Obesity is not associated with the poor pregnancy outcome following intracytoplasmic sperm injection in women with polycystic ovary syndrome

Funda Akpınar, Berfu Demir, Serdar Dilbaz, İskender Kaplanoğlu, Berna Dilbaz

Department of In Vitro Fertilization, Etlik Zübeyde Hanım Maternity & Women's Health Teaching Research Hospital, Ankara, Turkey

Abstract

Objective: To determine if body mass index has an effect on the outcome of *in vitro* fertilization in patients with polycystic ovary syndrome undergoing controlled ovarian hyperstimulation.

Material and Methods: The study included 337 cycles. Patients were stratified into the following 3 groups: normal weight, overweight, and obese. The primary outcome measures were response to ovarian hyperstimulation, the fertilization rate, the implantation rate, and the clinical and ongoing pregnancy rates.

Results: Total gonadotropin consumption increased, and the number of retrieved oocytes decreased as the body mass index increased. The implantation rate and clinical pregnancy rate were similar in all 3 groups. In response to the mid-luteal long protocol, the cycle cancellation rate was lower and the number of retrieved oocytes was higher in the overweight and obese groups, as compared to the antagonist protocol.

Conclusion: The body mass index did not affect the outcome of *in vitro* fertilization in women with polycystic ovary syndrome. Additional research is required to better understand the role of stimulation protocols on the cycle outcome. (J Turk Ger Gynecol Assoc 2014; 15: 144-8)

Key words: *In vitro* fertilization, polycystic ovary syndrome, body mass index

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age (1, 2). High luteinizing hormone and androgen levels in PCOS have a detrimental effect on oocyte maturity and fertilization (3) and are associated with a decrease in the pregnancy rate and an increase in the miscarriage rate (4). In addition, PCOS patients undergoing *in vitro* fertilization (IVF) have a high risk of ovarian hyperstimulation syndrome (OHSS) - an iatrogenic complication of controlled ovarian hyperstimulation (COH) (5).

Obesity is an epidemic that is affecting more women of reproductive age every year (6). Some IVF studies have reported that obesity is associated with the need for higher gonadotropin doses, an increase in the cycle cancellation rate, lower oocyte yield, and an increase in the miscarriage rate (7-9), whereas others have not noted any negative effects of obesity on IVF outcome (10, 11).The discrepancy in findings might be due to differences in the degree of obesity analyzed, stimulation protocols, and causes of infertility, and the overlapping features of PCOS and obesity, which makes it difficult to determine which factors affect IVF outcome (12, 13).

The primary aim of the present study was to investigate the effect of body mass index (BMI) on the outcome of IVF via intracytoplasmic sperm injection (ICSI) in women with PCOS. The study's secondary aim was to determine if there are any differences in cycle performance associated with the mid-luteal long gonadotropin releasing hormone (GnRH) agonist and flexible GnRH antagonist protocols in PCOS patients according to BMI.

Material and Methods

Data stored in a computer database on women with PCOS that underwent IVF treatment between May 2007 and August 2012 were retrospectively analyzed. The study protocol was approved by the Etlik Zübeyde Hanim Training and Research Institutional Review Board and written informed consent was obtained from the patients related to the treatment procedure. The study cohort consisted of PCOS patients that met the following criteria: BMI of 18.5-35 kg m^{-2}; undergoing ovarian stimulation using the mid-luteal long GnRH agonist protocol or the flexible GnRH antagonist protocol; and age ≤35 years. Women that underwent freeze-thaw cycles were excluded. All participants were stratified into 3 BMI groups according to the World Health Organization (WHO) classification system for obesity (14): normal weight (BMI: 18.5-24.9 kg m^{-2} [group 1]); overweight (BMI: 25-29.9 kg m^{-2} [group 2]); and obese (BMI: 30-34.9 kg m^{-2} [group3]).

