The additional value of ovarian hyperstimulation in intrauterine insemination for couples with an abnormal postcoital test and a poor prognosis: a randomized clinical trial

Pieternel Steures, M.D., Jan Willem van der Steeg, M.D., Peter G. A. Hompes, M.D., Ph.D., Patrick M. M. Bossuyt, Ph.D., J. Dik F. Habbema, Ph.D., Marinus J. C. Eijkemans, M.Sc., Ph.D., Caroline A. M. Koks, M.D., Petra Boudrez, M.D., Fulco van der Veen, M.D., Ph.D., and Ben W. J. Mol, M.D., Ph.D.

Objective: To assess the effectiveness of controlled ovarian hyperstimulation (COH) in intrauterine insemination (IUI) for subfertile couples with an abnormal postcoital test and a poor prognosis.

Design: Randomized clinical trial.

Setting: Twenty-four fertility centers in the Netherlands.

Patient(s): Subfertile couples with a well-timed nonprogressive PCT and additional factors that reduce fertility.

Intervention(s): Couples were randomly allocated to three cycles of IUI with COH or three cycles of IUI without COH.

Main Outcome Measure(s): Ongoing pregnancy within three IUI cycles.

Result(s): We randomly allocated 132 couples to IUI with COH, and 133, to IUI without COH. We observed 33 pregnancies (25%) in the couples allocated to IUI with COH, of which 28 were ongoing (21%), vs. 28 pregnancies (21%) in the couples allocated to IUI without COH, of which 23 were ongoing (17%; relative risk of an ongoing pregnancy, 1.2; 95% confidence interval, 0.75 to 2.0). Two multiple pregnancies occurred in the IUI with COH group, and one, in the IUI without COH group.

Conclusion(s): In couples with an abnormal PCT and a poor prognosis, IUI with COH leads to pregnancy rates comparable to those for IUI without COH. We propose to perform IUI without COH in couples with an abnormal PCT. (Fertil Steril 2007;88:1618–24. ©2007 by American Society for Reproductive Medicine.)

Key Words: Intrauterine insemination, cervical factor, subfertility, postcoital test, randomized

Intrauterine insemination (IUI) is a common treatment in unexplained subfertile couples as well as in male subfertility and cervical-factor subfertility. It can be performed with or without controlled ovarian hyperstimulation (COH). Controlled ovarian hyperstimulation carries the risk of multiple pregnancies. It poses a burden to the couple and is costly because of the use of gonadotropins and the need for monitoring of follicular development and growth (1). These drawbacks are warranted only by a substantial gain in ongoing-pregnancy rate from using IUI with COH compared with IUI without COH.

In cases of unexplained subfertility, IUI is not effective when the couple’s spontaneous-pregnancy likelihood is >30% in the next 12 months (2). When IUI is performed in unexplained subfertile couples, COH doubles the pregnancy rates, compared with IUI without COH (3, 4).

In cases of male subfertility, IUI improves pregnancy rates. Intrauterine insemination without COH has been proven to be equally effective as IUI with COH and should therefore be the first choice of treatment (5), but couples with less severe

Received July 24, 2006; revised and accepted January 22, 2007.

This randomized controlled trial is registered in the Dutch Trial Register and as an International Standard Randomized Clinical Trial (ISRCTN90142795). Supported by grant 945-12-002 from ZonMW, the Netherlands Organization for Health Research and Development, the Hague, the Netherlands. Presented orally at the Conjoint Annual Meeting of the American Society for Reproductive Medicine and the Canadian Fertility and Andrology Society, ASRM/CFAS 2005, Montreal, Quebec, Canada, October 15–19, 2005.

Reprint requests: Pieternel Steures, M.D., Center of Reproductive Medicine, Room H4-213, Department of Obstetrics and Gynecology, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands (FAX: 31-20-6963489; E-mail: pn.steures@amc.uva.nl).
sperm defects benefit from the addition of COH (6). In none of the studies on IUI in male subfertility was the prognosis of the couple taken into account.

