♦Thieme

Obesity Does not Compromise Ovarian Reserve Markers in Infertile Women

Übergewicht führt zu keiner Beeinträchtigung der ovariellen Reserve bei unfruchtbaren Frauen

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ABSTRACT

Introduction In the literature, conflicting results from studies examining the relationship between obesity and ovarian reserve have been reported. The purpose of the study is to investigate whether obesity adversely affects serum concentrations of ovarian reserve markers in infertile women with different ovarian reserve status.

Materials and Methods A total of 402 women were assigned to three groups according to body mass index (BMI; < 25 kg/m²: normal, n = 198; 25.0–29.9 kg/m²: overweight, n = 126; and ≥ 30 kg/m²: obese, n = 78). The women were also divided into two groups according to waist circumference (WC; < 80 cm: normal, n = 103; and ≥ 80 cm: obese, n = 299). Participants were also categorized into three types of ovarian reserve patterns: normal (n = 146), high (n = 112), and poor ovarian reserve (n = 144). The serum anti-Mullerian hormone (AMH), estradiol (E2), and follicle-stimulating hormone (FSH) levels were assayed and compared in all groups.

Results There were no significant differences in BMI and WC in the three ovarian reserve groups. There were significant differences between all ovarian reserve groups for AMH, E2, and FSH (p < 0.001 for all). The comparisons of ovarian reserve parameters (AMH, E2, and FSH) and obesity parameters (BMI and WC) revealed no significant differences in women with all ovarian reserve patterns.

Conclusion The parameters of ovarian reserve do not seem to be affected by increased BMI and WC. Thus, AMH may be considered as a reliable marker of ovarian reserve.

ZUSAMMENFASSUNG

Einleitung In der Literatur werden aus Studien, welche die Beziehung zwischen Übergewicht und ovarieller Reserve untersuchten, widersprüchliche Ergebnisse gemeldet. Ziel dieser Studie war es, zu untersuchen, ob Übergewicht negative Auswirkungen auf Konzentrationen von Markern von ovarieller Reserve im Blut bei unfruchtbaren Frauen mit unterschiedlicher ovarieller Reserve hat.

Material und Methoden Insgesamt wurden 402 Frauen in die Studie aufgenommen und gemäß ihrem Body-Mass-Index in 3 verschiedene Gruppen eingeteilt (BMI; < 25 kg/m²: normal, n = 198; 25.0–29.9 kg/m²: übergewichtig, n = 126; ≥ 30 kg/m²: adipös, n = 78). Die Frauen wurden auch gemäß ihrem Taillenumfang in 2 Gruppen eingeteilt (TU; < 80 cm: normal, n = 103; sowie ≥ 80 cm: adipös, n = 299). Die Teilnehmerinnen wurden auch nach ihrer ovariellen Reserve in eine von 3 Kategorien eingeteilt: normale (n = 146), hohe (n = 112) und mangelhafte ovarielle Reserve (n = 144). Der Anti-Müller-

Hormon-(AMH-)Spiegel, die Serum-Estradiol-(E2)-Werte und die FSH-Werte (FSH: follikelstimulierendes Hormon) wurden bei allen Gruppen untersucht und verglichen.

Ergebnisse Es gab keine signifikanten Unterschiede bezüglich BMI und TU zwischen den 3 Gruppen mit unterschiedlicher ovarieller Reserve. Es gab signifikante Unterschiede zwischen allen 3 Gruppen mit unterschiedlicher ovarieller Reserve bezüglich der AMH-, E2- und FSH-Werte (p < 0,001 für alle). Ein Vergleich der Parameter für die ovarielle Reserve (AMH, E2 und FSH) und der Adipositasparameter (BMI und TU) zeigte keine signifikanten Unterschiede zwischen Frauen mit unterschiedlicher ovariellen Reserve.

Schlussfolgerung Es scheint, dass die Parameter der ovariellen Reserve nicht durch einen höheren BMI oder einen weiten Taillenumfang beeinflusst werden. AMH darf daher als zuverlässiger Marker für die ovarielle Reserve betrachtet werden.

