# Clinical effects of ovulation induction with recombinant follicle-stimulating hormone supplemented with recombinant luteinizing hormone or low-dose recombinant human chorionic gonadotropin in the midfollicular phase in microdose cycles in poor responders

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**Objective:** To assess the clinical effects of recombinant luteinizing hormone (LH) or low-dose recombinant human chorionic gonadotropin (hCG) supplementation administered in the midfollicular phase in microdose gonadotropin-releasing hormone analogue (GnRH-a) flare-up cycles.
**Design:** Prospective randomized study.
**Setting:** Private infertility clinic.
**Patient(s):** A total of 170 women enrolled, with 145 women eligible for randomization.
**Intervention(s):** After randomization, 51 patients (group A) received only 600 IU of recombinant follicle-stimulating hormone (FSH) as the control group, 46 patients (group B) received 600 IU of recombinant FSH plus daily supplementation with 75 IU of recombinant luteinizing hormone, and 48 patients (group C) received 600 IU of recombinant FSH plus daily supplementation with 75 IU of recombinant hCG.
**Main Outcome Measure(s):** Peak estradiol ($E_2$) levels, days of stimulation with recombinant FSH, total recombinant FSH dosage, metaphase II oocytes retrieved, pregnancy rate (positive hCG levels), clinical pregnancy rate (positive fetal cardiac activity), and cancellation rates of stimulation and embryo transfer.
**Result(s):** The pregnancy rates were 35.1%, 27.6% and 31.2% for groups A, B, and C, respectively. Clinical pregnancy rates were 27.1%, 27.5, and 21.8% for groups A, B, and C, respectively. There were no statistically significant differences in the age, peak serum $E_2$ concentration, total recombinant FSH dosage, days of stimulation with recombinant FSH, total number of metaphase II oocytes retrieved, number of embryos transferred, pregnancy rates, clinical pregnancy rates, or cancellation rates of stimulation and embryo transfer among the three groups.
**Conclusion(s):** Additional exogenous LH activity in the form of either recombinant luteinizing hormone or low-dose recombinant hCG is unnecessary in microdose cycles to increase pregnancy rates. (Fertil Steril® 2007; 88:665–9. ©2007 by American Society for Reproductive Medicine.)

**Key Words:** Recombinant hCG, LH, FSH, microdose cycle, pregnancy rate

Diminished ovarian reserve is a condition that can occur in women at any adult age, although it is more frequently found in women in their 30s. There are several tests to diagnose this problem. These include basal tests for follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol ($E_2$), and inhibin B, or dynamic tests such as the clomiphene citrate challenge test and gonadotropin analogue stimulating test. In recent years, great attention has been given to direct tests such as the antral follicle count. One study has shown that good responders have a mean number of 13 antral follicles (1).

Women with diminished ovarian reserve are candidates for poor responder treatment. During controlled ovarian hyperstimulation (COH) for assisted reproductive technologies (ART), poor-response patients are those who show poor follicle recruitment in terms of number (generally three or four follicles) or size and have low levels of peak serum $E_2$ despite the high dose of gonadotropin administered. An ideal approach to patients who respond poorly to traditional COH regimens in preparation for ART has yet to be established. Some investigators have sought to take advantage of the initial endogenous gonadotropin "flare" induced by gonadotropin-releasing hormone analogue (GnRH-a) by using microdoses of an agonist in the early follicular phase to enhance the effect of exogenous gonadotropins (2–4). Since 2002, our clinic has preferred to use a microdose flare protocol for women who have diminished ovarian reserve, defined as having fewer than 12 antral follicles on baseline ultrasound examination.

The role of exogenous LH supplementation during COH also has been a matter of debate since the very beginning of ART. There are several unresolved issues, namely, the

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population of patients with whom LH could be beneficial (i.e., all patients, poor responders, and/or normal responders with low levels of basal LH), the type of stimulation protocol, and the type of preparation: human menopausal gonadotropin (hMG), recombinant LH, or a small amount of urinary human chorionic gonadotropin (hCG). Recombinant hCG has been recently developed and has started to be used for triggering ovulation in assisted conception (5). Our aim in this prospective, randomized study was to assess the clinical effects of recombinant LH or low-dose recombinant hCG supplementation when administered in the midfollicular phase in microdose GnRH-a flare cycles.

