The influence of body mass index on FSH dose and pregnancy rate in women undergoing ICSI-embryo transfer

ICSI-embryo transferi yapılan hastalarda vücut kitle indeksinin FSH dozu ve gebelik oranına etkisi

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Abstract

Objective: The aim of this study was to evaluate the influence of body mass index (BMI) on follicle stimulating hormone (FSH) dose and pregnancy rate in women undergoing ICSI- embryo transfer (ET).

Material and Method: This prospective study included 604 women undergoing ICSI-ET between January 2006 and December 2007. Patients were classified into five groups according to their BMI: Group A (BMI <18.5 kg/m^2), Group B (BMI 18.5 to 24.9 kg/m^2),Group C (BMI between 25 and 29.9 kg/m^2), Group D (BMI 30 to 35.9 kg/m^2), Group E (BMI: ≥36 kg/m^2).

Results: Total FSH doses for groups were 2087,5 I U(1200-4800), 2200 IU (750-7575), 2362,5 IU (900-7650), 3000 IU (1050-6975) and 3525 IU(1600-7800) respectively. The total FSH dose was significantly higher in Group E compared with those women in Groups A, B, C (p=0.001). Cancelled cycle rates were similar in all groups. The pregnancy rates per cycle were 30%, 40.9%, 32.8%, 14.4% and 18.2% respectively. The pregnancy rate per cycle was significantly higher in Group B than those women in Groups D and E, and it was also higher in Group C compared with those patients in Group D (p=0.038). The total FSH doses were significantly lower in Groups B and C than those in Groups D and E in patients with male infertility and in women with PCOS (p<0,001). The total FSH doses were similar in all five groups in patients with tubal factor infertility and in women with unexplained infertility.

Conclusions: Obese women (BMI >30 kg/m^2) required higher dose of gonadotropin for stimulation and they face a lower likelihood of pregnancy after ICSI. (J Turkish-German Gynecol Assoc 2009; 10: 1-5)

Key words: Body mass index, ICSI, Ovarian response, Pregnancy rate

Özet

Amaç: Bu çalışmanın amacı kliniğimizde ICSI-ET uygulanmış olan hastalarda vücut kitle indeksinin (VKİ) FSH dozu ve gebelik oranlarına etkisini ortaya koymaktır.

Gereç ve Yöntemler: Ocak 2006 ile Aralık 2007 tarihleri arasında ICSI-ET yapılan 604 hastanın verileri prospektif olarak kaydedildi. Hastalar VKİ'lerine göre beş gruba ayrıldı: A grubu (VKİ <18.5 kg/m^2); B grubu (VKİ 18.5-24.9 kg/m^2); C grubu (VKİ 25-29.9 kg/m2); D grubu (VKİ 30-35.9 kg/m2); E grubu (VKİ ≥36 kg/m^2).

Bulgular: Ovulasyon indüksiyonu için gerekli gonadotropin dozları gruplara göre: A grubunda 2087,5 I U(1200-4800); B grubunda 2200 IU (750-7575), C grubunda 2362,5 IU (900-7650), D grubunda 3000 IU (1050-6975) ve E grubunda 3525 IU(1600-7800)olarak bulundu. A, B ve C gruplarında gonadotropin dozarı E grubuna göre anlamlı olarak daha düşük bulundu (p< 0.001). İptal edilen sikus sayılarında gruplar arasında anlamlı fark saptanamadı. Siklus başına gebelik oranları ise: A grubunda %30, B grubuna %40.9, C grubunda %32.8, D grubunda %14.4 ve E grubunda %18.2 olarak bulundu. Siklus başına gebelik oranları B grubunda D ve E grubundan C grubunda ise D gubundan anlamlı olarak daha yüksek saptandı (p=0.038). İnfertilite nedenlerine göre hastalar aynı kriterlerle VKİ'lerine göre sınıflandırıldıklarında, açıklanamayan infertilite ve tubal faktör saptanan hastalarda gruplar arasında gonadotropin dozları açısından fark saptanmadı. PCOS ve erkek faktörü olan hastalarda gonadotropin dozları B ve C gruplarında D ve E gruplarına göre anlamlı olarak daha düşük saptandı (p<0,001).

