doi: 10.24074/tjrms.2017-54841

The Impact of Body Mass Index on ART Outcomes of High-Responders: Prospective Cohort Study

Yüksek Ovaryen Yanıtlı Olgularda, Beden Kitle İndeksinin ART Sonuçları Üzerine Etkinliğinin Araştırılması: Prospektif Kohort Çalışma

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ABSTRACT

Objective: Is to evaluate the impact of body mass index (BMI) levels on pregnancy outcomes in high-responders undergoing assisted reproductive technology (ART). **Material and Methods:** Total of 120 high responders was allocated to the study. High response was defined as having high serum AMH levels (>4 ng/ml). Subjects were divided into three groups according to their BMI values; normal weight 57 (BMI 18.5–24.9 kg/m^2), overweight 42 (25-29.9 kg/m^2) and obese 21 subjects (BMI ≥30 kg/m^2) were compared for pregnancy outcomes and Ovarian Hyperstimulation Syndrome (OHSS) rates. Gonadotropin starting dose was fixed to 150 IU/day in antagonist co-treated cycles for all subjects. **Results:** A total of 120 cycles were evaluated. In patients with BMI ≥30 kg/m^2, the total gonadotropin use was significantly higher ($p<0.001$) and number of retrieved oocytes was significantly lower ($p=0.001$) when compared to other groups. In normal weight patients, significantly higher numbers of mature oocytes and 2PN embryos were obtained when compared with other groups ($p<0.001$). Other parameters including number of good quality embryos available for transfer, implantation, biochemical, clinical pregnancy and OHSS rates were similar between all groups. **Conclusion:** Our results did not reveal a significant effect of BMI on the ART outcomes of high responder infertile women. Although higher BMI was correlated with less number of retrieved oocytes, it did not resulted with a negative impact on pregnancy outcomes. Another interesting finding was the trend to a less OHSS incidence with the increase in BMI of high responder patients.

Key Words: AMH, BMI, high responder, OHSS, pregnancy

ÖZET

Amaç: Yardımla üreme teknikleri (YÜT) uygulanan yüksek ovaryen yanıtlı olgularda, farklı beden kitle indeksinin (BKİ), gebelik sonuçları üzerine etkisini incelemek. **Gereç ve Yöntemler:** Farklı BKİ değerlerine sahip toplam 120 yüksek ovaryen yanıtlı olgu çalışmaya dahil edildi. Yüksek yanıt kriteri olarak olgudaki serum AMH değerinin >4 ng/ml olması kabul edildi. BKİ değerlerine göre olgular 3 gruba ayrıldı: normal kilolu 57 olgu (BKİ 18,5-24,9 kg/m^2), fazla kilolu 42 olgu (BKİ 25-29,9 kg/m^2), obez 21 olgu (BKİ >30 kg/m^2), gebelik ve ovaryen hiperstimulasyon sendromu (OHSS) oranları açısından karşılaştırıldı. **Bulgular:** Obez grupta, hem kullanılan gonadotropin dozu hem de toplanan oosit sayısı, diğer 2 gruba göre anlamlı olarak daha az saptandı ($p<0,05$). Fertilizasyon, gebelik oranları ve diğer parametreler açısından gruplar arasında farklılık saptanmadı. **Sonuç:** YÜT uygulaması yapılan yüksek yanıtlı olgularda, BKİ değerlerinin, YÜT sonuçlarına belirgin etkisinin olmadığı ortaya konulmuştur. Obez olgularda toplanan oosit sayısının az olmasının yanında, gebelik oranlarında farklılık saptanmamıştır. OHSS oranlarının, BKİ arttıkça bir miktar azaldığı gözlenmiştir.

