insemination

Fine-tuning a treatment

Inge Custers

Intrauterine insemination: Fine-tuning a treatment

Inge Maria Custers

Intrauterine Insemination: Fine-tuning a treatment
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Intrauterine Insemination: Fine-tuning a treatment

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Contents

Chapter 1

General introduction

GENERAL INTRODUCTION

Intrauterine insemination (IUI) is the most widely used fertility enhancing treatment in the world. In many guidelines it is the first step in the treatment cascade in couples with unexplained subfertility and male subfertility.[1-3] In an IUI cycle, the partner's semen is processed and inseminated directly in the uterine cavity at the time of ovulation. The rationale for performing IUI is that motile spermatozoa are concentrated in a small volume and inseminated directly into the uterine cavity near to the released oocyte, thus bypassing the cervix.[4,5]

There is a wide variation in practice in how to perform IUI. This variation is due to the complexity of IUI. An IUI cycle is a cascade of several interventions in each of which modifications can be made, such as the use of controlled ovarian stimulation to achieve growth of more than one follicle. This multifollicular growth can be performed with various drugs and stimulation regimens.[6,7] At the same time monitoring of follicular growth must be performed to optimize timing and induction of ovulation.[8] These interventions in the follicular phase are then followed by techniques in the second phase of the IUI treatment cycle, i.e. preparation of semen samples, optimal timing of insemination (which can be performed once or twice) and (im-) mobilisation immediately after the insemination.[9-11] All these interventions may vary considerably from centre to centre.

This variation in daily practice and the ensuing need for uniformity in treatment has lead to a growing number of randomized controlled trials en meta-analyses.

In the past decades several variations of conventional IUI were developed to optimize pregnancy rates. To solve the possible problem of progressive decline of the number of spermatozoa along the length of the genital tract- just a minor amount of spermatozoa are found in the Pouch of Douglas after conventional IUI- fallopian tube sperm perfusion (FSP) was introduced in 1992.[12] With this method some millilitres of processed sperm are flushed into the fallopian tubes under pressure with the hypothetical effect of enhancing pregnancy chances. A meta-analysis of RCT's with 595 couples showed however that there is no evidence that this technique generates higher pregnancy rates than normal IUI.[13]

Intra uterine insemination as a treatment for unexplained en mild male subfertility is usually combined with mild ovarian hyperstimulation (MOH). Since ovarian stimulation is associated with an increased risk of multiple pregnancies and therefore increased maternal/ perinatal morbidity and perinatal mortality, stimulation regimens have been developed with the ultimate goal of enhancing live-birth rates and keeping multiple pregnancies to a minimum.[14,15] In comparing several treatment regimens for MOH in IUI it was found that gonadotropins seem the most effective drugs. Anti-oestrogens appear cost-effective, but seem some-what less effective compared to gonadotropins. When gonadotropins are used, a daily low-dosage protocol is advised.[16]

Some of the problems arising from mild ovarian stimulation are premature luteinization and asynchronous ovarian follicular development. Several RCT's have addressed this issue by adding GnRH-agonists or GnRH-antagonists. GnRH-agonists were found to increase the

number of multiple pregnancies and the risk for ovarian hyperstimulation but could not increase pregnancy rates. In adding GnRH-antagonists to the ovarian stimulation regime, it was found that premature LH-surges were significantly reduced but live birth rates remained unaffected. Therefore GnRH-agonists and antagonists are not recommended for use in IUI treatment protocols.[17]

When the actual insemination is to be performed, adequate timing is of great importance. It was suggested that differences in treatment outcome were partially related to the timing of insemination.[8] Therefore several study groups investigated the effect of double insemination versus one single insemination. The Cochrane meta-analysis updated in 2007 found, based on five small trials en one larger trial, a beneficial effect in favour of double insemination especially in couples with mild male subfertility.[10] However, several trials not included in the review published thereafter could not reproduce these findings and found no difference in live birth rate.[18,19]

Apart from optimizing treatment success through optimizing various aspects of the treatment, the prognosis of a couple on natural conception has recently been identified as an important issue and is nowadays part of clinical decision making; The quintessence of prognosis is that IUI is only offered to a couple if the probability of a treatment independent pregnancy is very low and the success rate after IUI clearly exceeds this probability. To be able to make adequate and reliable predictions in clinical practice, formal prediction models, in which the contribution of each fertility-determining factor is quantified, have been developed in the recent past. One model on natural conception has been validated in an external population and predicts accurately the chances of a treatment independent pregnancy among subfertile ovulatory couples.[20]

In 2004 an IUI prediction model was developed.[21] By calculating the chances of an ongoing pregnancy after IUI, benefit from IUI in comparison to expectant management can be determined. Before the model is available for clinical use external validation is yet to be performed.

By using these models and comparing the prognoses generated by the models for the couple, they can be counselled on an individual basis. Such an approach can prevent overtreatment, decrease the misuse of facilities and other resources and minimise the risk of multiple pregnancy generated by premature treatment.

In couples with unexplained subfertility or mild male subfertility and a treatment independent prognosis on pregnancy over 40% expectant management is generally advised. A prognosis below 30% should be an incentive to start treatment. In patients with an intermediate prognosis (30-40%) the threshold of treatment or expectant management was previously assessed. it was found that in these couples expectant management was just as effective as immediate start of treatment with IUI within the first six months after diagnosis.[22]

BACKGROUND

When we started the project described in this thesis, it was recognized that the need for an IUI prediction model for clinical use was urgent, because there were none available but one.[21] Because newly developed prediction models tend to generate chances which are better than realized in clinical practice, we decided to perform an external validation of this model.

When homologous intrauterine insemination is commenced, information on the optimum number of cycles to perform is essential. Exact data on the optimum number of cycles, as a possible limit to which insemination is effective, was lacking, and advices on the optimum number of cycles to perform varied between three to 12 cycle in literature.[23-26] We therefore aimed to perform a large cohort study to understand the effectiveness after six cycles.

When the actual insemination is performed, it seems important to consider the position of the woman right after the insemination. In most clinics it is common practice to immediately mobilize women after insemination in lithotomic position. The thought is that by inseminating spermatozoa in the uterus, the chance of conception is no longer influenced by the female position because of the rapid sperm transport inside the uterus and fallopian tubes.[27] However, one small randomized trial found contradictory results: significantly higher pregnancy rates were found in couples in which the women were immobilized for a short period of time directly after the insemination.[28] Because the trial was quite small and the difference between the study groups was remarkably large we decided a larger trial was needed.

As previously discussed, patients with unexplained and mild male subfertility and an intermediate prognosis, are advised to wait for another six months before to start with IUI-MOH.[22] If the advice not to start treatment in the first six months is valid, the issue of long-term effectiveness and cumulative costs becomes important to address. To answer this question, a long term follow up of this trial was needed.

When the decision to start IUI has been taken, the majority of couples with male and unexplained subfertility will be advised to start IUI with mild ovarian stimulation. Since this is associated with a high number of multiple pregnancies[15,29,30] it has been suggested that alternative treatments such as IVF with elective single embryo transfer (IVF-eSET) might reduce multiple pregnancies, while maintaining acceptable pregnancy rates. However no randomized trials comparing IUI-MOH with IVF-eSET in treatment naïve patients had been performed yet and the feasibility of such a trial was unknown. We decided to perform a pilot trial to explore this problem.

Finally we decided to address the problem of patient dropout. Drop out from fertility treatment is a well known phenomenon, even in reimbursed fertility programmes.[31,32] To understand the reasons for couples to stop IUI treatment and to understand the possible effect on pregnancy rates due to selective dropout, a large cohort study was needed.

OUTLINE OF THE THESIS

Chapter 2 Reports on the results of an external validation of a prediction model that predicts the outcome of intrauterine insemination. The study was a descriptive prospective validation study testing the accuracy and performance of the model by calibration and discriminative capacity.

Chapter 3 Reports on a multicentre retrospective cohort study analysing 3714 couples who underwent 15, 303 cycles of IUI. Ongoing pregnancy rates were calculated up to the ninth cycle. The aim of this study was to analyse if pregnancy rates after the sixth cycle are acceptable, justifying continuation of treatment up to nine cycles.

Chapter 4 Reports on the results of a randomised controlled trial evaluating the effect of 15 minutes of immobilisation versus immediate mobilisation after IUI. Main outcome measure was ongoing pregnancy rate per couple.

Chapter 5 Describes the long-term outcome in couples with unexplained subfertility and an intermediate prognosis initially randomized between expectant management and immediate treatment. The aim of this study was to evaluate if expectant management for six months in terms of long-term effectiveness is comparable to that of immediate treatment with IUI, while the cumulative long-term costs of expectant management remain lower.

Chapter 6 Is a randomized pilot trial comparing the effectiveness of in vitro fertilization with elective single embryo transfer versus intrauterine insemination with controlled ovarian stimulation in couples with unexplained subfertility and unfavorable prognosis. Main outcome was ongoing pregnancy rate per couple.

Chapter 7 Evaluates couples undergoing intrauterine insemination who continue treatment until six cycles or ongoing pregnancy versus couples that drop out from treatment. Prognostic profile and reasons for dropping out are reported.

Chapter 8 Presents the summary of this thesis and provides suggestions for future research.

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Chapter 2

External validation of a prediction model for an ongoing pregnancy after intrauterine insemination

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ABSTRACT

Objective: To assess the accuracy of our recently developed prediction model in a prospective validation study to predict the outcome of intrauterine insemination (IUI).
Design: Descriptive prospective validation study.
Setting: Seven fertility centres in the Netherlands.
Patient(s): Couples treated with IUI of whom the female partner had a regular cycle.
Intervention(s): Intrauterine insemination with or without controlled ovarian hyperstimulation.
Main Outcome Measure(s): Ongoing pregnancy after intrauterine insemination. Performance of the prediction model was assessed with calibration and discriminative capacity. Calibration was assessed by comparing the predicted ongoing pregnancy rate with the observed ongoing pregnancy rate. Discriminative capacity was assessed with receiver operation characteristic (ROC) analysis. For daily practice, a score worksheet of the validated model was developed to estimate the chance of an ongoing pregnancy after IUI per treatment cycle.
Result(s): We included 1,079 subfertile couples who underwent 4,244 cycles of IUI. There were 278 ongoing pregnancies, that is, an ongoing pregnancy rate of 6.6% per cycle. External validation of the model showed good calibration. The predicted probability never differed by more than 1.5% of the mean observed probability.
The area under the ROC curve was 0.56 (95% confidence interval, 0.53–0.59) at external validation.
Conclusion(s): The prediction model was able to make a good distinction between couples with a good pregnancy chance and those with a poor pregnancy chance after IUI. This model can help in deciding which couples will benefit from IUI and which couples will not.

INTRODUCTION

Intrauterine insemination (IUI) is an established treatment for subfertility due to cervical factor, male factor, or unexplained etiology.[1-3] To make a rational choice between IUI and other treatment options, accurate information on the expected ongoing pregnancy chance after treatment is therefore very important.

At present, several prediction models are available to calculate the chance of an ongoing pregnancy. For spontaneous pregnancy the model of Hunault *et al.* makes it possible to predict the chance of a treatment-independent ongoing pregnancy.[4] Templeton *et al.* developed a model to predict the probability of a pregnancy after IVF treatment.[5] Steures *et al.* developed a model for the prediction of ongoing pregnancy after IUI.[6] Since a model tends to perform better in the population in which it has been constructed, external validation is a crucial step before the model can be used in daily practice.[7] Both the model of Hunault *et al.* and the model of Templeton *et al.* have been validated.[8,9] For the prediction model for IUI there has so far been no external validation. The aim of this study was therefore to validate the IUI prediction model with prospectively collected data from an external population.

MATERIALS AND METHODS

Patients

From January 2000 to October 2005, consecutive subfertile couples undergoing IUI were included in this study. Data were collected from seven fertility centers in the Netherlands: Academic Medical Center, Amsterdam; TweeSteden Ziekenhuis, Tilburg; Gooi-Noord Ziekenhuis, Blaricum; Vie Curi Medical Center, Venlo; Zaans Medical Center, Zaandam; Scheper Ziekenhuis, Emmen; and Maxima Medical Center, Veldhoven. The local ethics committee of each participating center gave institutional review board approval for this study. All couples had been trying to conceive for at least 12 months and underwent a basic fertility workup according to

the guidelines of the Dutch Society of Obstetrics and Gynecology.[10] The basic fertility workup consisted of a medical and a fertility history, assessment of ovulation, semen analysis, postcoital test (PCT), and an assessment of the fallopian tubes. If the woman was ovulatory, which was confirmed by ultrasound, basal body temperature, and/or midluteal serum P, and had at least one patent tube as assessed by hysterosalpingography and/or laparoscopy, the couple was included in the study. If abnormalities were seen during hysterosalpingography, laparoscopy was performed to rule out tubal pathology. Only in these women was endometriosis assessed. The couples that received IUI were diagnosed with either male factor subfertility, cervical factor, or unexplained subfertility. Male factor subfertility was defined according to World Health Organization criteria: semen volume ≤2.0 mL, pH≤7.2, concentration ≤20 million/mL, progressive motile spermatozoa within 1

hour of ejaculation ≤50%, normal morphology of spermatozoa ≤15%, or sperm antibodies ≥50% resulted in a diagnosis of male factor subfertility.[11] Cervical factor subfertility was diagnosed by means of at least one well-timed PCT in which no progressive motile spermatozoa were seen in five high-power fields at a magnification of 400 X. If timing of the PCT was based on the basal body temperature curve, the PCT was timed 1 day before expected ovulation. If timing was based on ultrasound, the PCT was planned when the dominant follicle was at least 18mm in diameter. A cervical factor was only diagnosed if the total motile count of the semen analysis was at least 10 million. Unexplained subfertility was defined as subfertility without any demonstrable cause. For each treated couple, maternal age, duration of subfertility, primary or secondary subfertility, number of cycles, presence of male or cervical factor, presence of one-sided tubal pathology, uterine anomalies, and endometriosis were registered. The use and type of ovarian hyperstimulation was also documented.

IUI Protocol

Intrauterine insemination was performed with or without controlled ovarian hyperstimulation (COH). In case IUI was performed without COH, ovulation detection was performed with urine LH tests (a semiquantitative monoclonal antibody-based kit, OvuQuick, Quid San Diego) with a detection level of 40 IU, or by transvaginal ultrasound. When LH tests were used for ovulation detection, patients tested their urine samples once or twice a day, starting on an individually determined cycle day. Women were inseminated 20–30 hours after the endogenous LH surge had been detected in the urine sample. In the event of follicular growth monitoring by transvaginal ultrasound, hCG (Pregnyl, Organon, Oss, the Netherlands) was administered when a follicle had a diameter of at least 16 mm. Women were inseminated 36–40 hours later. In both cases, a suspension of processed spermatozoa was introduced into the uterine cavity with a catheter of 10 cm in length (International Medical, Zutphen, the Netherlands). Controlled ovarian hyperstimulation was performed to achieve the growth of two or three dominant follicles before administration of hCG; COH was performed with hMG, recombinant FSH, or clomiphene citrate. When at least one follicle with a diameter of 16 mm was seen during ultrasound monitoring, hCG was given. The administration of hCG was withheld and IUI was cancelled in the stimulation protocols when more than three follicles with a diameter of at least 16 mm or more than four follicles with a diameter of at least 14 mm were present.

Semen Preparation

Semen samples were processed within 1 hour after ejaculation, using a density gradient centrifugation followed by a washing step with culture medium. The volume of semen that was inseminated varied between 0.2 and 1.0 mL.

Data Analysis

The primary endpoint was ongoing pregnancy, which was defined as the presence of fetal cardiac activity seen at transvaginal ultrasound at a gestational age of at least 10 weeks. Twin pregnancies and high-order multiple pregnancies were also registered.

The analysis was done at cycle level, that is, each cycle was considered as a separate unit of analysis. The probability of an ongoing pregnancy after IUI was calculated for all IUI cycles according to the formula given in the IUI prediction model (see Appendix).

Calibration and discriminative capacity of the model were evaluated. Calibration was evaluated by comparing the agreement between the predicted ongoing pregnancy chance and the mean observed ongoing pregnancy rate. The predicted and the observed fraction were plotted in a calibration plot. In this plot, the association between the predicted pregnancy chance and the observed pregnancy chance is shown. In the ideal situation, all points are situated on the line that describes x=y (the predicted chance is the observed chance). All cycles were split into four groups of predicted pregnancy chance per cycle, that is, 0%–5%, 5%–8%, 8%–11%, and 11%–17%.[6] Discriminative performance of the model was assessed by the area under the receiver operating characteristic curve (ROC). Sensitivity was defined as the fraction of cycles not resulting in an ongoing pregnancy that was predicted correctly, and specificity was defined as the fraction of cycles that resulted in an ongoing pregnancy that was predicted correctly. Calculations were performed with SPSS version 11.5 (SPSS Inc., Chicago).

RESULTS

Overall, 1,079 couples who underwent 4,244 cycles were included. Baseline characteristics and pregnancy outcome are shown in Table 1. In total, 365 pregnancies occurred (8.6% per cycle), of which 278 were ongoing pregnancies (6.6% per cycle), 22 pregnancies were twins (7.9% per ongoing pregnancy), and six were high-order multiple pregnancies (2.1% per ongoing pregnancy, all triplets). In total there were 87 unsuccessful pregnancies, that is, seven ectopic pregnancies and 80 miscarriages (in total, 2% per cycle). The predicted probability of an ongoing pregnancy was compared with the observed ongoing pregnancy rate in that category. The difference between the mean observed chance and the mean predicted chance was less than 1.5% in all groups, which indicates a good calibration of the prediction model (Table 2). Calibration is shown in Figure 1. The model showed good calibration between 5% and 11%. For the predicted ongoing pregnancy rates above 11%, a slight overestimation was seen, whereas for pregnancy rates <5%, underestimation was seen. However, the confidence intervals of the group with a poor predicted chance (0%–5%) and the group with a good predicted chance (8%–11%) did not overlap, which indicates a reliable distinction between these prognostic groups. Discrimination showed a ROC curve with an area under the curve (AUC) of 0.56 (95% confidence interval, 0.53–0.59) (Fig. 2).