Patients treated with the mid-luteal long GnRH agonist protocol took an oral contraceptive pill (Desolett; Schering Plough Medical, İstanbul, Turkey) for 21 d starting on d 3 of spontaneous menses. The gonadotropin starting dose ranged from 75 IU to 300 IU based on BMI. On d 16, daily GnRH agonist

Address for Correspondence: *Funda Akpınar, Department of In Vitro Fertilization, Etlik Zübeyde Hanım Maternity & Women's Health Teaching Research Hospital, Ankara, Turkey. Phone: +90 533 564 77 81 e.mail: fundaakpinar@yahoo.com*

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Table 1. Demographic characteristics of groups

Variable	Group 1 (n=109)	Group 2 (n=84)	Group 3 (n=79)	p value
No. of patients	84	59	50	
Age (years)	28.1±4.6	29.0±3.9	29.2±4.2	NS
Hormone Profile				
FSH (IU/L)	5.9±1.7	5.9±1.4	5.4±1.3	NS
LH (IU/L)	8.6±6.0[a]	7.6±4.7	5.9±2.9	.006
E2 (pg/mL)	43.6±19.4[b]	37.0±14.1	40.4±13.2	.043
Antral follicle count	18.7±7.5	18.6±5.9	18.1±6.2	NS
Type of infertility				NS
Primary	87 (79.8%)	69 (82.1%)	56 (70.9%)	
Secondary	22 (20.2%)	15 (17.9%)	23 (29.1%)	
Duration of infertility (months)	68.8±44.2[a,b]	91.2±49.9	100.4±51.6	≤.001
Number of previous IVF cycles	1.6±1.0	1.6±1.0	1.8±1.1	NS
Causes of infertility				
Male factor	54 (49.5%)[b]	31 (36.9%)	25 (31.6%)	.035
Tuboperitoneal	4 (3.7%)	6 (7.1%)	-	
Ovulatory dysfunction	91 (83.5%)	69 (82.1%)	65 (82.3%)	NS
Unexplained	44 (40.4%)	41 (48.8%)	39 (49.4%)	NS

[a]: Group 1 vs Group 2 (p<.05). [b]: Group 1 vs Group 3 (p<.05). Data are expressed as mean±SD.
No: number; FSH: follicle-stimulating hormone; LH: luteinizing hormone; E2: estradiol; IVF: *in vitro* fertilization

(Lucrin; Abbott Laboratories, İstanbul, Turkey) was initiated until human chorionic gonadotropin (hCG) administration. On d 3 of the next menstruation, gonadotropin stimulation was initiated. Patients treated with the flexible GnRH antagonist protocol started gonadotropin stimulation on d 3 of spontaneous menses (starting dose of 75-300 IU based on BMI). Then, GnRH antagonist (Orgalutran; Schering Plough Medical, İstanbul, Turkey) was started when a follicle was >13 mm and/or E2 >250 pg/mL^{-1}.

Ovarian response was monitored via transvaginal ultrasound (Mindray DC-T6; Shenzhen, China) and serum estradiol measurement. When ≤3 lead follicles with a mean diameter >17 mm were measured, 250 μg of hCG (Ovitrelle; Merck Serono Medical, İstanbul, Turkey) was administered subcutaneously for final oocyte maturation. Oocyte retrieval was performed under general anesthesia and transvaginal ultrasound (Mindray DC-T6; Shenzhen, China) guidance 35.5 h after administration of hCG. Patients were considered high risk for OHSS if they had any of the following: serum estradiol level ≥5000 ng/L^{-1}on the day of hCG administration and retrieval of ≥18 follicles and/or a BMI <24 kg m^{-2}. To prevent OHSS in the high-risk patients cabergoline 0.25 mg once daily per oral (Dostinex; Pfizer, Ascoli Piceno, Italia) was initiated on the day of hCG administration and continued until the day of embryo transfer, and colloid of hydroxyethyl starch (Voluven; Fresenius Kabi, İstanbul, Turkey) was intravenously administered at the time of oocyte retrieval. ICSI was routinely performed with all oocytes. Embryo transfer was performed on d 3 or 5 after retrieval, based on the number and quality of embryos. Embryos were evaluated 40-45 h and 65-70 h after ICSI for cleavage stage and were scored according to previously reported embryo evaluation criteria as the number and quality of blastomeres, the percentage of fragmentation, and the existence of a multinucleus (15). Blastocyst-stage embryos were scored according to the expansion of the blastocyst and the structure of the inner cell mass and trophectoderm (15). Embryo transfer was performed using a soft catheter (Wallace; Smiths Medical, Dublin, USA) under transabdominal ultrasound guidance (Mindray DC-T6; Shenzhen, China).

