

Intrauterine insemination with controlled ovarian hyperstimulation versus expectant management for couples with unexplained subfertility and an intermediate prognosis: a randomised clinical trial

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Summary

Background Intrauterine insemination with controlled ovarian hyperstimulation is commonly used as first-line treatment for couples with unexplained subfertility. Since such treatment increases the risk of multiple pregnancy, a couple's chances of achieving an ongoing pregnancy without it should be considered to identify those most likely to benefit from treatment. We aimed to assess the incremental effectiveness of intrauterine insemination with controlled ovarian hyperstimulation compared with expectant management in couples with unexplained subfertility and an intermediate prognosis of a spontaneous ongoing pregnancy.

Methods 253 couples with unexplained subfertility and a 30–40% probability of a spontaneous ongoing pregnancy within 12 months were randomly assigned either intrauterine insemination with controlled ovarian hyperstimulation for 6 months or expectant management for 6 months. The primary endpoint of this hospital-based study was ongoing pregnancy within 6 months. Analysis was by intention to treat. This trial is registered with the Dutch Trial Register and as an International Standard Randomised Clinical Trial, number ISRCTN72675518.

Findings Of the 253 couples enrolled, 127 were assigned intrauterine insemination with controlled ovarian hyperstimulation and 126 expectant management. In the intervention group, 42 (33%) women conceived and 29 (23%) pregnancies were ongoing. In the expectant management group, 40 (32%) women conceived and 34 (27%) pregnancies were ongoing (relative risk 0.85, 95% CI 0.63–1.1). There was one twin pregnancy in each study group, and one woman in the intervention group conceived triplets.

Interpretation A large beneficial effect of intrauterine insemination with controlled ovarian hyperstimulation in couples with unexplained subfertility and an intermediate prognosis can be excluded. Expectant management for 6 months is therefore justified in these couples.

Introduction

About 10% of couples who want to have a child fail to conceive within a year of regular unprotected intercourse.¹ In 20–30% of these couples, basic fertility investigations do not identify a cause of the subfertility.² For these couples, intrauterine insemination with controlled ovarian hyperstimulation is reported to be more effective than intrauterine insemination without controlled ovarian hyperstimulation, intracervical insemination, or timed intercourse.^{3–9}

Although the idea of intrauterine insemination is fairly straightforward, there are some drawbacks. Treatment itself can be a burden to the couple, is associated with high financial costs, and the addition of controlled ovarian hyperstimulation increases the risk of multiple pregnancy.¹⁰ For this reason, an appropriate balance of effectiveness and safety is essential. There have been no data available that allow distinction between couples with unexplained subfertility who would benefit from intrauterine insemination with controlled ovarian hyperstimulation and those who would not. The only way to make such a distinction would be to use a couple's prognostic profile.¹¹

For couples with an intermediate probability of achieving an ongoing pregnancy in the next few months, intrauterine insemination with controlled ovarian hyperstimulation should lead to a substantial increase in the pregnancy rate to warrant the drawbacks of this treatment.

We designed a trial to assess the effectiveness of intrauterine insemination with controlled ovarian hyperstimulation compared with expectant management in couples with unexplained subfertility and an intermediate prognosis of a spontaneous ongoing pregnancy in the next 12 months.

Methods

Patients

Between June 1, 2002, and July 1, 2005, 26 fertility centres in the Netherlands recruited couples for this study. The eligibility criteria were: that the couple had not conceived after at least a year of frequent unprotected intercourse; the woman was younger than 39 years; and the woman had a regular menstrual cycle. The local ethics committee of each participating centre approved the study, and written informed consent was obtained.

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Procedures

We did a basic fertility assessment of each couple according to the guidelines of the Dutch Society of Obstetrics and Gynaecology.¹² This assessment included a medical history, cycle monitoring, semen analysis, postcoital test, and investigation of tubal function. In the medical history, female age, duration of subfertility, and whether subfertility was a primary or secondary disorder for the woman were documented. Duration of subfertility was defined as the time from when the couple started actively trying to conceive to the time of randomisation. If the couple had a previous pregnancy that had not resulted in a livebirth, duration of subfertility was defined as the time from the first day of the pregnancy to the time of randomisation. Subfertility was judged to be a secondary disorder if the woman had previously conceived in the current or in a previous relationship, irrespective of pregnancy outcome.