## MATERIALS AND METHODS

### Patients and Protocols

The study group included 170 women who had fewer than 12 antral follicles and were undergoing a microdose protocol with GnRH-a followed by recombinant FSH administration. The diagnoses in the study population comprised tubal factors (18.3%), endometriosis (11.6%), unexplained infertility (13.3%), and male factor infertility (56.5%). Excluded were women older than 42 years, women with only one ovary, and women with a basal FSH concentration of >12 IU/L. To minimize selection bias, only the first intracytoplasmic sperm injection (ICSI) cycle was analyzed. The study protocol was approved by the institutional review board, and all patients gave informed consent.

### Stimulation Protocol

Following 3 weeks of oral contraceptive use (Gynera, Schering A.G., Istanbul, Turkey), 40 μg of leuprolide acetate (Lucrin, Abbott, Paris, France) two times daily was started on day 1 of withdrawal bleeding, and 600 IU of recombinant FSH (Gonal F, Serono, Bari, Italy; Puregon, Organon, Oss, Holland) was started on day 3. On the seventh day of stimulation, the patient's treatment cycle was canceled if she had fewer than three growing follicles.

The remaining 145 patients were randomized to three groups (Table 1). The control group (group A) received only 600 IU of recombinant FSH. Group B received 600 IU of recombinant FSH supplemented by 75 IU/day of recombinant LH (Luveris, Serono). Group C received 600 IU of recombinant FSH supplemented by 75 IU/day of recombinant hCG (Ovitrelle, Serono).

A patient's treatment was canceled if the follicles failed to grow. When at least two follicles were greater than 17 mm, 10,000 IU hCG (Pregnyl, Organon) was administered. Oocyte retrieval was performed 35 hours later.

After ICSI, embryo transfers were routinely performed on day 2. The luteal phase was supported using 90 mg twice daily of intravaginal progesterone gel (Crinone gel 8%, Serono). Twelve days after embryo transfer, serum was taken for β-hCG assessment. At 6-weeks' gestation, an ultrasound scan was performed to confirm the number of sacs and fetal viability.

### Ultrasound and Laboratory Assays

All ultrasound measurements were performed using a 6.5-MHz vaginal probe (Siemens Sonoline Sienna; Semens AG, Erlangen, Germany). Antral follicles were counted on cycle day 3 before initiation of the stimulation protocol. On day 3, serum FSH was also measured using a chemiluminescent immunoassay (Immulite; Euro/DPC, Glyn Rhonwy, Llanberis, Gwynedd, United Kingdom).

The stimulation response was monitored with serial measurements of serum $E_2$ and transvaginal ultrasonic evaluation of follicle number and size. Serum $E_2$ was measured using a chemiluminescent immunoassay (Immulite, Euro/DPC).

### Statistical Analysis

Age, percentage of patients over 37 years of age, antral follicle count, basal (day-3) FSH, peak $E_2$ levels, days of stimulation with recombinant FSH, the total recombinant FSH dose, metaphase II (M2) oocytes retrieved, pregnancy rate (positive hCG results), clinical pregnancy rate (positive fetal cardiac activity), cancellation rates of COH (after day 7), and embryo transfers were compared among the groups.

Analysis of variance (ANOVA) and the chi-square test were used for statistical comparisons. $P<.05$ was considered statistically significant. Statistical calculations were

**TABLE 1**

**Stimulation protocol.**

| Protocol | Group A (n = 51) | Group B (n = 46) | Group C (n = 48) |
|---|---|---|---|
| Oral contraceptive usage before stimulation (3 weeks) | Yes | Yes | Yes |
| Leuprolide acetate (started on day 1) | Yes | Yes | Yes |
| Recombinant FSH (started on day 3) | Yes | Yes | Yes |
| Recombinant LH (started on day 7) | No | Yes | No |
| Recombinant hCG (started on day 7) | No | No | Yes |