Anahtar Kelimeler: AMH, BKİ, yüksek yanıt, OHSS, gebelik

TJRMS 2017;1(1):7-12

Geliş Tarihi/*Received:* 18.01.2017 Kabul Tarihi/*Accepted:* 06.02.2017

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There is general consensus that obesity is associated with increased risk of infertility, pregnancy complications or long-term adverse health outcomes among women at reproductive age attempting to conceive.[1-3] However, these associations are not confirmed in those undergoing assisted reproductive technology.[4,5] Recent meta-analyses demonstrated that obese patients yield lower number of oocytes, require higher gonadotropins and are more likely to have cancelled cycles during ART cycles.[4-6]

A group of individuals defined as high-responders demonstrate slightly different hormonal dynamics with a prevalance estimated to be around 7%.[7] The high-responder definition is actually based on high basal antral follicle count (AFC) or elevated serum Anti-Mullerian Hormone (AMH) levels.[7] Since a single AMH measurement predicts high ovarian response independent from age and presence of Polycystic Ovary Syndrome (PCOS), this marker has eventually been implemented in daily practice.[8] Several adverse ART outcomes have been linked with excessive ovarian response. Being a well-known one, direct correlation was revealed between high numbers of harvested oocytes (>20) and increased OHSS rates.[9] Moreover, decreased live births, increased cycle cancellations and adverse perinatal outcomes were also linked with excessive ovarian response.[9-11] Ovarian hyperstimulation Syndrome is such a life-threatening complication of ovarian stimulation cycles that several recommendations have been revealed to preclude morbidities and mortalities.[12] In this context, quite a few data exists about the association between BMI and common complications of ART, as OHSS.

Despite large cohort studies evaluating the impact of body mass index (BMI) on ART outcomes, the data specifically evaluating high responders is quite limited. Primary outcome of the study is to compare pregnancy rates and secondary outcomes are OHSS and fertilization rates.

MATERIAL AND METHODS

This prospective study was conducted between March 2014 and May 2015 at a single private ART center. The Institutional Review Board and Ethics Committee approved the study protocol on 24 January 2014 (IRB reference number: 24/2014). All patients provided written informed consent to participate in the study, which was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. All subjects were at their first fresh ART cycles and one cycle of each case was included in the study. Inclusion cirteria were: patients >18 and <40 year of age, serum AMH level of ≥ 4 ng/mL, normal uterine anatomy confirmed with ultrasound or hysterosalpingography. Cases with a history of ovarian surgery or endometriosis, testicular sperm extraction and preimplantation genetic screening cycles, cryopreserved/thawed embryo cycles, with >2 prior unsuccesful ART history or cycle cancellations were excluded from the study. Heights and weights of all subjects were measured within the month of the cycle start date. The women were grouped into three categories based on World Health Organization (WHO) guidelines, namely normal: 18.5–24.9 kg/m^2; overweight: 25–29.9 kg/m^2 and obese: >30 kg/m^2. Patients in the obese group were all consulted with an endocrinologist to exclude any internal/endocrine disease that could worsen in a pregnancy state. The diagnosis of PCOS was made as proposed at the Rotterdam Consensus Meeting.[13] AMH concentrations were determined one month before starting the treatment. Circulating level of AMH was analyzed by a second-generation commercially available ELISA kit (Beckman Coulter Gen II Elisa Kit, Webster, NY). The AMH assay had a sensitivity of 0.08 ng/ml and total imprecision (% coefficient of variation) of < 7,7.

OVARIAN STIMULATION PROTOCOL

One ART cycle of each patient was included in the study. Ovarian stimulation was carried out with recombinant FSH (Gonal-F, Merck Serono) beginning from the second day of the menstrual cycle with a *fixed starting dose of 150 IU/day*. Dose adjustment was performed individually according to ovarian response. The GnRH antagonist (Cetrotide, Merck Serono) was introduced (0.25 mg/day) on the sixth day (fixed antagonist protocol) and continued throughout ovarian stimulation. When at least three follicles were ≥ 18 mm, rhCG (250 μg;

Ovitrelle, Merck Serono) was used for final oocyte maturation. Transvaginal ultrasound–guided oocyte retrieval and embryo transfer procedure was performed as previously described by Pabuçcu et al.[14] Embryos on the 2nd and 3rd days were classified as cleavage stage embryos and were graded based on cell numbers and the degree of fragmentation.[15] A biochemical pregnancy was defined as hCG concentration >20 IU/L on the twelfth day of the embryo transfer. A clinical pregnancy was defined as the presence of an intrauterine gestational sac with a heartbeat. The criteria for classification of OHSS as defined by Navot et al. were utilized to assess relative severity of OHSS.[16]

