Cost-effectiveness in reproductive medicine
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Cost-effectiveness of Assisted Conception for Male Subfertility

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Submitted
Abstract

Objective Intrauterine insemination (IUI) with or without controlled ovarian stimulation (COH), in-vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) are frequently used treatments for couples with male subfertility. There is no consensus regarding specific cut-off values for semen parameters, at which IVF would be advocated over IUI and ICSI over IVF. The aim of this study was to evaluate the cost-effectiveness of interventions for male subfertility according to the TMSC.

Design Cost-effectiveness analysis.

Setting Decision analytic framework.

Population Computer-simulated cohort of subfertile women aged 30 with a partner with a pre-wash TMSC of 0 to 10 million.

Methods We evaluated three treatments IUI with and without controlled ovarian stimulation, IVF and ICSI.

Main outcome measures Expected live birth. Secondary outcomes were cost per couple and the incremental cost-effectiveness ratio (ICER).

Results Comparing one cycle IUI-COH to one cycle of IVF, IVF was always more effective but also more costly with an extra cost per live birth ranging from €12,260 to €15,296. IVF had a lower cost per live birth compared to IUI-COH if the pre-wash TMSC was below 3 million. The comparison of one cycle of IUI in natural cycle to one cycle of IVF was unreliable. Comparing one cycle IVF to one cycle of ICSI showed that ICSI was more effective but also more costly. ICSI had a lower cost per live birth compared to IVF if the pre-wash TMSC was below 3 million.

Conclusions The choice of IVF over IUI-COH 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.
Cost-effectiveness of Male Subfertility

Introduction

Male subfertility is a common condition, diagnosed in 30% of all couples presenting with subfertility and as a contributory factor in another 20% (Hull et al., 1985; Crosignani et al., 1994). Intrauterine insemination (IUI) with or without controlled ovarian stimulation (COH), in-vitro fertilisation (IVF) and intracytoplasmatic sperm injection (ICSI) are frequently used treatments for couples with male subfertility (Goverde et al., 2000; Cohlen et al., 2005; Tournaye et al., 2012). Despite their widespread use, their cost-effectiveness has never been compared.

In a large prospective study among subfertile couples on the prognostic capacity of semen quality for fathering a child after natural conception, we observed that there was a strong correlation between semen parameters and the probability of natural conception (van der Steeg, 2011). A population based study in first time pregnancy planners found a strong predictive capacity of semen volume, sperm motility, and sperm concentration for natural conception (Bonde et al., 1998). Furthermore, the total motile sperm count (TMSC) appears to have a consistent, direct relationship with the pregnancy rate per cycle after IUI, but there is no definite predictive threshold for success (Tijani et al., 2010).

Knowledge on the effectiveness of the available treatments, i.e. IUI, IVF and ICSI for male subfertility with different grades of severity is limited. The role of IUI with or without COH in couples with mild male subfertility has been the subject of much debate. For the comparison IUI versus timed intercourse both in natural cycles no evidence of difference between the probabilities of pregnancy rates per woman was found (OR 5.3; 95% CI 0.42-67). No statistically significant difference between pregnancy rates per couple for IUI-COH versus IUI in natural cycle could be found (OR 1.5; 95% CI 0.92-2.4) (Bensdorp et al., 2007). In couples with moderate or severe male subfertility, i.e. a TMSC between 1 to 3 million, performing IUI before IVF, is not based on comparative studies. It also remains unclear at which TMSC ICSI becomes more effective than IVF (Rhemrev et al., 2001; Repping et al., 2002). As a consequence, ICSI is recommended when extreme male subfertility is present, TMSC below 1 million, although epidemiologic data to support such cut offs are lacking. The few studies that compared IVF or ICSI in couples with male subfertility showed a higher incidence of fertilization failure in IVF compared to ICSI (Pisarska et al., 1999; Plachot et al., 2002; van der Westerlaken, 2006). A meta-analysis showed that the risk ratio for an oocyte to become fertilized was 1.9 (95% CI 1.4-2.5) in favour of ICSI, and 3.1 ICSI cycles may be needed to avoid one complete fertilization failure after conventional IVF (95% CI 1.7-12.4) (Tournaye et al., 2002). The probability of total fertilization failure is therefore crucial in the choice between IVF or ICSI treatment in couples presenting with male subfertility. Once there is fertilization, pregnancy rates between IVF and ICSI do not differ (Repping et al., 2002).