Sonuç: Obez hastalarda ICSI uygulamalarında ovulasyon indüksiyonu için daha yüksek gonadotropin dozları gereklidir. Siklus başına gebelik oranları obez olanlarda azalmış olarak saptandı.

(J Turkish-German Gynecol Assoc 2009; 10: 1-5)

Anahtar kelimeler: Vücut kitle indeksi, İCSİ, Over yanıtı, Gebelik oranı

Introduction

The prevalence of obesity increases worldwide. Together with other conditions like diabetes mellitus, hypertension cardiovascular diseases, obese women are more likely to experience reproductive problems such as menstrual irregularities, anovulation, hirsutism, infertility and miscarriage (1). Obesity may impair human reproduction through different ways such as altered secretion of pulsatile gonadotropin-releasing hormone (GnRH), reduced sex hormone binding globulin (SHBG) leading to an alteration of androgen and estrogen delivery to target tissues, insulin resistance, hyperandrogenism and elevated leptin levels.

The data related to the impact of obesity on assisted reproduction treatment (ART) outcomes are conflicting. Many studies revealed that obese women require higher dose of gona-

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dotrophins for ovarian stimulation, increased cycle cancellation rates, fewer oocytes retrieved (2-5). In contrast, other studies found no significant effect of obesity on response to ovarian stimulation (6-9). Moreover, some studies suggested no negative impact of obesity on pregnancy rate and outcome of pregnancies conceived by ART (2, 6, 7, 10). In contrast, other studies have demonstrated that obesity may negatively affect ART outcome (3-5, 11-16).

We, therefore, conducted a prospective study to determine the influence of body mass index (BMI), which is calculated by dividing the weight in kilograms by height in meters squared (kg/m^2), on follicle stimulating hormone (FSH) dose and pregnancy rate in women undergoing ICSI- embryo transfer.

Materials and Methods

Study Population

This prospective study included 604 women undergoing ICSI with fresh embryo transfer at the Obstetrics and Gynecology Department, Erciyes University School of Medicine, between January 2006 and December 2007. The Ethics Review Committee approved the study, and informed consent was obtained before participation. The patients had their BMI recorded at the beginning of ovulation induction. Only the first ART cycle for each patient and only day 3 transfer cycles were included. Exclusion criteria are: (1) women >42 years old; (2) patients with an accompanying medical problem which may lead to abnormal BMI such as diabetes mellitus, hyper or hypothyroidism; (3) patients with basal FSH level >15IU/L; (4) women with thawed embryo transfer; (5) treatment cycles with surgical sperm retrieval, (6) patients with prior ovarian surgery, (7) poor responders patients defined as presence of three or less dominant follicles on the day of human chorionic gonadotropin (hCG) administration or a peak E2 level of <500 pg/ml, and (8) couples with more than one etiologies for their infertility.

Routine infertility investigations were performed in all couples. Semen analysis was evaluated according to the World Health Organization (WHO) criteria (17). Hormonal assessment consisted of measurement of LH, FSH, prolactin, TSH, estradiol (E2), testosterone, androstenedione, dehydroepiandrosterone sulphate (DHEAS), 17-hydroxyprogesteone on day 3 of a spontaneous or progesterone-induced menstrual bleed. Polycystic ovary syndrome (PCOS) was diagnosed according to 2003 Rotterdam criteria (18). To document ovulatory status, serum progesterone level was assessed on cycle days 21 and 23. The uterine cavity and fallopian tubes were evaluated by hysterosalpingography (HSG), additionally hysteroscopy and laparoscopy were performed to confirm the pathologies detected by HSG. Unexplained infertility was diagnosed when all investigations revealed normal results. Patients were divided into five groups according to their BMI: Group A (BMI <18.5 kg/m^2), Group B (BMI 18.5 to 24.9 kg/m^2),Group C (BMI between 25 and 29.9 kg/m^2), Group D (BMI 30 to 35.9 kg/m^2), Group E (BMI: ≥36 kg/m^2). The first four groups were classified according to WHO classification system for obesity (19). The last group was chosen to define severe obesity based on a previous report (9)

