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Chapter 7

Long-term outcome in couples with unexplained subfertility and an intermediate prognosis initially randomized between expectant management and immediate treatment

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ABSTRACT

BACKGROUND We recently reported that treatment with intrauterine insemination and controlled ovarian stimulation (IUI-COS) did not increase ongoing pregnancy rates compared with expectant management (EM) in couples with unexplained subfertility and intermediate prognosis of natural conception. Long-term cost-effectiveness of a policy of initial EM is unknown. We investigated whether the recommendation not to treat during the first 6 months is valid, regarding the long-term effectiveness and cumulative costs.

METHODS Couples with unexplained subfertility and intermediate prognosis of natural conception (n=253, at 26 public clinics, the Netherlands) were randomly allocated to 6 months EM or immediate start with IUI-COS. The couples were then treated according to local protocol, usually IUI-COS followed by IVF. We followed couples until 3 years after randomization and registered pregnancies and resources used. Primary outcome was time to ongoing pregnancy. Secondary outcome was treatment costs. Analysis was by intention-to-treat. Economic evaluation was performed from the perspective of the health care institution.

RESULTS Time to ongoing pregnancy did not differ between groups (log-rank test P=0.98). Cumulative ongoing pregnancy rates were 72–73% for EM and IUI-COS groups, respectively (relative risk 0.99; 95% confidence interval (CI) 0.85–1.1). Estimated mean costs per couple were €3424 (95% CI €880–€5968) in the EM group and €6040 (95% CI €4055–€8125) in the IUI-COS group resulting in an estimated saving of v2616 per couple (95% CI €385–€4847) in favour of EM.

CONCLUSIONS In couples with unexplained subfertility and an intermediate prognosis of natural conception, initial EM for 6 months results in a considerable cost-saving with no delay in achieving pregnancy or jeopardizing the chance of pregnancy. Further comparisons between aggressive and milder forms of ovarian stimulation should be performed.

INTRODUCTION

Intrauterine insemination with controlled ovarian stimulation (IUI-COS) is commonly used as first-line treatment for couples with unexplained subfertility. Evidence for the effectiveness of this treatment has been lacking, which is worrisome in view of the increased risk of multiple pregnancies in this treatment as a result of ovarian stimulation.[1,2] In couples with a chance of a treatment-independent pregnancy between 30 and 40%, we therefore assessed the effectiveness of IUI-COS compared with expectant management (EM) and found that IUI-COS was not more effective than EM over a period of 6 months.[3] We concluded that in these couples EM should be advocated.

The recommendation not to treat during the first 6 months only holds if the long-term effectiveness is comparable with that of immediate treatment, while the cumulative long-term costs of EM remain lower. Therefore, we followed all couples until 3 years after randomization and registered pregnancies, initiated treatments and costs.

MATERIALS AND METHODS

Patients

We report the 3-year follow-up of the couples who had previously been assigned randomly to IUI-COS (immediate treatment group, 127 couples) or EM (EM group, 126 couples) for a period of 6 months.[3] This RCT was performed between June 2002 and July 2005 in 26 fertility centres in the Netherlands. Couples were eligible for the trial in case of unexplained subfertility for at least 1 year, a female partner younger than 39 years with a regular cycle and an intermediate prognosis for an ongoing pregnancy. This prognosis was calculated by the validated prediction model of Hunault and colleagues, which predicts the chance for a spontaneous pregnancy in the next 12 months resulting in a live birth.[4,5] An intermediate prognosis was defined as a probability of a treatment-independent ongoing pregnancy between 30 and 40%.

Procedures

The original sample size for the RCT had been based on a non-inferiority design to exclude a difference larger than 13% from the assumed ongoing pregnancy rate in the EM group of 22% (α=5%, β=80%). With a sample size of 126 women in each group, we would have a power of 80% to detect a relative risk (RR) of 1.21 or larger for the long-term live birth rate, using a 5% significance level and two-sided testing and assuming a live birth rate of 70% in the control group.

After the initial study period of 6 months, couples who had been unsuccessful in getting pregnant were usually treated according to the guidelines of the Dutch Society of

Obstetrics and Gynaecology.[6] According to these guidelines, primary treatment is six cycles of IUI-COS followed by IVF for three cycles. Couples who were initially allocated to IUI-COS usually continued with three cycles of IVF.

