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Predictors of Total Gonadotropin Dose Required for Follicular Growth in Controlled Ovarian Stimulation with Intrauterin Insemination Cycles in Patients with Unexplained Infertility or Male Subfertility

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OBJECTIVE: The aim of this study was to determine the possible predictors of total gonadotropin dose (TGD) required to achieve ovulation in patients with unexplained infertility or male subfertility.

STUDY DESIGN: A prospective study on 230 patients (n:178 unexplained infertility, n:52 male subfertility) scheduled for controlled ovarian stimulation (COH) and intrauterine insemination (IUI) was designed to determine the association between basal follicle stimulating hormone (FSH), luteinizing hormone (LH), estrodiol (E2) levels, antral follicle count (AFC), age and body mass index (BMI) and total gonadotropin doses needed to achieve follicular growth.

RESULT: Regression analysis revealed an association between basal FSH level, BMI and AFC with total gonadotropin dose (P=0.001, P=0.002, P=0.045). BMI was positively correlated with TGD (r:0.400, P=0.001). Mean BMI of patients who required a total dosage of >1500 IUs of gonadotropin was 29.7±4.8kg/ m^2 where as it was 24.9±3.2kg/ m^2 for patients who received <1500 IU to achieve follicle growth (P=0.001).

CONCLUSION: Our study results imply that basal BMI is the essential parameter in determining the total dose of gonadotropin used to achieve follicular growth.

Key Words: Male subfertility, Unexplained infertility, Total gonadortopin dose, Body mass index, FSH, Estrodiol, LH, Antral follicle count.

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Introduction

Approximately 15% to 30% of couples will be diagnosed as having unexplained infertility after standart infertility evaluation.[1] Use of controlled ovarian stimulation (COH) with intrauterine insemination (IUI) in patients with unexplained infertility and male subfertility is based on the intention to maximize the chance of fertilization by providing ovulation with an increased number of eggs and introducing washed sperm with increased density of motile sperms into the uterine cavity. Various treatment protocols have been investigated for ovarian stimulation in patients with unexplained infertility.[1,2] Individual patient characteristics, treatment efficacy and cost of the treatment should be considered when developing an optimal treatment strategy.[3] Studies in the field of infertility focus on identification of prognostic factors that predict the treatment outcome and thus provide a personalized management strategy with optimum results for each couple.[4]

Follicular development is known to directly effect the pregnancy rates. Follicular development is related with ovarian reserve and diminished ovarian reserve is observed in most women with advancing age.[5] Ovarian aging reflects the processes of follicular depletion and decline in oocyte quality.[6] Increasing age is associated with decline in natural fecundity and pregnancy rates.[7] Age is held to be a better predictor of artificial reproduction technique outcome than basal follicule stimulating hormone (FSH) levels in younger women, and seems to affect egg quality more than quantity.[8,9] Depletion of ovarian follicles is followed by increased production of FSH from the pituitary gland. A combination of early follicular FSH

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and age has been claimed to be better than age alone in predicting outcome in women undergoing invitro fertilization (IVF).[8] Limitations of measurement of basal FSH include the lack of a clear cut off threshold value, presence of monthly variations and disparities between different laboratory assays.[10] Lower baseline levels of FSH-with a cutoff level of 8 IU/L and estradiol (E2), but not LH levels, are correlated with improved ovarian response and higher pregnancy rates in IVF cycles using a gonadotropin-releasing hormone (GnRH) antagonist.[11]

It has been suggested that measurement of basal E2 in addition to FSH might improve prediction of fertility potential compared with basal FSH and chronological age alone.[12] Evidence suggests that elevated early follicular E2 levels are associated with poorer prognosis.[13] The number of antral follicles in the early follicular phase correlates with ovarian reserve.[14] Low numbers of antral follicles are a sign of ovarian ageing, and are observable earlier than a rise in FSH serum level.[15] Problems with antral follicle count (AFC) include observed cycle–cycle differences, biological variation and intraobserver differences.[16] However, it has been proposed that AFC is possibly a better prognostic indicator than age or endocrine markers.[17]

The aim of this study was to determine the most significant parameter in distinguishing patients who need larger amounts of gonadotropin to achieve follicle growth during controlled ovarian hyperstimulation for treatment of unexplained infertility or male subfertility in order to design individual treatment modalities with improved outcomes.

