Original Article

Comparison of serum antimullerian hormone levels among four different phenotypes of polycystic ovary syndrome

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Abstract

Aim: Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders, with a prevalence of 5-10% among women of reproductive. Antimullerian hormone (AMH) may play important role in the pathophysiology and diagnosis of this syndrome. The goal of the current report was to compare serum AMH levels and clinical and hormonal features among four PCOS phenotypes.

Materials and Methods: Participants included women diagnosed with PCOS (n = 116), as defined by the Rotterdam consensus, and healthy subjects (n = 30). PCOS subjects were segregated into four phenotype groups based on the presence of oligo-ovulation or anovulation (OA), hyperandrogenism (HA), and polycystic ovarian morphology (POM) as follows: Group 1 (HA+OA+POM), Group 2 (HA+OA), Group 3 (HA+POM), Group 4 (OA+POM). The primary outcome measure used in the analysis was AMH serum level.

Results: Serum AMH levels were 10.2 ± 6.4 in Group 1, 4.5 ± 2.8 in Group 2, 7.4 ± 2.7 in Group 3, 7.9 ± 3.7 in Group 4, and 4.5 ± 1.8 in control group. AMH levels were markedly elevated in Group 1 compared to Groups 2, 3, 4, and control group. Free testosterone (fT) levels were similar in Groups 1 and 2 and markedly higher than in Groups 3 and 4. Insulin levels and results from the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) were significantly higher in all four phenotype groups than in the controls group Insulin and HOMA-IR values were similar among the phenotype groups.

Conclusion: Ovulatory dysfunction and POM may contribute to increased AMH levels. There may be an association between increased AMH levels and the severity of PCOS.

Keywords: Antimullerian hormone; phenotype; polycystic ovary syndrome

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders, with a prevalence of 5-10% among women of reproductive age (1,2). Clinical and/or biochemical hyperandrogenism (HA), oligo-ovulation or anovulation (OA), and polycystic ovarian morphology (POM) on ultrasonographic screening are the three cardinal features of PCOS. According to the Rotterdam consensus, the diagnosis of PCOS is based on the presence of at least two of these criteria and the exclusion of other commonly related diseases, including hyperprolactinemia, non-classical adrenal hyperplasia, and thyroid dysfunction (3). Subsequently, four different phenotypes were identified: phenotype 1 (HA+OA+POM), phenotype 2 (HA+OA), phenotype 3 (HA+POM), and phenotype 4 (OA+POM) (4).

The etiopathogenesis of PCOS has been poorly understood to date. Heterogeneity in clinical and biochemical presentations may reflect possible differences in the underlying pathophysiology of PCOS. Moreover, the long-term health outcomes and the risk of metabolic disorders may vary between the different phenotypes. Women with

severe PCOS have greater androgen excess, total and abdominal fat, menstrual irregularity and resistance to insulin and polycystic ovaries on ultrasound; and also have more severe risk factors for cardiovascular disease and diabetes than women with less severe forms of PCOS. Therefore, the phenotypic group with all three cardinal features is termed "severe" (5). Improved understanding of the characteristics of the different subtypes may help elucidate the underlying pathophysiology of the syndrome.

Antimullerian hormone (AMH) is a dimeric glycoprotein, a member of the transforming growth factor-β (TGF-β) superfamily. It is secreted by the granulosa cells of small antral and preantral follicles. AMH is considered to be a sensitive indicator of ovarian reserve and declines with age (6). The level of AMH may play important role in the pathophysiology and diagnosis of PCOS. AMH influences ovulatory dysfunction through paracrine pathway (7). Previous studies demonstrated that AMH levels were higher among PCOS subjects than among healthy controls (8,9). The mechanism responsible from increased AMH levels is still not fully understood. Some studies have indicated that insulin resistance, HA, and obesity contribute to

increased AMH levels (5,10). Moreover, increased AMH levels might be attributed to increased numbers of follicles and elevated AMH synthesis per follicle.

