

# Recombinant follicle-stimulating hormone in the treatment of patients with history of severe ovarian hyperstimulation syndrome\*

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**Objective:** To compare the low-dose recombinant FSH and hMG protocols in treatment of patients with history of severe ovarian hyperstimulation syndrome (OHSS).

**Design:** A prospective study on 22 patients with history of severe OHSS. Group A (n = 14) was treated with low-dose recombinant FSH in 40 cycles and group B (n = 8) was treated with low-dose hMG in 26 cycles.

**Setting:** The Egyptian IVF-ET Center, Cairo, Egypt.

**Patient(s):** Twenty-two patients with a history of severe OHSS.

**Intervention(s):** Ovulation induction.

**Main Outcome Measure(s):** Estradiol, number of follicles, number of hMG ampules, pregnancy rate (PR), and the development of OHSS.

**Result(s):** The cancellation rate, mean E<sub>2</sub> level on day of hCG, mean number of days of stimulation, and the mean number of ampules per cycle were 10%, 523 ± 166 pg/mL (conversion factor to SI unit, 3.671), 17.8 ± 5.4, and 19 ± 6.5 in group A and 19.2%, 554 ± 152 pg/mL, 14.6 ± 2.5, and 16.1 ± 3.6 in group B, respectively. Treatment resulted in eight pregnancies (20% per cycle) and two abortions (25%) in group A. In group B, four pregnancies resulted (15.4% per cycle) and two patients aborted (50%). No cases of OHSS developed in both groups. There were no significant differences in all parameters between the two groups.

**Conclusion(s):** Recombinant FSH low-dose protocol proved to be as effective as low-dose hMG in producing reasonable ovulation and PRS in polycystic ovary syndrome patients with a history of severe OHSS and the protocol was safe concerning the risk of development of OHSS. (Fertil Steril® 1996;66:757-60. ©1996 by American Society for Reproductive Medicine.)

**Key Words:** Recombinant FSH, prospective, ovarian hyperstimulation syndrome, low-dose protocol, hMG, polycystic ovaries

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Patients with a history of severe ovarian hyperstimulation syndrome (OHSS) after ovulation induction by gonadotropins represent a difficult clinical problem. It was reported previously that all patients who developed severe OHSS have some form of polycystic ovary syndrome (PCOS) (1). Repeated induction of ovulation in this group of patients using the conventional hMG protocol carries a high risk of development of OHSS once more.

Low-dose FSH protocol was tried successfully in the treatment of patients with PCOS and it achieved a reasonable ovulation and

pregnancy rates (PRs) and reduced the risk of the development of OHSS (2-6). Recently, biotechnology has made available for clinical use a recombinant FSH hormone preparation produced in vitro. Several reports demonstrated successful ovulation induction and establishment of pregnancy and birth using recombinant FSH (7, 8).

Recently, induction of ovulation and pregnancy were reported using recombinant FSH in patients with PCOS (9, 10). The objective of this study is to evaluate the safety of low-dose recombinant FSH stimulation protocol in pa-

tients with a history of severe OHSS and to compare it with the low-dose hMG protocols. To the best of our knowledge this is the first report in the literature on the use of recombinant FSH in patients with a history of severe OHSS.

## MATERIALS AND METHODS

Twenty-two women with a history of severe OHSS during ovarian stimulation in a previous cycle using conventional hMG or GnRH-a and hMG protocols are the subject of this study. The diagnosis of severe OHSS was based on the presence of dyspnea, abdominal pain, and gastrointestinal symptoms, in addition to enlarged ovaries >10 cm in diameter and the presence of ascites (11). In 15 cases, critical OHSS (12) was diagnosed with the presence of tense ascites, hemoconcentration, and oliguria. Our standard protocol of transvaginal aspiration of ascitic fluid and IV fluid therapy was performed in 19 of 22 patients (13).

Clinical examination and investigations of the study group revealed the presence of anovulatory infertility and PCOS criteria in all patients in the form of amenorrhea or oligomenorrhea, high basal LH, and ultrasonic picture of PCOS. Hirsutism was present in 10 patients. All women had patent tubes diagnosed by hysterosalpingography or laparoscopy.

All patients were informed about the nature of the study and they signed a consent. The protocol was accepted by our internal ethical committee.

