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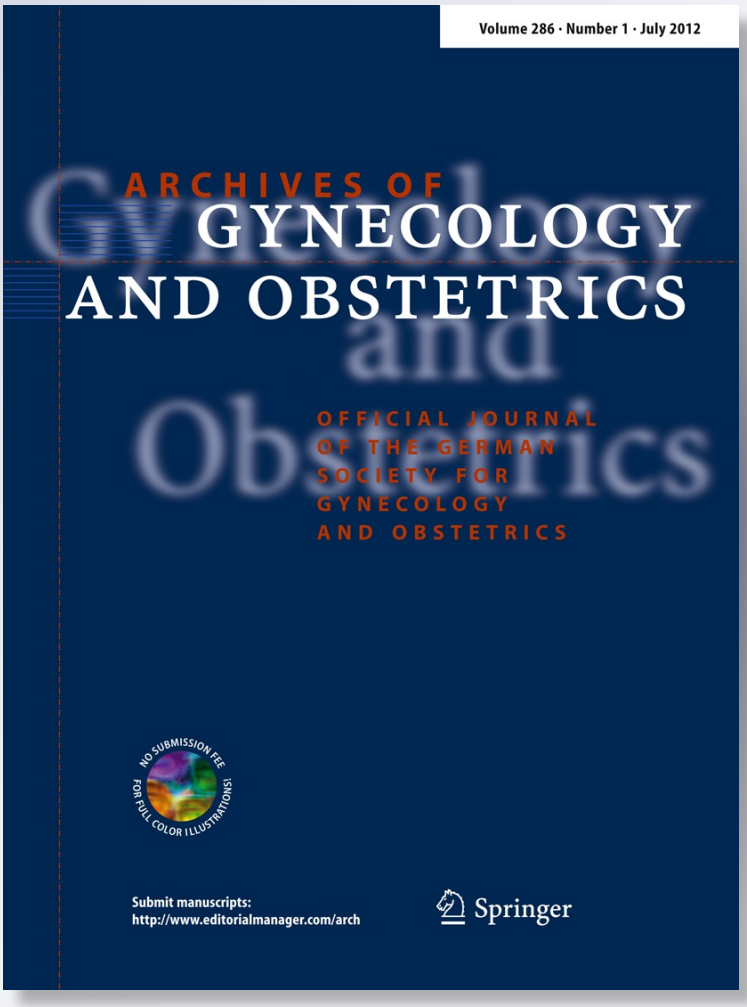

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GENERAL GYNECOLOGY

Is there any correlation between amh and obesity in premenopausal women?

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Abstract
Purpose To evaluate the correlation between the levels of anti-mullerian hormone and body mass index between obese and non-obese premenopausal women.
Methods Serum anti-mullerian hormone levels of women younger than 45 years admitted to our reproductive endocrinology clinic for investigation of infertility were examined in this cross-sectional study. Body mass indices were lower than 30 kg/m^2 in 222 patients and equal to or higher than 30 kg/m^2 in 37 patients. Levels of antimullerian hormone were analyzed in each group. Blood samples obtained from study subjects were assayed for levels of anti-mullerian hormone, follicle-stimulating hormone, luteinizing hormone, estradiol, prolactin and thyroid stimulating hormone.
Results There was no significant difference in terms of mean age between the two groups. There was no statistically significant difference between these two groups in terms of FSH, LH, estradiol and prolactin levels. Anti-mullerian hormone levels were 3.46 ± 2.79 ng/ml and 3.79 ± 2.93 ng/ml in non-obese and obese participants, respectively. No statistically significant correlation was found between Anti Müllerian Hormone (AMH) levels and BMI levels in either group ($P > 0.05$).
Conclusions Body mass index does not have an effect on serum AMH levels in women of reproductive age. Obesity has no association with levels of serum follicle stimulating hormone, luteinizing hormone, estradiol, prolactin and thyroid stimulating hormone. Obesity is unlikely to affect ovarian reserve in the premenopausal age group.

Keywords Anti-mullerian hormone · Body mass index · Obesity · Infertility

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Introduction

Anti Müllerian Hormone (AMH, also called Müllerian-inhibiting substance; MIS) is a homodimeric disulfide-linked glycoprotein and a member of the transforming growth factor-beta (TGF-β) superfamily [1]. Antral follicles are considered to be the primary source of circulating AMH, as they contain a large number of granulosa cells. Since AMH is secreted exclusively from follicles in the gonads, its serum concentrations in females are thought to reflect the size of the ovarian follicle pool [2, 3]. In general, AMH production rate is considered to reflect the amount of growing follicles in ovaries and the reservoir of ovarian function in females [4, 5]. Moreover, circulating AMH concentration predicts responsiveness to in vitro fertilization, decreases with aging and with possible gonadotoxic effects of chemotherapy and radiotherapy [6–9]. AMH was previously thought to have a sole role in the embryonic life as a male sex differentiation factor [10]. Today, it is a well-known indicator of ovarian reserve and potential fertility.