Broad differences in serum AMH levels among women with PCOS suggests a possible association between AMH levels and severity of PCOS. However, the function of AMH assessment as a diagnostic parameter and its potential association with the severity of PCOS is still unclear. The goal of the present paper was to compare the serum AMH levels and clinical, endocrine, and metabolic features associated with each of the four PCOS phenotypes and the control group.

MATERIALS and METHODS

Between September 2017 and May 2018, a total of 146 women were determined to be eligible and recruited to take part in this retrospective study. The study group consisted 116 women with PCOS who had complete medical records. PCOS subjects were further classified into four phenotype groups based on the presence of OA, HA, and POM as follows: Group 1 (HA+OA+POM), Group 2 (HA+OA), Group 3 (HA+POM), and Group 4 (OA+POM). Age- and body mass index (BMI)- matched 30 healthy women with regular menstrual cycles and without evidence of hirsutism and POM were included as control group. Ethical approval was obtained from the local ethics committee (Istanbul Training and Research Hospital Ethics Committee, number: 1299/2018).

Exclusion criteria included history of ovarian surgery, pregnancy, >36 or <18 years of age, hyperprolactinemia, thyroid dysfunction, androgen secreting tumors, history of hormonal medication in the previous six months, Cushing syndrome, and nonclassical adrenal hyperplasia. The primary outcome measure used in the analysis was AMH serum levels.

PCOS was defined according to the Rotterdam consensus (3). The presence of amenorrhea (no menstrual bleeding during last three months) or oligomenorrhea (6 or fewer menstrual cycles per year) was accepted as indicating OA. The presences of acne, hirsutism, and/or androgenic alopecia were defined as clinical HA. A Ferriman-Gallwey score >8 was indicated hirsutism (11). Biochemical HA was reported based on increased levels of free testosterone (fT) (12), as determined by the laboratory standard for the upper limit of the normal range for fT, 3.09 pg/ml. Increased ovarian volume of more than 10 ml or the presence of 12 or more follicles ranging in size from 2 mm to 9 mm diameter in each ovary was considered POM.

Anthropometric characteristics (including age, waist-to-hip ratio, weight, and height) and information from clinical examinations and ultrasound evaluations of participants were included. Biochemical data including the early follicular phase (days 2-5) follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2), as well as total testosterone (tT), fT, androstenedione (A), sex hormone binding-globulin (SHBG), dehydroepiandrosterone-sulfate (DHEA-S), 17-OH-progesterone (17-OH), fasting glucose, fasting insulin, thyroid-stimulating hormone, prolactin and AMH levels were obtained from medical records. Values for BMI were calculated using the following formula: body weight (kg) / height^2 (m). Waist circumference was measured at the smallest circumference between the xiphoid process and the umbilicus. Hip circumference was measured at the widest point over the buttocks. The waist to hip ratio (WHR) was calculated by dividing waist circumference by hip circumference. WHR ≥ 0.85 was considered abnormal (13). Insulin resistance was evaluated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) with the following formula: fasting glucose (mg / dL) x fasting insulin (mIU / mL) / 405 (14). Ultrasonographic examination was performed transvaginally (or by transrectal route in virgin patients) with 4-9-MHz transvaginal probe (Voluson E6 General Electric, Milwaukee, WI, USA).

Statistical Package for Social Sciences (SPSS) software for Windows (SPSS version 22.0; IBM Corp., Armonk, N.Y., USA) was used for the statistical analysis. The results are expressed as mean ± standard deviation. The normality of the distribution of continuous variables was evaluated using Kolmogorov-Smirnov statistics. Quantitative variables were compared using the Mann Whitney U test. Comparisons involving more than one group were calculated using the Kruskall Wallis test. The Chi-square test was used for the analysis of qualitative independent results. A p value < 0.05 was considered statistically significant.

RESULTS

Of the 116 participants with PCOS, 59 (50.4%) women with HA+OA+POM were included in Group 1, 10 (8.5%) women with HA+OA were included in Group 2, 14 (11.9%) women with HA+POM were included in Group 3, and 33 (28.2%) women with OA+POM were included in Group 4.