Table 1 Baseline characteristics and pregnancy outcome after IUI

	Missing data	Presence of the characteristic (n= 4,244 cycles)	Pregnancies (n= 365)
Maternal age (Y) (min-max)	0	33 (20-44)	
Duartion subfertility (Y) (min-max)	0	2.6 (1-13)	
Primairy subfertility (%)	0	3085 (73)	244
Secondary subfertility (%)	0	1159 (27)	121
Referred by family doctor (%)	16	3387 (80)	276
Referred by specialist (%) (or otherwise)	16	857 (20)	89
Unexplained subfertility (%)	0	1762 (42)	172
Cervical factor subfertility (%)	0	1072 (25)	99
Male subfertility (%)	0	852 (20)	52
One-sided tubal pathology (%)	0	415 (10)	31
Uterine anomaly (%)	0	167 (4)	11
Endometriosis (%)	0	499 (12)	28
No COH (%)	0	1106 (26)	72
Clomiphene citrate (%)	0	411 (10)	41
Recombinant FSH (%)	0	2373 (56)	225
Urinary FSH (%)	0	354 (8)	27
Cycle 1	0	1021	98
Cycle 2	0	891	75
Cycle 3	0	717	64
Cycle 4	0	538	45
Cycle 5	0	443	34
Cycle 6	0	338	32
Cycle 7	0	143	5
Cycle 8	0	67	7
Cycle 9-13	0	86	5

	Ongoing pregnancies (n= 278)	Abortion (n= 80)	Ectopic pregnancies (n= 7)	Twin pregnancies (n= 22)	High order multiple pregnancies (n= 6)
	192	46	6	16	5
	86	34	1	6	1
	211	61	4	16	5
	67	19	3	6	1
	130	40	2	12	2
	80	18	1	6	1
	39	12	1	3	2
	22	8	1	2	2
	9	2	0	2	0
	19	6	3	3	1
	57	13	2	0	0
	24	15	2	1	0
	176	47	2	19	4
	21	5	1	2	2
	72	24	2	4	1
	56	18	1	4	1
	52	10	2	4	2
	33	12	0	4	0
	24	9	1	1	0
	27	5	0	2	2
	5	0	0	1	0
	5	2	0	0	0
	4	0	1	2	0

Table 2 Mean predicted probability of an ongoing pregnancy versus the mean observed ongoing pregnancies.

Predicted chance	No. patients in group	Mean predicted probability	No. of pregnancies	Mean observed ongoing pregnancies
0-5%	665	3.9%	33	5.0%
5-8%	2,469	6.5%	171	6.9%
8-11%	1,043	9.0%	90	8.6%
11-17%	67	11.9%	7	10.4%

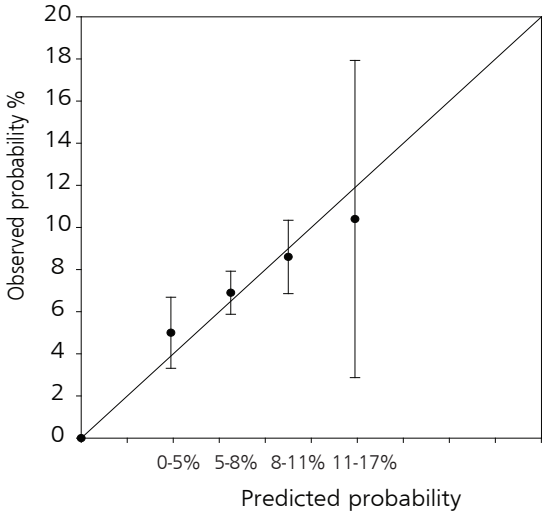

Figure 1 Calibration plot, showing the association between the predicted chance and observed chance of an ongoing pregnancy.

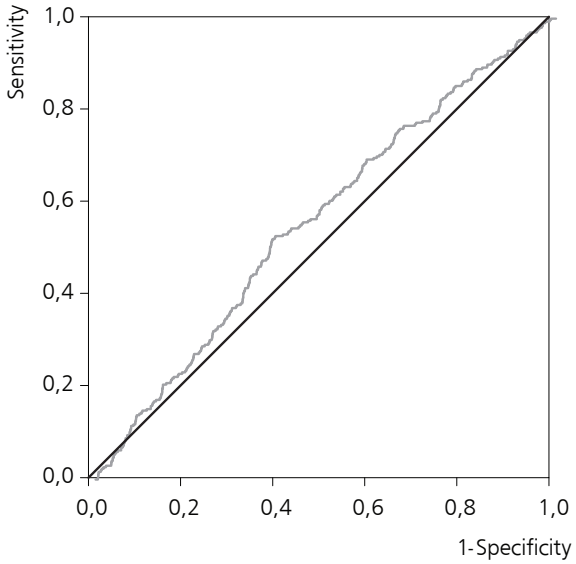

Figure 2 Receiver Operating Characteristic-curve

DISCUSSION

We assessed the external validity of our previously developed IUI prediction model in a large prospective cohort of more than 1,000 couples undergoing over 4,000 cycles of IUI. In this study we demonstrated that the prediction model previously published by Steures *et al.* is capable of predicting the chance of an ongoing pregnancy in different prognostic groups. In all four prognostic groups, the mean observed chance did not differ more than 1.5% from the mean predicted chance of an ongoing pregnancy.

A strong point of this study is the large number of cycles that was prospectively included and the complete and extensive follow-up. Also, since the patients were included in the study during a relatively short period (2000–2005), the chance of alterations in patient characteristics or changes in treatment protocol was limited.

The low area under the ROC curve might be explained by the homogeneous group of patients undergoing IUI, which have been filtered by time and diagnostic testing. Therefore, extreme differences can never be expected. In our validation sample, treatment was started at a median duration of subfertility of 2.6 years (min-max, 1-13 years), which means that probably most treatment-independent pregnancies would already have occurred, indicating a homogeneous population.

Furthermore, ROC analysis presumes to express the capacity to distinguish between pregnancy and nonpregnancy. However, even the couples with a very good prognosis (for example, pregnancy chance 30%) have a large chance of not getting pregnant. So even if the model could distinguish perfectly between couples with a 5% pregnancy chance and couples with a 30% pregnancy chance, the area under the ROC curve would maximally be 0.71. [13] We agree that an AUC of 0.56 is hardly better than perhaps flipping a coin. The problem, however, with these kinds of models is that because in fertility treatment pregnancy chances are never 0 or 100% and even seldom above 30%, the AUC will always be close to 0.5. This observation underscores the limitations of the area under the ROC curve, or c-index, as a method for determining model fit, despite its continued popular use in the medical literature. [14]

The AUC is particularly suited to retrospective case-control studies, in which the actual outcome probabilities cannot be estimated.[15] In the case of IUI, however, a very good prognosis of 30% per cycle implies that there is a 70% chance of nonpregnancy, which inevitably will affect the AUC. The discriminative capacity of such a model is also of limited clinical importance since couples are more interested in their own probability of conception within a certain treatment cycle (calibration) than in their chances of success compared with another couple (discrimination).

The effectiveness of IUI as a first treatment option for subfertile couples has been questioned, and some investigators advise performing IUI only for three cycles or not to start IUI at all.[16,17] It becomes therefore more important to underpin a treatment decision with reliable predicted success chances. Because chances for success and thus the choice for IUI or IVF are dependent on more than female age or sperm count alone, we feel that

Table 3 Prognostic score chart

						Prognostic score
Female age	20 to 25	26 to 31	32 to 35	36 to 39	40 to 43	
Score	7	9	10	11	12	–
Duration of subfertility	1 to 2	2 to 3	3 to 5	5 to 7	7 to 13	
Score	0	1	1	2	3	–
Diagnosis	Unexplained	Cervical factor	Male factor			
Score	0	-3	1			–
Pathology	Tubal	Uterine	Endometriosis			
Score	2	10	3			–
Ovarian hyperstimulation	No	CC	hMG or FSH			
Score	0	-2	-2			–
Cycle number	1	2	3	4	5 to 13	
Score	1	2	3	4	5	–
				Prognostic Index (sum score)		–

Circle the prognostic score for each of the variables and add them to the prognostic index. Use the curve in figure 3 to estimate the chance on an ongoing pregnancy after the IUI treatment cycle. (Example: a 33 year old woman, 2.5 years of unexplained subfertility, with no further pathology, and who will be treated with FSH has a prognostic index in the first cycle of: 10+1+0+0+-2+1=10. This score corresponds with 8.5% chance in the first treatment cycle)

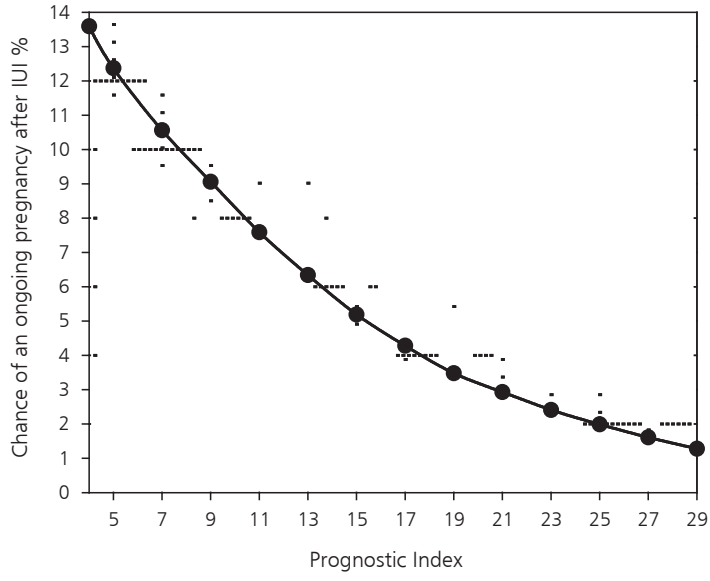

Figure 3 Prognostic index versus the chance on an ongoing pregnancy after IUI. The prognostic index is calculated form the score chart in Table 3

a decision to treat should be made based on a prediction model. The Steures *et al.* model is the first validated model that makes a reliable prediction of success possible in IUI.
In this study, we decided to externally validate an already existing model. As a consequence, factors not included in the original model, such as semen parameters, number of follicles, and endometrial type and thickness, were not taken into account. Future studies should evaluate whether the addition of other prognostic factors increases the performance of the model that we validated.
Because the issue of twin and high-order multiple pregnancies due to assisted reproduction is extremely important,[17,18] a next step in the development of prognostic models for IUI should be the prediction of multiple pregnancies.
In clinical practice, the IUI prediction model can also be used as a paper score worksheet (Table 3 and Fig. 3).The scores were derived from the beta coefficients (β) of multivariable analysis, in which e^{β} =odds ratio.[6] Variables were categorized into practical useful groups. The score per group was calculated as the product term of the group mean, the beta coefficient, and the factor -10.[12] For example, the variable age was grouped into maternal age 20–25, 26–31, 32–35, 36–39, and 40–43. The mean maternal age was 24.1 in the group 20–25, and the beta was -0.03. All women in this age group get an additional score of 7 points (24.1 x -0.03 x -10). The sum of all scores of the different variables resulted in a prognostic index. The prognostic index versus the chance of an ongoing pregnancy after IUI is plotted on a graph. Once the prognostic index is known, the chance of conceiving after IUI can be derived from this chart.
Although we did not perform a comparative study between IUI and IVF, the results of this study can be used to counsel patients to attempt IUI or to opt for an alternative treatment. If, for example, the success rate of IVF is more or less stable at about 20% per cycle, a decreased probability of success after IUI can be used as an argument to switch to IVF.
In conclusion, after external validation, the model proved to be accurate in predicting chances of success after IUI. It allows the clinician to identify couples who would benefit from IUI and those who would be better off with an alternative treatment.

APPENDIX

The formula for prediction of an ongoing pregnancy is as follows:
Probability = 1/ [1+exp (-β)], Where β = -1.41 + (maternal age x -0.03) + (duration of subfertility x -0.03) + (cervical factor x 0.27) + (male factor x -0.14) + (one-sided tubal pathology x -0.15) + (uterine anomaly x -0.98) + (endometriosis x -0.34) + (use of clomiphene citrate x 0.21) + (use of HMG or FSH x 0.23) + (cycle number [up to6] x -0.09)

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Chapter 3

Intrauterine insemination: how many cycles should we perform?

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ABSTRACT

Background In the past 20 years, various recommendations have been made about the maximum number of intrauterine insemination (IUI) cycles that should be performed, because evidence underpinning a possible limit is lacking.

Methods We performed a multicentre, retrospective cohort analysis among couples treated with IUI up to nine cycles. Primary outcome measure was ongoing pregnancy rate (OPR) per cycle. Cumulative OPRs (COPR) after three, six and nine cycles of IUI were calculated using life-table analysis. Univariable and multivariable logistic regression analysis was performed to identify variables possibly affecting OPR's.

Results Overall, 3,714 couples with male, cervical or unexplained subfertility underwent 15,303 cycles of IUI. In 70% of cycles, controlled ovarian hyperstimulation (COH) was used (51% clomiphene-citrate, 19% gonadotropins). Mean OPR rate was 5.6% per cycle. OPR in the seventh, eighth and ninth cycle were 5.1%, 6.7% and 4.6%, respectively. Taking censored patients into account, the calculated COPR was 18% after the third cycle, 30% after the seventh cycle and 41% after the ninth cycle. If censored patients were considered to have no chance of conception, a crude COPR of 25% after nine cycles was found. Multivariable regression analysis showed no significant impact of age, type of subfertility, diagnosis, use of hyperstimulation or cycle number on OPR after the sixth treatment cycle.

Conclusions OPR in high-order IUI cycles are acceptable, and do not offer a rationale for cancellation before nine cycles. Using this type of very mild COH, it may be reasonable to conduct up to nine cycles.

INTRODUCTION

Intrauterine insemination (IUI) is probably the most used treatment in subfertility. Various aspects of IUI, such as semen preparation techniques, natural versus stimulated cycles and single versus double insemination, have been well studied. [1-3] Data on the optimum number of IUI treatment cycles, however, are inconsistent, and recommendations on the number of treatment cycles that should be offered vary strongly.[4-13] Most authors recommend not to continue IUI after three to four cycles, [4-8,11-13] whereas two authors advise to repeat IUI even after six or more cycles. [9-10] However, most studies based their recommendations on relatively small patient populations varying from 200 to 600 couples. [4-8,11-13] In addition, all studies were single centre studies, thus affecting the generalizability of their findings. In view of these issues, we aimed to document cumulative ongoing pregnancy rates (COPR) after three, six and up to a maximum of nine cycles in a large cohort of IUI cycles in a retrospective analysis of data from four centres.

MATERIALS & METHODS

Patients

We performed a retrospective cohort study among consecutive couples treated with IUI from1986 to 2002. Data were collected from four fertility centres in The Netherlands: Medical Centre Alkmaar, Catharina Hospital Eindhoven, Onze Lieve Vrouwe Gasthuis Amsterdam and Vrije Universiteit Medical Centre Amsterdam.

All couples had been trying to conceive for at least 12 months. They had undergone a basic fertility workup that consisted of medical history, confirmation of an ovulatory cycle by ultrasound, basal body temperature and/or midluteal progesterone, semen analysis and assessment of tubal patency by laparoscopy or hysterosalpingography.

Indications for IUI were male subfertility, cervical factor subfertility and unexplained subfertility. Patency of at least one tube had to be confirmed. For detailed description of the definition of male subfertility, cervical factor subfertility and unexplained subfertility, as well as for the IUI protocol and semen preparation, we refer to a previous report on these data.[14]

For all couples, maternal age, duration of subfertility, diagnosis, tubal patency, semen parameters, primary or secondary subfertility and the use and type of controlled ovarian hyperstimulation (COH) were registered.

Data analysis

The primary outcome measure was ongoing pregnancy, defined as presence of fetal cardiac activity at transvaginal ultrasonography at a gestational age beyond 12 weeks. OPR per cycle and COPRs up to the ninth cycle were calculated. On the basis of COPRs,

a curve was constructed showing the time to pregnancy over multiple cycles. Univariable and multivariable logistic regression analysis was performed for variables possibly affecting the OPR. Variables considered in the analysis were female age, fertility history, diagnosis, use and type of COH and cycle number. Logistic regression analysis was done at cycle level, in data sets with cycle number one to six and cycle number seven to nine, separately. OPRs from the second until the ninth treatment cycle were also compared with the first treatment cycle with univariable logistic regression. For all variables, odds ratios, 95%-confidence intervals and P-values were calculated. A value of $P < 0.05$ was considered significant.

To evaluate whether patients who had a maximum of six cycles were different from patients proceeding treatment after six attempts, we analysed baseline characteristics in these two groups.

Data analysis was carried out using the Statistical Package for the Social Sciences (SPSS 11.5) (SPSS Inc., Chicago, IL, USA).

RESULTS

We included 3,714 couples who had undergone 15,303 treatment cycles. Analysis was limited up to the ninth treatment cycle (15,245 cycles). Baseline characteristics of the

Table 1. Characteristics of patients undergoing intrauterine insemination (IUI) cycles

	Cases n=3,714 mean (±SD)	**% of total**	**Missing n (%)**
Female Age (years)	33 (±4.2)		1
Infertility duration (years)	3.5 (±2.1)		344 (9)
History			7
Primary	2417	65	
Secondary	1290	35	
Diagnosis			0
Unexplained	1609	43	
Cervical	416	11	
Male	1314	35	
Combined	375	11	
Treatment cycles performed			
≥ 1	3714	100	
> 6	430	12	
Use of COH in treatment cycle	Total cycles n=15,245		1067 (7)
none	3552	23	
Clomiphene citrate	7775	51	
FSH/HMG	2851	19	

COH: controlled ovarian hyperstimulation

couples are summarized in Table 1. The characteristics of patients who had undergone a maximum of six attempts and patients who had more than six IUI cycles are shown in Table 2. There were no major differences between the two groups. There were 935 ongoing pregnancies, resulting in a mean OPR of 5.6% per cycle. OPR varied between 7.4% in the first and 4.4% in the fifth cycle (Table 3). The OPRs were relatively high in the first two cycles, with 7.4% and 7.0%, respectively, compared with around 5% in higher order cycles. The COPR after three cycles was 18%, to increase to 30% and 41% after six and nine cycles, respectively (Table 3, Fig.1). When the first cycle was considered as reference, the pregnancy rates in the third, fifth and sixth cycle were significantly lower after univariable logistic regression (Table 3). To analyse whether OPRs were influenced by possible prognostic factors, we performed a stepwise logistic regression analysis. In treatment cycles one to six, we found female age, presence of a cervical factor and cycle number to be significant after univariable analysis and multivariable logistic regression analysis. After univariable and multivariable analysis, none of the potential predictors was statistically significant in treatment cycles seven to nine (Table 4).