The menstrual cycle was regarded as being regular if the duration was between 23 days and 35 days, with variation between cycles of less than 8 days. Presence of ovulation was assessed by means of a basal body temperature curve, a midluteal serum progesterone concentration, or by sonographic monitoring of the cycle. Semen analysis was done for each couple at least once; volume, concentration, and motility were assessed, and a total motile count was calculated. At least one postcoital test was done for each couple during the basic fertility assessment. The test was planned according to the basal body temperature curve or findings of ultrasonography. If the timing was based on the basal body temperature curve, the postcoital test was scheduled the day before the expected ovulation. If it was based on ultrasonography, the postcoital test was done when the dominant follicle was at least 18 mm in diameter. The postcoital test result was regarded as normal if at least one progressive spermatozoon was seen in one of five high-power fields at 400 times magnification.

For the assessment of tubal function, the participating centres had two different approaches. With the first approach, tubal function was assessed by a chlamydia antibody test that used immunofluorescence technique or an EIA (BioMerieux, Paris, France; Medac, Wedel, Germany; Savyon Diagnostics, Marne La Valle, France). The result was judged to be positive if the titre was greater than 1 to 16 with the immunofluorescence technique or greater than 1·1 with the EIA. If the result was positive, the woman was scheduled for hysterosalpingography or laparoscopy. Tubal pathology was judged to be absent if the chlamydia antibody test was negative or subsequent hysterosalpingography, laparoscopy, or both showed two normal patent tubes. With the second approach, tubal function was directly assessed by hysterosalpingography or laparoscopy.

After completion of the basic fertility assessment, we calculated the prognosis of a spontaneous ongoing pregnancy resulting in a livebirth during the next year. We defined a spontaneous pregnancy as one that occurred without treatment. Ongoing pregnancy was defined as the

presence of fetal cardiac activity at transvaginal sonography at a duration of gestation of at least 12 weeks. We calculated the prognosis using the prediction model of Hunault and colleagues.¹³ This model incorporates the woman's age, duration of subfertility, primary or secondary subfertility, referral status, result of the postcoital test, and percentage of progressive motile semen as variables. Each variable is converted into a point score. The total point score of each couple corresponds to a prognosis of a spontaneous ongoing pregnancy. Couples with unexplained subfertility and an intermediate prognosis of a spontaneous ongoing pregnancy within the next 12 months were eligible for this study. An intermediate prognosis was defined as the chance of a spontaneous ongoing pregnancy between 30% and 40% within the next 12 months.

Couples were randomly allocated intrauterine insemination with controlled ovarian hyperstimulation or expectant management for 6 months. The randomisation sequence was computer generated in balanced block multiples of two or four, stratified by centre. The sequence was concealed, and sealed opaque envelopes containing details of the treatment allocation were assembled by an independent person. Clinicians in the participating centres enrolled the couple and subsequently opened the next envelope. The inclusion was then confirmed to the trial coordinator by fax.

Couples assigned intrauterine insemination with controlled ovarian hyperstimulation started treatment during the next menstrual cycle. Those for whom the tubal function had been assessed only by chlamydia antibody test at the time of randomisation sometimes had hysterosalpingography or laparoscopy before the first cycle or after three cycles of treatment.

Controlled ovarian hyperstimulation, semen preparation, and insemination regimens were done according to hospital-specific protocols. The study protocol recommended the use of follicle-stimulating hormone for controlled ovarian hyperstimulation. In general, baseline transvaginal sonography was done on cycle day 3 to exclude ovarian cysts larger than 20 mm. Thereafter, the women started daily subcutaneous injections of follicle-stimulating hormone (Gonal F [Serono Benelux, The Hague, Netherlands] or Puregon [Organon, Oss, Netherlands]) or human menopausal gonadotropin (Menopur [Ferring, Hoofddorp, Netherlands]) in mean doses of 75 IU, ranging from 37 IU to 150 IU, until transvaginal sonography showed at least one follicle of at least 16 mm in diameter. Ovulation was then induced with 5000 IU or 10000 IU of human chorionic gonadotropin (Pregnyl [Organon]) and women were inseminated 36–40 h later. We withheld human chorionic gonadotropin and intrauterine insemination if there were more than three follicles of diameter at least 16 mm, or five of diameter at least 12 mm. 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

The prediction model can be used from the following URL: <http://www.freya.nl/probability.php>

0.2 mL and 1.0 mL. We did the insemination irrespective of the total motile count after preparation on the scheduled day.

