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ARTICLE

Cost-effectiveness of assisted conception for male subfertility

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Abstract Intrauterine insemination (IUI), with or without ovarian stimulation, IVF and intracytoplasmatic sperm injection (ICSI) are frequently used treatments for couples with male subfertility. No consensus has been reached on 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 total motile sperm count (TMSC). A computer-simulated cohort of subfertile women aged 30 years with a partner was analysed with a pre-wash TMSC of 0 to 10 million. Three treatments were evaluated: IUI with and without controlled ovarian stimulation; IVF; and ICSI. Main outcome was expected live birth; secondary outcomes were cost per couple and the incremental cost-effectiveness ratio. The choice of IVF over IUI with ovarian stimulation and ICSI over IVF depends on the willingness to pay for an extra live birth. If only cost per live birth is considered 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. RBMOnline

KEYWORDS: cost-effectiveness, intracytoplasmic sperm injection, intrauterine insemination, in vitro fertilization, male subfertility

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Introduction

Male subfertility is a common condition, diagnosed as the sole cause in 30% of all couples presenting with subfertility and as a contributory factor in another 20% (Crosignani and Walters, 1994; Hull et al., 1985). Intrauterine insemination (IUI) with or without ovarian stimulation, IVF and intracytoplasmatic sperm injection (ICSI) are frequently used treatments for couples with male subfertility (Cohlen, 2005; Goverde et al., 2000; Tournaye, 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, a strong correlation was observed between semen parameters and the probability of natural conception (van der Steeg et al., 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) seems to have a consistent, direct relationship with the pregnancy rate per cycle after IUI, but no definite predictive threshold exists for success (Tijani and Bhattacharya, 2010).

Knowledge of 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 ovarian stimulation in couples with mild male subfertility has been subject to much debate. No evidence of difference between the probabilities of pregnancy rates per woman was found when IUI was compared with timed intercourse in both natural cycles (odds ratio [OR] 5.3; 95% confidence interval [CI] 0.42 to 67). No statistically significant difference between pregnancy rates per couple for IUI with ovarian stimulation compared with IUI in natural cycle could be found (OR 1.5; 95% CI 0.92 to 2.4) (Bensdorp et al., 2007). In couples with moderate or severe male subfertility, i.e. a TMSC between 1 and 3 million, carrying out IUI before IVF is not based on comparative studies. It also remains unclear at which TMSC ICSI becomes more effective than IVF (Repping et al., 2002; Rhemrev et al., 2001). As a consequence, ICSI is recommended when extreme male subfertility is present (TMSC below 1 million), although epidemiological data to support such cut-offs are lacking. The few studies that compared IVF with ICSI in couples with male subfertility showed a higher incidence of fertilization failure in IVF compared with ICSI (Pisarska et al., 1999; Plachot et al., 2002; van der Westerlaken et al., 2006). A meta-analysis showed that the risk ratio for an oocyte to become fertilized was 1.9 (95% CI 1.4 to 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 to 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 fertilization occurs, 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 with IUI with ovarian stimulation and IVF (Goverde et al., 2000). The costs per pregnancy resulting in at least one live birth were US$ 4511–5710 for IUI and IUI with ovarian stimulation, and US$ 14,679 for IVF. This study, however, was conducted 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 to be drawn on this issue. A retrospective cohort study evaluated 3479 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, a computer-simulated cohort study was conducted on the subject. The aim was to compare the cost and effectiveness of IUI, IVF and ICSI in subfertile women aged 30 years with a partner with a pre-wash TMSC between 0 and 10 million.

Materials and methods

Three Markov decision trees were constructed for couples presenting with male subfertility who completed their basic fertility work-up. To evaluate the most cost-effective treatment, one cycle of IUI with ovarian stimulation was compared with one cycle of IVF; one cycle of IUI in the natural cycle was compared with one cycle of IVF; and one cycle of IVF was compared with 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 compared with its next best alternative.

Details of computer simulation model

Patient characteristics

The 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 and 10 million. A 30-year-old woman was selected, as the studies of pregnancy probabilities according to pre-wash TMSC were based on couples in whom the woman had a mean age near 30 years (Campana et al., 1996; Cohlen et al., 1998; Dickey et al., 1999; Dorjpurev et al., 2011; Van Voorhis et al., 2001; Zhao et al., 2004).

