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ORIGINAL ARTICLE

Serum anti-müllerian hormone concentrations in reproductive age women with and without polycystic ovary syndrome: the influence of body mass index

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Abstract
Purpose To evaluate the correlation between anti-müllerian hormone (AMH) and body mass index (BMI) in patients with and without polycystic ovarian syndrome (PCOS).
Methods Serum AMH levels of 332 women in their reproductive period and below 45 years of age who were admitted to our reproductive endocrinology clinic with infertility were investigated in a cross-sectional study. Patients were divided into two groups as BMI under and equal or over 25 kg/m^2. Both groups were divided into two subgroups as PCOS and non-PCOS. AMH levels of patients were analyzed for each group.
Results Mean AMH values of BMI <25 and ≥25 kg/m^2 groups were 3.87 ± 2.95 and 3.58 ± 2.93 ng/mL, respectively ($P > 0.05$) in all patients. Means of AMH were not significantly different in BMI quartiles ($r = -0.008401$, $P = 0.96$). Among 107 patients with PCOS, means of AMH were 6.85 ± 2.95 ng/mL in 56 patients with BMI <25 kg/m^2 and 6.66 ± 3.18 ng/mL in 51 patients with BMI ≥25 kg/m^2 ($P > 0.05$). In the group of 225 non-PCOS patients, means of AMH were 2.27 ± 1.12 ng/mL in 104 patients with BMI <25 kg/m^2 and 2.28 ± 1.49 ng/mL in 121 patients with BMI ≥25 kg/m^2 ($P > 0.05$).
Conclusions Body mass index does not seem to have an effect on serum AMH levels in reproductive age women both with and without PCOS.

Keywords Anti-müllerian hormone · Body mass index · Ovarian reserve · Overweight · Polycystic ovarian syndrome

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Introduction

Anti-müllerian hormone (AMH) is a member of the transforming growth factor-β (TGF-β) family. In females, AMH is mainly secreted by the granulosa cells of early developing ovarian follicles [1]. The expression of AMH is localized in granulosa cells of primary, pre-antral and small antral follicles, suggesting an important role of AMH in human folliculogenesis [2].

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 [6, 7], decreases with aging [8] and with possible gonadotoxic effects of chemotherapy and radiotherapy. [9]. On the other hand, in women with PCOS, circulating AMH concentrations are two- to threefold higher than those in healthy women of reproductive age [10, 11].

There is abundant evidence that increased body mass index (BMI) has a significant adverse effect on pregnancy and miscarriage rates in women seeking to become

pregnant naturally [12, 13]. Attention has been paid to the causes of poor fertility outcomes in overweight women, seeking to determine whether these outcomes are due to an ovarian or endometrial effect [13].

Exploring the relationship between AMH and obesity may clarify the association of obesity and infertility, especially in terms of ovarian response. A number of studies have evaluated the association between AMH and BMI. In these studies, the evaluation of the relationship between AMH concentrations and BMI generally showed contradictory results. In some studies [14, 15] a significant inverse association between AMH levels and BMI was found, whereas some others [16–19] found no relationship between AMH and BMI.

The presence of paradoxical results in the literature led us to investigate whether or not AMH levels change with body mass index (BMI).

Materials and methods

Serum basal AMH levels of 332 patients under 45 years of age who were admitted to our reproductive endocrinology clinic with infertility were investigated, retrospectively. Patients who had FSH $\geq$15 mIU/mL, prolactin $\geq$50 ng/ml, TSH $\geq$5.0 mIU/L were excluded. We divided all patients into two groups as BMI $<$25 kg/m^2 ($n = 160$) and $\geq$25 kg/m^2 ($n = 172$).

Since AMH is known to increase in PCOS [20], we sought to determine whether AMH levels differ according to BMI in two different populations: namely women with PCOS ($n = 107$) and women without PCOS ($n = 225$). The Rotterdam 2003 criteria were used on clinical evaluation of PCOS.

All patients evaluated into two main groups according to body mass index (BMI), under and equal or over 25 kg/m^2, and each group was further subdivided into two subgroups based on the presence of PCOS, as PCOS and non-PCOS groups.

