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Valorisation
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In this valorisation paragraph the potential societal impact of the research presented in this thesis will be discussed. This thesis presents the results of a follow-up study in 9-year-old children born after IVF. During an IVF treatment, embryos are cultured in culture medium that may contain a variety of different ingredients. We showed in a previous study that this culture medium can affect the birthweight of children born after IVF. It is also known that birthweight is an important parameter predicting future health risks, and therefore it is important to perform structured follow-up. In this thesis, we present the results of such a follow-up study. We showed that the group of children who were heavier at birth, were on average still heavier and had a higher BMI at 9 years of age if compared to the other group. Cardiovascular development and cognitive development were comparable. Our study was the first to show that culture medium can have an effect on postnatal development.

Relevance
Since the first successful IVF treatment in 1978, the use of this treatment has increased significantly worldwide. In 2018, it was reported that already more than 8 million babies conceived after IVF/ICSI treatments were born. Research focusing on long-term health and development of the IVF offspring is still scarce. However, there is increasing evidence that pregnancies after ART are associated with a higher risk of adverse outcomes such as low birthweight and also that children born after ART show different outcomes with possible long-term health risks. We have shown that culture medium can affect not only birthweight, but also postnatal weight and growth patterns. Lower birthweight and accelerated postnatal growth are known to be associated with a higher risk for cardiovascular diseases in later life, which underlines the importance of structured and long-term follow-up of the children born after IVF.

Embryo culture media are an essential part of the IVF treatment and all cells within the embryo (and thus, indirectly, also all cells within the child’s body) are exposed to the culture medium. At present, in contrast to the drugs used in IVF, there is no uniform regulation or statutory oversight of the composition of embryo culture media. In Europe, the majority of media carry the CE mark, but non-CE media can still be used. Overall, fertility centers choose the media they want to use according to their own preferences. Manufacturers differ on whether and how they give information on the composition of the culture media and the scientific rationale. They are allowed to change their composition without informing their end-users (embryologists) about the changes. In the EU covenant of 2009 it was agreed that the EU would regulate ART culture media and consider them medical devices (Class III). According to the EU medical device regulations, manufacturers are supposed
to perform structured and long-term follow-up of the offspring who as an embryo were cultured in their culture media, however this is not performed. It is worrisome that the exact quantitative composition is unknown, because this limits the option to correlate specific culture medium ingredients to IVF outcome. The strong financial aspect of this field has led to a lack of transparency regarding composition, which does not facilitate the scientific effort to refine IVF culture media and reach a consensus on which one to use in which circumstances.

Target groups
The results of this thesis are interesting mostly for IVF clinicians, embryologists and embryo culture medium manufacturers. In the future, it could also be potentially useful for health economists, insurance companies and politicians. The results are only to a limited extent interesting for couples that are currently undergoing fertility treatment or already have a child conceived via IVF. Since it is still very unclear to what extent culture media can influence outcome, and moreover, which culture medium (ingredient) would be better, it is too early to inform patients about this. Patients should be informed that the general health outcome of children born after IVF is reassuring, but that all techniques that are applied during the embryonic phase are possibly capable of creating an increase in risks in later life.

Activities/Innovations
All chapters in this thesis have been or will be published in high-ranked scientific journals. Also, we have discussed our findings at numerous national and international conferences to increase awareness and attention for this important topic. Also the findings were discussed in popular scientific journals and newspapers (New Scientist and Daily Mail) that are easy accessible to patients and other people interested in IVF. We are currently performing a new multicenter randomized controlled trial to compare pregnancy and perinatal outcome between a sequential culture medium and a single-step culture medium to increase the knowledge and corroborate the evidence on their effects.