Models

Three decision trees were built. In model one, one cycle of IUI with ovarian stimulation was compared with one cycle of IVF. In model two, one cycle of IUI in the natural cycle was compared with one cycle of IVF. In model three, one cycle of IVF was compared with one cycle of IVF–ICSI. The used probabilities are presented in **Table 1**.

Table 1 Base-case assumptions and distributions.

IUI ovarian stimulated live birth per cycle	*Pre-wash TMC *10^6*	*Probability per cycle (%)*	*Distribution (range)*	*Reference*
	0	0	–	Campana et al.,1996; Cohlen et al.,1998; Dickey et al.,1999; Van Voorhis et al., 2001; Zhao et al; 2004; Dorjpurev et al., 2011
	1	1.48	Normal (0.0074–0.0038)	
	2	2.96	Normal (0.0148–0.0444)	
	3	4.27	Normal (0.0213–0.0640)	
	4	5.58	Normal (0.0279–0.0836)	
	5	6.88	Normal (0.0344–0.1033)	
	6	8.19	Normal (0.0410–0.1229)	
	7	9.50	Normal (0.0275–0.1425)	
	8	9.73	Normal (0.0487–0.1460)	
	9	9.97	Normal (0.0498–0.1495)	
	>10	10.20	Normal (0.0510–0.1530)	

IVF and ICSI live birth per cycle	*Cycle*	*Probability per cycle*	*Distribution (range)*	*Reference*
	1	0.277	Normal (0.14–0.42)	Lintsen et al., 2007
	2	0.253	Normal (0.13–0.38)	
	3	0.219	Normal (0.11–0.33)	

Fertilization failure	*Pre-wash TMC*10^6*	*Probability per cycle (%)*	*Distribution (Range)*	*Reference*
	0.01	21.2	–	Reppingetal.,2002
	0.1	20.0	Normal (0.100–0.300)	
	0.5	15.2	Normal (0.076–0.228)	
	1	10.6	Normal (0.053–0.159)	
	2	4.9	Normal (0.025–0.074)	
	3	2.2	Normal (0.011–0.033)	
	4	1.0	Normal (0.005–0.015)	
	5	0.4	Normal (0.002–0.006)	
	6	0.2	Normal (0.001–0.003)	
	7	0.1	–	
	8	0.0	–	
	9	0.0	–	
	10	0.0	–	

Costs[a]		*Distribution (range)*	*Reference*
IVF	€ 3.271	Normal (2271–4271)	Merkus, 2006
ICSI cycle	€ 3.541	Normal (2541–4541)	Bouwmans et al., 2008; Merkus, 2006
IUI natural cycle	€ 416	Normal (289–543)	Merkus, 2006
IUI stimulated cycle	€ 595	Normal (413–777)	Merkus, 2006.

[a]Index year 2012.
ICSI = intracytoplasmic sperm injection; IUI = intrauterine insemination; TMC = total motile count

Live birth probabilities after IUI

A systematic search for studies on pregnancy and live birth probabilities after IUI according to pre-wash TMSC in couples with male subfertility was conducted. All studies, except for one randomized controlled trial (Cohlen et al., 1998), were retrospective (Campana et al., 1996; Dickey et al., 1999; Dorjpurev et al., 2011; Huang et al., 1996; Merviel et al., 2010; Van Voorhis et al., 2001; Zhao et al., 2004). Two studies were excluded as they only mentioned pregnancy probabilities but not the necessary number of cycles to achieve this (Huang et al., 1996; Merviel et al., 2010). Most studies showed pregnancy probabilities of IUI and ovarian stimulation with clomiphene citrate or FSH (Campana et al., 1996; Cohlen et al., 1998; Dickey et al., 1999; Dorjpurev et al., 2011; Van Voorhis et al., 2001; Zhao et al., 2004). The pregnancy probabilities after IUI were combined with clomiphene citrate and FSH, and pregnancy probabilities after IUI and ovarian stimulation were calcualted according to pre-wash TMSC. The total number of cycles were summed and the total number of achieved pregnancies per cycle calculated. 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 (Cohlen et al., 1998) concluded that, in couples with a pre-wash TMSC below 5 million, IUI in the natural cycle was more effective than IUI with ovarian stimulation. In these couples, pregnancy probabilities improved sevenfold (OR of 6.9; 95% CI 0.7 to 70), whereas, in couples with a pre-wash TMSC between 5 and 10 million, no advantage of IUI and ovarian stimulation was found over IUI in the natural cycle. Because data on IUI in the natural cycle were scarce, and the randomized controlled trial (Cohlen et al., 1998) did not show a significant effect and, if used, would lead to unreliable results, a decision was made not to compare IUI in the natural cycle with IVF.