Blood samples were collected during the early follicular phase of menses in normal women because this phase of follicular development is likely most similar to the stage of arrested folliculogenesis in PCOS women [21]. AMH, follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), prolactin, and thyroid stimulating hormone (TSH) levels of patients were analyzed for each group.

No woman reported use of any medication that could interfere with the normal function of the hypothalamic–pituitary–gonadal axis during the last 3 months. In all women, body weight and height were measured; BMI was calculated with electronic digital scales (Mercury, AMZ 14, Tokyo, Japan) and in light clothing; height was measured barefoot with a stadiometer (G-Tech International CO LTD, Kyonggi Province, Korea).

Anti-müllerian hormone concentrations were measured with an enzymatically amplified two-sided immunoassay [DSL-10-14400 Active Müllerian Inhibiting Substance/AMH enzyme-linked immunosorbent assay (ELISA) kit, Diagnostic Systems Laboratories (DSL), Webster, TX, USA]. The theoretical sensitivity of the method is 0.006 ng/ml, the intraassay coefficient of variation for high values is 3.3%, and the interassay coefficient of variation for high values is 6.7%.

Serum E2, LH, and FSH were measured on a Roche E-170 automated immunoassay analyzer. Between-batch coefficients of variation for these assays were 10%. Measurement of 17-OHP was by RIA with intraassay CV less than 7% (DSL, Webster, TX, USA). TSH was measured by 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 for the range of 0.01–50 mIU/L. The manufacturer's reference range was 0.34–4.82 mIU/L.

Transvaginal ultrasound scans of the ovaries were performed by experienced sonographers who participated in the study. The presence of PCO appearance was diagnosed by the presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter and/or increased ovarian volume ($>$10 cm^3).

Statistics

The data have been presented as the arithmetical means and the standard deviations were calculated for each group as well. Independent samples t test was performed for evaluating the statistical relations between the subgroups. Pearson correlation analyses were used for evaluation of correlations. A P value < 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Solutions for the Social Sciences (SPSS) software version 11.0.

Results

All patients ($n = 332$) were grouped as BMI, under 25 kg/m^2 and equal or over 25 kg/m^2. One hundred sixty patients consisted BMI $<$25 kg/m^2 group and 172 patients consisted BMI $\geq$25 kg/m^2 group. There was no statistically significant difference between these two groups in terms of AMH, age, FSH, estradiol and prolactin levels; however, LH was significantly higher and TSH was significantly

lower in BMI <25 kg/m^2 group compared to BMI ≥25 kg/m^2 group (Table 1).

Each body mass group was subdivided into PCOS and non-PCOS groups. Among 107 patients diagnosed with PCOS, mean values of AMH were found 6.85 ± 2.95 and 6.66 ± 3.18 ng/mL in 56 patients with BMI <25 kg/m^2 and 51 patients with BMI ≥25 kg/m^2, respectively ($P > 0.05$). In the group of 225 patients without clinical diagnosis of PCOS, mean values of AMH were 2.27 ± 1.12 and 2.28 ± 1.49 ng/mL in 104 patients with BMI <25 kg/m^2 and 121 patients with BMI ≥25 kg/m^2, respectively ($P > 0.05$). No statistically significant correlation was found AMH levels and BMI. In both BMI <25 and ≥25 kg/m^2 groups, comparison of the PCOS and non-PCOS subgroups showed significantly higher mean age, AMH and LH, and significantly lower mean FSH in PCOS compared to the non-PCOS subgroup. Differences in mean E2, prolactin, and TSH levels were nonsignificant in both subgroups.

All patients were divided into two groups as PCOS and non-PCOS. In the PCOS group, there were no statistical differences between BMI <25 and ≥25 kg/m^2 groups in terms of mean age, FSH, LH, E2, prolactin, and TSH levels. Similarly, in the non-PCOS group, there were no statistical differences between BMI <25 and ≥25 kg/m^2 groups in terms of mean age, FSH, E2, and prolactin, levels (Table 2).

