Unexplained subfertility
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Chapter 1

General Introduction
GENERAL INTRODUCTION

The first steps on the path to treatment: diagnosing unexplained subfertility
In the first 12 months of unprotected intercourse about 84% of couples will conceive naturally (te Velde et al., 2000). If couples do not conceive naturally, some will seek medical help. These couples will undergo a standard fertility work-up at the fertility clinics. The fertility work-up generally comprises a thorough medical history and physical examination directed at identifying signs and symptoms to establish a differential diagnosis. This is followed by semen analysis, specific assessments in case of anovulation and an assessment of tubal patency and the pelvic cavity (National Institute for Health and Care Excellence, 2013). On the basis of these findings approximately sixty percent of couples are diagnosed with male and/or female subfertility (Brandes et al., 2010). The remaining couples in whom no abnormalities are found during the fertility work-up, are diagnosed as having unexplained subfertility.

A fork in the road: available first-line treatments
Medically assisted reproduction is recommended for couples with unexplained subfertility when their chances to conceive naturally are deemed low and the chances of conception with treatment are estimated to exceed those without treatment (Dutch Society of Obstetrics and Gynaecology (NVOG), 2010; National Institute for Health and Care Excellence., 2013). In the Netherlands, the chances of natural conception in the year following completion of the fertility work-up are calculated with the synthesis prediction model of Hunault (Hunault et al., 2004; van der Steeg et al., 2006). If couples have less than a 30% chance to conceive naturally, they are counselled for medically assisted reproduction.

A treatment option is intrauterine insemination with ovarian stimulation. The concept behind intrauterine insemination is to bring motile spermatozoa into the uterine cavity, closer to the oocyte for fertilisation, when the woman is ovulating. The cervix, which might act as a barrier for semen, is thus bypassed. Anti-estrogens or gonadotropins are added to increase the number of mature oocytes available for fertilisation, which could lead to higher pregnancy rates, but also to more multiple pregnancies. Multiple pregnancies are associated with maternal morbidity, i.e. pre-eclampsia, gestational diabetes and premature delivery, resulting in high neonatal morbidity and mortality (Pinborg, 2005)

Another treatment option is in vitro fertilisation. This intervention includes ovarian stimulation, follicle aspiration, in vitro fertilisation of the oocyte with or without intracytoplasmic sperm
injection and embryo transfer. The rationale for this intervention is that in vitro fertilisation could bypass many obstacles that potentially derail conception, such as impaired follicle development, cervical barrier or failure of the oocyte to be fertilised by a spermatozoon. The transfer of multiple embryos, originally intended to increase pregnancy rates, may also lead to more multiple pregnancies.

The preferred path: comparative assessment of first-line treatments

There are four treatment dimensions to consider when deciding which first-line treatment to offer couples with unexplained subfertility: burden, effectiveness, safety and costs (Dancet et al., 2014). The burden of treatment refers to the impact of an intervention on the functioning and overall well-being of couples. Recurrent visits to the fertility clinic may lead to physical burden during treatment with intrauterine insemination with ovarian stimulation. In vitro fertilisation is associated with more pain than intrauterine insemination, specifically due to the side effects of medication during the stimulation phase, the follicle aspiration itself or enlargement of the ovaries in the luteal phase. Both interventions can also evoke feelings of anxiety and depression from cancelled or failed treatments, resulting in more psychological burden during or after treatment (Gameiro et al., 2012).

The effectiveness of each first-line treatment depends on its capability to produce a healthy child. Intrauterine insemination with ovarian stimulation results in delivery rates of approximately 8% per cycle, while pregnancy rates of 29% per cycle have been reported after in vitro fertilisation (Kupka et al., 2016). Although the pregnancy rates per cycle after in vitro fertilisation are higher than those following intrauterine insemination, no large differences have been reported in cumulative pregnancy rates in treatment naive couples with unexplained subfertility with female age between 18 and 38 years old when compared in a randomised setting (Goverde et al., 2000; Custers et al., 2011).

Treatment safety focuses on physical harm with an emphasis on maternal and neonatal risks. The most important safety concern is the increased risk of a multiple pregnancy after intrauterine insemination or in vitro fertilisation. Multiple pregnancy rates are estimated at 7% after intrauterine insemination and approximately 19% after in vitro fertilisation (Kupka et al., 2016). The results of two randomized controlled trials found similar multiple pregnancy rates for treatment naive couples, when comparing in vitro fertilisation to intrauterine insemination (Goverde et al., 2000; Custers et al., 2011). Characteristic for IVF is the risk of ovarian hyperstimulation syndrome, which is negligible in intrauterine insemination with mild ovarian stimulation.
The fourth dimension, the financial costs of treatment, reflects the expenditure necessary to achieve the desired result. In vitro fertilisation is significantly more costly than intrauterine insemination (Van Rumste et al., 2014).

Taking into account all four treatment dimensions, it would seem that intrauterine insemination with ovarian stimulation is the recommended first-line treatment as it can be regarded as a less burdensome and equally effective intervention with a better safety profile and lower costs compared to in vitro fertilisation.
BACKGROUND OF THE THESIS

Any decision to start treatment should depend on the relative burden, effectiveness, safety and costs in comparison to no treatment. To date there is insufficient evidence that intrauterine insemination or in vitro fertilisation are more effective than no treatment, while burden, safety and costs are obvious disadvantages to both interventions (Pandian et al., 2015; Veltman-Verhulst et al., 2016). Many clinicians seem unaware of the scientific evidence behind these interventions, and so we aim to bring this debate to the forefront.

