Embryo culture media update

Strategic delivery:	☒ Safe, ethical effective treatment	☐ Consistent outcomes and support	☐ Improving standards through intelligence
Details:			
Meeting	Scientific and Clinical Advances Advisory Committee (SCAAC)		
Agenda item	5		
Paper number	SCAAC(19/06/2017)03		
Meeting date	19 June 2017		
Author	Anna Quinn, Scientific Policy Manager		
Output:			
For information or decision?	For information		
Recommendation	Members are asked to: • consider the progress of research (since October 2015) 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 • reflect on their views to date and identify what (if anything) needs to be communicated to the MHRA.		
Resource implications	None		
Implementation date	N/A		
Communication(s)	None		
Organisational risk	☒ Low	☐ Medium	☐ High
Annexes	None		

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 highly 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 early embryo development and the long-term health of children conceived by assisted reproduction.

1.3. Concerns about the components of embryo culture media, how they are regulated and their potential effects have been discussed by SCAAC on several previous occasions, most recently in October 2015 where the committee expressed concerns about lacking of reporting from IVF clinics. 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.

Current regulation

1.4. In the UK, human embryo culture media use 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 MHRA within the UK under the European Medical Devices Directive 93/42/EC[1]. It is therefore not within the remit of the HFEA to regulate the composition and safety of culture media.

1.5. 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. Research

2.1. A Cochrane review carried out in 2015 (Youssef et al.) aimed to evaluate the safety and effectiveness of different embryo culture media used for IVF and ICSI. A total of 32 studies were included in the review and whilst the authors concluded that having an optimal embryo culture medium is important for

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

embryonic development during IVF or ICSI treatment, there was insufficient evidence to support or refute the use of any specific culture medium. Several studies have been carried out, however no two studies compared the same culture media and no studies found any differences between culture media. This report highlighted the need for well-designed and executed randomised controlled trials in this area.

Sequential versus single media

2.2. Bouillon et al. (2016) investigated the effects of two different embryo culture media on the health and development of children born after IVF. In this single centre cohort study, IVF attempts were randomised to a Single Step Media (SSM) group, or a Global medium (Global) group. Over a six month period, 371 IVF attempts were randomised; 179 into the Global group and 192 into the SSM group. The study was stopped prematurely as the researchers observed significantly lower pregnancy and implantation rates in the SSM group compared to the Global group. 73 singletons born following randomisation (42 for the Global group and 31 for the SSM group) were followed-up as part of the study up to five years of age. Whilst delivery rate was significantly lower in the SSM group than in the Global group, culture media was found to have no effect on birthweight, risk of malformation (minor and major), growth and frequency of medical concerns. However, the authors reported that children in the Global group were less likely than those in the SSM group to show developmental problems. The authors suggest that further studies investigating the epigenetic[2] profile of children born following the use of SSM and Global media would be of value.

2.3. In 2016, Ceschin et al. compared the fertilisation rates, cleavage and blastocyst formation development and pregnancy rates of two commercially available embryo culture media (G1-PLUS™/G2-PLUS™ sequential medium and GV BLAST™ sole medium). The authors reported no significant difference between the two media for any of the parameters that were measured.

2.4. In a study by Costa-Borges et al. (2016), a two-step protocol involving a single media which is renewed on the third day of culture was compared to a one-step protocol where the embryos are cultured without interruption for five days in a single medium which is not renewed. Both protocols involved culture of embryos in a time-lapse incubator. The study included embryos from 59 patients and the authors found no difference in embryo morphology and morphokinetic parameters, clinical pregnancy and take-home baby rates, and perinatal outcomes between the two groups. The authors suggest that using an uninterrupted culture system in a time-lapse incubator does not impact on embryo development and has practical advantages for clinics including reducing costs.

[2] Epigenetics refers to the information in the genome over and above that contained in the DNA sequence.

2.5. Werner et al. (2016) compared sequential (Quinn's Advantage Cleavage Medium, SAGE) versus monophasic (Continuous Single Culture, Irvine Scientific) media to determine which culture conditions yielded the best blastocyst development and implantation rates. Sequential media involves embryos being cultured for three days and then transferred to fresh media for blastocyst development. In monophasic media conditions the embryo is cultured in a single media from day 0 until blastocyst development. 192 patients were recruited into the study which included 2257 embryos. The authors noted that embryos cultured in sequential media had higher blastulation rate compared to those cultured in monophasic media. However, there were no significant differences in the timing of blastulation or aneuploidy rates, suggesting that the type of media did not impact on the reproductive potential of those embryos which did blastulate.