The procedure for IUI-COS was performed according to hospital-specific protocols. The study protocol recommended the use of recombinant FSH (rFSH) for COS. The women started daily s.c. injections of rFSH [Gonal F (Serono Benelux, The Hague, Netherlands) or Puregon (Organon, Oss, Netherlands)] or hMG [Menopur (Ferring, Hoofddorp, Netherlands)] in mean doses of 75 IU, ranging from 37 to 150 IU, until transvaginal sonography showed at least one follicle of at least 16 mm diameter. In some hospitals, clomiphene citrate was used for ovarian stimulation in a dose of 100 mg from Day 3 until Day 7. Ovulation was induced with 5,000 or 10,000 IU of hCG [Pregnyl (Organon)] and women were inseminated 36–40 h later. We withheld hCG and IUI if there were more than three follicles of at least 16 mm diameter, or five of at least 12 mm diameter. We did not give luteal support. We processed semen samples within 1 h of ejaculation by density-gradient centrifugation followed by washing with culture medium. The volume of semen that was inseminated varied between 0.2 and 1.0 ml. We performed the insemination irrespective of the total motile sperm count after preparation on the scheduled day.

Treatment with IVF was also performed according to local protocol. Patients undergoing IVF received COS after down-regulation with a GnRH agonist in a long protocol with a midluteal start. COS was started with 150 U rFSH. Treatment was continued until at least three follicles >18 mm had developed. Ovulation was induced by 10,000 IU hCG (Pregnyl®, Organon, Oss, The Netherlands) and cumulus–oocyte complexes were recovered by transvaginal ultrasound-guided retrieval 36 h thereafter. On Day 3 the embryo transfer took place. According to the number of available embryos and patient preferences, one or two embryos were transferred. Non-transferred good quality embryos were cryo-preserved. When necessary, the frozen embryos were thawed and transferred.

Couples were followed for 3 years after randomization or until an ongoing pregnancy occurred. Primary outcome was time to ongoing pregnancy within 3 years after randomization. Ongoing pregnancy was defined as the presence of fetal cardiac activity during transvaginal ultrasonography at 12 weeks gestation. Secondary end-points were clinical pregnancy, miscarriage and ectopic pregnancy. Clinical pregnancy was diagnosed if there was evidence of a pregnancy by clinical or ultrasound parameters. Miscarriage was defined as a non-viable pregnancy during ultrasonography or pregnancy loss before 12 weeks gestation. Ectopic pregnancy was defined as a pregnancy located outside the uterus that required medical or surgical treatment. After a miscarriage or an ectopic pregnancy, follow-up was further continued until a viable pregnancy occurred. Multiple pregnancy rates were calculated per ongoing pregnancy.

The number of IUI and IVF cycles in both groups were registered.

Analysis

Analysis was performed according to intention-to-treat, i.e. all pregnancies that occurred in the 3 years following randomization were accounted for per randomized group, whether they occurred spontaneously, after IUI-COS or after IVF.

Kaplan–Meier curves were plotted to illustrate the difference in time to pregnancy between the two groups and the curves were compared with a log-rank test. We performed a Cox regression analysis with age as covariable, where age was stratified into three groups: <32, 32–35 and >35 years. The young age group (<32 years) functioned as a reference group. Ongoing pregnancies, after natural conception or after treatment, in both groups were expressed as a RR with a 95% confidence interval (CI). In all analyses a P-value of 0.05 was considered to indicate statistical significance. Calculations were performed with the Statistical Package for the Social Sciences version 16® (SPSS Inc., Chicago, IL, USA).

