

Correlation Between Serum AMH Levels and Cardiometabolic Indices in PCOS Women

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Abstract

Introduction: Polycystic ovary syndrome (PCOS) has a predilection for several cardio-metabolic disorders in future. Levels of anti-Mullerian hormone (AMH), a marker of ovarian ageing, are higher in women with PCOS women than in controls. However, whether and how AMH concentrations influence the cardio-metabolic risk in PCOS is yet to be established. **Objectives:** This study was done to determine the correlation between AMH levels and various cardiometabolic parameters in women with PCOS and to compare AMH levels in PCOS with and without metabolic syndrome (MS). **Materials and Methods:** In total, 144 women aged 20–40 years and diagnosed as PCOS by the Rotterdam criteria were included in this cross-sectional study. Their anthropometry and blood pressure were recorded. Fasting lipid profile, fasting glucose, fasting insulin, homeostasis model assessment-insulin resistance, total testosterone, and AMH were estimated. The correlation between AMH and cardiometabolic parameters was determined. **Results:** Serum AMH levels had no correlation with any component of MS. The AMH values were comparable between those with and without MS despite differences in the metabolic profile (11.39 ± 5.31 vs 11.56 ± 5.64 ng/mL, $P = 0.861$). **Conclusion:** AMH levels do not correlate with components of MS so it may not be useful as an indicator of cardiovascular risk, insulin resistance, or MS in PCOS.

Keywords: Anti-Mullerian hormone, metabolic syndrome, polycystic ovary syndrome

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy encountered in women of child-bearing age with several long-term cardiometabolic sequel like insulin resistance (IR), metabolic syndrome (MS), type 2 diabetes mellitus, and coronary artery disease (CAD).^[1-3] Menopausal transition is characterized by declining ovarian reserve and function, and the time of menopause is determined by the inevitable decline of the ovarian follicle pool. Serum anti-Mullerian hormone (AMH), a glycoprotein secreted by the granulosa cells of the preantral and antral follicles of the ovary,^[4,5] has emerged as a promising single marker of reproductive ageing.^[6,7] Peri- and postmenopausal life stages are associated with deterioration of cardiovascular health.^[6,8] This is attributed to declining estrogen levels which in turn impacts lipid profile and coronary artery dynamics, thus playing a crucial role in the appearance and progression of subclinical CAD.^[9] There is growing research whether decreased AMH may serve as an early indicator of worsening cardiometabolic status. Studies in general premenopausal women have

demonstrated that lower AMH levels may portend a more unfavorable cardiometabolic health.^[8,10] Whether AMH relates to cardiometabolic markers differently in women with PCOS, a high risk group for future cardiovascular and metabolic disorders, is still uncertain. Compared to controls, AMH concentrations are higher in PCOS, and age-related decline in AMH levels is slower culminating in delayed ovarian ageing and longer reproductive lifespan.^[11-25] However, whether these higher levels of AMH affect or predict overall cardiovascular risk in PCOS, remains unclear as results from existing studies are conflicting. Obesity, high AMH, IR, and MS, though not in the diagnostic criteria of PCOS, are closely associated with this condition, but the precise association between AMH and

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metabolic disturbances is yet to be elucidated. Furthermore, MS, a harbinger of CAD, presents at an earlier age in PCOS. Therefore, early identification of potential biomarkers, long before menopause sets in, will help in stratification of CAD risk and encourage disease prevention in this high-risk population. Despite evidence of higher prevalence of PCOS as well as MS and CAD in South Asian women compared to other ethnicities, studies investigating the relationship between serum AMH levels and MS in Indian women with PCOS are scarce.

Therefore, this study was undertaken to elucidate the correlation between AMH levels and various cardiometabolic parameters in PCOS women of the reproductive age group in eastern India. We also sought to compare AMH levels in PCOS women with and without MS.

MATERIALS AND METHODS

This cross-sectional study was conducted at a tertiary care center in eastern India from January 2019 to December 2020. All women between 20 and 40 years of age diagnosed with PCOS were included after informed consent. Diagnosis of PCOS was established if woman fulfilled two out of three features in the Rotterdam 2003 criteria, i.e., chronic anovulation/oligoovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovaries (PCO) on ultrasound (USG).^[1] Those with cycle intervals of <21 days or >35 days, or <8 cycles per year were considered to have ovulatory dysfunction. Women with acne, hirsutism with modified Ferriman–Gallwey score ≥ 8 , and/or androgenic alopecia were considered to have clinical hyperandrogenism. Serum testosterone levels ≥ 80 ng/dL was indicative of biochemical hyperandrogenism. Polycystic ovarian morphology (PCOM) was defined as ovarian volume >10 cc. Those with menarche within 3 years before enrollment; history of use of any hormones like oral contraceptives, antiandrogens, ovulation induction agents, antidiabetic or lipid lowering agents in the last 3 months; conditions likely to decrease AMH levels like previous chemotherapy, ovarian surgery and/or pelvic irradiation were excluded. IEC approval was obtained on 6th Dec 2018.