Material and Method

A prospective study on 230 patients (n:178 unexplained infertility, n:52 male subfertility) was designed to determine the possible association between basal FSH, luteinizing hormone (LH), E2, AFC, age, body mass index (BMI) of patients and total gonadotropin doses (TDG) required to achieve ≥1 follicle with a diameter greater than ≥16 mm in mean diameter. Sample size was estimated as 230 with 95% confidence interval and ±6.45 precision. Between January 2008 and September 2009, a total of 230 couples with unexplained infertility or male subfertility signed a written informed consent to take part in this study. The study was approved by the local regulatory authorities.

All couples had primary subfertility for at least 24 months. They had undergone fertility investigation by taking a detailed medical history, and performing physical examination, confirmation of ovulation by ultrasound and/or mid-luteal serum progesterone, semen analysis, and laparoscopy and/or hysterosalpingography to confirm tubal patency. All women had regular spontaneous menstrual cycles with 21-35 day intervals. Semen analysis was performed according to standardized methods by trained technicians and World Health Organization (WHO) criteria for normal sperm analysis was used for evaluation (a sperm concentration of ≥20x106, ≥50% motility and ≥%30 normal morphology, ≥ 75% viability with ≤ 1×106 white blood cells),[18] Unexplained subfertility was defined if no abnormality was found during these infertility investigations. Male subfertile group consist of 52 males with low sperm concentration between 5.106 to 20.106 or sperm motility lower than 40% with normal morhphology. Exclusion criteria were being <18 years or >38 years of age, anovulation (mid-luteal serum progesteron level ≤ 4.0 ng/mL), polycystic ovary syndrome (PCOS), premature ovarian failure, history of previous assisted reproduction attempts or surgical operations of the reproductive tract, having endometriosis classification stage III or IV of the American Fertility Society, malignancies of ovaries, breast and/or uterus, contraindications for one of the investigated drugs, persisting ovarian cyst (>19 mm and >1 months) on Day-3 of the treatment cycle, or having a total motile sperm count <1 million after semen preparation. All patients had FSH, LH, E2 levels measured at Day-3 (Roche Diagnostics GmBH, Germany chemiluminescence) of the menstrual cycle. A basal ultrasonography was performed for AFC prior to treatment.

Weight and height were measured in light clothing without shoes. BMI was calculated, dividing the weight divided by square of height (kg/m^2). Waist circumference was measured at the narrowest level between the costal margin and iliac crest, and the hip circumference was measured at the widest level over the buttocks while the subjects were standing and breathing normally. The waist-to-hip ratio (WHR) was calculated. The BMI, WHR were assessed by a single investigator for all of the subjects.

Step-up protocol was planned with an initial dose of 75 IU/day FSH beginning with cycle day 3 and increased after 7th day of the treatment or more if no follicle> 10mm was determined during real-time transvaginal ultrasonography (Schimadzu 450 XL Mhz vaginal probe), and the dose was increased in small increments (37.5 IU) , at same intervals, until evidence of progressive follicular development is observed. The FSH daily dose at the time when the leading follicule reached 12 mm in diameter was maintained until follicular maturation was achieved. Successful stimulation was accepted when ≥1 follicule with a diameter ≥16 mm was observed during transvaginal ultrasonography. The criteria for abondoning the cycle was having 5 or more follicle>14 mm.[19] The sum of the gonadotropin doses used during the cycle was recorded as Total Gonadotropin Dose (TGD). High dose gonadotropin need was defined as values >1500IU. Approximately 36 hours after the human chorionic gonadotropin (HCG) injection a concentrated suspension of sperm was placed in the uterus using an insemination catheter. Sperm density and motility of the sperm suspension was recorded. Women with a delay in the menstrual period following insemination was evaluated for pregnancy with serum HCG levels and sonograms.

Statistical Analyses

Data analysis was performed using SPSS version 11.0 (SPSS Inc., Chicago, IL, USA). An independent samples T-test was used for comparison of continuous variables between groups. A multivariate general linear model was applied for comparisons between two groups after adjusting for specific variables. Linear correlations were examined using Pearson's correlation. A multiple regression analysis was performed to determine which variables predict TGD. Odds ratios within 95% confidence intervals (CIs) were calculated to estimate the association between BMI and TGD. By means of a logistic regression model, odds ratios were adjusted for possible confounders, such as age, FSH, LH, E2, AF. Chi square test was used to compare catagorical variables. P value of ≤0.05 was considered statistically significant.

