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ORIGINAL RESEARCH

Does Serum Delta FSH Level Provided with High Starting Dose FSH Differ Among Various Ovarian Responses?

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ABSTRACT

The objective of this study is to evaluate whether serum delta FSH levels (the percentage difference of serum FSH between antagonist starting day and basal serum FSH level) differ between patients with different COH responses (poor, suboptimal response and normoresponders) who stimulated with a high (300 IU) fixed Recombinant FSH dose during flexible antagonist cycles. This study is a retrospective cross sectional cohort study conducted in a tertiary ART Center. 122 women were evaluated, of which, 51 were poor responders, 52 had suboptimal response and 19 had normal response. The primary outcome is to evaluate the spot serum FSH levels on the first day of GnRH antagonist dose administration and the delta FSH levels between groups. Basal serum FSH levels differed significantly between (7[5.2-8.6], 5.7[4.6-7.2], 4.8[4.1-5.3] poor, suboptimal and normoresponders respectively; p<0.001). Median spot serum FSH level on the antagonist starting day was significantly lower in normoresponders than poor and suboptimal responders (p=0.001 and p=0.025). Delta serum FSH levels did not differ significantly between groups (p=0.39). Rate of response to COH was significantly higher for the normoresponder group compared to poor and suboptimal groups (p<0.001 and p=0.019). Delta serum FSH levels were positively correlated with the response to COH (r=0.24, p=0.008). Although Delta serum FSH percentage did not differ between groups, normoresponder patients had a better response to COH. In conclusion, poor responders are not positively affected by a high dose of FSH exposure due to the fact that poor responders have a limited number of antral follicles that have already been exposed to high levels of FSH.

Keywords: Serum FSH levels. Controlled ovarian hyperstimulation. IVF. ICSI. Ovarian reserve.

Yüksek Doz Başlangıç FSH ile Sağlanan Serum FSH Düzeyi Artışı Over Yanıtlarına Göre Farklılık Gösterir mi?

ÖZET

Çalışmanın amacı, antagonist kontrollü ovarian simülasyon (KOH) sikluslarında yüksek (300 IU) sabit rFSH dozu ile uyarılan ve farklı yanıtları (zayıf, suboptimal yanıt veya normal yanıt) olan hastalar arasında, antagonistin başlatıldığı gün serum FSH düzeyleri ve serum FSH düzeylerindeki simülasyon başlangıcına göre artışı retrospektif olarak değerlendirmekti. Çalışmaya toplam 122 kadın dahil edildi; bunların 51'i zayıf yanıtlı, 52'si suboptimal yanıtlı ve 19'u normal yanıtlı hastalar idi. Bazal serum FSH düzeyleri her üç grup arasında anlamlı farklı idi (7[5.2-8.6], 5.7[4.6-7.2], 4.8[4.1- 5,3] sırasıyla zayıf, suboptimal ve normal yanıt grupları; p<0,001). Antagonist başlangıç gününde medyan spot serum FSH seviyeleri, normal yanıt verenlerde zayıf ve suboptimal yanıtlı gruplara göre anlamlı derecede düşüktü (p=0,001 ve p=0,025). Antagonist başlangıç gününe kadar serum FSH düzeyindeki artış miktarı gruplar arasında anlamlı farklılık göstermedi (p=0,39). Normal yanıt veren grupta, zayıf ve suboptimal yanıtlı gruplarla karşılaştırıldığında, KOH' a yanıt oranı anlamlı derecede yüksekti (p<0,001 ve p=0,019). Antagonist başlangıç gününe kadar serum FSH düzeyindeki artış oranı, KOH yanıtı ile pozitif korelasyon gösterdi (r=0,24, p=0,008). Sonuç olarak, serum FSH düzeyinde başlangıçtan itibaren artış oranı gruplar arasında farklılık göstermese de, normal yanıt veren hastaların KOH' a yanıt verme oranı daha yüksekti. Bu bulgular şunu desteklemektedir; zayıf yanıt verenler, daha yüksek başlangıç FSH seviyeleri nedeniyle zaten ilerlemiş olan küçük antral foliküllerden oluşan sınırlı bir havuza sahiptir ve daha yüksek FSH başlangıç dozlarından yararlanamayabilir.

