Economic evaluation of embryo transfer protocols

Valorization

In this valorization paragraph the potential societal impact of the research described in this thesis is discussed. This thesis presents an estimate of the long-term costs and consequences of reducing the number of multiple pregnancies in in vitro fertilisation (IVF) by single embryo transfer (SET).

Relevance

Around 10-15% of couples trying to achieve a pregnancy are confronted with fertility problems. IVF treatment has become routine practice in reproductive medicine to overcome fertility problems in couples across the world. Since the first successful IVF treatment in 1978, the use of this technology has increased significantly worldwide and thereby the number of children born after IVF. In 2018, it was reported that already more than 8 million babies conceived by IVF or intracytoplasmic sperm injection (ICSI) were born. However, research focusing on long-term health and development of the IVF offspring is still scarce. The reliance on multiple embryo transfer during IVF treatment to compensate for initially low pregnancy rates has resulted in an increase in the number of multiple pregnancies as soon as its technique and procedures improved. Multiple pregnancy is however considered a complication of IVF treatment due to its relatively high risk of maternal, obstetric and neonatal complications and accompanying higher healthcare costs.[75] Due to those risks, elective single embryo transfer (eSET) is advocated in most European and other developed countries in an effort to reduce the multiple pregnancy rate to a minimum while maintaining an acceptable pregnancy rate. The policy of mandatory eSET has been adopted in several countries such as Belgium, Sweden and Quebec, resulting in a significant reduction of the multiple pregnancy rate and perinatal morbidity and mortality. An IVF treatment is an expensive procedure making cost-effectiveness considerations important in the decision on the number of embryos to transfer. From a cost-effectiveness point of view, eSET is only preferred when performed in good prognosis patients and when the transfer of frozen-and-thawed embryos are included.[54] However, most studies investigating the cost-effectiveness of embryo transfer strategies were limited by the chosen measure of effectiveness and time horizon. Those studies did not consider the long-term consequences and costs of the embryo transfer strategies, such as the health status of the singletons and multiples born, and instead used cost per live-birth as outcome measure. In accordance with the general opinion that multiples are a complication of IVF, multiple births were counted as one life-birth in those previous cost-effectiveness studies. Despite the continuing development in the direction of eSET, double embryo transfer (DET) is still performed in clinical practice in 'poor prognosis' women.

The TwinSing study

In the TwinSing study, we estimated the long-term costs and consequences of reducing the number of multiple pregnancies in IVF by single embryo transfer. Multiple births con-

ceived by IVF have considerably poorer neonatal outcomes and used more hospital resources during the first five years of their lives than singleton births conceived by IVF. However, when excluding the costs made during the birth admission, hospital costs of multiple births and singletons conceived by IVF or ICSI were comparable. The long-term cost-effectiveness of several alternative embryo transfer strategies was estimated with a Markov model. It is cost-effective to replace DET with single embryo transfer from a short-term perspective (1-year), but from an intermediate-term (5-year) or long-term (18-years) perspective DET is the preferred embryo transfer strategy from a cost-effectiveness point of view.

Target groups

The results of this thesis are interesting for IVF professionals, health economists and health care providers, health insurance companies, politicians and the European Society of Human Reproduction and Embryology (ESHRE). In several European countries the government or insurance pays for the IVF treatment. In these circumstances, the government has a stronger say in the decision about the number of embryos to transfer. Above all, our research results are of interest to infertile couples who may need to undergo an IVF treatment. It has been reported that a noteworthy amount of infertile couples prefer to transfer more than one embryo in order to achieve a twin pregnancy, even if they have knowledge about the associated risks. Together we need to determine what the best course of action is.

Activities and innovation

The TwinSing study is innovative and at the same time results are controversial as it is one of the first cost-utility analyses performed in the field of assisted reproductive technology that estimates the long-term costs and consequences of reducing the number of multiple pregnancies in IVF with SET. It differs from previous studies as the chosen measure of efficiency of our study is the cost to 'gain' an additional QALY of the child(ren) born from the fertility treatment, a measure that combines the duration and health-related quality of life. The selected outcome measure is considered a logical extension of the intermediate outcome thus far used in economic evaluations of embryo transfer strategies, that is, the cost per live birth. All our results have been, or will be, published in high-ranking scientific research journals. We have presented our findings at national and international conferences to gain more attention for this topic. We hope that this has led to increased awareness among health policy decision makers and health care professionals of the of the methodological decision to count a multiple birth as one life birth in economic evaluations of embryo transfer strategies. Despite the results of our study, the transition towards elective single embryo transfer is ongoing. This suggests that cost-effectiveness arguments do not fuel decisions regarding embryo transfer strategies in IVF.

Schedule and implementation

An IVF treatment is an expensive procedure making costs consideration important in the decision on the number of embryos to transfer. With the current study we have shown that multiple birth children do have poorer health outcomes (including death) and increased health care costs compared to singletons during the neonatal period. On the other hand most multiple birth children grow up in good health, comparable to that of singletons. Therefore, children from multiple pregnancies are not necessarily 'a complication' of IVF. Based on the assumption that costs and outcomes of all children (i.e. both children of a twin) should be counted and that the health outcomes can be expressed in QALYs, we have shown that DET is the preferred embryo transfer strategy on the long-term from a cost-effectiveness point of view. The results of this thesis may suggest that the movement to 'mandatory' eSET for all couples is irrational and DET should be implemented in clinical practice. We do, however, not advocate that clinical practice guidelines should be altered. Economic evaluations need to be complemented by further considerations upon introduction in daily clinical practice. An important ethical issue is whether it is acceptable to 'purposely' create children that have a higher chance of mortality and poorer (neonatal) health outcomes and reduced quality of life through DET, even if it is considered cost-effective. This requires careful attention from health policy decision makers and healthcare professionals. If the outcome of a careful and balanced discussion among healthcare professionals - in contrast to the result of our economic evaluation - is that multiples are a complication of IVF treatment, further efforts should be made to abandon DET and to improve the success rate after SET. In the end it will be up to the policymaker, healthcare professional and the infertile couples to decide, which embryo transfer strategy to be used.

It is unlikely that the movement from DET to eSET will be reversed. Supported by more than a few short-term studies investigating the cost-effectiveness of eSET compared with DET, several northern European countries advocate eSET followed by the transfer of a single frozen-thawed embryo in subsequent cycles for infertile couples with good prognosis. This policy aims to promote the birth of healthy singleton babies, reducing the costs of the management and care of complications of multiple pregnancies and multiple birth children. With extension of the duration of embryo culture from 2 to 3 days (cleavage stage) to 5 days (bastocyst stage), the embryo with the highest implantation potential may be selected for transfer. Together with improvements in the cryopreservation techniques this led to the appearance of the so-called "freeze-all" policy as alternative for fresh embryo transfer. With this strategy all embryos are electively cryopreserved and later transferred into the uterus. The long term cost-effectiveness of DET versus multiple sequential eSET and the freeze-all policy as alternative for fresh embryo transfer has yet to be thoroughly studied.