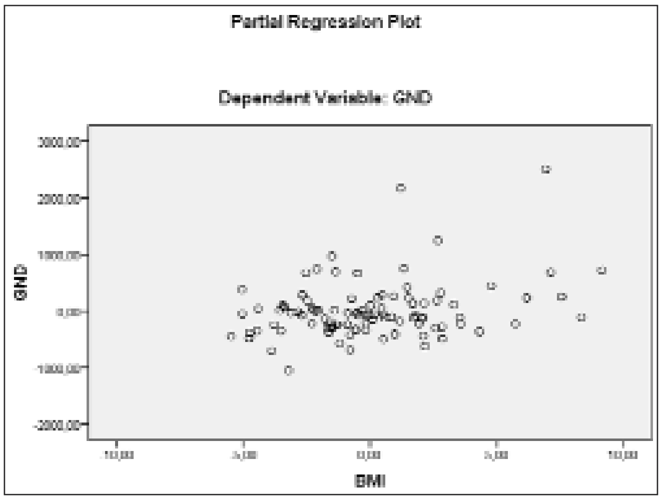

Figure1: BMI values and total gonadotropin doses

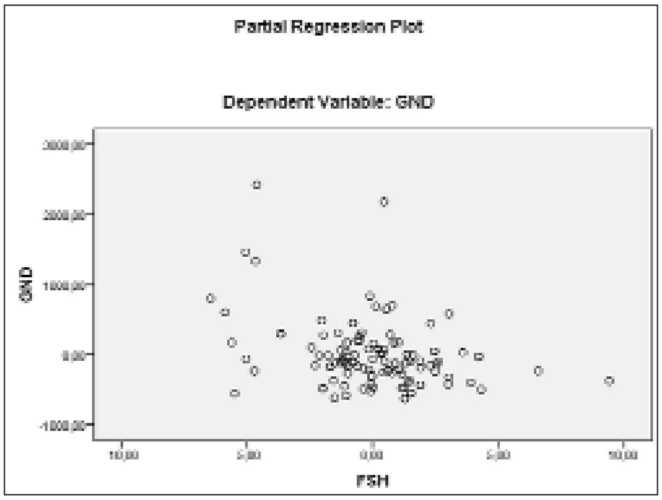

Figure2: FSH values and total gonadotropin doses

Results

Mean age, BMI, FSH, LH, E2, AFC and gonadotropin dose of the recruited patients were 29.7±5.3, 24.5±3.8 kg/m², 6.1±2.5 mIU/ml, 8.1±1.1 mIU/ml, 57.1±60.3 pg/ml, 6.4±2.8, 764.4±467.2 IU respectively. Multivariable regression analyses revealed association between basal FSH level, BMI and AFC with total gonadotropin dose (P=0.001, P=0.002, P=0.045) after adjustment of other parameters. Correlation coefficient between FSH and TGD was found to be r=–0.224 (P=0.001). BMI was positively correlated with TGD (r:0.400, P=0.001). AFC was not correlated with TGD (p=0.062). Mean BMI of patients who required a total dosage of >1500 IUs of gonadotropin was 29.7±4.8kg/m2 where as it was 24.9±3.2kg/m² for patients who received <1500 IU of gonadotropin to achieve optimum number of follicle growth (P=0.001, table 1). There were 61 (28%) patients with BMI>25 in group with low TGD, while 14 (77%) patients in high TGD group

Table 1: Patient characteristics of 230 women

	All patients N=230 (Mean ±SD)	TGD <1500 IU N=212 (Mean ±SD)	TGD >1500 IU N=18 (Mean ±SD)	P value
Age	29.6±5.2	29.7±5.2	29.2±6.2	0.815
FSH(Mıu/mL)**	6.2±2.4	6.2±2.3	4.7±3.9	0.56
LH (mIU/mL)***	8.6±12.3	7.5±9.2	12.6±24	0.385
E2 (pg/mL)****	57.9±64.9	59.2±66.7	30.1±15.2	0.058
AFC*****	6.3±2.8	6.5±2.9	4.6±1.5	0.042#
TGD (IU)******	765.4±484.2	664.3±282.9	1929.3±652.6	0.001 #
PREGNANCY	45(25.2%)	49(23.1%)	9(50%)	0.021#