Anahtar Kelimeler: Serum FSH düzeyleri. Kontrollü over stimülasyonu. IVF. ICSI. Over rezervi.

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The aim of controlled ovarian hyper-stimulation (COH) is to promote multifollicular growth By the use of gonadotropins. For this purpose, increased and sustained serum FSH concentrations during stimulation cycles exceed the physiologic threshold and consequently, achieving multifollicular growth[1,2].

While promoting multifollicular growth, the method to ensure an ideal response to controlled ovarian stimulation still remains a matter of debate. Although ovarian response to gonadotropins is not uniform among women, a recent study[3] have emphasized that 8 to 15 oocytes per cycle are required to obtain optimal responses associated with live births, with little variations in GnRH antagonist cycles[4]. Both poor and hyper-responses are associated with higher cycle cancellation rates and are both undesirable treatment outcomes[5]. Thats why the focus of treatment individualization has been mainly focused on FSH dose adjustment.

The essential therapeutic component leading to follicular growth is the follicular stimulating hormone (FSH)[6] FSH dose individualization based on an ovarian reserve test could theoretically improve IVF/ICSI treatment outcome.

Correlations between FSH doses and follicular recruitment during COH cycles have been defined in the literature[7]. Although correlations between FSH dose and ovarian response have been studied in a number of studies, there are limited data evaluating the effects of serum FSH levels on ovarian response[8]. Correlation between FSH dose Administration and achieved serum FSH concentrations are not clear. The relationship between too high serum FSH concentrations above the physiological FSH threshold and the ovarian response is another unknown.

The aim of this study was therefore to assess whether serum delta FSH levels differ between poor, suboptimal and normal responders to a fixed daily dose of recombinant(rec) FSH dose in flexible antagonist cycles. FSH dose administration is kept as a constant by using a high (300 IU) but fixed rFSH dose for all patients. In addition, the increment rate in serum FSH levels and its correlation with ovarian response to COH will be a secondary outcome for this study.

The question we are trying to find an answer to is: 'Who would benefit from a higher starting FSH dose during a controlled ovarian hyperstimulation (COH) cycle, poor responders or normoresponders?'.

Material and Method

This retrospective cohort study was approved by the research ethics committee of the local institutional review board of the University (2017-19/32). The participants were recruited from a Tertiary University Hospital ART Center, between May 2017- January 2018.

Women aged < 39 years with BMI < 35 kg/m^2 and serum FSH <10 IU/L, E2 < 80 pg/ml on cycle day (CD) 2 who underwent GnRH flexible antagonist cycles and stimulated with a fixed high dose of 300 IU recombinant FSH (rFSH) were included.

Exclusion criteria were COH cycles cancelled before oocyte pick up, cycles with gonadotropin dose alteration, patients with hypogonadotropic gonadism, cycles lack data for serum samples on CD2 and on GnRH antagonist starting day and patients with >15 oocytes retrieved were excluded.

Stimulation protocol

The total number of antral follicles measured between 8-10 mm in diameter on both ovaries was recorded for each participant on the starting day of COH (CD2). Flexible GnRH antagonist protocol with recombinant FSH was used for COH in a daily dose of 300 IU. From stimulation day 5 and subsequently, follicular growth was assessed. When at least one follicle reached 14 mm in diameter, 0.25 mg/0.ml ganirelix administered onward daily. When at least one follicle of ≥18 mm and 2 follicles of ≥17 mm in diameter were visualized, final oocyte maturation was induced by administrating 250 micrograms/0.5 ml of rhCG s.c. Thirty-four / thirty-six hours later oocyte pick-up was performed.

