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Controlled ovarian hyperstimulation and intrauterine insemination for treatment of unexplained infertility should be limited to a maximum of three trials

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Objective: To investigate the optimum number of cycles of controlled ovarian hyperstimulation and intrauterine insemination in the treatment of unexplained infertility.

Design: Observational prospective study.

Setting: In vitro fertilization embryo transfer center.

Patient(s): Five hundred ninety-four couples with unexplained infertility.

Intervention(s): Controlled ovarian hyperstimulation (COH), intrauterine insemination (IUI), in vitro fertilization (IVF), and intracytoplasmic sperm injection (ICSI).

Main Outcome Measure(s): Cycle fecundity.

Result(s): One to 3 cycles of COH/IUI were performed in 594 patients (group A) undergoing 1,112 cycles (mean, 1.9 cycles/patient). Up to 3 further trials (cycles 4–6) of COH/IUI were then performed in 91 of these women (group B), a total of 161 cycles (mean, 1.8 cycles/patient). A historical comparison group C consisted of 131 patients with 3 failed cycles of COH/IUI who underwent 1 cycle of IVF and ICSI at our center. In group A, 182 pregnancies occurred, with a cycle fecundity of 16.4% and a cumulative pregnancy rate (PR) of 39.2% after the first 3 cycles. In group B, 9 pregnancies occurred in cycles 4–6, with a cycle fecundity of 5.6%, significantly lower than that of group A ($P<.001$). The cumulative PR rose to 48.5% by cycle 6, a further increase of only 9.3%. In the women undergoing IVF and ICSI in group C, 48 pregnancies occurred, with a cycle fecundity of 36.6% per cycle, significantly higher than that of group B ($P<.001$).

Conclusion(s): In unexplained infertility, the cycle fecundity in the first three trials of COH and IUI was higher than in cycles 4–6, with a statistically significant difference. Patients should be offered IVF or ICSI if they fail to conceive after three trials of COH and IUI. (Fertil Steril® 2001;75:88–91. ©2001 by American Society for Reproductive Medicine.)

Key Words: Controlled ovarian hyperstimulation, intracytoplasmic sperm injection, intrauterine insemination, in vitro fertilization, unexplained infertility

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A couple is diagnosed with unexplained infertility when standard investigations are normal (1). This population includes fertile couples who have failed to conceive by chance alone and those with abnormalities as yet undetectable by current means. Estimates of the percentage of the infertile population with unexplained infertility range from 0% to 37% (2). The aggregate prevalence in a review of eight studies of 5,129 infertile couples was 16% (2).

Initially, expectant management may be warranted, especially in young women with a short duration of infertility (3). The reported variations in cumulative pregnancy rates (PRs) without treatment in couples with unexplained infertility are due to differences in female age and the infertility duration. Hull et al. found a cumulative PR over 3 years of 50%–80% as a function of female age and 30%–80% as a function of infertility duration (4). Because the diagnosis of unexplained infertility should include only couples with true (undetected) abnormalities, many investigators define the condition using a duration of involuntary infertility of 2–3 years (5).

Wang and Gemzell first reported the use of

gonadotropin therapy in ovulatory women with unexplained infertility in 1979 (6). Sher et al. then reported in 1984 on 14 couples with long-standing unexplained infertility who were treated with controlled ovarian hyperstimulation (COH) using menotropins, and intrauterine insemination (IUI). A PR of 35% was noted after a single cycle (7). Since that time, COH and IUI have become commonly used in the management of unexplained infertility in many clinics and assisted reproductive technology centers throughout the world (8, 9). The relative ease and noninvasiveness of the procedure have made it a popular option.

There is no consensus of opinion regarding the optimum number of COH/IUI trials in the treatment of unexplained infertility. Aboulghar et al. (9) and Chaffkin et al. (10) suggest 3 trials, Peterson et al. (11) recommend 4 trials, Martinez (12) proposes 6 trials, and Campana (13) performed up to 12 trials. With the marked improvement in results of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), there is a great need to determine the optimum number of COH/IUI cycles before resorting to IVF and ICSI. Therefore, we conducted this study.

MATERIALS AND METHODS

Subjects

The patient population consisted of 594 women with unexplained infertility of duaration ≥4 years. The criteria for diagnosis of unexplained infertility are regular menstrual cycles, midluteal-phase progesterone levels of 10 ng/mL, luteal-phase duration of >11 days, normal uterus and fallopian tubes on hysterosalpingography or laparoscopy, normal complement-dependent sperm immobilization test, and a semen analysis count of $>20 \times 106$/mL, >40% motility, and >60% normal forms on more than one sample. The patients underwent 1,273 cycles of COH/IUI with a range of 1–6 cycles per patient. Five hundred ninety-four patients had 1–3 cycles of treatment (group A), and 91 patients underwent 4–6 cycles of COH/IUI (group B) after failing to achieve pregnancy in the first 3 cycles. A historical comparison group (group C, n = 131) was treated by IVF with ICSI on sibling oocytes after failure of up to 3 trials of COH/IUI, according to a paper published previously by the authors (14). The internal ethics committee of our institution and the Institutional Review Board approved the study protocol. All women gave informed consent.