Stimulation protocol for ICSI treatment

Ovarian stimulation was facilitated by the standard 'long protocol'. Briefly, pituitary down-regulation was achieved by GnRH agonist (Lucrin daily; Abbott, Istanbul, Turkey) given daily from day 21 of the cycle preceding stimulation. Ovarian stimulation was carried out with recombinant FSH (Gonal F; Serono, Istanbul, Turkey) administered subcutaneously. The starting daily FSH dose was adjusted for age, ovarian volume, antral follicle count, day 3 FSH and BMI and it was 187.5-300 IU in women with PCOS and the remaining patients received 225-450 IU starting FSH dose. Subsequent gonadotropin doses adjusted based on ovarian response assessed by estradiol levels and follicular growth by serial transvaginal ultrasonograms. Ovulation was induced with 10 000 IU hCG (Pregnyl; Organon Istanbul, Turkey) when at least three follicles were 17 mm or more in maximum diameter. Oocyte retrieval was performed by transvaginal follicular aspiration under vaginal ultrasound guidance 36-38 hours after hCG administration. Oocytes were inseminated by ICSI and only ejaculated spermatozoa were microinjected. Embryos were transferred on day 3 and as a rule, and, when available, three embryos were transferred. However, transfers of four embryos were sometimes allowed in selected older women or in patients with poor embryo quality, after counseling the patients on the potential risks of multiple gestations. Ovulation induction, oocyte retrieval and embryo transfer were performed by two authors (EMA and YŞ). Luteal-phase support was achieved by daily administration of vaginal progesterone gel (Crinone 8% vaginal gel; Serono, Istanbul, Turkey) starting on the day of oocyte retrieval.

Pregnancy was defined as presence of fetal cardiac activity on transvaginal ultasonography at 7 weeks of gestation or later. The outcome of pregnancies were determined by reviewing of hospital records and contact with the women.

Statistics

Results are presented as median and interquartile range. Data were compared by Chi-square test. The total gonadotropin doses were compared by Kruskal Wallis test. Post-hoc comparisons were performed using the Dunn's procedure. For comparisons of two proportions, we used Minitab 14. All analyses were performed using SigmaStat 3.5. Statistical significance was set at $p<0.05$.

Results

Between January 2006 and December 2007, 604 subjects underwent their first ART cycles. The cause of infertility were male factor (n=314), Unexplained infertility (n=149), PCOS (n=90) and tubal factor (n=51). Table 1 shows the patients' median age, number of patients according to BMI groups and causes of infertility. There was no statistically significant difference with respect to patients' median age between groups. Table 2 summarizes total gonadotropin doses, cycle outcome and pregnancy rates of all five groups. The total FSH used for stimulation was significantly higher in women with a BMI ≥36 compared with those women in Groups A, B, C (p=0.001). The proportions of cancelled cycles were similar in all groups (Table 2). There were statistically significant more pregnancies in Groups B and C compared with those women in Groups A, D and E (p=0.001). The numbers of singleton, twin and triplet pregnancies were higher in Groups B and C than those in Groups A, D and E. The pregnancy rate per cycle was significantly higher in Group B than those women in Groups D and E, and it was

also higher in Group C compared with those patients in Group D (p=0.038). Table 3 examines total amount of gonadotropin used for stimulation according to BMI groups and causes of infertility. The total FSH doses were significantly lower in Groups B and C than those in Groups D and E in patients with male infertility and in women with PCOS (p<0,001). The total FSH doses were similar in all five groups in patients with tubal factor infertility and in women with unexplained infertility (Table 3).

Discussion

ART represent the choice of the treatment in cases of failure of pharmacologically induced ovulation. The risk of infertility is almost three times higher in obese women compared those in non-obese women (20). In obese women, endocrine and metabolic alterations, such as altered steroid metabolism, altered secretion and action of insulin and other hormones such as leptin, ghrelin, adiponectin and resistin, may impair ovarian function (21). These changes can affect follicular growth, embryo development and implantation in both natural and ART cycles (22). Ferlitsch et al. (15) reported that, by increasing BMI by one unit, the odds for pregnancy decreased by 0.84 in ART cycles. Similarly, each reduction of BMI by one unit increased the chance of pregnancy by 1.19. Additionally, Kably-Ambe and colleagues (23) observed a higher incidence of asynchronous follicular development in obese women undergoing ovarian stimulation. Moreover, in obese patients, decreased periovulatory intrafollicular hCG concentrations have been associated with decreased fertilization rates. Carrell and associates (24) reported an inverse association between BMI and intrafollicular hCG concentration, which was significantly lower in patients with BMI> 30kg/m^2 than those with a BMI< 30kg/m^2. The authors suggested that these findings could contribute to the concurrent decrease in embryo quality and pregnancy rates observed in their overweight and obese patients. Impaired oocyte quality may further contribute to the diminished ART success in obese patients (25). Bellver et al (26) studied 2656 first-cycle recipients of ovum donation and observed a tendency towards lower implantation and pregnancy rates and higher miscarriage rates in obese women. The authors concluded that the endometrium, or its environment, plays a subtle role in the more negative reproductive outcome of obese women.