Patients were divided into two groups, group A had 14 patients and group B had 8 patients. The first six patients included in this study were assigned prospectively to group A. The next 14 patients were divided on alternate basis between group A and group B. The original plan was to do a prospective study on 10 patients using the low-dose recombinant FSH, however, the response of our colleagues to refer cases and of our patients with history of severe OHSS to letters and telephone calls was high and, as a large number were turned in and wanted to join the study, we decided to divide the patients starting from patient 7 between low-dose recombinant FSH and low-dose hMG. The mean age in group A was  $29.6 \pm 7.1$  years and in group B was  $27 \pm 7.6$  years. The mean duration of infertility was  $5 \pm 2.1$  years in group A and  $4.8 \pm 1.3$  years in group B. The basal LH was  $16.6 \pm 2.1$  mIU/mL (conversion factor to SI unit, 1.00) in group A and  $17 \pm 1.3$  mIU/mL in group B and the basal FSH was  $4.5 \pm 1.3$  mIU/mL (conversion factor to SI unit, 1.00) in group A and  $5.4 \pm 1.3$  in group B. Seven patients in group A and three patients in group B had hirsutism. Three patients in group A and two patients in group B had amenorrhea; the rest of the patients in both groups had oligomenorrhea.

In group A, one ampule (75 IU) of recombinant FSH (Gonal F; Serono, Geneva, Switzerland) was given IM daily for 14 days and was increased by increments of 37.5 IU weekly if there was no adequate response as monitored by

serum  $E_2$  levels and transvaginal ultrasound (US) using a 7-MHz transducer (model 8538, 7 MHz ultrasound scanner model 1849 D, DK-2850; Bruel and Kjaer, Naerum, Denmark). The response was considered adequate if at least one follicle was growing steadily and the  $E_2$  level was rising. The first US was performed 1 week after the start of FSH administration and repeated every 2 to 3 days after appearance of follicular activity or increase in the endometrial thickness. Estradiol was measured two to three times during the course of stimulation and the last measurement was done on day of hCG administration. Human chorionic gonadotropin (5,000 IU, Profasi; EPICO, Cairo, Egypt) was given IM if at least one follicle reached 16 mm in diameter. If more than three follicles were >16 mm, the cycle was canceled.

In group B the same low-dose protocol was used and recombinant FSH was replaced by hMG (Pergonal; EPICO). In this study, the criteria for diagnosis of occurrence of OHSS were ovarian enlargement >10 mm in diameter, dyspnea, gastrointestinal symptoms, and abdominal distention. Clinical pregnancy was diagnosed by the presence of a gestational sac visualized by US.

## RESULTS

In group A, 14 patients underwent 40 cycles: 4 cycles were canceled due to poor response or irregular bleeding (10%) and the rest achieved adequate response. The mean  $E_2$  level on day of hCG injection was  $523 \pm 166$  pg/mL (conversion factor to SI unit, 3.671). In 15 cycles, there was more than one follicle >16 mm, the remaining 21 cycles showed monofollicular growth, the mean number of days of stimulation was  $17.8 \pm 5.4$  days and the mean number of ampules per cycle was  $19 \pm 6.5$ . Treatment resulted in eight pregnancies (20% per cycle), two patients aborted (25%), and there are six ongoing singleton pregnancies. There were no cases of OHSS.

In group B, eight patients underwent 26 cycles, and five cycles were canceled (19.2%) due to poor response. The mean  $E_2$  level on day of hCG was  $554 \pm 152$  pg/mL. In 11 cycles there was more than one follicle >16 mm. The remaining 10 cycles showed monofollicular growth. The mean number of days of stimulation was  $14.6 \pm 2.5$  days and the mean number of ampules per cycle was  $16.1 \pm 3.6$ . Treatment resulted in four pregnancies (15.4% per cycle), two patients aborted (50%) and there are two ongoing pregnancies. No cases of OHSS were reported. There was no statistically significant difference between the number of ampules, days of stimulation,  $E_2$  level on day of hCG, and the PRs between both groups.

The mean  $E_2$ , mean number of ampules, and mean days of stimulation were calculated for each patient and analysis was performed using the means of each patient. Comparison between the two groups was done using the Student's *t*-test.