Study Protocol

Patients undergoing COH/IUI received clomiphene citrate (Clomid; Merrell Dow SA, Neuilly-sur-Seine, France) 100 mg p.o. daily for 5 days from day 3 of the cycle. From days 6 to 10, 150 IU/day of human menopausal gonadotropin (hMG) (Humegon; Organon, Oss, The Netherlands; or Pergonal; Serono, Geneva, Switzerland) was administered intramuscularly (i.m.). From day 10 onward, daily vaginal ultrasound and urinary luteinizing hormone (LH) estimation (Clearplan; Unipath Limited, Bedford, United Kingdom) were performed.

IUI was performed 24 hours after detection of LH in the urine. If the leading follicle measured over 19 mm in diameter in the absence of LH in the urine, 10,000 U of human chorionic gonadotropin (hCG; Pregnyl; Nile Co., Egypt) were given i.m. and insemination was performed the next day. Treatment continued for up to 3 cycles in group A and 6 cycles in group B, with a no-treatment interval of 1–2 months.

Semen was prepared on the day of insemination using the swim-up technique as described previously (15). A serum βCG test was done to confirm pregnancy at the time of the first expected menstrual period. Clinical pregnancy was diagnosed 2 weeks after a positive test by the presence of a gestational sac with fetal echoes on ultrasound.

Results are presented as mean ± SD. Data were analyzed using Student's *t*-test and χ^2 test as appropriate. Cummulative pregnancy rates were calculated using Kaplan-Meier life-table analysis.

RESULTS

The 594 patients in Group A underwent 1,112 cycles of COH/IUI (cycles 1–3), with a mean of 1.9 cycles per patient. In group B, 91 women from group A underwent a total of 161 fourth, fifth, and sixth cycles of treatment, with a mean of 1.8 cycles per patient. The age of the patients (mean ± SD) in group A was 32 ± 4.5 years, in group B, 32.5 ± 4.6 years, and in group C, 32 ± 4.5 years. The duration of infertility (mean ± SD) was 6.5 ± 3.1 years in group A, 6.6 ± 3.2 years in group B, and 6.5 ± 3.1 years in group C. These differences were not statistically significant.

In group A, 182 pregnancies occurred in cycles 1–3, with an overall cycle fecundity of 16.4% per cycle and a cumulative PR of 39.2%. In group B, 9 clinical pregnancies occurred in patients undergoing their fourth, fifth, or sixth trial, with a cycle fecundity of 5.6% per cycle. The cumulative PR rose to 48.5% by cycle 6, a further increase of only 9.3%. The overall cycle fecundity in group B was significantly lower than that in group A (5.6% vs. 16.4%; $\chi^2 = 12.81$, $P<.001$).

In group C, in 131 women undergoing one cycle of IVF and ICSI after 3 failed cycles of COH/IUI, 48 clinical pregnancies occurred, giving a cycle fecundity of 36.6% per cycle. This is also significantly higher than the cycle fecundity in group B (36.6% vs. 5.6%; $\chi^2 = 44.33$, $P<.001$).

Twin pregnancies were reported in 18 patients (9.4%) in groups A and B and in 9 patients (18.7%) in group C. No high-order multiple pregnancies were reported in all groups.

Moderate OHSS (in the form of ovarian enlargment <10 cm, abdominal discomfort, and no clinically detected ascites) was reported in nine patients in groups A and B and

four patients in group C, but no one needed to be admitted to the hospital.

DISCUSSION

The effectiveness of ovulation induction and IUI in persistent infertility was the subject of a recent meta-analysis of 22 trials (16). The investigator concluded that average fecundability increased approximately fivefold when follicle-stimulating hormone (FSH) and IUI are used, compared with an untreated cycle. In another meta-analysis comparing COH and IUI with COH and timed intercourse in couples with unexplained infertility, patients undergoing IUI had a significantly higher PR (17). The results of these and other studies support the use of COH/IUI in the management of unexplained infertility. However, the optimum number of cycles of treatment is not stated in the above papers.

Several reports have been published on patients treated with ovulation induction and IUI, usually studied retrospectively, with infertility of differing etiologies treated with varying regimens (10, 11, 13, 18–26). Specific prognostic indicators have been sought to guide management and aid in counseling couples. Poor prognostic variables include increased female age (13, 18, 20–22, 25, 26), increased male age (21), longer duration of infertility (19, 25), greater hMG requirement (21), decreased endometrial thickness (19), lower number of follicles (18, 19, 25), poorer sperm motility (19, 24), and fewer inseminated sperm (13, 23). Patients with tubal factor, endometriosis, and male factor infertility have also been found to have lower PRs (10, 16, 25, 26).

