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van Rumste, M.M.E.

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Chapter 1

Introduction

INTRODUCTION

Subfertile couples undergo fertility treatments with the aim to get at least one healthy baby.[1] An ESHRE consensus report proposed that the primary outcome in fertility trials should be singleton live birth rate.[2] However, fertility trials mostly report on clinical or ongoing pregnancy rates. The side effects or complications, due to these fertility treatments, are poorly described, for the mother as well as for the fetus. How the pregnancy develops and what the obstetrical and neonatal outcome is, is often not mentioned. In 35% of clinical fertility trials, pregnancy loss is not reported and only a minority (7%) do report on serious adverse events, such as premature and very premature birth.[3] If important outcomes are incompletely reported, the value of fertility trials for counselling couples on the risk-benefit ratio of a treatment, for themselves or for their infants, is limited.

Subfertility is defined as the absence of conception in a period of 12 months of aiming for conception through unprotected intercourse.[4] Subfertile couples may undergo diagnostic or prognostic tests, such as assessment of ovulation, tubal patency testing and semen analysis.[5] When a cause for subfertility is found, the couple will receive therapy to either solve or bypass this problem to conceive. If a specific cause cannot be found, the couple is diagnosed with unexplained subfertility.[4]

In couples with unexplained subfertility the idea is to bring more gametes closer together: intrauterine insemination (IUI) with controlled ovarian stimulation (COS) is a common treatment.[4,6,7] In a meta-analysis of couples with unexplained subfertility, ovarian stimulation in combination with IUI has been shown to result in significantly higher pregnancy rates per woman as compared to IUI in the natural cycle.[8] The main driver behind the additional effectiveness of COS to IUI is multifollicular growth.[9] However, in the meta-analysis mentioned above, a comparison with no treatment or expectant management was not made. This is important, since in subfertile couples with a good prognosis for spontaneous conception, expectant management is a valid approach.[10,11] In couples with an intermediate prognosis, between 30 and 40%, the effectiveness of COS-IUI over a period of 6 months is similar to expectant management.[12] In fact, a 30-year old woman with a regular cycle and otherwise unexplained subfertility has 10 years with in total 120 ovulatory cycles ahead, in which she can conceive. It is questionable whether ovarian hyperstimulation for 6 cycles, which theoretically doubles the conception chances per cycle, really adds to the outcome of the 120 cycles that this woman still is going to get in her reproductive life. Evaluation of this additional value is therefore crucial.

In women undergoing ovarian stimulation in IVF, usually the next step in assisted conception if IUI has failed, the ovarian stimulation has serious drawbacks like ovarian hyperstimulation syndrome (OHSS) and the risk of multiple pregnancies.[13] The latter risk is also increased in women undergoing ovarian stimulation in IUI.

OHSS is characterized by the presence of multiple luteinized cysts within the ovaries. hCG causes the ovary to undergo extensive luteinization. In IVF, the use of hCG for final oocyte maturation and/or release, the continued use of hCG for luteal support, and the occurrence of a pregnancy resulting in hCG production, are risk factors for OHSS. When the risk of OHSS in IVF is thought to be high, the dosage of FSH can be changed during ovarian stimulation or hCG medication can be withheld. The incidence of OHSS varies widely, between 0.2% and 5%, of all assisted reproduction cycles.[14] Most cases of OHSS are mild, but it can be life threatening.[15,16] Two-dimensional ultrasound and serum estradiol determination is conventionally used in IVF to monitor the maturation of follicles and to ensure safe practice.

Another complication after IVF and COS-IUI is multiple pregnancy or, more specifically, pregnancy complications that occur as a result of such multiple pregnancies. Multiple pregnancies carry increased medical risks for mother and offspring, such as prematurity, preeclampsia, growth restriction and caesarean section, and increase the likelihood of social and economic problems in families and societies.[17-19] Since assisted reproductive technologies (ART), like COS-IUI and IVF became available, the number of multiple pregnancies has increased. In the United States there was an increase of 75% in twin births between 1980 and 2000. Over the same period the rate of triplet and higher order multiple pregnancies had risen four-fold.[20] Since the number of monozygotic twins has remained relatively constant (0.3-0.4% of all pregnancies), the increase in multiple pregnancies is the result of increasing numbers of dizygotic twins, triplets and higher order multiples. This is influenced by increasing maternal age, but mainly due to the use of agents for ovulation induction in ART.[21]

The incidence of multiple pregnancies after COS-IUI is poorly documented, but it is estimated that the multiple PR is 10-40% per cycle, and that 30-50% of all multiple pregnancies are due to COS-IUI.[20] The ESHRE consensus report on the risks and complications in ART concluded that the primary outcome measure in all fertility studies should ideally be singleton live birth rate and that twin and higher order multiple pregnancies should be considered complications.[22]

Multiple pregnancy rates in IVF can be reduced applying single embryo transfer (IVF-SET), instead of double embryo transfer (IVF-DET). A Cochrane review reported no significant difference in cumulative live birth rates following IVF-SET and one freeze-thaw, compared to one cycle of IVF-DET.[23] In IUI, the number of follicles per stimulated cycle can be lowered by milder ovarian stimulation, possibly resulting in less multiple pregnancies.