In cases of cervical-factor subfertility, IUI appears to be effective in couples with an isolated cervical factor without additional factors that reduce fertility (7). The incremental value of COH in IUI in couples with a cervical factor has been reported in only one retrospective study, which showed a nonsignificant increase in pregnancy rate after the use of COH (odds ratio, 1.4; 95% confidence interval [CI], 0.85 to 2.2) (8). To prevent undertreatment and overtreatment with COH, this low level of evidence needs to be confirmed or rejected in a randomized clinical trial.

At present, there are no randomized clinical trials on the incremental value of COH in IUI in cervical-factor subfertility and male subfertility, taking into account the prognosis of the couple. Therefore, we aimed to assess whether COH in IUI is of additional value in couples with an abnormal postcoital test (PCT) resulting from a cervical factor or a male factor and with a poor prognosis of an ongoing spontaneous pregnancy because of additional factors that reduce fertility.

MATERIALS AND METHODS

The study was performed between June 1, 2002 and July 1, 2005 in 24 fertility centers in the Netherlands. The study was approved by the local ethics committee of each participating center.

In couples who had an unfulfilled wish for a child and had ≥ 1 year with regular unprotected intercourse and in whom the woman had a regular cycle, a basic fertility workup was performed. This was done according to the guidelines of the Dutch Society of Obstetrics and Gynaecology and in the same way as reported in our study on the effectiveness of IUI with COH in unexplained subfertility (2, 9).

After completion of the basic fertility workup, in couples with an abnormal (negative) PCT, in other words, a well-timed, nonprogressive PCT that was caused by a cervical factor or a male factor, the prognosis was calculated for a spontaneous ongoing pregnancy resulting in a live-born child in the next 12 months. A spontaneous pregnancy was defined as a pregnancy that occurred without treatment. The prognosis was calculated according to the prediction model of Hunault et al. (10) by using a computer program or a paper score list (11). This model incorporates the variables of female age, duration of subfertility, primary or secondary subfertility, referral status, and percentage of progressive motile semen. Each variable is converted into a point score. The total point score of each couple corresponds to a prognosis for spontaneous ongoing pregnancy. The computer model can be used at the following URL: http://www.freyalibrary.html.

Couples with an abnormal PCT were invited to join the study if the model indicated a prognosis of ≤ 30% of a spontaneous ongoing pregnancy in the next 12 months, resulting in a live-born child.

Consenting eligible couples were randomly allocated to IUI with COH or to IUI without COH for three cycles, without a prespecified time horizon. The randomization sequence was computer generated in balanced-block multiples of two or four, stratified by center. Sealed opaque envelopes were prepared by an independent individual. Clinicians in the participating centers unsealed the first-in-order envelope after enrolling a couple. The inclusion was then confirmed by fax to the trial coordinator.

Cycle monitoring, detection and/or induction of ovulation, as well as semen preparation and insemination regimens were performed according to hospital-specific protocols. The study recommended for IUI with COH the use of FSH for COH. In general, a baseline transvaginal sonography was performed on cycle day 3 to exclude ovarian cysts of size > 20 mm. Thereafter, the women started with daily SC injections of FSH (Gonal F; Serono Benelux BV, Den Haag, the Netherlands or Puregon; Organon, Oss, the Netherlands) or human menopausal gonadotropin (Menopur; Ferring, Hoeftsdorp, the Netherlands) in doses of 75 IU, until transvaginal sonography showed at least one follicle with a diameter of 16 mm. Doses were adjusted in a range from 50 IU to 150 IU, depending on the ovarian response. The aim of mild ovarian hyperstimulation was to obtain multifollicular growth. Ovulation was then induced by the administration of 5,000 or 10,000 IU of hCG (Pregnyl, Organon), and women were inseminated 36 to 40 hours later. The administration of hCG was withheld, and IUI was not performed, if there were present more than three follicles with a diameter of ≥ 16 mm, or five follicles with a diameter of ≥ 12 mm.

Semen samples were processed within 1 hour after ejaculation by using a density gradient centrifugation, followed by a washing step with culture medium. The volume of semen that was inseminated varied between 0.3 mL and 0.5 mL.

