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van Rumste, M.M.E.

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Chapter 8

IVF with planned single embryo transfer versus IUI with ovarian stimulation in couples with unexplained subfertility, an economic analysis

Minouche M.E. van Rumste, Inge M. Custers, Madelon van Wely, Carolien A. Koks, Hans G.I. van Weering, Nicole G.M. Beckers, Gabrielle J. Scheffer, Frank J.M. Broekmans, Peter G.A. Hompes, Monique H. Mochtar, Fulco van der Veen, Ben Willem J. Mol

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ABSTRACT

Couples with unexplained subfertility are often treated with intra-uterine insemination with ovarian stimulation (IUI-COS), which carries the risk of multiple pregnancies. In couples with unexplained subfertility and a poor prognosis for natural conception, an explorative randomized controlled trial was performed comparing one cycle of in vitro fertilization (IVF) with elective single embryo transfer (eSET) versus three cycles of IUI-COS.

The aim of this study was to assess the economic burden of the treatment modalities. Main outcome measures were ongoing pregnancy rates and costs. We randomly assigned 58 couples to IVF-eSET and 58 couples to IUI-COS. The ongoing pregnancy rates were 24% in the IVF-eSET group, versus 21% in the IUI-COS group with two and three multiple pregnancies, respectively. The mean cost per included couple was significantly different, 2,781 Euro in the IVF-eSET group and 1,876 Euro in the IUI-COS group. The additional costs per ongoing pregnancy were 2,456 Euro for IVF-eSET. In couples with unexplained subfertility, one cycle of IVF-eSET costed an additional 900 Euro per couple compared to three cycles of IUI-COS, for no increase in ongoing pregnancy rates or decrease in multiple pregnancies. When IVF-eSET results in a 38% ongoing pregnancy rate, IVF would be the preferred treatment.

INTRODUCTION

In many countries, intra-uterine insemination with controlled ovarian stimulation (IUI-COS) is the first line of treatment in couples with unexplained subfertility. As IUI-COS finds her effectiveness in multiple ovulation, an inevitable side effect of ovarian stimulation is the occurrence of multiple pregnancies with a prevalence varying between 10 to 18% (Brandes et al., 2010; van Rumste et al., 2008; Steures et al., 2007;). Multiple pregnancies are associated with an increased risk for poor outcomes of both mother and children compared to singleton pregnancies, demonstrated for example by an increased rate of preeclampsia or preterm birth (Campbell and Templeton, 2004; The ESHRE Capri Workshop Group, 2000; Pinborg et al., 2004). They also impose a large burden on health care costs, due to the cost of obstetrical and neonatal complications, as well as to the cost of disability in the offspring (De Sutter et al., 2002; Gerris et al., 2004; Lukassen et al., 2004).
We recently conducted an explorative randomized controlled trial that evaluated whether IVF-eSET would lead to a similar pregnancy rate as three cycles of IUI-COS, but with a lower multiple pregnancy rate. This trial suggested that one cycle of IVF-eSET might be as effective as three cycles of IUI-COS as primary treatment (Custers et al., 2011). In view of this finding, costs may play an important role in the decision on one or the other treatment. The aim of our study was therefore to compare the costs of one IVF-eSET cycle versus three IUI-COS cycles in couples with unexplained subfertility.

MATERIALS AND METHODS

The initial study was performed as a multicenter randomized trial between November 2006 and February 2009. Nine clinics in the Netherlands participated, three University hospitals and six teaching hospitals. The institutional review board of the Academic Medical Centre approved the study, after which there was local approval from the boards of the other participating hospitals. The trial was registered in the clinical trial register as ISRCTN86744378.
All couples had undergone a standard fertility work-up, including assessment of ovulation by basal temperature curve or ultrasound, a tubal patency test and sperm analysis. All couples with unexplained or mild male subfertility, female age between 18 and 38 years and poor fertility prospects, defined as a 12 month prognosis of less than 30% for natural conception according to the model of Hunault (Hunault et al., 2004), were included. They were randomly allocated to one cycle of IVF-eSET followed by one cryo cycle, or to three cycles of IUI-COS. Follow-up ended four months after the first treatment cycle started.
In the IVF-eSET group couples underwent controlled ovarian hyperstimulation after down-regulation with a GnRH agonist in a long protocol with a midluteal start. One

