Scientific and Clinical Advances Advisory Committee Paper

Paper title	**Embryo Culture Media Update**
Paper number	SCAAC(02/14)01
Meeting date	05 February 2014
Agenda item	**4**
Author	Anjeli Kara
Information/decision	Information
Resource implications	None
Implementation	None
Communication	An update of will also be passed to the MHRA for information
Organisational risk	Low
Committee recommendation	Members are asked to: • consider the progress of research (since February 2012) into the effects of the components in culture media used for IVF treatment; • advise the Executive if they are aware of any other recent developments; and • reflect on their views to date and identify what needs to be communicated to the MHRA.
Evaluation	None
Annexes	Annex A: CE Marking guidance document

1. Lay summary

1.1 As a clinical in vitro fertilisation (IVF) system aims to imitate the conditions in vivo as comparably as possible, optimising the culture environment during IVF treatment is fundamental. The components of embryo culture media, therefore, require close scrutiny to ensure that gamete and embryo stress and risk is minimised, and embryo health is improved.

1.2 Although generally considered to be safe based on past and current experience, uncertainties remain about the effects of embryo culture media. Varying concentrations of components such as growth factors, amino acids, energy substrates and antibiotics may potentially impact early embryo development, and the long-term health of ART offspring.

1.3 Concerns surrounding embryo culture media components, its potential effects and its regulation have been previously discussed by the Scientific and Clinical Advances Advisory Committee (SCAAC). The careful consideration of changes to and the introduction of new technologies have also been stressed (Brison et al, 2013; Harper et al, 2012). SCAAC has agreed that new research should be monitored periodically to inform Members of the potential impact of culture media compositions on embryonic development and that discussion surrounding these findings should be passed to the MHRA for information. This paper presents an update summary of recent studies, looking at the impact of varying components in culture media.

2. Background

2.1 The body of literature surrounding components of embryo culture media currently suggests that suboptimal culture conditions have the potential to affect embryo viability after transfer, and potentially the health of ART offspring. Researchers have noted that culture media conditions can result in delayed cell division (Bowman and McLaren, 1970) and increased cell death (Brison and Schultz, 1997). Furthermore, studies have shown that the environment for preimplantation development can affect the expression and imprinting of key genes (Doherty et al, 2000; Fauque et al, 2007), which can result in chromosomal defects and abnormal embryos, and may act as markers of abnormal health in newborns. More recently, however, studies have also noted that the embryonic culture environment can affect development and future disease risk through epigenetic changes.[1] With such a spectrum of potential variations in embryo viability, it is important to consider the composition and balance of the constituents involved in culture media.

Current Regulation

2.2 In the UK, human embryo culture media (used for treatment purposes) must be CE marked by a Notified Body. Notified Bodies assess manufacturers for quality and safety, and these bodies are in turn assessed by the Medicines and Healthcare products Regulatory Agency (MHRA) within the UK under the

[1] A paper by Market-Velker et al (2010) was brought to the Committee's attention to support this statement.

European Medical Devices Directive 93/42/EC.[2] It is therefore not currently within the remit of the HFEA to regulate the composition and safety of culture media.

2.3 The MHRA currently classifies culture media used for treatment purposes as a high risk class III medical device. Therefore, manufacturers are required to note and justify any changes to culture media composition in their technical documentation. Manufacturers are also expected to ensure post-market surveillance is carried out to monitor the long-term safety of culture media, which is reviewed by a Notified Body.

2.4 In February 2011, SCAAC raised the following issues regarding culture media:

- Inclusion of culture media storage period and conditions in the clinical investigation stage of CE marking
- CE marking for the oil used in embryo culture, cryoprotectants and ICSI medium
- MHRA classification of purely synthetic culture media
- Consistent regulation of culture media CE marking across Europe

2.5 In April 2012, the HFEA Executive worked with the MHRA and a SCAAC working group to produce a CE marking guidance document for UK-licensed fertility clinics, which was thereafter circulated to the sector (Annex A). The bulletin sought to clarify the requirements and responsibilities of the standard licence condition T30, addressed questions around CE marking, and provided information relating to CE marked culture media and how it should be modified. The Executive also provided guidance on the reporting of any adverse incidents and links to further guidance on medical devices.

2.6 Ongoing updates have been provided to SCAAC on research progress regarding culture media and their components, and relevant information has been shared with the MHRA as part of the Executive's joint-working strategy and regulatory remit. This paper is a further update and summarises key research findings between January 2012 and January 2014.