Introduction

As simple definitions, obesity is an excess storage of triglycerides in adipose tissues and overweight is having a body weight, including muscles, fat, and body water, in excess of a standard or ideal body weight [1]. According to the World Health Organization (WHO), the term overweight has been defined as having a body mass index (BMI) equal to or greater than 25 kg/m², while obesity is having a BMI equal to or greater than 30 kg/m² [2]. The BMI is a practical and globally-used measure of obesity. However, it does not consider the person's degree of abdominal obesity [3]. On the other hand, waist circumference (WC) is an easy and reliable measure of visceral adipose tissue and can be used as a simple index of cardiovascular risk [4]. The WHO has reported sex-specific cutoff values that define overweight and obesity [3]. With regard to abdominal obesity, the WC cutoff value specific to the population of Turkish women is ≥ 80 cm estimated as 80 cm [5].

Obesity has emerged as a global epidemic. The International Obesity Task Force reported that 1.1 billion adults are overweight, and 312 million of these are women who are considered obese [6]. The WHO has reported that 60 % of women are overweight in the United States and most European countries, and 30 % of these women are considered obese [2, 6]. The prevalence of obesity has reached more than one third of the adult population in Turkey, similar to most of the worldwide populations [7, 8].

Obesity is associated with numerous personal characteristics including social, psychological, and demographical issues, and health problems. Moreover, being obese has a detrimental impact on most organ systems, including the reproductive system. Although the mechanisms are complex and multifactorial, obese women are more prone to anovulation and having abnormal uterine bleeding, endometrial hyperplasia, gynecological cancers, infertility, miscarriage, and antenatal and neonatal complications [9 – 11]. Obese women also exhibit impairments in ovarian, follicular, and oocyte development, fertilization, and embryo development and implantation [12, 13].

The quality and quantity of the oocyte reservoir has been described as ovarian reserve. This refers to an indirect index of a female's reproductive capacity [14]. Like all screening tests, ovarian reserve tests are aimed at identifying individuals at risk for diminished ovarian reserve. Over the past two decades, several methods have been described to predict the ovarian reserve. Anti-Mullerian hormone (AMH) is a member of the transforming growth factor β superfamily of glycoproteins and is produced by the granulosa cells of the preantral and small antral follicles [15]. AMH reflects the quantity of growing follicles and the ovarian follicular pool [16]. Although basal follicle-stimulating hormone (FSH) levels are the most commonly used ovarian reserve test, antral follicle counts and AMH levels are promising predictors with significant potential advantages [17]. For now, AMH is considered as a reliable indicator of declining ovarian function since AMH exhibits minimal inter- and intra-cycle variations [18].

There are numerous publications stating that the obesity leads to infertity through various pathways, including impaired follicular development, quantitative and qualitative development of the oocyte [12, 19]. In the existing literature, conflicting results from studies examining the relationship between obesity and ovarian reserve have been reported. While some studies have demonstrated a significant reverse correlation [20, 21], others have demonstrated no relationship between ovarian reserve markers and obesity [22 – 24].

Therefore, we aimed to investigate whether obesity adversely affects serum concentrations of ovarian reserve markers in women with different ovarian reserve status in the present study.

Material and Methods

Study population

A total of 485 infertile women who had attended the Reproductive Endocrinology Department at Hitit University Hospital between February and December 2015 were included in this prospective cross-sectional study. The study was performed in accordance with the Declaration of Helsinki 2013 Brazil version and was approved by the local ethics board of Ankara Numune Education and Research Hospital (20796219–724.087). All participants gave their written informed consent prior to the beginning of the study. The comprehensive personal and family histories were obtained from all participants. The participants who had a history of pelvic surgery, endometriosis, tubo-ovarian masses, cardiovascular, hepatic, renal and respiratory diseases, diabetes mellitus, malignancies, chemotherapy, or radiotherapy were excluded from the study. The current use of hormones or drugs that may have affected ovarian functions, smoking, pregnancy and lactation, an FSH level > 15 IU/L, hyperprolactinemia, and an age ≥ 45 years were also considered exclusion criteria. In total, 402 participants who met the inclusion criteria were included into the study.