STATISTICAL ANALYSES

Data analyses were performed by using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, United States). Whether the distribution of continuous variables were normal or not was determined by Kolmogorov Smirnov test. Levene test was used for the evaluation of homogeneity of variances. Data were shown as mean ± SD or number of cases and (%). While the differences in normally distributed variables between groups were compared by Student's t test, Mann Whitney U test was applied for comparison of the not normally distributed data. While the differences in normally distributed variables among more than two independent groups were analyzed by One-Way ANOVA, Kruskal Wallis test was applied for comparison of the uneven data. When the p value from One-Way ANOVA or Kruskal Wallis test statistics were statistically significant, post hoc Tukey HSD or Conover's non-parametric multiple comparison tests were used to learn which group was different from others. Categorical data were analyzed by Pearson's chi-square, Fisher's exact or Likelihood Ratio test, where applicable. A p value less than 0.05 was considered statistically significant.

RESULTS

Total of 139 patients were defined as eligible for prospective follow-up. Ten subjects refused to participate, thus leaving a population of 129 eligible patients. In cycles that have ended up with serum estradiol levels >4500 pg/mL and/or high number of follicles (>15) measuring >12 mm during the late follicular phase, GnRH agonist (leuprolide acetate 1 mg) was used for final oocyte maturation with (n=2) or without (n=7) total freezing of all embryos. These patients were also excluded from the final analyses (n=9). The mean age and BMI of the overall group were 28,3±5,2 years and 26,1±5,0 kg/m^2, respectively. A total of 23% (28/120) of subjects had PCOS diagnosis of which mean AMH levels were 5,5±1,5 ng/mL. Mean fasting glucose and insulin levels were 80,0±6,5 mg/dl and 11.1±5.7 mIU/ml respectively. Among the entire cohort, the clinical pregnancy rate was 30% (36/120) and 10 mild early OHSS cases were observed (5, 4 and 1 OHSS cases in normal weight, overweight and obese groups respectively).

When subjects were categorized according to BMI, 57 of them had BMI 18.5-24.9 kg/m^2 (mean: 22,28±1,94 kg/m^2), 42 had BMI 25-29.9 kg/m^2 (mean: 27,2±1,35 kg/m^2), and 21 had BMI ≥30 kg/m^2 (mean: 34,3±4 kg/m^2). Demographic characteristics of the BMI groups are given in Table 1, as results were quite comperable. Polycystic ovary Syndrome prevalance was found as 19%, 33.3% and 14.2% in normal weight, overweight and obese group respectively (p>0.05). Maximal endometrial thickness, peak estradiol levels and cycle duration were also similar. In patients with BMI ≥30 kg/m^2, the total gonadotropin use was significantly higher (p<0.001) and number of retrieved oocytes was significantly lower (p=0.001) compared to other groups. In normal weight patients, significantly higher numbers of mature oocytes and 2PN embryos were obtained compared to other groups (p<0.001). Outcome measures of the BMI groups are given in Table 2. Fertilization, implantation, biochemical and clinical pregnancy rates were statistically similar between all BMI groups (p>0.05) (Table 3).

DISCUSSION

According to the current study, increasing BMI values do not to influence ART outcomes in high responders with regard to pregnancy and OHSS rates, when fixed starting dose is selected in antag-

TABLE 1: Demographic characteristics of BMI groups.

BMI kg/m²	18-24.9 (N:57)	25-29.9 (N:42)	>30 (N:21)	P value
Age (years)	27.3 ± 5.6	29.8 ± 4.5	27.9 ± 4.8	0.054
Duration of infertility (months)	51.0 (8.0-72)	48.0 (12.0-84)	53.0 (10-96)	0.701
PCOS diagnosis (%)	11/57 (19%)	14/42 (33.3%)	3/21 (14.2%)	0.152
Basal AFC	12.1 ± 3.2	11.7 ± 4.0	12.2 ± 3.7	0.827
Basal FSH (IU/L)	6.9 ± 2.1	6.3 ±1.6	6.4 ± 2.7	0.378
	6.6 (1.9-14.0)	6.3 (3.3-11.0)	5.9 (2.3-14.0)	
Basal E2 (mIU/mL)	59.3 ± 16.4 [a]	53.1 ± 14.8 [a]	55.3 ± 17.1	0.047*
	59.3 (11.2-113.0)	53.1 (20.0-90.0)	55.4 (20.0-98.0)	
AMH (ng/mL)	5.4 ± 1.3	5.8 ± 1.9	5.3 ± 1.3	0.547
	5.0 (4.0-11.2)	5.4 (4.1-15.2)	5.0 (4.1-8.3)	
Fasting plasma glucose (mg/dL)	80.7 ± 69.0	79.4 ± 5.7	79.5 ± 7.1	0.500
	80.7 (70.0-100.0)	79.4 (70.0-91.0)	77.0 (70.0-94.0)	
BMI (kg/m²)	22.28±1.94 [a, b, c]	27.2±1.35 [a, b, c]	34.3±4 [a, b, c]	<0.001*
	22.9 (18-24.9)	27.1 (25-26.6)	33 (30-43)	