3. Research

Effects of culture media composition on fetal development and birth weight in clinical IVF

3.1 Animal studies have shown that culture media constituents are responsible for changes in the birth weight of newborns; however, in human IVF little knowledge is available on the effect of media type on fetal development and birth weight.

[2] Council Directive 93/42/EEC of 14 June 1993 concerning medical devices: http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31993L0042:EN:HTML

3.2 A recent retrospective study conducted by Eskild et al (2013) investigated changes to the birth weight or placental weight of singletons conceived between 1991 and 2011, in single or sequential culture media (Medicult Universal IVF Medium; Medicult Universal and Medicult ISMI; and Vitrolife G-IVF PLUS and Vitrolife G-1 PLUS). The group also sought to assess whether changes to birth and placental weight differed from the trends seen in newborns from spontaneous conceptions over the same period. Changes in culture media used for IVF were associated with significant differences in newborn birth weight and in the placental weight to birth weight ratio when compared with the trend from spontaneous conceptions.

3.3 This correlation is supported by Nelissen et al (2012) who sought to determine whether in vitro culture of embryos (Cook and Vitrolife) during the first few days of preimplantation development affects perinatal outcome in singletons, twins and in children born after transfer of frozen embryos. The group found that in vitro culture of embryos in Cook media resulted in singletons with a lower mean birth weight when compared with singletons born after culture in Vitrolife. This follows the group's 2011 study that suggested the use of different culture media leads to variations in fetal development as early as the second trimester; a finding that was further investigated in their 2013 study and noted apparent differences in fetal development after the culture of embryos in both Cook and Vitrolife media, as early as the second trimester of pregnancy.

3.4 While Eskild et al (2013) and Nelissen et al (2012) report correlations between culture media and birth weight, recent studies contradict these findings. As presented at the 2013 annual meeting of the European Society of Human Reproduction and Embryology (ESHRE), Carrasco et al (2013) conducted a prospective study where newborn birth weight following the randomised use of Cook and Vitrolife culture media were compared. A retrospective analysis was subsequently carried out as a second strand to the study, where birth weight was assessed against three sequential media – Cook, Medicult and Vitrolife. No significant difference was observed between the embryo culture media used and newborn birth weight.

3.5 These results are consistent with those published by Lin et al (2013) who retrospectively observed no significant difference in newborn length and birth weight among Vitrolife, Global and Quinn single stage culture media. Eaton et al (2012) also noted no significant association between culture media and birth weight in either singleton deliveries (Vitrolife G1.3, Global, and Vitrolife G1.5) or in twin deliveries (Vitrolife G1.3, Global, and Vitrolife G1.5). The same conclusions were obtained in the study by Vergouw et al (2012), in which the analysis of singletons born after a fresh single embryo transfer and singletons born after frozen–thawed single embryo transfer showed no significant difference in birth weight between HTF and Sage culture media.

3.6 While research has been conducted on a number of embryo culture media (eg, Vitrolife and Cook), the abovementioned results cannot be extrapolated to reflect all other culture media available for clinical use. It is therefore necessary that the analysis of all culture media and the long-term effects on the health of children conceived through ART remain monitored. It is also

important that studies understand the effect of compounding factors, as Lin et al (2013) and others have shown that compounding factors such as maternal weight and height, gestational age and infant gender are significantly related to birth weight.

Effects of differential pH on embryo culture media

3.7 A recently conducted review by Swain (2013) sought to highlight the importance of optimising pH in human preimplantation embryo development and to discuss recommendations for clinical practice. The review emphasised the importance of both internal pH (pHi) and external pH (pHe) in determining embryo quality.

3.8 Swain (2013) found it problematic to determine an optimal pHe due to the difficulty in isolating it from variables such as CO_2 and bicarbonate. Various commercial media companies were found to recommend varying pHe ranges, most within the range of 7.2-7.4, while others recommend that pHe should be altered based on the gamete or stage of the embryo; however, changing pHe during culture has not been shown to improve outcomes. It was also highlighted that media components can impact intracellular pH (pHi); therefore, media with differing concentrations of components (eg, lactate or amino acids), may have varying pHi despite being the same pHe.

3.9 Due to variations in optimum pH between multiple culture media and the absence of comparative studies, Swain (2013) advised adherence to manufacturer recommendations and maintenance of a small acceptable pH range for clinical IVF.

