Experimental
&
Clinical Article

The Effect of Elevated Basal Follicle Stimulating Hormone Levels on Assisted Reproductive Technology Cycle Outcomes

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ABSTRACT

OBJECTIVE: Despite the availability of better biomarkers, basal day 3 follicle-stimulating hormone is widely available and often used as the first-line test in ovarian reserve evaluation. The aim of this study was to evaluate the outcomes of cycles with elevated (>12 IU/mL) basal follicle-stimulating hormone values.

STUDY DESIGN: Cycles with basal day 3 follicle-stimulating hormone values >12 IU/mL were divided into four cohorts according to follicle-stimulating hormone levels: group I, follicle-stimulating hormone between 12-15 IU/m, group II between 15-20 IU/mL, group III between 20-25 IU/mL and group IV >25 IU/mL. Both demographic characteristics and controlled ovarian stimulation parameters were retrospectively reviewed.

RESULTS: Total antral follicle count was significantly higher in group I compared to the other three groups (p=0.001). Number of follicles ≥17 mm on human chorionic gonadotropin (hCG) day, number of retrieved oocytes, mature oocytes and fertilized oocytes were significantly higher in group I compared to the other groups (p=0.003, p=0.001, p=0.001, and p=0.001, respectively). No significant difference was found between groups regarding cancellation rates. The rate of embryo transfer per started cycle was significantly higher in group I compared to group III and group IV (p=0.001). Clinical pregnancy rates per embryo transfer were comparable among the groups.

CONCLUSION: Despite the retrieval of lower quantities of oocytes, reasonable pregnancy rates could be achieved if embryo transfer was performed in cycles with follicle-stimulating hormone values over 12 IU/mL.

Keywords: Assisted reproductive technologies, Clinical pregnancy, Follicle-stimulating hormone, Poor ovarian response,

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Introduction

Major determinants of the success of assisted reproductive technologies (ART) depend on women's age and ovarian reserve, which indicate reproductive potential as a function of the number and quality of remaining oocytes (1). Despite the availability of better biomarkers of ovarian reserve such as antral follicle count (AFC) and anti-Müllerian hormone (AMH), basal day 3 follicle-stimulating hormone (FSH) is widely available and often used as either the first-line or the only test in ovarian reserve evaluation (2). It is routinely used to determine the ovarian reserve in many ART units prior to starting ART treatment (3). Elevated basal FSH level is thought to reflect ovarian aging and is associated, at least in

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older women undergoing in vitro fertilization (IVF), with poor ovarian response and low pregnancy rates (4,5) and a higher chance of fetal loss (6). It is a common practice in many IVF center to defer treatment when the FSH values are high (7).

The purpose of the present study was to evaluate the success rates of ART cycles with elevated basal FSH values and to present a tool to the clinician for realistic opinion and proper consultation with the patient.

Material and Method

Medical records of patients who underwent treatment in the center of assisted reproduction of a tertiary hospital from September 2007 to December 2016 were reviewed. Cycles with basal day 3 FSH values >12 IU/mL were identified. All cycles were divided into four cohorts according to FSH levels: group I, FSH between 12-15 IU/mL, group II between 15-20 IU/mL, group III between 20-25 IU/mL and group IV >25 IU/mL. Cycles with no sperm retrieval, with FSH values <12 IU/mL, and frozen embryo transfer cycles were excluded from the study. The consent for using data was obtained and the study was approved by the institutional review board (21/12/2016-Number: 219). The study was performed in accordance with the Declaration of Helsinki.

Both demographic characteristics and controlled ovarian stimulation (COS) parameters were retrospectively reviewed based on patient files and the computer database. Controlled ovarian hyperstimulation was performed using long GnRH agonist, microdose flare or antagonist protocols. Either pure recombinant FSH or human menopausal gonadotropin (HMG) was used. The dose of gonadotropins was individualized according to the patient's age, baseline serum FSH concentration on day 3 and body mass index (BMI). Cycles were monitored by serial transvaginal ultrasound evaluation and serum estradiol determination. When at least three follicles reached a mean diameter of 17 mm, final oocyte maturation was triggered with the administration of recombinant human chorionic gonadotropin (hCG) (Ovitrelle; Merck-Serono, Istanbul, Turkey) (250 mg when BMI <29 kg/m^2 and 500 mg when BMI >29 kg/m^2).

