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Relationship between antimullerian hormone and the diagnostic features of polycystic ovarian syndrome

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Abstract

Background: Antimullerian hormone (AMH) is a promising marker of polycystic ovary syndrome (PCOS) and polycystic ovarian morphology (PCOM). Limited data are available regarding its utility among Bangladeshi women with PCOS.

Objectives: This study aimed to see the association between AMH and diagnostic markers of PCOS.

Methods: This cross-sectional comparative study included 100 women with PCOS based on Rotterdam criteria and 78 matched healthy controls. Following the collection of clinical information, fasting blood was collected during the follicular phase of the menstrual cycle to measure total testosterone (TT), luteinizing hormone (LH), follicle-stimulating hormone (FSH) by chemiluminescence and AMH by ELISA method. An ultrasonogram of the ovaries was done either transvaginal or transabdominal route depending on the patient's marital status.

Results: Women with PCOS had higher AMH levels than controls [6.49 (2.31, 10.3) vs. 2.78 (1.38, 7.01), median (IQR), p<0.001). Among women with PCOS, AMH levels were lower with hyperandrogenemia (TT>4.6 ng/mL) than with normoandrogenemia [3.99 (2.0, 9.18) vs. 8.13 (4.84, 12.25), p=0.008]. AMH levels did not vary with the status of the menstrual cycle, hirsutism, PCOM, LH/FSH ratio (>2.0), and phenotypes of PCOS. AMH negatively correlated with TT among women with PCOS (ρ= -0.26, p= 0.010). Serum AMH was a poor marker of PCOS (AUC: 0.67) and not for PCOM at all.

Conclusion: Serum AMH levels were higher in women with PCOS than controls with a negative association with TT. Serum AMH had little utility for the diagnosis of PCOS and PCOM. *[J Assoc Clin Endocrinol Diabetol Bangladesh, January 2024; 3 (1): 16-21]*

Keywords: Polycystic ovary syndrome, Polycystic ovarian morphology, Total testosterone, Irregular cycle, Hirsutism, Luteinizing/follicle-stimulating hormone ratio

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Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrinopathy of reproductive-aged females with unknown pathophysiology.[1] Currently, there is no single diagnostic test, and it is diagnosed according to consensus diagnostic criteria.[2] However, there are several markers of PCOS. Among them, antimullerian hormone (AMH) or mullerian inhibiting substance is a promising marker of PCOS as well as polycystic ovarian morphology (PCOM). This glycoprotein is a member of the superfamily transforming growth factor β and is exclusively expressed in granulosa cells of preantral and small antral follicles of ovaries. Its primary role is to inhibit follicular recruitment and maturation. The circulating levels of AMH indicate the pool of primordial follicles, thus providing an indirect measure of ovarian reserve.[3,4]

In women with PCOS, the levels of AMH are increased due to a higher number of follicles as well

as increased per-follicle production.[5] Apart from its role in folliculogenesis, it is also associated with neuroendocrine dysregulation and placental malfunction in women with PCOS. Placental dysfunction promotes a hyperandrogenic environment during pregnancy and plays an important role in the reprogramming of the reproductive axis of the female fetus.[6] Not only its importance in the pathogenesis of PCOS including anovulation and hyperandrogenemia, but its role as a diagnostic tool for PCOS as well as PCOM, and, its prognostic role during ovulation induction are areas of current research interest.[7] However, results are contradictory in many aspects and it needs age, race, and method-specific cut-off levels of AMH before using it as a universal tool for PCOS.[8] Very limited data are available from Bangladesh regarding the association of AMH with PCOS and its diagnostic features. This study aimed to see AMH levels with different diagnostic features as well as phenotypes of PCOS, and its utility as a marker of PCOS.

Methods

This cross-sectional comparative study was done in the Endocrinology Department of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. The ethical approval was taken from the institutional review board of the University. The study was conducted according to good clinical practice and following the Helsinki Declaration.

