

Chapter | 8

General Discussion



The aim of this thesis is to discuss the optimal way to define success in IVF and to show how the implementation of new outcome parameters can contribute to the development of alternative approaches of success in IVF in different patient groups. Firstly a meta-analysis was conducted to compare outcomes of IVF in women presenting with polycystic ovary syndrome (PCOS), characterized by 2 out of 3 of the following criteria: Oligo and/or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries. Furthermore two randomised controlled trials were performed. One feasibility trial comparing a dual embryo transfer policy and a triple embryo transfer policy in women of 38 years and older. Secondly, a randomised effectiveness trial was performed evaluating the cumulative term live birth rate of two different treatment strategies; the mild stimulation/ gonadotropin releasing hormone (GnRH) antagonist co-treatment protocol combined with single embryo transfer or a standard stimulation/GnRH agonist long-protocol in combination with the transfer of two embryos. This trial only involves 2 arms instead of the four possible combinations for conceptual and practical reasons. Conceptual, because the mild stimulation, (due to shorter duration and better patient tolerance), was expected to enable subjects to have more cycles in the same time period. More cycles means additional pregnancy chances, which can compensate for a possibly reduction in live birth per cycle due to the use of GnRH antagonist co-treatment along with the transfer of a single embryo transfer. In addition it makes sense to combine a mild approach, generating a reduced number of multiple follicles with the transfer of a reduced number of embryos. Practical because, given the number of participants that could feasibly be recruited over a given period of time, the statistical power of a four arm trial would significantly reduced.

The proposed optimal outcome parameter in this thesis is the cumulative term live birth rate per time period or per treatment period. This should be weighed against the associated discomfort, complications and costs. The first randomised trial presented in this thesis showed that in women of 38 years and older the transfer of 2 embryos after IVF may result in similar cumulative term live birth rates compared with the transfer of three embryos provided that a higher number of treatment cycles is accepted. The principle finding presented in this thesis is that the application of a mild strategy in women under 38 does not reduce the chance of achieving the goal of a term live birth within 1 year. Recent studies have shown that even in patients younger than 38 years where at least 3 good quality embryos are available, single embryo transfer yields reduced ongoing pregnancy rates compared to the transfer of two embryos (43). However, these studies provide no insight into outcome over a series of cycles. Our findings also imply that the mild strategy will reduce the per cycle chance of pregnancy. However, cumulative term live birth rates of approximately 45% are still possible if the necessity of an additional treatment cycle is accepted. This is shown by the absence of a significant difference between the cumulative term live birth within 1 year comparing both strategies. As such,

the couple will face no reduction in the overall potential to have a child, provided they undergo more 'mild' cycles in the same period of time. This will probably also count for PCOS women because the meta-analysis presented in this thesis has shown that IVF outcome is comparable between PCOS and non-PCOS women. However more research is necessary to develop patient friendly mild stimulation protocols for PCOS women. In general, PCOS women are excluded in studies investigating new milder stimulation protocols.

If the mild approach is to be adapted into daily practice, it is important that, instead of considering success from IVF treatment in terms of ongoing pregnancy rate per cycle both physicians and patients regard success in terms of a treatment period while also taking the risks, complications and patient discomfort into account (163). The debate as to whether twins should be regarded as a successful outcome continues (6). From a clinical perspective, a term twin birth without complications may be considered as a success. However, the increased rate of complicated deliveries, preterm births, and low birth weight (99,225) (which gives rise to increased perinatal and longterm morbidity) have led to the opinion that medical intervention in infertility should aim primarily at establishing a singleton pregnancy (6). The perinatal morbidity and mortality directly related to multiple births overwhelm any argument in favour of more rapid family building by means of multiple births. In addition, the incidence of stress fatigue and depression is increased in patients from twins (21). Yet, both patients (21,86,226) and infertility doctors (90) remain insufficiently aware of medical complications and parent stress associated with multiple births.

As mentioned before similar cumulative 1-year pregnancy rates leading to term live birth were shown to occur in both groups. In this study the Kaplan Meier method was applied in a different way than usually applied in calculating cumulative success rates in infertility (107). Generally it is assumed that drop outs have a similar chance for pregnancy as patients continuing treatment (censoring). Because all information concerning pregnancies occurring in 1 year was available, an intention to treat analysis including all pregnancies could be performed to calculate the real life cumulative term live birth rate without making assumptions with regard to the chance of pregnancies of the drop outs (no censoring). Therefore, this cumulative term live birth rate is lower than usually found in the literature. Censoring does not take into account the effects of high drop out rates during treatment (for example due to patient discomfort) and is therefore not appropriate when outcome parameters are employed which take patient discomfort into account.