top-quality embryo was transferred on day three. If no top-quality embryo was present, double embryo transfer (DET) was performed. Spare embryos were cryo-preserved on the fourth day (conventional slow freezing) when possible. If the thawed embryo was of good quality, again only one embryo was transferred. The results of the freeze-thaw cycles were also included in this study, providing they were within the timeframe of four months after starting the first treatment. Further details, such as scoring of the quality of the embryo, have been previously described (Custers et al., 2011).

Women in the IUI-COS group underwent controlled ovarian hyperstimulation with 50 to 75IU rFSH (Puregon®, MSD, Oss, the Netherlands). When necessary the dose rFSH was increased. One teaching hospital used 100mg clomiphene citrate for 5 days, starting cycle day three. The goal of ovarian hyperstimulation was to achieve the growth of up to a maximum of three dominant follicles (>18mm). The detailed stimulation protocol and other clinical details for IUI-COS have been previously described (Custers et al., 2011).

The primary outcome was an ongoing pregnancy, defined by an intra-uterine pregnancy with positive heart activity seen by ultrasound at 12 weeks' gestation. We also assessed the number of multiple pregnancies, live birth and financial costs. All analyses were done by intention-to-treat and all randomized couples were included.

Economic analysis

In the Netherlands, an unlimited number of IUI-COS cycles and up to three cycles of IVF (including cryo-preserved cycles) are covered by health care insurance. The economic analysis was therefore performed from the perspective of the health care institution. We followed the EURONHEED sub-checklist as a guideline for our economic evaluation (Nixon et al., 2009).

We used prices set at November 2010 by the Dutch Health Care Authority (NZa), which were nationwide agreed fixed prices for treatments (http://ctg.bit-ic.nl/Nzatarieven/top.do). The costs for IVF-eSET and IUI-COS included hospital costs, such as clinical and laboratory costs, the specialist fee and the costs of medication. These costs are specified in Table 1. Hospital costs like overhead costs were not included but assumed to be equal. The clinical component includes costs regarding the monitoring of the cycle during treatment, diagnostic tests, visits to the outpatient-clinic, medical equipment, and follow-up of the couple after IUI or embryo transfer in case a pregnancy occurred. The laboratory component includes costs regarding the procedures concerning sperm preparation, in vitro fertilization, embryo scoring and embryo transfer. Medication costs comprises of the total units of rFSH or clomiphene citrate were registered per cycle. Multiple imputations were used in case total units of FSH per cycle were missing. Couples were followed until there was an ongoing pregnancy or until the follow-up period ended. Costs generated by a pregnancy developing beyond 12 weeks' gestation and delivery were not taken into account.

We registered the number of cycles with IVF-eSET and IUI-COS, as well as the ongoing pregnancy rates in both groups. The mean costs per couple per randomized group were calculated. The 95% confidence intervals of the mean costs were estimated by non-parametric bootstrapping to account for the expected skewing of the data.
Cost-effectiveness was defined as the ratio of the sum of the total costs per randomized group divided by the number of couples with an ongoing pregnancy. A scenario analysis was done to explore the cost effectiveness of IVF versus IUI at different ongoing pregnancy rates following IVF using bootstrapping.
To explore the effect of plausible variations in stimulation medication, we performed four sensitivity analyses. First, we calculated the total costs assuming that IUI was performed with clomiphene citrate. Second, total costs were calculated assuming that IUI was performed with the highest dosage of FSH. Third, costs were calculated assuming the lowest dosage of FSH was used in the IVF group. Fourth, costs were calculated using the highest dosage of FSH in the IVF group.