One hundred newly detected adult women with PCOS and 78 age-matched healthy controls were enrolled consecutively by convenient sampling during August 2014 to July 2015. PCOS was diagnosed according to Rotterdam criteria.[2] Women having regular menstrual cycles with insignificant hirsutism as well as normoandrogenemia were considered healthy controls. Both the study groups were selected after excluding thyroid dysfunctions, hyperprolactinemia, and hormonal contraceptive use within three months of enrollment. After taking informed written consent, relevant history was taken and physical examinations were done. Venous blood in a fasting state during the follicular phase of the menstrual cycle was drawn to measure total testosterone (TT), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and AMH. AMH was analyzed by an enzyme-linked immunosorbent assay, AMH GEN II ELISA kit (Beckman Coulter, Inc. USA) with an intra-assay coefficient of variation of 3.4 – 5.4% and inter-assay variation of 4.0 – 5.6%. Other hormones were measured by chemiluminescent microparticle immunoassay. A TT >4.6 ng/mL and a LH/FSH ratio (LFR) >2.0 were considered hyperandrogenemia and altered LFR respectively.[9] USG of ovaries was performed in the follicular phase of the menstrual cycle by trans-abdominal or trans-vaginal route depending on marital status only in patients with PCOS.

Statistical analysis was performed by SPSS software version 25.0. Data were expressed in median (inter-quartile range, IQR) and frequency (%) according to their types. Association between two groups was done by Mann Whitney U test and association among more than two groups was done by Kruskal Wallis one-way ANOVA test for quantitative variables. Pearson's chi-square or Fisher's exact test was done to see the association between qualitative variables. The correlation of serum AMH with the clinical and biochemical variables was done by Spearman's correlation test and point-biserial correlation test. At last, a receiver operating characteristics curve (ROC) analysis was performed to see serum AMH as a marker of PCOS and PCOM. Statistical significance was set at a two-sided p-value below 0.05.

Results

The baseline characteristics of the study population showed that women with PCOS had poor metabolic status including BMI ($p < 0.001$), WC ($p < 0.001$), systolic ($p < 0.001$) & diastolic ($p < 0.001$) blood pressure, and acanthosis nigricans ($p < 0.001$) than in the control group. The percentage of acne was also higher ($p < 0.001$) in the PCOS group than in the control group (Table-I).

Serum AMH levels were significantly higher in the PCOS group than in the control group ($p < 0.001$). Among patients with PCOS, serum AMH levels were statistically similar among the phenotypes. Only, phenotype A had higher levels of AMH than the control group ($p = 0.002$) (Figure-1). The AMH levels were also similar between phenotype A and other phenotypes in combination (B+C+D) in the PCOS group ($p = 0.813$).

Table-I: Characteristics of the study population (n= 178)

Variables	PCOS (n= 100)	Control (n= 78)	p
Age, years	25.0 (23.0 – 27.0)	26.0 (24.0 – 29.0)	0.073*
BMI, kg/m^2	26.88 (24.38 – 29.0)	21.34 (19.91 (23.08)	<0.001*
Waist circumference, cm	88.0 (80.63 – 97.75)	78.0 (77.0 – 79.0)	<0.001*
Systolic BP, mm-Hg	110.0 (100.0 – 120.0)	100.0 (90.0 – 100.0)	<0.001*
Diastolic BP, mm-Hg	80.0 (70.0 – 80.0)	70.0 (60.0 – 80.0)	<0.001*
Acne	29 (29.0)	5 (6.4)	<0.001†
Acanthosis nigricans	36 (36.0)	1 (1.3)	<0.001‡

*Mann Whitney U test, †Pearson's chi-square test, and ‡Fisher's exact test were done