In the IUI cycles without COH, ovulation detection was performed with urine LH tests (a semi-quantitative monoclonal antibody–based kit; OvuQuick, Quid, San Diego, CA) with a detection level of 40 IU, or by transvaginal sonography. If ovulation was detected with LH tests, patients tested their urine samples once or twice per day, starting on an individually calculated cycle day. Women were inseminated 20 to 30 hours after the endogenous LH surge had been detected in the urine sample. In case follicular growth was monitored by transvaginal sonography, hCG (Pregnyl, Organon) was administered when the dominant follicle had a diameter of ≥ 16 mm. Women were inseminated 36 to 40 hours thereafter. Semen was processed and inseminated in the same way as in the IUI cycles with COH.

Couples were followed until an ongoing pregnancy occurred. If pregnancy had not occurred, follow-up ended after the third IUI cycle or at drop out. If a pregnancy miscarried, follow-up continued until the next pregnancy, or the last of the three IUI cycles.
The primary endpoint was ongoing pregnancy within three IUI cycles. Ongoing pregnancy was defined as the presence of fetal cardiac activity at transvaginal sonography at a gestational age of ≥12 weeks. Secondary endpoints were clinical pregnancies, miscarriages, ectopic pregnancies, multiple pregnancies, and live birth. 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, either seen at transvaginal sonography or as a result of the loss of a visible pregnancy.

We designed our study as a noninferiority trial. Our hypothesis was that IUI without COH would not be inferior to IUI with COH. If this were to be true, IUI without COH would be the preferred strategy. We considered IUI without COH not to be inferior to IUI with COH if we could exclude that the pregnancy rate without COH was ≥12.5% lower, using a 5% significance level. A smaller difference was judged to be clinically irrelevant, because the cost and adverse effects of COH would outweigh the slight increase in pregnancy rate. Assuming an 18% ongoing-pregnancy rate after three cycles of IUI, 117 couples had to be enrolled in each group to achieve an 80% level of power.

All pregnancies occurring within the three IUI cycles were included in the analyses, as well as spontaneous pregnancies occurring before or between these IUI cycles. The treatment effect of IUI with COH was expressed as relative risk and as a number needed to treat, both with their 95% CI. We plotted Kaplan-Meier curves to visualize the time to pregnancy in the two groups, and we compared these curves by using a log rank test.

We performed additional analyses in which we evaluated the pregnancy rate per IUI cycle with or without COH and expressed the treatment effect as relative risk and number needed to treat. We compared the effectiveness of IUI with COH with that of IUI without COH in the subgroup of couples with a total motile sperm count (TMC) of ≥10 million and in the subgroup of couples with a TMC of <10 million (severe male subfertility). In the IUI with COH group, we also assessed the relation between follicular growth patterns and the occurrence of pregnancy.

RESULTS

In total, 657 consecutive couples with an abnormal PCT and a poor prognosis of a spontaneous ongoing pregnancy in the next year were registered in one of the participating centers. Informed consent was obtained from 272 couples (41%), among whom 136 couples were randomly allocated to IUI with COH and 136 couples to IUI without COH (Fig. 1).

Seven randomized couples had to be excluded from the analyses who did not meet the inclusion criteria because they had a positive PCT, a short duration of subfertility

![Flowchart of trial population, with inclusion and outcome. Ong = ongoing.](image-url)
(<12 mo), or two-sided tubal occlusion, known at the time of randomization.

The baseline characteristics of the two groups were comparable (Table 1). All women included in the study had their tubes assessed before randomization by chlamydia antibody test (CAT), hysterosalpingography, or diagnostic laparoscopy (DLS). In 101 women (77%) allocated to IUI with COH and 107 women (80%) allocated to IUI without COH, tubal function had been assessed by hysterosalpingography or laparoscopy before randomization. In 8 women (7.9%) and 9 women (8.4%), respectively, one-sided tubal occlusion was found. In the follow-up time for three IUI cycles, two and five women, respectively, underwent a hysterosalpingography or laparoscopy. In these women, both tubes were patent. Taken together, 103 women (78%) allocated to IUI with COH and 112 women (84%) allocated to IUI without COH, tubal function had been assessed by hysterosalpingography or laparoscopy, among whom 8 women (7.8%) and 9 women (8.0%), respectively, had one-sided tubal occlusion.