**BMI: Body Mass Index, **FSH: Follicule stimulating Hormone, ***LH: Luteinizing Hormone, ****E2: Estradiol, *****AFC: Antral Follicle Count ******TGD: Total Gonadotropin Dose, p<0.05: Statistically Significant, # Statistically significant* (p<0.001). Odds ratio of BMI>25 for need of high gonadotropin dose was found to be 8.585(95% CI, 2.702-27.281, P=0.001). Odds ratio of BMI>30 for need of high gonadotropin dose was found to be 27.344(95% CI, 8.495-88.010, P=0.001). There were 9 (4%) patients with BMI>25 in group with low TGD, while 10 (55%) patients in high TGD group (p<0.001).There were 49 (23.1%) pregnancies in patients who needed lower doses of gonadotropins while 9(50%) patients conceived in high dose gonadotropin group (p:0.021). Mean age of patients who concieved (27.5±4 years) was lower than those who did not concieve (30.4±5.4 years, p:0.001). Mean gonadotropin dose used for ovarian stimulation was also higher in patients who conceived but difference was not statistically significant (p:0.210). BMI and FSH adjusted gonadotropin doses between pregnant and non pregnant group were not significantly different (p:0.065). Mean age, BMI, FSH, LH, E2, AFC, TGD and pregnancy rates were similar between male subfertile and unexplained infertile group (Table 2).

Table2: Patient characteristics of different infertile groups

	Male subfertility N=52 (Mean ±SD)	Unexplained infertility N=178 (Mean ±SD)	P value
Age	29.9±5.8	29.6±5.2	0.748
BMI (kg/m²)*	24.4±3.8	24.5±3.8	0.935
FSH(Mıu/mL)**	6.±2.5	6.1±2.5	0.794
LH (mIU/mL)***	5.8±3.9	8.6±12.3	0.008
E2 (pg/mL)****	54.3±41.2	57.9±64.9	0.699
AFC*****	6.6±2.7	6.3±2.8	0.724
TGD (IU)******	761.5±406	765.5±484.3	0.958
PREGNANCY	13(25%)	45(25.3%)	0.967

****BMI:*** *Body Mass Index,* ****FSH:*** *Follicule stimulating Hormone,* *****LH:*** *Luteinizing Hormone,* ******E2:*** *Estradiol,* *******AFC:*** *Antral Follicle Count,* ********TGD:*** *Total Gonadotropin Dose, p<0.05: Statistically Significant,*

Discussion

The use of ovulation induction and intrauterine insemination for the treatment of unexplained infertility is known to improve the conception rates, however the data given in the published clinical trials have a limited value due to the heterogeneity of the treated couples and treatment protocols and methodologies of these studies besides the fact that there is limited data about the costs and cost-effectiveness of the treatment modalities,[20,21]

In IUI cycles the aim is to achieve optimal number of follicles with minimum cost and avoid ovarian hyperstimulation. Although predictors of ovarian response have been studied in IVF cycles, we have not encountered a study related with predictors total gonadotropin dose to achieve ovarian response in IUI cycles in this manner.

The aim of the present study was to explore the significance of the parameters of ovarian reserve tests to predict the need for high doses of gonadotropin required to achieve optimum follicler growth. The predictors in the model were high FSH, LH, AFC, E2, BMI and age of patient.

BMI index was found to be significantly higher in patients who needed higher doses of gonadotropin in our study group . Özgün et al reported that obese women (BMI >30 kg/m^2) required higher dose of gonadotropin for stimulation and faced a lower likelihood of pregnancy after ICSI.[22] The effect of obesity on fertility and fertility treatments have been investigated by various authors. Obesity can affect follicular development and ovulation by changing gonadotropin releasing hormone secretion and increasing circulating insulin levels and ovarian and adrenal androgen production and decreasing sex hormone binding globulin and altering steroid production from ovarian theca and granulosa cells through elevated serum peptin levels.[23-26] Other factors that are suggested to adversely effect the pregnancy rates during treatment cycles in obese women are increased endometrial thickness at the time of retrieval in obese patients[27] and lower intra-follicular hCG concentrations related to high BMI.[28]

