Cost-effectiveness in reproductive medicine
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Conclusions and Implications for Future Research
Conclusions and Implications for future research

This thesis had three aims. The first aim was to identify the quality of cost-effectiveness studies performed in reproductive medicine, the second aim was to assess the long-term economic benefits attributed to IVF conceived individuals in the Netherlands and the third aim was to explore cost-effectiveness of various diagnostic strategies and therapeutic interventions in reproductive medicine.

From the present thesis we can conclude the following:

- There is still room for improvement in reporting cost-effectiveness studies in reproductive medicine. Adequately applying and reporting the methodology of cost-effectiveness analysis is critical for researchers, editors, and readers to accurately interpret results.
- In the Netherlands, both IVF-conceived children as well as non-IVF conceived children have a negative net present value at the end of their life. This finding contrasts with similar analyses in countries like the US, UK and Sweden. Since both IVF conceived children and non IVF conceived have a negative net present value, this should not be a reason to stop covering IVF-treatment.
- For a 30 year-old woman, with otherwise unexplained subfertility for 12 months, not testing tubal patency and expectant management for another year was the most cost-effective strategy. Three year cumulative live birth rates were 78.4% and absolute costs were €5,063. The extra cost per live birth compared to no tubal patency testing and no treatment was €19,046. Invasive diagnostic tubal test in the fertility work-up is thus not cost-effective. Applying this model to other ages, we found that not performing tubal patency testing and delayed treatment for one year until the age of 38 and not performing tubal patency testing and direct treatment from the age of 39 were the most cost-effective strategies.
- In couples undergoing up to three cycles of IVF, we found that dose individualization of gonadotropins according to ovarian reserve seems the most cost-effective strategy. Cumulative live birth over 1 year was 70.6% and absolute costs were €6,678. The extra costs per live birth compared to no treatment were €10,837. 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 a female age of 45 years compared to no dose individualization.
- In women with PCOS who did not conceive after 6 ovulatory cycles with Clomiphene Citrate (CC) we found that continuation of CC with six cycles, followed by three cycles of IVF was the lowest cost option. Two year cumulative live birth was 74% and absolute costs were €7,530. If one is willing to pay €629 per extra live birth, continuation of CC with six cycles, six cycles of Gonadotrophins and three cycles of IVF was the next most cost-effective option with a two year cumulative live birth of 93% and absolute cost were €7,651. If one is willing to pay €630 per extra live birth, continuation of CC with six cycles, twelve cycles of Gonadotrophins and three cycles of IVF was the next most cost effective option with a two year cumulative live birth of 98% and absolute cost were €7,684. Time to pregnancy had no effect on our conclusions.
In couples with male subfertility and a pre-wash TMSC between 0 and 10 million comparing one cycle IUI with COH to one cycle of IVF, IVF was always more effective but also more costly. The extra costs per live birth (ICER) varied from €12,260 for a prewash TMSC of 0.1 million to €15,296 for a pre wash TMSC of 10 million. The absolute costs per live birth were lower for IVF compared to IUI when the pre-wash TMSC was below 3 million. 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. Applying more IUI or IVF cycles did not alter our conclusions.

Comparing eSET and DET in women undergoing IVF, showed that up to the age of 32 eSET is more cost-effective. In women of 33 or older double embryo transfer is more effective than SET but also more costly. The extra cost per live birth (ICER) for women aged 32 was €50,348. The ICER decreased rapidly with increasing female age, resulting in an ICER of €54 at the age of 43. Whether single or double embryo transfer should be performed in women of 33 years or older depends on the willingness to pay for an extra child.

We evaluated the cost and effects of oocyte freezing compared to IVF treatment. Oocyte freezing at the age of 35 and collecting them at the age of 40 resulted in a 5 year cumulative live birth rate of 84% and absolute costs of €10,419. No oocyte freezing and IVF at the age of 41 resulted in a cumulative 5 year live birth rate of 64% and absolute costs of €7,798. Oocyte freezing at age 35 is cost effective if the return rate after oocyte storage is higher than 61% and one is willing to pay €19,560 extra per additional live birth (ICER) compared to IVF.

An overview of the outcomes of the cost-effectiveness studies is given in table 1.

Cost-effectiveness studies are crucial in positioning randomized controlled trials; since model-based cost-effectiveness studies are based on the best available evidence and reflect current knowledge. Model based cost-effectiveness studies facilitate identification of the knowledge gaps and can show the critical values at which randomized controlled trials should be positioned. After model-based cost-effectiveness studies it is imperative to test them in randomized controlled trials before implementing them in current practice.

