Controlled ovarian hyperstimulation and intrauterine insemination for treating male subfertility: a controlled study

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In this randomized crossover trial we investigated whether the use of controlled ovarian hyperstimulation with low-dose human menopausal gonadotrophin in couples with male subfertility leads to a higher probability of conception when intrauterine insemination (IUI) is applied. We also investigated whether the efficacy of IUI in natural or stimulated cycles was related to the severity of male subfertility. Seventy-four couples completed 308 treatment cycles. Thirteen pregnancies occurred after IUI in a natural cycle (pregnancy rate per completed cycle: 8.4%) and 21 after IUI in a stimulated cycle (pregnancy rate per completed cycle: 13.7%). The difference between the two treatment modalities was not statistically significant. The efficacy of IUI in stimulated cycles was related to the severity of the semen defect. In couples with a total motile sperm count $<10^9$ or $10^6$, ovarian stimulation did not improve treatment outcome, while it did in couples with a total motile sperm count $\geq10^9$. Compared with the expected chance of conceiving spontaneously without treatment, both natural and stimulated cycles improved the probability of conception. We conclude that, for the group as a whole, ovarian stimulation did not improve the probability of conception. However, in couples with less severe semen defects, ovarian stimulation did improve the probability of conception.

Key words: intrauterine insemination/male subfertility/ovarian stimulation/randomized and crossover study

Introduction

To determine whether the combination of intrauterine insemination (IUI) and ovarian stimulation improves the probability of conception in couples with male subfertility, two controlled comparisons must be made: IUI versus timed intercourse in natural cycles (to prove a beneficial effect of IUI), and IUI in natural cycles versus IUI in cycles with ovarian stimulation (to prove a beneficial effect of ovarian stimulation) (Cohlen et al., 1995b). Interpretation of the usefulness of either treatment modality is hampered by the fact that only a few controlled studies performing these comparisons have been published and that criteria for male subfertility are either ill-defined or differ widely. Regarding the results of randomized studies, IUI in natural cycles seems to improve the probability of conception in the case of a severe semen defect (Kerin and Quinn, 1987; Kirby et al., 1991). Whether ovarian stimulation further improves the probability of conception, when IUI is applied for male subfertility, and whether treatment outcome in ovarian stimulation cycles is related to the severity of the semen defect have not been investigated prospectively. Therefore a randomized, controlled study of the treatment of couples with male subfertility as the only identifiable cause was performed. Its aim was twofold: first, to determine whether IUI in cycles with ovarian stimulation improves the probability of conception compared to IUI in natural cycles and, second, to investigate whether the outcome of each treatment modality is related to the severity of semen defects.

Materials and methods

Seventy-four couples with subfertility possibly related to male subfertility signed an informed consent form to take part in this study, and the protocol was approved by the Ethical Committee of the University Hospital Utrecht. Subfertility was primary in 61 couples (82%). The average age of the women was 30.7 years (range 24–39 years) and of the men 33.5 years (range 25–46 years). The mean duration of infertility was 3.1 years (range 2–9 years). We used the same definition of male subfertility as in our previous studies (te Velde et al., 1989; Nan et al., 1994), namely that in each of at least two subsequent semen analyses, one or more of the classical semen parameters were abnormal: sperm concentration $<20\times10^6$/ml; motility $<40%$; normal morphology $<40%$. Men with anti-sperm antibodies, as detected by a direct mixed agglutination reaction, were excluded. All women had regular cycles within 25 to 35 days, with a biphasic basal body temperature and a normal midluteal progesterone concentration of $>9.7$ ng/ml (conversion factor to SI unit: 3.180). Progesterone concentration was determined using competitive enzyme immunoassay with the biotin–streptavidin technology, inter-assay variability $<4.5%$. (Boehringer Mannheim GmbH, Diagnostica, Mannheim, Germany). No abnormalities on hysterosalpingography and/or laparoscopy were present that could explain the subfertility of the couple. Intrauterine insemination has proven effective in treating cervical hostility (te Velde et al., 1989; Kirby et al., 1991; Check and Spirito, 1995). To avoid a possible bias we excluded couples with a cervical factor. Therefore, the result of a well-timed post-coital test, performed 9 to 12 h after intercourse, indicated either progressive motile spermatozoa or, in the case of a negative post-coital test due to the semen factor, an optimum quality of the cervical mucus, i.e. mucus score $\geq11$ (scale 0–12) and pH $>6.3$ (Eimers et al., 1994a).

