1

Introduction
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Subfertility is defined as the failure to conceive after regular unprotected intercourse for one year. About 10-15% of couples trying to conceive will be confronted with subfertility and 8% of couples will remain childless even after two years of trying (Bongaarts, 1982; Evers, 2002). In the western world 55-80% of these subfertile couples seek medical help for their problem (Boivin et al., 2007). A large part of the couples who seek help for their subfertility eventually conceive spontaneously, namely 45% of the couples after 60 months (Evers, 2002).

The standard fertility work-up starts with a thorough medical history and physical examination followed by the assessment of ovulation. In a couple presenting with anovulation, the cause can be categorized in three groups. Type 1 anovulation, hypogonadotrophic hypogonadism, is the cause of anovulation in 10% of the women presenting with anovulation. Type 2 anovulation, predominantly polycystic ovary syndrome, is the cause in 80% of the cases. Type 3 anovulation, ovarian failure, is the cause in 5% of women (World Health Organization, 1993).

The standard fertility work-up also consists of a semen analysis to diagnose the presence of male subfertility. Male subfertility is a common condition, diagnosed in 26% of all couples presenting with subfertility and as a contributory factor in another 11% (Brandes et al., 2010).

Assessment of tubal patency is usually reserved as last test in this work-up. Tubal disease includes tubal obstruction and pelvic adhesions due to infection, endometriosis and previous surgery. The prevalence of bilateral tubal pathology accounts for subfertility in 12% of the couples. (Broeze et al., 2012 ).

Cost-effectiveness

The choices for one fertility treatment over the other are currently driven by knowledge on their effectiveness but not by financial considerations and cost-effectiveness. In reproductive medicine costs play an important role, due to the rise in healthcare costs and since infertility care is not a covered benefit in many countries. Fertility treatment pathways generally move from low-cost, low-technology treatments such as intrauterine insemination (IUI) to high-cost, more invasive assisted reproductive technologies (ART) with in vitro fertilization (IVF) (National Collaborating Centre for Women’s and Children’s Health, 2004; Royal College of Obstetrics and Gynaecology Infertility Guidelines Group, 2006). It is questionable if this is the most cost-effective treatment pathway, since different causes are responsible for subfertility. Therefore, from a cost-effectiveness point of view, the standard pathway of moving from a low-cost, low technology to a high-cost, more invasive reproductive technology might not be applicable to all diagnoses.

Data on cost-effectiveness are instrumental since healthcare costs are rising and becoming unsustainable for future generations. Infertility treatment is sometimes seen by politicians, policy makers and the general public as a medical luxury product and therefore prone to health care cuts. The profession needs to take the responsibility for their work and associated costs. We are the ones that are responsible to make our healthcare payable. Therefore it is important to perform cost-effectiveness studies to ensure that reproductive techniques are available for couples who will benefit from the treatment and
also for future generations. As such, economic analyses underpinning decision-making are gaining importance. This thesis tries to contribute to this domain.

**Background and outline of thesis**

Quality standards have been set on how to perform high-quality economic evaluations, with the aim to improve performance (Drummond and Jefferson, 1996; Gold et al., 1996; Siegel et al., 1996). So far it is unknown what the quality is of the studies published in reproductive medicine; therefore our first aim was to evaluate the methodological quality of these studies. Insight into the quality of economical analysis in reproductive medicine is important for valuing the performed studies and to assess whether these studies are of such quality that they can be used for decision-making.

In vitro fertilization (IVF) is sometimes seen by politicians, policy makers and the general public as a medical luxury product and therefore prone to health care cuts. In 2009, one out of 38 individuals born in the Netherlands was a result from IVF. (Nederlandse Vereniging voor Obstetrie en Gynaecologie (Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG), 2010). If IVF is cut from public financing, a percentage of these individuals will not be born, because many couples are unable to pay for IVF themselves. On short term, cutting costly IVF treatment from the government’s expenditure is cost minimizing, but this is questionable on the long term. The birth of IVF individuals will, apart from fulfilling a wish for a child for a couple, lead to tax revenues in the future, as these children will mostly become economic active adults in society. A calculation of lifetime tax revenues of IVF conceived individuals in the United Kingdom, United States and Sweden showed positive tax revenues attributed to investments in IVF, suggesting that IVF is a good use of public resources (Connolly et al., 2009; Connolly et al., 2008; Svensson et al., 2008). Since social security transfers and tax rates differ across countries, our second aim was to assess the long-term economic benefits attributed to IVF conceived individuals in the Netherlands.

There are several topics in reproductive medicine in which the cost-effectiveness of diagnostic and/or treatment strategies are still unclear. In this thesis we will explore the following knowledge gaps:

- Cost-effectiveness of testing for tubal pathology,
- Cost-effectiveness of dose adjustment in IVF treatment according to ovarian reserve,
- Cost-effectiveness of treatment strategies for couples presenting with PCOS who fail to conceive after six cycles of Clomiphene Citrate,
- Cost-effectiveness of assisted reproduction for male subfertility,
- Cost-effectiveness of single versus double embryo transfer and;
- Cost-effectiveness of oocyte freezing for expanding the reproductive life span.