Body mass index levels were also evaluated as quartiles, and Pearson correlation analysis showed that there was no statistically significant correlation between BMI and AMH. ($r = -0.008401$, 95% confidence interval −0.3561 to 0.3414. The two-tailed P value is 0.9636, considered not significant) (Table 3).

The groups were separated as BMI <30 and ≥30. LH was correlated with BMI in <30 kg/m^2 group ($r = -0.1945$, 95% CI −0.3272 to −0.05438, P 0.007) but not in ≥30 kg/m^2 group ($r = 0.009461$, 95% CI −0.3404 to 0.3571, $P = 0.95$).

Table 1 Comparison of BMI <25 and ≥25 groups

	BMI <25 ($N = 160$)	BMI ≥25 ($N = 172$)	P value
BMI (kg/m^2)	22.15 ± 1.86	29.22 ± 3.96	**<0.0001**
AMH (ng/mL)	3.87 ± 2.95	3.58 ± 2.93	NS
Age (years)	31.01 ± 5.20	32.2 ± 5.80	NS
FSH (mIU/ml)	6.22 ± 2.71	6.12 ± 2.14	NS
LH (mIU/ml)	4.43 ± 2.76	3.66 ± 2.00	**0.0037**
Estradiol (pg/ml)	45.77 ± 27.38	42.68 ± 23.29	NS
Prolactin (ng/ml)	17.66 ± 7.37	17.58 ± 8.62	NS
TSH (mIU/L)	1.62 ± 0.97	1.92 ± 1.05	**0.0088**

Groups were not divided according to polycystic ovarian syndrome. There's no explanation for the significant increase in mean LH and TSH

AMH anti-müllerian hormone, *BMI* body-mass index, *FSH* follicle stimulating hormone, *LH* luteinizing hormone, *TSH* thyroid stimulating hormone

Bold values are statistically significant ($P > 0.05$)

Discussion

Obesity is well-known to impair human fertility. Different mechanisms such as insulin resistance, hyperandrogenism, and elevated leptin levels and leptin resistance have been proposed and investigated for elucidating infertility mechanisms in obese women. There is some evidence that those proposed mechanisms may adversely affect the ovulation, fertilization, and implantation in obese women [12, 13].

Obesity may impair the oocyte and embryo quality, and thus, decrease the fertilization rates. Endometrial receptivity may be impaired in obese women. These mechanisms

Table 2 Comparison of BMI <25 and ≥25 subgroups in PCOS and non-PCOS patients

BMI (kg/m^2)	PCOS PATIENTS ($n = 107$)			NON-PCOS PATIENTS ($n = 225$)		
	BMI <25 ($N = 56$)	BMI ≥25 ($N = 51$)	P value (NS)	BMI <25 ($N = 104$)	BMI ≥25 ($N = 121$)	P value
AMH (ng/mL)	6.85 ± 2.95	6.66 ± 3.18	0.7609	2.27 ± 1.12	2.28 ± 1.49	0.9555 **NS**
Age (years)	28.66 ± 4.51	29.47 ± 4.09	0.3347	32.28 ± 5.12	33.41 ± 5.77	0.1264 **NS**
FSH (mIU/ml)	5.36 ± 1.27	5.07 ± 1.55	0.2823	6.47 ± 2.33	6.55 ± 2.20	0.7925 **NS**
LH (mIU/ml)	5.32 ± 2.95	4.66 ± 2.85	0.2508	3.96 ± 2.54	3.25 ± 1.36	**0.0086**
Estradiol (pg/ml)	42.16 ± 26.07	34.51 ± 11.78	0.0817	47.73 ± 28.00	45.87 ± 25.81	0.6094 **NS**
Prolactin (ng/ml)	18.02 ± 6.99	17.02 ± 8.24	0.5932	17.46 ± 7.59	17.80 ± 8.79	0.7510 **NS**
TSH (mIU/L)	1.62 ± 0.97	1.95 ± 0.99	0.0976	1.91 ± 1.28	1.91 ± 1.07	0.9750 **NS**