The first cycle was randomized for IUI in a natural cycle or for IUI in a cycle with ovarian stimulation using sealed opaque envelopes. This treatment was alternated according to a crossover design. Each
A couple was offered six treatment cycles: three with IUI in natural cycles, and three with IUI in cycles with ovarian stimulation. To achieve mild ovarian stimulation, we administered one ampoule containing 75 IU human menopausal gonadotrophin (HMG) per day (Humeqon, Organon, Oss, The Netherlands) starting on cycle day 3. When mono-follicular growth was achieved, each patient received 1.5 ampoule HMG per day in the next stimulation cycle, or two ampoules HMG per day in the third ovarian stimulation cycle if monofollicular growth persisted. Before starting ovarian stimulation, a transvaginal ultrasound scan was performed on cycle day 2 or 3 to preclude abnormalities of the ovaries. From cycle day 10 onwards, the stimulation was monitored every other day or daily with a transvaginal ultrasound scan to determine the number and diameter of the developing follicles, and with determination of serum oestradiol and luteinizing hormone (LH) concentrations. Oestradiol was measured using radioimmunoassay with anti-oestradiol antisera: inter-assay variability <21%, intra-assay variability <6.3% (DPC, Los Angeles, CA, USA). LH was measured using a radioimmunoassay with a specific polyclonal anti-LH antisera: inter-assay variability <6.7%, intra-assay variability <7.0% (DPC). Stimulation was stopped when the leading follicle(s) reached a mean diameter ≥18 mm or when an LH surge was detected (LH ≥24 IU/l). Ovulation was induced with 5000 IU human chorionic gonadotrophin (HCG, Pregnyl, Organon) and IUI was scheduled for 38 to 40 h later. In the case of a premature LH surge, HCG was administered as soon as possible and the insemination was planned for the following morning. Intrauterine insemination was performed once in every cycle. All couples were asked to abstain from intercourse starting at least 2 days before the insemination (to obtain optimal semen samples) until 4 days after the insemination (to measure solely the efficacy of IUI). To minimize the risk of a multiple pregnancy or ovarian hyperstimulation syndrome, HCG was withheld if ≥4 follicles with a mean diameter of ≥18 mm were seen on the ultrasound scan, or if the oestradiol concentration exceeded 1635 pg/ml (conversion factor to SI unit: 3.671).

In the case of a natural cycle, IUI was timed with daily determination of serum LH concentrations from cycle day 10 onwards. Insemination was scheduled for 26 h after the onset of the LH surge was detected (LH ≥24 IU/l). Again the couples were asked to abstain from intercourse. Preparation of the spermatozoa and insemination technique have been described previously (Nan et al., 1994). Pregnancy were detected with an HCG urine test (HCG-plus test, Abbott B.V., Amstelveen, The Netherlands), and confirmed with a transvaginal ultrasound scan at 6 to 7 weeks of gestation.

For all calculations of classical semen parameters we used the average value of the first and the second semen analysis. The effect of ovarian stimulation was estimated by survival analysis in order to estimate pregnancy rates over time (in cycles). Survival analysis with discrete timing of events (‘proportional odds’) was used to account for the aspect of time (Kalbfleisch and Prentice, 1980). In contrast to Cox proportional hazards, the cycle number was entered as a nominal variable to handle time and ovarian stimulation as a time-dependent explanatory variable. Such an analysis takes into account the fact that each woman might have had several treatment cycles and that pregnancy rates drop as a result of selection. To investigate whether treatment outcome differed between couples with a severe semen defect and couples with a less severe semen defect, we calculated regression lines for the pregnancy rate per cycle of IUI in natural cycles and of IUI in stimulated cycles for different parameters of semen quality. The regression lines were fitted to the individual semen parameter of each of the 74 couples. We used the average value of the first and second semen analysis to reduce intra-individual variability of semen parameters. A recent study showed that combining the results of two semen analyses increases the association between semen quality and the probability of conception, compared with the results of the first semen analysis only (Tielemans et al., 1997).

To define the severity of male subfertility, we used several combined semen parameters as advised by Glazener et al. (1987): motile sperm count (sperm concentration × percentage motile spermatozoa); total motile sperm count (volume × sperm concentration × percentage motile spermatozoa); motile normal sperm count (sperm concentration × percentage motile spermatozoa × percentage normal morphology); and the total motile normal sperm count (volume × sperm concentration × percentage motile spermatozoa × percentage normal morphology). We also investigated whether the total motile sperm count of the semen sample produced on the day of IUI, before and after sperm preparation, significantly influenced treatment outcome.