Cost-effectiveness studies on interventions for male subfertility are scarce. A randomized controlled trial with a subset of 77 couples with mild male subfertility (TMSC between 1 and 20 million), reported IUI to be more cost-effective compared to IUI-COH and IVF (Goverde et al., 2000). The costs per pregnancy resulting in at least one live birth were US$ 4,511-5,710 for IUI and IUI-COH and US$ 14,679 for IVF. However, this study was performed 15 years ago, when IVF success rates were rather low, and the small subset of couples with mild male subfertility did not allow robust conclusions on this issue. A retrospective cohort study
evaluated 3,479 IUI cycles and 551 IVF cycles and evaluated their cost-effectiveness (van Voorhis et al., 2001). This study concluded that if the pre-wash TMSC was below 10 million, IVF/ICSI was more effective and less costly than IUI. As further comparative studies on IUI, IVF and ICSI are lacking, we performed a computer-simulated cohort study on the subject. Our aim was to compare the cost and effectiveness of IUI, IVF and ICSI in subfertile women aged 30 with a partner with a pre-wash TMSC between 0 and 10 million.

**Material and Methods**

We constructed three Markov decision trees for couples presenting with male subfertility who finished their basic fertility work up. To evaluate the most cost-effective treatment we evaluated one cycle of IUI with controlled ovarian stimulation versus one cycle of IVF, one cycle of IUI in the natural cycle versus one cycle of IVF and one cycle of IVF versus one cycle of ICSI according to pre-wash TMSC.

A Markov model is a more complicated decision model used to analyse recurring events over time. Therefore, it is a useful tool for the evaluation of cost-effectiveness analyses in reproductive medicine, because in every cycle there is a new chance to conceive. Markov models can be used to compute the costs per live birth and the incremental cost-effectiveness ratio (ICER). The ICER represents the extra costs per live birth between two scenarios. These costs are calculated by dividing the differences in costs by the differences in live births of two scenarios. Normal practice is to order strategies or scenarios from the least to the most effective. Dominated strategies are then eliminated and the ICERs are calculated for each strategy in comparison with its next best alternative.

**Details of computer simulation model**

**Patient characteristics**

Our base-case calculation was centred on a 30-year old woman with a regular menstrual cycle, normal Fallopian tubes and a partner with a pre-wash TMSC between 0 to 10 million. We centred our calculation on a 30-year-old woman, since the majority of the studies regarding pregnancy probabilities according to pre-wash TMSC were based on couples where the female had a mean age near 30 (van Voorhis et al., 2001; Cohlen et al., 1998; Dickey et al., 1999; Dorjpurev et al., 2011; Zhao et al., 2004; Campana et al., 1996).

**Models**

We built three decision trees. In Model one, we compared one cycle of IUI-COH with one cycle of IVF. In Model two we compared one cycle of IUI in the natural cycle with one cycle of IVF. In Model three we compared one cycle of IVF with one cycle of IVF/ICSI. The used probabilities are presented in table 1.

**Live birth probabilities after IUI**

We performed a systematic search for studies on pregnancy and live birth probabilities after IUI according to pre-wash TMSC in couples with male subfertility. All studies except
for one randomized controlled trial, were retrospective (van Voorhis et al., 2001; Cohlen et al., 1998; Dickey et al., 1999; Dorjpurev et al., 2011; Zhao et al., 2004; Campana et al., 1996; Merviel et al., 2010; Huang et al., 1996). Two studies were excluded since they only mentioned pregnancy probabilities but not the necessary number of cycles to achieve this (Merviel et al., 2010; Huang et al., 1996). Most studies showed pregnancy probabilities of IUI-COH with clomiphene citrate (CC) or follicle-stimulating hormone (FSH) (Voorhis et al., 2001; Cohlen et al., 1998; Dickey et al., 1999; Dorjpurev et al., 2011; Zhao et al., 2004; Campana et al., 1996). We therefore combined the pregnancy probabilities after IUI with CC and FSH and calculated the pregnancy probabilities after IUI-COH according to pre-wash TMSC. We summed the total number of cycles and calculated the total number of achieved pregnancies per cycle. Intermediate numbers were computed with smoothing.

Pregnancy probabilities after IUI according to pre-wash TMSC in the natural cycle were scarce. The only randomized controlled trial concluded that, in couples with a pre-wash TMSC below 5 million, IUI in the natural cycle was more effective than IUI-COH (Cohlen et al., 1998). In these couples, pregnancy probabilities improved sevenfold (OR of 6.9 (95% CI 0.7-70)), while in couples with a pre-wash TMSC between 5 to 10 million, there was no advantage of IUI-COH over IUI in the natural cycle. Because data on IUI in the natural cycle was scarce and the performed randomized controlled trial did not show a significant effect and if used would lead to unreliable results, we decided not to perform an analysis comparing IUI in the natural cycle to IVF.