Table 2. Patient characteristics of couples who underwent one to six or seven to nine cycles of IUI

	1-6 cycles	7-9 cycles
Female age (years, mean ± SD)	33.2 (±4.2)	33.5 (±4.1)
Duration subfertility (years, mean ± SD)	3.5 (±2.1)	3.7 (±2.0)
Primary subfertility (%)	65.1	65.1
Cervical factor (%)	11.3	10.2
Male Factor (%)	35.1	37.4
Unexplained (%)	43.1	44.7

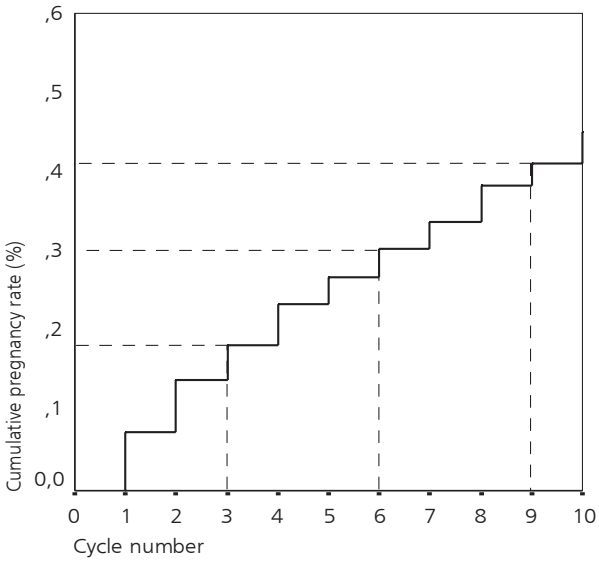

Figure 1. Cumulative OPR's from first to ninth IUI treatment cycle

Table 3. OPR's per cycle and cumulative PR's.

Cycle number	Patients	Pregnancies	Cumulative pregnancies	PR/cycle	Cumulative PR	OR	95% CI	P
1	3714	274	274	7.4	7.4	1.00		
2	3134	220	494	7.0	13.9	0.95	0.79-1.14	0.57
3	2615	134	628	5.1	18.3	0.68	0.55-0.84	<0.01*
4	2058	131	759	5.4	23.5	0.85	0.69-1.06	0.15
5	1657	73	832	4.4	26.9	0.60	0.44-0.75	<0.01*
6	1319	62	894	4.7	30.3	0.62	0.47-0.82	<0.01*
7	430	22	916	5.1	33.9	0.68	0.43-1.05	0.09
8	207	14	930	6.7	38.3	0.91	0.52-1.58	0.74
9	108	5	935	4.6	41.2	0.61	0.25-1.50	0.28

Odd's ratios calculated per cycle in comparison to the first treatment cycle. OR, odds ratio; CI, confidence interval, *versus first cycle.

DISCUSSION

In this large retrospective multicentre cohort study in couples undergoing over 15,000 IUI cycles, we report on the outcome of IUI after nine cycles.

We found that continuing IUI after six failed cycles still resulted in acceptable pregnancy rates; other prognostic factors had a limited impact on these pregnancy rates. Up to the

Table 4. Results of univariable and multivariable analysis of factors influencing pregnancy outcome from cycle 1-6 and cycle 7-9.

	Cycle number 1-6					
	univariable			multivariable		
	OR	95% CI	P	OR	95% CI	P
Age	0.97*	0.95-0.98	<0.01	0.97*	0.95-0.98	<0.01
History						
Primary	1.00					
Secondary	0.94	0.82-1.09	0.43	1.05	0.89-1.24	0.55
Diagnosis						
Unexplained	1.00					
Cervical	1.39*	1.13-1.70	0.02	1.37*	1.11-1.69	<0.01
Male	0.87	0.75-1.02	0.09	0.87	0.73-1.02	0.08
COH						
none	1.00					
Clomiphene citrate	1.01	0.86-1.19	0.91	0.97	0.83-1.15	0.79
FSH/HMG	1.07	0.82-1.39	0.62	1.01	0.77-1.34	0.94
Cyclenumber	0.90*	0.86-0.94	<0.01	0.89*	0.85-0.93	<0.01

Analysis performed on cycle-level. *Significant value

ninth treatment cycle, we found pregnancy rates to be quite stable. Our reported results are comparable to two previous studies.[9,10] The fact that our pregnancy rates are somewhat lower might be explained by the fact we reported on OPRs and the limited use of COH.

After logistic regression analysis, we found COH not to be of significant influence on pregnancy outcome. This is probably explained by the fact that in the Netherlands patients are stimulated rather mildly and mono or bifollicular cycles are quite common.[15]

As the outcome of IUI is subject to chance, the quintessence of IUI is repeating the cycles. Small consecutive chances will then result in acceptable pregnancy rates.

Reasons to stop IUI are numerous: for a couple with repeated failed attempts continuing IUI can become a frustrating experience. From the perspective of the doctor repeating IUI cycles can be time-consuming and offering alternative options may seem easier than motivating patients who have lost confidence. Despite these understandable emotions, our data show that continuing treatment after several failed attempts is rewarding. Since a patient's opinion is partially dependent on the way she is counselled,[9,16] it is especially important for a physician to discuss the benefits of repeating IUI cycles.

Psychology in terms of fear of failure is a well known and important factor in fertility treatment.[9,17,18] This fear of failure must not be ignored when a couple is treated during some cycles. Appropriate counselling, i.e. emphasizing COPR instead of pregnancy rates per cycle, is therefore of paramount importance to help a couple to understand the principle of repeated cycles. Also, proper psychological guidance during fertility treatment may help couples continue treatment after failed attempts.

	Cycle number 7-9					
	univariable			multivariable		
	OR	95% CI	P	OR	95% CI	P
	0.98	0.91-1.05	0.57	1.02	0.93-1.10	0.66
	1.00					
	0.96	0.49-1.86	0.89	0.58	0.24-1.42	0.23
	1.00					
	0.18	0.02-1.35	0.10	0.22	0.03-1.67	0.14
	0.33	0.33-1.32	0.24	0.62	0.28-1.39	0.24
	1.00					
	1.05	0.49-2.22	91	1.13	0.48-2.63	0.78
	0.72	0.15-3.39	0.68	0.68	0.14-3.40	0.64
	1.04	0.68-1.58	0.87	0.98	0.58-1.66	0.93

If patients drop out of an IUI programme and no correction is made in the analysis, one underestimates pregnancy rates of the IUI programme. This is only correct if all patients that were censored, i.e. dropped out of the programme, would indeed not have conceived upon continuation of the IUI. In that case, the pregnancy rates would have been around 25% instead of 41%. To see if censored patients, i.e. patients who stopped treatment before the seventh IUI cycle, were different from patients who continued treatment (i.e. patients whom had undergone seven cycles or more), we analysed patient characteristics in these two groups. Since we found no major differences, an overestimation of the pregnancy rates is rather unlikely.

Since we performed a retrospective cohort analysis, our study does not allow for cost effectiveness comparisons between IUI and IVF. Also, we had no complete record on multiple pregnancies in this cohort. On the basis of the use and type of ovarian stimulation, we estimated our multiple rate to be around 9%.

Cost-effectiveness of IVF with single embryo-transfer in a population of patients undergoing IUI is of great interest, but data on this topic are so far lacking.

On the basis of this large retrospective cohort study, we feel that couples should have the possibility to continue IUI treatment after six failed attempts, especially when couples are young (female age below 35 years) and still have a considerable time ahead in which they are able to conceive.

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Chapter 4

Immobilisation versus immediate mobilisation after intrauterine insemination: randomised controlled trial

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ABSTRACT

Objective To evaluate the effectiveness of 15 minutes of immobilisation versus immediate mobilisation after intrauterine insemination.

Design Randomised controlled trial.

Setting One academic teaching hospital and six non-academic teaching hospitals.

Participants Women having intrauterine insemination for unexplained, cervical factor, or male subfertility.

Interventions 15 minutes of immobilisation or immediate mobilisation after insemination.

Main outcome measure Ongoing pregnancy per couple.

Results 391 couples were randomised; 199 couples were allocated to 15 minutes of immobilisation after intrauterine insemination, and 192 couples were allocated to immediate mobilisation (control). The ongoing pregnancy rate per couple was significantly higher in the immobilisation group than in the control group: 27% (n=54) versus 18% (34); relative risk 1.5, 95% confidence interval 1.1 to 2.2 (crude difference in ongoing pregnancy rates: 9.4%, 1.2% to 17%). Live birth rates were 27% (53) in the immobilisation group and 17% (32) in the control group: relative risk 1.6, 1.1 to 2.4 (crude difference for live birth rates: 10%, 1.8% to 18%). In the immobilisation group, the ongoing pregnancy rates in the first, second, and third treatment cycles were 10%, 10%, and 7%. The corresponding rates in the mobilisation group were 7%, 5%, and 5%.

Conclusion In treatment with intrauterine insemination, 15 minutes' immobilisation after insemination is an effective modification. Immobilisation for 15 minutes should be offered to all women treated with intrauterine insemination.

Trial registration Current Controlled Trials ISRCTN53294431.

INTRODUCTION

Intrauterine insemination with or without ovarian hyperstimulation is probably the most frequently applied fertility treatment in the world. One of the questions that has remained unresolved is whether pregnancy rates are positively influenced by immobilisation after insemination.

Several studies have investigated sperm migration and survival in the female genital tract. Spermatozoa may reach the fallopian tube—the site of fertilisation—within two to 10 minutes.[1-4] These data suggest that sperm migration to the site of fertilisation is independent of the position of the woman directly after intrauterine insemination.

In 2000, however, Saleh *et al* reported that if a woman remained in a supine position for 10 minutes after intrauterine insemination, the pregnancy rates increased significantly compared with immediate mobilisation (13% v 4% per cycle).[5] Unfortunately, this randomised controlled trial was rather small and unbalanced, as 40 couples were compared with 55 couples. Also, the outcome of pregnancy was not defined. As the subject has not been studied since then, we assessed the effectiveness of immobilisation after intrauterine insemination in a large multicentre randomised clinical trial.

METHODS

Subfertile women between 18 and 43 years of age with an indication for treatment with intrauterine insemination were eligible for the trial. Couples using donor semen (fresh or cryopreserved) could also be included in the trial. We made no restrictions with regard to the use and type of controlled ovarian hyperstimulation during treatment cycles.

All couples had been investigated for infertility according to the guidelines of the Dutch Society of Obstetrics and Gynaecology.[6] This included a medical history, cycle monitoring, semen analysis, postcoital test, and assessment of tubal patency. The woman's age, duration of subfertility, and whether subfertility was primary or secondary were documented. We defined duration of subfertility as the time from when the couple started actively trying to conceive to the time of start of treatment. If the couple had a previous pregnancy that had not resulted in a live birth, we defined duration of subfertility as the time from the first day of the pregnancy to the time of start of treatment. We defined primary subfertility as the absence of pregnancy in the current relationship.

If cryopreserved donor sperm was used, we defined subfertility as at least 12 cycles of unsuccessful intracervical insemination before intrauterine insemination. Ovulation was confirmed by basal body temperature curve, midluteal serum progesterone, or sonographic monitoring of the cycle. We included anovulatory women in the trial only after ovulation had been induced for at least six to 12 months without conception or if a male factor was also present, as in these instances an indication for intrauterine insemination existed.

At least one well timed postcoital test was done (except in couples using cryopreserved donor sperm) during the basic assessment of fertility. The test was planned according to the basal body temperature curve or findings of ultrasonography. A cervical factor was diagnosed if no progressive spermatozoa were seen in five high power fields at 400 times magnification and the total motile sperm count was less than 10×10^6 spermatozoa/ml. Tubal pathology was assessed by a chlamydia antibody test, a hysterosalpingogram, or laparoscopy. In the case of a positive chlamydia antibody test, the tubal status was subsequently evaluated with a hysterosalpingogram or laparoscopy; in women with a negative chlamydia antibody test, tubal pathology was considered to be absent. Patients had to have at least one patent tube to be eligible for the study. We defined male subfertility as total motile sperm count less than 10×10^6 spermatozoa/ml and unexplained subfertility as total motile sperm count more than 10×10^6 spermatozoa/ml and exclusion of a cervical factor.

Controlled ovarian hyperstimulation, semen preparation, and insemination regimens were done according to hospital specific protocols. Controlled ovarian hyperstimulation was done with clomiphene citrate 50-150 mg on days five to nine of the cycle or subcutaneous injections of recombinant or urinary follicle stimulating hormone daily (Gonal F, Serono Benelux, The Hague, Netherlands; Puregon, Organon, Oss, Netherlands; or Menopur, Ferring, Hoofddorp, Netherlands). Controlled ovarian hyperstimulation was primarily done with recombinant follicle stimulating hormone in all clinics but one, where clomiphene citrate was used as a first line treatment. Ovulation was induced with 5000 IU or 10,000 IU of human chorionic gonadotrophin (Pregnyl, Organon), and women were inseminated 36-40 hours later. If more than three dominant follicles (>16 mm) were present, the treatment cycle was cancelled. Semen samples were processed within one hour of ejaculation by density gradient centrifugation followed by washing with culture medium. The volume of semen that was inseminated varied between 0.2 ml and 1.0 ml.

Patients were asked to participate before start of the first intrauterine insemination cycle. After giving written informed consent, the couples were randomly assigned to have three cycles of intrauterine insemination followed by 15 minutes of immobilisation (intervention group) or three cycles of intrauterine insemination with immediate mobilisation (control group). We randomised the couples before the first insemination, by using a web based computer program with a stratification procedure for age (18-34 years and 35-43 years) and centre. Women were inseminated in the lithotomy position in a Trendelenburg tilt. Depending on their allocation, women remained in the supine position for 15 minutes (timed by an alarm clock) or were mobilised immediately.

The primary outcome measure was the occurrence of an ongoing, viable intrauterine pregnancy (within four months after randomisation), defined as fetal heart beat seen by transvaginal ultrasonography at 12 weeks' gestation. Secondary outcomes included live birth, biochemical pregnancy, ectopic pregnancy, and miscarriage. Pregnancy was determined by a qualitative urine test for β human chorionic gonadotrophin if no menstruation occurred 14 days after insemination.

Assuming an ongoing pregnancy rate of 10% per cycle in the mobilisation group, we believed that an increase in the ongoing pregnancy rate from 10% to 14% per cycle would be relevant. This corresponds to a 12% difference after three cycles. As expecting that 15 minutes of immobilisation would perform worse than immediate mobilisation would not be logical, we used one sided statistical tests. Using an α error of 0.05 and a β error of 0.20, and assuming a dropout rate of 10%, we needed 185 couples in each arm.

We calculated the rates of ongoing pregnancy per couple in each group and the corresponding relative risk with 95% confidence intervals. We used a two tailed Fisher's exact test to test for significance. We used Kaplan-Meier analysis to calculate time to pregnancy. We initially analysed data according to the intention to treat principle and followed this with a per protocol analysis.

RESULTS

Between September 2005 and October 2007, we randomly assigned 391 couples to immobilisation in a supine position for 15 minutes (199 couples; intervention group) or immediate mobilisation (192 couples; control group). Figure 1 shows the trial profile. The baseline characteristics were comparable in the two groups; very small differences existed only in distribution of diagnoses and use of controlled ovarian hyperstimulation (table).

The ongoing pregnancy rate per couple was significantly higher in the immobilisation group than in the control group: 27% (54/199) versus 18% (34/192); relative risk 1.5, 95% confidence interval 1.1 to 2.2; P=0.03. The crude difference in ongoing pregnancy rates was 9.4% (95% confidence interval 1.2% to 17%). Live birth rates were 27% (53/199) in the immobilisation group and 17% (32/192) in the mobilisation group (relative risk 1.6, 1.1 to 2.4; P=0.02). The crude difference in live birth rates was 10% (1.8% to 18%).

During the study, nine spontaneous pregnancies occurred between treatment cycles: four in the immobilisation group (one after the first cycle, three after the second cycle) and five in the mobilisation group (two after the first cycle, three after the second cycle) (fig 1). One treatment cycle in the immobilisation group was converted to in vitro fertilisation because of ovarian hyper-response, and this cycle resulted in an ongoing pregnancy.

In the per protocol analysis, we excluded these 10 ongoing pregnancies that did not result from intrauterine insemination. Again, the ongoing pregnancy rate in the immobilisation group was significantly higher: 25% (49/199) versus 15% (29/192); relative risk 1.6, 1.1 to 2.5; P=0.01.

One patient was randomised twice in the study: the first time she was allocated to immediate mobilisation. An ongoing pregnancy occurred but was terminated at 20 weeks' gestation because of multiple congenital abnormalities. The second time, the patient was randomised to immobilisation. Again an ongoing pregnancy occurred; this time it resulted in a live birth.