values are given as mean±SD or median (min-max)
AFC: Antral follicle count; FSH: Follicle stimulating hormone; E2: Estradiol; AMH: Anti-Mullerian Hormone.
Tukey HSD and Conover-Inman tests were performed for the binary comparisons among the groups and the p value was set at 0.05.
Significant differences were found between;
a: BMI 18-24,9 vs BMI 25-29,9
b: BMI 18-24,9 vs BMI>30
c: BMI 25-29,9 vs BMI>30.
*: statistically significant (p<0.05).

TABLE 2: Ovarian stimulation outcomes of BMI groups.

BMI kg/m²	18-24.9 (N:57)	25-29.9 (N:42)	>30 (N:21)	P value
E2 level on hCG day (mIU/mL)	3217.9 ± 1398.6	3104.6 ± 1504.2	2470.9 ± 1182.8	0.112
Maximal endometrial thickness (mm)	11.4 ± 1.5	11.0 ± 1.4	11.6 ± 1.9	0.158
	11.0 (8.0-15.0)	11.0 (8.5-15.0)	12.0 (8.0-16.0)	
Cycle duration (days)	11.1 ± 1.8	11.5 ± 2.2	11.8 ± 2.9	0.735
	11.0 (8.0-17.0)	11.0 (8.0-17.0)	11.0 (8.0-20.0)	
Total gonadotropin use (IU)	1752.6 ± 637.9 [b]	1802.3 ± 561.6 [c]	2714.6 ± 730.7 [b, c]	<0.001*
No of oocytes retrieved	13.9 ± 3.1 [b]	13.8 ± 4.0 [c]	10.8 ± 2.9 [b, c]	0.001*
Mature (MII) oocytes	10.8 ± 2.6 [a, b]	8.0 ± 4.6 [a]	6.5 ± 2.6 [b]	<0.001*
	11.0 (4.0-17.0)	7.5 (2.0-21.0)	6.0 (3.0-12.0)	
No of 2PN	9.0 ± 2.6 [a, b]	6.4 ± 3.8 [a]	5.6 ± 2.6 [b]	<0.001*
	9.0 (4.0-15.0)	6.5 (1.0-19.0)	5.0 (2.0-11.0)	
No of good quality embryos available on day 2	2.1 ± 2.0	2.4 ± 2.0	2.5 ± 2.6	0.745
	2 (0-10.0)	2.0 (0-8.0)	2.0 (0-9.0)	
No of transferred embryos	1.6 ± 0.6	1.6 ± 0.5	1.7 ± 0.5	0.851
	2.0 (0-3.0)	2.0 (1.0-2.0)	2.0 (1.0-2.0)	

values are given as mean±SD or median (min-max)
Tukey HSD and Conover-Inman tests were performed for the binary comparisons among the groups and the p value was set at 0.05.
Significant differences were found between;
a: BMI 18-24,9 vs BMI 25-29,9
b: BMI 18-24,9 vs BMI>30
c: BMI 25-29,9 vs BMI>30
*: statistically significant (p<0.05).

onist co-treated cycles. In the literature, high BMI is generally associated with increased gonadotropin requirements in ovarian stimulation cycles.[17,18] A large cohort analysis investigating more than 150.000 ART cycles demonstrated significantly increased FSH dosages as BMI increased.[6] Obese pa-

TABLE 3: Major cycle outcomes of BMI groups.