Study design

A physical examination and measurements for weight, height, and WC were performed on all participants. BMI was calculated by dividing the weight in kilograms by the height in square me-

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ters. WC values were measured at the level of the iliac processes and umbilicus with the same scale to evaluate abdominal obesity. The transvaginal ultrasound examinations were also performed during the early follicular phase of the menstrual cycle (day 2 to 4) by means of a transvaginal 7.5 MHz probe (Toshiba Xario 100, Toshiba Medical Systems Co., Nasu, Japan) by the same clinician. The total antral follicle count (AFC) was the sum of the small follicles (2–10 mm in diameter) in each ovary.

All participants were assigned to three groups according to BMI (< 25 kg/m^2: normal group, n = 198; 25.0–29.9 kg/m^2: overweight group, n = 126; and ≥ 30 kg/m^2: obese group, n = 78). The women were also divided into two groups according to WC (< 80 cm: normal group, n = 103; and ≥ 80 cm: obese group, n = 299). Additionally, all participants were categorized into three types of ovarian reserve patterns. These patterns included the normal ovarian group (n = 146), which included women with an adequate reserve pattern (women with ≥ 7 baseline AFC), the high ovarian group (n = 112) including women with a high reserve pattern according to the Rotterdam Consensus on Diagnostic Criteria for polycystic ovarian syndrome (PCOS) [25], and the poor ovarian group (n = 144) that included women with a diminished reserve pattern (women with < 7 baseline AFC), based on a committee opinion concerning ovarian reserve by the American College of Obstetricians and Gynecologists [26]. The comparisons of all data in all ovarian reserve groups were then drawn.

Data collection and assays

The blood samples were obtained from the antecubital vein after an overnight fast between 8:00 a.m. and 10:00 a.m. in the early follicular phase on day 2 or 3. The blood samples were collected into 5 mL serum separator tubes (BD Vacutainer, Becton Dickinson, New Jersey, USA). The samples were allowed to clot completely at room temperature and were then centrifuged at 1500 g for 4 min within 30 min. Serums were analyzed daily for es-

tradiol (E2) and FSH with an electrochemiluminescence immunoassay (ECLIA) method using an autoanalyzer (Cobas 6000, E 601 Roche Diagnostics, GmbH, Mannheim, Germany). To obtain minimal fluctuations in the samples, the serum for AMH measurements were frozen at $-20\,°C$ within 2 hours for a maximum of 7 days and then analyzed. All analyses of AMH samples were also performed on a weekly basis by the ECLIA method using an autoanalyzer (Cobas 6000, E 601 Roche Diagnostics, GmbH, Mannheim, Germany).

Statistical analyses

All analyses were performed using SPSS (Statistical Packages for The Social Sciences) software version 21 (SPSS Inc., Chicago, IL, USA). For the categorical variables, chi-square tests were used. The continuous variables were first evaluated for normality of statistical distribution by Shapiro-Wilk tests. As the continuous variables were not normally distributed, non-parametric methods (Mann-Whitney U tests) were used to perform statistical analyses. The descriptive statistics were expressed as a median (minimum-maximum) and number (percentage %). The Spearman correlation tests were used to determine the correlations of continuous variables. A p value of < 0.05 and a confidence interval of 95% were considered as statistically significant.

Results

Baseline demographic and biochemical characteristics

The demographic and biochemical characteristics of the study population regarding the aspects of ovarian reserve groups are presented in ▶ Table 1. The comparisons of the mean ages in all ovarian reserve groups demonstrated a statistically significant difference ($p < 0.001$). The median age was 29 years (18–34) for the normal reserve group, 27.5 years (18–34) for the high reserve

▶ Table 1 The demographic and biochemical charecteristics of the study population.