Hormonal assay

Basal (cd2) FSH, estradiol(E2), LH and anti-Mullerian hormone (AMH) levels were analysed for all the participants. After starting COH, blood samples were taken on the GnRH antagonist starting day for serum FSH levels, E2 levels and also for serum progesterone and E2 on the day of hCG trigger.

COH response assessment

Patients with retrieved oocytes number less than 5 are defined as the poor response group, suboptimal response was defined as the retrieval of 5-9 oocytes and rest of the patients who had 10-15 oocytes retrieved formed the normoresponder group.

Outcome measure

Primary outcome is the serum FSH levels on the first day of GnRH antagonist dose administration and the delta FSH percentage level (which is calculated as; serum FSH level on the day of first GnRH antagonist dose administrated – CD2 serum FSH level / CD2 serum FSH level x100 and expressed as a percentage) between the groups.

Secondary outcomes are correlations between serum delta FSH percentage and cycle outcomes (retrieved

oocyte number and the rate of COH response, P and E2 levels on hCG trigger day). The rate of response to COH is calculated as; retrieved oocyte number / AFC x 100 and expressed as a percentage. The rate of response to COH should be evaluated as a clinical performance indicator as many parameters which had been evaluated as laboratory indicators in the Vienna concensus[9].

Statistical analysis:

Study data were summarized using descriptive statistics values (median with %25-%75 percentile for categorical variables). Statistical analyses used the the Kruskal–Wallis (to compare more than two groups) and Mann–Whitney U (for comparison of ranks between two groups) non-parametric tests. For the correlations of categorical variables analyses, Spearman Rho test was performed. All the analysess were performed using the SPSS software package for Mac (Statistical Package for Social Sciences, version 23.0, SPSS Inc., Chicago, Illinois, USA). A two-tailed $p<0.05$ was considered statistically significant.

Results

Of 122 women, 51 were categorized as poor responders, 52 had suboptimal response and 19 had normal response. Baseline characteristics for the 3 groups are shown in Table I.

Table I. Patient baseline characteristics

	Poor Response (< 5 oocytes) (n=51)	Suboptimal Response (4< oocytes<10) (n=52)	Normal Response (9< oocytes<16) (n=19)	*p* value
Age (year)	35.0 (33.0-38.0)	34.0 (32.0-37.0)	34.0 (32.0-35.0)	0.15[a]
BMI (kg/m2)	26.0 (22.8-29.0)	25.15 (22.0-28.5)	27.0 (22.0-32.0)	0.9[a]
Duration of infertility (years)	7.0 (4.0-11.0)[x]	7.0 (4.0-11.0)[x]	6.0 (4.0-11.0)[x]	0.72[a]
Diagnosis				
Poor ovarian reserve (POR)	43 (84.3%)	38 (73.1%)	9 (47.4%)	
Male Factor	6 (11.8%)	3 (5.8%)	5 (26.3%)	
Unexplained	2 (3.9%)	6 (11.5%)	4 (21.05%)	
PCOS	-	2 (3.8%)	1 (5.3%)	
Endometriosis	-	3 (5.8%)	-	
Baseline AMH	0,76 (0.26-1.4)[x]	1,26 (0.75-2.0)[y]	2.38 (1.1-3.1)[z]	**<0.001**[a]
AFC	4.0 (3.0-7.0)[x]	7.0 (4.0-9.0)[y]	8.0 (5.0-12.0)[y,z]	**<0.001**[a]

Data are given as Median (%25-%75 percentile)

[a]The Kruskal–Wallis test (for comparison more than two groups)

[x,y,z] The different letters show statistically significance (The Mann–Whitney U test for comparison of ranks between two groups)

A significant difference was found in serum AMH levels (μg/L), this was due to the difference between suboptimal response group and poor response group (1,26 [0.75-2.0] versus 0.76 [0.26-1.4] respectively ;p= 0.005) and suboptimal versus normal response group (1,26 [0.75-2.0] versus 2.38 [1.1-3.1] respectively, p= 0.007). A significant difference was also found between groups for AFC. Poor responders had significantly lower AFC compared to suboptimal and normal response groups (P<0.001 and p<0.001) (Table I).