The demographic, hormonal, and clinical parameters of all groups are displayed in Table 1. Age and BMI were consistent across all groups. The control group had a significantly lower average WHR compared with those of the four phenotype groups. Average WHR did not differ significantly among the four PCOS groups.

The serum AMH levels were 10.2 ± 6.4 in Group 1, 4.5 ± 2.8 in Group 2, 7.4 ± 2.7 in Group 3, 7.9 ± 3.7 in Group 4, and 4.5 ± 1.8 in the control group. The highest serum AMH levels were observed in Group 1. AMH levels were significantly higher in Groups 1, 3, and 4 compared with controls. Group 2 had significantly lower AMH levels than Groups 1, 3, and 4. Groups 3 and 4 had similar AMH levels.

Levels of fT were similar in Groups 1 and 2 and markedly higher than those in Groups 3 and 4. There was no significant difference between control group and Groups 3 and 4 regarding levels of fT. (Figure 1). Levels of tT levels were markedly elevated in Groups 1 and 2 compared to those of the control group. There was no significant difference among the PCOS phenotypes in terms of tT levels. Levels of DHEA-S were significantly higher in Group 2 compared with controls and Groups 1, 3, and 4. In addition, DHEA-S levels were similar in Groups 1, 3, and 4.

Table 1. Demographic, clinical and biochemical parameters of groups

| Variables	Group 1 HA+OA+POM (n=59)	Group 2 HA+OA (n=10)	Group 3 HA+POM (n=14)	Group 4 OA+POM (n=33)	Controls (n=30)	Group 1 vs. 2	Group 1 vs. 3	Group 1 vs. 4	Group 1 vs. controls	Group 2 vs. 3	Group 2 vs. 4	Group 2 vs. controls	Group 3 vs. 4	Group 3 vs. controls	Group 4 vs. controls
Age (years)	22.0	25.0	23.0	24.0	24.0	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
BMI (kg/m²)	24.8	23.3	24.4	25.0	24.2	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
WHR	0.88	0.86	0.85	0.86	0.79	NS	NS	NS	<.05	NS	NS	<.05	NS	<.05	<.05
FSH (mIU/mL)	7.0	7.0	5.5	6.3	5.7	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
LH (mIU/mL)	10.6	10.4	6.9	7.7	6.3	NS	NS	NS	<.05	NS	NS	<.05	NS	NS	NS
E2 (pg/ml)	45.0	48.5	45.5	41.0	35.0	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
FG (mg/dL)	88.0	91.0	90.5	92.0	91.0	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
tT (ng/dL)	69.5	68.7	54.1	60.2	53.7	NS	NS	NS	<.05	NS	NS	<.05	NS	NS	NS
fT (pg/ml)	2.93	3.08	2.06	2.37	2.10	NS	<.05	<.05	<.05	<.05	<.05	<.05	NS	NS	NS
A (ng/ml)	1.92	1.96	1.41	1.48	1.45	NS	NS	NS	<.05	NS	NS	<.05	NS	NS	NS
DHEA-S (µg/dL)	279.6	345.3	241.1	212.7	256.4	<.05	NS	NS	NS	<.05	<.05	<.05	NS	NS	NS
17 OHP (ng/ml)	0.7	0.4	0.5	0.5	0.5	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
SHBG (nmol/L)	42.1	35.2	49.1	46.8	38.2	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
AMH (ng/ml)	9.6	4.6	7.4	8.6	4.1	<.05	<.05	<.05	<.05	<.05	<.05	NS	NS	<.05	<.05
Insulin (µU/mL)	8.6	7.7	5.8	11.0	4.2	NS	NS	NS	<.05	NS	NS	<.05	NS	<.05	<.05
HOMA-IR	1.80	1.68	1.27	1.48	0.93	NS	NS	NS	<.05	NS	NS	<.05	NS	<.05	<.05