Mean AMH was higher in PCOS patients compared to non-PCOS patients although means of BMI were not significantly different between two groups

AMH anti-müllerian hormone, *BMI* body-mass index, *FSH* follicle stimulating hormone, *LH* luteinizing hormone, *PCOS* polycystic ovary syndrome, *TSH* thyroid stimulating hormone

Bold values are statistically significant ($P > 0.05$)

Table 3 Mean AMH levels according to BMI quartiles

Quartile (%)	BMI (kg/m^2)	Number of patients	Mean age (year)*	Mean FSH (mIU/ml)*	Mean BMI (kg/m^2)	Mean AMH (ng/ml)**
<25	<22.5	82	31.09	6.25	20.65	3.72
25–50	22.6–24.9	78	30.95	6.20	23.73	4.03
50–75	25–27.9	86	31.76	6.05	26.37	3.45
>75	>28	86	32.73	6.20	32.08	3.72

Means of AMH do not change in different BMI groups

AMH anti-müllerian hormone, *BMI* body mass index

*Pearson Correlation test: $r = 0.1936$, 95% CI −0.5920 to 0.7905, $P = 0.6460$

**Pearson Correlation test: $r = -0.008401$, 95% CI −0.3561 to 0.3414, $P = 0.9636$

may be responsible for a decrease in implantation and pregnancy rates as well as an increase in miscarriage rate, yielding to a poorer outcome in obese women in assisted reproduction [12, 13].

The mechanism underlying the inverse relationship between obesity and AMH is not entirely clear. Nevertheless, two different possible explanations for the inverse association of AMH and obesity are that (1) obesity is associated with decreased ovarian reserve [22], or (2) obesity is associated with follicular dysfunction [14, 23].

The first explanation is supported by the association between obesity and decreased ovarian response to ovarian stimulation, which has been identified in studies of assisted reproductive technologies [22]. The second explanation, that decreased levels of AMH in obese women signify impaired follicular function, is supported by evidence that obese women have fewer ovulatory cycles than normal weight women during the menopausal transition [23, 24]. Further studies to clarify the role of obesity in both follicular function and reserve are needed [14].

It is well-established by several studies that serum AMH level is a good indicator of ovarian reserve. Also, in many other studies, the relationship between AMH and ovarian response has been investigated. Our study results showed that decreased serum AMH level is associated with decrease in ovarian response (poor responder) [7].

Women with PCOS have higher AMH concentrations than normal women, probably due to both larger ovarian follicular mass and enhanced production of AMH per granulosa cell [10, 11, 25, 26]. Therefore, to prevent bias, instead of measuring the AMH levels in general population, we preferred to divide women with PCOS and without PCOS in this study. We evaluated the association between BMI and AMH in each group.

A number of studies have evaluated the association between AMH and BMI [11, 14–20, 27–31]. (Table 4) These study results can be classified under two groups: (1) studies which suggest presence of a negative correlation between AMH levels and BMI, (2) studies which suggest that there is no correlation between BMI and AMH levels. Georgopoulos et al. [15] observed that serum AMH levels were negatively correlated with BMI for both women with PCOS and ovulatory women. Indeed, by dividing all women according to BMI (limit 25 kg/m^2), the serum AMH levels were 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, $P < 0.001$). These AMH levels were consistent with our findings; however, there was no change with BMI in our study.

In support of our study, recent studies on non-obese ovulating women have found no relationship between AMH and BMI. [16, 17] Park et al. [18] also did not detect any statistically significant relationship between AMH and anthropometric parameters (BMI, waist circumference, and waist-hip ratio) after adjusting for age. Exploring the relationship between AMH and obesity may clarify the association of obesity and infertility.