Sample size was calculated based on correlation coefficients between the components of MS and AMH levels, taken from a previous study.^[26] A total of 144 women were recruited. All participants were categorized into one of the four phenotypes as per Rotterdam criteria – phenotype A/frank PCOS, phenotype B/non-PCO PCOS, phenotype C/ovulatory PCOS, and phenotype D/normoandrogenic PCOS. History was elicited pertaining to age, menstrual pattern, androgenic symptoms, and parity. Clinical examination was performed to identify acne, hirsutism, androgenic alopecia, and acanthosis nigricans. Their height, weight, body mass index (BMI), waist circumference (WC), waist: hip circumference ratio, and systolic and diastolic blood pressure (BP) were recorded. Weight was measured using a digital scale to the nearest 100 g, with the women dressed in light clothing and barefoot. Height was determined using a tape measure, with

the women standing upright, barefoot, with their shoulders aligned normally. Those with BMI ≥ 23 kg/m² and ≥ 25 kg/m² were considered to be overweight and obese, respectively. Waist and hip circumference were measured as per the WHO STEPS (STEPwise approach to noncommunicable disease risk factor surveillance) protocol, wherein WC was measured at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest at the end of a normal expiration, while hip circumference was measured around the widest portion of the buttocks, using a stretch-resistant tape that wrapped snugly but not constricting and held parallel to the floor. USG was performed either transvaginally or transabdominally depending upon marital status. Since determination of follicle number per ovary (FNPO) by transabdominal USG can be unreliable, especially in obese or unmarried women, ovarian volume was measured in all cases rather than FNPO.

Blood was collected from the antecubital vein of all participants under all aseptic conditions on days 2–4 of the spontaneous menstrual cycle or on any day for women with amenorrhea after overnight fasting of 8–12 h. Serum was analyzed for total testosterone and insulin by the chemiluminescence method in Siemens Advia Centaur XP immunoassay analyzer. Serum fasting lipid profile and fasting plasma glucose were estimated by Beckmann Coulter AU5800 autoanalyzer using reagents from Beckmann Coulter, Inc., USA. Quality control in both the analyzers were maintained by using Bio-Rad internal quality control samples daily and external quality control monitored by monthly samples from the Association of Clinical Biochemists of India prepared by Christian Medical College, Vellore. For analysis of AMH, the serum samples were stored at temperature of -80 °C. The analysis was later performed by the ELISA-based kit method from Epitope Diagnostics, Inc., San Diego, USA.

IR was defined as homeostasis model assessment-insulin resistance (HOMA-IR) value >2.5, as calculated by the formula $HOMA-IR = [\text{fasting insulin } (\mu\text{U/mL}) \times \text{fasting glucose (mg/dL)}] / 405$. MS was diagnosed if any three of the following five risk factors are present as per the cutoffs for Asian Indians – WC >80 cm, triglycerides (TG) ≥ 150 mg/dL, high-density lipoprotein cholesterol (HDL-C) <50 mg/dL, systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg, and fasting glucose ≥ 100 mg/dL.^[27] The clinico-endocrine profile was compared between those with MS and those without MS.

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics 20.0 for Windows. Normality of data was established by Kolmogorov–Smirnov test. Continuous and categorical variables were expressed as mean \pm SD and frequency with percentages, respectively. Pearson's correlation coefficient was used for assessing the correlation between serum AMH levels and cardiometabolic risk factors. Student's *t*-test was employed for comparison of continuous variables, while Chi-square test was used for comparing proportions between

MS and non-MS groups. P value < 0.05 was considered as statistically significant.

RESULTS

Table 1 summarizes the baseline characteristics of the study participants. The mean age of the participants was 24.73 ± 3.37 years. Almost two-third of the participants (69.4%) were overweight/obese with a mean BMI of 25.58 ± 4.71 kg/m². Only eight women had no menstrual abnormality. Majority of them (70.8%) had clinical and/or biochemical hyperandrogenism. Acanthosis nigricans, a clinical indicator of IR, was found in 45.8% women, but biochemical IR, as estimated by HOMA-IR >2.5 , was observed only in 18 subjects (12.5%). Nearly one-third had MS (31.3%). Mean AMH levels were 11.51 ± 5.52 ng/mL.