To compare cycle characteristics we used the Student’s two-tailed t-test. A significance level of 5% was accepted. The results of our two previous studies (te Velde et al., 1989; Nan et al., 1994) showed a pregnancy rate per cycle of approximately 2.5%, when IUI was applied in natural cycles, and of 10.5%, after IUI in cycles with ovarian stimulation. To detect a difference of this magnitude (as opposed to our zero hypothesis of no difference), we calculated that we would need 150 cycles for each treatment modality with α set at 0.05 and β at 0.20 (power = 1 – β = 80%).

Results

Seventy-four couples started 320 treatment cycles (mean number of cycles, 4.3). Table I shows the pregnancy rate per completed IUI cycle and the number of drop-outs before starting a new treatment cycle. Altogether nine patients dropped out before completing six cycles for reasons other than pregnancy: six patients for personal reasons, and three patients became pregnant during a non-treatment cycle. Of the 320 started cycles, 161 were natural cycles while in 159 cycles ovarian stimulation was administered. Six natural cycles (3.7% of the started natural cycles) were cancelled because of a premature or missed LH surge. Six stimulated cycles (3.8% of the started stimulated cycles) were cancelled: one because of a premature LH surge with the largest follicle 11 mm, and five to prevent multiple pregnancies or ovarian hyperstimulation syndrome. Thus 308 cycles were completed, 155 without and 153 with ovarian stimulation.

Table II shows the proportional odds ratios (OR) and 95% confidence intervals (CI) of the pregnancy rates and live birth rates per started and completed IUI cycle between the two treatment modalities. Although there was a tendency towards greater success with ovarian stimulation, none of the differences reached statistical significance (P = 0.15 to 0.18). Age of the woman and duration of subfertility did not significantly influence treatment outcome. Including both parameters in a multivariate regression analysis also did not change the OR. Of the 34 pregnancies, 32 were singleton and 2 were twins. Six pregnancies ended in a spontaneous abortion (three in each treatment modality), and the other 28 pregnancies resulted in the birth of one (n = 26) or two (n = 2) healthy children. Including the 3 patients who became pregnant during non-treatment cycles, 37 of the original 74 couples became pregnant (50%), 34 after IUI (pregnancy rate per couple: 46%; live birth rate per couple: 38%).

In 37 of the 153 stimulated cycles, a premature LH surge occurred and two pregnancies were achieved (pregnancy rate...
Table I. Pregnancy rate per completed intrauterine insemination cycle and number of drop-outs for reasons other than pregnancy before starting a new treatment cycle

<table>
<thead>
<tr>
<th>Cycle no.</th>
<th>Natural cycles</th>
<th></th>
<th>Stimulated cycles</th>
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<th>No. of cycles</th>
<th>Pregnancies (%)</th>
<th>No. of cycles</th>
<th>Pregnancies (%)</th>
<th>No. of drop-outs</th>
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<tbody>
<tr>
<td>1</td>
<td>38 (38)</td>
<td>4 (10.5)</td>
<td>36 (36)</td>
<td>3 (8.3)</td>
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<td>2</td>
<td>32 (33)</td>
<td>2 (6.3)</td>
<td>32 (34)</td>
<td>5 (15.6)</td>
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<td>3</td>
<td>26 (29)</td>
<td>6 (23.1)</td>
<td>29 (30)</td>
<td>5 (17.2)</td>
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<td>4</td>
<td>25 (25)</td>
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<td>19 (21)</td>
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<td>5</td>
<td>15 (17)</td>
<td>1 (6.7)</td>
<td>22 (23)</td>
<td>3 (13.6)</td>
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<td>6</td>
<td>19 (19)</td>
<td>0</td>
<td>15 (15)</td>
<td>3 (20.0)</td>
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<td>Total after 6 cycles</td>
<td>155 (161)</td>
<td>13 (8.4)</td>
<td>153 (159)</td>
<td>21 (13.7)</td>
<td>9</td>
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*a* Values in parentheses are number of started cycles.