From a different point of view, Thomson et al. [31] recruited 52 overweight and obese women with PCOS and reproductive impairment; they followed a 20-week weight loss program to assess AMH, weight, menstrual cyclicity, and ovulatory function, which were assessed at baseline and post-intervention. They found that in overweight and obese women with PCOS and reproductive dysfunction, a 20-week weight loss intervention resulted in improvements in reproductive function, but no change in AMH levels. As in our study, this study supports the idea that AMH does not change with obesity (BMI). Women with higher levels of AMH at baseline experienced greater ovarian dysfunction (fewer ovulatory cycles, greater cycle irregularity, and cycle length variation), and had higher levels of testosterone, suggesting that high AMH levels are associated with impairment of reproductive function. Moreover, women who demonstrated improvements in reproductive function had significantly lower AMH levels at baseline and experienced greater weight loss following the intervention

Table 4 Summary of studies on AMH and BMI relationship

References	Year	Design	Number of patients	Age group	Comment
Studies suggesting negative correlation between AMH and BMI					
Freeman et al. [14]	2007	Cohort	122 Women	Late reproductive age	Obese women have lower AMH levels compared to non-obese women ($P = 0.016$)
Chen et al. [20]	2008	Cross-sectional	99 Women with PCOS	Median 26 years (range 21–35)	AMH had a significant negative association with BMI (γ 20.213, $P = 0.035$)
Piouka et al. [27]	2009	Cohort	200 Women with PCOS [100 normal weight and 100 obese and overweight (BMI >25 kg/m^2)] and 50 healthy women (25 normal weight and 25 obese and overweight)	Reproductive age	AMH levels were negatively correlated with BMI ($r = -0.310$, $P = 0.001$)
Georgopoulos et al. [15]	2009	Prospective	50 Ovulatory women as controls and 200 women with PCOS	Reproductive age	Serum AMH levels were also negatively correlated with BMI for both women with PCOS ($r = -0.222$, $P = 0.007$) and ovulatory women ($r = -0.696$, $P < 0.001$).
Utriainen et al. [28]	2010	Cohort	52 Girls with premature adrenarche (PA) and 48 prepubertal girls	Prepubertal	Serum AMH concentration was negatively correlated with BMI SDS ($r = -0.23$, $P = 0.019$)
Steiner et al. [29]	2010	Exploratory	Normal (<25 kg/m^2; $n = 10$) and obese (>30 kg/m^2; $n = 10$) women who received a low-dose OC (20 mcg ethinyl estradiol/100 mcg levonorgestrel) for two cycles	Range 18–35 years	AMH levels are significantly lower in obese women.
Studies suggesting no relationship between AMH and BMI					
Pigny et al. [11]	2003	Prospective	104 Women (59 symptomatic PCOS, 45 controls)	PCOS: mean 28.3 years (range 24–33) Controls: mean 27.4 years (range 21.3–33.1)	The mean serum AMH level tended to be lower in obese than in nonobese controls (15.0 ± 9.3 vs. 22.0 ± 12.7 pmol/L, respectively; $P = 0.07$), whereas no difference was observed between obese and nonobese women with PCOS (44.5 ± 16.6 vs. 50.8 ± 27.6 pmol/L, respectively; $P = 0.32$). In addition, in controls exclusively, the BMI was negatively and significantly related to the serum AMH level.
Siow et al. [22]	2005	Prospective cohort	31 Adolescents with PCOS and 17 girls with normal menstrual cycles	Adolescents	Serum AMH levels in PCOS were not influenced by BMI.
Wunder et al. [17]	2007	Longitudinal	36 Young, healthy, normal weight Caucasian women without medication	Median age ± SD: (25.5 ± 5.5 years)	No correlation between AMH and the BMI
Nardo et al. [16]	2009	Cross-sectional	232 IVF candidates (49 of whom had PCOS)	22–41 years	No significant relationships were found between circulating AMH levels and BMI
Hart et al. [30]	2009	Prospective cohort	244 Adolescent girls	Median 15.1 years (range 14.5–17.6 years)	The association between AMH concentrations and BMI did not reach statistical significance (P = 0.070)
Thomson et al. [31]	2009	Prospective	52 Overweight and obese women with PCOS and reproductive impairment underwent a 20-week weight loss intervention	Median: 29.8 years	AMH levels did not change with weight loss in both responders and non-responders