Live birth probabilities after IVF and ICSI

Live birth probabilities were derived for IVF–ICSI from a prospective cohort study conducted between 2002 and 2004 (Lintsen et al., 2007). These live birth probabilities were used 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 was assumed only to occur in IVF cycles. Fertilization failure also occurs in ICSI cycles, in that case mostly as a result of poor oocyte quality. Woman's age was assumed to be 30 years in our calculaton, and therefore fertilization failure was assumed not to occur when using ICSI.

Fertilization failure

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

Cycle length

In the base-case scenario, the time frame was one cycle and therefore our cycle length was set at 1 month. As the duration of our base-case analysis was one cycle, no discounting was applied. In sensitivity analysis, the effect of applying more cycles was evaluated.

Costs

The model was built from a healthcare 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**).

It was assumed that, in this period, no significant cost changes in the treatment protocol occurred except for inflation. The costs were €416 for one cycle of IUI in the natural cycle and €595 for one cycle of IUI with ovarian stimulation. In this study, the average costs of IVF–ICSI were available, in the Netherlands, IVF and ICSI has a similar reimbursement from a health insurance perspective. As our calculations were made from a healthcare perspective, it was assumed that the average cost of the IVF–ICSI cycle were equivalent to the costs of one IVF cycle, namely €3271. In another study, a distinction between IVF and ICSI costs was made. The ratio between the IVF and ICSI cycle was used to calculate the costs of one ICSI cycle, resulting in a cost per ICSI cycle of €3541 (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. No distinction was made between singleton or multiple gestations. Using these values, the costs per live birth and the ICER were calculated.

Sensitivity analysis

To address the uncertainty about our assumptions, one-way and probabilistic (Monte Carlo simulations) sensitivity analyses was conducted. In one-way sensitivity analysis, variables were varied independently. A threshold analysis was conducted 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. Normal distributions were fitted as beta-distributions for probabilities could not be 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, 5000 iterations of 5000 women were carried out.

In the present model, one cycle was evaluated, and, in sensitivity analysis, the effect of comparing more cycles was evaluated. Six cycles of IUI were compared with three cycles of IVF, as it is common practice to apply six cycles of IUI and three cycles of IVF, if treatment with IUI or IVF is instigated. The effect of three cycles of IVF compared with three cycles of ICSI was examined.

Estimates for the base-case analysis and ranges for sensitivity analyses are presented in **Table 1** and were derived from peer-reviewed literature, as referenced. A computer-generated Markov model (TreeAge Pro 2009, Tree Age Inc, Williamstown, MA, USA) was used to conduct the analysis. International Review Board approval was not required for this research.

Results

Model one cycle IUI with ovarian stimulation compared with one cycle of IVF

Live birth rate after IUI with ovarian stimulation 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 €5833 for a pre-wash TMSC of 10 million. Cost per live birth varied