Live birth probabilities after IVF and ICSI

We derived live birth probabilities for IVF/ICSI from a prospective cohort study performed between 2002 and 2004 (Lintsen et al., 2007). We used these live birth probabilities to compute live birth rate after IVF and ICSI. The only difference between the live birth rates and ongoing pregnancy rates is the risk of fertilization failure, which we assumed only occurs in IVF cycles.

Fertilization failure

We calculated the probability of fertilization failure according to pre-wash TMSC based upon a previously published prediction model (Repping et al., 2002).

Cycle length

In our base case scenario the time frame was one cycle and thus our cycle length was set at one month. Since the duration of our base case analysis was one cycle, no discounting was applied. In sensitivity analysis we evaluated the effect of applying more cycles.

Costs

The model was built from a health care perspective; therefore only direct medical costs were included. Costs per cycle were derived from the Dutch Umbrella study on fertility treatment (Merkus, 2006). The cost calculation was made according to the Dutch situation in the year 2012; hence costs were adjusted according to the consumer price index (CBS, Statistics Netherlands, 2013). (Table 1)
### Table 1. Base case assumptions and distributions

<table>
<thead>
<tr>
<th>IUI COH live birth per cycle</th>
<th>Pre Wash TMC ( \times 10^6 )</th>
<th>Probability per cycle</th>
<th>Distribution (Range)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>1,48%</td>
<td>Normal (0.0074-0.0038)</td>
<td>-</td>
<td>Dorjpurev et al, Zhao et al, Cohlen et al, Campana et al, Bradley et al, Dickey et al.</td>
</tr>
<tr>
<td>2</td>
<td>2,96%</td>
<td>Normal (0.0148-0.0444)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>4,27%</td>
<td>Normal (0.0213-0.0640)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>5,58%</td>
<td>Normal (0.0279-0.0836)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>6,88%</td>
<td>Normal (0.0344-0.1033)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>8,19%</td>
<td>Normal (0.0410-0.1229)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>9,50%</td>
<td>Normal (0.0275-0.1425)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>9,73%</td>
<td>Normal (0.0487-0.1460)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>9,97%</td>
<td>Normal (0.0498-0.1495)</td>
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<td>-</td>
</tr>
<tr>
<td>&gt;10</td>
<td>10,20%</td>
<td>Normal (0.0510-0.1530)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IVF &amp; ICSI live birth per cycle</th>
<th>Cycle</th>
<th>Probability per cycle</th>
<th>Distribution (Range)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0,277</td>
<td>Normal (0.14-0.42)</td>
<td>-</td>
<td>Lintsen et al.</td>
</tr>
<tr>
<td>2</td>
<td>0,253</td>
<td>Normal (0.13-0.38)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>0,219</td>
<td>Normal (0.11-0.33)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Fertilisation Failure</th>
<th>Pre Wash TMC ( \times 10^6 )</th>
<th>Probability per cycle</th>
<th>Distribution (Range)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>21,2%</td>
<td>-</td>
<td>-</td>
<td>Repping et al.</td>
</tr>
<tr>
<td>0.1</td>
<td>20,0%</td>
<td>Normal (0.100-0.300)</td>
<td>-</td>
<td>-</td>
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<tr>
<td>0.5</td>
<td>15,2%</td>
<td>Normal (0.076-0.228)</td>
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<td>-</td>
</tr>
<tr>
<td>1</td>
<td>10,6%</td>
<td>Normal (0.053-0.159)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>4,9%</td>
<td>Normal (0.025-0.074)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>2,2%</td>
<td>Normal (0.011-0.033)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>1,0%</td>
<td>Normal (0.005-0.015)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>0,4%</td>
<td>Normal (0.002-0.006)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>0,2%</td>
<td>Normal (0.001-0.003)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>0,1%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>0,0%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>0,0%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>0,0%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Costs*</th>
<th>Distribution (Range)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVF</td>
<td>€ 3 271 Normal (2271-4271)</td>
<td>Umbrellastudy, Merkus</td>
</tr>
<tr>
<td>ICSI cycle</td>
<td>€ 3 541 Normal (2541-4541)</td>
<td>Bouwmans et al* Umbrellastudy</td>
</tr>
<tr>
<td>IUI natural cycle</td>
<td>€ 416 Normal (289-543)</td>
<td>Umbrellastudy</td>
</tr>
<tr>
<td>IUI stimulated cycle</td>
<td>€ 595 Normal (413-777)</td>
<td>Umbrellastudy</td>
</tr>
</tbody>
</table>