Oocyte pick up (OPU) was performed by transvaginal ultrasound-guided aspiration 35.5-36 h after the hCG injection. As a policy of the clinic, intracytoplasmic sperm injection (ICSI) was performed for all oocytes. Signs of fertilization (presence of two pronuclei and two polar bodies) was checked 16-18 h after ICSI was performed. Embryo transfer (ET) was performed on the second, third or fifth day after ICSI.

Cycle cancellation was defined as the lack of ovarian response to stimulation (no follicular recruitment and/or inadequate serum estradiol increase), retrieval of no oocytes, total fertilization failure or developmental arrest of the embryo.

Luteal support was given by either vaginal progesterone (Crinone 8% gel, Merk, Istanbul) twice daily or vaginal progesterone plus 100 mg intramuscular progesterone (Progestan ampul 50 mg/mL i.m., Kocak Farma, Istanbul) from ET to the pregnancy test. A pregnancy test was performed 12 days following ET and clinical pregnancy was defined as the presence of a gestational sac with accompanying fetal heartbeat by ultrasound 4 weeks following the ET procedure.

Statistical analysis was performed using IBM SPSS Statistics Software (20.0, SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test was used to test the distribution of variables. Analysis of variance (ANOVA) test was used for multiple comparisons. Post-hoc analysis was done using Tukey's HSD test. Data are presented as mean ± standard error (SE). Statistical significance was assumed with a probability error of p <0.05.

Results

A total of 393 cycles with basal day 3 FSH values >12 IU/mL were selected for the study; 179 cycles in group I, 116 cycles in group II and 44 and 54 were in group III and group IV, respectively. Mean basal FSH levels in groups I, II, III, and IV were 13.3±0.8, 17.4±1.5, 22.2 ± 1.4, and 31.4±6.1 IU/mL, respectively.

There were no statistically significant differences regarding female age and duration of infertility. Total AFC was significantly higher in group I compared to the other three groups (p=0.001). Total gonadotropin dose was comparable among groups (p=0.328). The duration of stimulation was significantly shorter in group IV compared to the other three groups (p=0.034). The number of follicles ≥17 mm on hCG day, number of retrieved oocytes, mature oocytes, and fertilized oocytes were significantly higher in group I compared to the other groups (p=0.003, p=0.001, p=0.001, and p=0.001, respectively) (Table I).

Regarding cancellation rates, although there was no difference among groups (p=0.056), there was a tendency towards decreased cancellation rates with lower basal FSH values. The rate of ET per started cycle was significantly higher in group I compared to group III and group IV (p=0.001). However, rates of clinical pregnancy per ET were comparable among the groups (p=0.615) (Table II).

ROC curve analysis revealed an FSH threshold value of 15.85 IU/mL with 52.5% sensitivity and 66.7% specificity for prediction of pregnancy (AUC 0.61) (Figure 1) and a threshold value of 15.22 IU/mL with 55.1% sensitivity and 67.6% specificity for prediction of clinical pregnancy (AUC 0.60) (Figure 2).

Table I: *Demographic characteristics and controlled ovarian stimulation parameters of the cycles*