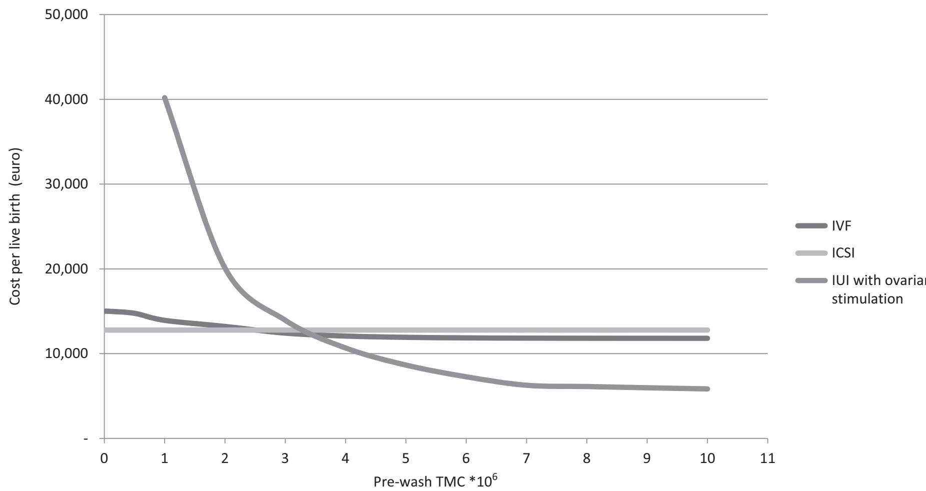

Figure 1 Cost per live birth. IUI = intrauterine insemination; ICSI = intracytoplasmic sperm injection; TMC = total motile count.

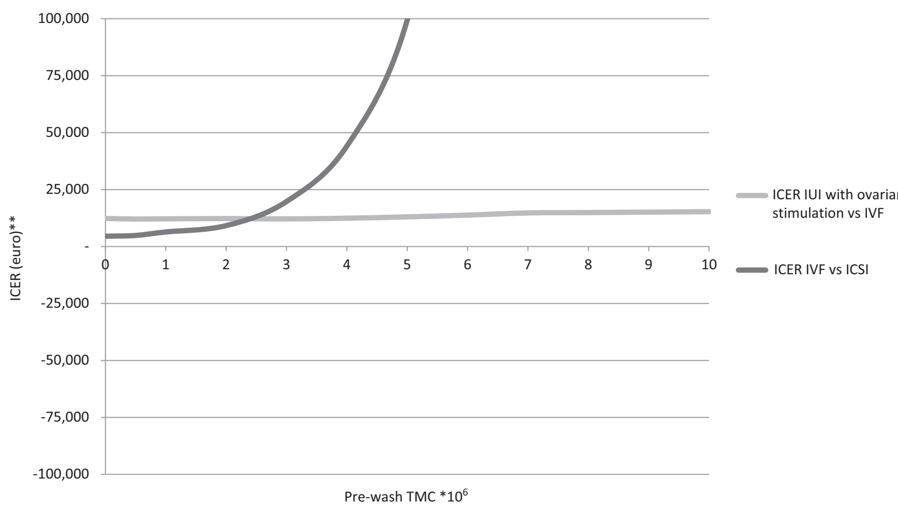

Figure 2 Incremental cost-effectiveness ratios.** The scale of the Y-axis was adjusted so the threshold would become readable; the total cost reached €4,873,646. ICER = incremental cost-effectiveness ratio; ICSI = intracytoplasmic sperm injection; IUI = intrauterine insemination; TMC = total motile count.

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. Per live birth, IUI with ovarian stimulation had a lower cost compared with 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 with one cycle of 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. Per live birth, ICSI had a lower cost compared with IVF if the pre-wash TMSC was less than 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 with ovarian stimulation compared with one cycle IVF

In one-way sensitivity analysis, the probability of fertilization failure varied. 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, as IUI is also cheaper. Below a fertilization failure of 63.2%, the choice of treatment depends on the willingness to pay. And with a pre-wash TMSC of 1 million, the probability of fertilization failure should be above 93.7% before IUI becomes more effective.

The probability of live birth after IUI with ovarian stimulation also varied. 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. Also, if the probability of live birth was above 24.4%, extra costs per live birth are above €80,000. 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. 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. For a pre-wash TMSC, ICER of 0.1 million was €13,207 (95% CI €6441–€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 with one cycle ICSI

In one-way sensitivity analysis, the probability of fertilization failure varied. No threshold was found. If the probability of fertilization failure was above 1.2%, the extra cost per live birth for ICSI would be below €80,000 per extra live birth. If the probability of fertilization failure was above 5%, extra costs per live birth is below €20,000.

In probabilistic sensitivity analysis, 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 dependent on the willingness to pay per extra live birth.