No correlation was observed between AMH and components of MS as well as with other cardiometabolic parameters, as shown in Table 2. However, there was a significant positive correlation of AMH with ovarian volume and testosterone levels and negative correlation with age.

Table 3 depicts the clinicometabolic profile of PCOS women with and without MS. Hirsutism, obesity, and acanthosis nigricans were more prevalent MS group, while menstrual dysfunction was more common in those without MS. Although women with MS had a more unfavorable cardiometabolic profile in terms of anthropometry, BP, lipid profile, and measures of IR, AMH levels did not differ from those without MS (11.39 ± 5.31 vs 11.56 ± 5.64 ng/mL, $P = 0.861$).

AMH concentrations were comparable between obese and lean PCOS, as also between those with and without IR (data not shown in table).

DISCUSSION

The main findings of this study are that AMH do not correlate with any component of MS. Serum AMH concentrations do not differ between those with or without MS despite differences in the clinicometabolic profile.

Because menopause has been associated with a depleted follicular pool as well as worsening of cardiometabolic status, there has been growing interest to investigate whether markers of ovarian reserve like AMH might predict cardiovascular health. Serum AMH concentrations are higher in South Asian women than in other ethnicities.^[28] Given the higher risk of CAD and MS in South Asians compared to the Western counterparts, it is intriguing to investigate how these higher AMH levels impact cardiovascular risk in a vulnerable population like PCOS women who, as such, present with an altered metabolic profile. Although the longitudinal impact of the high prevalence of conventional cardiovascular risk factors on coronary morbidity and mortality in PCOS is not known precisely, appropriate risk triage in reproductive age women with PCOS is advisable. Feldman *et al.*^[26] have concluded that in women with PCOS, low AMH levels predict

Table 1: Clinicometabolic characteristics of women with PCOS

Parameter	Mean \pm SD/ Frequency (%)
Age (years)	24.73 \pm 3.37
Menstrual dysfunction*	136 (94.4)
Acne*	78 (54.2)
Hirsutism*	49 (34.0)
mFG score	6.36 \pm 5.43
Acanthosis nigricans*	66 (45.8)
BMI (kg/m ²)	25.58 \pm 4.71
Waist circumference (cm)	85.90 \pm 10.88
Hip circumference (cm)	97.63 \pm 9.05
Waist hip ratio	0.87 \pm 0.06
Systolic blood pressure (mmHg)	115.59 \pm 14.43
Diastolic blood pressure (mmHg)	75.06 \pm 10.79
Average ovarian volume (cc)	13.72 \pm 4.99
AMH (ng/mL)	11.51 \pm 5.52
Fasting glucose (mg/dL)	92.58 \pm 12.63
Total cholesterol (mg/dL)	168.64 \pm 31.57
Triglycerides (mg/dL)	115.47 \pm 52.18
Low-density lipoprotein-cholesterol (mg/dL)	106.26 \pm 25.76
High-density lipoprotein-cholesterol (mg/dL)	45.26 \pm 8.50
Very-low-density lipoprotein-cholesterol (mg/dL)	23.09 \pm 10.43
Testosterone (ng/dL)	60.94 \pm 34.86
Fasting insulin (μ U/mL)	6.32 \pm 6.47
HOMA-IR	1.47 \pm 1.64

*Expressed as frequency and percentages. AMH: Anti-Mullerian hormone, BMI: Body mass index, HOMA-IR: Homeostasis model assessment-insulin resistance, mFG : modified Ferriman-Gallwey

Table 2: Correlation between AMH and cardio-metabolic parameters

AMH vs	r	P
Age	-0.179	0.032
Weight	-0.095	0.257
BMI	-0.097	0.247
Waist circumference	-0.097	0.246
Hip circumference	-0.071	0.397
Waist hip ratio	-0.092	0.272
Systolic blood pressure	-0.072	0.394
Diastolic blood pressure	-0.004	0.957
Average ovarian volume	0.258	0.002
Total cholesterol	0.121	0.149
Triglycerides	-0.020	0.816
Low density lipoprotein-cholesterol	0.025	0.768
High density lipoprotein-cholesterol	0.147	0.079
Very low density lipoprotein-cholesterol	-0.020	0.816
Fasting glucose	0.097	0.248
Fasting insulin	-0.126	0.133
HOMA-IR	-0.113	0.179
Testosterone	0.305	<0.001