Economic evaluation

The economic evaluation was performed from the perspective of the health care institution. Indirect costs, such as travel expenses or productivity loss, and external costs borne by society were not included. All the participating hospitals were public hospitals and costs were covered by health care insurance. In case of comparable ongoing pregnancy rates in the immediate treatment group and the EM group a cost-minimization study would be performed with focus on the cost-difference between the two strategies within a time horizon of 3 years. In case of a difference in ongoing pregnancy rate, a cost-effectiveness analysis would be performed. We followed the EURONHEED sub-checklist as a guideline for our economic evaluation.[7]

We recorded the number of IUI-COS and IVF treatments and we used data from an inventory study of mean costs of each treatment cycle in The Netherlands in 2005.[8,9] All cycles of therapy were included, including those started in the waiting period. We assumed that the costs for couples who received no treatment were equal to zero, since no additional visits to the clinic were made. The average total dose of gonadotrophins used for the ovarian stimulation in IUI was estimated and was set at 800 IU of FSH per cycle.[8,9] To reflect the concept of time preference, meaning that an amount of money spent or saved in the future is worth less than the same amount today, costs were calculated using a discount rate of 5%, as is consistent with conventional practice.[10,11] The unit costs for one cycle of IVF and one cycle of IUI-COS were estimated at €2139 and €773, respectively. The costs for the hospital component, specialist fee and medication for IUI-COS and IVF are specified in Table 1. The mean costs and the confidence boundaries were estimated by non-parametric bootstrapping to account for the expected skewing of the data owing to the relatively high proportion of patients with no, or very low, costs.[12]

The costs for one ongoing pregnancy per randomized group were calculated by dividing the mean total costs made by the number of ongoing pregnancies per randomized group.

Table 1. Costs per resource unit for IUI-COS and IVF

Resource unit	IUI-COS	IVF
Hospital component	€ 340	€ 984
Specialist fee	€ 99	€ 230
Medication	€ 334	€ 925
Total	€ 773	€ 2.139

In IUI-COS cycles, clomiphene citrate can replace FSH.[13] Clomiphene citrate use is low in cost, whereas FSH is expensive. To explore the effect of plausible variations in FSH use, we calculated the total costs for the case where clomiphene citrate would have been used and in the case where a high dose of 1000 IU FSH per cycle had been used.

RESULTS

In the initial study, 126 couples were assigned to EM and 127 couples to IUI-COS for 6 months. Baseline characteristics at the time of randomization were comparable between the two groups, and have been published in the original article.[3] Mean female age was 33 years, mean duration of subfertility was 2 years, 77% of the couples had primary subfertility and the mean prognosis of the couples was a 35% ongoing pregnancy rate without additional treatment in 12 months. In 47 (11%) cycles of the initial trial, clomiphene citrate was used for COS, resulting in three ongoing pregnancies (6.4% per started cycle). Overall, of the 444 started cycles in the immediate treatment group, 63 cycles (14%) were cancelled because of the risk of high-order multiple pregnancies. Multifollicular growth, defined as more than one follicle with a diameter >15 mm, was achieved in 42% of the inseminated cycles. If follicles >10 mm were included, 70% of the inseminated cycles were multifollicular. In the immediate treatment group, one twin and one triplet pregnancy occurred, and both of these pregnancies resulted from multifollicular cycles in which only one follicle >15 mm was present.

After the initial 6 months, 34 couples (27%) had an ongoing pregnancy in the EM group and 29 couples (23%) in the immediate treatment group. Time to pregnancy showed no significant difference between the two groups. The remaining couples (92 and 98 couples, in the EM group and immediate treatment group, respectively) were followed until they achieved an ongoing pregnancy or for a maximum of 2.5 years. Twelve couples in the EM group (10%) and nine couples in the immediate treatment group (7%) were lost to follow-up, mainly because they had moved to untraceable locations.

Both in the EM group and in the immediate treatment group eight couples (16 couples overall) refrained from further treatment. In the EM group, 82 couples started IUI-COS and two couples immediately started IVF. Of the 52 couples who did not conceive after IUI-COS 42 couples continued with IVF.