Table 4 continued

References	Year	Design	Number of patients	Age group	Comment
Park et al. [19]	2010	Prospective comparative	Adolescents: Oligomenorrheic ($n = 24$), PCOS ($n = 153$), normal controls ($n = 39$), adults: PCOS ($n = 73$), normal ($n = 36$)	Adolescents (median approx 15.5) and adults (median approx 30)	Pearson correlation analysis demonstrated a significant inverse correlation between AMH and BMI for the adolescent subjects ($P = 0.002$) and the adult subjects with PCOS ($P = 0.002$). In the NC women, mean AMH levels were greater in the nonobese compared with the obese controls but did not achieve statistical significance.
Park et al. [18]	2010	Longitudinal	120 Healthy women	Mean age ± SD 37 ± 24 years, range 30–44 years)	No correlation between AMH and the BMI ($r = -0.087$, $P > 0.05$)

As it is seen, relationship between AMH and BMI can be evaluated in two groups as either "not correlated" or "negatively correlated". The sample size of our study was superior to all other studies

AMH anti-müllerian hormone, *BMI* body-mass index, *PCOS* polycystic ovary syndrome

compared with non-responders. Importantly, however, the responders had lower levels of AMH at baseline compared with the non-responders [31]. This study supports the results of our study. We also suggest that AMH level does not play a role in the mechanism that obesity interferes with reproductive function. The relationship between AMH concentrations and both hormonal profile and insulin resistance is still unclear, and additional research is required to specifically investigate potential weight loss effects on additional hormonal and insulin parameters that may influence reproductive function [31].

In our study there was no association between BMI and AMH levels or other parameters like age, FSH, LH, prolactin and estradiol. Similarly, no association between BMI and inhibin B, estradiol, FSH, or prolactin has been shown until now.

There is no logical explanation for the significant difference in LH groups. However, there is a positive correlation between AMH and LH. This positive correlation between AMH and LH is possibly the result of the pathophysiology of PCOS rather than the interaction between LH and AMH. In our study, LH was significantly high in BMI <25 group compared to BMI >25 group, and a similar result was also seen in AMH although it remained non-significant. However, when we separate the patients as PCOS and non-PCOS, these differences disappear in PCOS group. When we separate the groups as BMI <30 and ≥30, we have seen that LH was correlated with BMI in <30 kg/m^2 group ($r = -0.1945$, 95% CI −0.3272 to −0.05438, $P = 0.007$) but not in ≥30 kg/m^2 group ($r = 0.009461$, 95% CI −0.3404 to 0.3571, $P = 0.95$).

Means of age in BMI <25 and >25 kg/m^2 groups were not significantly different. Moreover, there is no statistically significant difference in mean age and FSH between the groups which might have potentially affected AMH levels (Table 3).

Considering that there are no changes in FSH and inhibin B which are used as ovarian reserve tests, the relationship between obesity and infertility and the relationship between obesity and ovarian reserve should be interpreted as two distinct subjects. However, the relationship between obesity and AMH has not been fully explained. Obesity has been associated with reduced fertility, even in the presence of ovulatory menstrual cycles, and with increased probability of miscarriage compared with normal weight women [13, 32, 33]. Mean TSH was significantly higher in BMI ≥25 kg/m^2 group compared to BMI <25 kg/m^2 group, although both mean values were consistent with euthyroid levels. There are many other studies which suggest that BMI and TSH levels are positively correlated [34–37], and very few which suggest that there is no association between the latter two [38].

It is not possible to explain the relationship between BMI and reproductive function with AMH levels. The decrease in fertility is difficult to explain in studies which suggest that AMH decreases as BMI increases. Similarly, finding that increased AMH levels in PCOS are responsible from fertility impairment is paradoxical. Therefore, we suggest that AMH is a good marker of follicle reserve irrespective of BMI. The decrease in fertility in obesity arises from the negative interactions in 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.

In conclusion, we found that there is no relationship between AMH levels and BMI, and also that BMI did not influence the circulating AMH concentrations in women with and without PCOS.

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