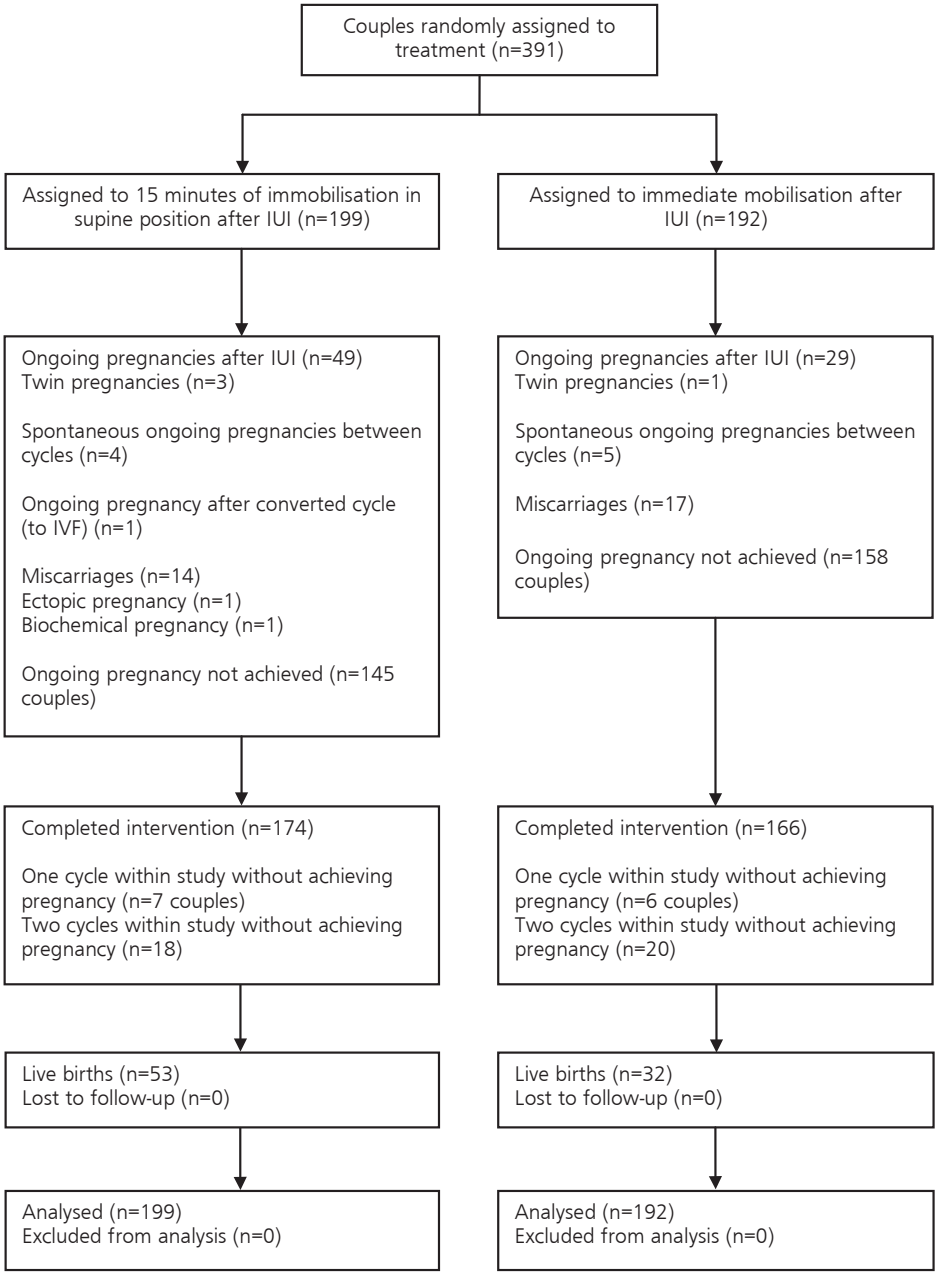

Figure 1. Trial profile: Couples who completed the intervention where those who underwent three cycles of IUI within 4 months or achieved pregnancy.

Table Baseline characteristics of the couples

Characteristics	15 Minutes of immobilization (n=199)	Immediate mobilization (n=192)
Mean (SD) womans age (years)	33.9 (3.8)	33.3 ± 3.9
Mean (SD) duration of subfertility (years)	2.7 (1.4)	2.7 ± 2.5
Primary subfertility	145 (73)	148 (77)
Cause of subfertility		
Male factor *	23 (12)	24(12)
Unexplained	118 (59)	105 (55)
Cervical Factor	58 (29)	63 (33)
One sided tubal path.	21 (11)	24 (13)
Anovulation	11 (6)	16 (8)
More than one diagnosis	31 (16)	39 (20)
Use of controlled ovarian hyperstimulation	118 (60)	124 (65)
Clomiphene citrate	26 (13)	25 (13)
Recombinant FSH	91 (46)	99 (52)
GnRh	1 (<1)	0

Values are numbers (percentages) unless stated otherwise
FSH=follicle stimulation hormone; GnRH=gonadotrophin releasing hormone.
*Total motile sperm count less than $10*10^6$/ml

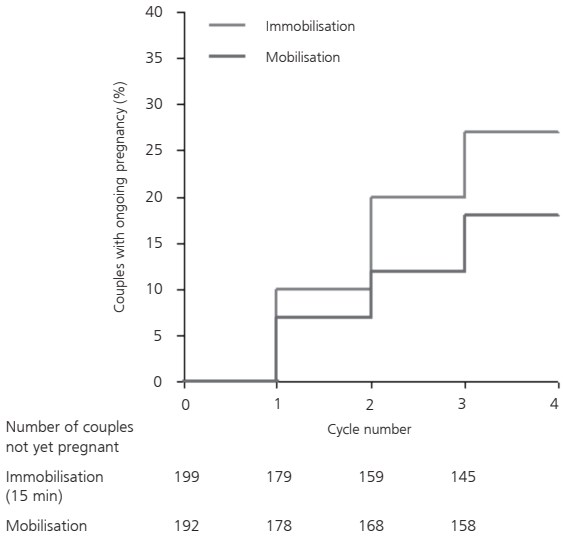

Figure 2. Kaplan-Meier curve of time to ongoing pregnancy

The Kaplan-Meier curve in figure 2 shows time to ongoing pregnancy. We found a significant difference in time to pregnancy in favour of immobilisation (log rank test, P=0.026). The mean number of cycles per couple during the study was 2.4 in the immobilisation group and 2.5 in the control group. In the immobilisation group, ongoing pregnancy rates in the first, second, and third cycles were 10%, 10%, and 7%. The corresponding rates in the immediate mobilisation group were 7%, 5%, and 5%.

In the immobilisation group, 25 (13%) patients did not complete three cycles or achieve pregnancy within the study period compared with 26 (14%) in the mobilisation group (fig 1). Reasons for not completing three cycles were delay by the patient between cycles, burden of the treatment, or doctor's advice to stop intrauterine insemination treatment.

DISCUSSION

In this large randomised controlled trial, we found that 15 minutes of immobilisation after intrauterine insemination significantly increased ongoing pregnancy rates. Although the difference in ongoing pregnancy rate per couple was somewhat lower than assumed in the power analysis (9.5% observed versus 12% expected), we consider this difference to be clinically relevant, especially as 15 minutes of immobilisation is a simple intervention with low additional costs. Although immobilisation takes more time and occupies more space in busy rooms, the intervention will be economic in the long run, as pregnant patients will not return in subsequent cycles.

The mechanism of the effect of immobilisation after insemination is unclear. After coitus, spermatozoa enter the cervix through the cervical mucus into the uterus, leaving the seminal plasma behind in the vagina. In intrauterine insemination, spermatozoa are inseminated in a small volume of fluid directly into the uterus. As a consequence, immediate mobilisation might cause leakage of this volume together with spermatozoa out of the uterus; alternatively, movement of processed sperm to and up the fallopian tubes may take longer than after intercourse.[7]

Small differences in treatment protocols among participating centres existed in this multicentre study, such as inseminated volume of semen and type of hyperstimulation. However, randomisation generated an equal distribution of the couples over the two treatment groups. Also, as heterogeneity in treatment protocols is likely among different fertility clinics, our findings represent daily practice and are therefore more generalisable to other populations.

Protocol violation in the control group was unlikely, as the woman was immediately mobilised with the physician in the room. In most centres, this was the standard approach before start of the study. In the immobilisation group, prolongation of the period of immobilisation at the initiative of the patient may have occurred in some cases.

CONCLUSION

We found a clinically relevant and statistically significant improvement in ongoing pregnancy rates after 15 minutes of immobilisation, confirming the results of a previous study.[5] As immobilisation is easily done and carries very little cost, we suggest incorporating immobilisation as a standard procedure in intrauterine insemination treatment.

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Chapter 5

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.

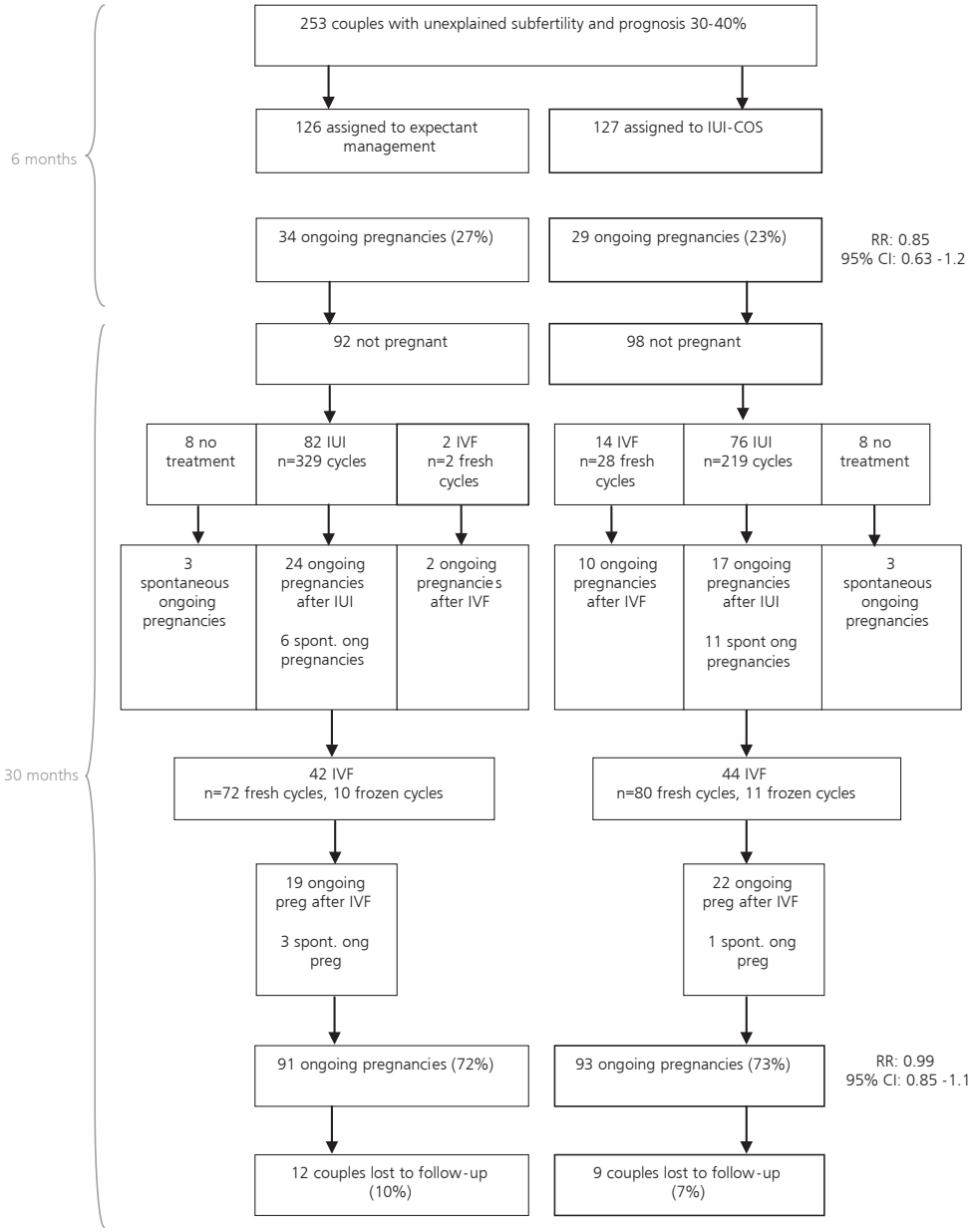

Figure 1 Flow chart of treatment and pregnancy outcome over 3 years for couples with unexplained subfertility and an intermediate prognosis, initially randomized between EM and immediate treatment IUI-COS, intrauterine insemination and controlled ovarian stimulation; RR, relative risk; CI, confidence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

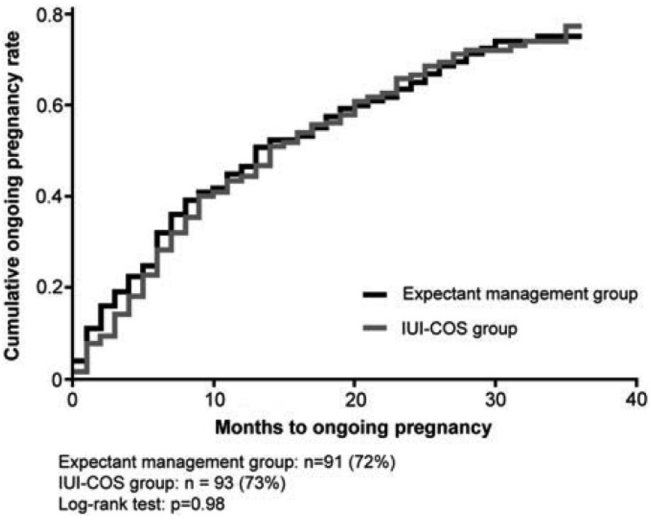

Figure 2 Time to ongoing pregnancy in couples who were initially randomized between EM and immediate treatment.

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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Chapter 6

Couples with unexplained subfertility and unfavourable prognosis; A randomized pilot trial comparing the effectiveness of IVF-eSET and IUI-COS

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ABSTRACT

Objective: To evaluate the effectiveness of IVF with elective single embryo transfer (IVF-eSET) vs. IUI with controlled ovarian stimulation (IUI-COS) as an alternative treatment to reduce the risk for a multiple pregnancy.
Design: Randomized pilot trial.
Setting: Three Academic and six teaching hospitals in the Netherlands
Patient(s): Couples with unexplained or mild male subfertility and an unfavourable prognosis for natural conception.
Intervention(s): One cycle of IVF-eSET or three cycles of IUI-COS.
Main outcome measure(s): Ongoing pregnancy per couple.
Result(s): We randomly allocated 116 women to IVF-eSET (n=58) or IUI-COS (n=58). There were 14 ongoing pregnancies (24%) in the IVF-eSET group and 12 pregnancies (21%) in the IUI-COS group (relative ratio 1.17; 95% confidence interval 0.60 to 2.30). There were two twin pregnancies in the IVF-eSET (14%) group and two twin and one triplet pregnancy in the IUI-COS group (25%).
Conclusions: In patients with unexplained or mild male subfertility and a poor prognosis for natural conception, one cycle of IVF-eSET might be as effective as 3 cycles of IUI-COS as primary treatment. Elective single embryo-transfer does not seem an effective strategy in preventing multiple pregnancies in this particular population. In the future a strict SET policy (i.e., compulsory SET) might be an option. Our trial provides evidence for the feasibility and highlights the importance of a large definitive trial to determine the effectiveness and side effects of both strategies.

INTRODUCTION

At present at least 1 out of 10 couples in Western countries is facing subfertility.[1,2] In a large proportion of these couples unexplained subfertility or mild male subfertility is diagnosed.[3] To avoid over- and under-treatment in these couples prediction models are used, which estimate the chances of a treatment-independent pregnancy. In couples with a favorable prognosis, >30% in 1 year, the guidelines of the Dutch Society for Obstetrics and Gynecology recommend expectant management. The National Institute for Health and Clinical Excellence guidelines also mention that each subfertile couple should be informed about the possibility of natural conception before assisted reproductive technology (ART).[4-6] If the prognosis for a live-born child in the next 12 months is <30%, treatment should be commenced.

In these poor-prognosis couples two empirical treatments are available: IUI with controlled ovarian stimulation (IUI-COS) or IVF with double embryo transfer (IVF-DET). Both treatments result in considerable pregnancy rates but also in a considerable number of multiple pregnancies.[7-9] Women with a multiple pregnancy are at increased risk for obstetric and neonatal complications, such as preterm birth, intrauterine growth retardation, and pre-eclampsia.

In vitro fertilization with elective single embryo transfer (IVF-eSET) can reduce multiple pregnancies considerably in an IVF population. In these couples, ongoing pregnancy rates varying from 21% to 38%, with multiple pregnancy rates from 0 to 4.5%, have been reported in several trials.[10,11] These data open up the possibility of considering IVF-eSET as an alternative for IUI-COS in reducing multiple pregnancy while maintaining success rates in couples with a prognosis for a live-born child in the next 12 months of <30% and who qualify for IUI-COS.

In these trials patients were included who primarily had an indication for IVF treatment or who had previous failed IUI cycles without taking the prognosis for natural conception into account. In addition, inclusion and randomization of couples was performed just before ET, and by then the availability of at least two top-quality embryos is certain.

In view of this, the question remains whether these data can be generalized to subfertile couples with a poor prognosis who are therapy naïve and are to start with IUI or IVF-eSET. Therefore, we decided to conduct a randomized pilot trial comparing one cycle of IVF-eSET with three cycles of IUI-COS in treatment-naïve couples with mild male or unexplained subfertility and a poor prognosis for natural conception, to determine whether one cycle of IVF-eSET might be as effective as three cycles of IUI-COS as primary treatment, while preventing multiple pregnancies.

MATERIALS AND METHODS

Our trial took place between November 2006 and February 2009 in three academic and six teaching hospitals in the Netherlands. Couples were invited to participate if they were diagnosed with unexplained or mild male subfertility. Couples had to have poor fertility prospects as calculated by the validated model of Hunault.[3,12] Poor fertility prospects were defined as a chance of natural conception <30% within 12 months. Exclusion criteria were other causes of subfertility, including severe male subfertility, cervical factor, and polycystic ovary syndrome; female age ≥38 years; or prior treatment within this subfertility episode. The age limit was based on concerns that IUI-COS may compromise pregnancy rates in older women.