Table 1. Specified costs per treatment of IVF or IUI-COS

	IVF-eSET	IUI
Hospital component	€ 1852.20	€ 436.69
Costs without follicle aspiration and ET	€ 1131.37	
Specialist fee	€ 332.60	€ 66.58
Medication		
50mg clomiphene citrate		€ 0.454
1 IU FSH	€ 0.409	€ 0.409
10,000 IU hCG	€ 8.68	€ 8.68
14 days progesterone	€ 14	

Funding

An unconditional grant from Organon, Oss, the Netherlands was received for the initial clinical trial. Patients did not receive compensation for treatment, since IVF and IUI were completely reimbursed by health insurance.

RESULTS

We randomized 116 couples, of which 58 couples were allocated to IVF-eSET and 58 to IUI-COS (Figure 1). Baseline characteristics of both groups were comparable, with a mean female age of 34 years and duration of subfertility of 2.3 years (Custers et al., 2011). The outcomes per randomized group are shown in Table 2. In the couples treated with IVF-eSET there were 14 ongoing pregnancies (24%). Two of those pregnancies were twin

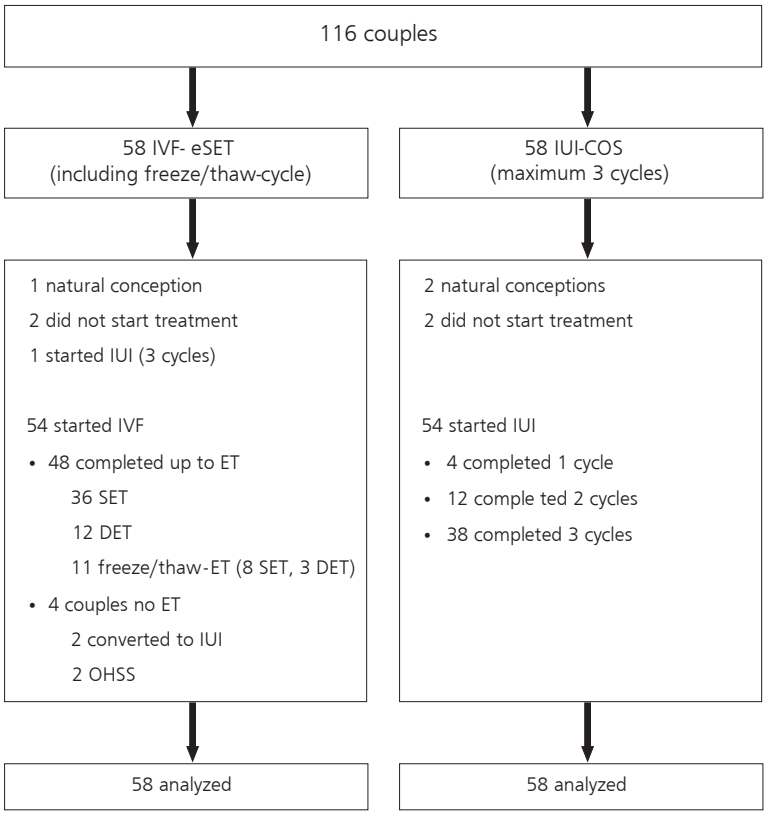

Figure 1. Flow chart of randomized couples

pregnancies (multiple pregnancy rate of 14%). Both resulted from transfer of two fresh embryos. In the couples treated with IUI-COS there were 12 ongoing pregnancies (21%), of which two twins and one triplet pregnancy (multiple pregnancy rate of 25%). The triplet pregnancy was reduced to a twin pregnancy and the twins were born at term. All twins were dichorial diamniotic. The pregnancy rates per started treatment cycle were 25.9% for IVF-eSET (54 cycles) and 8.5% for IUI-COS (142 cycles).