Obesity is a condition characterized by excessive storage of triglycerides in adipose cells. World Health Organization (WHO) has defined obesity as a body mass index (BMI) greater than 30 kg/m^2. BMI provides the most

useful population-level measure of overweight and obesity, since it is the same in both sexes and in all adult age groups. Calculating BMI is one of the best methods for population assessment of overweight and obesity. BMI is easy to calculate and inexpensive for clinical or public use, since calculation only requires the parameters of height and weight. BMI allows people to compare their own weight to that of the general population. Obesity and overweight are common conditions that have impacts not only on general health, but also on reproductive health to a great extent. Several studies have reported abundant evidence that obesity has a significant adverse effect on pregnancy in women seeking to become pregnant by natural means [11, 12]. Increased body mass index (BMI) has been associated with reduced fertility, and an increased risk of miscarriage compared with normal-weight women [13]. During pregnancy, overweight and obesity are associated with an increased risk of adverse maternal and infant health outcomes. Attention to weight loss before conception might improve fertility, and maternal and infant health outcomes of pregnancy. Once pregnancy is achieved in a woman with a high BMI, there is a substantially increased risk of miscarriage and pregnancy complications [12]. The etiology of poor fertility outcomes in overweight women has been searched, seeking to determine whether these outcomes are due to an ovarian or endometrial effect [12]. In addition to impairing spontaneous conception, high BMI might impair the probability of achieving pregnancy with assisted reproductive technology (ART). There is a high prevalence of obese women in the infertile population, and numerous studies have highlighted the link between obesity and infertility. Obesity contributes to anovulation and menstrual irregularities, reduced conception rate and a reduced response to fertility treatment. Markers of ovarian reserve, including baseline FSH, E2, inhibin B, antral follicle count, ovarian volume, and, recently, AMH, have been used to counsel patients regarding their reproductive outcomes [13]. Serum AMH concentrations remain stable throughout the menstrual cycle, which is a major advantage over other markers of fertility such as FSH and inhibin [13]. The cycle stability and operator independency make AMH a most appealing single marker of ovarian reserve [13]. Exploring the relationship between AMH and obesity might clarify the association between obesity and infertility, especially in terms of ovarian response. The evaluation of the level of AMH has clinical value in predicting the success of in vitro fertilization (IVF). Various studies have evaluated the association between AMH and BMI, but reported contradictory results overall. On the other hand, some of the studies in the literature have reported a significant inverse correlation between AMH levels and BMI [14, 15], whereas others found no relationship between AMH and BMI [16–18]. In the process of clinical decision making, we need to know whether obesity affects AMH levels. In this study, our objective was to investigate the effect of obesity on the level of AMH in obese and non-obese premenopausal women.

Materials and methods

Participants

This study was conducted in Reproductive Endocrinology and Infertility Clinic of Department of Obstetrics and Gynecology, Cerrahpasa School of Medicine, Istanbul University between May 2009 and April 2010. Serum basal AMH levels of volunteering patients under 45 years of age, who were admitted to our infertility clinic to investigate infertility were examined in a cross-sectional study. Inclusion criteria were having no history of gynecological operations, having a regular menstrual cycle, no signs of hyper-androgenemia, and normal sonographic appearance of the ovaries. Potential participants were excluded if they were using fertility drugs, oral contraceptives or metformin were smokers, pregnant, breastfeeding or had history of cardiovascular, liver, kidney or respiratory disease, uncontrolled hypertension, diabetes or malignancy. Additionally, patients who had FSH $\geq$15 mIU/ml, hyperprolactinemia, and were 45 years or older, were excluded from the study population. Totally 373 women were screened for inclusion and 259 patients met the study inclusion criteria and did not have any of the exclusion criteria. None of the study patients reported the use of any medications in the last 3 months that could interfere with the normal functioning of the hypothalamic–pituitary–gonadal axis.