All couples had undergone a basic fertility workup according to the guidelines of the Dutch Society of Obstetrics and Gynecology. This workup included a medical history, cycle monitoring, postcoital test, semen analysis, and assessment of tubal patency. Female age, duration of subfertility, and whether subfertility was primary or secondary were documented. Duration of subfertility was defined as the time from when the couple started actively trying to conceive (or had their last nonviable pregnancy) to the time of inclusion in the trial. If the couple had a previous pregnancy that had not resulted in a live birth, duration of subfertility was defined as the time from the first day of the pregnancy to the time of inclusion in the study. Primary subfertility was defined as the absence of pregnancy in the current relationship.

In case (cryopreserved) donor sperm was used, subfertility was defined as at least 12 cycles of unsuccessful intracervical inseminations. Ovulation was confirmed by basal body temperature curve, midluteal serum P level, or sonographic monitoring of the cycle.

At least one well-timed postcoital test was performed (except in couples using cryopreserved donor sperm) during the basic fertility assessment to exclude a cervical factor. Tubal pathology was assessed by a chlamydia antibody test and hysterosalpingogram or laparoscopy. Patients had to have at least one patent tube to be eligible for the study. Mild male subfertility was defined as a total motile count (TMC) of $3–10 \times 10^6$ spermatozoa/mL. Unexplained subfertility was defined as a TMC $>10 \times 10^6$ spermatozoa/mL and exclusion of a cervical factor.

The study protocol was approved by the institutional review board of the University of Amsterdam and had local approval from the boards of the other participating hospitals. The trial was registered in the clinical trial register as ISRCTN86744378. None of the authors had a conflict of interest.

Couples who gave informed consent were randomized by a central Internet-based randomization stratified for center. They were allocated either to IVF-eSET followed by a cryo cycle or to IUI-COH for three cycles, within 4 months from the moment of randomization. Randomization was thus performed before start of treatment by the couple's own physician.

IVF-eSET

Patients allocated to receive IVF-eSET underwent controlled ovarian hyperstimulation after down-regulation with the GnRH agonist triptorelin (Ferring) in a long protocol with a midluteal start. Controlled ovarian hyperstimulation was started with 100–150 U recombinant FSH (rFSH). Treatment was continued until at least three follicles >18 mm had developed. Ovulation was induced by 10,000 IU hCG (Pregnyl; Organon), and cumulus–oocyte complexes were recovered by transvaginal ultrasound–guided retrieval 36 hours thereafter.

Embryos were scored with the use of validated morphologic scoring criteria at the time of fertilization (pronuclear morphology) and daily until the time of transfer. Embryos were assessed for their morphology daily by an embryologist/IVF technician using an Olympus IX71 inverted microscope equipped with Relief Contrast optics at a magnification of ×320 or a similar kind of microscope. On day 3 one embryo was selected for transfer if one or more embryos of good quality were available.

In case there were no good-quality embryos available, two embryos were transferred. Nontransferred good-quality embryos were cryopreserved on the fourth day (conventional slow freezing). When implantation was not successful or early miscarriage occurred, the frozen embryos were thawed and transferred. Again, only one embryo was transferred per freeze–thaw cycle if it was of good quality.

Good-quality embryos were defined as embryos having a cumulative embryo score of ≥24 (in the cumulative embryo score the number of cells is amplified with the morphologic score, which ranges from 1 [excellent, 4 points] to 4 [poor, 1 point]; for instance, a score 2, good-quality eight-cell embryo, will receive 8 × 3 = 24 points). Morulae were considered top-quality if <10% fragments were present and at least 50% of the cells were part of the compacting process.

IUI-COS

In couples allocated to receive IUI-COS, women underwent ovarian stimulation with 50–75 IU rFSH (Puregon; Organon) in a low-dose step-up protocol to achieve the growth of one to (maximally) three dominant follicles. In case the cycle was monofollicular, the amount of rFSH was raised in the subsequent cycle. Cycles with one dominant follicle (≥15 mm) and at least one more follicle >10 mm at the time of hCG administration were considered multifollicular. In case more than three dominant follicles were present the cycle was cancelled. Ovulation was induced with 5,000 or 10,000 IU of hCG (Pregnyl).

Semen samples were processed within 1 hour of ejaculation by density-gradient centrifugation followed by washing with culture medium. The volume of semen that was inseminated varied between 0.2 mL and 1.0 mL. Women were inseminated 36 to 40 hours after hCG administration.

Statistical Analysis

The primary endpoint was an ongoing pregnancy occurring within 4 months from time of randomization, defined as a viable intrauterine pregnancy of at least 12 weeks' duration. Secondary endpoints were multiple pregnancy miscarriage and ectopic pregnancy. Follow-up was continued until live birth. Treatment-specific variables, such as number of follicles in IUI-COS cycles, number of oocytes after follicle aspiration, and number of embryos, SETs, and DETs, were also registered.

The effectiveness of IVF-eSET compared with IUI-COS was expressed as a relative rate ratio (RR) with corresponding 95% confidence intervals (CIs). We used the log–rank test and Kaplan-Meier curves to compare cumulative pregnancy rates over time. All outcomes were analyzed on an intention-to-treat basis. Because these strategies have never been compared before, our aim was to perform a pilot trial evaluating the feasibility of such a study. We planned to include 50 couples in both study arms.

Funding

We received an unconditional grant from Organon (Oss, the Netherlands). Because, at the time, IVF and IUI were completely reimbursed by health insurance, patients did not receive further compensation for treatment.

RESULTS

Overall, 116 couples were included in our study, of whom 58 were allocated to IVF-eSET and 58 were allocated to IUI-COS (Fig.1). The baseline characteristics of both groups were comparable (Table1).

In the IVF-eSET group three couples did not start treatment: one because of natural conception, one because of a newly discovered hepatitis C infection in the male partner,

Table 1. Characteristics of couples allocated to IVF-eSET or IUI-COS

Baseline characteristic	**IVF-eSET (n=58)**	**IUI-COS (n=58)**
Female age (y), mean (SD)	33.6 (3.0)	34.0 (2.9)
Duration of subfertility (y), median (25^{th} percentile)	2.3 (1.9)	2.2 (1.8)
Primary subfertility, n (%)	53 (91)	46 (79)
TMC (×106 spermatozoa/mL), median (25th percentile)	56.5 (22.1)	47.3 (18.8)
FSH cycle day 2-5 (IU/L), mean (SD)	7.5 (2.2)	7.4 (2.6)
One-sided tubal pathology, n (%)	0	2 (3)
Diagnosis, n (%)		
Unexplained subfertility	54 (93)	51 (88)
Mild male subfertility	4 (7)	7 (12)
Chance of spontaneous pregnancy: % next 12 mo, mean (SD)	23.0 (6.5)	23.8 (6.1)

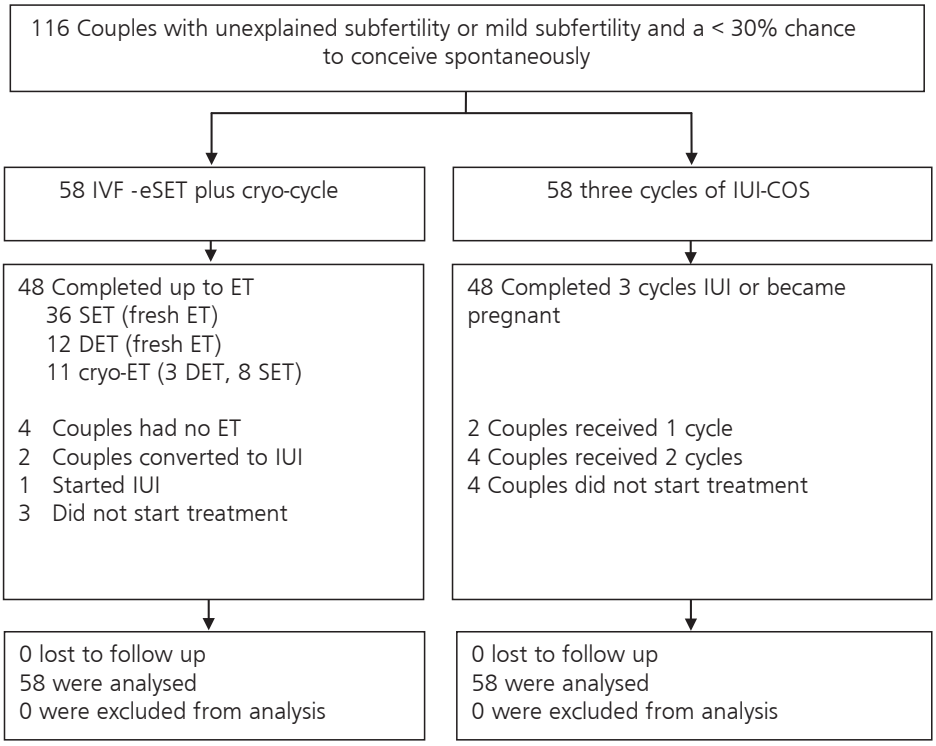

Figure 1. Flow Chart

and one because of personal reasons. One couple reverted to IUI-COS treatment after being tested positive for hepatitis B because cryopreservation of embryos of hepatitis B–infected patients was not performed in the treating hospital. Therefore, 54 patients started IVF treatment, of whom 52 (93%) had an oocyte retrieval and 48 (90%) had ET. In 36 patients (75%) SET was performed, and in 12 patients (25%) DET. In two couples intracytoplasmic sperm injection was performed because of unexpected low semen count on the day of oocyte retrieval.

In the IUI-COS group four couples did not start IUI-COS: two because of natural conception, one because of obesity that made follicle monitoring impossible during COS, and one because of relationship problems. Therefore, 54 couples started treatment and underwent a total of 142 IUI cycles. In five patients ovarian hyperstimulation was performed with clomiphene citrate instead of rFSH. In 74% of all IUI-COS cycles multifollicular growth was achieved (105 of 142 started cycles). Of the 142 started cycles, 14 cycles were cancelled because of the risk of high-order multiple pregnancy (10%).

The cumulative ongoing pregnancy rates over time from IVF-eSET and IUI-COS are shown in Figure 2. The ongoing pregnancy rate at 4 months from randomization was 14 (24%) in the IVF-eSET group and 12 (21%) in the IUI-COS group (RR 1.2, 95% CI 0.60–2.3). Pregnancy rates in the two treatment arms over 4 months did not differ (log–rank score

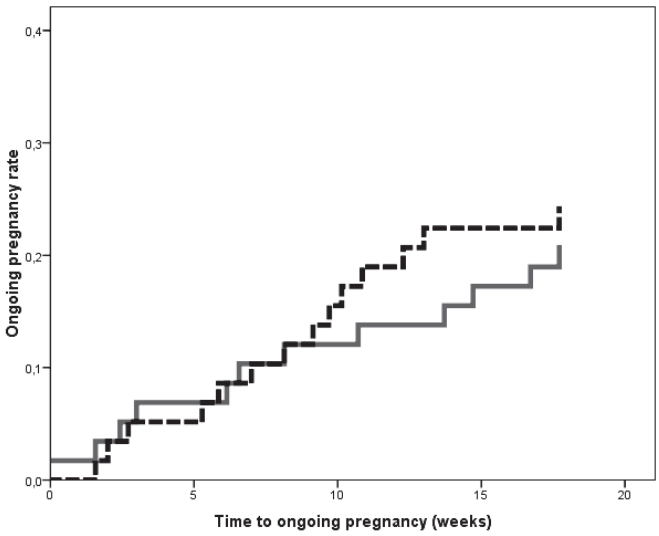

Figure 2. Cumulative ongoing pregnancy rate over time from one cycle of IVF-eSET or three cycles of IUI-COH

0.200, P=.65). Outcomes are summarized in Table 2. The multiple pregnancy rate per ongoing pregnancy was 14% (n = 2) in the IVF-eSET group and 25% (n = 3) in the IUI-COS group. The two twin pregnancies in the IVF arm both occurred after transfer of two fresh embryos of lower quality. The triplet pregnancy in the IUI-COS arm occurred after an IUI cycle in which four follicles were present of 16, 15, 14, and 13 mm at the time of hCG administration. The couple decided to reduce the pregnancy to a twin pregnancy.

Additional treatment outcomes for IVF-eSET and IUI-COS are described in Supplemental Table 1. In the IVF-eSET group 25 couples had cryopreserved spare embryos. Of the ongoing pregnancies seven occurred after SET, four after DET, two after transfer of a cryo-SET, and one spontaneous pregnancy occurred. In the IUI-COS group the mean number of follicles remained largely unaltered in the three IUI cycles. Of the ongoing

Table 2. Pregnancy outcomes at 4 months from randomization.

Outcome measures	IVF-eSET (n=58)	IUI-COS (n=58)	RR (95 % CI)
Clinical pregnancies	15	14	1.07 (0.57-2.01)
Ongoing pregnancies	14 (24)[a]	12 (21)[b]	1.17 (0.60-2.30)
Multiple pregnancies	2 (14)	3 (25)	
twin	2	2	
triplet	0	1	
Live births	13[c] (22)	12 (21)	1.08 (0.55-2.16)
Miscarriage	1 (2)	2 (3)	
Ectopic pregnancy	0	1 (2)	

Note: Values are numbers (percentage).
[a]One spontaneous pregnancy (IVF-eSET).
[b]Two spontaneous pregnancies (IUI-COS).
[c]One couple was lost to follow up.

Supplemental table 1. Treatment outcomes for IVF-eSET and IUI-COS

Treatment outcomes	
IVF-eSET	**Value**
No oocytes retrieved, mean (SD)	11.7 (7.2)
No embryos on day ET, mean (SD)	7.0 (5.5)
Number embryo's cryopreserved, mean (SD)	2.5 (4.0)
Ongoing pregnancy per ET, n (%)	
SET	7/36 (19)
DET	4/12 (33)
Cryo-SET	2/8 (25)
Cryo-DET	0/3 (0)
Spontaneous pregnancy	1
IUI-COS	
Mean no of follicles >10mm*, mean (SD)	
First IUI cycle	2.3 (1.4)
Second IUI cycle	2.2 (1.2)
Third IUI cycle	2.7 (1.6)
Mean no of follicles ≥ 15mm, mean (SD)	
First IUI cycle	1.6 (0.7)
Second IUI cycle	1.8 (0.9)
Third IUI cycle	1.9 (1.0)
Ongoing pregnancy, n (%)	
First IUI cycle	1/54 (2)
Second IUI cycle	5/51 (10)
Third IUI cycle	4/42 (10)
Spontaneous pregnancy	2

pregnancies one occurred in the first IUI cycle, five in the second IUI cycle, and four in the third IUI cycle. In this treatment arm two spontaneous pregnancies occurred.

DISCUSSION

In this pilot trial one cycle of IVF-eSET followed by transfer of frozen–thawed embryos generated in that cycle if present was as effective as three cycles of IUI-COS in couples with unexplained or mild male subfertility. With this sample size, we had a 47% power to detect a difference of 20% between the two groups (α error 5%, two-sided test).

When we started this trial we expected IVF-eSET to be a useful tool to prevent multiple pregnancies in patients with unexplained or mild male subfertiltiy and a poor prognosis for natural conception. To our surprise we found a rather high multiple pregnancy rate (14% per ongoing pregnancy) caused by a considerable rate of double embryo transfers (25%).

Possibly this can be explained by the relatively young population in our trial (women aged ≥38 years were excluded from the trial), who did not have previously failed IUI-COS cycles. Earlier studies have shown maternal age to be one of the most important predictors of pregnancy outcome after IVF.[13] Additionally, embryo quality based on morphology alone is not an excellent predictor of pregnancy outcome. Selection between poor (four-cell score3) and excellent embryos (blastocyst) seems clear cut; the difficulty probably lies in differentiating moderately good embryos from sub–top-quality embryos, which defines the difference in double or single embryo transfer.[14,15] The absence of international scoring criteria and the presence of inter- and intraobserver variability in the morphologic assessment of early-stage embryos create a further problem in selecting the proper embryos for single transfer.[16,17]

We found a low ongoing pregnancy rate after three cycles of IUI-COS, mainly due a very low ongoing pregnancy rate in the first treatment cycle (2%). Possibly dose finding in the first cycle was partly responsible for this low rate, considering the relatively high cancellation rate in the first cycle (9.2%, vs. 5.8% in the second cycle). Still, this illustrates the fear for multiple pregnancies, which in this pragmatic multicenter study led to the high cancellation rate in the first cycle, to avoid running the risk of multiple pregnancies. Moreover, patients were not offered to convert these cycles to IVF because this is not common practice in the Netherlands.

Our study is the first study that evaluates the effectiveness of IVF-eSET vs. IUI-COS as a tool to prevent multiple pregnancies while maintaining acceptable pregnancy rates in patients with unexplained or mild male subfertility and a poor prognosis for natural conception, in whom standard treatment would have been IUI-COS.

Because of the time horizon of 4 months, only 11 of the 25 couples who had frozen embryos did actually receive them after a failed IVF cycle. The ongoing pregnancy rate after a single cycle of IVF-eSET therefore will in practice be higher than the 24% we found, given that several couples still had spare embryos. Therefore, the potential effect from IVF-eSET could be higher than observed in his study. In future trials a longer follow-up period is clearly important.

In summary, in patients with unexplained or mild male subfertility and a poor prognosis, one cycle of IVF-eSET seems as effective as three cycles of IUI-COS but does not seem a very effective tool in preventing multiple pregnancies. Our trial provides evidence for the feasibility and highlights the importance of a large definitive trial with a longer treatment time and longer follow-up period to determine more precisely the pregnancy rates and multiple pregnancy rates of both treatments. In further studies a strict SET policy (compulsory SET) should be compared with IUI-COS instead of eSET.