In induced cycles, longer induction period with the use of a high dose of total gonadotropin is observed in obese patients in a large number of the studies[29-31] although Martinuzzi et al reported no increase in the total dose of gonadotropin required and no negative impact of BMI in IVF cycles in women with high BMI.[32]The outcome of infertility treatment in obese patients is controversial as in some studies higher cycle cancellations and lower pregnancy rates are shown in tretament.[27,33] Some authors reported no difference in cancellation, implantation or pregnancy rates while peak E2 levels were found to be lower in obese women without any impact on the pregnancy rate by other studies.[30,34] Furthermore, fat distribution, especially abdominal fatness is thought to have more impact on pregnancy rates in IVF cycles than obesity itself.[35] Health insurance in our country pays for 1500 IU gonadotropin doses per cycle, so patients were divided into two according to need for gonadotropin doses below and above this value.

It is known that female fertility declines with age.[36,37] However, it is also perceived that age per se can be a poor determinant of female fertility, since there is a wide range in the relationship between ovarian reserve and age.[38,39]

Basal FSH concentration is an indirect estimate of ovarian reserve, being a measure of the magnitude of negative feedback exerted on the pituitary by ovarian inhibin and E2 secretion.[39] An elevated basal FSH level has been shown to be a better predictor of poor IVF outcome and reproductive potential than chronological age alone.[8,40] Women with AFC less than four were 8.7 times more likely not to get pregnant after

IVF (two studies; 95% CI, 2.4-31.7) than women with AFC four or more. The sensitivity and specificity of AFC to predict cycle cancellation was 66.7% and 94.7%, respectively. Women with an AFC of less than four were 37 times (two studies; 95% CI, 13.68-100.45) more likely to have their cycle cancelled than women with AFC of four or more.[41] The clinical applicability for basal estradiol as a test before starting IVF is prevented by the very low predictive accuracy, both for poor response and non-pregnancy.[42] In our patient group with unexplained infertility, no statistically significant difference was found in the AFC of the patients who concieved and who failed to conceive.

Among the known parameters used for evaluation of the ovarian reserve; only BMI was found to be significantly associated with the total gonadotropin dose needed for ovarian stimulation rather than age, FSH, LH, AFC and E2 in the presented study. Prospective follow up with optimum number of patients is the major advantage of this study but further studies with higher number of patients are required for further clarification of the predictors of outcome and hence tailoring an individualized treatment protocol in patients with unexplained infertility.

Açıklanamayan ve Erkek Faktör İnfertilitesi Olan Hastalarda Ovaryen Stimulasyon-Intrauterin Inseminasyon Sikluslarında Folikül Gelişimi için Gereken Gonadotropin Dozu Prediktörleri

AMAÇ: Bu çalışmada amaç açıklanamayan ve erkek faktör infertilitesi olan hastalarda ovaryen stimulasyon-intrauterin inseminasyon sikluslarında folikül gelişimi için gereken gonadotropin dozu prediktörlerini araştırmaktır.

GEREÇ VE YÖNTEM: Bazal folikül stimüle edici hormon (FSH), luteinize edici hormon (LH), estrodiol (E2) levels, antral follikül sayısı (AFC), yaş ve vücut kitle indeksi (VKI) ile total gonadotropin doz arasındaki ilişki araştırılmak üzere ovaryen stimulasyon-inseminasyon prokolüne alınan 230 (178 açıklanamayan, 52 erkek faktör infertilitesi)hastada prospektif çalışma planlandı.

BULGULAR: Regresyon analizinde FSH, AFC ve VKI ve total gonadotropin dozu arasında ilişki anlamlı saptandı (P=0,001, P=0,002, P=0,045). VKI total gonadotropin dozu ile anlamlı korele idi (r:0,400, P=0,001). Folikül gelişimi için 1500 ıu nün üstünde gonadotropin ihtiyacı olan hastaların ortalama VKI 29,7±4,8kg/ m^2,1500 ıu nün altında gonadotropin ihtiyacı olan hastaların ortalama VKI 24,9±3,2kg/m^2 .

SONUÇ: Çalışmamızın sonuçlarına göre foliküler büyümeyi sağlayacak gonadotropin dozunu belirlemede VKI gerekli bir parametredir.

Anahtar Kelimeler: Erkek subfertility, Açıklanamayan infertilite, Total gonadortopin doz, Vücut kitle indeksi, FSH, Estrodiol, LH, Antral folikül sayısı.

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