All patients received luteal support with vaginal progesterone gel (Crinone gel 8%; Serono Medical, Istanbul, Turkey) t.i.d. beginning the day of oocyte retrieval. Serum βhCG levels were measured 12 d after embryo transfer. Severe OHSS was considered the development of OHSS (16) with hematocrit >45%, WBC count >15,000 mm^{-3}, electrolyte imbalance, elevated liver enzymes, and a serum creatinine level >1.2 mg/dL^{-1}.

Data analysis was performed using SPSS v. 11.5 for Windows (SPSS, Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to determine if the distribution of continuous variables was normal or not. Levene's test was used to evaluate the homogeneity of variances. Data are shown as mean±SD or median (range), where applicable. Nominal data are expressed as n and percentage. Mean differences between groups were compared via one-way ANOVA, and the Kruskal-Wallis test was used to compare median values. When the P value for one-way ANOVA or Kruskal-Wallis test results was statistically significant, post hoc Tukey's HSD or Conover's non-parametric multiple comparison tests, respectively, was used to determine which groups

Table 2. Cycle outcomes of groups

Variable	Group 1 (n=109)	Group 2 (n=84)	Group 3 (n=79)	p value
No. of patients	84	59	50	
Cycle cancellation n (%)	2 (1.8%)	5 (6.0%)	2 (2.5%)	NS
Poor response	2 (1.8%)	1 (1.2%)	2 (2.5%)	NS
OHSS	-	2 (2.4%)	-	NS
Follicular discordance	-	2 (2.4%)	-	NS
Stimulation protocol n (%)				NS
Midluteal long GnRH agonist	83 (76.1%)	55 (65.5%)	61 (77.2%)	
Flexible GnRH antagonist	26 (23.9%)	29 (34.5%)	18 (22.8%)	
Duration of stimulation (days)	9.9±2.3	9.6±2.4	10.4±2.9	NS
Total gonadotropin dose (IU)	1558.6±632.0[a,b]	1731.0±657.6[c]	2094.6±796.9	≤.001
Mean progesterone level on the day of HCG	1.6±1.0	1.6±1.0	1.8±1.1	NS
Estradiol level on the hCG day (pg/mL)	3240.1±1857.0[b]	2813.3±1621.0[c]	2287.4±1333.6	≤.001
Endometrial thickness on hCG day (mm)	10.3±2.3	9.6±2.3	9.7±2.1	NS
No. of total oocytes	17.6±9.0[b]	16.8±8.1[c]	13.8±7.1	.015
No. of mature oocytes	12.7±6.6[b]	11.8±6.8	9.5±5.2	.008
No. of G1 embryo	1.25±1.04[b]	1.25±1.00[c]	1.64±1.03	.035
Severe OHSS	8 (7.3%)[b]	5 (6.0%)	0 (0%)	.009

[a]: Group 1 vs Group 2 (p<.05). [b]: Group 1 vs Group 3 (p<.05). [c]: Group 2 vs Group 3 (p<.05) . Data are expressed as mean±SD.
No: number; OHSS: ovarian hyperstimulation syndrome; GnRH: gonadotropin-releasing hormone; hCG: human chorionic gonadotropin; G1: Grade 1

differed from each other. Nominal data were analyzed using Pearson's chi-square or Fisher's exact test, where applicable. The level of statistical significance was set at $p<0.05$.

Results

In total, 337 cycles in 193 PCOS patients were analyzed. Patient baseline characteristics, including age, basal hormone profile, antral follicle count, type of infertility, number of previous IVF cycles, and cause of infertility, were similar in all 3 groups (Table 1). The response to COH in each group is shown in Table 2. Total gonadotropin consumption was highest in group 3, followed by group 2 (group 3 vs. group 2: $p=0.004$; group 3 vs. group 1: $p<0.001$; group 2 vs. group 1: $p=0.022$). The estradiol level on the day of hCG administration was lower in group 3 than in group 2 and group 1 (group 3 vs. group 2: $p=0.029$; group 3 vs. group 1: $p<0.001$). The number of oocytes retrieved was lower in group 3 than in group 2 and group 1 (group 3 vs. group 2: $p=0.017$; group 3 vs. group 1: $p=0.005$). The number of mature oocytes was lower in group 3 than in group 1 ($p<0.001$). None of the patients in group 3 had severe OHSS, as compared to 8 patients in group 1; the difference was significant ($p=0.022$).