Effects of amino acids on embryo culture media

3.10 The main difference seen among culture media is found in the composition of amino acids; a component that is important for the metabolic and homeostatic regulation of the preimplantation embryo and embryo development. Carrasco et al (2013) noted that Cook, Medicult and Vitrolife culture media show variety in composition with respect to non-essential amino acids, such as alanine, asparagine, glutamine, proline and serine. Regarding essential amino acids, Vitrolife possesses methionine, whereas Cook and Medicult contain methionine, isoleucine, leucine, threonine, tryptophan, tyrosine and valine.

Effects of proteins on embryo culture media

3.11 While embryo culture media is available pre-supplemented with human serum albumin (HSA), poorly defined protein supplements that contain immune globulins are also used. However, unlike HSA, the composition of these supplements is unknown and represents a source of variation that may impact the quality of the culture environment. Wolff et al (2013) questioned whether the composition of complex protein supplements affect timing of mouse embryo development. When presenting at ESHRE 2013, Wolff et al noted that variations in protein supplements vary notably for oxidative metals (eg, iron) and that these supplements affect the time embryos spent at the two-cell stage, as well as synchrony of the second and third cycles, although there was no impact on blastocyst rate. However, a complete compositional

analysis was not performed and factors such as growth factors may be responsible for these differences.

3.12 Ziebe et al (2013) conducted a multicentre, randomised, placebo-controlled, double-blinded prospective design to evaluate the effect of granulocyte-macrophage colony-stimulating factor (GM-CSF)[3] in embryo culture media on ongoing implantation rate. Addition of GM-CSF was seen to elicit a significant increase in survival of transferred embryos to week 12 gestation and live birth.[4] These results are consistent with an established protective effect of GM-CSF on culture-induced embryo stress and it was noted that the effect of GM-CSF was influenced by HSA concentration in the culture media.

3.13 The presence of ammonium in culture media in both animal and human studies has shown detrimental effects on embryonic development and pregnancy rate. Most embryo culture media contain amino acids, some of which break down into ammonium; a process that is dependent on temperature. At the 2013 annual conference of ESHRE, Kleijkers et al (2013) presented that the concentration of ammonium accumulates in culture media during storage and incubation at 4-7°C and 37°C, respectively. These levels, however, were not seen to significantly affect IVF outcomes including fertilisation rate, embryonic development, pregnancy rate and the birth weight of ART offspring.

3.14 Due to the poor definition of complex protein supplements and varying amino acid composition of embryo culture media, ongoing analysis of the potentially adverse effects on embryo development is necessary to establish an optimal clinical consistency.

Effects of oxygen on embryo culture media

3.15 In addition to being a source of reactive oxygen species,[5] oxygen and its concentration may affect the performance and pH of various culture media. To determine differences in the interaction of oxygen concentration with culture media composition, Morbeck et al (2013) analysed its effect on mouse embryo development in a cross-sectional study. Mouse embryo development kinetics[6] were monitored for seven culture media (Cook, In Vitro Care, Origio, Sage, Vitrolife, Irvine CSC and Global) in low (5%) and atmospheric (20%) oxygen for duration of two-, four- and eight-cell stages. Cell division kinetics, particularly at the two- to four-cell stage, was culture media dependant and showed a strong interaction with oxygen concentration. Although further

[3] A multifunctional cytokine identified in mice as essential for normal blastocyst development and subsequent fetal viability and health.

[4] It was highlighted to the Committee that this significant increase was shown in a small non-specified subgroup of patients with previous miscarriage and requires confirmation in a prospective study. There was no beneficial effect of GM-CSF in all patients with no previous miscarriage.

[5] Chemically reactive molecules that form as a natural by-product of oxygen metabolism and play key roles in cell signalling and homeostasis. During times of environmental stress, ROS levels can dramatically increase and result in significant damage to cell structures.

[6] The study of rates of chemical processes, including how experimental conditions can influence the speed of a chemical reaction.

testing is essential prior to extrapolation to human embryos, this shows that variations in culture media in relation to oxygen could induce metabolic stress that may have long-term consequences.

Effects of single and sequential embryo culture media on embryo development

3.16 Three protocol types are currently used for the in vitro culture of embryos: culture using a single media, culture using a single medium sequentially and culture using two media sequentially. While the sequential protocol has been considered favourable by some, other studies have shown no difference (Biggers and Summers, 2008).

3.17 Summers et al (2013) compared the development of embryos in single and sequential media systems, using Global and Quinn's Advantage, respectively. The study comprised of two arms: the development of embryos from days one to three and day three to five/six. No significant difference was observed between the two media with respect to embryo quality during the preimplantation phase, in the rates of blastocyst development, inner cell mass and trophectoderm scores, or with the proportion of blastocysts chosen for transfer or cryopreservation. Together, these results support the view that two-step sequential media protocols are sufficient, though not necessary for the in vitro culture of embryos.