	FSH 12-15 IU/mL (n=179)	FSH 15-20 IU/mL (n=116)	FSH 20-25 IU/mL (n=44)	FSH > 25 IU/mL (n=54)	*p* value
Female age (years)	34.23±5.93	35.26±5.12	33.77±6.06	34±5.79	0.316
BMI (kg/m^2)	25.86±4.86	26.03±4.3	25.29±4.15	23.67±3.81	0.015
Total AFC	6.01±3.7	4.53±3.02	3.83±2.49	4.46±4.16	0.001
Duration of infertility (months)	69.47±61.74	67.24±67.79	70.93±71.12	46.09±47.58	0.107
Duration of stimulation (days)	9.27±2.75	9.23±2.8	8.25±3.34	8.21±3.52	0.034
Total dose of gonadotropin (IU)	3143.96±1323.69	3094.47±1235	3086.27±1295.62	2751.42±1756	0.328
Number of follicles ≥17 mm on hCG day	1.96±1.59	1.35±1.09	1.43±2.51	1.51±1.07	0.003
Number of retrieved oocytes	5.92±4.5	4.27±2.89	3.25±3.38	2.65±2.8	0.001
Number of mature oocytes	4.63±3.68	2.83±2.44	1.75±2.36	1.53±2.01	0.001
Number of fertilized oocytes	2.35±2.09	1.4±1.84	0.91±0.92	1.03±1.77	0.001

FSH, follicle-stimulating hormone; BMI, body mass index; AFC, antral follicle count; hCG, human chorionic gonadotropin.

Table II: *Outcomes of the cycles.*

	FSH 12-15 IU/mL (n = 179)	FSH 15-20 IU/mL (n = 116)	FSH 20-25 IU/mL (n = 44)	FSH > 25 IU/mL (n = 54)	p value
Cycle cancellation rates (%)	17.7	26.9	35.7	25.5	0.056
ET/started cycle (%)	55.3	42.2	20.5	37.0	0.001
Clinical pregnancy/ET (%)	24.2	18.4	11.1	15.0	0.615

FSH: Follicle-stimulating hormone, ET: Embryo transfer

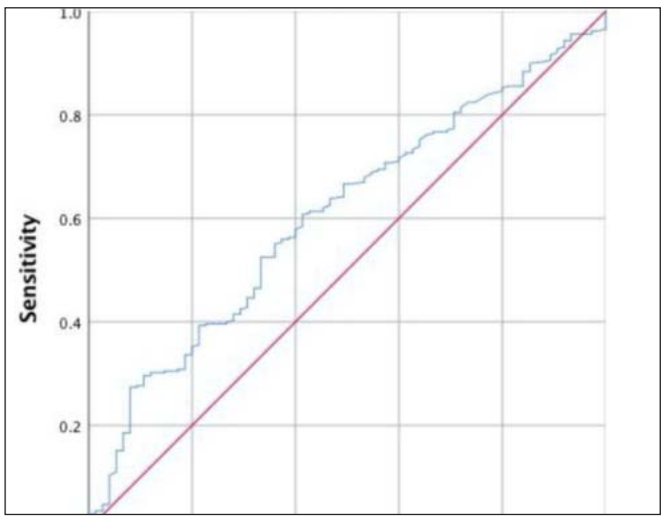


Figure 1: *Receiver-operator curve analysis for the performance of basal serum follicle-stimulating hormone in the prediction of pregnancy.*

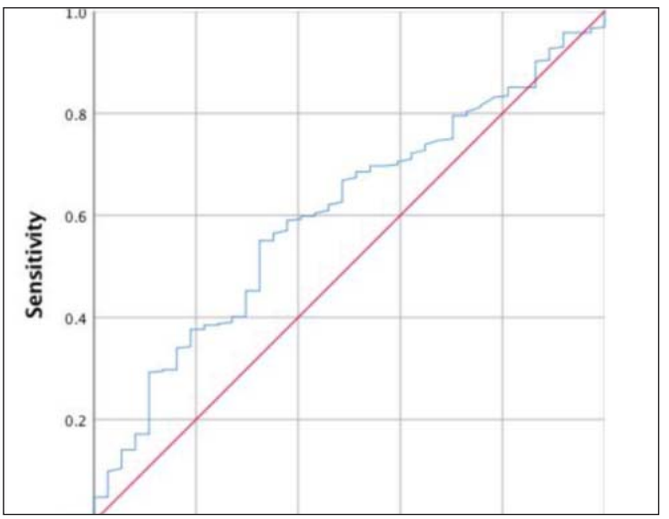


Figure 2: *Receiver-operator curve analysis for the performance of basal serum follicle-stimulating hormone in the prediction of clinical pregnancy.*

Discussion

In this retrospective study, we assessed the effect of elevated basal FSH value (>12 IU/mL) on controlled ovarian stimulation parameters and cycle outcomes. Our results revealed that the number of retrieved oocytes, mature oocytes, and fertilized oocytes decreased with increasing FSH values. Also, the number of embryo transfer cycles decreased significantly with FSH values over 20 IU/L. However, when an embryo developed and was transferred, clinical pregnancy rates per transfer seemed not to be affected by the FSH values.