The present study has demonstrated that obese women (BMI>30 kg/m^2) required higher dose of gonadotropin for stimulation and they face a lower likelihood of pregnancy after ICSI, suggesting that the response to FSH stimulation is diminished by obesity. During ovarian stimulation with gonadotropin, serum FSH concentration should exceed a 'threshold' for gro-

Table 1. The patients' median age, number of patients according to BMI groups and causes of infertility

	BMI (kg/m^2)					
	A **<18.5**	**B** **18.5-24.9**	**C** **25-29.9**	**D** **30-35.9**	**E** **≥36**	**P**
No of women	10	232	229	111	22	
Age (years)	26.5±3.54 (20-32)	26.46±4.66 (19-40)	27.38±4.79 (20-44)	28.11±5.00 (21-40)	29.18±4.49 (25-41)	>0.05
Unexplained infertility	3(30%)	58 (25%)	59(25.8%)	23 (20.7%)	6 (27.3%)	>0.05
Male Factor	5(50%)	128 (55.2%)	116(50.6%)	55 (49.6%)	10 (45.5%)	<0.001
PCOS	1(10%)	34(14.7%)	32(14%)	18 (16.2%)	5 (22.7%)	<0.001
Tubal Factor	1(10%)	12 (5.1%)	22(9.6%)	15 (13.5%)	1 (4.5%)	>0.05

Table 2. Total gonadotropin doses, cycle outcome and pregnancy rates

	BMI (kg/m^2)					
	A **<18.5**	**B** **18.5-24.9**	**C** **25-29.9**	**D** **30-35.9**	**E** **≥36**	**P**
Total FSH dose (IU)	2087,5^a (1200-4800)	2200^a (750-7575)	2362,5^a (900-7650)	3000^{ab} (1050-6975)	3525^b (1600-7800)	0.001
No of Cancelled cycles	1	25	29	21	4	0.291
No of Pregnancy	3^b	95^a	75^a	16^b	4^b	0.001
No of Singleton	2^b	61^a	48^a	8^b	2^b	0.021
No of Twin	1^b	26^a	23^a	7^b	2^b	0.024
No of Triplet	0^b	8^a	4^a	1^b	0^b	0.016
Pregnancy per cycle (%)	30^{a,c}	40.9^{a,c}	32.8^{a,c}	14.4^b	18.2^{b,c}	0.038

Statistically significant difference is not present in groups sharing the same letter

Table 3. Total amount of gonadotropin used for stimulation according to BMI groups and causes of infertility

	BMI (kg/m²)					
	A <18.5	**B 18.5-24.9**	**C 25-29.9**	**D 30-35.9**	**E ≥36**	**P**
Unexplained infertility	2700 (1350-4800)	2400 (1225-5400)	2700 (1350- 7200)	3375 (1912-6975)	3337.5 (2025-4200)	0.11
Male Factor	1800[a,b] (1350-4050)	2237.5[a] (1100-7575)	2287.5[a] (1125-7650)	3037.5[b] (1050-5550)	4050[b] (1800-7800)	<0.001
PCOS	2650[a,b] (2650-2650)	1425[a] (750-4800)	1731,25[a] (900-4950)	2700[b] (1500-4050)	3675[b] (1600-6600)	<0.001
Tubal Factor	1200 (1200-1200)	3000 (1687.5-4950)	2725 (1200-6075)	2800 (2100-5100)	3375 (3375-3375)	0.54