Values presented as median. A, androstenodione; AMH, antimullerian hormone; BMI, body mass index; DHEA-S, dehydroepiandrosterone-sulfate; E2, estradiol; FG, fasting glucose; FSH, follicle-stimulating hormone; fT, free testosterone; HOMA-IR, homeostatic model assessment for insulin resistance; HA, hyperandrogenism; LH, luteinizing hormone; OA, oligo-ovulation or anovulation; 17-OH, 17-OH-progesteron; POM, polycystic ovarian morphology; SHBG, sex hormone binding-globulin; tT, total testosterone; WHR, waist-to-hip ratio

Insulin and HOMA-IR levels among the phenotype groups were similar (Figure 2, 3) and markedly increased compared to levels in the control group. Groups 1 and 2 showed significantly higher LH and androstenedione levels than did the control group. No difference was observed among other groups in terms of LH and androstenedione. No significant differences were found in the FSH, E2, SHBG, 17-OHP, and fasting glucose levels among all groups.
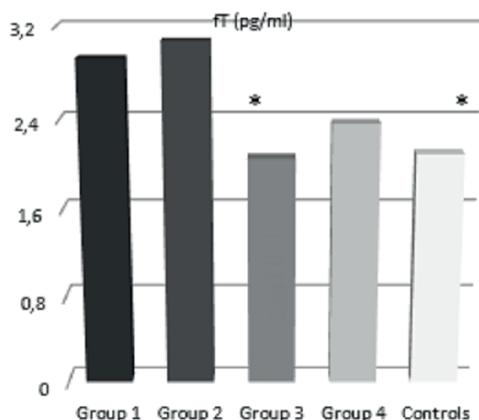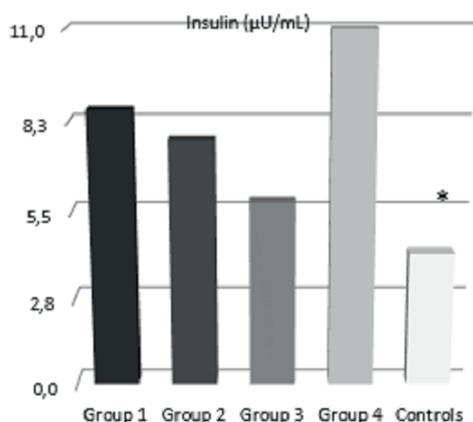

*p < 0.05 compared with Groups 1 and 2

Figure 1. Free testosterone (fT) (pg/ml) levels of all groups
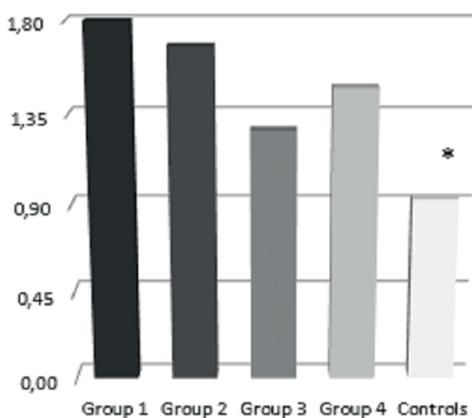
*p < 0.05 compared with Groups 1, 2, 3, and 4

Figure 2. Homeostatis model of assessment of insulin resistance (HOMA-IR) values in women with and without polycystic ovary syndrome

*p < 0.05 compared with Groups 1, 2, 3, and 4

Figure 3. Insulin (µU/mL) levels of all groups

DISCUSSION

PCOS is a condition that includes several heterogeneous phenotypes. Better understanding of PCOS phenotypes could facilitate elucidation of the etiology and improve diagnosis and treatment of the syndrome. It is important to evaluate patients individually because the long-term effects of PCOS can be improved with individualized screening and treatment strategies.

As reported in prior studies, the HA+OA+POM phenotype was the most prevalent phenotype (50.4%) observed in our study population while the OA+HA phenotype was the least common (8.5%) (15,16). Some studies indicated marked difference in BMI among the phenotypes of PCOS (16,17). Katsikis et al. suggested that BMI may influence phenotypic expression of PCOS (18). In contrast, other reports, including the current study, demonstrated no marked differences in BMI among PCOS phenotypes (5,19). Thus, the homogeneity of the groups regarding BMI may provide an advantage in interpretation of the data. Recent guideline on PCOS state that DHEA-S has limited value for detecting biochemical HA (12). Consistent with this guideline, our findings revealed DHEA-S levels in Groups 1 and 3 were similar to those in Group 4, the phenotype that does not include HA feature. The present study supports the conclusion that DHEA-S is a weak indicator of biochemical HA.