*Index year 2012
We assumed that in this period no significant cost changes in the treatment protocol occurred except for inflation. The costs were €416 for one cycle IUI in the natural cycle and €595 for one cycle IUI-COH. In this study the average costs of IVF/ICSI was given, since in the Netherlands IVF and ICSI has a similar reimbursement from a health insurance perspective. Since our calculations were made from a health care perspective, we assumed the average cost of the IVF/ICSI cycle were the costs of one IVF cycle, namely €3,271. In another study the distinction between IVF and ICSI costs, was made, we used the ratio between the IVF and ICSI cycle to calculate the costs of one ICSI cycle, resulting in a cost per ICSI cycle of €3,541 (Bouwmans et al., 2008).

**Outcomes**

Live birth probabilities were determined for each scenario, as were the estimated costs. Live birth probabilities were defined as ongoing pregnancies resulting in a live birth of at least one child. There was no distinction between singleton or multiple gestations. Using these values, we computed the costs per live birth and the incremental cost-effectiveness ratio (ICER).

**Sensitivity analysis**

To address the uncertainty regarding our assumptions we carried out one-way and probabilistic (Monte Carlo simulations) sensitivity analyses. In one-way sensitivity analysis we varied variables independently. A threshold analysis was performed to determine if and when a variable changed the threshold value. This represents the value of a variable above which another treatment is preferred. In probabilistic sensitivity analysis the uncertainty of each parameter is quantified in terms of a probability distribution of this parameter. For this analysis distributions were fitted for all parameters in the model. As we were not able to fit beta-distributions for probabilities, normal distributions were fitted. The normal distributions were calculated according to the confidence interval from the study or by the plausible range provided by expert opinion (Briggs et al., 2006). For the probabilistic sensitivity analysis, 5,000 iterations of 5,000 women were performed.

In our model we evaluated one cycle, in sensitivity analysis we evaluated the effect of comparing more cycles. We compared six cycles of IUI to three cycles of IVF, since it is common practice to apply six cycles of IUI and three cycles of IVF, if treatment with IUI or IVF is instigated. We also evaluated the effect of three cycles of IVF versus three cycles of ICSI.

Estimates for the base-case analysis and ranges for sensitivity analyses are summarised in Table 1 and were derived from peer reviewed literature, as referenced. We performed our analysis by using a computer-generated Markov model (TreeAge Pro 2009, Tree Age Inc, Williamstown, MA, USA). We did not need IRB approval for this research.

**Results**

*Model one cycle IUI-COH compared to one cycle IVF*

Live birth rate after IUI-COH varied from 0% with a pre-wash TMSC of 0.1 million to 10.2% with a pre-wash TMSC of 10 million. Live birth rate after IVF varied from 21.8% with a
pre-wash TMSC of 0.1 million to 27.7% with a pre-wash TMSC of 10 million. Cost per live birth for an IUI cycle varied from €40,203 for a pre-wash TMSC of 1 million to €5,833 for a pre-wash TMSC of 10 million. Cost per live birth varied for an IVF cycle from €14,986 for a pre-wash TMSC of 0.1 million to €11,811 for a pre-wash TMSC of 10 million. IUI-COH had a lower cost per live birth compared to IVF if the pre-wash TMSC was above 3 million (Figure 1). 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, therefore IVF was always more effective and also more expensive (Figure 2).

**Model one cycle IVF compared to one cycle ICSI**

Live birth rate after ICSI was stable with 27.7% after one cycle ICSI. Live birth rate after IVF varied from 21.8% with a pre-wash TMSC of 0.1 million to 27.7% with a pre-wash TMSC of 10 million. Cost per live birth varied for an IVF cycle from €14,986 for a pre-wash TMSC of 0.1 million to €11,811 for a pre-wash TMSC of 10 million. Cost per live birth for an ICSI cycle irrespective of pre-wash TMSC was €12,783. ICSI had a lower cost per live birth compared to IVF if the pre-wash TMSC was < 3 million, from 3 million IVF had a lower cost per live birth (Figure 1). The extra costs per live birth (ICER) varied from €4,598 for a pre-wash TMSC of 0.1 million to €4,873,646 for a pre-wash TMSC of 10 million, therefore ICSI was more expensive but also more effective. (Figure 2)

**Sensitivity analysis**

**Model one cycle IUI-COH compared to one cycle IVF**

In one-way sensitivity analysis we varied the probability of fertilization failure. If at a pre-wash TMSC of 10 million the probability of fertilization failure is above 63.2% IUI becomes more effective than IVF and therefore the dominant treatment. Since IUI is also cheaper. Below a fertilization failure of 63.2% the choice of treatment is dependable on the willingness to pay (WTP). And with a pre-wash TMSC of 1 million the probability of fertilization failure should be above 93.7% before IUI becomes more effective.

