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# Ovarian Stimulation in Obese and Non-obese Polycystic Ovary Syndrome Using a Low-dose Step-up Regimen with Two Different Starting Doses of Recombinant Follicle-stimulating Hormone

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**Sixty-seven infertile women with polycystic ovary syndrome (PCOS) were divided into two groups, obese and non-obese, according to their body mass index. Waist-to-hip ratio, insulin resistance, total testosterone and dehydroepiandrosterone sulphate levels were significantly elevated in obese, compared with non-obese, patients. Both groups were treated with a low-dose step-up protocol of recombinant follicle-stimulating hormone (rFSH) with a starting dose of 50 IU/day and, every third day, a 25-IU increase in the dose until the appropriate dose was achieved for each individual, up to a maximum of 175 IU/day. In the obese group only, repeat therapy commenced in the second ovulatory cycle in women who had not become pregnant, however a starting dose of 75 IU/day was then used, with incremental and maximum dose as before. The results of the starting dose of 75 IU/day rFSH were compared with the results of a 50 IU/day rFSH starting dose in the obese group. A starting dose of 50 IU/day rFSH in a low-dose step-up regimen was found to be effective, safe and well-tolerated for inducing follicular development in non-obese infertile women with PCOS. However, for obese PCOS patients, a starting dose of 75 IU/day rFSH is recommended.**

KEY WORDS: POLYCYSTIC OVARY SYNDROME; RECOMBINANT FOLLICLE-STIMULATING HORMONE; LOW-DOSE STEP-UP REGIMEN; OBESITY; OVULATION INDUCTION

## Introduction

Polycystic ovarian syndrome (PCOS) is the most common hormone disorder in women of reproductive age, characterized by hyper-androgenism and chronic anovulation; it is estimated to affect 5% – 10% of women.[1] PCOS may be diagnosed on the Rotterdam criteria, which is based on having two of the following three features: (i) oligo-ovulation or anovulation; (ii) clinical and/or

biochemical signs of hyperandrogenism; and (iii) polycystic ovaries on ultrasound examination (defined as the presence of ≥ 12 follicles measuring 2 – 9 mm in diameter and/or ovarian volume > 10 $cm^3$).[2]

Insulin resistance, defined as reduced utilization of insulin-mediated glucose, has been found in 10% – 25% of the obese population in sophisticated, dynamic studies of insulin action.[3] Insulin resistance is most commonly found in obese PCOS women (65%), but can also occur in about 20% of lean PCOS women.[4] Obesity has profound effects on both the pathophysiology and the clinical manifestation of PCOS by different mechanisms, leading to androgen excess and increased free androgen availability, and to alterations in granulosa cell function and follicle development.[5]

Most cycles in patients with infertility and PCOS are anovulatory. Infertility is due to anovulation in approximately 75% of women:[6] serum and ovarian androgen levels are raised and associated with impaired folliculogenesis.[7] Although the anti-oestrogen, clomiphene citrate, is the first-choice agent for ovulation induction in infertile women with PCOS, a woman who fails to conceive on this medication after three or four ovulatory cycles is unlikely to respond to this medication and should be considered as clomiphene citrate-resistant.[8] In addition, the frequent development of multiple follicles leads to the risk of multiple pregnancy and ovarian hyperstimulation syndrome. To overcome these risks, a low-dose step-up protocol with recombinant follicle-stimulating hormone (rFSH) is an effective and safe choice for inducing ovulation in clomiphene citrate-resistant infertile PCOS cases.[9]

In the present study, ovulation induction with rFSH in a low-dose step-up regimen in obese and non-obese groups of patients with PCOS was evaluated to determine the appropriate starting dose of rFSH in both groups.