	Normal ovarian reserve group (n = 146)	High ovarian reserve group (n = 112)	Poor ovarian reserve group (n = 144)	p
Age (years)	29 (18–34)	27.5 (18–34)	36 (20–45)	0.000*
BMI (kg/m^2)				
▪ < 25.0 (n = 198)	77 (38.9%)	55 (27.8%)	66 (33.3%)	0.813
▪ 25.0–29.9 (n = 126)	44 (34.9%)	35 (27.8%)	47 (37.3%)	
▪ ≥ 30.0 (n = 78)	25 (32.1%)	22 (28.2%)	31 (39.7%)	
WC (cm)				
▪ < 80 (n = 103)	37 (43.1%)	29 (36.1%)	37 (20.8%)	0.065
▪ ≥ 80 (n = 299)	109 (31.6%)	83 (30.6)%	107 (37.8%)	
AMH (ng/dL)	2.3 (0.1–11.3)	5.4 (1.6–20.0)	1.2 (0.1–10.7)	0.000*
E2 (pg/mL)	44.0 (3.0–263.0)	37.0 (5–167.1)	46.0 (5.0–347.0)	0.002*
FSH (IU/L)	7.0 (0.1–13.8)	6.0 (3.3–9.9)	7.6 (0.2–15.0)	0.000*

Values are shown as median (minimum-maximum). BMI = Body mass index; WC = Waist circumference; AMH = Anti-müllerian hormone; E2 = Estradiol; FSH = Follicular stimulating hormone.

* p-values indicate statistically significant ($p < 0.05$).

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▶ **Table 2** The comparisons of ovarian reserve parameters and BMI in different ovarian reserve groups.

BMI (kg/m²)	Normal ovarian reserve group (n = 146)				High ovarian reserve group (n = 112)				Poor ovarian reserve group (n = 144)			
	<25 (n = 77)	25.0–29.9 (n = 44)	≥30 (n = 25)	p*	<25 (n = 55)	25.0–29.9 (n = 35)	≥30 (n = 22)	p*	<25 (n = 66)	25.0–29.9 (n = 47)	≥30 (n = 31)	p*
AMH (ng/dL)	2.3 (0.1–9.4)	2.3 (0.1–11.3)	1.9 (0.1–7.0)	0.485	5.5 (1.7–20.0)	5.4 (1.6–19.2)	5.6 (1.8–14.0)	0.687	1.3 (0.1–10.7)	1.02 (0.1–8.7)	1.1 (0.1–6.7)	0.394
E2 (pg/mL)	52.0 (5.0–263.0)	38.3 (8–158.0)	40.0 (3.0–81.0)	0.004*	35.0 (5.0–73.0)	40.6 (5.0–167.1)	37.0 (18.0–77.0)	0.097	46.2 (5.0–193.0)	47.0 (9.8–337.0)	40.0 (19.0–347.0)	0.827
FSH (IU/L)	7.2 (3.1–13.0)	6.7 (4.4–13.4)	6.5 (0.1–13.8)	0.187	6.2 (3.3–9.1)	6.0 (3.4–9.9)	5.5 (3.7–9.5)	0.325	7.8 (0.2–15.5)	7.4 (3.6–13.4)	7.2 (2.9–12.4)	0.630

Values are shown as median (minimum–maximum). BMI = Body mass index; AMH = Anti-Müllerian hormone; E2 = Estradiol; FSH = Follicular stimulating hormone.
* p-values indicate statistically significant (p < 0.05).

group, and 36 years (20–45) for the poor reserve group (p < 0.001). There were no significant differences in BMI and WC between the three ovarian reserve groups (p = 0.813 and p = 0.065, respectively). As expected, significant differences between all ovarian reserve groups with regard to AMH, E2, and FSH levels were detected. The median AMH values of the normal, high, and poor ovarian groups were 2.3 (0.1–11.3) ng/dL, 5.4 (1.6–20.0) ng/dL, and 1.2 (0.1–10.7) ng/dL respectively, (p < 0.001). Thus, the women with poor ovarian reserve had lower AMH concentrations. The median E2 values of the normal, high, and poor ovarian groups were 44.0 (3.0–263.0) pg/mL, 37.0 (5.0–167.1) pg/mL, and 46.0 (5.0–347) pg/mL (p < 0.001), respectively. The normal, high, and poor ovarian groups also had statistically different median FSH levels with values of 7.0 (0.1–13.8) IU/L, 6.0 (3.3–9.9) IU/L, and 7.6 (0.2–15.5) IU/L respectively, (p < 0.001).