We also varied the probability of live birth after IUI-COH. If the probability of live birth at a pre-wash TMSC of 10 million was above 14.4% the extra cost per live birth for IVF would come above €20,000 per extra live birth. And if the probability of live birth was above 24.4% extra costs per live birth are above €80,000. And if the probability of live birth at a pre-wash TMSC of 1 million was above 10.2% the extra cost per live birth for IVF would come above €20,000 per extra live birth. And if the probability of live birth was above 20.2% extra costs per live birth are above €80,000.

Probabilistic sensitivity analysis showed that IVF was always more effective and also more costly for all ranges. ICER for a pre-wash TMSC of 0.1 million was €13,207 (95% CI €6,441 - €25,994) and was €65,535 (95% CI €6,422 - €71,842) for a pre-wash TMSC of 10 million. Which treatment is cost-effective, depends on the willingness to pay.

**Model one cycle IVF compared to one cycle ICSI**

In one-way sensitivity analysis we varied the probability of fertilization failure. We found no threshold. If the probability of fertilization failure was above 1.2% the extra cost per
Cost-effectiveness of Male Subfertility

live birth for ICSI would be below €80,000 per extra live birth. And if the probability of fertilization failure was above 5% extra costs per live birth is below €20,000.

In probabilistic sensitivity analysis we found that ICSI was always more effective according to the 95% confidence interval until a pre-wash TMSC of 6 million and could be more or less expensive than IVF. Therefore, ICSI was the dominant strategy or cost-effectiveness was dependable on the WTP per extra live birth.
Model six cycles IUI-COH compared to three cycles IVF
Live birth rate after six cycles of IUI-COH varied from 0% with a pre-wash TMSC of 0.1 million to 47.6% with a pre-wash TMSC of 10 million. Live birth rate after three cycles of IVF varied from 48.2% with a pre-wash TMSC of 0.1 million to 57.8% with a pre-wash TMSC of 10 million. Total costs varied from €3,570 to €2,774 for IUI-COH and from €7,875 to €7,403 for IVF. Cost per live birth after six cycles of IUI-COH varied from €40,203 for a pre-wash TMSC of 1 million to €5,833 for a pre-wash TMSC of 10 million. Cost per live birth varied for an IVF cycle from €16,334 for a pre-wash TMSC of 0.1 million to €12,805 for a pre-wash TMSC of 10 million. IUI-COH had a lower cost per live birth compared to IVF if the pre-wash TMSC was above 3 million. The extra cost per live birth (ICER) varied from €8,930 for a pre-wash TMSC of 0.1 million to €45,154 for a pre-wash TMSC of 10 million, IVF was always more effective and also more expensive.

Model three cycles IVF compared to three cycles ICSI
Live birth rate after three cycles of ICSI was stable with 57.8%. Live birth rate after IVF varied from 48.2% with a pre-wash TMSC of 0.1 million to 57.8% with a pre-wash TMSC of 10 million. Total cost varied between €7,878 to €7,403 for three cycles of IVF and €8,014 for three cycles of ICSI. Cost per live birth varied for three cycles of IVF cycle from €16,362 for a pre-wash TMSC of 0.1 million to €12,805 for a pre-wash TMSC of 10 million. Cost per live birth for an ICSI cycle irrespective of pre-wash TMSC was €13,860. ICSI had a lower cost per live birth compared to IVF if the pre-wash TMSC was below 3 million, from 3 million IVF had a lower cost per live birth. The extra cost per live birth (ICER) varied from €1,400 for a pre-wash TMSC of 0.1 million to €7,221,382 for a pre-wash TMSC of 10 million, ICSI was always more expensive but also more effective.

We’ve also tested the probability of fertilization failure. If the probability of fertilization failure is more than 27.3% per cycle, three cycles of ICSI is less expensive and more effective than three cycles of IVF, IVF is dominated.