As described in the publication on the clinical outcomes of this trial in 74% of all IUI-COS cycles multifollicular growth was achieved. Fourteen IUI-COS cycles were cancelled because of the risk of high order multiple pregnancy (10%). In 116 IUI-COS cycles the number of follicles larger than 15mm was registered. In 59/116 IUI-COS cycles (50.8%) there was more than one follicle larger than 15mm.

Economic analysis

In 9 couples in the IVF-eSET group and 7 couples in the IUI-COS group the units of FSH used were imputed. In 5 couples receiving IUI-COS treatment, ovarian stimulation was

performed with clomiphene citrate. All of these couples received three cycles of IUI-COS. The number of treatment cycles, amounts of rFSH and clomiphene citrate used and costs per randomization group, are shown in Table 2.

The total costs per randomized group were € 161,327 for the IVF-eSET group and € 108,808 for the IUI-COS group (Table 2), suggesting a potential additional cost of € 52,519 for IVF-eSET. The mean cost per included couple was € 2,781 (95% CI: € 2,293 to € 3,270) in the IVF-eSET group and € 1,876 (95% CI: € 1,462 to € 2,270) in the IUI-COS group ($p<0.01$). The bootstrapped mean difference (95%CI) in costs per couple suggested a cost of € 915 (95% CI 183 to 1,647) for IVF-eSET versus IUI ($p<0.01$). The costs expressed per ongoing pregnancy were € 11,523 and € 9,067, per randomized group respectively. Costs per ongoing pregnancy were € 2,456 higher for IVF-eSET (95% CI 898 to 4,014).

Sensitivity analysis

In the IVF group the lowest used dosage was 1,050 IU FSH. Applying this low dosage to all couples would have resulted in total costs for the whole randomized group of k€ 141. In this low dose calculation IVF-eSET would still result in € 558 higher cost per couple than IUI-COS.

When assuming the highest used dosage of 3,000 IU FSH for all couples that underwent IVF, the total costs for the whole randomized group would have been k€ 184. In this high dose calculation, the additional costs for IVF-eSET would have been € 1,300 per couple.

Sensitivity analysis showed that if all couples receiving IUI-COS would have received clomiphene citrate, the total costs in the IUI-COS group would have been € 72,617, resulting in a mean cost per included couple of € 1,252. Hence, the potential additional costs per couple would then rise from € 915 to € 1,529 for IVF-eSET.

In the IUI-COS group the highest dosage of FSH was 3,575 IU resulting in a total cost of € 291,703, if this high quantity of FSH would have been used in all IUI-COS cycles. The potential savings per couple after a single IVF-eSET cycle would then be € 2,248. The costs in the two randomized groups would be the same (k€ 155) if a mean dosage of 1,522 IU FSH had been used per IUI-COS cycle by each couple in the IUI-COS group.

Scenario analysis

We performed a scenario analysis in which we increased the ongoing pregnancy rate in the IVF-eSET group up to 50% (Table 3). IUI-COS was dominant over IVF-eSET at a relative ongoing pregnancy rate of 1.2 or below for IVF-eSET versus IUI-COS. IVF-eSET would be the dominant treatment if the ongoing pregnancy rate would be 1.8 or higher after IVF-eSET versus IUI-COS. In the present study that would relate to a 38% ongoing pregnancy rate after IVF-eSET versus the observed 21% after IUI-COS.

Table 2. Outcomes per randomized group

	IVF-eSET (N=58)				
	natural conception	**IUI**	**IVF**	**cryo-ET**	**total IVF (%)**
clinical outcomes					
ongoing pregnancies (N)	1	0	11	2	14 (24)
multiples (N)	0	0	2	0	2 (14)
live birth (N)	1	0	11	1	13 (22)
live birth singletons (N)	1	0	10	1	12 (92)
live birth twins (N)	0	0	1	0	1 (8)
live birth unknown (N)	0	0	1	0	1 (7)
medication					
cycles rFSH (N)		3	54		54
total rFSH (IU)		1,165	98,072		99,237
mean rFSH (IU)		388	1,816		1,837
cycles CC (N)					
total CC (mg)					
mean CC (mg)					
costs					
total costs (€)					161,327
mean costs per couple (€)					2,781
mean costs per cycle (€)					2,933
mean costs per pregnancy (€)					11,523