Apart from effectiveness and complications also costs should be considered when discussing assisted conception in couples with unexplained infertility. Costs consist of cost of treatment and cost of obstetrical and neonatal complications, as well as the long-term cost related to disabilities in the offspring. In this respect, multiple pregnancies impose a large burden on health care costs.[24-26]

One ART treatment cycle itself can be cheaper as compared to another treatment, but might increase costs due to complications. Moreover, multiple cycles might be necessary to achieve an ongoing pregnancy.[27,28]

BACKGROUND

In fertility trials it is unusual to describe obstetrical outcomes. Although the endpoint of a treatment in fertility trials is usually an ongoing pregnancy, such a pregnancy does not guarantee the live birth of a baby.[1] This resulted in a change from pregnancy to live birth as the primary outcome in trials. However, this change is not based on clinical data and we hypothesized that pregnancy rates and live birth rates are not that different in subfertility studies.

A complication in ART is the occurrence of OHSS. Although OHSS is a serious complication in IVF, intensive monitoring during ovarian stimulation is inconvenient and expensive. A simplification could be restricting monitoring to ultrasonography.

Another complication is multiple pregnancies. The dilemma in COS-IUI is finding the balance in reducing the number of multiple pregnancies, for a still acceptable pregnancy rate. We wanted to evaluate the role of the number of follicles in COS-IUI in relation to ongoing pregnancy rate and multiple pregnancies in couples treated for unexplained non-conception. Hence we performed a retrospective cohort analysis. Although the rationale for addition of COS to IUI is to increase the pregnancy rate by multifollicular growth, studies reporting on the number of preovulatory follicles in relation to pregnancy rates in ovarian hyperstimulation with IUI showed contradictory results. Whereas the majority of the studies report a positive association between the number of follicles and pregnancy rate, we failed to find such a positive association in previous studies.[12,29-34] To address this contradiction, we performed a systematic review of the literature on the subject.

Furthermore, it remained questionable, whether it is possible to design and conduct high quality pragmatic randomized controlled trials studying the impact of prevention strategies to reduce multiple pregnancies after ART.

Since cost-effectiveness is becoming more important, we wondered whether the recommendation for expectant management in couples with an intermediate prognosis for pregnancy, would hold after three years. An economic evaluation, considering ongoing pregnancies and cumulative costs, was conducted.

Recently, an explorative randomized controlled trial was performed that evaluated whether IVF-eSET would lead to a similar pregnancy rate as three cycles of IUI-COS, but with a lower multiple pregnancy rate. This trial suggested that one cycle of IVF-eSET might be as effective as three cycles of IUI-COS as primary treatment.[35] In view of this finding, costs may play an important role in the decision on one or the other treatment.

OUTLINE OF THE THESIS

In **chapter 2**, we report the results of a meta-analysis on the estimates of treatment effect in 143 randomized clinical trials in reproductive medicine comparing clinical pregnancies with live birth as outcome measure.

In **chapter 3**, we report the effects of ovarian monitoring by ultrasound only versus ultrasound plus serum estradiol measurement on IVF outcomes in women undergoing stimulated cycles in IVF and intracytoplasmic sperm injection (ICSI) treatment. Two randomized controlled trials were included this review. The clinical pregnancy rates and the occurrence of OHSS were compared.

In **chapter 4**, we report the results of a retrospective cohort study among 300 couples with unexplained subfertility undergoing IUI-COS in a university clinic. An inventory of the relationship between the number of follicles in IUI-COS cycles and the ongoing pregnancy rates and multiple pregnancies was made.

In **chapter 5**, we report a systematic review and meta-analysis to express the relation between the number of follicles and pregnancy rates. Relevant papers reporting follicle numbers in IUI cycles were included.

In **chapter 6**, we report whether studies evaluating strategies to prevent multiple pregnancies have sufficient power to reduce multiple pregnancies. Finally, we report if randomized controlled trials on subfertility, which describe multiple pregnancies, can show a reduction of 50% in the number of multiple pregnancies.

In **chapter 7**, we report the long-term effectiveness of expectant management or treatment with IUI-COS in couples with unexplained subfertility and intermediate prognosis of natural conception. Couples were randomly allocated to 6 months expectant management or immediate start with IUI-COS. We followed couples until 3 years after randomization and registered pregnancies and resources used. We investigated whether the recommendation not to treat during the first 6 months is valid, regarding the long-term effectiveness and cumulative costs. Economic evaluation was performed from the perspective of the health care institution.

In **chapter 8**, we report the economic analysis of an explorative randomized controlled trial comparing one cycle of in vitro fertilization (IVF) with elective single embryo transfer (eSET) versus three cycles of IUI-COS in couples with unexplained or mild male factor subfertility. The costs per included couple and per ongoing pregnancy were calculated and compared.

In **chapter 9** we summarize the results of the studies presented in this thesis.

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