Discussion
In this decision analysis, we found that in couples with a pre-wash TMSC above 3 million, the cost per live birth were lower for IUI-COH compared to IVF. Below a pre-wash TMSC of 3 million ICSI had a lower cost per live birth. IVF was always more expensive and effective than IUI-COH and ICSI was always more expensive and effective than IVF. Whether IVF is considered cost-effective over IUI-COH and ICSI over IVF depends on the WTP per extra live birth. Unfortunately it is unknown what the payer (health provider or couple) is prepared to pay for an extra live birth. Changing the variables, within plausible ranges, did not alter our conclusions.

Since in current practice more cycles are given to a couple, we also explored the effect on the cost-effectiveness when comparing more cycles. If six cycles of IUI-COH were applied and three cycles of IVF, our conclusions remained the same. If the pre-wash TMSC was above three million, IUI-COH had a lower cost per live birth compared to IVF and IVF was always more effective and expensive. Therefore application of IVF over IUI-COH is
Our findings were similar to another cost-effectiveness study on this topic, only we found that below a pre-wash TMSC of 3 million, IVF had a lower cost per live birth (Goverde et al., 2000). This small randomized controlled trial also reported that IUI had a lower cost per live birth in couples with a pre-wash TMSC between 1 to 20 million, only no cut-off values were studied (Goverde et al., 2000). Another study on this topic concluded that if the pre-wash TMSC was below 10 million, IVF/ICSI was more effective and less costly than IUI (van Voorhis et al., 2001). This is in contrast with our findings. We found that IVF or ICSI was always more effective and more costly.

Our study has some limitations. First, although empirical data and true healthcare costs were used as input parameters for the model, data on live birth according to pre-wash TMSC were limited. For example, due to unreliable data we were not able to perform analysis comparing IUI in the natural cycle to IVF.

Second, ideally, we also should have compared IUI to timed intercourse. However, the only model available for the prediction of natural conception is not applicable in couples with male subfertility (Hunault et al., 2004).

Third, we considered pregnancy probabilities were equal to the live birth probabilities, since data on miscarriage rates were lacking. Possibly, the live birth probabilities are a bit lower than estimated.

Fourth, to compute live birth rates after IVF and ICSI we derived live birth probabilities for IVF/ICSI from a prospective cohort study performed between 2002 and 2004 (Lintsen et al., 2007). The only difference between the live birth rates and ongoing pregnancy rates was the risk of fertilization failure, which we assumed only occurs in IVF cycles. The risk of fertilization failure was based on a previously published prediction model (Repping et al., 2002) that has not been validated externally. A sensitivity analysis on the risk of fertilization failure showed that irrespective of the risk of fertilization failure, ICSI was always more effective and more costly. The risk of fertilization failure only had an influence on the extra cost per live birth.

Fifth, our base-case calculation was centred on 30 year old women. We were unable to specify the model by different groups of age due to lack of evidence. Since the majority of the studies regarding pregnancy probabilities according to pre-wash TMSC have a mean female age around 30, this model is applicable to this population (Voorhis et al., 2001; Cohlen et al., 1998; Dickey et al., 1999; Dorjpurev et al., 2011; Zhao et al., 2004; Campana et al., 1996).

Sixth, in reproductive medicine the WTP for an extra live birth is unknown. Therefore it is very difficult to make a clear statement whether IUI, IVF or ICSI is considered cost-effective, since it is highly dependable on the WTP.

A strength of this study is that this is the first study that used a model to explore the cost-effectiveness in couples with male subfertility. Although we searched extensively for data on the subject, we have to conclude that high level evidence is scarce. Consequently, our model-based approach is at present the most optimal approach on this subject. Our outcomes define important knowledge gaps and a large randomized controlled trial is needed to support these calculations. In the Netherlands a large randomized
controlled trial, the MASTER trial, is started and will validate the indications for expectant management, IUI, IVF and ICSI in couples with male subfertility by taking the cost-effectiveness of these treatments into account. (NTR3820,NTR3822,NTR3823)

Furthermore, in this study, we made great effort to be transparent in our reporting, which should allow researchers and decision-makers to judge the applicability of this work to their own setting.

In conclusion, in this study we were able to compare IUI, IVF and ICSI in couples with male subfertility. The choice of IVF over IUI and ICSI over IVF depends on the willingness to pay for extra live birth. However, above a pre-wash TMSC of three million costs per live birth are lower for IUI and below a pre-wash TMSC of three million costs per live birth are lower for ICSI.
References


Chapter 7