3.18 Another recent study investigating the morphokinetics[7] of growing embryos affected by two culture media (single, Global; sequential, Sage Cleavage) supports these findings. Basile et al (2013) found no statistical difference between either media for the timing of 2-, 3-, 4- and 5-cells and the length of the second cycle. Yang et al (2013) also sought to determine differences in the morphokinetics and number of set chromosomes of human embryos cultured in single (Irvine Scientific CSC) versus sequential (Vitrolife G1 and G2) media. No significant differences in the percentage of blastocysts with optimal morphokinetics between single and sequential culture were observed, and a non-significant trend towards more embryos developing to euploid blastocysts in single compared to sequential media was found.

Effect of tilting embryo culture system on embryo development

3.19 To apply appropriate stimuli to embryos, Hara et al (2013) developed a tilting embryo culture system to assess whether it could improve the grade of fresh human embryos compared with a control static culture system. Eggs were randomly assigned to the tilting or conventional system and embryos were evaluated at days three and five using standard grading criteria for embryo quality.

3.20 The fertilisation rate was similar across both groups and the rates of blastocyst formation at day five, including those highly graded, were significantly higher using the tilting system. There is therefore suggestion that

[7] The changes in the appearance of an embryo during a period of time.

embryo movement or mechanical stimulation during embryo culture may be beneficial for the in vitro culture of embryos.

4. Conclusion

4.1 Although the number of studies relating to the impact of culture media has risen over recent years, research remains inconclusive and on-going. The data currently available on the composition and factors affecting culture media, fetal development and newborn birth weight is limited to predominantly retrospective studies.

4.2 More rigorously designed large-scaled, randomised control trials remain to be conducted, which also address the long-term outcomes of variations in culture media. In turn, this will ensure that culture media for treatment is both safe for use and contains components optimal for embryo, fetal and long-term development. Further studies exploring the wider culture environment and how factors may affect the variations in culture media should also continue.

5. Recommendations

5.1 Members are asked to:

- consider the progress of research (since February 2012) into the effects of the components in culture media used for IVF treatment;
- advise the Executive if they are aware of any other recent developments; and
- reflect on their views to date and identify what needs to be communicated to the MHRA.

6. References

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ANNEX A – CE marking and ART

It is a standard condition of all HFEA licences that wherever possible only CE marked medical devices should be used (standard licence condition T30). Centres often report that CE marked products are not available or that some CE marked products prove to be unsuitable. This article clarifies the requirements of this standard licence condition and what we expect centres to do.

What is CE marking?

The CE mark on a product represents the manufacturer's declaration that the product meets the relevant EU regulations. For products used in Assisted Reproductive Technologies (ART) (including IVF, IUI and any other treatment involving the handling of human gametes or embryos in a laboratory), the relevant regulations are the Medical Devices Regulations.

There are three classes (risk categories) of medical device: class I, class II (which is further subdivided into classes IIa and IIb) and class III. The higher the classification, the greater the level of assessment of the product before a CE mark is awarded.

HFEA centres should not be using any media or consumables that have not been CE marked at a classification suitable for the purpose for which the device is being used. In the UK it is illegal for manufacturers to sell non-CE marked products that would fall under the remit of a classified medical device (for a particular intended purpose). If you are aware of any non-CE marked products being sold for use in an ART setting, we would encourage you to notify the Medicines and Healthcare Products Regulatory Agency (MHRA).

The media used in IVF are usually defined as Class III Medical Devices because they contain medicinal products or substances acting in an ancillary manner. Other products specifically intended for ART purposes, such as plastic ware, may have a different medical device classification. Centres should ensure that they use only plastic ware that has been CE marked for use in humans where appropriate. General purpose laboratory equipment is not classified as a medical device and therefore does not need to be CE marked.

CE marked culture media

For class IIa, IIb and III products, manufacturers are required to submit information on the product and the manufacturing processes to an external body (called a Notified Body) as part of the CE marking process. Notified bodies undertake a review of the manufacturer's design dossier prior to the approval of Class III medical devices.