AMH: Anti-Mullerian hormone, BMI: Body mass index, HOMA-IR: Homeostasis model assessment-insulin resistance

a greater risk of MS as a single unit decrease in AMH was associated with an 11% increase in odds of MS, indicating an

Table 3: Clinicometabolic profile of PCOS women with and without metabolic syndrome

Parameter	PCOS without metabolic syndrome (n=99)	PCOS with metabolic syndrome (n=45)	P
Age (years)	24.30±3.23	25.68±4.43	0.064
Menstrual dysfunction*	95 (95.95)	41 (91.12)	0.026
FG score	5.62±5.35	7.97±5.33	0.016
Hirsutism*	27 (27.27)	22 (48.89)	0.011
Acne*	52 (52.53)	26 (57.78)	0.592
Overweight and obesity*	59 (59.60)	41 (91.12)	<0.001
Acanthosis nigricans*	32 (32.32)	34 (75.56)	<0.001
Height (m)	1.54±0.05	1.55±0.06	0.237
Weight (kg)	58.15±10.59	68.73±12.09	<0.001
BMI (kg/m ²)	24.38±4.40	28.23±4.29	<0.001
Waist circumference (cm)	83.08±10.70	92.10±8.53	<0.001
Hip circumference (cm)	95.19±8.27	103.01±8.42	<0.001
Systolic blood pressure (mmHg)	111.31±11.24	125.00±16.24	<0.001
Diastolic blood pressure (mmHg)	71.97±9.31	81.86±10.80	<0.001
Average ovarian volume (cc)	13.60±5.40	13.98±3.99	0.637
Fasting glucose (mg/dL)	89.24±6.56	99.94±18.49	<0.001
Total cholesterol (mg/dL)	161.71±29.20	183.91±31.54	<0.001
Triglycerides (mg/dL)	94.52±28.52	161.54±62.28	<0.001
Low-density lipoprotein-cholesterol (mg/dL)	100.32±24.19	119.32±24.49	<0.001
High-density lipoprotein-cholesterol (mg/dL)	47.27±8.85	40.83±5.59	<0.001
Very-low-density lipoprotein-cholesterol (mg/dL)	18.90±5.70	32.30±12.45	<0.001
Fasting insulin (μU/mL)	5.12±4.14	8.94±9.36	0.011
HOMA-IR	1.13±0.93	2.22±2.44	0.005
Testosterone (ng/dL)	58.56±33.69	66.24±37.26	0.294
AMH (ng/mL)	11.56±5.64	11.39±5.31	0.861

*Expressed as frequency and percentages, rest parameters as mean±SD. AMH: Anti-Mullerian hormone, BMI: body mass index, HOMA-IR: homeostasis model assessment-insulin resistance

independent role for AMH in cardiovascular risk stratification in these women. Jun *et al.*^[29] also propounded that AMH is a potential cardiometabolic risk factor as low levels are related to higher HOMA-IR values and TG levels, and lower HDL-C levels. Conversely, Lin YH *et al.*^[17] did not find significant differences in glucose tolerance, IR, lipid profile or risk of MS among the low (<4 ng/mL), moderate (4–11 ng/mL), and high (>11 ng/mL) AMH groups. In line with the latter findings, we too did not find any association between AMH levels and MS as evident from lack of correlation between AMH and various components of MS as well as from comparable AMH levels between MS and non-MS groups. There is also evidence that in PCOS, high AMH levels increase the risk for IR but not MS.^[30] Some authors have observed that the association between AMH and some cardiometabolic risk factors is abolished or attenuated after controlling for potential confounders like age and BMI.^[20,22,24,31] This implies that obesity may mediate the relationship between AMH and MS, and AMH may not be a significant and independent predictor of MS or future CAD risk. This is further supported from an inverse association between AMH and markers of obesity reported in most studies,^[15,17,20,22-24,26,31] which is probably due to a toxic suppressive effect of obesity on granulosa cell function and follicular AMH production, or due to a dilutional effect on serum AMH concentrations.^[31] Conversely, some studies, including ours, have found no association between AMH and

obesity.^[11,14,16,18,19,21,25] In addition, we found no differences in AMH levels between obese and nonobese PCOS women. It is postulated that any impact of BMI on AMH in young women is probably weak as the association was found in normal weight PCOS but not in overweight or all PCOS subjects and weight reduction did not decrease AMH levels despite improvement in reproductive function.^[18,24] All these observations suggest that the variance of serum AMH in PCOS may not primarily be due to metabolic factors like BMI. Consequently, serum AMH may have a minor role in influencing risk of MS, which is mainly characterized by obesity. Additionally, in clinical practice, it is not useful to establish different thresholds of AMH according to BMI.