Controlled ovarian stimulation (COH) characteristics and serum level results for hormone parameters are shown in Table II.

Table II. Controlled ovarian stimulation (COH) characteristics and serum level results for hormone parameters

	Poor Response (< 4 oocytes) (n=51)	Suboptimal Response (4< oocytes<9) (n=52)	Normal Response (10< oocytes<15) (n=19)	*p* value
Baseline FSH	7.0 (5.2-8.6)[x]	5.7 (4.6-7.2)[y]	4.8[x] (4.1-5.3)[z]	**<0.001**[a]
Baseline LH	3.4 (1.8-3.4)	3.45 (1.5-3.5)	2.6 (1.2-2.6)	0.09[a]
Baseline E_2	47.0 (35.0-59.0)	43.0 (34.0-55.0)	47.0 (35.0-56.0)	0.85[a]
Day of first antagonist	8.0 (6.0-9.0)	7.0 (6.0-8.0)	8.0 (6.0-9.0)	0.8[a]
Antagonist day E_2	227.0 (123.0-356.0)[x]	379.5 (180.0-710.0)[y]	399.5 (320.0-1030.0)[y]	**<0.001**[a]
Antagonist day FSH	18.0 (14.8-21.0)[x]	16.8 (13.6-20.1)[x]	14.5 (11.6-16.8)[y]	**0.004**[a]
Gonadotropin dose till to antagonist day	2100.0 (1800.0-2400.0)	1800.0 (1500.0-2100.0)	2100.0 (1800.0-2400.0)	0.63[a]
Total Gonadotropin dose	3000.0 (2400.0-3450.0)	3000.0 (2700.0-3300.0)	3300.0 (3000.0-3600.0)	0.24[a]
hCG days	11.0 (8.0-11.0)	11.0 (8.0-11.0)	11.0 (9.0-11.0)	0.91[a]
hCG day P_4	0.3 (0.2-0.6)[x]	0.5 (0.3-0.8)[y]	0.6 (0.3-0.9)[y]	**0.002**[a]
hCG day E_2	507.0 (292.0-892.0)[x]	980.0[x] (761.0-1783.0)[y]	1483.0 (937.0-2471.0)[z]	**<0.001**[a]
Rate of increment in serum FSH levels(%)	147.0[x]	188.0[x]	190.0[x]	0.39[a]
Retrieved total oocyte number	3(2-4) [x]	7(6-8) [y]	11(10-13) [z]	**<0.001**[a]
COH success (Oocyte/AFC x100) (%)	57.14% [x]	100.0 % [y]	144.4 % [z]	**<0.001**[a]

Data are given as Median (%25-%75 percentile)

[a]The Kruskal–Wallis test (for comparison more than two groups)

[x,y,z] The different letters show statistically significance (The Mann–Whitney U test for comparison of ranks between two groups)

P values were found as p=0.85 and p=0.09, respectively for baseline serum estradiol and LH levels between the groups. Baseline (cd 2) serum FSH levels (IU/L) differed significantly between all three groups (7[5.2-8.6] versus 5.7[4.6-7.2] versus 4.8[4.1-

5.3], in poor, suboptimal and normal response groups respectively; p<0.001) (Table II). No significant differences were found for the starting day of GnRH antagonist (p=0.8). Also r FSH doses used up to antagonist starting day and total used rFSH doses were not different between the groups (p=0,63 and p=0.24, respectively).

Median serum FSH level on the antagonist starting day was significantly lower in the normoresponders compared to poor and suboptimal response groups (p=0.001 and p=0.025). For normoresponder, poor and suboptimal groups the median FSH levels were 14.5 IU/L(11.6-16.8), 18 IU/L (14.8-21) and 16.8 IU/L (13.6-20.1), respectively (p=0.004). The rate of increase in serum FSH levels (delta FSH percentage) until the antagonist starting day was not significantly different between groups (p=0.39) (Table II).