Term live birth rates should not be the only outcome used when comparing both IVF treatment options. The costs and psychological burden associated with the treatments should also be part of the equation. In section 7 of this thesis we measured the economic consequences of both IVF treatment strategies in order to provide an integrated evaluation of the effects and costs. In this study, the total costs were related to the success rate

in a cost-effectiveness analysis we clearly demonstrate that costs of pregnancy, delivery and neonatal care differ between both strategies and that the overall costs are influenced heavily by the higher costs due to multiple pregnancies. Despite the slightly higher average number of cycles for the mild strategy, and thereby high treatment costs, we found in our study that overall costs per ongoing pregnancy were cheaper compared to the standard treatment strategy, mainly due to the health economic benefits of the reduction of multiple pregnancies in the mild stimulation approach indicating that mild ovarian stimulation with single embryo transfer represents a reasonable approach not only medically and ethically, but also from an economical point of view.

Patient discomfort should also be considered when comparing IVF treatment strategies. By developing treatment strategies with less psychological complaints the drop out rate during treatment may decrease and as a consequence the term live birth rate per treatment (period) may increase. Pituitary down-regulation with GnRH agonist is associated with elevated levels of physical discomfort (29). In the week before the start of ovarian stimulation, women who were undergoing pituitary down-regulation reported more often symptoms like headache, abdominal pain and sore muscles than the control group (210). During subsequent treatment stages, however, no differences were found in physical discomfort between the two study groups. This suggests that “milder” ovarian stimulation might not result in reduced patient discomfort. However, since average treatment duration is shorter when using mild stimulation, patients suffer from physical complaints for a shorter period of time. In addition, overall discomfort within a year is comparable in both groups despite the fact that the average number of IVF cycles is increased in the mild strategy group.

The way to define success in IVF proposed in this thesis and the described study can contribute to the introduction of single embryo transfer on a large scale. Evidence is also provided that triple embryo transfer in women of 38 years and older will not increase success rates per treatment and as such opens the possibility of restricting the number of replaced embryos to 2 even in this supposed low prognosis group as the individual potential for pregnancy will not become forfeited. Introducing single embryo transfer in women under 38 years may require big efforts from both the clinician and the couple. The couple and the clinician have to be aware that (less than) an extra treatment cycle within 1 year seems a reasonable price for the prevention of chances for the lifelong consequences of (severely) damaged children related to multiple birth (173). The couple should be made aware of the balance between their short-term desire for offspring and their long term appreciation of raising healthy children. In addition, the interest of the child itself and his/her quality of life and financial burden for society related to live long handicaps should be taken into consideration. If structured, written and oral information about risks and complications of multiple pregnancies is provided reassuring overall similar chances for offspring per started treatment, patients will probably become more

inclined to the transfer of 1 embryo rather than 2. The development of patient friendly stimulation protocols can contribute to the introduction of single embryo transfer at large. Introducing single embryo transfer as a standard policy, from which deviation is not allowed as a principle, patients may not easily put pressure on the physician to obtain consent for a 2 embryos transfer. In Sweden and Belgium the law obliges single embryo transfer in women younger than 36 years (173,48). This has resulted in the transfer of 1 embryo in the majority of patients and in a decrease in multiple pregnancies. However, if patients have to pay for IVF themselves, choosing for single embryo transfer after being informed about the associated lower pregnancy rate may be difficult. If a country has an adequate reimbursement system there is an important task for the politicians and health insurance providers to modify the legislation in such a manner that single embryo transfer in women of 37 years and younger is stimulated (48). Part of this requires that the reimbursement system *per cycle* has to be replaced for a system of payment per overall treatment or per healthy child born.

Society will carry a large part of the costs for the complications associated with multiple pregnancy and birth. Governments therefore might have regulatory interest in how IVF is performed. By covering IVF by health insurance, they will accrue costs in the short term, but might also be able to establish guidelines for the number of embryos transferred. The possible need for a higher number of treatment cycles to achieve pregnancy after single embryo transfer will increase treatment costs. However, in the long run, governments may profit from reimbursing IVF treatments, which are restricted to one-embryo transfer, by saving the costs of complications associated with multiple pregnancies. In addition, much more attention should be focussed towards additional pregnancies from cryopreserved surplus embryos (since the transfer of a single embryo will result in more embryos for cryostorage) and patient selection for single ET based on multi-variate models rather than chronological age *per se*.