The optimum number of cycles of COH/IUI is a pragmatic question when counseling a couple, and the literature suggests various answers. Some papers limit the number of cycles studied to 3 or 4. Several publications state that the PR decreases significantly after 3 (10) or 4 (20, 25) cycles. Recommendations include a maximum of 3 (9, 10, 18, 24), 4 (11, 20, 25), or 6 (12, 13) cycles of treatment. Some papers suggest a range of numbers: 3 to 6 cycles, depending on the etiology of infertility (26); 3 to 4 cycles (27); or several cycles (28).

This question arises because of the availability of the alternative treatments of IVF and ICSI. Several papers, including one from our center, have studied these techniques in couples with unexplained infertility and failed COH/IUI, with encouraging results (14, 29–31). Of note is the relatively higher rate of failed fertilization after IVF in these couples, a possible explanation for their unexplained infertility. For this reason, our policy is to perform IVF with ICSI on sibling oocytes in these patients. The oocytes were divided between IVF and ICSI, to avoid the possibility of total failure of fertilization by IVF, which occurs in 17.6% of cases of unexplained infertility (14).

The relative cost-effectiveness of COH/IUI and IVF must be considered, and it is important not to resort to IVF too soon at a much greater cost before the maximum chance of pregnancy with COH/IUI has been achieved. Alternatively, it is important not to waste time or money on ineffective treatments for a large number of cycles of COH/IUI if the chances of success are low. Guzick et al. (28) found a cost per pregnancy in women with unexplained infertility of $10,000 for clomiphene citrate (CC) and IUI, $17,000 for hMG/IUI, and $50,000 for IVF. They recommend that several cycles of CC and IUI be offered first. Van Voorhis et al. (32) found COH/IUI to be more cost-effective than assisted reproductive technology (ART) and recommend its use in women with open fallopian tubes, although the optimum number of cycles is not given. Another paper published this year also found that COH/IUI is cost-effective in unexplained infertility (33).

However, it must be remembered that cost-effectiveness compares the price per pregnancy for specific treatments, and a more cost-effective option can have a lower overall chance of pregnancy. A prospective trial in the UK of stimulated IUI vs. IVF in unexplained and mild male factor infertility did find similar PRs at approximately half the cost after 1 cycle. They concluded it to be the appropriate form of management (34). Although Van Voorhis et al. found COH/IUI to be cost-effective, with ART costing over three times more per delivery, the PR per cycle was lower with COH/IUI (32). In our center, the total cost of 3 cycles of COH/IUI is equivalent to 50% of the cost of 1 IVF/ICSI cycle. The low cost of COH/IUI makes it an attractive alternative and cost-effective option for the treatment of unexplained infertility. However, starting from the fourth cycle onward, this study has shown that the PR is disappointingly low and IVF/ICSI is more cost-effective after failure of three COH/IUI trials.

According to our results, women with unexplained infertility should undergo 3 cycles of COH/IUI with an expected cumulative PR of 39.2%. Not all women failing to conceive completed 3 cycles; if they had, a higher proportion of patients starting treatment would conceive. In group C, the cycle fecundity was 36.6% after 1 cycle of IVF with ICSI in women with three previous failed COH/IUI trials. This is consistent with the findings of Peterson et al., who found a course of up to 4 cycles of COH/IUI as effective as 1 cycle of IVF in achieving pregnancy, at a lower cost (11). Continuing COH/IUI for 4 to 6 cycles in our study gave a further increase of only 9.3% in the cumulative chance of pregnancy, compared with a cycle fecundity of 36.6% per cycle of IVF/ICSI after failure of three trials of COH/IUI.

An aggressive stimulation protocol in IUI cycles using GnRH analogues and large doses of FSH probably would have achieved a higher cycle fecundity compared with our conservative stimulation protocol. However, an increased rate of high-order multiple pregnancy and OHSS would have also occurred. In our large series of COH/IUI, no severe OHSS or high-order multiple pregnancy was reported.

The side effects and complications of the management

options must be considered when counseling couples. Results of studies on obstetric and neonatal outcome in COH/IUI are reassuring, but the high rate of multiple pregnancy is of concern (35). The risk of hyperstimulation is also important and was particularly mentioned in the report of the European Society of Human Reproduction and Embryology Capri Workshop (36). The complications of IVF, particularly multiple pregnancy, are well documented and emphasize the importance of a firm indication for this form of treatment.

In conclusion, our paper seeks to address the pragmatic problem of what to advise couples with unexplained infertility who have failed to conceive after 3 cycles of COH/IUI. The overall PR per cycle in cycles 4 to 6 of COH/IUI was significantly lower than in the first 3 cycles, and a markedly higher PR was achieved in the group receiving IVF/ICSI after 3 failed cycles of COH/IUI. These results should aid in counseling women as to the optimum management of their unexplained infertility.

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