Cost-effectiveness in reproductive medicine
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Summary

This thesis reports on cost-effectiveness in reproductive medicine. Firstly, we evaluated the methodologic quality of studies in reproductive medicine. 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. Secondly, we assessed the long-term economic benefits attributed to IVF conceived individuals in the Netherlands. Thirdly, we evaluated various topics in reproductive medicine in which the cost-effectiveness of diagnostic and/or treatment strategies are still unclear. We explored the cost-effectiveness of: testing for tubal pathology, dose adjustment in IVF treatment according to ovarian reserve, treatment strategies for couples presenting with PCOS and fail to conceive after six cycles of Clomifene Citrate, assisted reproduction for male subfertility according to pre-wash total motile sperm count, single versus double embryo transfer according to female age and the cost-effectiveness of oocyte freezing for expanding the reproductive life span.

Chapter 1

In chapter 1 we describe the background of the economic evaluations that we performed. We describe that management of the fertility workup and therapeutic interventions are currently driven by evidence regarding effectiveness but usually not by cost-effectiveness. Fertility treatments 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. It is questionable if this is the most cost-effective treatment pathway, since different causes are responsible for subfertility. Therefore, the standard pathway of moving from a low-cost, low technology to a high-cost, more invasive reproductive technology might not be applicable for all diagnoses looking at it from a cost-effectiveness point of view.

Chapter 2

In chapter 2 we evaluated the methodologic quality of economic analyses published in the field of reproductive medicine. Insight into the quality of economical analyses in reproductive medicine is important for valuing the performed studies and to assess whether these studies can be used for decision-making. Therefore we performed a systematic review of existing economical analyses in Reproductive Medicine. We systematically scored all articles according to a checklist based on the available guidelines. We found that there is still room for improvement in the quality of economical evaluations in reproductive medicine. Of the 85 evaluated articles published between 1997 and 2011, only one article met all quality criteria. The mean number of criteria adhered to was 20 out of 30. If at least one author was from a methodologic department, the number of criteria adhered to was higher. Improvement can be gained by more clear and transparent reporting of the design (perspective, study horizon) as well as used values for costs, probabilities, outcomes and the performance of sensitivity analysis. Understanding and adequately applying and reporting the methodology of cost-effectiveness analysis is critical for researchers, editors,
and readers to accurately interpret results. As decision making – both for clinical and health policy decisions – should be based on high quality evidence on clinical and economic consequences, researchers in reproductive medicine should strive to further improve the quality of their economic evaluation studies and related publications.

Chapter 3
In chapter 3 we evaluated if an IVF-conceived child in the Netherlands results in a positive return at the end of live. Previous studies conducted 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). Therefore, we assessed the long-term economic benefits attributed to IVF-conceived individuals in the Netherlands. Furthermore, we extended the previous analytic framework by considering differences in net tax revenue that may arise following the birth of an IVF-conceived boy or girl.

According to our analysis the net present value at the end of life of IVF conceived individuals is negative, for both men and women. The same is true for naturally conceived individuals in the Netherlands. These results are consistent with a generational accounting analysis conducted in 1995 in the Netherlands; this analysis also showed a negative return at the end of live (Bovenberg et al., 1999). This is in contrast with the results found in the United States, United Kingdom and Sweden. The differences between the countries can be explained by differences in taxing, social benefits and labour participation.

This is the first analysis that differentiates between men and women. In our analysis both men and women had a negative return at the end of life, but the negative return of women ( - €123,177) was much higher compared to that of men ( - €47,091). This can partly be explained by the lower labour participation of women compared to men. (CBS, Statistics Netherlands 2010) Also, if women work, this is more likely to be part-time, compared to men and the income of women is still lower than that of men, resulting in less income tax and VAT. (CBS, Statistics Netherlands, 2011) Another explanation for the difference between men and women are the health care costs. During working life, the costs are approximately the same, but from retirement to the end of life, women consume more health care. This is probably because women live longer than men and as age progresses healthcare costs increase more rapidly (National Institute for public health and the environment, 2008).

Our analysis showed a negative return at the end of life, for an average IVF individual, for both men and women. Because an IVF individual does not result in a positive return, the government could decide not to invest in IVF, but on the other hand, naturally conceived individuals also give a negative return at the end of life.