The first topic that we wanted to explore was the cost-effectiveness of testing for tubal pathology. Subfertile women who are diagnosed with bilateral tubal occlusion are usually advised to begin in vitro fertilization (IVF) treatment, where women with patent tubes are either advised to adhere to a period of expectant management, if they have a favorable prognosis to accomplish a natural pregnancy (Hunault et al., 2004; Steures et al., 2006).
Since diagnosis steers treatment, it is important to diagnose bilateral tubal occlusion. Current most important diagnostic tests that are used to detect tubal occlusion consist of the hysterosalpingogram (HSG) and Diagnostic Laparoscopy (DL) and dye. Falloscopy, Hystero-contrast-sonography and transvaginal hydrolaparoscopy are used less frequent (Schlief and Deichert., 1991; Kiss et al., 1993; Dechaud et al., 1998; Lundberg et al., 1998; Gords et al., 1998). Diagnostic laparoscopy and dye is considered as the gold standard. The current guidelines are not in agreement on the most effective diagnostic scenario for tubal patency testing, i.e. there is no consensus on which test should initially be used, and there is no consensus on the sequence of tests in the fertility workup (American Society for Reproductive Medicine (ASRM), 2006; Bosteels et al., 2007; den Hartog et al., 2008; Fatum et al., 2002; National Institute for Clinical Excellence, 2004; Perquin et al., 2006). In view of this lack of agreement and lack of knowledge on the most cost-effective diagnostic-treatment strategy our aim was to compare cost and effectiveness of different invasive diagnostic scenarios for the detection of tubal pathology.

The second knowledge gap we explored was the cost-effectiveness of dose-adjustment according to ovarian reserve for IVF treatment. In vitro fertilization is less effective in older women due to their diminished ovarian reserve (Broekmans et al., 2006). Because there are at present no means for improving ovarian reserve, the question arises as to how to best integrate the data on ovarian reserve in clinical management to obtain the best possible outcome for women. So far, the evidence on this topic is limited. A systematic review on the predictive value of ovarian reserve testing and IVF outcome concluded that poor response, defined as fewer than four oocytes after ovarian stimulation, can be predicted by ovarian reserve tests and that these tests could be useful to determine the most appropriate gonadotropin dosage for an individual woman (Broekmans et al., 2006). A few small randomized controlled trials tested the effect of dose individualization, but revealed conflicting results (Klinkert et al., 2005; Olivennes et al., 2009). One larger randomized controlled trial comparing ovarian hyperstimulation with a standard dose of gonadotropins to ovarian hyperstimulation with a dose based on ovarian reserve showed an increase in pregnancy rates in women allocated to the individualized dosing of gonadotropins, but the confidence intervals on the estimates of the treatment effect were wide (Popovic-Todorovic et al., 2003). In view of this limited data, we compared the cost effectiveness of several treatment scenarios with and without ovarian reserve testing in IVF.

In case a woman presents with an ovulations disorder, treatment of type 1 and the lack of treatment for type 3 anovulation is obvious. In case of type 1 treatment is very effective, 80-90% of the couples is pregnant within 1 year after ovulation induction with GNrH (Braat et al., 1991; Balen et al., 1994). For type 3 anovulation, ovarian failure, there no treatment available but oocyte donation. The treatment of couples with polycystic ovary syndrome isn’t straight forward. Treatment starting with the oral anti estrogen Clomiphene Citrate is effective and inexpensive, making this the logical first line therapy. After failing to conceive with three to six cycles of Clomiphene Citrate women traditionally proceed to ovulation induction with gonadotropins. At present, it is unclear for how many cycles ovulation induction with Clomiphene Citrate should be repeated before proceeding to gonadotropins (Fauser et al.,...
Therefore our third aim was to evaluate the cost-effectiveness of various treatment strategies in women with PCOS who fail to conceive after 6 cycles of Clomiphene Citrate and the choice whether to continue with CC or Gonadotrophins from a cost-effective point of view.

Male subfertility is common in the subfertile population. Male subfertility is authority based categorized in mild, moderate and severe male factor on the basis of semen laboratory characteristics. Since there is no treatment to improve semen quality, current treatment of male subfertility is based on optimizing the chances of fertilization by delivering motile sperm close to (intra-uterine insemination), very close to (in vitro fertilization), or even inside the oocyte (intra cytoplasmatics sperm injection). Despite the widespread use of IUI, IVF and ICSI, these treatments have seldom been tested on their relative effectiveness and cost-effectiveness in couples presenting with male subfertility. Little is known on the value of classifying severity of male subfertility on basis of semen laboratory characteristics and its consequences on determining the optimal treatment strategy. Although the treatment options IUI, IVF and ICSI are listed in the Dutch Network Guideline on Subfertility, high level evidence is lacking for nearly all recommendations, such as the treatment of first choice and the appropriate number of treatment cycles before switching to a second line treatment option (Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG), 2010). Therefore our fourth aim was to evaluate assisted reproduction for couples with male subfertility according to the pre-wash total motile sperm count.