Table II. 'Proportional odds' ratios and 95% confidence intervals (CI) of pregnancy and live birth rates per started and completed cycle (intrauterine insemination in natural cycles versus intrauterine insemination in stimulated cycles)

<table>
<thead>
<tr>
<th>Proportional odds ratio (95% CI)</th>
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<tr>
<td>Pregnancy rate per started cycle</td>
<td>1.71 (0.82–3.57)</td>
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<td>Pregnancy rate per completed cycle</td>
<td>1.68 (0.80–3.51)</td>
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<td>Live birth rate per started cycle</td>
<td>1.78 (0.79–4.03)</td>
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<tr>
<td>Live birth rate per completed cycle</td>
<td>1.76 (0.77–3.99)</td>
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Figure 1. Pregnancy rate per cycle (%) after intrauterine insemination (IUI) in natural cycles and after IUI in stimulated cycles in relation to the average total motile sperm count of the couple.

per cycle: 5.4%). In the 116 stimulated cycles without a premature LH surge, 19 pregnancies were achieved (pregnancy rate per cycle 16.4%). Thus, LH surges tended to influence treatment outcome negatively, although significance was not reached (OR: 0.30, 0.07–1.36).

With regard to the question of whether the semen quality influenced the outcome of either treatment modality, we compared regression lines for IUI in natural cycles and for IUI in stimulated cycles as a function of increasing semen quality. Figure 1 shows the results for the total motile sperm count. The figure shows that, with an increasing total motile sperm count, the probability of conception obtained with IUI in stimulated cycles increased (dotted line; $P = 0.04$). The probability of conception obtained with IUI in natural cycles was not significantly correlated with the total motile sperm count (continuous line; $P = 0.79$). The pregnancy rate per cycle of the two treatment modalities crossed at a level of $8.7 \times 10^6$ motile spermatozoa. However, the difference in slope between the two regression lines was not significant ($P = 0.08$). Similar tendencies and $P$ values were observed for the other three parameters of semen quality (motile sperm count, motile normal sperm count, and total motile normal sperm count) without reaching significance. The four combined semen parameters that we tested were apparently highly correlated, and hence we will focus on the total motile sperm count only. We found that the total motile sperm count of the first semen analysis was highly correlated with the total motile sperm count of the second semen analysis (Spearman’s correlation coefficient 0.82, $P < 0.0001$).

Because Figure 1 suggested that couples with low total motile sperm counts should undergo IUI in natural cycles, while couples with high total motile sperm counts should undergo IUI in cycles with ovarian stimulation, we divided our population into subgroups according to their total motile sperm count. We found that, in couples with a total motile sperm count $<5 \times 10^6$ ($n = 11$), IUI in natural cycles resulted in a higher pregnancy rate per cycle compared with IUI in stimulated cycles (OR with 95% CI: 6.9, 0.7–70), while in couples with a total motile sperm count $\geq 10^7$ ($n = 52$), the opposite was true (OR with 95% CI: 3.15, 1.25–7.92), see Figure 2. No difference in pregnancy rate per cycle between the two treatment modalities could be observed in couples with a total motile sperm count between 5 and $10^6$ ($n = 11$) (OR with 95% CI: 0.68, 0.10–4.57). The total motile sperm count of the semen sample obtained on the day of IUI before and after sperm preparation did not significantly influence treatment outcome ($P = 0.47$ and 0.66, respectively). However, cycles in which $>1 \times 10^6$ motile spermatozoa were inseminated resulted in significantly higher pregnancy rates (29 pregnancies in 259 cycles: 11.2%) than those cycles in which $\leq 1 \times 10^6$ motile spermatozoa were inseminated (one pregnancy in 38 cycles: 2.6%; $P = 0.046$). The total motile sperm counts of 11 cycles, which resulted in four pregnancies,
were not known, although all these men produced $>1 \times 10^6$ motile spermatozoa in the inseminate on other occasions.

In 70% of the completed stimulation cycles, multifollicular development occurred. The number of follicles $\geq 12$ mm or $\geq 16$ mm at midcycle did not influence treatment outcome significantly ($P = 0.66$ and 0.98, respectively). Only one patient had monofollicular development ($\geq 12$ mm) in all stimulated cycles despite increasing HMG doses. Regarding the number of follicles $\geq 12$ mm at midcycle, ovarian stimulation resulted in multifollicular development in 83% of the stimulated cycles of couples with a total motile sperm count $<5 \times 10^6$, in 81% of the stimulated cycles of couples with a total motile sperm count $5-10 \times 10^6$, and in 66% of the stimulated cycles of couples with a total motile sperm count $\geq 10 \times 10^6$. Regarding the number of follicles $\geq 16$ mm at midcycle, ovarian stimulation resulted in multifollicular development in 57% of the stimulated cycles of couples with a total motile sperm count $<5 \times 10^6$, in 57% of the stimulated cycles of couples with a total motile sperm count $5-10 \times 10^6$, and in 44% of the stimulated cycles of couples with a total motile sperm count $\geq 10 \times 10^6$.