Our cost-effectiveness study regarding dose adjustment according to ovarian reserve is currently being tested in the OPTIMIST trial (NTR2657)(van Tilborg et al., 2012). This study compares the routine use of ovarian reserve tests and subsequent use of individualized FSH dosages in predicted poor and hyper responders as compared to a policy without ovarian reserve test using standard dosages of FSH.

The cost-effectiveness of IUI vs. IVF vs. ICSI in couples with male subfertility will be tested in de MASTER trials. These trials compare three treatment protocols. In the first randomized controlled trial (NTR3820) (RCT) couples with a pre-wash TMSC of 6 to 10 million are randomized between three cycles of IUI in the natural cycle (NAT), followed by three cycles of IUI controlled ovarian hyperstimulation (COH) and expectant management for 6 months. In the second (NTR3822) couples with a pre-wash TMSC of 3 to 6 million are randomized between three cycles of IVF, including transfer of cryo-embryos and three
Table 1. Summary cost-effectiveness studies in this thesis

| Chapter 4 Tubal Patency Tests | 30–year-old women with a regular menstrual cycle, who had finished the initial fertility work-up, except for the assessment of tubal patency, and had a partner with a normal semen analysis. | Expected cumulative live births after 3 years; Cost per couple; Incremental cost-effectiveness ratio. | (SC 1) no tests and no treatment | (SC 1) €0 | (SC 1) Reference scenario |
| (SC 2) immediate treatment without tubal testing | (SC 2) €8,927 | (SC 2) €26,541 |
| (SC 3) delayed treatment without tubal testing | (SC 3) €6,459 | (SC 3) €19,046 |
| (SC 4) hysterosalpingogram (HSG), followed by immediate or delayed treatment, according to diagnosis (tailored treatment) | (SC 4) €6,904 | (SC 4) €20,372 |
| (SC 5) HSG and a diagnostic laparoscopy (DL) in case HSG does not prove tubal patency, followed by tailored treatment | (SC 5) €6,874 | (SC 5) €20,150 |
| (SC 6) DL followed by tailored treatment | (SC 6) €7,862 | (SC 6) €23,184 |

| Chapter 5 Ovarian reserve testing in IVF | Cohort of subfertile women aged 20 to 45 years who are eligible for IVF | Expected cumulative live births after 1 years; Cost per couple; Incremental cost-effectiveness ratio. | (SC 1) No treatment | (SC 1) €0 | (SC 1) Reference scenario |
| (SC 2) up to three cycles of IVF limited to women under 41 and no ovarian reserve testing | (SC 2) €12,628 | (SC 2) €15,166 |
| (SC 3) up to three cycles of IVF with dose individualization of gonadotropins according to ovarian reserve | (SC 3) €9,454 | (SC 3) €10,837 |
| (SC 4) up to three cycles of IVF with ovarian reserve testing and exclusion of expected poor responders after the first cycle | (SC 4) €11,356 | (SC 4) €13,743 |

| Chapter 6 PCOS | 30 year old women with PCOS who ovulate on Clomiphene Citrate (CC) but did not conceive after 6 cycles | Expected cumulative live births after 1 years; Cost per couple; Incremental cost-effectiveness ratio. | (SC 1) Three cycles of IVF | (SC 1) €16,461 | (SC 1) €12,616 |
| (SC 2) continuation of CC with six cycles, followed by three cycles of IVF in case of no birth | (SC 2) €10,234 | (SC 2) €15,166 |
| (SC 3) six cycles of Gonadotrophins and three cycles of IVF | (SC 3) €10,906 | (SC 3) €14,518 |
| (SC 4) twelve cycles of Gonadotrophins and three cycles of IVF | (SC 4) €10,074 | (SC 4) €9,571 |
| (SC 5) continuation of CC with six cycles, six cycles of Gonadotrophins and three cycles of IVF | (SC 5) €8,239 | (SC 5) €629 |
| (SC 6) continuation of CC with six cycles, twelve cycles of Gonadotrophins and three cycles of IVF | (SC 6) €7,836 | (SC 6) €630 |
### Table 1. Continued