BMI kg/m²	18-24.9 (N:57)	25-29.9 (N:42)	>30 (N:21)	P value
Fertilization rate (%)	87.0 ± 13.3	80.6 ± 16.7	85.9 ± 19.9	0.101
Implantation rate (%)	31.6 ± 42.0	27.4 ± 41.6	30.9 ± 43.2	0.906
Positive hCG (%)	23/57 (40.4%)	15/42 (35,7%)	8/21 (38.1%)	0.896
Clinical pregnancy (%)	17/57 (29.8%)	13/42 (31.0%)	6/21 (28.6%)	0.981
OHSS (%)	5/57 (8.8%)	4/42 (9.5%)	1/21 (4.8%)	0.779

values are given as mean±SD or median (min-max)
hCG: Human chorionic gonadotropin; OHSS: Ovarian hyperstimulation syndrome.
Tukey HSD and Conover-Inman tests were performed for the binary comparisons among the groups and the p value was set at 0.05.
Significant differences were found between;
a: BMI 18-24,9 vs BMI 25-29,9
b: BMI 18-24,9 vs BMI>30
c: BMI 25-29,9 vs BMI>30
*: statistically significant (p<0.05).

tients required nearly two-fold higher gonadotropins compared to normal weight subjects in our study. Relatively higher gonadotropin may be related to the altered drug distribution in the presence of large body surface. Moreover, increased requirement may be due to reduced gonadotropin responsiveness secondary to increased serum leptin concentrations in the presence of high body fat.[19]

In case of predicted high responders, a dose adjustment for BMI is usually not applied. According to a recent nomogram, the calculated starting dose of gonadotropin is 150 IU/daily for high responders (AMH: 4 ng/ml), regardless of BMI.[20] Considering this data, all the participants in our study received 150 IU of daily recombinant gonadotropin for COS. However, with this standard dose, obese patients yielded significantly lower number of mature oocytes (6,5± 2,6) compared to other BMI groups. Similar to our results, high BMI was associated with a decline in oocyte number either in different infertile populations or in high responders.[17,18,21] In our study, despite lower oocyte yield, no significant effect of BMI was found on oocyte fertilization, embryo implantation and pregnancy outcomes, which is consistent with the previous findings.[18,22] Relatively less but considerable number of mature oocytes in obese high responders is thought to contribute to an acceptable number of good quality embryos in our study.

Although the pathophysiology remains unresolved, several reports suggest unfavorable endometrial changes associated with obesity.[22] A recent data analyzing more than 9500 first cycles of ovum donation with ova from normal weight donors revealed that implantation and live birth rates were significantly reduced with increasing BMI.[23] Even if some authors suggest that the probable cause of unfavorable outcomes was linked with reduced uterine receptivity in obesity, we failed to reach such a conclusion as peak echo measurements and implantation rates were all comparable among BMI groups.

According to OHSS outcomes in our data, two important points should be addressed. *First*; we failed to detect any significant relation between OHSS rates and different BMI levels that is consistent with the recent meta-analysis.[6] Interestingly, a lower trend of OHSS was observed as body mass increased. Two recent retrospective analyses revealed a similar trend.[21,24] Since excess numbers of oocytes was shown to correlate positively with OHSS rates, relatively lower oocyte yield in overweight and especially in obese patients seems to justify the less OHSS incidence.[10] *Secondly;* despite preventive measures, we still detected 8.3% overall OHSS rate in our dataset. High ovarian reserve of our population might be the explanation of such OHSS prevalence in our study as mean AMH levels were 5,5±1,5 ng/mL. Since basal AMH level

could be utilized effectively to predict OHSS with 3,36 ng/mL cut-off, our basal levels were considered to be quite high revealing pretty high OHSS rates.[25] Therefore, high responders especially for those with AMH >4 ng/ml should be carefully evaluated and monitorized even though they are under preventive measures. As our study population is too limited to be conclusive for a precise recommendation, further studies would be beneficial.

In conclusion, our results did not reveal a significant effect of BMI on the ART outcomes of high responder infertile women. However, well-designed randomized controlled trials particularly evaluating metabolic influence on ovarian stimulation dynamics are necessary.

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