Table 3. Scenario analysis

IVF – ongoing pregnancy (%)	IUI – ongoing pregnancy (%)	RR	cost-effectiveness	dominant treatment
24%	21%	1.17	0.79	IUI
31%	21%	1.5	1	
38%	21%	1.83	1.24	IVF

DISCUSSION

In couples with unexplained subfertility, we found that IVF-eSET was equally effective as IUI-COS for a similar multiple pregnancy risk, while the mean cost per included couple was € 2,781 (95% CI: € 2,293 to € 3,270) in the IVF-eSET group and € 1,876 (95% CI: € 1,462 to € 2,270) in the IUI-COS group. The additional costs for IVF-eSET per couple were € 915 (95% CI 183 to 1,647) ($p<0.01$) and per ongoing pregnancy € 2,456 (95% CI 898 to 4,014).

	IUI-COS (N=58)			
natural conception	IUI1	IUI2	IUI3	total IUI (%)
2	1	5	4	12 (21)
0	0	2	1	3 (25)
2	1	5	2	10 (17)
2	1	3	1	7 (70)
0	0	2	1	3 (30)
0	0	0	2	2 (17)
	49	45	34	128
	30,666	34,103	23,991	88,76
	626	758	706	963
	5	5	5	15
	2,25	2,5	2,5	7,25
	450	500	500	483
				108,808
				1,876
				761
				9,067

Our pregnancy rate of 24% in the IVF group was rather low. However, it was comparable to the overall average ongoing pregnancy rate for IVF in the participating clinics (on average 18.7% during the period of this trial for SET and DET). If IVF success rates were higher, like the ones reached in for instance the USA, IVF-eSET would be more cost-effective than IUI-COS. This seems to be feasible, since a cumulative live birth rate, including one freeze-thaw cycle, of 38% was found for IVF-eSET in a systematic review comparing IVF-eSET with IVF-DET (McLernon et al., 2010). Recent developments show that transfer of blastocyst embryos, as compared to day three embryos, will result in a significantly higher live birth rate (Glujovsky et al., 2012). Vitrification of blastocysts results in a significant higher post-thawing survival rate over slow freezing (Kolibianakis et al., 2009). Both modern developments might possibly make IVF the more favourable treatment, but are awaiting assessment through randomized trials.

No pregnancies occurred after IUI-COS with clomiphene citrate, but the number of couples receiving clomiphene citrate in our study was limited to five couples. We feel that they should be included, because of the intention-to-treat analysis and because clomiphene citrate leads to the same pregnancy rates as FSH in IUI-COS (Dankert et al., 2007).

Sensitivity analysis showed that using clomiphene citrate instead of rFSH in all IUI cycles would enlarge the difference in costs for IVF-eSET as compared to IUI-COS. Using 1,522 IU FSH in the IUI-COS group would result in the same costs for IVF-eSET as IUI-COS. The mean use of FSH in IUI cycles found in our study was 580 IU. This is far below the break-even point of 1,522 IU FSH. If all couples included for IUI-COS used FSH, IVF-eSET would still be more costly for the same pregnancy results. Even the lowest dose of medication in IVF-eSET did not alter the fact that IVF-eSET remained more expensive than IUI-COS.

A limitation of our study is the small sample size and the short time horizon of 4 months of the original RCT. We are at present performing a larger study on a similar question (Bensdorp et al., 2009). That study compares similar strategies in two groups of 200 couples over an interval of one year. Moreover, a third arm is added, evaluating IVF treatment in a modified natural cycle (Pelinck et al., 2006), which might lower the costs and therefore might have a better cost-effectiveness.

