Follicle stimulating hormone as a predictor of ovarian response in women undergoing controlled ovarian hyperstimulation for IVF

M. Ashrafi, T. Madani, A. Seirafi Tehranian, F. Malekzadeh

Department of Endocrinology and Female Infertility, Royan Institute, P.O. Box 19395-4644, 36 Simin Alley, Assef Cross, Zaferanieh, Tehran, Iran
Akbar Abadi Hospital Iran University of Medical Science and Health Services, Tehran, Iran
Azad University of Islamic Medical Science, Tehran, Iran

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Abstract

Objective: To evaluate the effect of basal follicle stimulating hormone (FHS) level on ovarian response in women undergoing controlled ovarian hyperstimulation for in vitro fertilization. Methods: A descriptive and analytic study of 212 cycles of IVF chosen from about 2200 files of women treated at Royan Institute, Tehran, Iran, from 1991 to 1999. Treatment was started with intranasal or subcutaneous buserlin (0.5 cm³), on day 21 (long protocol). On day 2 of the next cycle, stimulation with human menopausal gonadotropin (hMG) was initiated. When the number and size of follicles were suitable, human chorionic gonadotropin (hCG) was given intramuscularly for ovulation induction, followed by oocyte retrieval 36 to 40 h later. Embryos were transferred about 48 to 72 h after oocyte retrieval. The women were assigned to 2 groups on the basis of day 3 serum FSH levels (<15 IU/mL, group 1 and ≥15 IU/mL, group 2). Results: There were statistically significant differences between the 2 groups in number of follicles, number of oocytes retrieved and embryos transferred (lower in group 1), and level of serum luteinizing hormone and number of canceled cycles (higher in group 1). There were no statistical differences in number of ampoules of hMG used or age of...
1. Introduction

Because of the time, financial, and emotional expenditure incurred by patients undergoing in vitro fertilization (IVF), identifying poor responders prior to initiation of treatment is extremely important.

The unavailability of quality of oocytes in a suitable number because of reduced ovarian reserve is one of the most important causes of failure of IVF treatment. While a universally accepted definition of “poor responders” is not currently available [1,2], most agree that women who have produced less than 3 to 4 oocytes or had a low peak Estradiol (E2) level (upper limit, 500 pg/mL on the day of human chorionic gonadotropin (hCG) administration) in a previous stimulation cycle could be so characterized [3,4].

Some of the signs and symptoms of poor responders were reviewed as follows:

(A) Age: The reproductive potential of a woman decreases as she advances in age. In 1994 Navot et al. [5] found a relation between changes in oocyte number and decreases in the possibility of fertility. They also stipulated that age-related decline in female fertility is not due to a diminished capacity of the uterus to sustain embryo implantation.

(B) Serum follicle stimulating hormone (FSH) level: Women may begin to have a subtle increase in their serum FSH concentrations in their mid-thirties, coinciding with the time at which fertility begins to decline [6,7]. The most suitable time for measuring FSH is in the third day of menstruation [8]. A basal FSH level above 25 IU/mL reduces the fertility rate by up to 2% [9]. In 2003 Saadat et al. [10] showed poor IVF responses among women with an increased basal FSH and indicated that conventional therapy was more effective in these women than using clomiphen citrate and human menopausal gonadotropin (hMG) together.

(C) Basal estradiol levels: Measuring basal E2 along with basal FSH in patients who undergo IVF cycles is of great importance. Although there is inconsistency among investigators [4,11,12], cancellation rates were significantly increased in patients with basal E2 levels of $\geq 80$ pg/mL.

(D) The clomiphen citrate challenge test: This test was first introduced by Navot et al. in 1987 to determine follicle reserve in women aged 35 years or older. It shows the level of FSH after administration of clomiphen from day 5 up to the ninth IVF cycle. An FSH elevation compared with basal level in the 10th day indicated a greater ovarian reserve [13,14].

(E) Evaluation of serum inhibin-B: Studies show that reduced day 3 serum inhibin-B concentration correlates with reduced fertility rate [15,16]. Many investigators do not mention serum inhibin-B because its reduction always correlates with increased basal FSH and E2 [17].

(F) A study by Syrop et al. [18] shows a relation between ovarian volume and its response to exogenous gonadotropin. The authors consider this relationship more important than increased basal FSH levels. However, until now, there is no exact measure for ovarian volume, but a volume less than 2 cm$^3$ is consistent with experience.

(G) Antral follicle count: Some investigators show that the antral follicle count correlates well with ovarian response to exogenous gonadotropin stimulation and number of oocytes produced. However, no precise number of follicle supported this finding in this study. A group of investigators consider fewer than 3 follicles as a poor ovarian response [19].

Today the ovarian stimulation protocol in women with a decreased ovarian reserve are flare GnRH analogue [20], GnRH antagonist [21], high-dose GnRH analogue [22,23], and, at last, oocyte donation.

The objective of this study is to evaluate the outcome of increasing basal FSH on ovarian response in women undergoing IVF and ET.

2. Materials and methods

This is a descriptive and analytic study. Among 2200 patients who were referred to Royan Institute from 1991 to 1999, 212 were found eligible for the study. Eligibility factors were less than 6 months between
measuring basal FSH and initiating controlled ovarian stimulation (GnRHa plus hMG) and no endometriosis.