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**TABLE 2**

**Demographic features.**

| | Group A (rFSH) (n = 51) | Group B (rFSH + rLH) (n = 46) | Group C (rFSH + r-hCG) (n = 48) | *P* value |
|---|---|---|---|---|
| Age | 34.9 ± 0.5 | 36.3 ± 0.7 | 35.2 ± 0.9 | .26 |
| Patients >37 years (%) | 29.4 | 41 | 36.9 | .37 |
| No antral follicles | 5.8 ± 0.4 | 6.6 ± 0.6 | 6.3 ± 0.5 | .69 |
| Day-3 FSH (IU/L) | 6.8 ± 1.7 | 7.3 ± 1.8 | 7.1 ± 1.9 | .98 |
| Peak $E_2$ levels | 1897.1 ± 427 | 2003.1 ± 468 | 2362.7 ± 292 | .44 |
| Days of stimulation | 9.1 ± 0.3 | 8.5 ± 0.3 | 8.1 ± 0.2 | .06 |
| Recombinant FSH dosage (IU) | 5454.5 ± 177 | 5125.7 ± 165 | 4902.4 ± 148 | .053 |
| M2 oocytes retrieved | 5.6 ± 0.7 | 4.8 ± 0.6 | 3.8 ± 0.4 | .19 |
| Embryos transferred | 2.5 ± 0.2 | 2.4 ± 0.3 | 2.1 ± 0.2 | .46 |

*Note:* Values are mean ± standard error of mean.

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performed using Sigmastat for Windows, version 3.0 (Jardel Scientific Corporation, San Rafael, CA).

## RESULTS

Among the three groups, there were no statistically significant differences in age, percentage of patients over 37 years of age, total number of antral follicles, basal FSH, peak $E_2$ level, days of stimulation with recombinant FSH, dosage of recombinant FSH used, total number of M2 oocytes retrieved, or number of embryos transferred (Table 2). However, a decrease in the mean days of stimulation with recombinant FSH in groups C and B compared with group A was detected that was very close to statistical significance ($P$=.06). Furthermore, in terms of the mean number of M2 oocytes retrieved in each group, a trend toward decrease was shown in groups C and B compared with group A ($P$=.053).

In addition, the cancellation rate for COH and embryo transfers, and the pregnancy rate among the three groups showed no statistically significant difference (Table 3). The cancellation rate of stimulation after day 7 was 13.7% for group A, 10.2% for group B, and 10.8% for group C. The cancellation rate of embryo transfer was 15.9% for group A, 17.1% for group B, and 21.9% for group C. Overall cancellation rates, including cancellation rates of both stimulation and embryo transfer, were 27.4% for group A, 25.6% for group B, and 30.4% group C. The pregnancy rates for groups A, B, and C were 35.1%, 27.6%, and 31.2%, respectively. The clinical pregnancy rates were 27.1%, 27.5%, and 21.8%, respectively.

## DISCUSSION

The ideal approach to patients who respond poorly to traditional COH regimens in preparation for ART has yet to be established. There are several debates about the type of COH regimens and the dosage of gonadotropins. Researchers have analyzed the effect of increasing gonadotropin dosages as a means of enhancing ovarian response (6, 7). Microdose GnRH-a flare cycles have been shown to be efficacious in women who have diminished ovarian reserve or are poor responders to luteal phase protocols (8).

Alongside these debates, LH supplementation in ART cycles has been controversial as well. Exogenous LH

**TABLE 3**

**Clinical outcomes.**

| Outcome | Group A | Group B | Group C | *P* value |
|---|---|---|---|---|
| Cancellation rate of COH (%) | 13.7 | 10.2 | 10.8 | .85 |
| Cancellation rate of ET (%) | 15.9 | 17.1 | 21.9 | .75 |
| Cancellation rate of COH + ET (%) | 27.4 | 25.6 | 30.4 | .88 |
| Pregnancy rate (%) per transfer | 35.1 | 27.6 | 31.2 | .80 |
| Clinical pregnancy rate (%) per transfer | 27.1 | 27.5 | 21.8 | .65 |

*Note:* COH, controlled ovarian hyperstimulation; ET, embryo transfer.