Couples assigned expectant management were followed up until an ongoing pregnancy occurred or for 6 months if no pregnancy occurred. If a pregnancy miscarried, follow-up continued until the next pregnancy or the end of the 6 months. Hysterosalpingography or laparoscopy was allowed in these 6 months.

The primary endpoint was ongoing pregnancy within 6 months. Secondary endpoints were clinical pregnancies, miscarriages, ectopic pregnancies, multiple pregnancies, and livebirth. Clinical pregnancy was defined as the presence of a yolk sac at transvaginal sonography at a gestational age of 7 weeks. Miscarriage was defined as non-vital pregnancy at transvaginal sonography or at the loss of a visible pregnancy.

Statistical analysis

We assumed an ongoing pregnancy rate in the expectant management group of 22% in 6 months (ie, 30–40% in 12 months) based on the model of Hunault and colleagues,¹³ and stated that intrauterine insemination with controlled

ovarian hyperstimulation would be warranted only with an ongoing pregnancy rate after 6 months of 35% or more. To exclude a difference larger than 13%, 125 couples were needed in each group ($\alpha=5\%$, $\beta=80\%$).

We did the analyses by intention to treat. We included all pregnancies that occurred in intrauterine insemination cycles done within 6 months after randomisation, as well as those that occurred spontaneously in this period. We expressed the treatment effect of intrauterine insemination with controlled ovarian hyperstimulation both as relative risk and as absolute risk with their 95% CI. We plotted Kaplan-Meier curves to illustrate the differences in time to pregnancy between the groups, and compared these curves by log-rank test. In subgroup analyses, we investigated the pregnancy rate per intrauterine insemination cycle and the relation of the follicular growth patterns to the occurrence of pregnancy. This trial is registered with the Dutch Trial Register and as an International Standard Randomised Clinical Trial, number ISRCTN72675518.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

4588 consecutively presenting couples with regular cycles underwent basic fertility assessment in the participating centres. All variables needed for calculation of prognosis were available for 3221 couples (figure 1). Of the couples with unexplained subfertility and an intermediate prognosis of a spontaneous ongoing pregnancy within 12 months, 256 were not invited or declined to participate. Informed consent was obtained from the remaining couples (figure 1). Baseline characteristics are shown in table 1. Some couples had a prognosis of less than 30% or greater than 40%. These couples were erroneously included owing to miscalculations at baseline, but according to the intention-to-treat principle we kept them in the analysis. 17 (7%) men had a total motile count of less than 10 million, seven in the intervention group and ten in the expectant management group. However, the motility of the semen is the only variable taken into account in the prognostic model; after all data had been entered into the prediction model, these couples still had a prognosis of between 30% and 40%, making them eligible for the study. Although we applied an upper limit for maternal age of 38 years, one woman assigned intrauterine insemination with controlled ovarian hyperstimulation was aged 40 years, and according to the intention-to-treat principle we included her in the final analysis.

All women included in the study had their fallopian tubes assessed by a chlamydia antibody test, hysterosalpingography, or laparoscopy before randomisation. In 96 (76%) women assigned to the intervention group and in