Study design

Body weight and height were measured in all participating women. All patients were divided into two groups according to BMI. Study group consisted of patients with a BMI $<$30 kg/m^2 (non-obese, $n = 222$) and BMI $\geq$30 kg/m^2 (obese, $n = 37$). Levels of AMH, follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), prolactin, and thyroid stimulating hormone (TSH) were examined in all patients. Body weight and height were also measured in all patients. All study procedures were performed in accordance with the Declaration of Helsinki. Institutional ethics committee approval was obtained, and all the subjects were informed of the study protocol, potential risks and benefits of the study, and a written informed consent was obtained from each subject prior to the performance of any study procedures.

Clinical and biochemical measurements

Blood samples were collected during the early follicular phase of menstrual cycle in normal women. AMH, FSH, LH, E2, prolactin, and TSH levels of patients were analyzed in each group. Body weight was measured in each subject in light clothing using electronic digital scales (Mercury, AMZ14, Tokyo, Japan) and height was measured barefoot with a stadiometer, and BMI was calculated from these values (G-Tech International Co. Ltd., Kyonggi Province, Korea). Anti-mullerian hormone concentrations were measured with an enzymatically amplified two-sided immunoassay [DSL-10-14400 Active Mullerian Inhibiting Substance/AMH enzyme-linked immune sorbent assay (ELISA) kit, Diagnostic Systems Laboratories (DSL), Webster, Tx, USA]. The theoretical sensitivity of this method is 0.006 ng/ml, the intra-assay coefficient of variation (CV) for high values is 3.3 %, and the inter-assay CV for high values is 6.7 %. The levels of serum FSH, LH, and E2 were measured with Roche E-170 automated immunoassay analyzer (Roche Diagnostics, Mannheim, Germany). Inter-batch CV for these assays was 10 %. The measurement of 17-OHP was performed with RIA using intra-assay CV less than 7 % (DSL, Webster, Tx, USA). TSH was measured with colorimetric immunoassay (Dimension RxL clinical chemistry analyzer; Dade, Newark, DE, USA) with a sensitivity of 0.01 mIU/l, a precision of less than 6.2 % at all concentrations tested, and calibrated to the range of 0.01–50 mIU/l. The manufacturer's reference range was 0.34–4.82 mIU/l.

Data analysis

The Computer version of Statistical Package for the Social Sciences software version 11.1 (SPSS, Chicago, IL, USA) was used to perform statistical analyses. The data were presented as arithmetic means and standard deviations were calculated in each group. Pearson correlation analyses were used for the evaluation of correlations. Independent samples *t* test was performed to evaluate the statistical relations between subgroups. A *P* value of <0.05 was considered to be statistically significant.

Results

All participants ($n = 259$) were grouped according to BMI; subjects with a BMI less than 30 kg/m^2 constituted the non-obese group ($n = 222$) and subjects with a BMI of 30 kg/m^2 or more constituted the obese group ($n = 37$). The mean age of female participants was 32.05 ± 4.9 in non-obese (BMI <30) and 32.89 ± 5.78 in obese (BMI ≥30), and there were no statistically significant differences in terms of mean female age between the two groups ($P > 0.05$, Table 1). Mean BMI was found to be 24.22 ± 3.06 kg/m^2 in non-obese and 33.62 ± 3.2 in obese group. Level of FSH was 6.42 ± 2.28 in non-obese and 5.81 ± 1.89 in obese subjects at day 3 of the cycle. There were no statistically significant differences in terms of the FSH level ($P > 0.05$, Table 1). AMH levels were 3.46 ± 2.79 ng/ml in non-obese participants and 3.79 ± 2.93 ng/ml in obese participants (Table 1). No statistically significant correlation was found between the levels of AMH and BMI ($P > 0.05$), (Table 1). In addition, no statistically significant difference was determined between the two groups in terms of LH, estradiol and prolactin levels ($P > 0.05$, Table 1).

Table 1 Age of female participants, Body Mass Index and other features

	BMI <30 (*N*:222)	BMI ≥30 (*N*:37)	*P* value
Age (years)	32.05 ± 4.9	32.89 ± 5.78	>0.05*
FSH (mIU/ml)	6.42 ± 2.28	5.81 ± 1.89	>0.05*
LH (mIU/ml)	4.26 ± 3.54	4.40 ± 3.39	>0.05*
TSH (mIU/liter)	1.80 ± 1.03	1.98 ± 1.13	>0.05*
Prolactin (ng/ml)	17.72 ± 8.34	15.64 ± 5.51	>0.05*
BMI (kg/m^2)	24.22 ± 3.06	33.62 ± 3.2	**<0.0001****
AMH (ng/ml)	3.46 ± 2.79	3.79 ± 2.93	>0.05*

Values are given as mean ± SD

BMI body mass index, *FSH* follicle stimulating hormone, *LH* luteinizing hormone, *TSH* thyroid stimulating hormone