The European Society of Human Reproduction and Embryology (ESHRE) has appointed a working group on culture media with members from the special interest groups Embryology, Safety and Quality in ART, and Genetics. This working group encourages constructive co-operations with IVF culture media manufacturers regarding transparency, composition and quality control parameters. Also, in 2016 the Oxford University Press published a press release in Human Reproduction from the working group that received worldwide attention. The results of our study will be presented to this working group and will add valuable information and therefore enforce the working groups' position in the lobby with manufacturers to become transparent on the composition of their culture media.
It is very important to acknowledge the possibility that IVF culture media composition, other culture conditions and techniques applied during the IVF treatment can affect post-natal development of the offspring. However, the extent of the adverse outcome is still uncertain and large basic research studies and randomized clinical studies are essential to investigate the aetiology of the adverse outcome.

**Schedule and implementation**

Introduction of new techniques, changes in culture media composition and laboratory protocols should be preceded by thorough and structured research upon introduction into daily practice. In reproductive medicine not infrequently a treatment forces itself upon the practitioner long before a suitable theory of the mechanism of action has been developed. Too often, new techniques are introduced into daily practice after just some appealing findings in a few small, underpowered, mostly observational studies. Well-designed and properly powered research is indispensible for improving the techniques used in IVF. With regard to culture media development, changes should be made to the existing regulatory system to achieve transparency and improve monitoring of outcomes to the long-term benefit of ART children. At the moment, only basic quality control and a proof-of-principle from mouse embryo testing is necessary before a new culture medium can be applied in the human IVF clinic. This is not enough to safeguard the health of future IVF children.

An important step forward would be that researchers are allowed to culture embryos just for research purposes. Animal models are in many ways a very good first step for research in the field of reproductive medicine, but the results might not always translate well to the human situation. The most important advantage of animal research is the shorter lifespan of for example mice, with a timespan of a couple of months “long-term” effects of culture medium can be investigated. However, humans have a fecundity that is not at all comparable to that of mice and sheep and also there are differences in the nutritional requirements of the embryos. Therefore animal models should not be the only way to gain more insight in the (patho)physiology and to test effectiveness of new techniques, but it should also be performed in human embryos. Unfortunately in The Netherlands, it is not allowed to culture embryos for research and in the latest political coalition agreement, in October 2017, the new Government announced that this will not be allowed for at least the next 4 years. This is a great set-back for research in the field of ART and it should be carefully reconsidered. In comparison to culture media for mouse embryos, media for human embryos are not truly optimized and probably will never be without proper research in human embryos. In order to optimize basic culture parameters for mice, to optimize mouse embryo culture medium, several thousand mouse embryos were used. To achieve similar experiments in humans, the number...
of human embryos would be very high and numerous ethical issues would be raised. However the consequence of this is the introduction of embryo culture media without proper testing in the human.

**Challenges involved in the field of reproductive medicine**

Although ART has changed the life of many people in a positive way, it is also an increasingly commercial industry. Couples who are trying to conceive are willing to try anything to achieve their biggest wish, i.e. becoming parents. The field of ART is rapidly changing and improving, but many new technologies and methods have been introduced in clinical practice without appropriate evidence to show that the procedure is beneficial to the patient and moreover that the benefits outweigh its potential harms. The biggest difference with other fields in medicine is that fertility patients attend clinics with a “wish” instead of a “complaint”. Their attitude is therefore quite different from patients who attend their doctor for example for high blood pressure. Infertility patients are often well informed, either by reading on the internet but also by taking in a lot of (not always correct) advice from their friends and family. Professionals involved in IVF treatments should inform their patients carefully and the main objective should be to be honest about the (im)possibility and usefulness of adding extra techniques. Shared decision making together with well-informed couples is one of the challenges of IVF clinicians.

We hope that the results described in this thesis will increase awareness for the existing legislation and most importantly more strict regulations concerning the clinical implementation of culture media. More stringent regulation on the production of IVF culture media and more flexible legislation on embryo research is required to keep moving forward with the best interest of the patients and their offspring in mind. It is the duty of healthcare professionals and researchers to focus on unravelling the aetiology of the observed differences to be able to improve the techniques in order to reduce the potential lifetime health risks of the IVF offspring.