PCOS; polycystic ovary syndrome
Statistically significant difference is not present in groups sharing the same letter

wing multiple follicles (27). Imani and co-workers (28) showed that the threshold effect of exogenous FSH is reduced in obese women, which finally may result in a requirement for higher FSH doses for stimulation, as demonstrated in the present study. Additionally, Steinkampf et al. (29) demonstrated lower absorption of recombinant FSH in obese women with both intramuscular and subcutaneous administration. This mechanism may contribute to higher gonadotropin requirement in obese patients undergoing ART. Fedorasack and collaborators (3) published a retrospective study of 2660 subjects undergoing 5019 ART cycles comparing four BMI categories (<18.5 to ≥30 kg/m²) and the starting dose of FSH was not fixed as in the present study. They found that increased BMI was associated with an increased FSH requirement. Furthermore, they analyzed the 2660 first treatment cycles and the results were similar to those obtained with all cycles, indicating that the relationship between increased BMI and increased FSH requirement was not due to a dose adjustment in successive cycles of the same couple. Therefore, using adjusted starting dose of FSH was not a disadvantage in the present study. A meta-analysis of 13 studies confirmed a positive relationship between degree of obesity and the amount of gonadotropin required for ovarian stimulation, with a weighted mean difference of 771 IU more needed in obese women (30).

Our study detected that the total FSH doses were higher in obese participants compared with normal and overweight women with PCOS and male infertility. However, we did not demonstrate such effect in patients with tubal factor or unexplained infertility. This may be explained by the fact that male factor infertility group included more than the half of the study population and failure to detect an association between obesity and higher gonadotropin requirement may be a reflection of smaller group size in tubal factor and unexplained infertility groups. Therefore, we have planned to expand our data. Moreover, in many studies, it has been proven that obese patients with PCOS required higher dose of gonadotropin for ovarian stimulation compared with normal counterparts and our results were consistent with these studies (31, 32).

The relationship between obesity and ART outcome is controversial. As in the present study, many authors have reported lower pregnancy rates in obese women following ART (2, 12-14, 24). It is well known that obesity is associated with changes of sex steroid hormone and SHBG levels. Obesity is related to a decrease in SHBG concentration and this leads to alteration of androgen and estrogen delivery to target tissues, which results in functional hyperandrogenism. Different studies have shown that intrafollicular hCG levels correlated inversely with BMI (14, 24). Additionally alteration of leptin levels associated with obesity, which may affect sex hormone levels, has been reported. Insulin resistance is an important factor for hyperandrogenism especially in patients with PCOS. Obesity and all associated endocrine changes may affect the function of the corpus luteum, that of the trofoblast function and early embryonic development and endometrial receptivity (16). Oocyte quality can also be impaired as a result of obesity. However, other studies have demonstrated similar pregnancy rates between obese and normal patients (7, 33-35).

It has been postulated that underweight has a deleterious effect on ART outcome as overweight and obesity (10, 12). Although our results revealed that the number of pregnancy was lower in underweight group (Table 2), we carefully avoided emphasizing this result because there were only 10 patients in this group and the result of underweight group may suffer from low statistical power. Therefore, larger studies are required to clarify this issue.

The study has some significant strength. First of all, the major strength was its prospective nature. In the literature, most of the data about this topic has been based on retrospective studies or pooled data, thus allowing potential for observer bias. Another advantage of the study was the homogeneity of ovarian stimulation protocol. In the literature most of the studies included patients with different stimulation protocols, which may effect gonadotropin doses and even outcome. Additionally, this study included only first ART cycle. There are many studies including more than one cycle of the same participants. In this situation, undiagnosed bad prognostic factors of an individual may cumulatively effect on results. Lastly, we calculated BMI of the participants at the beginning of ovarian stimulation. In the Literature, some studies encompassed patients with BMI assessed within the last one year or last six months. However, there is no doubt that significant weight changes may have occurred in this time interval.

The study has a significant disadvantage. The main limitation of the study was collecting data on a sufficient number of cases in

some groups. The number of cases studied was sufficient in Group B, C and D. However, for groups A and E far greater numbers needed to be studied. Additionally, it should be emphasized that there is only one patient in some subgroups (Table 1).

In conclusion, our results indicate that obesity and overweight is associated with reduced pregnancy rates and increased requirement gonadotropin for ovulation induction. This information is valuable for counseling couples before initiation of ART. Obese and overweight patients should be strongly encouraged to loose weight before starting ART.

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