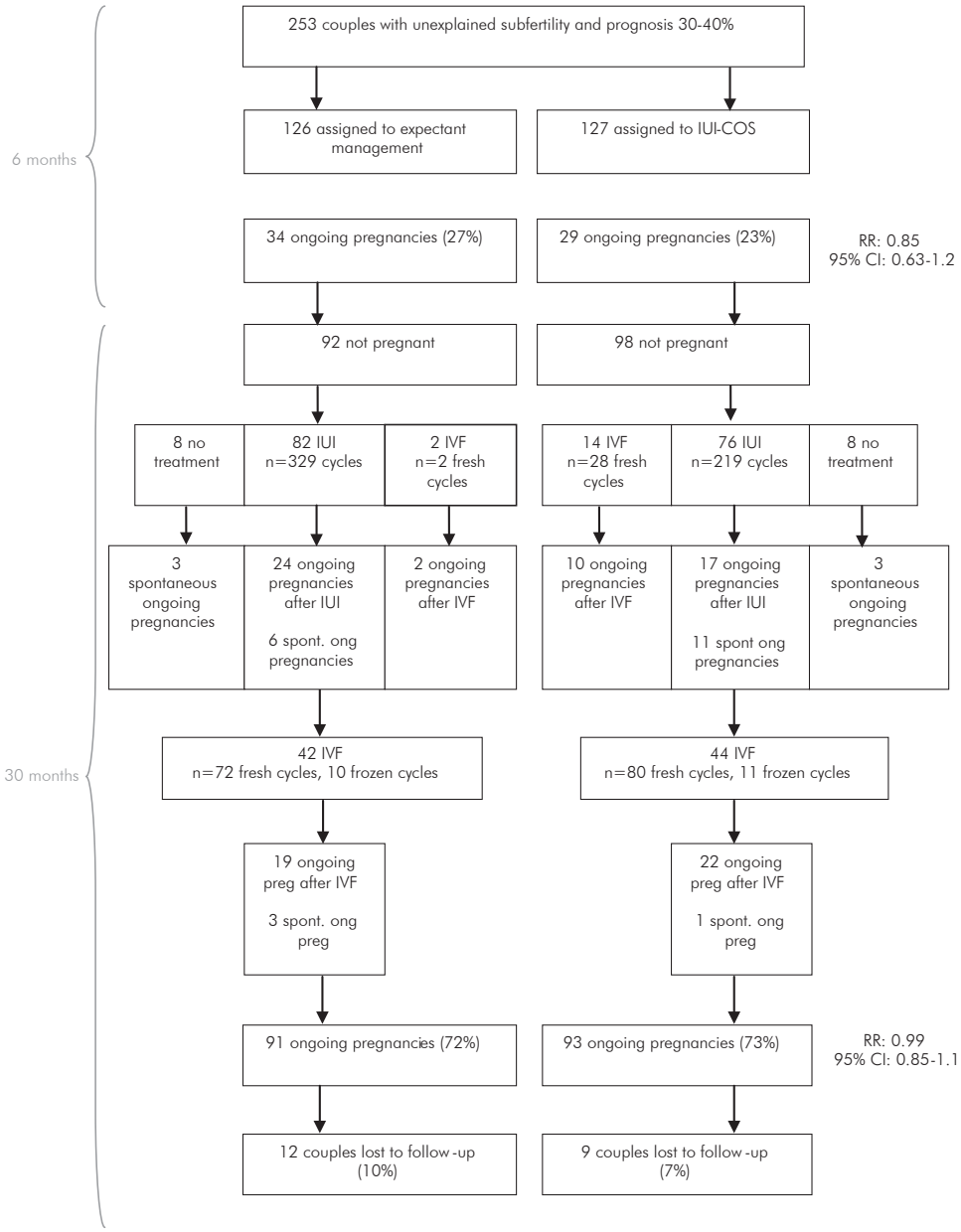

Figure 1 Flow chart of treatment and pregnancy outcome over 3 years for couples with unexplained subfertility and an intermediate prognosis, initially randomized between EM and immediate treatment IUI-COS, intrauterine insemination and controlled ovarian stimulation; RR, relative risk; CI, confidence interval.