Relationship of ovarian reserve parameters to BMI subgroups

The comparisons of ovarian reserve parameters (AMH, FSH, and E2) and BMI subgroups are shown in ▶ **Table 2**. All participants (n = 402) were grouped according to ovarian reserve status: normal (n = 146), high (n = 112), and poor (n = 144) reserve groups. The mean serum AMH and FSH concentrations were statistically similar in all ovarian reserve groups and their BMI subgroups (p > 0.05, for all). By comparison of the mean E2 level, a significant difference was detected in the normal ovarian reserve group (p = 0.004). In this group, the women of normal weight (BMI < 25) had the highest E2 (52.0 pg/mL) level. However, the high and poor ovarian reserve groups did not possessed any significant difference (p > 0.05, for all).

Relationship of ovarian reserve parameters to WC subgroups

The ovarian reserve parameters of study population were compared according to their WC subgroups, as demonstrated in ▶ **Table 3**. Although the mean FSH levels of normal ovarian reserve group were 7.2 IU/L and 6.7 IU/L respectively, no statistical significance was found (p = 0.177). On the contrary to E2 comparisons in the normal ovarian BMI subgroups, the mean E2 levels in all ovarian reserve groups and WC subgroups were statistically similar (p > 0.05, for all). We also demonstrated that the mean AMH levels were not statistically different from each other in the three ovarian reserve groups (p > 0.05, for all).

Discussion

The overall aim of this study was to investigate whether obesity has an impact on the measures of ovarian reserve. Specifically, we conducted a comprehensive evaluation of this impact by assigning participants to three ovarian reserve groups. We hypothesized that obesity and body size would influence ovarian reserve markers. However, our findings did not support the notion that ovarian reserve is impaired in obese women.

In an earlier study, higher BMI levels were associated with lower inhibin B levels in premenopausal women, while the opposite results were observed in postmenopausal women [15]. A cross-sec-

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► **Table 3** The comparisons of ovarian reserve parameters and WC in different ovarian reserve groups.

WC (cm)	Normal ovarian reserve group (n = 146)			High ovarian reserve group (n = 112)			Poor ovarian reserve group (n = 144)		
	< 80 (n = 37)	≥ 80 (n = 109)	p*	< 80 (n = 29)	≥ 80 (n = 83)	p*	< 80 (n = 37)	≥ 80 (n = 107)	p*
AMH (ng/dL)	2.3 (0.4–9.2)	2.3 (0.1–9.4)	0.775	5.0 (1.6–19.2)	5.5 (1.8–20.0)	0.132	0.8 (0.1–4.3)	1.2 (0.1–10.7)	0.529
E2 (pg/mL)	41.3 (11.0–230.0)	43.0 (3.0–263.0)	0.898	35.4 (15.0–65.0)	37.5 (5.0–167.1)	0.692	46.0 (27.0–193)	46.7 (9.8–123.0)	0.963
FSH (IU/L)	7.2 (4.7–12.6)	6.7 (0.14–13.4)	0.177	6.3 (3.4–8.7)	6.0 (3.3–9.9)	0.880	8.3 (4.7–12.6)	7.2 (2.1–15.5)	0.178

Values are shown as median (minimum-maximum). WC = Waist circumference; AMH = Anti-Müllerian hormone; E2 = Estradiol; FSH = Follicular stimulating hormone.
* p-values indicate statistically significant (p < 0.05).

tional study by Su et al. explored the association between obesity and serum and ultrasound measures of ovarian reserve in women of late reproductive age. This group reported that AMH was lower in obese women, while antral follicle count did not differ in accordance with body size [27].