If the medium contains an ancillary medicinal substance which assists the physical mode of action of the media by acting in a pharmacological, immunological or metabolic manner (see MHRA Guide to what is a Medicinal Product, paragraph 13),

then the classification of the medium may need to be considered by the European Medicines Authority prior to CE marking or require a consultation with an EU medicines authority (the MHRA in the UK) to determine whether these products should still be classified as medical devices or whether the product composition means that the product should be classified as a medicine. **If a manufacturer makes any changes to these products they need to be re-assessed.**

Modifying CE marked culture media

Modifying existing devices (for example, adding calcium ionophore to culture medium) or using them 'off-label' for purposes not intended by the manufacturer (for example, using a medium for a different purpose from the one for which it was specified) has safety implications. It may also count as manufacture of a new device under the Medical Devices Regulations. The original manufacturer's liability will be limited and liability may be partly or wholly transferred to the organisation or person making the modifications if the device is implicated in an adverse incident.

If you choose to modify an existing product or use a product 'off label', you risk becoming the 'manufacturer' and you should perform a suitable risk analysis and validation to ensure the product or process is safe. The HFEA would not recommend the modification of products or the 'off-label' use of products as this is potentially non-compliant with the requirements of standard licence conditions.

The MHRA has issued advice on 'off-label' use in Medical Device Alert: Medical devices in general and non-medical products (MDA/2010/001). This advice clarifies that if you modify a product you are then required to validate the safety and efficacy of each and every combination of products used and have robust evidence to support their efficacy and long term safety.

Adverse Incident Reporting

Individual clinics should report problems with media and/or other devices in generating pregnancies or long term health of children to the MHRA and the HFEA. It is important that clinic staff are vigilant so that adverse incidents, including near misses, are reported. Guidance on what should be reported to the MHRA can be found in section 5.1.1 of MEDDEV 2.12-1 rev 8 Guidelines on a medical devices vigilance system.

The HFEA is aware of the recall of a device used in cryopreservation and this is an example of where adverse incident reporting was important in minimising the impact of a faulty product. Manufacturers have a legal responsibility to report any suspected problems with their products to the relevant Competent Authorities (MHRA in the UK) as soon as they become apparent. Users may also have a legal responsibility to report to the relevant agencies. Reports where user error is suspected are also valuable to the MHRA as this can provide evidence of the need for an improvement in the instructions for use.

We would strongly encourage you to notify the HFEA (using the normal incident reporting system) and the MHRA (using the MHRA's online adverse incidents reporting system) of all relevant incidents.

What you should do now

You should check the CE mark status of culture medium used in your clinic. If these products are not CE marked appropriately, you should contact the manufacturer to establish whether they are in the process of obtaining a CE mark.

If medium is not CE marked, you should assess the risks of continuing to use the product. We would not wish you to make precipitous changes that might impact on the quality of treatment that you are providing to your patients. However, in the absence of any prospect that the products that you use will meet the requirements of licence conditions, you should consider implementing a plan of action to ensure compliance within the next year.

You should also ensure that laboratory plastic ware that comes into contact with gametes or embryos is appropriately CE marked. As above, in the absence of any prospect that the products that you use will meet the requirements of licence conditions, you should consider implementing a plan of action to ensure compliance within the next year.

If you conclude that you are being offered products for use in ART that are not CE marked as required, you should also contact the MHRA to report this.

Further Information

MHRA website: www.mhra.gov.uk/Howweregulate/Devices/index.htm

MHRA Device Bulletin – Managing Medical Devices DB 2006(05) (guidance on the purchasing, deployment, maintenance, repair and disposal of medical devices): www.mhra.gov.uk/Publications/Safetyguidance/DeviceBulletins/CON2025142

Council Directive 93/42/EEC of 14 June 1993 concerning medical devices: http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31993L0042:EN:HTML

European Commission Manual on borderline and classification in the community framework for medical devices (see section 4.3: In-Vitro Fertilisation (IVF) and Assisted Reproductive Technologies (ART) products): http://ec.europa.eu/health/medical-devices/documents/borderline/index_en.htm

MEDDEV 2.2/4 Guidelines for conformity assessment of In Vitro Fertilisation (IVF) and Assisted Reproduction Technologies (ART) products (guidelines that relate to CE marking of culture media): http://ec.europa.eu/health/medical-devices/files/meddev/2_2_4_ol_en.pdf

MEDDEV 2.12-1 rev 8 Guidelines on a Medical Devices Vigilance System (guidance on vigilance with specific reference to ART): http://ec.europa.eu/health/medical-devices/files/meddev/2_12_1_ol_en.pdf

MEDDEV 2.1/3 (section C explains the process and the documentation that must be submitted to the Medicines Authority / EMA by the Notified Body): http://ec.europa.eu/health/medical-devices/files/meddev/2_1_3_rev_3-12_2009_en.pdf

Manual of decisions on medical devices (section 4.3): http://ec.europa.eu/health/medical-devices/documents/borderline/index_en.htm

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