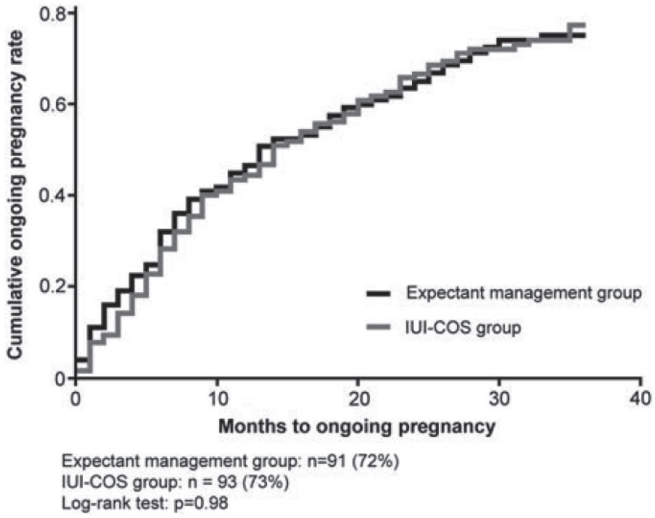

Figure 2 Time to ongoing pregnancy in couples who were initially randomized between EM and immediate treatment.

In the immediate treatment group, 76 couples continued IUI-COS and 14 couples started IVF. Of the 51 couples who did not conceive after IUI-COS, 44 couples continued with IVF (Fig. 1).

At 3 years, the total number of pregnancies was 109 in the EM group and 125 in the immediate treatment group. The number of ongoing pregnancies was 91 (72%) in the EM group and 93 (73%) in the immediate treatment group, resulting in an RR of 0.99 (95% CI: 0.85–1.1) (Fig. 1).The median time to pregnancy was 13 months (95% CI: 8–18) in the EM group versus 14 months (95% CI: 10–18) in the immediate treatment group. Time to pregnancy showed no significant difference, log-rank test P=0.98, RR 0.99 (95% CI: 0.85–1.1) (Fig. 2). Age was not significantly associated with time to pregnancy in the two treatment groups, the hazard rate (HR) for the 32–35 years group versus <32 years group was 1.2 (P=0.41) the HR for the >35 versus <32 years group was 1.1 (P=0.59).

In the EM group 45 of the 91 ongoing pregnancies occurred after either IUI or IVF treatment, three pregnancies occurred spontaneously in couples refraining from further treatment and nine between treatment cycles, whereas 34 ongoing pregnancies already had occurred in the first 6 months. In the immediate treatment group 49 of the 93 ongoing pregnancies were the result of IUI or IVF treatment and 15 occurred spontaneously, of which 12 occurred between treatment cycles, whereas 29 ongoing pregnancies already occurred in the first 6 months (Fig. 1).

The total number of miscarriages was 17 in the EM group (13% per couple) versus 31 in the immediate treatment group (24% per couple) (RR 0.54, 95% CI: 0.32–0.92). In each group one ectopic pregnancy occurred. In the EM group, there were nine twin pregnancies (multiple pregnancy rate 10% per ongoing pregnancy) with one spontaneously conceived, three after IUI-COS and five after IVF, versus seven twins and one triplet in the immediate

Table 2. Pregnancy outcome after three years in couples with unexplained subfertility and an intermediate prognosis initially randomized between EM and immediate treatment.

	Expectant management group (n=126)	Immediate treatment group (n=127)	RR (95%CI)
All pregnancies	109	125	0.88 (0.82-0.94)
Ongoing pregnancies, n (%)	91 (72)	93 (73)	0.99 (0.85-1.1)
Miscarriages, n (%)	17 (13)	31 (24)	0.54 (0.32-0.92)
Ectopic pregnancies, n (%)	1 (0.8)	1 (0.8)	1.0 (0.06-15.9)
Multiple pregnancies, n (%)	9 (8)	8 (6)	1.1 (0.45-2.8)

RR, relative risk; CI, confidence interval.

Table 3. Ongoing pregnancies per group and per treatment cycle (IUI and IVF).

	Expectant management group (n=126)	Immediate treatment group (n=127)	RR (95% CI)
Spontaneous ongoing pregnancies, n (%)	46 (37)	26 (20)	1.8 (1.2-2.7)
Number of IUI cycles	364	661	
Ongoing pregnancies after IUI, n (%)	24 (19)	35 (28)	0.7 (0.4-1.1)
% ongoing pregnancy per IUI cycle	6.6	5.3	1.2 (0.8-2.1)
Number of IVF cycles	75	108	
Ongoing pregnancies after IVF, n (%)	21 (17)	32 (25)	0.7 (0.4-1.1)
% ongoing pregnancy per IVF cycle	28	30	0.9 (0.6-1.5)

treatment group (multiple pregnancy rate 9% per ongoing pregnancy), with three twins and one triplet after IUI-COS (IUI-COS group) and four twins after IVF (Table 2).
In the EM group 364 IUI cycles were started which resulted in 24 ongoing pregnancies (6.6% per started cycle). In the immediate treatment group 661 IUI cycles were started, resulting in 35 ongoing pregnancies (5.3% per started cycle).
In the EM group 75 IVF cycles were started resulting in 21 ongoing pregnancies (28% per started IVF cycle) versus 108 IVF cycles in the immediate treatment group resulting in 32 ongoing pregnancies (30% per started cycle) (Table 3).