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Chapter 7

Couples dropping out of a reimbursed intrauterine insemination program: what is their prognostic profile and why do they drop out?

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Fertility and Sterility, in press

ABSTRACT

Objective: To evaluate whether baseline characteristics and prognostic profiles differed between couples who drop-out from IUI and couples that continue IUI, and the reasons for couples dropping-out from IUI programs.
Design: Retrospective observational cohort study
Setting: Three fertility centres in the Netherlands
Patients: Consecutive subfertile couples undergoing IUI.
Interventions: None
Main Outcome Measure: Characteristics and prognosis on ongoing pregnancy after IUI, calculated by the model of Steures *et al.,* at the start of treatment, of couples that dropped-out compared to couples that continued treatment or achieved an ongoing pregnancy.
Results: We studied 803 couples who underwent 3,579 IUI cycles of whom 221 couples dropped-out (28%). Couples dropping-out completed 2.8(SD±1.4) cycles per couple compared to 4.5(SD±2.3) cycles per couple for those continuing treatment. Couples dropping-out had a higher female age, longer subfertility duration and higher basal FSH. Mean prognosis to achieve an ongoing pregnancy after IUI at start of treatment was 7.9% (SD±2.4) per cycle for couples who dropped-out, and 8.5%(SD±2.5) per cycle for couples continuing treatment. Of the dropouts, 100 couples (45%) were actively censored from the IUI-programme of whom 87 couples (39%) because of poor prognosis. 121 Couples (55%) were passively censored from the program of whom 62 (28%) dropped-out due to personal reasons. 59 Couples (27%) were lost-to-follow-up.
Conclusions: We found significant differences in prognostic profile between couples continuing treatment and couples dropping-out, although these differences seem limited from a clinical perspective. We conclude that overestimation of ongoing pregnancy rates after IUI due to couples dropping-out is limited.

INTRODUCTION

The majority of couples that face involuntarily childlessness seek medical help.[1] Although most couples are very motivated in achieving their ultimate goal of parenthood at the start of their fertility treatment, many couples -up to 60%- stop treatment before an ongoing pregnancy is achieved.[2,3] Even in countries where fertility treatment is completely reimbursed, dropout is a well known phenomenon.[4,5]

Studies on couples who drop out from fertility treatment have so far almost solely focused on couples receiving IVF.[6-15] Reasons why many couples withdraw from IVF appear to be a poor prognosis for achieving a pregnancy after the actual treatment, psychological distress associated with IVF[4,16,17] or financial reasons.[18] Thus far, only a few studies focused on drop out during the entire period of fertility work-up and subsequent treatment.[19,20] Until now, no single study has addressed drop out in a population undergoing intra uterine inseminations (IUI) as a first line treatment.

Since couples who drop out from an IUI program typically disappear from our sight, they usually are not included in analyses of success of IUI programs. This is worrisome, because selective dropout of poor prognostic couples might lead to over-estimation of cumulative pregnancy rates[12] and this hampers us to counsel couples realistically on their chances of ongoing pregnancy after intra-uterine insemination.

The aim of this cohort study was therefore to evaluate in retrospect, whether baseline characteristics and prognostic profiles differed between couples who drop out from IUI and couples that continue IUI, and to register the reasons for couples dropping out from IUI programs.

MATERIALS AND METHODS

Patients and procedures

Consecutive subfertile couples undergoing IUI between January 2000 and January 2008 were included in the study. For these patients, IUI treatments as well as the use of necessary medication was covered by their reimbursement programme. Data were collected from three fertility centres in the Netherlands: Academic Medical Center, Amsterdam; TweeSteden Hospital, Tilburg and Onze Lieve Vrouwe Gasthuis, Amsterdam. All couples had been trying to conceive for at least 12 months and underwent a basic fertility workup according to the guidelines of the Dutch Society of Obstetrics and Gynaecology (http://nvog-documenten.nl).

Couples had not been pre-selected by the use of a prognostic model. IUI was offered for the diagnoses male subfertility, cervical factor subfertility, unexplained subfertility or one-sided tubal pathology according to National guidelines and local protocols. Male subfertility was defined as a Total Motile Count (TMC) < $10*10^6$ /mL. Cervical factor subfertility was diagnosed by means of at least one well-timed post coital test (PCT) in which no

progressive motile spermatozoa were seen in five high-power fields at a magnification of 400 (TMC at least 10 million). For each treated couple, female age, duration of subfertility, primary or secondary subfertility, total motile semen count, type of controlled ovarian stimulation (COS), basal FSH level and diagnosis was registered.

For couples dropping out from treatment as well as for couples continuing treatment, the baseline characteristics were recorded and with these variables the prognosis on an ongoing pregnancy after IUI at the start of the first cycle was retrospectively calculated by a validated prediction model for IUI by Steures *et al.,* 2004[21] (formula see appendix). In case the type of COS (Clomiphene citrate or gonadotropins) was not registered, we assumed gonadotropins had been used, since this is the most widely used protocol in the Netherlands.

A couple was considered a dropout if they had not utilized six completed cycles of IUI, which are reimbursed by Dutch healthcare companies or achieved an ongoing pregnancy. Pregnancies were divided in treatment related pregnancies and spontaneous pregnancies in between treatment cycles. A treatment cycle was considered complete if processed semen was inseminated; all other cycles were registered as started cycles. Couples who intended to proceed to in vitro fertilization were also registered. If a couple dropped out, their record was assessed for the reason for dropping out, at least 6 months after their last visit. All outcomes of basic fertility work-up and treatment had been registered in an electronical database at the time of treatment of the couple as well conventional written charts.

Reasons for dropping out were divided in four categories: poor prognosis as estimated by the treating physician, technical IUI related problems, personal reasons (burden of treatment, no confidence in IUI, health problems not IUI related, relational problems, moving house or adoption), or unknown reasons (lost to follow up).

We defined couples that were advised to stop treatment by their doctor because of poor prognosis or IUI related, technical problems as actively censored drop outs. Couples that dropped out by their own choice due to personal reasons, or couples lost to follow up were defined as passively censored drop outs.

Because the study is a retrospective observational cohort study, Institutional Review Board approval was not required.

Statistics

Differences in baseline characteristics, including prognostic profiles between couples dropping out of treatment and couples continuing treatment, as well as subgroups, were calculated with ANOVA or Mann-Whitney test as appropriate using Spss 18.

RESULTS

We studied 803 couples who started 3,579 IUI cycles, of which 3,237 were completed cycles. There were 221 (28%) couples that stopped treatment before finishing six completed cycles of IUI and did not achieve an ongoing pregnancy. 152 Couples (69% of all dropouts) had stopped treatment after the third insemination. Of the remaining 582 couples that continued treatment, 307 had an ongoing pregnancy (38% of all couples) of which 264 were IUI related and 43 occurred spontaneously between treatment cycles (Figure 1).

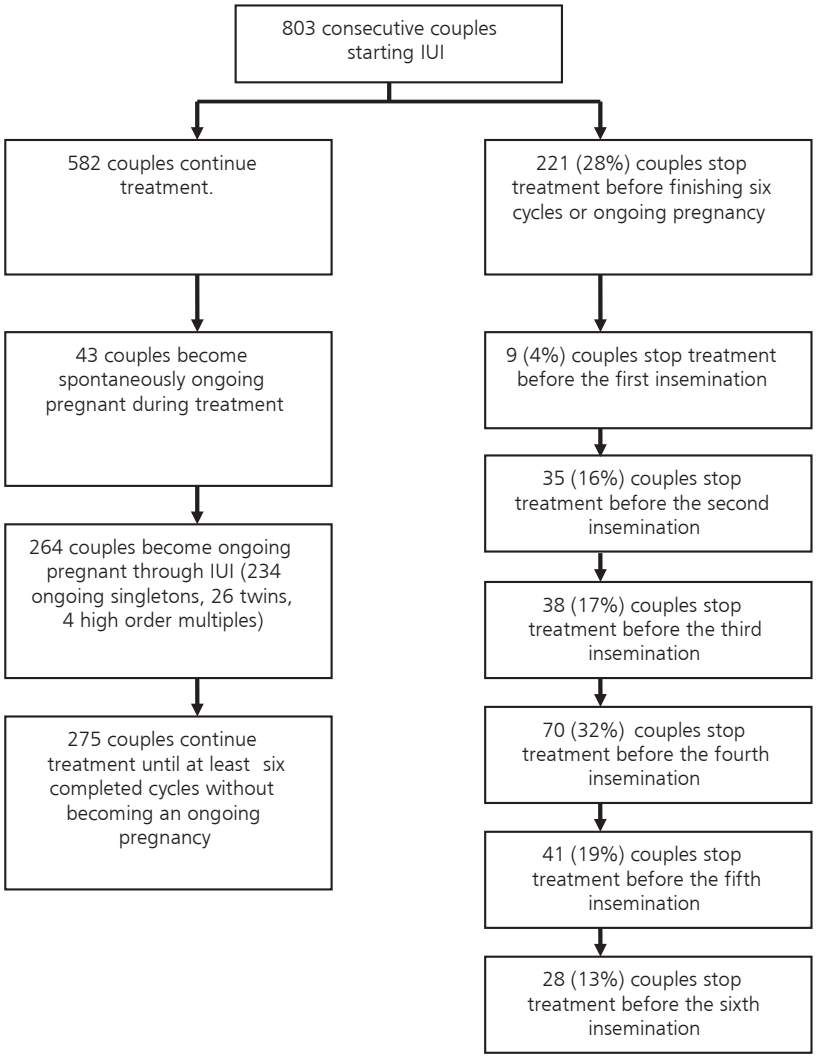

Figure 1. Flowcharts of couples continuing IUI and couples dropping out during intra-uterine insemination

Baseline characteristics of couples that dropped out and couples that continued IUI are summarized in table 1. Mean female age (SD) was higher in the group of dropouts (34.2 ± 4.2 versus 33.5 ± 3.9 years; p 0.04) as well as the duration of subfertility (3.4 ± 2.1 versus 3.0 ± 1.7 years; p 0.00) and baseline FSH (7.5 ± 6.5 versus 6.7 ± 4.3 U/l; p 0.02). We found no significant differences in all other characteristics. The overall prognosis (SD), calculated retrospectively by the model of Steures *et al.,* at start of treatment on an ongoing pregnancy was 7.9% (2.4) per cycle for couples dropping out and 8.5% (2.2) per cycle for couples continuing treatment (p=<0.001) (Table 1).
The mean number (SD) of started cycles was 3.2 (1.4) for couples that dropped out versus 4.9 (2.6) for couples continuing IUI. The mean number (SD) of completed treatment cycles was 2.8 (1.4) versus 4.5 (2.3) (Table 2).
Of the 221 couples that dropped out, 100 couples (45%) were actively censored from the programme (table 3). From these 100 couples 87 (39%) were advised to stop because

Table 1 Baseline characteristics dropouts versus couples continuing treatment

	Drop outs (n=221)	**Patients continuing (n=582)**	**P-value**
Female age in years, mean (SD)	34.2 (4.2)	33.5 (3.9)	0.04
Duration subfertility in years, mean (SD) median	3.4 (2.1) 2.9	3.0 (1.7) 2.6	0.00
Primairy subfertility(%)	192 (87)	538 (92)	
Diagnosis			
Cervical (%)	48 (22)	141 (24)	
Male (%)	45 (20)	109 (19)	
Unexplained (%)	94 (43)	241 (41)	
Tubal pathology (%)	26 (12)	66 (11)	
Multiple diagnoses (%)	8 (4)	25 (4)	
TMC mean (SD)	78.8 (126)	88.8 (117)	0.18
median	47.5	55.0	
FSH U/l, mean (SD)	7.5 (6.5)	6.7 (4.3)	0.02
median	6.8	6.0	
Chance ongoing pregnancy/ cycle at start treatment (SD)	7.9 (2.4)	8.5 (2.2)	0.00

Table 2 Treatment characteristics dropouts versus patients continuing treatment

	Dropouts (n=221)	**Patients continuing (n=582)**
Total number started cycles	713	2866
Total number completed cycles	625	2612
Total number unfinished or cancelled cycles (%/ started)	88 (12)	254 (8.9)
Mean number started cycles (SD)	3.2 (1.4)	4.9 (2.6)
Mean number completed treatments (SD)	2.8 (1.4)	4.5 (2.3)

Table 3 Reasons for dropping out and prognoses at start of treatment for subgroups

	Patients n (%)		Prognosis per subgroup % (SD)
Active censoring	**100 (45)**		7.7 (± 2.2)
Poor prognosis		87 (39)	7.6 (± 2.4)
Treatment problems, IUI related		13 (5.9)	8.1 (± 1.2)
Passive censoring	**121(55)**		8.0 (± 2.4)
Personal reasons		62 (28)	8.0 (± 2.1)
Removal		8 (3.6)	
Relational		2 (0.9)	
Adoption		1 (0.4)	
Health problems, not IUI related		14 (6.3)	
Burden of the treatment		14 (6.3)	
No confidence in treatment		23 (10)	
Lost to follow up		59 (27)	8.0 (± 2.8)
Total	**221**		

of poor prognosis. A poor prognosis was expected in case of advanced female age, long duration of subfertility or unexpected poor semen quality during treatment. The retrospectively calculated prognosis with the IUI prediction model of Steures *et al.,* in these couples was an ongoing pregnancy chance of 7.6% per cycle at the start of their treatment which was only slightly lower than the overall prognosis for the total group of couples that dropped out (7.9%). Thirteen couples (5.9%) were advised to stop IUI because of treatment related technical problems, such as repeatedly premature ovulation, repeated cycle-cancellation due to risk of a high-order multiple pregnancy or failure to monitor the cycle due to poor visibility of the ovaries. All of these 100 actively censored couples that dropped out were planned to continue with in vitro fertilization after stopping IUI.

Passive censoring occurred in 121 couples (55%). Of these couples, 62 couples (28%) dropped out because of personal reasons. Fifty-nine couples (27%) were lost to follow up: 54 did not return for treatment without further notice and five couples had a spontaneous pregnancy in between treatment cycles of which four women miscarried. Of one couple we were not able to find out if the pregnancy was ongoing or not.

DISCUSSION

The present cohort study in couples that underwent IUI showed that couples dropping out of an IUI program have a significantly different prognostic profile as compared to couples that continue IUI. Women were significantly older, duration of subfertility was longer and the prognosis for an ongoing pregnancy at the start of IUI treatment was significantly lower for couples that dropped out. Although statistically significant, the absolute difference of

this prognosis for an ongoing pregnancy at the start of treatment was very small (only 0.6%; 7.9% and 8.5 % respectively) and therefore seems to be clinically irrelevant.

Assuming that pregnancy chances only declined at increasing cycle number and all couples would continue treatment until six cycles, we calculated that the cumulative ongoing pregnancy rate after 6 cycles in the entire population would add up to 41%, in patients who dropped out of treatment 39% and in patients who continued treatment 42%. The observed ongoing pregnancy rate was 38% (307 ongoing pregnancies in 803 couples), which corresponds exactly with these calculations based on the prediction model of Steures *et al*.

The subgroup of couples who were adviced to stop treatment because of alleged poor prognosis would reach an estimated cumulative ongoing pregnancy rate of 37%. It is possible that other considerations such as patients preference or relative efficacy of IVF for the individual couple also played a role in decision making to stop IUI-treatment, but it is likely that doctors are not effective in estimating the patients' prognosis if they do not use a prediction model. This is in line with a previous study that found that gynaecologists differed widely in their estimation of prognosis on a spontaneous pregnancy of subfertile couples.[22]

This emphasizes that the use of prediction models in counselling couples to stop or continue treatment is essential; it might prevent premature referral to more invasive treatments as IVF.

In our cohort, the treatment cycles were completely reimbursed. Decision making by couples and physicians to stop or continue treatment was therefore not influenced by direct costs through treatment. Indirect costs by foregone wages were not mentioned by any of the couples as a reason to stop treatment.

We could not differentiate between the commitments of couples using clomiphene or gonadotropins as the vast majority had used gonadotropins which was the standard protocol at the time of the study.

Furthermore, psychological distress did not appear to be a main reason for dropping out of treatment: dropping-out due to the "burden of the treatment" and "no confidence in treatment" occurred in 16% of the couples. However, 27% of the couples that did not return for further treatment were lost to follow-up. It is possible that in this group a portion of the couples found the treatment too burdensome. An important issue and possible shortcoming of the present study is that "burden of the treatment" and no "confidence in treatment", classified as psychological distress, was interpreted by the treating physician and not by standard interviews or a questionnaire because of the retrospective nature of the study.

In IVF poor prognosis and psychological distress are the main reasons for dropping out.[5,16,17] It is possible that the main reasons for dropping out differs between IUI and IVF because after IUI there are still alternative options to achieve pregnancy, whereas IVF might be considered as "last resort".

In conclusion, we found that the observed pregnancy rates after IUI are overestimated due to patient drop out. This overestimation however is limited and it is therefore unlikely that we counsel our patients too optimistically.

Appendix:

The formula for prediction of an ongoing pregnancy is as follows:
Probability = $1/[1+\exp(-\beta)]$,
Where β = -1.41+ (maternal age x -0.03)+(duration of subfertility x -0.03)+(cervical factor x 0.27)+(male factor x -0.14)+one-sided tubal pathology x -0.15)+(uterine anomaly x -0.98)+(endometriosis x -0.34)+(use of clomiphene citrate x 0.21)+(use of HMG or FSH x 0.23)+(cycle number [up to six] x -0.09).