Cycle performance and pregnancy outcome in group 1 were similar for those treated with the mid-luteal long GnRH agonist and flexible GnRH antagonist protocols. In group 2, the cycle cancellation rate and duration of stimulation were significantly higher in those that received the flexible GnRH antagonist protocol, as compared to the mid-luteal long GnRH agonist protocol ($p=0.004$ and $p=0.016$, respectively). In group 3, the number of oocytes and number of mature oocytes were significantly higher in those that received the mid-luteal long GnRH agonist protocol, as compared to the flexible GnRH antagonist protocol ($p=0.01$ and $p=0.01$, respectively). Pregnancy outcomes associated with both protocols were similar in all 3 groups (Table 3).

Discussion

Obesity and PCOS are closely related disorders with overlapping features (17), including a possible negative effect on the outcome of ICSI. The present study aimed to determine the effect of BMI on the outcome of ICSI in women with PCOS. The present findings show that PCOS patients in the normal weight group (Group 1) had the best cycle outcomes; however, the pregnancy rate in Group 1 and Group 3 (obese group) was similar.

Age of the female is the most important factor associated with IVF success. Regardless of BMI, as female age increases the risk for poor IVF outcome increases. Age-related decline in oocyte quality and the IVF fertilization rate is well documented; as such, maximum age in the present study was restricted to 35 years.

A significant association was observed in the present study between BMI and gonadotrophin requirement, which is in agreement with earlier reports of "gonadotrophin resistance" (7, 8, 11, 13, 18). Gonadotrophin resistance in obesity could be related to the volume of distribution or peripheral metabolic clearance.

Table 3. Cycle and pregnancy outcomes of the groups according to protocol

Variable	Group 1 (n=109)			Group 2 (n=84)			Group 3 (n=79)		
	Agonist (n=83)	Antagonist (n=26)	p	Agonist (n=55)	Antagonist (n=29)	p	Agonist (n=61)	Antagonist (n=18)	p
Cycle cancellation n (%)	2 (2.4%)	0 (0%)	NS	0 (0%)	5 (17.2%)	.004	2 (3.3%)	0 (0%)	NS
Duration of stimulation (days)	9.5±1.9	10.8±2.9	NS	9.2±2.4	10.3±2.0	.016	10.3±3.0	10.5±2,4	NS
Total gonadotropin dose (IU)	1567.0±574.3	1532.8±798.1	NS	1727.8±663.6	1738.1±657.8	NS	2109.6±833.5	2044.4±679.3	NS
No. of total oocytes	18.4±9.4	15.4±7.6	NS	16.3±7.4	18.0±9.6	NS	14.9±7.3	10.1±4.7	.010
No. of mature oocytes	13.5±6.6	10.5±6.3	NS	11.5±6.2	12.6±8.0	NS	10.4±5.3	6.6±4.2	.010
Severe OHSS	6 (7.2%)	2 (7.7%)	NS	4 (7.3%)	1 (3.4%)	NS	0 (0%)	0 (0%)	NS
Fertilization rate (%)	44.5±21.5	41.1±22.6	NS	42.4±19.7	44.7±24.2	NS	48.3±23.5	40.2±30.9	NS
Implantation rate/ET (%)	36 (54.5%)	11 (44.0%)	NS	26 (51.0%)	10 (50.0%)	NS	19 (38.8%)	5 (41.7%)	NS
Biochemical pregnancy/ET n (%)	5 (7.6%)	3 (12.0%)	NS	8 (15.7%)	2 (10.0%)	NS	6 (12.2%)	0 (0.0%)	NS
Clinical pregnancy/ET n (%)	31 (47.0%)	8 (32.0%)	NS	18 (35.3%)	8 (40.0%)	NS	13 (26.5%)	5 (41.7%)	NS
Miscarriage/ET n (%)	11 (16.7%)	2 (8.0%)	NS	6 (11.8%)	2 (10.0%)	NS	4 (8.2%)	2 (16.7%)	NS
Ongoing pregnancy/ET n (%)	20 (30.3%)	6 (24.0%)	NS	12 (23.5%)	6 (30.0%)	NS	9 (18.4%)	3 (25.0%)	NS
Multiple pregnancy/ET n (%)	8 (12.1%)	0 (0.0%)	NS	3 (5.9%)	1 (5.0%)	NS	4 (8.2%)	1 (8.3%)	NS

Data are expressed as mean±SD.
No: number; OHSS: ovarian hyperstimulation syndrome; ET: embryo transfer

Exogenous FSH was shown to course different absorption and metabolism in lean versus obese women with PCOS (19, 20).