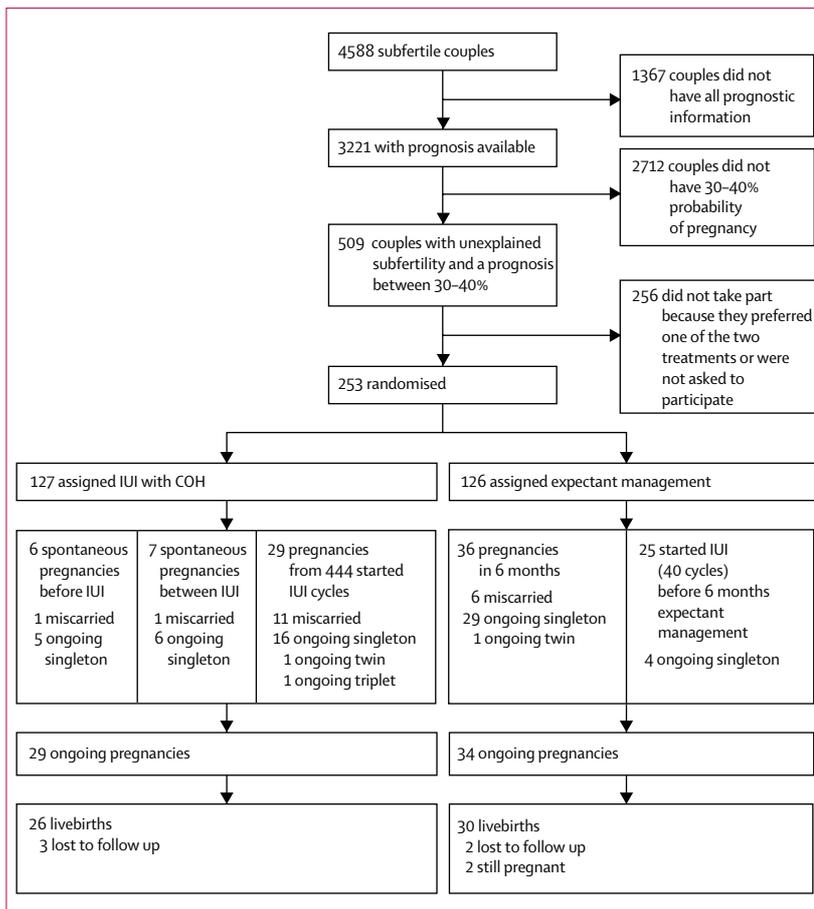


Figure 1: Trial profile
IUI=intrauterine insemination. COH=controlled ovarian hyperstimulation.

94 (75%) assigned expectant management, tubal function had been assessed by hysterosalpingography or laparoscopy before randomisation. One-sided tubal occlusion was found in five (5%) women in the intervention group, and two (2%) in the expectant management group. At 6-month follow-up, eight women in the intervention group and ten women in the expectant management group underwent hysterosalpingography or laparoscopy. Of these women, only one, in the expectant management group, had one-sided tubal occlusion. Taken together, in both groups, 104 (82%) women underwent hysterosalpingography or laparoscopy; of these women, five (5%) in the intervention group and three women (3%) in the expectant management group had one-sided tubal occlusion. No couples were lost to follow-up.

Pregnancy data are shown in figure 1. In the intervention group, six women conceived spontaneously; one miscarried. Of the 121 couples who started treatment, seven conceived spontaneously between cycles; again, one miscarried. 29 pregnancies occurred after treatment, of which 11 miscarried. Three couples in the intervention group continued the treatment after miscarriage. In these couples, one ongoing pregnancy occurred. Overall in the treatment group, one twin pregnancy, and one triplet pregnancy occurred. In 26 of the ongoing pregnancies, the infants were born alive. Both infants were born alive from the twin pregnancy. The triplet pregnancy was reduced to a twin pregnancy and both infants were born alive. In three couples, follow-up until livebirth was not possible because they changed address.

In the group assigned expectant management for 6 months, 25 (20%) couples started intrauterine insemination with controlled ovarian hyperstimulation before 6 months: four couples after 3 months, five after 4 months, and 16 after 5 months. The four (3%) pregnancies that occurred in these cycles were all ongoing. 36 (29%) women conceived spontaneously; six miscarried. All pregnancies that were followed up until livebirth (30, 88%) resulted in livebirth of at least one child. Both infants were born alive in the twin pregnancy. In two couples, follow-up until livebirth was not possible because they changed address.

After 6 months, 42 (33%) pregnancies had occurred in the intervention group and 40 (32%) in the expectant-management group (figure 1). The miscarriage rates were 31% and 15%, respectively. The number of ongoing pregnancies was 29 (23%) in the intervention group and 34 (27%) in the expectant-management group; thus, the relative risk of ongoing pregnancy was 0.85 (95% CI 0.63–1.1), and the absolute risk difference in favour of the expectant-management group was 4% (95% CI from 15% in favour of the expectant-management group to 6% in favour of the intervention group). The relative risk for livebirth was 0.86 (0.54–1.4).