# Patients and methods

## PATIENTS

Women with PCOS diagnosed on the Rotterdam criteria[2] who had been referred to Yuzuncu Yil University Hospital for fertility treatment were enrolled into this study. There was no age limit for inclusion. The patients were divided into two groups according to body mass index (BMI): an obese group (BMI ≥ 25 $kg/m^2$) and a non-obese group (BMI < 25 $kg/m^2$). All patients had primary infertility, a normal hysterosalpingogram or laparoscopy, no history of pelvic surgery or pelvic inflammatory disease recorded prior to ovulation induction and male partners with normal semen parameters. According to the Guidelines of the Social Insurance Institution of Turkey, ovulation induction should be attempted with gonadotrophin in all patients with PCOS and the expenses will be covered for a maximum of three cycles.[10] None of the patients had used gonadotrophins before enrolment in this study.

The study was approved by the Yuzuncu Yil University Ethics Committee for Clinical and Laboratory Research. Written, informed consent to participate in the study was obtained from each patient.

## TREATMENTS, MEASUREMENTS AND EVALUATIONS

Both BMI and waist-to-hip ratio (WHR) were measured for each patient. BMI was calculated as weight (kg)/height $(m)^2$. The WHR was calculated by dividing the minimal waist circumference by the hip circumference at the level of the greater trochanters. The degree of hirsutism was

determined using the Ferriman–Gallwey score.[11]

A morning blood sample was taken after an overnight fast of ≥ 12 h during the follicular phase (between days 3 and 5) of each patient's spontaneous or progestin-induced menstrual cycle. The homeostasis model assessment of insulin resistance (HOMA-IR) was used to evaluate insulin resistance, using the following formula:[12] HOMA-IR = (IRI × FPG)/22.5, where IRI is fasting plasma immunoreactive insulin (μU/l) and FPG is fasting plasma glucose (mmol/l).

Treatment with rFSH (follitropin beta; Puregon®, NV Organon, Oss, The Netherlands) commenced 2 days after spontaneous or progestin-induced withdrawal bleeding. A low-dose step-up regimen was used, starting with 50 IU/day rFSH and followed by a 25-IU increase in the dose every third day until the appropriate dose was achieved for each individual. The dose was increased up to a maximum of 175 IU/day. Ovulation was induced using 5000 – 10 000 IU human chorionic gonadotrophin (hCG) when the leading follicle was ≥ 18 mm in diameter, with no other follicles > 14 mm. In the obese group, repeat therapy commenced in women who did not become pregnant after the first ovulatory cycle, however a starting dose of 75 IU/day rFSH was then used with dose increases and maximum dose as before.

Ovarian response was monitored prospectively by ultrasound using a 7.5 MHz Philips HD X11 transvaginal transducer (Philips, Eindhoven, The Netherlands). Serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone (TT) and dehydroepiandrosterone sulphate (DHEAS) concentrations were measured by chemiluminescent immunoassay (Immulite®, Diagnostic Products Corporation, Los Angeles, CA, USA) in single assays. The main outcome measures were treatment duration, total doses of rFSH, threshold dose and number of follicles ≥ 18 mm on the day of hCG administration.

### STATISTICAL ANALYSIS

Statistical evaluation of the data was carried out using the Statistical Package for Social Sciences (SPSS® version 15.0; SPSS Inc., Chicago, IL, USA). When evaluating the data (in addition to the definitive statistical methods of median and SD calculations for comparison of the quantitative data), Student's *t*-test was used for intergroup comparisons of the normal distribution parameters and the Mann–Whitney *U*-test was used for the intergroup comparisons of the abnormal distribution parameters. The paired sample *t*-test was used for intragroup comparisons of the normal distribution parameters and the Wilcoxon signed-rank test was used for intragroup comparisons of the abnormal distribution parameters. The results were evaluated with a confidence interval of 95% and a significance level of $P < 0.05$.