As regard BP, we did not find a statistically significant negative correlation with AMH levels, similar to few.^[23] In contrast, Feldman observed a negative correlation which was, however, attenuated after adjusting for BMI.^[26] This indicates that low AMH may not worsen cardiometabolic risk in PCOS as significantly or independently as obesity.

The association between AMH and lipid profile is inconsistent as well as differential with various lipid parameters in different studies.^[17-20,22,26,29,31] Few have found a positive correlation with total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C) even after controlling for age, BMI, and androgen levels postulating that in women with

PCOS, AMH has an independent association with adverse lipid profile.^[18,31] Increased AMH levels may lead to increased androgens which in turn may contribute to atherogenic dyslipidemia. However, despite a positive correlation between AMH and testosterone levels in our study, we did not observe any correlation between AMH and lipid profile parameters, partly in concordance with few.^[18-20,22,26] This suggests that hyperlipidemia in PCOS is independent of androgens and pathways for elevations are different for different lipid parameters.^[31]

The relationship between indices of IR and AMH has been a source of controversy. Some have found a positive correlation between AMH and fasting glucose, fasting insulin, and HOMA-IR.^[14,15,18,30] This is further supported by reduction in insulin and AMH levels after treatment with insulin sensitizers.^[12,32] This positive association may reflect indirect regulation through androgens as hyperinsulinemia leads to hyperandrogenism in PCOS which in turn causes a derangement in folliculogenesis, thus contributing to the PCOM and a higher than normal AMH levels.^[21,32] Conversely, some have found improvement in IR parameters, but not AMH levels, with metformin use,^[33] thus adding credence to the fact that AMH levels are not associated with IR. In our study also, AMH levels were not correlated with measures of IR, similar to most studies.^[11,14-17,19-23,25] Nonetheless, a negative correlation has also been reported in literature attributable to the oxidative stress on ovarian granulosa cell function caused by IR.^[17,24,26,29,31]

Compared to PCOS women without MS, those with MS had a more adverse cardiometabolic risk profile in terms of measures of obesity, dyslipidemia, and IR, but AMH levels did not differ, in agreement with few reports.^[30] Additionally, AMH levels were comparable between those with and without IR and obesity, which conforms to certain studies.^[11,18,19,25] It is not surprising that an association between AMH and several adverse cardiometabolic parameters like HOMA-IR, WC, BMI, androgens, TC, and LDL-C has been found to be restricted only to obese PCOS cohort, thus hinting that the relationship between low AMH levels and cardiovascular risk is entirely explained by the strong inverse association between AMH and BMI.^[20,25,31] This means that early identification and treatment of obesity, IR, and MS in all PCOS women is priority to prevent future adverse cardiovascular events rather than triaging them based on AMH values as AMH levels do not directly influence the risk of these metabolic disorders.

Our study has some limitations, the main being the absence of an age and BMI-matched non-PCOS control group. The subjects evaluated in the present study were recruited from a tertiary care hospital on outpatient basis and do not reflect the true distribution of the general population. It is a cross-sectional study with small sample size so longitudinal changes in the relationship between AMH and cardiometabolic parameters cannot be assessed. Results cannot be applied to adolescent or perimenopausal PCOS as we studied women between 20

and 40 years. Number of participants aged 30 years and above was small, which may have obscured the relationship between AMH and conventional cardiometabolic risk factors, which tend to increase with advancing age. The discrepancies in the available evidence regarding the association between AMH and cardiometabolic risk factors could be due to considerable differences in geographical, ethnic, and anthropometric characteristics of study population, PCOS diagnostic criteria, study design and sample size, cutoffs used for defining MS, test assays, etc.

CONCLUSION

There is no correlation between AMH and components of MS in PCOS. AMH levels are comparable in those with and without MS, obesity, and IR. Therefore, serum AMH concentrations may not be useful as a predictor for cardiovascular risk, IR, or MS. Longitudinal cohort studies of large sample size and long-term follow-up are needed to investigate the nature, mechanisms, and direction of the complex relationship between AMH and cardiometabolic risk factors as reproductive age women with PCOS transition to menopause.

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Conflicts of interest

There are no conflicts of interest.

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