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Chapter 8

General discussion and summary

GENERAL DISCUSSION

Intrauterine insemination has been a treatment of all times. The first scientifically described homologous insemination was performed in London by the Scottish physiologist and surgeon John Hunter in 1790. He advised a man with severe hypospadia to collect his semen directly after coitus in a syringe and introduce it into the vagina of his wife. The woman conceived after this procedure.[1] Initially, the techniques of insemination were rather curious and the success rates were amazingly high; homologous insemination was practiced in France by Girault as early as 1838 and appeared to be successful in 8 out of ten cases.[2] Numerous scientific reports appeared between the mid eighteen hundreds and the beginning of 1900 in which it appeared that homologous insemination was successfully practiced by medical experts in France, England, Germany and the United States.[1,2] Between 1900 and World War II the number of reports on homologous insemination declined since there was a growing interest in artificial insemination with donor semen. Methods for freezing and thawing of semen were developed which led to the possibility of insemination without the necessity of freshly produced semen by husbands or donors. A new indication for insemination arose from this newly developed technique, called the "distance indication": wives of soldiers sent to war could be inseminated with their husband frozen and thawed semen.[3]

It took until 1984 before the first randomised clinical trial was published in The Lancet.[4] This trial investigated the effectiveness of intra uterine insemination in 35 couples with men with poor semen quality. The paper described a cross-over-trial design in which the couples were initially randomised into three groups: 14 couples started with a single act of natural intercourse based on the basal body temperature, 7 couples started with a single act of natural intercourse the day after the LH-surge and 14 couples started with a single IUI of washed sperm on the day after the LH-surge. After completing four cycles of each procedure patients switched to one of the other two alternatives. They registered 8 pregnancies out of 39 IUI cycles versus one pregnancy after 34 cycles of BBT-timed intercourse and no pregnancies after 38 cycles of LH-timed intercourse. Since the trial was small the effectiveness of IUI could not be proven.[5-8] Soon more and more randomised and non randomised studies were published and the effectiveness was no longer doubted.[9-11] Studies on IUI now focussed on spreading the number of indications[12,13] and fine-tuning the treatment in terms of sperm washing procedures and use of superovulating medication.[14]

Intrauterine insemination for unexplained and male subfertility

During the writing of this manuscript, a critical re-appraisal of the literature and updating of Cochrane reports resulted in questioning the actual contribution of intrauterine insemination for unexplained or male subfertility.[15,16] In unexplained subfertility there is evidence that IUI with ovarian stimulation increases the live birth rate compared to IUI alone. The likelihood of pregnancy was also increased for treatment with IUI compared to

timed intercourse in stimulated cycles. One adequately powered multicentre trial showed no evidence of effect of IUI in natural cycles compared with expectant management.[17]
When we decided to perform a long-term follow up of the randomized trial of Steures *et al.,* (IUI-MOH versus expectant management in unexplained subfertility), our initial hypothesis was that after the first six months with more or less equal numbers of live births between the two groups, the non-treated group would take a leap in time-to-pregnancy when they would start IUI-MOH. However, in three years time in which couples underwent IUI-MOH, IVF/ICSI or refrained from further treatment we found no difference in time to ongoing pregnancy between the immediate treatment group and expectant management group. However, the expectant management group underwent significantly less IUI and IVF treatment cycles compared to the group that received immediate treatment with IUI-MOH.[18]
Overlooking these results the effect of IUI alone is questionable; the major effect- if any- is possibly due to aggressive ovarian stimulation, which in turn increases the risk of multiple pregnancies.
As advised in the Cochrane analyses couples should be informed on the risk of IUI-MOH and the possibility of alternative options.[15]

Risk of multiple pregnancies, search for alternatives

IVF with elective single embryo-transfer is considered as a possible effective tool in preventing multiple pregnancies in an IVF population. Reports of multiple rates between 0-5% have been reported in trials.[19-20] Continuing on these data, our hypothesis was that IVF-eSET might also be an effective tool to prevent multiple pregnancies in a treatment-naïve IUI population. In our pilot study, to our surprise, we found a rather high multiple pregnancy rate (14% per ongoing pregnancy) caused by a considerable rate of double embryo transfers (25%). More-over, in the limited time-horizon of four months, we found equal numbers of ongoing pregnancies and live-births, suggesting that IVF-eSET does not seem a superior treatment in these couples in prevention of multiple pregnancies and achieving an ongoing pregnancy. One possible explanation might be the difficulty of selecting the embryo with the highest implantation potential for transfer.[21-24] These preliminary results emphasize the need for large definitive trials with a longer treatment time and longer follow-up period to determine more precisely the pregnancy rates and multiple pregnancy rates of both treatments IVF-eSET and IUI-MOH.
From the recently published Cochrane review on IVF for unexplained subfertility, also no definitive conclusions could be drawn to choose for IVF as a superior treatment since adverse effects and costs are unsufficiently clarified.[25]
If the decision has been made to start IUI, usually with MOH, pregnancy rates up to 40% are achievable after nine cycles. Since the quintessence in fertility treatment is repeating treatment cycles, couples should not be motivated to skip or discontinue IUI prematurely and to switch to more aggressive treatments such as IVF/ICS before superiority has been proven.

In modern society this is a moot point. A shift to premature and more aggressive treatment with IVF-ICSI is visible and this is worrisome. Current society is shifting towards a situation in which couples should obtain a family in the shortest period possible and the possibility of expectant management is increasingly difficult for a couple.[17] Besides this, family planning is increasingly becoming merchandise in which desperate couples are willing to pay large amounts of money.[26] Moreover, there is emerging evidence to indicate that IVF may predispose individuals to increased incidence of obesity, elevated blood pressure, fasting glucose and triglycerides and subclinical hypothyroidism.[27]

Implications for future research

In The Netherlands IUI with or without MOH is performed in 90% of the hospitals with over 28 000 cycles each year. About 10% of all ongoing pregnancies resulted in a multiple pregnancy.[28] In a relatively young population with unexplained or mild male subfertility, in which only gonadotropins are used, multiple rates are sometimes higher.[29]

For some the use of gonadotroping has become a "20th century relic" and the use of alternative medications mostly Clomiphene citrate is advocated as a more cost-effective alternative.[30] Available studies on the subject are relatively small and larger trials are needed.[31,32]

In prevention of multiple pregnancies, the search for alternative treatment strategies is an ongoing quest. Hopefully the INeS-study which compares IUI-MOH, IVF with single embryo transfer and Modified Natural cycle IVF will bring light to this question.[33]

Although more and more difficult nowadays, also larger trials evaluating expectant management versus IUI-MOH and IVF are needed to identify the actual contribution of these treatments in patients with unexplained subfertility.

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SUMMARY

This thesis reports on various aspects that determine optimal treatment of subfertile couples with intrauterine insemination (IUI). It describes the first step in clinical decision making that is deciding whether IUI is a suitable option for the subfertile couple. The first developed multivariate model, predicting an ongoing pregnancy after IUI, was externally validated and found to be suitable for daily clinical use. The number of IUI treatment cycles to perform is discussed as well as the effect of a short period of bedrest after intrauterine insemination. We performed a long-term follow up of couples with unexplained subfertility who were initially randomized for expected management or immediate treatment with IUI and mild ovarian hyperstimulation (IUI-MOH). In search of an alternative treatment-option to prevent multiple pregnancies after IUI-MOH, but to maintain acceptable pregnancy rates we performed a pilot trial evaluating the effect of IVF with elective single embryo-transfer (IVF-eSET) versus IUI-MOH in treatment-naïve subfertile couples. Finally, we evaluated the effect of drop-out of subfertile couples from an IUI programme on cumulative pregnancy rates after IUI.

In **chapter 1** we describe that IUI is still one of the most frequently applied treatments for male and unexplained subfertility. There is a wide variation in practice in how to perform IUI due to the complexity of the treatment: such as type and use of ovarian stimulation, follicular monitoring and timing of ovulation, and the number of inseminations to perform. This variation in daily practice and the ensuing need for best practice has lead to a growing number of randomized controlled trials en meta-analyses. A number of the most relevant Cochrane reviews, RCT's and cohort-studies are summarized in short.

In **Chapter 2** the performance of a prediction model for an ongoing pregnancy after intra-uterine insemination is assessed in a general subfertile population by means of accuracy (calibration) and discriminative capacity. The prediction model has been evaluated among 1079 couples whom underwent 4244 IUI cycles in seven fertility clinics. There were 278 ongoing pregnancies that is an ongoing pregnancy rate of 6.6% per cycle. External validation of the model shows good calibration. The predicted probability never differed by more than 1.5% of the mean observed probability. The discriminative capacity is comparable to the one of the developement model (c-statistic 0.56).

Chapter 3 reports on the number of IUI treatment cycles that should be performed in terms of cumulative pregnancy rates. In total 3714 couples who underwent 15303 cycles of IUI were included. In 70% of cycles, mild ovarian hyperstimulation was used. Mean ongoing pregnancy rate was 5.6% per cycle. Ongoing pregnancy rates in the seventh, eighth and ninth cycle were 5.1%, 6.7% and 4.6%, respectively. The calculated cumulative ongoing pregnancy rate was 18% after the third cycle, 30% after the seventh cycle and 41% after the ninth cycle. We conclude that conducting IUI up to nine cycles instead of six is a valid option for subfertile couples.

In **chapter 4** we describe a randomized clinical trial which addresses the effectiveness of 15 minutes of immobilization in supine position subsequent to intrauterine insemination

versus immediate mobilization. In total 391 couples were randomised; 199 couples were allocated to 15 minutes of immobilisation after intrauterine insemination, and 192 couples were allocated to immediate mobilisation (control group). The ongoing pregnancy rate per couple was significantly higher in the immobilisation group than in the control group: 27% versus 18%; RR 1.5 (CI 1.1-2.2). Live birth rates were 27% in the immobilisation group and 17% in the control group: RR 1.6 (1.1-2.4). In the immobilisation group, the ongoing pregnancy rates in the first, second, and third treatment cycles were 10%, 10%, and 7%. The corresponding rates in the mobilisation group were 7%, 5%, and 5%. We conclude that in treatment with intrauterine insemination, 15 minutes' immobilisation after insemination is an effective modification and should be offered to all women treated with intrauterine insemination.

Chapter 5 reports on the long-term outcome in couples with unexplained subfertility and an intermediate prognosis initially randomized between expectant management and immediate treatment. The original randomized trial had found 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 in the first six months after diagnosis. The long-term cost-effectiveness of a policy of initial expectant management was unknown.

After the first six months couples (n=253, at 26 public clinics, the Netherlands) were 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. We found that 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, RR 0.99 (CI 0.85-1.1). Estimated mean costs per couple were € 3424 (CI € 880-€ 5968) in the EM group and € 6040 (CI € 4055-€ 8125) in the IUI-COS group resulting in an estimated saving of € 2616 per couple (CI € 385-€ 4847) in favour of EM. We conclude that initial EM for 6 months results in a considerable cost-saving with no delay in achieving pregnancy or jeopardizing the chance of pregnancy.

Chapter 6 describes a randomized controlled pilot trial in couples with unexplained subfertility and unfavorable prognosis for a spontaneous pregnancy, comparing the effectiveness of in vitro fertilization with elective single embryo transfer versus intrauterine insemination with controlled ovarian stimulation. We randomly allocated 116 women to IVF-eSET (n = 58) or IUI-COH (n = 58). There were 14 ongoing pregnancies (24%) in the IVF-eSET group and 12 pregnancies (21%) in the IUI-COS group (RR 1.17; CI 0.60-2.30). There were two twin pregnancies in the IVF-eSET group (14%) and two twin pregnancies and one triplet pregnancy in the IUI-COH group (25%). The conclusion was that one cycle of IVF-eSET might be as effective as three cycles of IUI-COS as primary treatment. However, elective single embryo transfer does not seem an effective strategy in preventing multiple pregnancies in this particular population. This trial provides evidence for the feasibility and highlights the importance of a large definitive trial to determine the effectiveness and side effects of both strategies.

Chapter 7 evaluates whether baseline characteristics and prognostic profiles differ between couples who drop-out from IUI and couples that continue IUI, and the reasons for couples dropping-out from IUI programs. A retrospective observational cohort study was performed in three fertility centres in the Netherlands. We studied 803 couples who underwent 3 579 IUI cycles. 221 Couples dropped-out (28%) which meant they had not reached an ongoing pregnancy or completed six cycles. Couples dropping-out completed 2.8(SD±1.4) cycles per couple compared to 4.5(SD±2.3) cycles per couple for those continuing treatment. Couples dropping-out had a higher female age, longer duration of subfertility and higher basal FSH. Mean prognosis to achieve an ongoing pregnancy after IUI at start of treatment was significantly lower (7.9%; SD±2.4) per cycle for couples who dropped-out compared to couples continuing treatment (8.5%; SD±2.5). Of the dropouts, 100 couples (45%) were actively censored from the IUI-programme. The other 121 couples (55%) who dropped-out did so due to personal reasons. 54 couples (24%) were lost to follow-up.

We found significant differences in prognostic profile between couples continuing treatment and couples dropping-out, although these differences seem limited from a clinical perspective. We conclude that overestimation of ongoing pregnancy rates after IUI due to couples dropping-out is limited.

Chapter 9

Algemene discussie en samenvatting

ALGEMENE DISCUSSIE

Intra-uteriene inseminatie (IUI) is een eeuwenoude behandelingsmethode. De eerste wetenschappelijke beschrijving van een homologe inseminatie was van de hand van de Schotse arts John Hunter in 1790. Hij adviseerde een man met ernstige hypospadie zijn semen direct na coïtus op te vangen in een spuitje en het in te brengen in de vagina van zijn vrouw. De vrouw werd zwanger na deze procedure.[1]

In het begin waren inseminatie-technieken vaak curieus en werden buitengewoon hoge succespercentages behaald. Zo werd in 1838 in Frankrijk een case serie beschreven door Girault, waarbij homologe inseminatie in 8 van de 10 gevallen succesvol bleek.[2] Diverse wetenschappelijke publicaties volgden tussen midden 1800 en begin 1900, waaruit bleek dat inseminatie succesvol werd toegepast door medische experts in Frankrijk, Engeland, Duitsland en de Verenigde Staten.[1,2] Tussen 1900 en de Tweede Wereld oorlog nam het aantal publicaties met betrekking tot homologe inseminatie af, door een groeiende interesse in kunstmatige inseminatie met donorsemen (KID). Tevens werden methoden voor cryopreservatie en ontdooien van semen ontwikkeld, hetgeen inseminatie met eerder door partner of donor geproduceerd semen mogelijk maakte. Hierdoor ontstond een nieuwe indicatie: "de afstandsindicatie": vrouwen van soldaten aan het front konden worden geïnsemineerd met het semen dat voor vertrek naar het front ingevroren was.[3]

Het duurde tot 1984 voordat de eerste echte gerandomiseerde klinische studie in The Lancet werd gepubliceerd.[4] Deze trial onderzocht de effectiviteit van IUI in 35 koppels waarvan de man verminderde semenkwaliteit had. Het artikel beschrijft in een cross-over design, de randomisatie van koppels in drie groepen: 14 koppels startten met eenmalig ovulatiegerichte coïtus gebaseerd op een basaal-temperatuur-curve (BTC), 7 koppels startten met eenmalig coïtus een dag na de LH-piek en 14 koppels startten met intra-uteriene inseminatie met bewerkt semen de dag na de LH-piek. Na 4 cycli switchten de koppels naar een van de twee andere procedures. Er ontstonden 8 zwangerschappen uit 39 IUI cycli, 1 zwangerschap na 34 cycli coïtus met een BTC en 0 zwangerschappen na LH-piek getimede coïtus. Gezien het feit dat de trial erg klein was kon de effectiviteit van IUI niet onomstotelijk bewezen worden.[5-8] Desalniettemin werd na deze studie nog maar weinig getwijfeld aan de effectiviteit van IUI als behandeling en het aantal publicaties van gerandomiseerde en non-gerandomiseerde studies nam exponentieel toe. [9-11] Het focus lag vanaf dat moment hoofdzakelijk op het uitbreiden van het aantal indicaties waarvoor IUI kon worden toegepast[12,13] en het perfectioneren van onderdelen van de IUI behandeling, zoals sperma-bewerkingsprocedures en evaluatie van follikelstimulerende medicatie.[14]

Intra-uteriene inseminatie voor onverklaarde en mannelijke subfertiliteit.

Ten tijde van de synthese van dit manuscript, vond een kritische herwaardering van bestaande en nieuwe literatuur plaats en werden Cochrane meta-analyses ge-update. Hieruit ontstond een hernieuwde vraagstelling naar de daadwerkelijke bijdrage van IUI

in de behandeling van onverklaarde en mannelijke subfertiliteit.[15,16] In het geval van onverklaarde subfertiliteit is er evidence dat IUI met ovariële stimulatie het percentage levendgeborenen vergroot in vergelijking tot IUI zonder stimulatie. Tevens is de likelihood op zwangerschap vergroot in de vergelijking van IUI versus getimede coïtus, beide in gestimuleerde cycli. Een goed gepowerde multi-center studie liet geen effect van IUI zonder stimulatie zien in vergelijking tot een afwachtende beleid.[17]

In de trial van Steures *et al.,* werd na randomisatie tussen IUI-MOH versus afwachtend beleid, bij onverklaarde subfertiliteit, na zes maanden geen verschil gevonden in aantal levendgeboren kinderen tussen beide armen. In een lange termijn follow-up van de studiepopulatie van deze trial, was de primaire hypothese dat na zes maanden min of meer gelijke aantallen levend geboren kinderen tussen beide groepen, de onbehandelde groep een voorsprong zou nemen in de tijd-tot-zwangerschap wanneer zij zouden starten met IUI-MOH. Echter, in de drie jaar tijd dat koppels uit beide groepen IUI-MOH, IVF/ICSI of geen verdere behandeling ondergingen, werd geen verschil gezien in tijd tot een doorgaande zwangerschap tussen de groep die initieel een afwachtend beleid had versus koppels die direct waren gestart met IUI-MOH. De groep die aanvankelijk voor een afwachtend beleid was gerandomiseerd had echter significant minder IUI en IVF cycli ondergaan.[18]

Kritische beschouwing van deze resultaten doet de vraag rijzen wat de effectiviteit van intra-uteriene inseminatie *an sich* is; de effectiviteit van de totale behandeling, indien überhaupt aanwezig, valt mogelijk eerder toe te schrijven aan ovariële hyperstimulatie, met als negatief bij-effect een vergroot risico op meerlingzwangerschappen.