The effect of BMI on oocyte and embryo quality remains contentious. Some studies reported poorer embryologic outcome in obese patients (12, 13, 21, 22), whereas others did not observe a similar association (7, 12, 23). Some studies indicate that adverse follicular conditions associated with insulin resistance, endocrine alterations, and possibly embryo- toxic cytokines are responsible for low embryo quality (12, 13, 21, 22), whereas others indicate that obesity-associated impaired embryo quality is only theoretical if age- and ovarian reserve-matched controls are compared (7, 11, 23). In the present study the number of grade 1 embryos was significantly higher in Group 3 (obese PCOS patients). The significantly higher LH level observed in Group 1 (normal weight) might have negatively effected oocyte quality (3, 24), resulting in a lower number of grade 1 embryos. The higher quality embryos might have resulted in a better than expected pregnancy rate in Group 3 (obese group).

In the present study patients in Group 2 (overweight) and Group 3 (obese) that received the mid-luteal long GnRH-agonist (agonist) protocol had better cycle characteristics -including a lower cycle cancellation rate- than those that received the flexible GnRH-antagonist (antagonist) protocol. Discordance of follicular growth was the primary cause of cycle cancellation in the patients that received the flexible GnRH-antagonist protocol. During the early follicular phase, early antral follicles present noticeable size heterogeneities that may be amplified during ovarian stimulation (25). Use of oral contraceptive in previous cycles in the patients that received the mid-luteal long GnRH-agonist protocol might have supplied cohort coordination. To have similar homogeneity of antral follicles in antagonist cycles luteal FSH suppression by either estrogen or GnRH antagonist administration could have been tried which we did not cross our mind due to lack of enough clinical experience in antagonist protocol. A meta-analysis by Griesinger et al. (26) that included 305 PCOS patients treated with antagonist and agonist protocols reported comparable IVF outcomes in both groups. The researchers concluded that more prospective studies are required to determine the optimal stimulation protocol based on BMI in PCOS patients.

In the present study the number of severe OHSS patients and the estradiol level on the day of hCG administration were both significantly higher in Group 1(normal weight) than in Group 3(obese). It is well known that low body weight and PCOS are risk factors for OHSS (5). In the present study obesity was observed to protect against OHSS in population of PCOS women.

The present study's retrospective design is its primary limitation. Mild and moderate OHSS cases were not included because they were treated as outpatients and they were not included in our computerized patient database. Furthermore, patients that were morbidly obese (BMI >40 kgm^{-2}, n=4) and underweight (BMI <18.5 kg m^{-2}, n=5) were not included in the analysis because of their small numbers. The prevalence of morbid obesity in Turkey

might be different than in other countries due to the potential effect of a Mediterranean diet and coincidence of PCOS and being underweight occurs with a low prevalence with insulin resistance observed in PCOS. These might result smaller sample sizes in morbid obese and underweight groups.

The number of collected oocytes in the present study was lower and the required gonadotrophin dose was higher in obese women with PCOS, but obesity was not associated with a lower pregnancy rate. Cycle performance, embryologic, and pregnancy outcomes were similar in the overweight and normal weight women with PCOS, indicating the possibility that overweight PCOS patients may be within the spectrum of normal (27), or that obesity is the cut-off point for compensatory mechanisms. Although the number of mature oocytes was higher and the cycle cancellation rate was lower in the overweight and obese patients that received the mid-luteal long GnRH-agonist protocol than in those that received the flexible GnRH-antagonist protocol, the pregnancy rate was similar for both protocols. In conclusion, additional research is required to determine the optimal stimulation protocol in PCOS patients based on BMI.

Ethics Committee Approval: *Ethics committee approval was received for this study from Etlik Zübeyde Hanim Training and Research Hospital Institutional Review Board.*

Informed Consent: *Written informed consent was obtained from patients who participated in this study.*

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