Pregnancy data are summarized in Figure 1. Complete follow-up was obtained for all couples. In the group allocated to IUI with COH, three women (2%) conceived spontaneously before the start of IUI. All pregnancies were ongoing. In 124 couples, IUI was started. Four women (3%) conceived spontaneously between IUI cycles. Three of these pregnancies were ongoing, and one miscarried. After IUI, 26 pregnancies (20%) occurred. Twenty-two of these pregnancies were ongoing, 3 miscarried, and 1 was an ectopic pregnancy. There were 2 twin pregnancies. Of the 28 ongoing pregnancies, all 26 singleton pregnancies (100%) resulted in a live birth of one child; 1 twin pregnancy resulted in the live birth of both children; and in the other twin pregnancy, one child was healthy and the other one died. Eighteen couples did not complete three IUI cycles because of the burden of the treatment, insurance problems, personal reasons, or having switched earlier to IVF (13.6%). The latest IUI cycle took place within 6 months of follow-up.

In the group allocated to IUI without COH, three women (2%) conceived spontaneously before the start of IUI. All three pregnancies were ongoing. After IUI, 22 pregnancies (17%) occurred. Seventeen of these pregnancies were ongoing, four miscarried, and one was an ectopic pregnancy. There was one twin pregnancy. Finally, of the 23 ongoing pregnancies, 21 singleton pregnancies resulted in a live birth of one child, one singleton pregnancy resulted in an intrauterine fetal death, and the twin pregnancies resulted in the live birth of both children. Ten couples did not complete three IUI cycles because of burden

**TABLE 1**

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>IUI with COH (n = 132)</th>
<th>IUI without COH (n = 133)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean maternal age, y (min–max)</td>
<td>33 (23–41)</td>
<td>33 (21–41)</td>
</tr>
<tr>
<td>Mean duration of subfertility, y (min–max)</td>
<td>2.5 (1–10)</td>
<td>2.7 (1–10)</td>
</tr>
<tr>
<td>Primary subfertility, n (%)</td>
<td>114 (86)</td>
<td>112 (84)</td>
</tr>
<tr>
<td>Menstrual cycles per y, n (min–max)</td>
<td>13 (10–16)</td>
<td>13 (10–16)</td>
</tr>
<tr>
<td>Mean FSH, IU/L (min–max)</td>
<td>7.2 (3–27)</td>
<td>6.8 (2–15)</td>
</tr>
<tr>
<td>Median E2, nmol/L (min–max)</td>
<td>0.13 (0.03–0.89)</td>
<td>0.14 (0.02–1.24)</td>
</tr>
<tr>
<td>Median semen analyses, TMC (min–max)</td>
<td>28 (1–542)</td>
<td>21 (1–587)</td>
</tr>
<tr>
<td>% Progressive motile semen (min–max)</td>
<td>32 (2–87)</td>
<td>29 (1–76)</td>
</tr>
<tr>
<td>Chlamydia antibody test positive test results, n (%)</td>
<td>14/100 (14)</td>
<td>18/101 (18)</td>
</tr>
<tr>
<td>Hysterosalpingography 1-sided tubal pathology, n (%)</td>
<td>1/72 (1.4)</td>
<td>5/66 (7.6)</td>
</tr>
<tr>
<td>DLS 1-sided tubal pathology, n (%)</td>
<td>7/29 (24)</td>
<td>4/41 (9.8)</td>
</tr>
<tr>
<td>Mean prognosis, % (min–max)</td>
<td>13 (4–22)</td>
<td>13 (0–26)</td>
</tr>
</tbody>
</table>

aData available at time of randomization in 117 and 115 women in the IUI with COH group and expectant-management group, respectively.

bData available at time of randomization in 64 and 65 women in the IUI with COH group and expectant-management group, respectively.

cData available at time of randomization in 100 and 101 women in the IUI with COH group and expectant-management group, respectively.

dData available at time of randomization in 72 and 66 women in the IUI with COH group and expectant-management group, respectively.

eData available at time of randomization in 29 and 41 women in the IUI with COH group and expectant-management group, respectively.

of the treatment, insurance problems, personal reasons, or having switched earlier to IVF (7.5%). The latest IUI cycle took place within 6 months of follow-up.