Economic evaluation

Given the comparable ongoing pregnancy rates in the two groups, we did a cost-minimization and focused on the cost-difference. The costs for one cycle of IUI-COS and one cycle of IVF in the Netherlands were calculated at €773 and €2139, respectively (Table I). In the EM group, 364 IUI cycles and 75 IVF cycles resulted in total costs of €442k. In the immediate treatment group, 661 IUI cycles and 108 IVF cycles resulted in total costs of €742k, suggesting a potential saving of €300k in favour of the EM group. The mean estimated costs per couple

in the EM group were €3424 (95% CI €880–€5968) and in the immediate treatment group €6040 (95% CI €4055–€8125), resulting in an estimated saving of €2616 per couple (95% CI €385–€4847). The estimated costs expressed per ongoing pregnancy were €4741 (SD 545) and €8248 (SD 578) for the EM and immediate treatment group, respectively.
To explore the effect of plausible variations in stimulation medication, sensitivity analyses were performed. First, we evaluated the consequence of the use of clomiphene citrate instead of gonadotrophins. This resulted in IUI-COS costs of €445 per cycle instead of the €773 with FSH. With clomiphene citrate use, the saving in the EM group in comparison with the immediate treatment group was still €203k. Subsequently, we evaluated the effect of the use of a high quantity of 1000 IU FSH per IUI cycle. Medication costs for FSH will rise from €334 to €417 per cycle for 800 and 1000 IU, respectively. This resulted in IUI-COS costs of €856 per cycle. If a high quantity of FSH had been used, potential savings for EM would have been higher, up to €325k.

DISCUSSION

We compared the long-term consequences of EM for 6 months versus immediate start of treatment with IUI-COS in couples with unexplained subfertility and an intermediate prognosis of a natural conception. Three years after randomization, the time to ongoing pregnancy and cumulative ongoing pregnancy rates were comparable in the two groups but initial EM, followed by IUI-COS and IVF in case of no pregnancy, resulted in an average potential saving of more than €2500 per couple.
If female age is under 39 years, as in our study, and the chance of conception without treatment is between 30 and 40%, a certain delay in treatment is thus extremely cost-effective. Our results are in line with a recent publication that found EM to be more cost-effective in patients with unexplained subfertility compared with a first-line treatment of unstimulated IUI cycles or stimulated clomiphene citrate cycles without IUI.[14]
The recently published FASST trial (a randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment trial[15]) studied more aggressive treatment protocols in similar patients as our study. The FASTT trial compared three cycles of IUI/clomiphene citrate and three cycles IUI/FSH followed by three IVF cycles versus the short track i.e. three cycles of IUI/clomiphene citrate immediately followed by IVF. It is intriguing to see that women in both studies had a mean age of 33 years and that other baseline characteristics were comparable between both trials. However, the FASTT trial included 18% patients with diagnoses other than unexplained subfertility (hypo-gonadotrophic/hypo-estrogenic or polycystic ovary syndrome) and the overall prognoses for treatment-independent pregnancy were not reported. Despite the differences in aggressiveness of treatment, nearly 75% of all couples undergoing

comprehensive treatment in both studies had a viable pregnancy. Indeed, median time to pregnancy was shorter in the FASST trial. However, in view of the fact that final viable pregnancy rates were comparable and that assisted reproduction technology (ART) has rarely been evaluated against EM, and also in view of the known and unknown side effects of ART, we feel that more comparisons between aggressive forms of ART and milder forms should be made. Until then, subfertile couples should be informed that ART might reduce time to pregnancy but does not increase the overall pregnancy rates. Also, side effects of ART should be discussed with those couples.