Comparison between PRs and abortion rates in both groups was done using the Fisher's exact test.

## DISCUSSION

Severe OHSS is a serious iatrogenic complication of ovulation induction by gonadotropins (14). Polycystic ovary syndrome was found to be an important risk factor for the development of OHSS (1). Several methods for prediction and prevention of the syndrome have been suggested. Nevertheless, with the available means, complete prevention of the syndrome is impossible (15).

Successful induction of ovulation in patients with PCOS remains a difficult problem and no single method has emerged as the treatment of choice. Inclusion in this study was based on the past history of development of severe OHSS during conventional stimulation protocols using hMG, however, all patients were found to have PCOS. This extremely high risk group of patients constituted a major threat if conventional methods of ovulation induction would have been attempted.

Several reports in the recent literature have demonstrated the effectiveness and safety of the low-dose hMG protocol for induction of ovulation in PCOS patients (2, 4, 6). Using the low-dose protocol, Homburg et al. (5) reported a PR that compared favorably with the conventional hMG protocol in patients with PCOS and they reported nil incidence of OHSS and multiple pregnancies. The main problem when using conventional hMG protocol is the high frequency of multifollicular development that is responsible for high rates of OHSS (16). Meldrum (17) suggested that the various benefits of low-dose gonadotropin protocol should prompt reconsideration and probably replace conventional gonadotropin therapy.

Considering all the above reasons, the low-dose stimulation protocol was chosen for this work. The rationale behind this study was inducing the growth of one follicle and at most three follicles. We followed the previous protocols published by Polson et al. (3), Sagle et al. (18), and Shoham et al. (6).

The aim is to use the smallest effective dose to achieve ovulation. The cancellation rate due to failure to induce adequate response was 10% in recombinant FSH group, which is comparable to cancellation rates of 8% to 15% using low-dose FSH and hMG reported in the literature (3, 4, 19).

Clinical PRs of 20% per cycle in group A and 15.4% per cycle in group B in this study compare favorably with previous reports using low-dose therapy for PCOS patients (5, 6). It was reported previously that the miscarriage rate is rather high in PCOS patients irrespective of the stimulation protocol used (20–22). However, the number of pregnancies and abortions is too small in our study to give a high power

of significance. Although there was no significant difference between recombinant FSH and hMG in this study, these findings should be taken cautiously because of the small sample size.

Patients with PCOS are known to have a peculiar hypersensitivity to gonadotropins, however, this sensitivity varies from one patient to another for some unknown reason. Severe OHSS develops in one patient with a high level of  $E_2$  and a large number of follicles and does not develop in another patient with the same number of follicles and  $E_2$  levels. All patients included in this study proved to have PCOS and were highly sensitive to gonadotropins. In this most sensitive group of patients, the low-dose protocol using recombinant FSH or hMG was effective in inducing reasonable ovulation and PRs without the risk of development of OHSS. This is in support of Brown's theory (23) of the ovarian threshold requirements of FSH during gonadotropin treatment.

The present work showed no significant difference in the age,  $E_2$  level on day of hCG, number of hMG and recombinant FSH ampules, duration of treatment, and PRs. No multiple pregnancy or OHSS occurred in both groups.

The endocrine profile of PCOS patients is characterized by high endogenous LH levels. This could be detrimental on low conception and high abortion rates (24). As FSH preparations derived from recombinant sources are devoid of intrinsic LH activity, theoretically speaking their use in PCOS patients might be beneficial (6). However, the use of pure FSH previously did not prove to be superior to the use of hMG in PCOS patients (18).

This might denote that the LH content of hMG has no deleterious effect on ovulation. Shoham et al. (6) found that the level of LH is significantly lower on day of hCG when they compared low-dose with conventional hMG therapy. This may be an important advantage of the low-dose protocol.

In the present study, the recombinant FSH, which is completely devoid of LH activity, was found to be equivalent to hMG. However, the expected better batch-to-batch consistency because the FSH isoform profile is controlled and the high purity, which may allow SC administration, may give both the clinician and the patient greater confidence and convenience. In conclusion, low-dose recombinant FSH ovulation induction protocol was effective and safe in patients with a history of severe OHSS.

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