In total, 33 pregnancies (25%) occurred in the group allocated to IUI with COH, and 28 pregnancies (21%), in the group allocated to IUI without COH (Fig. 1). The miscarriage rates in both groups were 15% and 18%, respectively. The number of ongoing pregnancies in the IUI with and without COH groups were 28 (21%) and 23 (17%), resulting in a relative risk of 1.2 (95% CI, 0.75 to 2.0). The corresponding absolute risk difference was +4% (95% CI, –6% to +13%), corresponding with a number needed to treat of 26 (95% CI, 10 to infinity). The Kaplan-Meier curves showed no significant difference in the time to pregnancy in both groups (Fig. 2; log-rank test \( P \) value, .47).

In the group allocated to IUI with COH, 325 IUI cycles were started, of which 43 cycles (13%) were canceled. The pregnancy rate per started cycle was 8.0%, with an ongoing-pregnancy rate of 6.8% per started cycle. In 23 IUI cycles (7.1%), COH was performed with antiestrogenic medication (clomiphene citrate). In these IUI cycles, two ongoing pregnancies occurred (8.7% per started cycle). In the group allocated to IUI without COH, 345 IUI cycles were started, of which 34 cycles (9.9%) were canceled. The pregnancy rate per started cycle was 6.4%, with an ongoing-pregnancy rate of 4.9% per started cycle. When calculations were performed at a cycle level, the relative risk was 1.4 (95% CI, 0.74 to 2.5).

The number of cycles needed to treat for COH was 54 to achieve one additional ongoing pregnancy (95% CI, 18 to infinity).

The pregnancies in relation to the TMC for IUI with and without COH are shown in Table 2. The effectiveness of IUI with COH in couples with a TMC of \( \geq 10 \) million was not different from that in the total group (relative risk, 1.25; 95% CI, 0.93 to 1.7). Multifollicular growth was registered in 230 (82%) of the 282 inseminated cycles. Multifollicular growth, defined as more than one follicle with a diameter of 10 mm, occurred in 62% of the inseminated cycles with COH. In 38% of the inseminated cycles with COH, more than one follicle with a diameter of 15 mm was present at the time of hCG injection. The pregnancies in relation to the follicular growth for the group allocated to IUI with COH are shown in Table 3. No clear differences in the pregnancy rates were seen between the cycles with monofollicular and multifollicular growth.

**DISCUSSION**

This is the first randomized clinical trial that evaluated the additional value of COH in IUI in couples with an abnormal PCT. Our data show an almost similar effect of IUI with and without COH in these couples. The estimates of treatment effect were not different in couples with a TMC of 10 million.
>10 million and in couples with a TMC of <10 million, but because the study was not powered for the additional analysis of the relation between pregnancies and the total motile sperm count, this result should be interpreted with caution.

A strength of this study is that we used the prognostic profile of each couple, in addition to their diagnosis, as an inclusion criterion. This way, we included both couples with an abnormal PCT and a long duration of their subfertility, as well as couples with an abnormal PCT and poor semen quality or couples with an advanced maternal age. This approach led to a selection of a more specific and homogeneous group from the prognostic profile. Because the treatment effect in subfertile couples may be dependent not only on diagnosis but also on prognosis, documenting the prognostic profile of the included couples makes our study results easy to interpret and to generalize for each fertility clinic (12).

There are some possible limitations of this study. We erroneously included seven couples who did not meet the inclusion criteria. These couples were distributed equally over the two treatment policies, and therefore either inclusion or exclusion would not affect the results and conclusion of our study. Because the aim of this trial was to assess whether addition of COH is effective in subfertile couples with a negative PCT and at least one patent tube, we believe that postrandomization exclusion is a better option than leaving these couples in the analysis.

