In vitro culture of human embryos : effects on fetal development and the role of the placenta

Chapter 8

Valorisation

Why is this thesis relevant?

In this valorisation paragraph, I want to consider the potential impact of our research and to valorise what is of societal and economic value.

Relevance

The number of IVF children increases every year, while the etiology of the adverse perinatal outcome of singletons conceived after assisted reproduction technology (ART) is still incompletely understood. In humans, these phenotypic differences, such as birthweight, appear less pronounced than in animals. However, the apparently normal newborn infants after ART might be carrying lifetime health risks. Safety of ART is of vital importance, however research in this field has been very limited so far. We have shown that the type of culture medium used has a significant effect on fetal development and birthweight. Moreover, human placentas display epigenetic disturbances after ART when compared to placentas from spontaneous pregnancies.

Although ART has led to substantial knowledge of human embryology, it has also turned into a multi-million dollar industry. Worldwide, ART is mainly provided in the private health care sector. IVF clinics want to deliver as many healthy babies as possible. But as in some countries success rates of IVF clinics are published, ranking ART clinics according to their success rates in league tables could increase the pressure to use the latest technology in order to achieve the best results. IVF patients are very www-literate, so ART clinics may also be under strong pressure from patients to go ahead with innovations if expected benefits were already set out on the web or in the press. In ART there are many examples of new technologies and methods which have been introduced in clinical practice without appropriate evidence-base to show that the procedure is safe and beneficial to the patient, that it is cost-effective, and that its benefits outweigh its potential harms, for instance DHEA administration to 'rejuvenate' old eggs, time-lapse monitoring of embryo development, endometrial 'scratching', assisted hatching, *in vitro* maturation, blastocyst transfer, vitrification and preimplantation genetic screening (PGS) (Harper *et al.*, 2012). Furthermore, changes to culture media composition (supplementation with growth factors, antioxidants, cytokines and vitamins), stimulation regimens and laboratory protocols are often established internationally without adequate validation. "Assisted reproduction has been technologically driven rather than evidence

based. Treatment tends to be empirical, and existing evidence can be ignored in favour of novel interventions" (Bhattacharya *et al.*, 2001).

Target groups

The results of this thesis are interesting for IVF professionals, culture medium manufacturers, pharmaceutical and other industries, health economists and health care providers/insurers, politicians and the European Society of Human Reproduction and Embryology (ESHRE). Together we need to determine what the best course of action is. Above all, our research results are of interest to patients. What do patients want? Why do they accept or even insist on receiving treatments without any evidence? Are patients aware of the adverse outcome after ART or of the possible long-term health effects? Do they care? Infertility couples belong to a very vulnerable group. They will do everything to achieve their goal, a baby. They should not be exploited.

Activities/innovation

All our results have been published in high-ranking scientific research journals. We have had the opportunity to discuss our findings nationally and internationally to gain more attention for this important topic. This has led to more and more research groups worldwide investigating the effect of culture medium on human perinatal outcome. In the Netherlands, a multi-centre trial has been initiated comparing two commercially available culture media with respect to live birth rate and perinatal outcome. We played a role in the formation of the ESHRE working group on culture media with members from the special interest groups Embryology, Safety and Quality in ART, and Genetics. This working group held meetings with the largest ART culture media producers to encourage constructive co-operation over transparency, composition and quality control parameters. Regular expert meetings for instance organised by ESHRE, should raise global awareness and the development of recommendations and official guidelines.

The possibility that media and other culture conditions are partly responsible for an adverse perinatal outcome in IVF children should not be ignored. The extend of this adverse outcome however is still uncertain. Therefore, larger studies are required to investigate the etiology of this adverse perinatal outcome. Culture media manufacturers need to disclose the exact composition of their media, including concentrations of components, to enable a better comparison of culture media.

Schedule and implementation

IVF professionals need to consider the safety of future changes to culture media composition, stimulation regimens and laboratory protocols before introducing them into the clinical setting. New technologies should be evaluated for effectiveness, safety and cost-effectiveness. Also, they should further investigate the effects of those technologies that have already been introduced. We need more relevant preclinical testing, preferably using a more appropriate test than the mouse embryo assay. Subsequently, human embryos should be made available for research, and research should be performed on human eggs/sperm or embryos donated for research. This should be followed by large clinical trials with follow-up of IVF pregnancies and children. Innovation is important, however we need to be critical before introducing these innovations in human ART.

According to EU regulations, culture media intended for use in the IVF process to support the growth and/or storage of embryos are generally to be considered as Class III medical devices (EU Manual, 2014). These medical devices must meet certain essential requirements that are set out in the Medical Devices Directive 93/42/EEC and further explained in an EU Guideline (2014). In these guidelines it is stated that culture media must be CE (European Conformity) marked and that pre-clinical testing (including tests for genotoxicity, carcinogenicity and reproductive toxicity) should be performed in order to evaluate the risk due to the IVF product (e.g. culture media). Furthermore, manufacturers of such medical devices must perform pre-clinical and clinical evaluations and should plan a post-market clinical follow-up programme in order to provide the clinical safety and performance data on the use of the culture medium in clinical practice.

In view of the results described in this thesis, we hope to achieve more awareness for the existing legislation and most importantly its clinical implementation. Tighter regulation of the production of IVF culture media via national and European legislation is required to eventually disclose the exact composition of media.

Lastly, we believe that ART patients and their offspring should be fully informed of the adverse outcome after ART and the possible long-term health effects. A patient-preference investigation could enhance our knowledge on what patients want with regard to this very important topic.

References

Bhattacharya S, Hamilton MP, Shaaban M, Khalaf Y, Seddler M, Ghobara T, Braude P, Kennedy R, Rutherford A, Hartshorne G, *et al.* Conventional in-vitro fertilisation versus intracytoplasmic sperm injection for the treatment of non-male-factor infertility: a randomised controlled trial. *Lancet* 2001;**357**:(9274): 2075-2079.

Harper J, Magli MC, Lundin K, Barratt CL,Brison D. When and how should new technology be introduced into the IVF laboratory? *Hum Reprod* 2012;**27**:(2): 303-313.