## Results

Sixty-seven women with PCOS (28 in the obese group; 39 in the non-obese group), diagnosed on the Rotterdam criteria,[2] were included in the study and their baseline clinical and biochemical features are given in Table 1. Their ages and duration of infertility were similar between the groups. Compared with the non-obese group, BMI, HOMA-IR, WHR, TT and DHEAS were all significantly elevated in the obese group ($P < 0.01$). Ferriman–Gallwey scores and LH levels were slightly higher in the obese group compared with the non-obese group, but the difference was not significant. Levels of FSH and LH, and the LH/FSH ratio were similar in both the obese and non-obese groups.

The outcome of rFSH treatment with a

**TABLE 1:**
**Baseline clinical and biochemical features (mean ± SD) of obese and non-obese patients with polycystic ovary syndrome (PCOS) included in the study of ovulation induction with a low-dose step-up regimen of recombinant follicle stimulating hormone (rFSH)**

| Parameter | Obese PCOS ($n$ = 28) | Non-obese PCOS ($n$ = 39) | Statistical significance |
|---|---|---|---|
| Age (years) | 28.46 ± 4.42 | 25.82 ± 3.07 | NS |
| Duration of infertility (years) | 4.03 ± 1.73 | 4.00 ± 1.83 | NS |
| Body mass index (kg/m$^2$) | 29.74 ± 2.59 | 22.26 ± 1.89 | $P < 0.01$ |
| Waist-to-hip ratio | 0.82 ± 0.02 | 0.77 ± 0.03 | $P < 0.01$ |
| HOMA-IR | 3.55 ± 0.61 | 2.61 ± 0.29 | $P < 0.01$ |
| Ferriman–Gallwey score | 12.82 ± 2.73 | 11.74 ± 2.24 | NS |
| LH (mIU/ml) | 10.46 ± 2.65 | 9.35 ± 2.10 | NS |
| FSH (mIU/ml) | 5.31 ± 1.20 | 4.90 ± 1.03 | NS |
| LH/FSH ratio | 1.98 ± 0.33 | 1.91 ± 0.25 | NS |
| Total testosterone (ng/dl) | 110.75 ± 17.64 | 95.61 ± 14.28 | $P < 0.01$ |
| DHEAS (µg/dl) | 323.89 ± 27.08 | 280.87 ± 39.90 | $P < 0.01$ |

Data all analysed using Student's *t*-test.
NS, not statistically significant ($P > 0.05$); HOMA-IR, homeostasis model assessment of insulin resistance; LH, luteinizing hormone; FSH, follicle-stimulating hormone; DHEAS, dehydroepiandrosterone sulphate.

starting dose of 50 IU/day for all patients with PCOS is shown in Table 2. Treatment duration was significantly longer ($P < 0.01$) and the total dose of rFSH was significantly higher ($P < 0.01$) in obese patients compared with non-obese patients. The threshold dose was also significantly elevated in the obese group compared with the non-obese group ($P < 0.01$), as was the median threshold dose ($P < 0.01$). No significant difference between the two groups was found between the mean number of follicles ≥ 18 mm on the day of hCG administration.

At the second ovulatory cycle, in the obese

**TABLE 2:**
**Outcome measures (mean ± SD and median) for obese and non-obese patients with polycystic ovary syndrome (PCOS), treated with a low-dose step-up regimen of recombinant follicle-stimulating hormone (rFSH) administration (starting dose 50 IU/day, followed by 25-IU incremental doses every third day)**

| Outcome measure | Obese PCOS ($n$=28) | Non-obese PCOS ($n$=39) | Statistical significance |
|---|---|---|---|
| Treatment duration (days) | 16.28 ± 1.65 | 12.18 ± 1.62 | $P < 0.01$[a] |
| Total rFSH dose, IU (median) | 1297.32 ± 168.65 (1275) | 632.69 ± 120.19 (600) | $P < 0.01$[b] |
| Threshold dose of rFSH, IU/day (median) | 81.25 ± 11.02 (75) | 55.13 ± 10.22 (50) | $P < 0.01$[b] |
| No. of follicles ≥ 18 mm on day of hCG administration (median) | 1.25 ± 0.44 (1) | 1.33 ± 0.48 (1) | NS[b] |