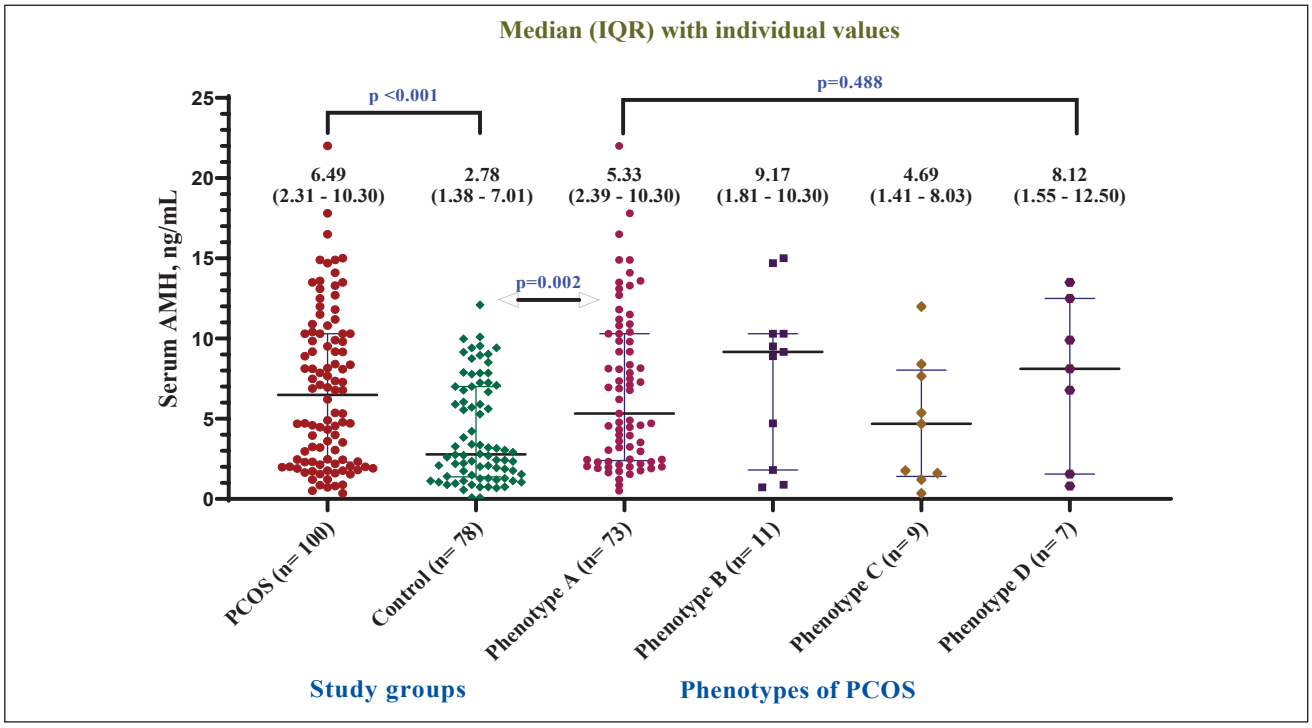

Figure 1: Serum AMH level in the study population and different phenotypes of PCOS (n= 178)

Mann Whitney U test was done
Kruskal Wallis one-way ANOVA test was done
Phenotypes of PCOS: A (hyperandrogenism, HA + ovulatory dysfunction, OD + polycystic ovarian morphology, PCOM); B (HA + OD); C (HA + PCOM); D (OD + PCOM)

Among patients with PCOS, those with hyperandrogenemia had significantly lower levels of serum AMH than those with normal total testosterone (p=0.008). Serum AMH levels did not vary according to the status of the menstrual cycle, hirsutism, hyperandrogenism, PCOM, and LH/FSH ratio subgroups (Table-II).

Among the diagnostic features, Serum AMH levels had a weak negative correlation with only serum TT (p= -0.26, p= 0.010) (Figure-2), but not with the menstrual cycle (r= 0.13, p=0.191), hirsutism (r=0.04, r=0.672), PCOM (p=0.08, p=0.434), LH (p=0.05, p=0.618), FSH (p=-0.07, p=0.498), or LH/FSH ratio (p=0.02, p=0.817).

Serum AMH was a poor marker of PCOS [area (95% CI) = 0.67 (0.59 – 0.75)]. At serum AMH levels of 3.5 ng/mL, the highest Youden index was found with a sensitivity and specificity of 66.0% and 60.3% respectively (Figure-3). It could not be used as a marker of PCOM in women with PCOS [area (95% CI) = 0.57 (0.36 – 0.77), SE= 0.10, p= 0.481].