De Pergola et al. proposed that overweight and fertile women with obesity have lower FSH, LH, inhibin B, and E2 concentrations. They concluded that a possible inhibitory effect of obesity on gonadotropins and E2 production may be one of the elucidative mechanisms [28]. Other authors have also reported similar results. Freeman et al. noted a negative correlation between BMI and AMH in later reproductive-age women. They found that obese women had 65% lower AMH levels compared to women of normal weight [20]. Steiner et al. also reported that obese women had 34% lower levels of AMH [29]. However, other authors have suggested that lower AMH levels in late reproductive-age obese women result from physiological processes other than decreased ovarian reserve [20, 27].

In contrast to the studies in which ovarian reserve has been negatively affected by high BMI levels, several studies have demonstrated that serum and ovarian markers of diminished ovarian reserve (DOR) did not exhibit consistent changes with body size [30–32]. In parallel with our study, some authors have reported no significant relationships between circulating AMH levels and obesity. Nardo et al. and Halawaty et al. did not detect any differences in FSH, AMH, AFC, and ovarian volume [22, 33]. Furthermore, in a prospective case-controlled study, Shaw et al. found no correlation between AMH levels and increased BMI levels in 135 Caucasian premenopausal women, 16% of whom were obese women younger than 45 years of age [34]. In a cross-sectional study from Turkey, Sahmay et al. also evaluated 259 premenopausal women, 14% of whom were were obese women under 45 years of age. They concluded there was no significant association between AMH and obesity [35].

Moy et al. sought to determine whether the association between obesity and AMH would be dependent on racial factors. They performed a study that included 350 women, 99 of whom were African-Americans, 59 were Caucasians, 58 were Hispanics, and 34 were Asians. They concluded that obesity is inversely correlated with AMH in Caucasian women, but not in other racial groups. Interestingly, when women with DOR were examined independently, an association between BMI and AMH was reported. However, this same study demonstrated no association between BMI and AMH in women with normal ovarian reserve [36]. Moreover, all ovarian reserve patterns, including normal, high, and poor patterns, were not affected by increased BMI and body size. However, in our study there was no such relationship between obesity and AMH in 402 Caucasian premenopausal women. Moreover, we did not demonstrate any association between BMI and AMH in women with normal, high, and poor reserves.

In contrast to the present study, a very recent systematic review and meta-analysis conducted by Moslehi et al. reported that ovarian reserve markers of AMH and FSH were significantly lower in obese than in non-obese women [37].

Interestingly, another finding is that the mean E2 level was higher only in the women of normal weight of the normal ovarian reserve group. In a study, it was demonstrated that higher serum levels of leptin in obese women correlate with higher levels of leptin in the follicular fluid [38]. In vitro studies have shown that leptin affects steroidogenic pathways in granulose cells, decreasing estrogen and progesterone production in a dose dependent manner [39, 40]. This mechanism for the adipokines might be the explanation of the highest E2 level in the group of women of normal weight. Nevertheless, it is essential to accomplish further studies in order to reveal the causal relationship between E2 and BMI subgroups in other ovarian reserve groups.

The main strength of our study is the large sample size compared to many prior studies evaluating the effects of obesity on ovarian reserve markers. Another strength is that we included WC as another marker of abdominal obesity. In addition to these strengths, three groups of ovarian reserve (normal, high, and poor) were evaluated to determine the effect of obesity on different levels of ovarian reserve. A potential limitation of this study is that the study population primarily consisted of women who were being treated for infertility, and we did not have any fecundity data for the study group.

In summary, our findings do not support any effect of obesity on ovarian reserve markers. In other words, the parameters of ovarian reserve do not seem to be affected by increased BMI and WC. Nevertheless, the decrease in fecundity in infertile obese

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women may arise from other multiple factors including folliculogenesis and endometrial receptivity. Because there is no relationship between obesity and AMH, AMH may be considered as a reliable marker of ovarian reserve. The etiologies for diminished ovarian reserve other than obesity also may be necessary to investigate. Further clinical and basic research studies are needed to elucidate the role of obesity on ovarian reserve and reproductive functions.

Funding

Conflict of Interest

The authors declare that they have no conflict of interest.

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