Chapter 4
In chapter 4 we evaluated the cost-effectiveness of testing for tubal pathology. 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 work-up. Therefore we evaluated the cost-effectiveness of invasive tubal testing in subfertile couples. We performed a cost-effectiveness analysis,
Summary

using a decision analytic framework based on a computer-simulated cohort of sibfertile women. We evaluated six diagnostic and treatment scenarios: [1] No test or treatment. [2] Direct treatment without tubal testing. [3] Delayed treatment without tubal testing [4] Hysterosalpingogram (HSG), followed by direct or delayed treatment, according to diagnosis (tailored treatment) [5] HSG and a diagnostic laparoscopy (DL) in case HSG does not prove tubal patency, followed by tailored treatment. [6] DL followed by tailored treatment. Main outcome was expected cumulative live birth after three years. Secondary outcomes were cost per couple and the incremental cost-effectiveness ratio. For a 30 year old women, with otherwise unexplained subfertility for 12 months, three year cumulative live birth rates were 51.8%, 78.1%, 78.4%, 78.6% and 78.4% and costs per couple were €0, €6,968, €5,063 €5,410 €5,405 and €6,163 for scenario 1,2,3,4,5 and 6, respectively. The incremental cost-effectiveness ratio compared with scenario 1 (reference strategy), were €26,541, €19,046, €20,372, €20,150 and €23,184 for scenario 2,3,4,5 and 6, respectively. Sensitivity analysis showed the model to be robust over a wide range of values for the variables. Invasive diagnostic tubal test in the fertility work-up is thus not cost-effective.

Chapter 5

In chapter 5 we evaluated the cost-effectiveness of dose-adjustment according to ovarian reserve. We tested the following scenarios in a decision analytic model: [1] No treatment, [2] up to three cycles of IVF limited to women under 41 years and no ovarian reserve testing, [3] up to three cycles of IVF with dose individualization of gonadotropins according to ovarian reserve, and [4] up to three cycles of IVF with ovarian reserve testing and exclusion of expected poor responders after the first cycle, with no treatment scenario as the reference scenario. Cumulative live birth over 1 year was 9.0% in the no treatment scenario, 54.8% for scenario 2, 70.6% for scenario 3 and 51.9% for scenario 4. Absolute costs per woman for these scenarios were €0, €6,917, €6,678, and €5,892 for scenarios 1, 2, 3, and 4, respectively. Incremental cost-effectiveness ratios (ICER) for scenarios 2, 3, and 4 were €15,166, €10,837, and €13,743 per additional live birth. We found that dose-individualisation of the dose of gonadotropins according to ovarian reserve increases live births in a model in which a maximum of 3 cycles of IVF was offered until the female age of 45 years. The dose individualisation leads to lower costs and increased live birth. We also demonstrated in sensitivity analysis that even if the population aged above 40 years quadruples, the scenario of dose individualisation of gonadotropins according to ovarian reserve remains cost-effective. A limitations of this study is that data on the effectiveness of dose individualisation based on ovarian reserve testing are derived from one small study.(Popovic-Todorovic et al., 2003) Hence, this scenario needs to be tested in a larger population to confirm or refute the effect of dose individualisation prior to IVF especially in relation to female age.

Chapter 6

In chapter 6, we evaluated the cost-effectiveness of various treatment strategies for women with PCOS who did not conceive after 6 ovulatory cycles with CC. We evaluated the following strategies: [1] Three cycles of IVF [2] Continuation of CC with six cycles, followed by three cycles of IVF in case of no birth [3] Six cycles of Gonadotrophins and three cycles of IVF [4]
Chapter 10

Twelve cycles of Gonadotrophins and three cycles of IVF [5] Continuation of CC with six cycles, six cycles of Gonadotrophins and three cycles of IVF [6] Continuation of CC with six cycles, twelve cycles of Gonadotrophins and three cycles of IVF. Two year cumulative birth rates were 58%, 74%, 89%, 97%, 93% and 98% and costs per couple were €9,518, €7,530, €9,711, €9,764, €7,651 and €7,684 for scenario 1, 2, 3, 4, 5 and 6 respectively. Scenario 2 was the lowest cost option. The extra cost per at least one live birth for scenario 5 was €629 and for scenario 6 €630. Our study showed that, after an initial failed number of 6 cycles, a continuation with CC for 6 cycles followed by 3 cycles of IVF (scenario 2) was the least expensive strategy. Continuation of CC with 6 cycles, followed by 6 to 12 cycles of gonadotrophins and 3 cycles of IVF in case of no pregnancy (scenario 5 and 6), was more expensive but also generated a higher pregnancy rate, i.e. 93% versus 98%. Whether this scenario is considered to be cost-effective depends on the willingness to pay per extra live birth. Since not only the achievement of a live birth, but also the time to pregnancy is an important factor, we also tested the effect of time to pregnancy on outcome. We discounted live birth and found that the issue of time to pregnancy had no influence from a cost-effectiveness point of view. The major limitations of this study were that data on long term treatment scenarios are not available in couples with CC failure. Therefore, it is essential to quantify the assumptions used in this model in a randomized controlled trial.