We realize that health care costs due to multiple pregnancies were not included. However, costs until a gestational age of 12 weeks would be comparable for a multiple pregnancy as compared to a singleton pregnancy. Since the number of multiple pregnancies in both groups was small and comparable, alterations in the results of the economic analysis are not expected. However, we realize that health care for a triplet pregnancy beyond 12 weeks' gestation till weeks after delivery would significantly increase the costs.

In our analysis we did not include the costs made by the couple themselves, which might influence the 'costs per couple'. Since the economic analysis was performed from the perspective of the health care institution, couples included were not asked to keep track of their expenses in so-called cost diaries. These costs include out-of-pocket costs, such as leave of absence, non-prescription drugs and travel expenses (Fiddelers et al., 2009; Reindollar et al., 2010). These costs made outside the health care institution might influence the outcome. In a recent large study cost diaries were included and approximately only 1% of the total costs of couples were due to costs outside the health care institution (Reindollar et al., 2010). Consequently, this would hardly influence the costs per couple as calculated in our study.

Studies on economic analyses on IUI and IVF are scarce. In 2006 a paper was published on the cost-effectiveness of IVF versus IUI followed by IVF (Pashayan et al., 2006). This paper concluded that primary treatment by an IVF cycle would be more cost-effective than first offering IUI followed by IVF. However, this study used pregnancy rates based on previously performed studies or assumptions and used a hypothetical cohort. Also eSET or multiple pregnancies were not taken into account. A second study, the FASST-trial, concluded that IUI with FSH had no additional value to the ART treatment fertility couples received (Reindollar et al., 2010). Although their study seems comparable to ours, their study protocol was different. Both strategies in the FASST-trial included IUI. They compared treatment of IUI with clomiphene citrate followed by IVF (the accelerated arm), with treatment of IUI with clomiphene citrate, followed by IUI with FSH and IVF. The pregnancy rates in FSH-IUI

cycles were comparable to ours (9.8% in the FASST-trial versus 9.6% in our trial), but the women receiving FSH-IUI in the FASST-trial received 150 U FSH per day which is twice as much as in our study. Applying 75 IU FSH would substantially have lowered the costs for FSH stimulated IUI and would result in a more cost-effective therapy. A retrospective cohort study compared one cycle of IVF with two cycles of IUI-COS and concluded that IVF was more effective, but costlier (Chambers et al., 2010). It should be noted that in this study 10% of the included couples with unexplained subfertility tried to conceive for less than 12 months, and thus had a good prognosis for pregnancy. Also, 10% of the couples starting IUI-COS converted to IVF after only one cycle of IUI. These two aspects may have increased healthcare costs. In a randomized controlled trial comparing IUI, IUI-COS, and IVF, for 6 cycles, the cumulative pregnancy rate for IVF was not significantly better than that for IUI (Goverde et al., 2000). IUI was found to be a more cost-effective treatment than IVF. The multiple pregnancy rate in the IVF group was high (21%, including one set of triplets), and does not represent the modern embryo transfer policy of eSET or SET.

We found high multiple pregnancy rates compared to European data published by ESHRE (Ferraretti et al., 2012). Our twin rate after IUI was 25% versus a 10.6% rate (per ongoing pregnancy) in Europe. After IVF-eSET 14% twins were found in our study compared to 20.7% twins after IVF in Europe. If we would implement the European multiple pregnancy rates in our cost-effectiveness analysis, this would result in an even larger difference of cost-effectiveness between IUI-COS and IVF, in favour of IUI. However, using strict SET rather than eSET in IVF, would probably result in a lower multiple pregnancy rate in the IVF arm.

In conclusion, in couples with unexplained subfertility, one cycle of IVF-eSET cost in our setting an additional € 900 per couple compared to three cycles IUI-COS, for no increase in ongoing pregnancy rates or decrease in multiple pregnancies. However, if a clinic has ongoing pregnancy rates of 38% or higher with IVF-eSET, the treatment of choice should be IVF-eSET.

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