Zoals geadviseerd in de Cochrane meta-analyse, dienen koppels dan ook adequaat geadviseerd worden over het risico van IUI-MOH en de mogelijkheid van alternatieve opties.[15]

Het risico op meerlingzwangerschappen, de zoektocht naar alternatieven

IVF met electieve single embryo transfer (IVF-eSET) wordt beschouwd als een mogelijk effectief middel in het voorkomen van meerlingzwangerschappen in een IVF-populatie. In verschillende studies.naar IVF-eSET worden meerlingpercentages van 0-5% gerapporteerd.[19-20] Op grond van deze data ontstond de hypothese dat IVF-eSET een effectief middel zou kunnen zijn om meerlingzwangerschappen te voorkomen in een behandelings-naïeve IUI-populatie. Verrassenderwijs werd in onze pilot-studie, waarbij gekeken werd naar IVF-eSET versus IUI een hoog meerlingpercentage (14% per doorgaande zwangerschap) gevonden, veroorzaakt door een aanzienlijk percentage double-embryo transfers (25%). Tevens werd in de beperkte tijd van 4 maanden, gelijke aantallen doorgaande zwangerschappen en levend geboren kinderen gevonden, hetgeen suggereert dat IVF-eSET met betrekking tot doorgaande zwangerschap en reductie van meerlingen niet superieur is aan IUI-MOH bij koppels met onverklaarde subfertiliteit. Een mogelijke verklaring voor onze bevindingen is de moeilijkheid van het selecteren van het embryo met het hoogste implantatiepotentieel.[21-24] Deze pilot-studie onderschrijft dan

ook de noodzaak tot het verrichten van een grote gerandomiseerde trial waarin IVF-eSET en IUI-MOH vergeleken worden, met een langere behandelduur en follow-up periode.
Recentelijk is de waarde van IVF bij onverklaarde subfertiliteit gepubliceerd in een Cochrane meta-analyse. In deze meta-analyse wordt geconcludeerd dat voor IVF nog onvoldoende is bewezen dat dit de beste behandelresultaten biedt voor onverklaarde subfertiliteit, mede ook aangezien de mogelijke bijwerkingen en kosten nog onvoldoende zijn onderzocht.[25]
Wanneer de beslissing tot het starten van een behandeling met IUI, doorgaans met ovariële stimulatie, is gemaakt, zijn zwangerschapspercentages tot 40% na 9 behandelcycli haalbaar. Aangezien de essentie van voortplantingstechnieken zit in de herhaling van een behandeling, zouden koppels niet gemotiveerd moeten worden IUI over te slaan of voortijdig te staken en (te) snel over te gaan naar meer invasieve behandelmethoden als IVF/ICSI voordat meerwaarde van deze behandeling onomstotelijk bewezen is.
In de huidige tijd is een zorgwekkende verschuiving zichtbaar naar het eerder, frequenter en agressiever behandelen met invasieve voortplantingstechnieken zoals IVF-ICSI. In de maatschappij van nu wordt van een koppel verwacht in een zo kort mogelijke tijd een gezin te stichten. De mogelijkheid van een aanvullende periode afwachtend beleid na diagnostiek in geval van subfertiliteit is buitengewoon lastig voor een koppel.[17]
Voortplantingstechnieken lijken in toenemende mate verworden te zijn tot producten waarvoor wanhopige koppels bereid zijn veel geld neer te leggen.[26] Tenslotte zijn er steeds meer aanwijzingen dat IVF de mogelijke aanzet zou kunnen zijn voor de toenemende incidentie van obesitas, hypertensie, gestoorde bloedglucose, triglyceriden levels en subklinische hypothyreoïdie bij nageslacht ontstaan na IVF.[27]

Implicaties voor toekomstig onderzoek

In Nederland wordt in 90% van de ziekenhuizen IUI met of zonder stimulatie verricht, wat resulteert in meer dan 28.000 cycli per jaar. Ongeveer 10% van alle doorgaande zwangerschappen resulteerde in een meerlingzwangerschap.[28] In een relatieve jonge populatie met onverklaarde of milde mannelijke subfertiliteit waarbij gonadotrofinen worden gebruikt, ligt dit meerlingpercentage soms zelfs hoger.[29]
Voor sommigen is het gebruik van gonadotrofinen een "20ste eeuw-relikwie" geworden en wordt er gepleit voor het gebruik van kosten-effectieve alternatieven zoals Clomifeencitraat.[30] Voorhanden zijnde studies over dit onderwerp zijn echter relatief beperkt in aantal en grootte en er is dan ook behoefte aan grotere studies.[31,32]
In de preventie van meerlingzwangerschappen is de zoektocht naar alternatieve behandelstrategieën nog geenszins een gesloten boek. Mogelijk zal de INeS-studie waarin IUI-MOH, IVF-SET en IVF in de gemodificeerde natuurlijke cyclus onderzocht wordt, een antwoord op deze vraag geven.[33]
Hoewel tegenwoordig steeds gecompliceerder, zijn grotere trials nodig die het effect van afwachtend beleid evalueren versus IUI-MOH en IVF om het daadwerkelijke effect van deze behandelingen vast te stellen bij patiënten met onverklaarde subfertiliteit.

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SAMENVATTING

Dit proefschrift rapporteert over diverse aspecten van een optimale behandeling van subfertiele koppels met intra-uteriene inseminatie (IUI).

Allereerst wordt de klinische besluitvorming beschreven, de beslissing of IUI een geschikte behandeling is voor het subfertiele koppel. Hiertoe werd een eerder ontwikkeld multivariabel prognostisch model, dat de kans op een doorgaande zwangerschap voorspelt na IUI, extern gevalideerd en geschikt bevonden voor dagelijks klinisch gebruik.

Vervolgens wordt in dit proefschrift besproken hoeveel IUI-behandelcycli moeten worden uitgevoerd voor een optimaal behandelresultaat, alsmede het effect van een korte tijd bedrust na een intra-uteriene inseminatie.

Verder wordt een lange termijn follow up beschreven van koppels met onverklaarde subfertiliteit, initieel gerandomiseerd voor een afwachtend beleid of directe behandeling met IUI en milde ovariële hyperstimulatie (IUI-MOH).

In de zoektocht naar een alternatieve behandeling ter voorkoming van meerlingen na IUI-MOH en behoud van acceptabele zwangerschapscijfers, worden de resultaten van een pilot-trial gerapporteerd, waarin het effect van IVF-eSET versus IUI-MOH werd geëvalueerd in behandelingsnaïeve subfertiele koppels. Ten slotte wordt in dit proefschrift gekeken naar het effect van uitval van subfertiele koppels uit een IUI-programma op de cumulatieve zwangerschapscijfers na deze behandeling.

In **hoofdstuk 1** beschrijven we dat IUI nog steeds een van de meest toegepaste behandelingen is voor mannelijke en onverklaarde subfertiliteit. Er is een enorme variatie in klinische praktijk tussen centra ten gevolge van de complexiteit van de behandeling. Voorbeelden zijn: het gebruik van, en de soort ovariële stimulatie, monitoring van folliculaire ontwikkeling en timing van ovulatie, en het aantal inseminaties dat kan worden verricht in een behandeling. Deze variatie in dagelijkse praktijk en de toenemende behoefte aan "best practice" heeft geleid tot een groeiend aantal klinische trials en meta-analyses. Een aantal van de meest relevante Cochrane reviews, gerandomiseerde studies en cohortstudies wordt in het kort besproken.

In **hoofdstuk 2** wordt beschreven hoe goed het eerder ontwikkelde predictiemodel de kans op een doorgaande zwangerschap na IUI voorspelt in een subfertiele populatie, in termen van calibratie en onderscheidend vermogen. Hiertoe werd dit model geëvalueerd op 1079 koppels die 4244 IUI cycli ondergingen in zeven Nederlands ziekenhuizen. Er ontstonden 278 doorgaande zwangerschappen, hetgeen neerkomt op een zwangerschapspercentage van 6,6% per cyclus.

De calibratie van het model was goed. De voorspelde kans op een zwangerschap verschilde nooit meer dan 1,5% van het gemiddelde geobserveerde percentage. Het discriminerend vermogen van het predictie model in deze populatie was vergelijkbaar met dat van de populatie waarmee het model was ontwikkeld (c-statistic 0,56).

Hoofdstuk 3 rapporteert over het aantal IUI cycli dat bijdraagt aan een verhoging van het cumulatieve zwangerschapscijfer. In totaal werden 3714 koppels geïncludeerd die in totaal

15303 IUI cycli ondergingen. In 70% van de cycli werd milde ovariële hyperstimulatie toegepast. Het gemiddeld doorgaande zwangerschapspercentage was 5,6% per cyclus. Doorgaande zwangerschapspercentages in de zevende achtste en negende cyclus waren respectievelijk 5,1%, 5,7% en 4,6%. Het cumulatief zwangerschapscijfer was 18% na de derde cyclus, 30% na de zevende cyclus en 41% na de negende cyclus. Hieruit werd geconcludeerd dat het continueren van IUI tot en met 9 cycli, in plaats van zes, een goede optie is voor subfertiele koppels.

In **hoofdstuk 4** wordt een gerandomiseerde studie beschreven waarin de effectiviteit van 15 minuten immobilisatie in steensnede ligging in aansluiting op IUI wordt onderzocht. In totaal werden er 391 koppels gerandomiseerd waarvan er 199 werden gerandomiseerd voor 15 minuten immobilisatie en 192 koppels voor directe mobilisatie in aansluiting op IUI (de controlegroep). Het doorgaand zwangerschapscijfer per koppel was significant hoger in de groep waarbij immobilisatie werd toegepast: 27% versus 18%; RR 1.5 (CI 1.1-2.2). Het percentage levend geboren kinderen was 27% in de immobilisatie-groep en 17% in de controle groep: RR 1.6 (1.1-2.4). In de immobilisatie-groep was het doorgaand zwangerschapspercentage in de eerste, tweede en derde cyclus 10%, 10% en 7%, in de controlegroep respectievelijk 7%, 5% en 5% per cyclus. Hieruit kon geconcludeerd worden dat 15 minuten blijven liggen in aansluiting aan de intra-uteriene inseminatie een effectieve en eenvoudig toepasbare aanpassing is van de behandeling en hierom moet worden aangeboden aan alle vrouwen die worden behandeld met IUI.

Hoofdstuk 5 rapporteert over de lange termijn uitkomsten van koppels met onverklaarde subfertiliteit en een intermediaire prognose, eerder behandeld in een trial waarbij gerandomiseerd werd tussen een afwachtend beleid (AB) en IUI-MOH.

Uit deze gerandomiseerde trial bleek dat behandeling met IUI-MOH geen toename in het aantal doorgaande zwangerschappen liet zien in vergelijking tot een afwachtend beleid in de eerste zes maanden nadat de diagnose onverklaarde subfertiliteit was gesteld. Naast lange termijn zwangerschapscijfers werd in onze studie ook gekeken naar de kosteneffectiviteit van AB.

Na de eerste zes maanden (einde van de trial) werden koppels behandeld conform lokaal protocol (n=253 koppels in 26 Nederlands ziekenhuizen), hetgeen doorgaans starten van of continueren met IUI-MOH betekende, gevolgd door IVF. Koppels werden tot 3 jaar na randomisatie gevolgd . Zowel doorgaande zwangerschappen als aard en frequentie van reproductieve technieken werden hierbij bekeken.

Er werd geen statistisch significant verschil gevonden in tijd tot een doorgaande zwangerschap tussen beide groepen (log rank test P=0.98). Cumulatieve doorgaande zwangerschapscijfers waren in de AB-groep en de IUI-MOH groep respectievelijk 72% en 73%, RR 0.99 (CI 0.85-1.1). Geschatte gemiddelde kosten per koppel in de AB-groep waren: € 3424 (CI € 880-€ 5968), versus € 6040 (CI € 4055-€ 8125) in de IUI-MOH groep. Derhalve resulteert een afwachtend beleid in een gemiddelde kostenbesparing van € 2616 per koppel (CI € 385-€ 4847)

De conclusie van deze studie is dan ook dat een initieel afwachtend beleid van zes maanden tot een aanzienlijke kostenbesparing leidt, zonder compromittering van tijd tot een doorgaande zwangerschap of zwangerschapscijfer.

In hoofdstuk 6 wordt een gerandomiseerde pilot-trial onder koppels met onverklaarde subfertiliteit en een ongunstige prognose op spontane zwangerschap beschreven, waarbij de effectiviteit van IVF-eSET wordt vergeleken met IUI-MOH. 116 koppels werden in deze studie gerandomiseerd tussen 1 cyclus IVF-eSET (n=58) of 3 cycli IUI-MOH (n=58). In de IVF-eSET groep ontstonden 14 doorgaande zwangerschappen (24%) versus 12 (21%) in de IUI-MOH groep (RR 1.17; CI 0.60-2.30). In de IVF-eSET groep was sprake van twee tweelingzwangerschappen (14% per doorgaande zwangerschap) en in de IUI-MOH groep werden twee tweeling- en één drieling zwangerschap gezien (25% per doorgaande zwangerschap). De conclusie van deze pilot-trial was dat één cyclus IVF-eSET mogelijk even effectief is als drie cycli IUI-MOH in deze populatie. Electieve single embryo transfer lijkt echter geen effectieve strategie ter voorkoming van meerlingzwangerschappen in deze specifieke populatie. Op basis van de aangetoonde haalbaarheid en pilotdata van deze studie lijkt een grote gerandomiseerde studie opportuun, waarin effectiviteit en bijwerkingen van beide behandelstrategieën vastgesteld kunnen worden.

Hoofdstuk 7 beschrijft karakteristieken en prognostische profielen van koppels die uit een IUI-programma vallen ten opzichte van koppels die de behandeling voort zetten. Hiertoe werd een retrospectieve, observationele cohortstudie verricht onder patiënten uit drie klinieken in Nederland. 803 Koppels die 3579 IUI cycli ondergingen werden onderzocht. Van deze koppels stopten 221 koppels (28%) voortijdig (voor het bereiken van een doorgaande zwangerschap of afronding van 6 IUI cycli) met de behandeling. Koppels die de IUI behandeling staakten, ondergingen gemiddeld 2.8 (SD±1.4) afgeronde IUI cycli per koppel in vergelijking tot 4.5 (SD±2.3) cycli per koppel die de IUI behandeling continueerden. Bij koppels die de behandeling voortijdig stopten werd een hogere leeftijd van de vrouw, een langere subfertiliteitsduur en een hoger basaal FSH gezien. De gemiddelde kans op zwangerschap per cyclus aan het begin van de behandeling was significant lager voor koppels die hun behandeling waren gestopt (7.9%; SD±2.4) in vergelijk tot koppels die de behandeling hadden voortgezet (8.5%; SD±2.5). Van de 221 koppels die stopten werd aan 100 koppels (45%) actief geadviseerd de behandeling te staken. Bij de resterende 121 koppels (55%) werd de behandeling om persoonlijke redenen gestaakt. Van 59 koppels (27%) kon de reden voor het voortijdig stoppen van de behandeling niet worden achterhaald, zij verschenen niet meer in het ziekenhuis waar zij behandeld werden.

Concluderend werden statistisch significante, maar klinisch weinig relevante verschillen gevonden in prognostische profielen tussen koppels die een IUI behandeling voortijdig staken in vergelijk tot koppels die deze behandeling wel afronden. Overschatting van cumulatieve zwangerschapscijfers na IUI ten gevolge van selectieve uitval van patiënten is derhalve zeer gering.

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Portfolio

PORTFOLIO

Course

Clinical epidemiology and biostatistics.

Oral- and poster presentations

Custers IM, Veen van der F, Steures P, Steeg van der JW, Hompes PGA, Mol BWJ. Impact of patient dropout on the estimates of pregnancy rates after intrauterine insemination.
Posterpresentation, ESHRE 2005, Copenhagen, Denmark.

Custers IM, Steures P, van der Steeg JW, van Dessel HJHM, Bernardus RE, Bourdrez P, Koks CAM, Riedijk WJ, Burggraaff JM, van der Veen F, Mol BWJ.External validation of a prediction model for an ongoing pregnancy after intrauterine insemination.
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Custers IM, Steures P, Hompes PGA, Flierman PA, van Kasteren Y, van Dop PA, van der Veen F, Mol BWJ. Intrauterine insemination: How many cycles should we perform?
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van Rumste MME, **Custers IM**, van der Veen F, van Wely M, Evers JLH and Mol BWJ. Does the number of follicles influence pregnancy rates in intrauterine insemination with mild ovarian hyperstimulation: a meta-analysis.
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Curriculum vitae

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Inge Custers werd op 21 juli 1978 geboren als tweede van drie kinderen van Angèle en Hans Custers in Nijmegen. Ze groeide op in Malden. In 1996 behaalde zij haar Atheneum diploma aan de Stedelijke Scholengemeenschap Nijmegen. In datzelfde jaar startte zij met de studie geneeskunde aan de Vrije Universiteit in Amsterdam.

In 2002 kreeg zij in aansluiting op haar oudste co-schap een baan als ANIOS in het Spaarne Ziekenhuis op de afdeling Obstetrie en Gynaecologie. Twee jaar later, in 2004, ging zij als IVF-arts aan het werk bij het Centrum Voor Voortplantingsgeneeskunde van het AMC. In datzelfde jaar begon zij aan een promotietraject onder leiding van Prof. dr. F. van der Veen en Prof. dr. B.W.J. Mol over verschillende aspecten van de intra-uteriene inseminatie behandeling.

In 2008 startte zij haar opleiding tot gynaecoloog binnen het cluster AMC, in het Spaarne Ziekenhuis in Hoofddorp (opleiders Dr. M.H. Emanuel en Dr. A. Vollebregt). In 2010 vervolgde zij haar opleiding in het AMC Amsterdam (opleiders Prof. dr. M.J. Heineman en Prof. dr. J.A.M. van der Post).

Inge is getrouwd met Dannis van Vuurden en zij hebben samen drie kinderen: Madelief, Max & Gijs.