Decreased ovarian reserve is a rather common problem among subfertile women, with approximately 31% of ART cycles using fresh non-donor eggs or embryos reported by the Society of Assisted Reproductive Technology being complicated by a diminished ovarian reserve in 2015 (8). The inverse relationship between elevated early follicular phase FSH and

the diminished ovarian reserve is universally accepted (9). Several studies demonstrated that high day-3 basal concentrations of FSH are associated with a low response to ovarian stimulation, high cancellation rates, and a low chance of success in patients undergoing ART treatment (4,5,10). Thum et al. compared the results of 1368 patients with normal basal FSH ≤10 IU/L with 492 patients with high basal FSH (>10 IU/L). The average number of oocytes retrieved was lower among women with elevated FSH (10.12±5.6 vs 6.16±3.9) (9). In another study, Kojima et al. demonstrated a higher number of retrieved oocytes, fertilized oocytes and transferred embryos in patients with FSH values <10 IU/L (8.7±6.1, 4.6± 3.9, and 1.8±0.8, respectively) compared to patients with FSH values <15 IU/L (2.2±2.0, 1.4±2.0, and 0.9±0.7, respectively, p <0.001) (3). The results of our study were in line with the mentioned studies, demonstrating decreased oocyte yield with increasing FSH levels.

However, the link between elevated FSH values and quality of the resultant embryos is a matter of debate, unlike the decreased number of oocytes retrieved. Various authors have suggested a negative effect of elevated FSH on embryonic quality and outcome of ART (11-13). However, other reports have suggested that the basal FSH level was useful as an indicator of a quantitative rather than qualitative ovarian response for ovarian hyperstimulation, meaning basal FSH level did not reflect on the quality of the oocytes (14,15). Abdalla and Thum analyzed 3401 cycles of four groups divided according to FSH levels: group A, FSH <10 IU/mL, group B, 10.1-15 IU/mL, group C, 15.1-20 IU/mL, and group D, FSH >20 IU/mL. In patients aged <38, the pregnancy rate and live birth rate were reduced, though not significantly, as FSH levels increased. A live birth rate of at least 20% was always achieved in patients with FSH between 10 and 20 IU/l, and 16.7% in patients with FSH >20 IU/l (15). Another study by the same group also showed that women with elevated serum FSH levels had lower numbers of oocytes retrieved and lower clinical pregnancy rates compared to women with FSH levels in the normal range. However, women with an elevated basal FSH level who responded well to gonadotropin stimulation and generated a good number of oocytes/embryos had similar chances of becoming pregnant and having a live birth as women in the same age range with normal levels of FSH (9). The results of our study also demonstrated comparable clinical pregnancy rates per ET among the four groups, despite the retrieval of a decreasing number of retrieved oocytes with increasing FSH values, which was in line with the above-mentioned studies. The mean age of the patients in our study was approximately 35 in all groups. It could be hypothesized from these results that a proportion of these patients with elevated basal FSH who reach the embryo transfer stage of the treatment may have a chance of pregnancy. Increased basal FSH levels should not discourage women from attempting a cycle of IVF.

The study is not without limitations. Retrospective nature and small sample size were the main limitations of the study. Despite these limitations, comparison of groups demonstrates us the importance of the reaching of embryo transfer stage in patients with high FSH values.

In conclusion, the results of this study suggest that high basal FSH levels should not be the sole indication for withholding treatment. Despite the retrieval of lower quantities of oocytes, reasonable pregnancy rates could be achieved if embryo transfer could be performed.

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