Data analysed by: [a]Student's *t*-test; [b]Mann–Whitney *U*-test.
hCG, human chorionic gonadotrophin; NS, not statistically significant ($P > 0.05$).

group only, rFSH treatment was started with 75 IU/day and results were compared with those of the 50 IU/day rFSH starting dose (Table 3). Since the patients in the first cycle were the same as those in the second cycle, in order to apply the matched-sample test, three patients were excluded from the study in the second cycle because they became pregnant; these patients were also excluded from the first cycle evaluation for this comparison.

None of the women developed ovarian hyperstimulation syndrome during the study. In the obese group, giving 75 IU/day rFSH instead of 50 IU/day significantly shortened the duration of treatment ($P < 0.01$) and reduced the total rFSH dosage ($P < 0.01$), but there was no significant difference between the mean numbers of follicles ≥ 18 mm or the threshold doses.

## Discussion

To minimize the likelihood of ovarian hyperstimulation syndrome and multiple pregnancy, it may be useful to estimate an individual's FSH threshold before starting rFSH treatment. The present study was undertaken to compare the results after ovarian stimulation in obese and non-obese PCOS, using a low-dose step-up regimen with two different starting doses of rFSH. The obese and non-obese women with PCOS who were studied had similar Ferriman–Gallwey scores, LH/FSH ratios and serum concentrations of FSH and LH. Significant increases in the baseline clinical and biochemical features of BMI, WHR, HOMA-IR, TT and DHEAS were found in obese infertile women with PCOS compared with non-obese infertile women with PCOS. Obesity also affected treatment duration and total rFSH dose: obese women needed higher doses of rFSH to induce follicular development; non-obese women received significantly lower doses of rFSH. No significant difference was found between the number of follicles ≥ 18 mm on the day of

**TABLE 3:**
**Outcome measures (mean ± SD and median) for obese patients with polycystic ovary syndrome (PCOS) who were treated with a low-dose step-up protocol of recombinant follicle-stimulating hormone (rFSH) at a starting dose for the first cycle of 50 IU/day followed by 25-IU incremental doses every third day and at a starting dose for the second cycle of 75 IU/day followed by 25-IU incremental doses every third day**

| | Obese PCOS | | |
|---|---|---|---|
| **Outcome measure** | **First cycle (50 IU/day) ($n$ = 25)[a]** | **Second cycle (75 IU/day) ($n$ = 25)[a]** | **Statistical significance** |
| Duration of treatment (days) | 16.28 ± 1.59 | 12.72 ± 0.84 | $P < 0.01$[b] |
| Total rFSH dose, IU (median) | 1296.00 ± 163.40 (1275) | 1023.00 ± 141.96 (975) | $P < 0.01$[c] |
| Threshold dose of rFSH, IU/day (median) | 81.00 ± 10.90 (75) | 84.00 ± 12.25 (75) | NS[c] |
| No. of follicles ≥18 mm on day of hCG administration (median) | 1.24 ± 0.43 (1) | 1.40 ± 0.64 (1) | NS[c] |

[a]Since the patients in the first cycle were the same as those in the second cycle, in order to apply the matched-sample test, three patients were excluded from the study in the second cycle because they became pregnant; they were also excluded from the first cycle evaluation for this comparison.
Data analysed by: [b]Student's *t*-test; [c]Mann-Whitney *U*-test.
hCG, human chorionic gonadotrophin; NS, not statistically significant ($P > 0.05$).

hCG administration between the obese and non-obese groups.