Kaplan-Meier analysis showed no significant differences in time to pregnancy (figure 2, log-rank test, $p=0.41$). Of

	IUI with COH (n=127)	Expectant management (n=126)
Mean maternal age, years (SD; range)	33 (3.4; 23–40)	33 (3.1; 24–38)
Mean duration of subfertility, years (SD; range)	2.0 (0.5; 1–3)	1.9 (0.5; 1–3)
Primary subfertility, number (%)	99 (78%)	96 (76%)
Median menstrual cycles per year (IQR; range)	13 (2.0; 10–15)	13 (1.0; 10–15)
Mean FSH IU/L (SD; range)	7.0 (2.1; 2–15)	6.7 (2.2; 3–15)
Median oestradiol nmol/L (IQR; range)	0.14 (0.12; 0.01–0.75)	0.14 (0.14; 0.05–0.75)
Median semen analyses: TMC (IQR; range)	68 (109; 1.3–460)	60 (125; 1.4–507)
Mean % progressive motile semen (SD; range)	44 (17; 16–92)	41 (19; 6–90)
Positive CAT result	10/92 (11%)	14/95 (15%)
HSG one-sided tubal pathology	3/70 (4%)	2/77 (3%)
Laparoscopy one-sided tubal pathology	2/26 (8%)	0/17
Mean prognosis % (SD; range)	35 (5.5; 17–49)	35 (6.2; 14–55)

IUI=intrauterine insemination. COH=controlled ovarian hyperstimulation. FSH=follicle-stimulating hormone. TMC=total motile count. CAT=chlamydia antibody test. HSG=hysterosalpingography. *Data available at time of randomisation for 100 couples in the intervention group and 106 in expectant-management group for FSH; 57 and 58 couples, respectively, for oestradiol; in 92 and 95 couples for CAT results; 70 and 77 couples for HSG; and 26 and 17 couples for laparoscopy.

Table 1: Baseline characteristics

the 444 cycles of intrauterine insemination started in the couples assigned to the intervention group, 63 (14%) cycles were cancelled. The pregnancy rate per started cycle was 6.5%, with an ongoing pregnancy rate of 4.1% per started cycle. In 47 (11%) cycles, anti-oestrogenic medication (clomifene citrate) was used for controlled ovarian hyperstimulation. In these cycles, three ongoing pregnancies occurred (6.4% per started cycle). Multifollicular growth, defined as more than one follicle with a diameter of at least 15 mm, occurred in 42% of the inseminated cycles. In 70% of the inseminated cycles more than one follicle with a diameter of 10 mm was present at the time of human chorionic gonadotropin

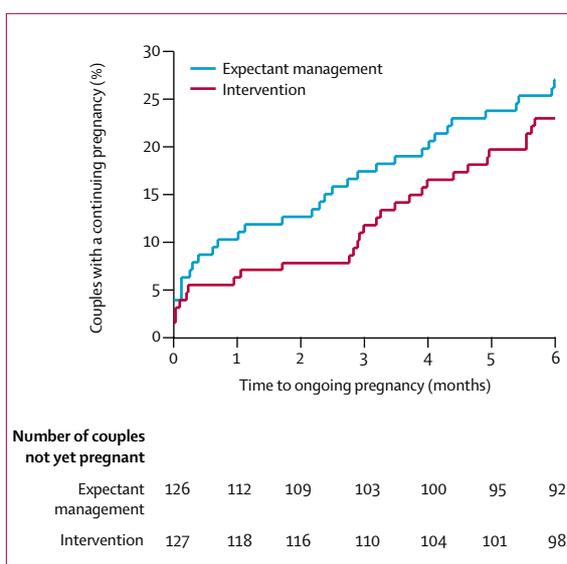


Figure 2: Kaplan-Meier analysis of time to ongoing pregnancy in the two groups

	Cycles (n=353)	All ongoing pregnancies (% per cycle)	Twin pregnancies	Triplet pregnancies
>10 mm				
Monofollicular growth	106 (30%)	4 (4%)	0	0
Multifollicular growth	247 (70%)	12 (5%)	1	1
>15 mm				
Monofollicular growth	204 (58%)	8 (4%)	1	1
Multifollicular growth	149 (42%)	8 (5%)	0	0

Table 2: Pregnancies after intrauterine insemination in relation to follicular growth patterns

injection. Table 2 shows the pregnancies in relation to follicular growth. No clear differences in pregnancy rates were seen between the cycles with monofollicular and multifollicular growth.

Discussion

We compared the effectiveness of intrauterine insemination and controlled ovarian hyperstimulation with that of expectant management in couples with unexplained subfertility and an intermediate prognosis.¹⁴ Our findings exclude a large beneficial effect of intrauterine insemination with controlled ovarian hyperstimulation in these couples.