Table-II: Serum AMH levels with different diagnostic characteristics in women with PCOS (n= 100)

Features	Categories	No.	Serum AMH	p
Menstrual cycle (cycle length <21 or >35 days)	Irregular cycle	91	6.78 (2.33 – 10.30)	0.152
	Regular	9	4.69 (1.41 – 8.03)	
Hirsutism (mFG score ≥8)	Significant	84	5.79 (2.36 – 9.84)	0.899
	Insignificant	16	7.45 (1.94 – 11.73)	
Hyperandrogenemia (>4.6 ng/mL)	Hyperandrogenemia	63	3.99 (2.0 – 9.18)	0.008
	Normoandrogenemia	37	8.13 (4.84 – 12.25)	
PCOM (OV >10 mL and/or FNPO ≥12)	Present	89	5.37 (2.31 – 10.10)	0.481
	Absent	11	9.17 (1.81 – 10.30)	
LH/FSH ratio (>2.0)	Altered	29	4.71 (2.26 – 10.10)	0.770
	Normal	71	6.78 (2.30 – 10.30)	

Mann Whitney U test was done

PCOM (polycystic ovarian morphology), OV (ovarian volume), FNPO (follicle number per ovary), LH (luteinizing hormone), FSH (follicle-stimulating hormone)

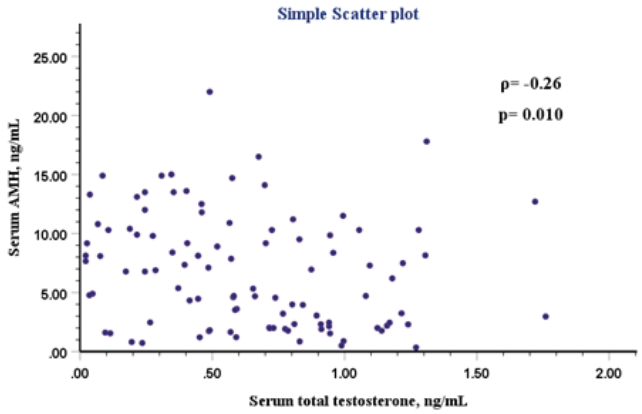

Figure 2: Correlation between serum AMH and total testosterone among women with PCOS (n= 100)

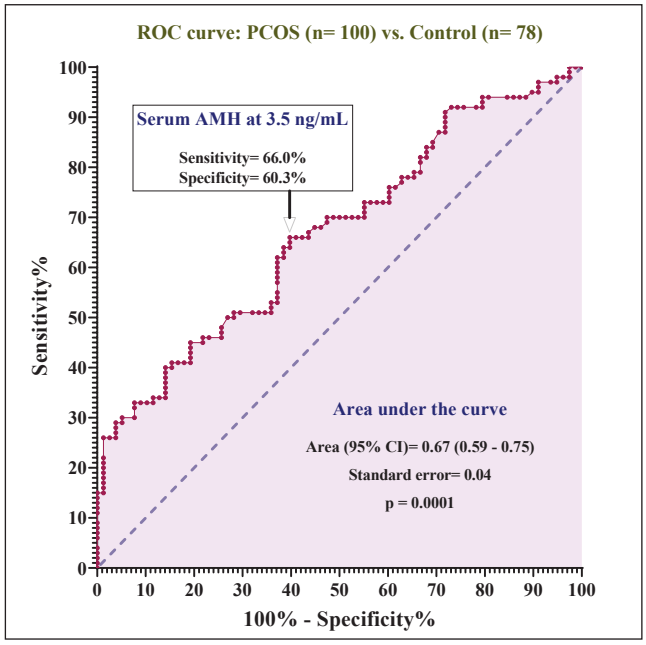

Figure 3: Receiver operating characteristics curve analysis of serum AMH as a marker of PCOS

Discussion

We found higher serum AMH levels in women with PCOS than in control. The main PCOS phenotypes did not differ in AMH levels. Only, those with phenotype A had higher levels of AMH than in the control. A reciprocal association between AMH and serum TT was observed in patients with PCOS. Serum AMH was a poor marker of PCOS with an optimal cut-off of 3.5 ng/mL.

Women with PCOS had median AMH levels 2.33 times higher than those in the control group. AMH levels are influenced by several variables, most significantly the assay method, age, and race.[10,11] Using a more recent immunoassay, a meta-analysis found that the PCOS group had four times greater levels of AMH than the control.[12] Therefore, to identify both PCOS and PCOM, a cut-off of AMH that is specific to age, demographic, and assay is needed.