<table>
<thead>
<tr>
<th>Patient(s)</th>
<th>Outcome's</th>
<th>Scenario's (SC) / Model</th>
<th>Cost per live birth</th>
<th>Incremental-Cost-effectiveness ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chapter 7</strong>&lt;br&gt;Male Subfertility</td>
<td>subfertile women aged 30 with a partner with a pre-wash TMSC of 0 to 10 million.</td>
<td>Expected live birth after 1 cycle; Cost per couple; Incremental cost-effectiveness ratio's.</td>
<td>(Model 1) One cycle IUI-COH compared to one cycle of IVF&lt;br&gt;U cycle: pre-wash TMSC of 1 million €40,203 pre-wash TMSC of 10 million €5,833&lt;br&gt;IVF cycle: pre-wash TMSC of 0.1 million €14,986 pre-wash TMSC of 10 million €11,811</td>
<td>(Model 1)</td>
</tr>
<tr>
<td><strong>Chapter 8</strong>&lt;br&gt;SET versus DET in IVF</td>
<td>subfertile women aged 30-43 undergoing IVF</td>
<td>Expected live birth after 1 cycle; Cost per couple; Incremental cost-effectiveness ratio's.</td>
<td>(SC 1) Single embryo transfer with one frozen-thawed embryo transfer (SET)&lt;br&gt;(SC 2) Double embryo transfer (DET)</td>
<td>(Model 2) One cycle of IVF compared to one cycle of ICSI&lt;br&gt;IVF cycle: pre-wash TMSC of 0.1 million €14,986 pre-wash TMSC of 10 million €11,811 ICSI cycle: Irrespective of pre-wash TMSC €12,783&lt;br&gt;(Model 2) IVF cycle: Reference ICSI cycle: pre-wash TMSC of 0.1 million €4,598 pre-wash TMSC of 10 million to €4,873,646</td>
</tr>
<tr>
<td><strong>Chapter 9</strong>&lt;br&gt;Oocyte Freezing</td>
<td>35-year-old women who want to postpone pregnancy till the age of 40</td>
<td>Expected live birth after 10 years; Cost; Incremental cost-effectiveness ratio's.</td>
<td>(Reference SC) women at age 40 attempt to conceive and, if not pregnant after 1 year, undergo IVF&lt;br&gt;(SC 1) Women undergo three cycles of ovarian hyperstimulation at age 35 for oocyte freezing, then at age 40, use these frozen oocytes for IVF&lt;br&gt;(SC 2) Women at age 40 attempt to conceive without treatment</td>
<td>(SC Reference) €12,071</td>
</tr>
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</table>
cycles of IUI in the natural cycle (NAT), followed by three cycles of IUI-COH. In the third
RCT couples with a pre-wash TMSC below 3 million and post-wash TMSC > 300,000 are
randomized between three cycles of IVF, including transfer of cryo-embryos and three
cycles of ICSI, including transfer of cryo-embryos (NTR3823).

The cost-effectiveness of treatment with Clomiphene Citrate or Gonadotropins after
CC-failure is currently tested in the M-OVIN study (NTR1449). In this study patients
are randomly allocated to four treatment arms: extended CC treatment for 6 months,
ovulation induction with gonadotropins for 6 months, extended CC treatment with IUI for
6 months and ovulation induction with gonadotropins with IUI for 6 months.

Whether our base case assumption in our cost-effectiveness study of oocyte freezing
is sound will become clear in the future when more cohort data becomes available.

In our review we showed that there is still room for quality improvement in cost-
effectiveness studies in reproductive medicine. None of the studies were based on time
to pregnancy, which is also a crucial element for economic evaluations in reproductive
medicine, since not only the birth of a child is important, but also the time within it occurs.
Time to pregnancy is especially important in view of subsequent pregnancies, since most
couples desire more than one child, and as failure to conceive is most prevalent in couples
with relatively higher age, this time aspect is even more relevant.

The overwhelming majority of studies focussed on treatment, rather than on diagnosis.
Apparently, diagnostic issues are more complicated in economic analyses, specifically as
the end point is more difficult to define. We feel there is a need for economic analyses
of diagnostic issues, as a large part of the costs in reproductive medicine is spent on
diagnostic procedures.

Economic evaluations of fertility treatments are different from normal cost-effectiveness
analyses, where quality adjusted live year’s (Qaly’s) are often the preferred outcome. In
reproductive medicine there is little doubt that the outcome of interest is live birth. What
society is willing to pay for an extra quality adjusted live year is set at 80,000 euro in the
Netherlands.(Raad voor de Volksgezondheid en zorg and (Council for Public Health and
Healthcare) 2006) What we are willing to pay for an extra live birth is unknown. To interpret
and compare cost-effectiveness studies in reproductive medicine it is essential to set a
willingness to pay. If a willingness to pay is set, researchers and decision makers are able to
decide which treatment or diagnostic test is cost-effective. Therefore it is essential for future
research to evaluate what society is willing to pay per live birth.
References