Only couples with a probability of a spontaneous ongoing pregnancy within 12 months of between 30% and 40% were recruited—ie, a probability of 22% within 6 months. Since we could rule out a substantial treatment effect in this group, treatment is unlikely to be effective in couples with a greater probability of pregnancy than 40%. Thus, even though we narrowed down our population by using a prognostic profile, our findings are generalisable to a larger population—ie, all couples with unexplained subfertility and a probability of pregnancy of more than 30%.

There are at least three possible limitations of this study. First, the study protocol recommended use of follicle-stimulating hormone for controlled ovarian hyperstimulation, but in 11% of cycles, an anti-oestrogenic drug (clomifene citrate) was used. However, a Cochrane Review found no significant difference in livebirth rates per couple between intrauterine insemination with follicle-stimulating hormone or with anti-oestrogenic drugs.¹⁵ Second, differences in local intrauterine-insemination protocols among the 26 participating centres might have affected the results. Such variation is likely to occur in routine fertility treatment. Third, our ongoing-pregnancy rate per started cycle of 4.1% is lower than the 9% per intrauterine-insemination cycle described in previous studies.^{5,6} The explanation for this difference can be found in our study population as well as in the results of previous studies. Some of the couples participating in our study had male subfertility, and in some cases the presence of endometriosis, non-occlusive tubal pathology, and one-sided tubal pathology could not be ruled out since hysterosalpingography or laparoscopy were not done. Nevertheless, all couples had an intermediate prognosis, and, more importantly, randomisation generated equal distribution of the couples over the two treatment groups.

Since the pregnancy rate in the expectant-management group was in accordance with that predicted, these issues are unlikely to have had a substantial effect on the overall pregnancy rate in either group. Our findings are similar to those of Guzick and co-workers.⁶ In both studies, 33% of the couples conceived within four treatment cycles, either as a result of treatment or spontaneously. In both studies, 23% of the couples had an ongoing pregnancy, and miscarriage rates were around 30%. Guzick and colleagues' study reported only the overall pregnancy rate, not the ongoing pregnancy rate. The pregnancy rate was given per inseminated cycle and not per started cycle. After recalculation of their data, the ongoing pregnancy rates per started cycle are much lower (5.5%) and fairly similar to ours. However, more than 30% of pregnancies in the previous study were multiple. Apparently, the higher pregnancy rate could be obtained only after stronger ovarian hyperstimulation, which inevitably results in the increased occurrence of twins and triplets. Similarly, in the study by Goverde and colleagues,⁵ the pregnancy rates after intrauterine insemination with controlled ovarian hyperstimulation were higher than those in our study, but there was also a high rate of multiple pregnancy (29%).

The UK National Institute for Health and Clinical Excellence recommends use of intrauterine insemination without controlled ovarian hyperstimulation in couples with unexplained subfertility.¹⁴ Our study shows there is no substantial benefit from this approach in couples with a probability of pregnancy of more than 30%. Although we did not study the effect of intrauterine insemination without controlled ovarian hyperstimulation, that intervention is highly unlikely to have a beneficial effect in these couples.

Our study shows that identification of couples who will not benefit from intrauterine insemination is possible. Through selection of these couples, the misuse of facilities and other resources can be avoided. Our trial also emphasises the importance of expectant management, which is an efficient way to prevent multiple pregnancy. So far, this approach has been ignored in the debate on multiple pregnancy.^{10,16,17} Since a large beneficial effect of intrauterine insemination with controlled ovarian hyperstimulation in couples with unexplained subfertility and an intermediate prognosis can be excluded, expectant management for 6 months is justified in these couples.

Contributors

Ben W J Mol, Fulco van der Veen, and Peter G A Hompes contributed to the study design. Pietermel Steures and Jan Willem van der Steeg promoted the study, sought ethical approval, coordinated trial management, and collected data. Frank J Broekmans and Harold R Verhoeve recruited participants and collected data. Pietermel Steures did the statistical analysis, under the supervision of Ben W J Mol and Patrick M M Bossuyt. J Dik F Habbema and Marinus J C Eijkemans provided statistical advice. All authors helped to prepare the final report.

Conflict of interest statement

We declare that we have no conflict of interest.

Collaborative Effort on the Clinical Evaluation in Reproductive Medicine study group investigators and participating centres in Netherlands

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