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supplementation could be provided by hMG, recombinant LH, urinary hCG, or recombinant hCG. Because the potency of hCG is approximately six times that of LH, and hCG has a longer half-life than LH (9), low-dose hCG has been used for LH supplementation (10). Filicori et al. (10), who used different doses of urinary hCG, including 50 IU/day, 100 IU/day, and 200 IU/day, showed that low-dose hCG administration can stimulate folliculogenesis. Therefore, we chose a regimen of 75 IU/day of recombinant hCG.

The literature has shown three main trends when discussing LH activity in ART. First, some investigators contend that LH supplementation has no role in treatment or that it even may have a negative impact (11–13). Our observation of no statistically significant differences in pregnancy rate or clinical pregnancy rate when comparing the women who received only recombinant FSH (group A), recombinant FSH plus LH (group B), or recombinant FSH plus recombinant hCG (group C) would seem to support this.

Second, some practitioners believe that LH should be used in all women because it increases the ovarian response to FSH, reducing the dosage needed and the length of stimulation (10, 14–17). In our study, we also saw a trend toward decrease in the days of stimulation with recombinant FSH and in the total dose of recombinant FSH in the group who received recombinant FSH and LH (group B) and recombinant FSH and recombinant hCG (group C), compared with the group who received only recombinant FSH (group A). On the other hand, this trend in activity was not detected by previous studies where FSH and hMG were compared (18, 19).

Third, LH can be useful in some clinical situations such as strong down-regulation due to a GnRH analogue, women of advanced age, or women who previously had required high levels of FSH to stimulate their ovaries (20–23). Research has shown that LH activity provided by urinary hCG supplementation in the midfollicular phase is associated with favorable pregnancy results in low responders using a long protocol (24). However, we did not observe a similar effect in microdose flare cycles with women who have diminished ovarian reserve.

Conflicting evidence also exists regarding the effects on $E_2$ levels and on oocyte and embryo quality. Studies have found that $E_2$ levels rise more slowly in patients treated with FSH alone than with combined FSH and LH (16, 17). Adding recombinant LH has resulted in higher peak serum $E_2$ levels without any affect on the outcome in IVF cycles stimulated under GnRH agonists (25) or GnRH antagonists (26). Although we found a trend of increase in $E_2$ levels in the groups who received recombinant FSH and LH (group B) and recombinant FSH and recombinant hCG (group C) when compared with the group who received only recombinant FSH (group A), the differences among the groups were not statistically significant.

Earlier studies found a higher percentage of mature oocytes in patients treated with FSH than in patients treated with hMG (19, 27); however, more recent studies could not identify any significant difference (28–30). Embryo quality also was found to be comparable (30).

Our study observed that the mean number of M2 oocytes was greater in the patients who had received only recombinant FSH (group A) than in those who had received recombinant FSH and LH (group B) or recombinant FSH and recombinant hCG (group C), but the difference was not statistically significant. The addition of LH activity may selectively achieve large follicle formation and curtail smaller, less mature follicle development. Filicori et al. (10) showed that low-dose hCG could exert its stimulatory action on larger ovarian follicles even when the administration of exogenous FSH was reduced or discontinued altogether. In addition, another study showed that there was a statistically significant inverse relationship between the amount of LH activity and the number of small preovulatory follicles (31).

A more complete understanding the underlying physiology would require measuring serum LH and androgen levels during the late follicular phase especially. Filicori et al. (32) observed no difference in serum levels of LH, $E_2$, progesterone, and testosterone when comparing the group who received only FSH and one who received FSH plus hCG in a long GnRH agonist regimen. A similar study could be designed for a microdose flare cycle.

In microdose flare cycles, there is an initial rise in endogenous gonadotropins. This protocol is associated with markedly elevated follicular-phase LH concentrations, which are actually higher than in patients treated with hMG in a long GnRH agonist regimen (33). Therefore, it can be assumed that this condition does not require additional exogenous LH activity in the form of either recombinant LH or low-dose recombinant hCG in microdose cycles in women with diminished ovarian reserve.

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