There were no complications resulting from either ovarian stimulation (moderate or severe ovarian hyperstimulation syndrome) or IUI (pelvic infection).

**Discussion**

The results of uncontrolled studies suggest that ovarian stimulation improves treatment outcome when IUI is applied in cases of male subfertility (Dodson and Haney, 1991). Therefore, this treatment modality is often advised before attempting more invasive therapies such as in-vitro fertilization or gamete intra-Fallopian transfer (Peterson et al., 1994). In this randomized and controlled study of 308 completed treatment cycles with male subfertility as the only identifiable cause, we found no statistically significant difference between IUI in a natural cycle and IUI after mild ovarian stimulation with gonadotropins ($P = 0.17$). The pregnancy rate per completed stimulated IUI cycle of 13.7% is in the range of those reported in other randomized and controlled studies (Nulsen et al., 1993; Balasch et al., 1994). Nulsen et al. (1993) performed the same comparison in 20 couples with male subfertility and found no significant improvement following ovarian stimulation. In a randomized and controlled study using clomiphene citrate, Arici et al. (1994) also found no difference. When comparing low-dose follicle stimulating hormone and clomiphene citrate both in combination with IUI, Balasch et al. (1994) found a tendency in favour of follicle stimulating hormone for male subfertility.

The pregnancy rate per completed natural IUI cycle of 8.4% is somewhat higher than that reported in previous studies (te Velde et al., 1989; Kirby et al., 1991; Nulsen et al., 1993). It is possible that this is due to the presence of a carry-over effect of gonadotrophins on the subsequent natural cycle, resulting in a higher pregnancy rate per natural cycle. However, in a previous study we showed that such an effect is unlikely (Cohen et al., 1995a). Considering our population as a whole, no statistically significant improvement in treatment outcome was obtained with ovarian stimulation but, for couples with less severe semen defects, ovarian stimulation did improve treatment outcome (Figure 2). We postulate that, in couples with a less severe semen defect, subfertility is probably due to a combination of male and subtle female factors, as has been reported for couples with moderate oligospermia or previously unexplained subfertility (Silber and Cohen, 1983; Dunphy et al., 1990). A recent meta-analysis by Hughes (1997), which evaluated the use of IUI and ovarian stimulation for persistent infertility (excluding male subfertility), showed that ovarian stimulation has an independent positive effect on treatment outcome (OR with 95% CI: 2.35, 1.87–2.94). In a large prospective cohort study of IUI in clomiphene citrate cycles for couples with male subfertility or an unsatisfactory post-coital test, Dickey and Holtkamp (1996) found pregnancy rates to be acceptable in couples with less severe semen defects only.

Both for couples with unexplained subfertility and for couples with a less severe semen defect, ovarian stimulation might improve the quality of the cycle, perhaps by overcoming ovulation defects or unfavourable oestadiol/progesterone ratios. Our standard fertility work-up was not able to detect these subtle defects. Not all patients received a laparoscopy before entering the trial. Crosignani and Walters (1994) have shown that endometriosis might influence the efficacy of IUI in couples with male subfertility. However, only 18% of their patients had endometriosis, women with endometriosis that might influence the ovum pick-up mechanism were excluded, and the severity of the endometriosis of the included women was not recorded. In our study it is not clear whether or not patients had endometriosis or other pelvic abnormalities, including adhesions. Neither endometriosis nor adhesions are (positively) influenced by ovarian stimulation. All patients
underwent a vaginal ultrasound at the start of each cycle to exclude ovarian cysts (including endometriotic cysts). Furthermore, through the use of a randomized crossover design, all women were randomly divided between the two treatment modalities and acted as their own control.

In the case of a severe semen defect, the subfertility of the couple probably mainly results from the subfertility of the man. Kirby et al. (1991) have shown that IUI significantly increases the probability of conception in couples with a severe semen defect only. The probability of conception is significantly increased merely by increasing the number of motile spermatozoa at the site of fertilization at the expected moment of ovulation. This is not further improved by ovarian stimulation. It is even possible that, in those women with predominantly normal cycles, ovarian stimulation might negatively influence the probability of conception. We observed that in couples with a total motile sperm count $<5 \times 10^6$ ($n = 11$), no pregnancy occurred in 23 stimulated cycles, while three women became pregnant in 27 natural cycles.