The difference in AMH levels between PCOS vs. control was mainly due to the differences between phenotype A vs. the control group in our study. We found similar levels of AMH among the phenotypes of PCOS. This is probably due to the small number of participants in the non-A phenotypes. Several studies showed different types of associations between the phenotypes. Santhia et al. did not find any significant differences in AMH levels among the phenotypes of PCOS.[13] Wiweko et al. found higher serum AMH in phenotype A than in C and D and higher serum AMH in phenotype B than in D.[14] Ozay et al. found higher AMH levels in phenotype A than in phenotype D only.[15]

We found similar levels of AMH in PCOS patients

with irregular cycles than those with regular cycles. This may be due to a small number of participants with regular menstrual cycles despite lower levels of AMH than those with irregular cycles. Abbara et al. also found higher levels of AMH among women with irregular cycles. Even, they found a trend of higher AMH levels with longer length of menstrual cycles within the group of normal cycle length.[16] Pigny et al. showed a graded increment of AMH levels with increasing the length of the menstrual cycle (amenorrhea > oligomenorrhea > eumenorrhea) among women with PCOS.[17] We were not able to show this type of relation due to a lack of descriptive data. Besides, classifying a single type of menstrual irregularity is difficult, as the same patient may experience a different type of menstrual irregularity over a period of time. Hence, the current PCOS guidelines excluded those terms (polymenorrhea, oligomenorrhea, etc.) and mentioned only irregular cycles.[8]

We found a negative association and correlation between AMH and TT. Hwang et al. also found a negative correlation between AMH with free testosterone.[18] However, both positive and null correlations were also reported.[19,20] We did not find a significant association between AMH levels with hirsutism status or combined clinical and biochemical androgenism. One study showed higher levels of AMH among PCOS women with significant hirsutism, hyperandrogenemia, and total hyperandrogenism than those without.[21] Sahmay et al. found a positive correlation of AMH with mFG score and hirsutism independent of androgen levels[20] Butt et al. did not get a significant association between AMH and hirsutism.[22] They also did not find any association between AMH levels and ovarian volume which was in agreement with our finding.[22] We did not find a significant association between AMH levels and LH, FSH, or their ratio in women with PCOS. A positive association with LH and a negative association with FSH were described in previous studies.[20] No associations were reported by others.[17,20,22] A discordance among different studies again indicates PCOS is a heterogeneous condition.

Serum AMH was found a poor marker of PCOS and could not be used as a marker of PCOM in our study. A meta-analysis found AMH as a fair marker of PCOS with a cut-off of 4.7 ng/mL with sensitivity and specificity were 79.4% and 82.8% respectively. Two other meta-analyses also showed AMH as a fair marker of PCOS. A review showed a wide range of AUC (0.67 – 0.92) and diagnostic cut-off for PCOS (8.9 – 13.6 ng/mL) with significant overlap between PCOS and control. An inappropriate selection of samples contributes the significant heterogeneity.[24,25] A pooled analysis showed heterogeneity especially when immunoassay and ELISA assay methods were used. The pooled sensitivity and specificity were nearly 80% for both and AMH is now recommended by international evidence-based guidelines, in 2023 as an alternative to USG-PCOM in adults.[8]

Limitations of this study include the measurement of AMH by immunoassay, small number of participants in different subgroups, and heterogeneity in ultrasound measurement for PCOM.

In conclusion, serum AMH levels are higher among women with PCOS than healthy controls. However, it is a poor marker of PCOS with limited utility for PCOM as a diagnostic tool. Serum AMH has a significant negative association with TT among the diagnostic features of PCOS. A population-based study with a larger sample size as well as the use of 3rd generation assay for measurement of AMH is required before using AMH as a diagnostic marker of PCOS and PCOM in the Bangladeshi population.

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Disclosure

The authors declare that no conflict of interest could be perceived as prejudicing the impartiality of the research reported.

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Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author upon reasonable request.

Ethical Approval and Consent to Participate

This study was approved by the Institutional Review Board (IRB) of BSMMU, All procedures performed in studies involving human participants were in accordance with the ethical standards of the IRB and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed written consent was obtained from each of the participants included in the study.

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