Trials comparing different culture media

2.6. A Chinese study by Yin et al., carried out in 2015 measured the impact of three different embryo culture media on laboratory outcomes and neonatal birth weight. The culture media under investigation were Quinn's Advantage (QA), Single Step Medium (SSM) and Continuous Single Culture Medium (CSC). The laboratory outcomes measured were fertilisation rate, normal fertilisation rate, cleavage rate, normal cleavage rate and good quality embryo rate. 673 patients were included over the two year study period and multiple linear regression analyses showed that the type of culture medium was correlated with fertilisation rate, normal fertilisation rate, cleavage rate and good quality embryo rate. The authors concluded that the type of culture media used during IVF/ICSI had potential influences on laboratory outcomes, it was not associated with neonatal birth weight.

2.7. Kleijkers et al. (2016) conducted a multicentre, double blind randomised controlled trial to compare the use of HTF embryo culture media with G5 media. 836 couples were recruited into the study between July 2010 and May 2012 (419 into the HTF group and 417 in the G5 group). Number of usable embryos, implantation rate after fresh embryo transfer and clinical pregnancy rate were all found to be significantly higher in the G5 group compared to the HTF group. Birthweight was found to be significantly lower in the G5 group compared to the HTF group (mean difference 158g, 95% confidence interval: 42g – 275g). This significant difference remained after adjusting for gestational age and gender. The authors reported that live birth rate was 6% higher in the G5 group and this was not statistically significant. However, the study was powered to detect a 10% difference in live birth rate and a smaller difference could still be clinically relevant. The authors go on to conclude that the G5 media provides greater IVF treatment success as other clinically relevant outcomes significantly favoured G5 media over HTF.

2.8. Following the publication of the Kleijkers et al. (2016) study, several responses were published which debated the reported findings. Most recently, a commentary published in Human Reproduction comments on the original

studies, the numerous responses and the interpretation of evidence (Roberts & Vail, 2017). Whilst the main focus of this paper was on the appropriate interpretation of evidence, the authors conclude that the evidence suggesting an association between culture media and birth weight should be taken seriously and further randomised controlled trials are needed better understand this finding. However, they also note the large participant numbers required to perform adequately powered trials which means large observational studies are still of value.

Effects of insulin supplementation

2.9. Fawzy et al. (2017) measured the impact on clinical pregnancy rate of supplementing embryo culture media with insulin. The study involved 5,142 sibling eggs retrieved from 360 patients. The insulin-supplemented group was found to have higher rates of clinical, ongoing and twin pregnancies compared to the non-insulin supplemented control group. The authors also reported higher embryo quality and compaction in the insulin supplemented group on day three, and on day five the insulin supplemented group was found to have higher rates of blastocyst formation, quality, and cryopreservation. The authors concluded by stating that these results require further confirmation through a multicentre randomised controlled trial and through using different culture media.

Effects of protein supplementation

2.10. A 2015 study investigated whether the protein supplement concentration in embryo transfer medium had any impact on clinical outcomes of IVF and ICSI cycles. 750 patients undergoing IVF/ICSI met the inclusion criteria for the study and Huang et al. divided these patients into three groups according to concentration of synthetic serum substitute in the embryo transfer medium: Group A (10%), Group B (20%) and Group C (50%). No statistically significant differences were found between the groups for clinical pregnancy rate, multiple pregnancies, implantation rate and live birth rate. The authors concluded that supplemental protein concentration in embryo transfer medium does not influence treatment outcomes.

Disclosing culture media composition

2.11. A 2016 literature review by Sunde et al. considered whether greater transparency is needed regarding the composition of culture media. The authors conclude that manufacturers should be required to disclose the composition of their culture media and that any changes in composition should be justified, validated and communicated to the end users. They also propose that the existing regulatory framework relating to culture media should be amended to ensure disclosure of composition and to improve monitoring of long term outcomes associated with each culture media used in the clinic.

3. Conclusions

3.1. Since SCAAC last considered embryo culture media in 2015, research in this area has continued to progress with a greater focus on the comparison between protocols where the embryo culture media is refreshed after three days, and protocols where the embryo is cultured for five to six days in a single medium.

3.2. 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.

3.3. Further research is required to further explore the relationship between embryo culture media and longer term health outcomes in children born.

4. Recommendations

4.1. Members are asked to:

- Consider the progress of research (since October 2015) 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
- Reflect on their views to date and identify what (if anything) needs to be communicated to the MHRA.

5. References

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