Obesity may affect infertility and reproduction in women in different ways by: (i) affecting spontaneous ovulation; (ii) interfering with the efficiency and outcomes of assisted reproductive technology; and (iii) a worsening of physiological processes and rates of pregnancy.[13]

Women with PCOS have significant insulin resistance that is independent of obesity, changes in body composition and impairment of glucose tolerance.[14] Obesity has been proven to be correlated with fertility problems, including anovulation, resistance to treatment (larger quantities of exogenous FSH are required) and decreased ongoing pregnancy rates.[15] The strong association between insulin resistance and ovarian hyperandrogenism suggests that insulin directly influences ovarian function.[16]

The 1991 – 1992 Annual Report of the Committee for Reproductive and Endocrine (Japan Society of Obstetrics and Gynecology)[17] demonstrated a significant difference in insulin resistance between non-obese and obese women with PCOS: it suggested that obesity was the factor that affected insulin resistance most strongly and that insulin resistance in Japanese PCOS women was a consequence of obesity rather than a feature of PCOS in itself.

Compared with non-obese women with PCOS, those with obesity are characterized by a worsened hyperandrogenic and metabolic state, poorer menses and ovulatory performance and, ultimately, poorer pregnancy rates.[5] Obese patients have a poorer outcome following assisted reproductive treatment, with an ongoing pregnancy rate of < 10%,[9] suggesting that the starting dose of FSH should be adjusted according to BMI and the response observed in previous stimulated cycles.[18] However, although Hamilton-Fairley *et al*.[19] also suggested that obese PCOS women often required higher doses of gonadotrophin and more time to achieve follicular maturation, they reported that cancellation and the pregnancy rates seemed to be the same as those observed for lean PCOS women.

The threshold dose required for unifollicular development can vary considerably from patient to patient; consequently, step-up regimens have become widely accepted strategies.[20] This is important because PCOS is a heterogeneous condition with distinct endocrine features and the FSH threshold varies between individual patients.[21] If starting doses and incremental dose adjustments are not carefully titrated, ovulation induction or intra-uterine insemination protocols with gonadotrophins may lead to high rates of multifollicular growth.[22] Even with low-dose FSH stimulation, obese and insulin-resistant women with PCOS have a much greater tendency to develop a multifollicular response and, thus, a relatively high cycle cancellation rate in order to avoid hyperstimulation.[23] Balen and Jacobs[20] showed that, if a low-dose step-up regimen is used, it is necessary to decide on both the starting dose and the incremental dose, and starting doses ranging from 37.5 to 150 IU/day have been used. Although this approach results in a serious reduction in multifollicular induction cycles and ovarian hyperstimulation, the duration of treatment is prolonged and requires a substantial amount of medication.[24]

Shoham *et al*.[25] showed that using a low-dose protocol starting at 75 IU/day and incremental doses of 37.5 IU gave a significantly higher rate of unifollicular growth compared with a conventional protocol. Another study showed that a low-

dose alternate-day regimen of rFSH (50 IU/day) successfully induced uni-ovulation in 10 patients with chronic anovulation secondary to PCOS.[26]

In conclusion, the present study investigated the relationship between BMI, WHR, HOMA-IR, total rFSH dose, treatment duration and clinical outcome in obese and non-obese infertile women with PCOS undergoing controlled ovarian hyperstimulation. The BMI, WHR and HOMA-IR indexes were appropriate for determining the starting dose of rFSH in infertile women with PCOS. Non-obese PCOS patients received significantly lower doses of rFSH. The results of this study indicate that a low-dose step-up regimen with a starting dose of 50 IU/day of rFSH and 25-IU incremental doses every third day is effective for inducing follicular development in non-obese women with PCOS. The study also found that insulin resistance detected with HOMA-IR is significantly higher in obese patients with PCOS than in non-obese patients. Based on these data, it is suggested that a starting dose of 75 IU/day of rFSH and 25-IU incremental doses every third day should be considered in a controlled ovarian hyperstimulation protocol for obese PCOS patients with a high HOMA-IR score.

## Conflicts of interest

The authors had no conflicts of interest to declare in relation to this article.

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