The prognostic model of Hunault *et al.* (2004)[4] has not been validated for women over 39 years old and therefore our data may not be generalized to older women. Usually, older women are offered ART earlier, although evidence on the superiority of such a strategy is lacking.

The number of multiple pregnancies was low in our study and equally divided over both treatment groups. We therefore did not include the extra costs of multiple pregnancies in our analysis. The calculated costs were based on health care cost in the Netherlands. As we implemented all items, except the costs of side effects (multiple pregnancies), of the guideline of EURONHEED[7] we believe our outcomes are transferable to other countries.

A strong point of our study is that we followed a strict treatment protocol with intention-to-treat analysis without the influence of commercial interests. Owing to the long period of follow up (3 years), couples were able to complete six cycles of IUI-COS followed by three cycles of IVF, if necessary. Therefore, we feel that this study reflects daily practice and the results should be applicable to all couples with unexplained subfertility and an intermediate prognosis of natural conception.

Our study can be criticized because of the low pregnancy rates in the cycles with IUI-COS. European registers report higher results for IUI-COS but the outcome is clinical pregnancy rate, not ongoing pregnancy rate.[16] However, within the context of clinical trials, other groups also do not report pregnancy rates over 10% per cycle.[1] The European Society of Human Reproduction and Embryology Capri Workshop Group on IUI[17] reported pregnancy rates of 7% with clomiphene citrate-stimulated IUI and 12% with FSH-stimulated IUI. In the same ESHRE report, it is indicated that pregnancy rates per cycle are high enough to merit clomphine citrate-stimulated IUI in couples with unexplained subfertility in lieu of more costly and complex FSH-stimulated IUI, with the risk of multiple pregnancies. In our study, the explanation of the lower pregnancy rates cannot be found in the medication used for ovarian stimulation, because clomiphene citrate was used in only ~11% of the IUI cycles. In the Netherlands only mild stimulation is common: usually IUI is only performed when one or two follicles are present. This 'dose-finding' may lead to cancellation of cycles, mainly in the first two cycles. However, performing IUI with only one or two follicles is in line with the recommendation of a previous report from van Rumste *et al.* (2008)[18] who found that COS resulting in more than two follicles only enhanced multiple pregnancy rates without an actual gain in number of pregnancies. Despite the low pregnancy rates per cycle after

IUI-COS, we found that >70% of the couples in this population eventually achieved an ongoing pregnancy within 3 years, which is, in counselling for EM, very encouraging for the couple.

One limitation of our study is that unfortunately the original data set did not provide us with a complete breakdown of the number of stimulated cycles for which there was only 1 follicle ≥16, 2 follicles ≥16, 3 follicles ≥16 and >3 follicles ≥16 mm. This information would improve our understanding of the low pregnancy rate for stimulated cycles and also of the circumstances which may help to keep the multiple pregnancy rate low.

Our study, in which we limited IUI-COS to couples with intermediate prospects for spontaneous pregnancies, was a multicentre study in 26 centres in The Netherlands, with a representative spectrum of the quality of care in the country. It is important to stress here that we observed more miscarriages in the early treatment group, which either might be a biological phenomenon or a consequence of the more intensive monitoring of treatment cycles, resulting in a higher detection rate.

As far as the economic evaluation is concerned, one could debate whether it is rational to perform a sensitivity analysis comparing the use of clomiphene citrate to the use of FSH in IUI treatment when a difference is found in pregnancy rates. We are convinced that it is very reasonable, since a large meta-analysis found that the difference in pregnancy rates with FSH or clomiphene citrate stimulation was not statistically significant.[19]

By following the strategy of initial EM in couples with unexplained subfertility and an intermediate prognosis, money can be saved and spent more economically. The savings in the EM group in health care costs of €2616 per couple could be made available to the 28% of the couples who did not conceive after 3 years: each of these couples could spend almost an extra €10 000 on additional treatment, which is equivalent to 12 additional cycles of IUI-COS or four cycles of IVF.

In conclusion, in couples with unexplained subfertility and an intermediate prognosis of natural conception, initial EM for 6 months results in a considerable cost-saving without jeopardizing the chances of having a child.

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