* Non-significant; * * Significant

Discussion

Obesity has become a major health problem across the world. There is a high prevalence of obese women in the infertile population and numerous studies have highlighted the link between obesity and infertility [19]. Obesity affects one-fifth of the female population, with 18.3 % of the female population in the reproductive age group (16–44 years) being classified as obese [20]. Overweight and obesity are significant and increasingly common health problems associated with increased risks of morbidity, quality of life, and metabolic and reproductive health consequences [19]. In women, being overweight or obese is associated with impaired fertility and decreased chance of conception both in natural and assisted reproductive technology births. Obesity, defined as a BMI of 30 or above by the WHO, contributes to anovulation and menstrual irregularities, reduced conception rate and a reduced response to fertility treatment. According to a global survey, more than 30 % of women between 25 and 44 years are overweight

(BMI 25 to 30 kg/m^2), and 20 % are obese [21]. Calculation of BMI is one of the best methods for population assessment of overweight and obesity. Obesity has been proven to impair human fertility. Many different mechanisms, such as insulin resistance, hyper-androgenism, elevated leptin levels and leptin resistance, have been proposed and investigated for elucidating the infertility in obese women. These proposed mechanisms may adversely affect the ovulation, fertilization and implantation in obese women [11, 22]. Attention to weight loss before conception might improve fertility, and maternal and infant health outcomes during pregnancy.

A number of studies have evaluated the association between AMH and BMI [12–18]. In a study conducted to examine the impact of oral contraceptive use on serum AMH levels, Steiner et al. [23] have determined that AMH levels are 34 % lower in the obese group. Supportive of these results, Freeman et al. [14] have stated that AMH levels tend to be 65 % lower in obese women and BMI remained significantly associated with AMH levels in multivariable models that included adjustments for menopausal status, age, race and day of the cycle. Georgopoulos et al. have observed that serum AMH levels were negatively correlated with BMI for both women with PCOS and ovulatory women [15]. They have stated that serum AMH levels are statistically significantly higher in normal-weight women with PCOS (6.88 ± 3.60 vs. 4.99 ± 2.16 ng/ml, $P < 0.001$) and in normal-weight ovulatory women (4.11 ± 1.29 vs. 2.41 ± 0.25 ng/ml, $P < 0.001$) when women are grouped by BMI (limit 25 kg/m^2) [15]. Nardo et al. have reported that no significant relationships were found between circulating AMH levels and BMI [16]. Halawaty et al. [24] have reported no statistically significant relationship between serum AMH levels and obesity in a cross-sectional study that included 100 premenopausal women. Park et al. [18] also have not detected any statistically significant relationship between the levels of AMH and anthropometric parameters (BMI, waist circumference, and waist-hip ratio) after adjusting for age. Thomson et al. [25] have recruited 52 overweight and obese women with PCOS and reproductive impairment and followed a 20-week weight loss program to assess the changes in AMH, weight, menstrual cyclicity, and ovulatory function compared to baseline. Authors have found that a 20-week weight loss intervention resulted in improvements in reproductive function, but no change in AMH levels in overweight and obese women with PCOS and reproductive dysfunction. Similar to ours, the latter study supports the idea that AMH does not change with obesity. Thomson's [25] study has also demonstrated that women had higher levels of testosterone, suggesting that high AMH levels are associated with the impairment of reproductive function. Moreover, women who demonstrated improvement in reproductive function had significantly lower AMH levels at baseline and experienced greater weight loss following the intervention compared to non-responders [25]. Similarly, the results of our study also suggest that the level of AMH does not play a role in the mechanism of interference of obesity with reproductive function. The relationship between AMH concentrations and both hormonal profile and insulin resistance is still not clear, and additional research is required to specifically investigate the potential effects of weight loss on additional hormonal and insulin parameters that might influence reproductive function [25]. In our study, we determined no association between BMI and AMH levels or other parameters including age, levels of FSH, LH, prolactin and estradiol.

According to the results of our study, obesity does not seem to have an effect on serum AMH levels. The decrease in rates of fertility in obese women arises from the negative interactions on follicular development or poor endometrial receptivity, rather than follicular reserve. In other words, AMH should better be considered as a good marker of ovarian reserve rather than a marker of fertility prediction. It is not possible to explain the relationship between BMI and reproductive function with AMH levels. This lack of relationship between serum AMH levels and obesity should be deemed as an advantage for AMH in terms of its clinical utilization as a stable marker.

Conflict of interest Authors declare no conflicts of interest.

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