As expected, retrieved total oocyte numbers were higher for the normoresponder group compared to poor and suboptimal response groups (p<0.001 and p<0.001). The median rate of response to COH was significantly higher for the normoresponder group compared to poor and suboptimal groups (p<0.001 and p=0.019) (Table II).

Rate of increase in serum FSH levels (delta FSH percentage) did not show correlation with initial serum AMH levels overall (r=0.036, p= 0.69). The increase rate in serum FSH levels until the antagonist starting day was positively correlated with the response to COH (r=0.24, p=0.008) (Figure 1).

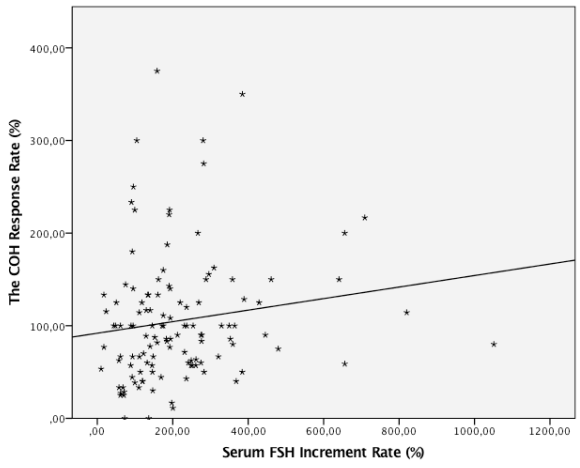

Figure 1.
Scatter plot COH response and Serum FSH Increment Rate. Correlation r=0.24, p=0.008, r^2 = 0.022.

Delta serum FSH percentage was also positively correlated with serum progesterone and estradiol levels on the day of hCG administration (respectively; r=0.21, p=0.021 and r=0.21, p= 0.022).

Discussion and Conclusion

In our study, we found out that spot serum FSH concentrations measured on the GnRH antagonist starting day with a fixed high dose of rFSH, were significantly lower in the group of women with normal response to stimulation. Based on the total number of oocytes retrieved following stimulation, actual ovarian reserve appears to be a more important determinant rather than serum FSH concentrations.

There are limited studies investigating serum FSH concentrations during COH cycles. A study conducted with women who were supposed to have a normal ovarian reserve stimulated with different doses of rFSH, reported a significantly higher serum FSH concentrations with higher doses of gonadotropins[8]. However, there was no difference between groups regarding the numbers of mature oocytes and embryos achieved. In our study women with different ovarian response whom received a fixed, high dose of rFSH, poor and suboptimal responders showed higher serum FSH concentrations when compared to normoresponders. In another recent study, although serum FSH concentrations were similar on the trigger day among poor responders and normal responders who received gonadotropins at the same dose (150 IU), significantly lower number of oocytes were retrieved among poor responders. This could indicate that the serum FSH concentration is not the primary contributing factor for yield oocyte number[10].

In our study, serum FSH concentrations were measured during the first phase of the cycle – follicular phase, before the administration of antagonists, unlike previous studies. The practical rationale is that endogenous serum FSH levels might be suppressed by the antagonist. Therefore, serum FSH monitoring is warranted during early phases, and can be useful in determination of COH response or determination of the doses to be administered. In a previous study, gonadotropin dose adjustment has been done in order to prevent poor responses. However, no improvements were observed in cycle cancellation rates and in the number of oocytes recruited[11]. Therefore, adjustment during the late periods of the cycle may not bring the desired benefits.