Another limitation may be the fact that the study protocol recommended FSH for COH, but in 7.1% of IUI cycles, COH was performed with anti-estrogenic medication (clomiphene citrate). However, in a Cochrane review, no significant difference in live birth rates per couple after IUI with FSH and IUI with anti-estrogenic medication was found (13). Although this study had a protocol for the performance of the PCT and the treatment of IUI, the very fact that 24 centers participated in the trial may have affected the results. Nevertheless, this limitation is relative because this multicenter approach reflects the performance of the PCT and the effectiveness of IUI in daily fertility practice. The ongoing-pregnancy rate per started IUI cycle with or without COH of 6.8% and 4.9%, respectively, is lower than the 10% and 13% that were described elsewhere in a retrospective study (7). This lower pregnancy rate can be explained by the prognostic profile of the couple. In the retrospective study, couples with cervical-factor subfertility were included independently of their prognosis, whereas in the present study, only couples with a poor prognosis were included.

The 4% difference in pregnancy rate that we found means that COH should not be applied in couples with an abnormal PCT. Because the 95% CI ranged from −6% to 13%, a beneficial effect of COH cannot be excluded completely. However, in clinical decision making, the risks of these two treatment policies also should be taken into account. In case of multifollicular growth, which is the primary aim of COH, there is a risk of multiple pregnancy, and couples are forced to trade off between the risks of a multiple pregnancy and cancellation of the IUI cycle, the latter obviously implying no pregnancy at all. Moreover, the risk of multiple pregnancies cannot always be foreseen, because in IUI with COH, these pregnancies also can arise from borderline or small follicles in cycles that are not canceled on the basis of existing guidelines. In contrast, IUI without COH bears no increased medical risk at a lower financial cost.

The PCT has been abandoned in many guidelines. However, performing the PCT enables identification of couples with a cervical factor and avoids misclassifying these couples as having unexplained infertility. This misdiagnosis would lead to the use of IUI with COH, which increases costs and the risk of multiple pregnancies, without increasing chances of pregnancy in these couples.

In conclusion, IUI with COH, in couples with an abnormal PCT and a poor prognosis, leads to pregnancy rates that are comparable to those obtained by using IUI without COH. Intruterine insemination without COH should be the treatment of first choice in these couples.

REFERENCES


APPENDIX

The CECERM (Collaborative Effort for Clinical Evaluation in Reproductive Medicine) study group investigators and their participating centers in the Netherlands are as follows:

Y. M. van Kasteren (Medisch Centrum Alkmaar, Alkmaar)
P. F. M. van der Heijden (Twenteborg Ziekenhuis, Almelo)
W. A. Schöls (Meander Medisch Centrum, Amersfoort)
M. H. Mochtar (Academisch Medisch Centrum, Amsterdam)
H. R. Verhoeve (Onze Lieve Vrouwe Gasthuis, Amsterdam)
P. G. A. Hompes (Vrij Universiteit Medisch Centrum, Amsterdam)
L. J. van Dam (Gelre Ziekenhuis, Apeldoorn)
A. V. Sluijmer (Wilhelmina Ziekenhuis, Assen)
R. E. Bernardus (Ziekenhuis Gooi-Noord, Blaricum)
J. P. Dörr (Westeinde Ziekenhuis, Den Haag)
P. J. Q. van der Linden (Ziekenhuis Deventer, Deventer)
J. M. Burggraaff (Scheper Ziekenhuis, Emmen)
G. J. E. Oosterhuis (Medisch Spectrum Twente, Enschede)
M. H. Schouwink (Sint Anna Ziekenhuis, Geldrop)
P. X. J. M. Bouckaert (Atrium Medisch Centrum, Heerlen)
F. M. C. Delemarre (Elkerliek Ziekenhuis, Helmond)
J. H. Schagen-Van Leeuwen (St. Antonius Ziekenhuis, Nieuwegein)
J. A. M. Kremer (UMC St. Radboud, Nijmegen)
H. J. H. M. Van Dessel (TweeSteden Ziekenhuis, Tilburg/Waalwijk)
F. J. M. Broekmans (UMC Utrecht, Utrecht)
C. A. M. Koks (Maxima Medisch Centrum, Veldhoven)
P. Bourdrez (Vie Curi Medisch Centrum, Venlo/Venray)
W. W. J. Riedijk (Zaans Medisch Centrum, Zaandam)
B. J. Cohlen (Isala Klinieken, Zwolle)