Evaluation of AMH levels has been suggested as a diagnostic tool for PCOS in conjunction with the existing Rotterdam criteria. Furthermore, it has been stated that AMH may be a good candidate to replace the POM criterion (20). However, whether AMH can be considered as a marker for PCOS is still unclear given the conflicting findings from earlier studies (21,22). Previous studies indicate that AMH has low specificity and sensitivity for diagnosing PCOS in population other than those with phenotype HA+OA+POM (22). We demonstrated that the Group 2 had similar AMH levels as the control group. Thus, using AMH as the sole diagnostic indicator would miss 8.5% of women with PCOS.

AMH levels have been shown to be elevated in many PCOS subjects compared to controls (23). The granulosa cells of small antral and preantral follicles synthesize AMH, suggesting an increase in the number of antral follicles may be responsible for elevated AMH levels (24). In a study that divided women into three groups according to AMH levels, researchers reported that 21% of participants with AMH levels lower than 4 ng/ml were diagnosed with PCOS, while 80% of those with AMH levels higher than 11 ng/ml were diagnosed with PCOS (25). Similarly, the current paper demonstrated that AMH levels were higher in phenotypes with POM than in women without PCOS. These findings support the theory that increased AMH levels may be a result of POM. Increased AMH levels could also facilitate diagnosis of PCOS in the OA+POM group, which is presented as having a normoandrogenic profile.

Jamil et al. reported that AMH levels increased 1.9 fold in the HA+OA+POM phenotype compared to the OA+HA phenotype. In addition, AMH levels have been reported to be markedly lower in the OA+HA group than in the HA+POM and OA+POM groups (26). In contrast, another study observed higher AMH levels in the OA+HA phenotype compared with those in the HA+POM and OA+POM phenotypes (5). A recent paper indicated that while AMH levels were markedly higher in the HA+OA+POM group compared to those of the OA+HA group, no marked difference was demonstrated between the other phenotypes (27).

Sahmay et al. reported a threefold elevation in AMH levels in the HA+OA+POM group over those in the OA+HA group. They demonstrated that POM was the discriminating feature between the two groups. They also found significantly higher AMH levels in the OA+POM and HA+POM groups than in the OA+HA group (25). Consistent with Sahmay's findings, we reported that AMH levels in Groups 1, 3, and 4 were markedly increased over those of Group 2. These findings support the suggestion that POM may be the main factor affecting circulating AMH levels. Our results also indicate that OA is a contributing factor in elevated AMH levels. AMH levels are recognized as a reflection the severity of PCOS, which is defined by the presence of three diagnostic criteria: HA, OA, and POM (5,25). Consistent with previous reports, the present study found the highest AMH levels in phenotype with three diagnostic features. This finding may support AMH as a useful marker for the severity of PCOS.

Although insulin resistance has been reported to have a positive association with AMH, this relationship remains controversial. One study reported higher AMH levels among women with PCOS who were insulin resistant than those who were not (28). In some previous studies, metabolic syndrome and insulin resistance were shown to be higher in HA phenotypes than in normoandrogenic phenotype (29,30). However, as in another study, no difference was demonstrated between groups based on HOMA-IR results (31). Similarly, no difference was observed between the groups in terms of HOMA-IR values in this study. This result might be due to the similar BMI averages of the study's groups and its small sample size.

CONCLUSION

In conclusion, the highest AMH values were found in the PCOS phenotype with all three diagnostic criteria. The findings of the current study emphasize the association between OA, POM and increased AMH levels in the different PCOS phenotypes. HA seems to have less effect on AMH values. Therefore, increased AMH levels may play a role in detecting the severity of PCOS. Further investigations with larger study populations may clarify the association between AMH and PCOS phenotype.

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