A recent study investigated associations between serum FSH concentrations in the predetermined 7th day of the cycle and COH outcomes, in a patient subgroup who received various rFSH doses (dose range: 200-300 IU); serum FSH concentrations above the cut-off value of 22 IU were found to be associated with poor response[12]. Additionally, this study underlined a negative correlation between serum FSH levels and the numbers of recruited oocytes and

embryos. However, delta serum FSH levels were not evaluated in none of the studies mentioned above.

Studies on pharmacokinetics of exogenous FSH demonstrated that serum FSH levels were determined not only by the doses administered but also by the body weight[13]. In our study, no significant intergroup differences were observed in BMI scores.

In tailored dose studies, using <11 AFC as cut-off to predict poor responders, particularly the counts of antral follicles 2 to 10 mm in diameter, were assessed by FSH doses of 150, 225 and 450 IU per day, and the administration of FSH at higher doses, for poor responders, dose increments did not provide any benefit for live birth Rate and were found to be associated with unnecessarily increased treatment costs[14]. The cut-off value of <11 is chosen in this study for AFC to predict poor responders which is significantly higher than our cut-off value. Considering higher rates of FSH receptor binding in patients with good ovarian reserves and adequate AFC, it is inevitable to wonder whether some dose increments could improve parameters of response to COH in those patients with better ovarian reserve rather than poor responders? We could not know the percentage of antral follicles which will respond to COH cycles.

As Vienna consensus aimed to create laboratory performance indicators for COH results, COH response rates have not been evaluated clinically[9]. To evaluate COH response success rates between groups, we calculated the ratio of retrieved total oocytes to AFC as percentage. Although there is a similar rate of increment for the serum FSH levels between the groups, COH response rate was higher for the normoresponder group in our study population. However randomized, controlled studies are needed to provide a definitive response to this question.

A comparative study of higher doses including 450 IU and 600 IU in patients with low ovarian reserve did not demonstrate any benefits associated with dose increments[15]. A more recent meta-analysis emphasized that it was impossible to suggest that dose increments were beneficial in poor responders, due to heterogeneity and different cut-off values used in those studies[16].

In our study, significant differences were observed between 3 groups for the baseline FSH concentrations. All of the studies performed with serum FSH levels up to date, evaluated spot serum FSH levels, but as serum FSH levels could be dependent on initial values, we also evaluated the delta serum FSH percentage levels. In our study, the rate of increment in serum FSH levels was found significantly correlated with COH response parameters.

In spite of similar delta serum FSH percentages observed between tdifferent groups, a better COH cycle success is achieved in normoresponder group (144.4%). This could be explained with the presence of FSH sensitive secondary or small antral follicles (2-5 mm) that could not be counted during the initial ultrasonography[17]. Due to higher initial baseline FSH levels within the poor responders, small antral follicles (2-5 mm) which have been already advanced to antral follicles (8-10 mm) would not respond to recombinant FSH. These findings also support that normoresponders with normal ovarian reserve and secondary follicles or small antral follicles, could benefit from a higher starting FSH dose.

Additionally, several limitations should be mentioned. Compared to the poor and suboptimal responders, the sample size of the normoresponders was too small to be discussed. Also, exclusion of cancelled cycles and inclusion of only flexible antagonist cycles could be additional limitations.

In general, the results of this study show that similar rate of increase in serum FSH levels between different COH response patients support that actual ovarian reserve appears to be a more important determinant rather than serum FSH concentrations, as a parameter of response to COH cycles. Limited studies have been conducted to assess serum FSH concentrations and COH cycle outcomes to date and in this study, our results demonstrated higher spot serum FSH levels and excessive amounts of circulating FSH would not reflect an appropriate direct relationship between COH response and FSH levels. Since our study is a retrospective study, unrecognized biases should be considered. These issues should be studied in a larger trial with poor responders and a true dose comparison design.

Ethics Committee Approval Information:
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Idea and design: G.U., I.K.; Data collection and processing: I.K., K.A., B.A.; Analysis and interpretation of data: I.K., G.K., C.Ç.; Writing of significant parts of the article: I.K., K.A., G.U.
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