Model six cycles IUI with ovarian stimulation compared with three cycles IVF

Live birth rate after six cycles of IUI with ovarian stimulation 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 with ovarian stimulation and from €7875 to €7403 for IVF. Cost per live birth after six cycles of IUI with ovarian stimulation varied from €40,203 for a pre-wash TMSC of 1 million to €5833 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. Per live birth, IUI with ovarian stimulation had a lower cost compared with IVF if the pre-wash TMSC was above 3 million. The extra cost per live birth (ICER) varied from €8930 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 with three cycles ICSI

Live birth rate after three cycles of ICSI was stable at 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 €7878 to €7403 for three cycles of IVF and €8014 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. Per live birth, ICSI had a lower cost compared with 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 €1400 for a pre-wash TMSC of 0.1 million to €7,221,382 for a pre-wash TMSC of 10 million. Here, ICSI was always more expensive but also more effective.

The probability of fertilization failure was also tested. 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 therefore dominant. The cost per pregnancy with a 27.5% fertilization failure are €13,860 for ICSI compared with €17,719 for IVF.

Discussion

In this decision analysis, in couples with a pre-wash TMSC above 3 million, the cost per live birth was lower for IUI with ovarian stimulation compared with IVF. Below a pre-wash TMSC of 3 million ICSI had a lower cost per live birth. Compared with IUI with ovarian stimulation, IVF was always more expensive and effective; compared with IVF, ICSI was always more expensive and effective. Whether IVF is considered cost-effective over IUI with ovarian stimulation and ICSI over IVF depends on the willingness to pay 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.

In current practice, more cycles are given to a couple; therefore, the effect on the cost-effectiveness when comparing more cycles was also explored. If six cycles of IUI with ovarian stimulaton were applied, and three cycles of IVF, our conclusions remained the same. If the pre-wash TMSC was above 3 million, IUI with ovarian stimulation had a lower cost per live birth compared with IVF, and IVF was always more effective and expensive. Therefore, application of IVF over IUI with ovarian stimulation depends on the willingness to pay. The conclusions also remained the same if three cycles of IVF were compared with three cycles of ICSI.

The findings were similar to another cost-effectiveness study on this topic; however, below a pre-wash TMSC of 3 million, we found that 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 and 20 million; however, 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.

The 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, because the data were unreliable, IUI in the natural cycle could not be compared with IVF.

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

Third, pregnancy probabilities were considered to be equal to live birth probabilities, as data on spontaneous abortion rates were lacking. Possibly, the live birth probabilities are a bit lower than estimated.

Fourth, to compute live birth rates after IVF and ICSI, live birth probabilities were derived for IVF–ICSI from a prospective cohort study carried out 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), which 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, the base-case calculation was centred on a 30-year old women. The model, however, could not be specified according to different groups of age owing to lack of evidence. As most of the studies on pregnancy probabilities according to pre-wash TMSC have a mean woman's age around 30 years, this model is applicable to this population (Campana et al., 1996; Cohlen et al., 1998; Dickey et al., 1999; Dorjpurev et al., 2011; Van Voorhis et al., 2001; Zhao et al., 2004).

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

A strength of this study is that, to the best of our knowledge, this is the first study that used a model to explore the cost-effectiveness in couples with male subfertility. Although data on the subject were searched extensively, we had to conclude that high level evidence is scarce. Consequently, the model-based approach is at present the most optimal approach on this subject. The outcomes define important knowledge gaps, and a large randomized controlled trial is needed to support these calculations. Particularly, knowledge about natural conception chances resulting from expectant management in relation to total motile sperm count are unavailable (Bhattacharya et al., 2008; Hughes et al., 2004; Steures et al., 2006); therefore, hampering such modelling. In the Netherlands, a large randomized controlled trial, the MASTER trial, has 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 the present study, a big effort was made to report transparently, which should allow researchers and decision-makers to judge the applicability of this work to their own setting.

In conclusion, in this study, IUI, IVF and ICSI in couples with male subfertility were compared. The choice of IVF over IUI and ICSI over IVF depends on the willingness to pay for extra live birth. Above a pre-wash TMSC of 3 million, however, costs per live birth are lower for IUI and below a pre-wash TMSC of 3 million costs per live birth are lower for ICSI.

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