To ultimately provide this evidence, randomised controlled trials are needed with a head to head comparison of the most cost-effective and least burdensome first-line treatment with a no treatment policy. Before these trials can be performed, we first need to establish which first-line treatment is the most cost-effective and least burdensome. When we started the projects described in this thesis, intrauterine insemination was the recommended first-line treatment for couples with unexplained subfertility (Dutch Society of Obstetrics and Gynaecology (NVOG), 2010).

In the years following the introduction of intrauterine insemination into clinical practice less aggressive ovarian stimulation protocols were being used. This resulted in less multiple pregnancies without decreasing ongoing pregnancy rates (van Rumste et al., 2008). Advancements in in vitro fertilisation resulted in a considerable increase in pregnancy rates, while multiple pregnancy rates remained high (de Mouzon et al., 2010; Ferraretti et al., 2013). Gradually, double embryo transfer was replaced by elective single embryo transfer (Bhattacharya and Kamath, 2014; Tobias et al., 2016). The birth rates following in vitro fertilisation with elective single embryo transfer were lower than those with double embryo transfer, but these differences were fully compensated by the frozen embryo transfers following single embryo transfer (Pandian et al., 2013). This has led to a debate whether single embryo transfer should be offered in any circumstance, the so-called compulsory SET (cSET) (Miller et al., 2016).

Next to conventional in vitro fertilisation, a less burdensome form of in vitro fertilisation became increasingly popular, specifically the modified natural cycle in vitro fertilisation which only uses the follicle that develops naturally for oocyte retrieval. Cumulative pregnancy rates of more than 30% with very low multiple pregnancy rates around 1% were reported after in vitro fertilisation in a modified natural cycle (Pelinck et al., 2007). We therefore designed a randomised controlled trial to explore the burden, effectiveness,
safety and costs of in vitro fertilisation with single embryo transfer and in vitro fertilisation in a modified natural cycle in comparison to intrauterine insemination with mild ovarian stimulation and strict cancellation criteria.

Conclusions of randomised controlled trials are intrinsically founded on the outcomes of all couples that received the allocated intervention, which overlooks the possibility that within these couples treatment could be effective for some, but not for others. This has opened up a new avenue of research, and we therefore set out to investigate potential treatment selection markers i.e. characteristics that could aid in identifying couples that would have had better pregnancy chances with in vitro fertilisation as first-line treatment.

Natural conception rates are crucial to clinical decision-making, so we evaluated the natural conception chances for couples with unexplained subfertility, taking into account the time before starting treatment, between treatments and after treatments. Additionally, we looked at differences between clinics in natural conception rates. Finally, we performed a systematic review and network meta-analysis incorporating all the available evidence of randomised controlled trials on first-line treatments and unassisted reproduction for couples with unexplained subfertility.
OUTLINE OF THE THESIS

Chapter 2 debates the scientific evidence of the effectiveness and safety of intrauterine insemination and in vitro fertilisation, compared with no treatment, for couples with unexplained subfertility.

Chapter 3 reports the results of a randomised controlled trial comparing in vitro fertilisation with single embryo transfer or in vitro fertilisation in a modified natural cycle with intrauterine insemination with controlled ovarian hyperstimulation as a first-line treatment in couples with unexplained or mild male subfertility and an unfavourable prognosis for natural conception.

Chapter 4 presents the results of an economic analysis alongside the randomised controlled trial discussed in chapter 3.

Chapter 5 presents the results of a study on treatment selection markers for unexplained subfertility in a randomized controlled trial of couples with unexplained or mild male subfertility randomised to one cycle of in vitro fertilisation with elective single embryo transfer or three cycles of intrauterine insemination with controlled ovarian hyperstimulation.

Chapter 6 builds on chapter 5, and reports a larger study on treatment selection markers. In a randomised setting we compared in vitro fertilisation with single embryo transfer or in vitro fertilisation in a modified natural cycle with intrauterine insemination with controlled ovarian hyperstimulation in couples with unexplained or mild male subfertility and an unfavourable prognosis for natural conception, described in chapter 3.

Chapter 7 reports an estimate of the natural conception rates for couples with unexplained or mild male subfertility after the completion of the fertility work-up. It is based on the randomised trial comparing in vitro fertilisation with single embryo transfer or in vitro fertilisation in a modified natural cycle with intrauterine insemination with controlled ovarian hyperstimulation as a first-line treatment in couples with unexplained or mild male subfertility and an unfavourable prognosis for natural conception described in chapter 3.

Chapter 8 reports on a study performed in 38 fertility clinics in the Netherlands. The aim of this study was to evaluate if there were differences in natural conception rates between couples going to these clinics.

Chapter 9 presents a protocol for a study using network meta-analysis on treatment strategies for couples with unexplained subfertility. In this study we evaluate all possible
interventions to identify the most effective treatment for these couples. This is done by incorporating all interventions being used for unexplained subfertility, not only evaluating head to head direct comparisons but also indirect comparison techniques for treatments that have not been directly assessed in randomised controlled trials.

**Chapter 10** presents the summary of this thesis and provides recommendations for practice and suggestions for future research.
REFERENCES