An important question that remains to be answered is how to distinguish between a severe and a less severe semen defect. In other words, which semen qualities indicate ‘true male subfertility’ in contrast to mild male subfertility, where female factors may also contribute to the subfertility of the couple. Large studies on the frequency distribution of sperm counts in fertile and subfertile men showed wide overlap in sperm counts between the two groups (Silber, 1989). Even men with very low sperm counts can achieve a pregnancy. Significant differences in pregnancy rates were observed only with threshold levels of sperm count of $10 \times 10^6$/ml or total motile sperm count of $12.5 \times 10^6$ (Smith et al., 1977; Zuckerman et al., 1977). To define clinically significant male subfertility, Bostofte et al. (1982) proposed an even lower borderline of a sperm count of $5 \times 10^6$/ml, Glazener et al. (1987) used a motile normal sperm count of $4 \times 10^6$/ml, and Hargreve and Elton (1983) proposed a motile sperm count of $<2 \times 10^6$/ml. Thus, all authors found considerably lower borderlines compared with the criteria of male subfertility proposed by the World Health Organization (WHO, 1992). Men with a semen defect according to the WHO criteria but with still reasonable sperm counts, whose partners are fertile, will probably achieve a pregnancy anyway and will, therefore, never visit a fertility clinic. Regarding the results of our study we would define couples with a severe semen defect, resembling ‘true male subfertility’, as those couples with an average total motile sperm count $<5 \times 10^6$, in line with the definitions of the above mentioned studies (Bostofte et al., 1982; Hargreve and Elton, 1983; Glazener et al., 1987). We postulate that, in couples with a total motile sperm count $\geq 10 \times 10^6$, subtle female factors may also contribute to the subfertility of the couple, which therefore almost resembles unexplained subfertility (Dunphy et al., 1990). The transition between these two groups, while not a distinct line, is likely to lie between total motile sperm counts of $5 \times 10^6$ and $10 \times 10^6$.

Ideally, a third modality should have been added to this study, in which patients would have received no treatment. However, because we considered it unethical to withhold treatment for patients with longstanding subfertility, we used the formula of Eimers et al. (1994b) to estimate, for each couple, the expected spontaneous chance of conception. We calculated a mean expected spontaneous pregnancy rate per cycle of 3.3% (range 2.1–6.0%), concurring with five pregnancies altogether. After six treatment cycles we observed 13 pregnancies after IUI in natural cycles, and after IUI in stimulated cycles we observed 21 pregnancies. Thus, both IUI in natural cycles and IUI in stimulated cycles significantly improved the probability of conception compared with the estimated spontaneous pregnancy rate per cycle ($P < 0.01$).

In this trial a crossover design was used. In 1993 Daya reopened the discussion as to whether crossover trials should be abandoned in infertility research (Daya, 1993). His main concern about a crossover design was that couples who drop out (because of pregnancy or other reasons) will leave the study, which may lead to unbalanced groups after the crossover point and therefore to over- or underestimation of the efficacy of one of the treatment modalities. The same group published the results of a meta-analysis comparing crossover and parallel designs, and concluded that a crossover design results in a significant overstimation of the efficacy of the most effective treatment modality (Khan et al., 1996). Recently, we performed a computer simulation comparing both designs under different assumptions. We found no statistically or clinically significant differences between the two designs (Cohen et al., 1998). We also re-analysed the study by Khan et al. (1996) and, after correcting certain inconsistencies, found that no significant difference between the two designs could be found (te Velde et al., 1998). Because of its practical advantages (couples are more motivated to participate and complete the entire trial because they are offered both treatment modalities), we strongly believe that a crossover design deserves a place in cycle-related infertility research.

We conclude that, for couples with a severe semen defect, IUI in a natural cycle significantly improves the probability of conception compared with the estimated spontaneous chance to conceive. In this group ovarian stimulation does not increase treatment outcome and may even have a negative effect. For couples with less severe semen defects, ovarian stimulation significantly improves treatment outcome. Regarding our results, we currently advise the combination of IUI and ovarian stimulation only in couples with an average total motile sperm count $\geq 10 \times 10^6$ derived from 2 semen samples, and the use of IUI in natural cycles in couples with lower total motile sperm counts. Randomized and controlled studies have to be initiated to confirm our results in other clinics under different circumstances.

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