Since the aim of in vitro fertilization (IVF) is achieving a live birth, clinical decision making in IVF is focused on maximizing a woman’s chances of becoming pregnant. In the 20th century, the most common approach to increase the likelihood of pregnancy in IVF was to transfer multiple embryos (Schieve et al., 1999). This approach indeed resulted in high pregnancy rates but also increased the risk of multiple pregnancies. In 2006, 20.8% of all pregnancies after IVF were a multiple pregnancy (de Mouzon et al., 2010). This high multiple pregnancy rates caused concern since multiple pregnancies are associated with increased maternal and perinatal morbidity and mortality, as well as costs (Bergh, 2005; European Society of Human Reproduction and Embryology (ESHRE), 2000). A logical solution to this recent epidemic of twins was to transfer only one embryo, but evidence on the effectiveness of elective single embryo transfer (eSET) in women with an intermediate or poor prognosis undergoing IVF is lacking (McLernon et al., 2010; Pandian et al., 2009). Despite this lack of evidence there is a strong trend towards implementing SET in women with an intermediate or poor prognosis, but before such a strategy is implemented, it is essential to know whether SET is cost-effective relative to DET in these women based on the best available evidence. We therefore evaluated the cost-effectiveness of single embryo transfer and double embryo transfer by decision analysis in subgroups defined by female age.

In the past decades, the average age of women bearing their first child has increased strongly (UNECE, 2007). This is an important reproductive health problem, as women steadily lose their oocytes from birth to menopause, with an accelerated loss of oocyte quantity and quality from the age of 35 (Baird et al., 2005). As a consequence, female fertility potential declines rapidly thereafter, resulting in an increase in involuntary childlessness (Leridon 2004; van Noord-Zaadstra et al., 1991). This risk of involuntary childlessness increases
from 2 to 3% for women younger than 30 years, to 36% for women of 40 years or older (Steenhof and de Jong., 2009; te Velde et al., 2008). Given the recent successes in oocyte freezing, fertility preservation for women is now possible (Antinori et al., 2007; Chian et al., 2009; Kuwayama et al., 2005; Noyes et al., 2009; Rienzi et al., 2010; Yoon et al., 2003). For women with cancer and needing chemotherapy, fertility preservation is already an accepted intervention, but oocyte freezing could also help women who want to extend their natural reproductive lifespan (Dondorp and De Wert, 2009; European Society of Human Reproduction and Embryology (ESHRE), 2004; Homburg et al., 2009; Society for Assisted Reproductive Technology (SART) and American Society for Reproductive Medicine (ASRM), 2008). To obtain oocytes for freezing, these healthy women must undergo IVF treatment, which is burdensome, not without health risk and involves extra costs. As a consequence, this strategy has been criticized (American Society for Reproductive Medicine (ASRM), 2009; Batty, 2006; Henderson, 2007; Khamsi, 2007). This may well have been premature, because oocyte freezing at a relatively younger age could potentially result in much higher pregnancy rates than natural conception or the currently applied strategy, which is IVF treatment at an advanced age. To facilitate the debate on oocyte freezing for women who want to extend their reproductive lifespan, our last aim was to perform a cost-effectiveness analysis and determine whether oocyte freezing at age 35 and using these oocytes at age 40 for IVF is cost-effective compared with either IVF at the age of 40 using freshly obtained oocytes or delayed natural conception without treatment.

In Chapter 2 we give an overview of the methodologic quality of economical analysis studies performed in Reproductive Medicine.

In Chapter 3 we address the affordability of public funded IVF from a broader point of view. We consider the live course of a child and its effect on society. We assess the lifetime net tax contribution of an average IVF-child and non IVF- conceived child.

In Chapter 4 we present a cost-effectiveness study of invasive diagnostic strategies for tubal pathology in the fertility work-up. For this a Markov decision analytic model was used, incorporation the risk of tubal pathology.

In Chapter 5 we present the cost-effectiveness of ovarian reserve testing in IVF. We used a Markov decision analytic model to address the effect of dose-individualisation according to ovarian reserve.

In Chapter 6 we present a cost-effectiveness study of treatment strategies in women with PCOS who failed to conceive after six ovulatory cycles with Clomiphene Citrate. We tested various treatment strategies concerning continuation with Clomifene citrate and/or treatment with gonadotrophins.

In Chapter 7 we present a cost-effectiveness study of treatment for couples with male factor. We used a pre-wash TMC < 10 million for the prediction of fertilization failure. Our aim was to find out when IUI, IVF or ICSI is preferred from a cost-effectiveness point of view.
In **Chapter 8** our aim was to evaluate until what age SET is cost-effective. We evaluated the costs and effectiveness of single embryo transfer with one frozen-thawed single embryo transfer compared to double embryo transfer, taking into account female age.

In **Chapter 9** we evaluated the cost-effectiveness of oocyte freezing because of anticipated gamete exhaustion. We evaluated the cost and effects of oocyte freezing compared to IVF treatment.

In **Chapter 10** we provide a general discussion of the results of the studies presented in this thesis and comment on the implications of these findings.

In **Chapter 11** we give a summary of the data presented in this thesis.
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Chapter 1

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