Chapter 7

In chapter 7, we evaluated the cost-effectiveness of assisted reproduction for couples with male subfertility according to pre-wash TMSC. We evaluated IUI with and without controlled ovarian stimulation (COH), IVF and ICSI. We compared one cycle of IUI-COH to one cycle of IVF, one cycle of IUI without COH to one cycle of IVF and one cycle of IVF to one cycle of ICSI. The model comparing one cycle of IUI with COH to one cycle of IVF, showed that the cost per live birth were lower for IUI-COH compared to IVF if the pre-wash TMSC was above 3 million. IVF was always more effective but also more costly than IUI-COH. The extra costs per live birth (ICER) varied from €12,260 for a pre wash TMSC of 0.1 million to €15,296 for a pre wash TMSC of 10 million. Whether IVF is considered cost-effective over IUI-COH depends on the willingness to pay (WTP) per extra live birth. The model comparing one cycle of IUI in the natural cycle to one cycle IVF, showed that the extra cost per live birth (ICER) grew exponentially since live birth rates after IUI were unreasonable due to unreliable data. high. The model comparing one cycle of IVF to one cycle of ICSI showed that if the prewash TMSC was below 3 million the cost per live birth for ICSI was lower than IVF. Above a pre-wash TMSC of 3 million, IVF had a lower cost per live birth. The extra cost per live birth (ICER) ranged from €4,598 to €4,873,646, since ICSI was more expensive but also more effective. Whether ICSI is considered cost-effective over IVF depends on the willingness to pay (WTP) per extra live birth. Sensitivity analysis, did not alter our conclusions. Also comparing six cycles of IUI-COH to three cycles of IVF did not alter our conclusions. The choice of IVF over IUI and ICSI over IVF depends on the willingness to pay for an extra live birth. If one only considers the cost per live birth for each treatment, above a pre-wash TMSC of 3 million, IUI is less costly than IVF and below a pre-wash TMSC of 3 million ICSI is less costly. Effectiveness needs to be confirmed in a large randomized controlled trial.
Chapter 8
In Chapter 8 we evaluated a policy of SET versus DET to reduce multiple pregnancies while maintaining reasonable pregnancy rates against reasonable costs. Single embryo transfer in selected groups of women is advocated as the only effective means of lowering the rate of twin pregnancies. The main aim of this study 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, looking at different female age groups. Our study showed that single embryo transfer with one frozen-thawed embryo transfer is cost-effective in women up to 32 years compared to DET. In women of 33 or older double embryo transfer is more effective than SET but also more costly. The ICER for women aged 32 was €50,348. The ICER decreased rapidly with increasing female, resulting in an ICER of €54 at the age of 43. Whether single or double embryo transfer should be performed in women of 32 years or older depends on how much society is willing to pay for an extra child. This study is the first cost-effectiveness study on single embryo transfer that included age as a continuous variable. Our main limitation was that all model parameters were based on cohort data, not on randomized controlled trials. Since trials comparing single embryo transfer with frozen and thawed single embryo transfers versus double embryo transfers have not been performed in women between 36 and 43 years, cohort data currently provide the best available evidence. We found that embryo transfer strategy has a profound impact on costs, effectiveness and adverse outcomes associated with treatment. Cost-effectiveness was dependent on female age and how much society is willing to pay for an extra child. Obviously, our data need confirmation by a large randomized clinical trial to evaluate which transfer policy is really (cost) effective.

Chapter 9
In chapter 9, we evaluated the cost-effectiveness off oocyte freezing on social indication. We evaluated the cost and effects of oocyte freezing compared to IVF treatment. Our study showed oocyte freezing at age 35 to be cost effective if the return rate after oocyte storage is higher than 61% and one is willing to pay €13,156 extra per additional live birth compared to our reference strategy, IVF. When changing the reference strategy to delayed natural conception without additional treatment, the ICER of oocyte freezing was €30,091 per additional live birth and the ICER of IVF was €47,874. Oocyte freezing is therefore more cost effective than IVF. The main limitation is that data on natural conception at 40 years or older are limited. The calculated pregnancy rates may not precisely reflect the ‘real’ pregnancy rates for women of 40 or older, but our sensitivity analyses showed that, even with higher or lower spontaneous pregnancy chances, the model remained stable. Also data on success rates after oocyte freezing are limited, most of the published papers used data on frozen oocytes of subfertile women (Antinori et al., 2007;Chian et al., 2009;Kuwayama et al., 2005;Noyes et al., 2009;Yoon et al., 2003). The women in our hypothetical cohort were not subfertile, but women of unproven fertility. This could result in an underestimation of pregnancy rates, but we believe that this potential underestimation is equalled out by the potential decline in quality and quantity of oocytes.
after freezing/thawing. Our study substantiates that oocyte freezing results in higher live birth rates compared to IVF or natural conception without additional treatment, but is also more costly. Our study also shows that oocyte freezing will be more cost effective if women use their frozen oocytes later in life, as older women have lower chances of conceiving naturally, but it will be less cost-effective if women use their frozen oocytes at younger age as they will then still have reasonably high chances of conceiving naturally.

**Chapter 10**

Finally, in this chapter we give the conclusions and recommendations for future research are made.
References


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