In addition to routine blood and urinary test results, levels of FSH, luteinizing hormone (LH), estradiol, prolactin, and DHEA on the third day of previous menstrual cycle were extracted from patients' files, as well as thyroid test results. For pituitary—ovarian suppression, patients were injected with 0.5 cm\(^3\) of buserlin (Superfact; Hoechst AG, Germany) subcutaneously and, for ovulation induction, 2 or 3 daily ampoules of hMG were injected (Humegon; Organon, France), according to the woman's age (3 for women 35 years and older, 2 for women younger than 35 years). Ovarian response was monitored 5 to 6 times using vaginal ultrasonography (Aloka 600 model; Aloka, Japan). When there were at least 2 follicles greater than 17 mm, 10,000 units of human chorionic gonadotropin (hCG) (Pregnyl N.U.; Organon, Holland) were administered and oocyte retrieval was performed 36 to 40 h after the hCG injection. Embryo transfer was performed 44 to 72 h following oocyte retrieval. Patients were categorized into 2 groups according to FSH level on day 3 of previous menstrual cycle [8]: group 1 consisted of 36 patients with a FSH level of 15 IU/mL or higher, and group 2 of 176 patients with FSH levels less than 15 IU/mL. The end points studied were: patient's age, duration of infertility, number of hMG ampoules, number of developing follicles, number of oocytes collected, and number of transferred embryos. Data analysis was performed using the \( t \) test, \( \chi^2 \) test, and Fisher exact test. \( P<0.05 \) was considered statistically significant.

### 3. Results

Mean ± SD age and duration of infertility were 34.1 ± 5.18 and 10.3 ± 7.19 years in group 1 and 32.2 ± 5.94 and 9.8 ± 5.82 years in group 2. The rate of primary infertility was 72.2% in group 1 and 71% in group 2. In group 1, LH levels were significantly elevated (\( P<0.05 \)) (Table 1). There were significant differences in the number of retrieved oocytes, transferred embryos, and canceled cycles between the 2 groups, but there were no significant differences in the number of hMG ampoules administered (Table 2).

### 4. Discussion

This study shows a significant relation between FSH levels measured on the third day of the cycle and ovarian response. Women with FSH levels of 15 IU/mL or higher have fewer developing follicles than those with FSH levels less than 15 IU/mL. This finding is consistent with those of Scott et al. [8], Cahill et al. [24], Sharif et al. [25], and Toner et al. [26] regarding the effect of basal FSH level on folliculogenesis, and shows that there is no significant association between patient age and elevated

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Developing follicles, 16—22 mm</th>
<th>Retrieved oocytes</th>
<th>Transferred embryos</th>
<th>hMG ampoules</th>
<th>Canceled cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (FSH ≥ 15 IU/mL)</td>
<td>3.3 ± 3.28</td>
<td>4.51 ± 7.75</td>
<td>1.4 ± 1.51</td>
<td>35.5 ± 17.30</td>
<td>11</td>
</tr>
<tr>
<td>Group 2 (FSH &lt; 15 IU/mL)</td>
<td>5.2 ± 2.90</td>
<td>7.0 ± 5.52</td>
<td>2.2 ± 1.68</td>
<td>30.66 ± 10.88</td>
<td>5</td>
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<tr>
<td>( P ) value</td>
<td>( 0.001^a )</td>
<td>( 0.022^a )</td>
<td>( 0.006^a )</td>
<td>( 0.170 )</td>
<td>( 0.001^a )</td>
</tr>
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\( a \) Significant differences between the 2 groups.

\( a \) Numbers in parenthesis are minimum and maximum of each item.
level of FSH. Therefore, patient age alone does not predict ovarian response.

Pruksananoda et al. [27], Basil et al. [28], and others [24,29] as well as this study found a reverse relation between day-3 FSH level and number of oocytes retrieved.

In this respect, the question whether the number and dosage of the hMG ampoules have any effects on ovarian response in poor responders has been addressed. The present study, in agreement with previous findings by Sharif [25]. Pruksananoda et al. [27], and Cahill et al. [24], noted no association between number of consumed hMG ampoules and ovarian response. Ovarian response depending on ovarian reserve, increasing the number of ampoules cannot result in better ovarian response in poor responders [13,17]. This knowledge not only helps the physicians who prescribe the drug, it also spares unneeded costs for the patients.

The findings in present study showed a predictive value for day-3 FSH level for estimating cancellation rate of IVF cycle. In group 1, in which serum FSH levels were 15 IU/mL or higher, the cancellation rate was 31%, whereas it was less than 3% in group 2. In 1998, Sharif et al. [25] found the possibility of a higher cancellation rate among women with FSH levels higher than 10 IU/mL. This study also showed that an elevation of FSH levels is associated with an elevation of serum LH.

The results of the present study show that basal FSH level is a predictive factor of the outcome of IVF treatment, as increased basal FSH is associated with insufficient ovarian response and treatment failure. Therefore, because of its predictive value regarding ovulation induction, measuring basal FSH level may guide the physician’s decision.

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