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Cardiometabolic markers and serum amh levels in PCOS: can AMH serve as a surrogate cardiometabolic markeR?

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Abstract

Objective To study the cardiometabolic markers in women in with polycystic ovary syndrome (PCOS) across all phenotypes and its correlation with serum anti-mullerian hormone (AMH) levels.

Methodology In cross-sectional community-based study aimed to determine the prevalence of PCOS among women aged 19–39 years over 5 years (2018–2022), 10,109 women were found to be eligible from 14,061 approached through a pre validated questionnaire. Out of this cohort, 201 women were diagnosed prior, and from the 2314 probable cases on detailed clinical, ultrasound and hormonal evaluation as per Rotterdam criteria, 860 were true cases. Healthy women from the same community matched for age and BMI, were taken as controls (1174). Both PCOS and healthy controls were assessed for cardio-metabolic indices, including anthropometry (BMI, Waist Circumference (WC), Waist to Hip Ratio (WHR), biochemistry (OGTT with 75 g glucose, lipid profile, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), visceral adiposity index [VAI], lipid accumulation product [LAP]) and fasting and post prandial insulin. Other hormone assays and AMH levels were also assessed in PCOS and controls. Correlation between serum AMH and cardiometabolic indices was calculated for cases using Pearson's method. Data was analysed using STATA version 18.

Main outcome measure(s) Cardio-metabolic profile including obesity/overweight, hypertension, insulin resistance, dyslipidemia among PCOS women and their different phenotypes, comparison with controls and correlation with serum AMH levels in cases.

Result(s) In the baseline characteristics, PCOS group had higher systolic and diastolic blood pressure, fasting blood sugar, 2 h oral glucose tolerance test (OGTT), fasting, 30 min and two hours post OGTT insulin levels than control group. In lipid profile, PCOS group had lower High Density Lipoprotein-Cholestrol (HDL-C) and higher low Density Lipoprotein-Cholestrol (LDL-C) levels. HOMA-IR, VAI, LAP were significantly higher in PCOS group. When AMH was correlated with various cardio-metabolic indices in women with PCOS, significant positive correlation was found with BMI, waist circumference, triglycerides and very low Density Lipoprotein cholestrol (VLDL-C) VLDL levels. While

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correlating AMH with cardio-metabolic indices in different phenotypes, PCOS phenotype A, C, and D suggested a significant positive correlation with BMI, waist circumference, post -prandial blood sugar at 30 min and VLDL-C, while phenotype B correlated only with BMI and VLDL levels.

Conclusion(s) A positive correlation could be seen between serum AMH and anthropometric and lipid profile parameters in Indian PCOS women. No such correlation can be established between other insulin resistance markers.

Keywords Polycystic ovary syndrome, Cardiometabolic markers, serum AMH levels

Introduction

Polycystic ovary syndrome is currently the commonest endocrinopathy among women in the reproductive age [1]. Symptoms of PCOS are seemingly unrelated to one another and the condition is often overlooked and under diagnosed especially in adolescents. Although, the disorder classically presents with features of an-ovulation and hyperandrogenism, a barrage of metabolic abnormalities are described which may manifest simultaneously or later in life and is a cause of concern, besides menstrual and reproductive dysfunctions [2, 3]. Currently PCOS is a significant public health problem in India including type 2 Diabetes Mellitus (DM) owing to its high prevalence and association with metabolic aberrations such as obesity, abnormal glucose tolerance, insulin resistance, metabolic syndrome, cardiovascular disease risk, sub-inflammation, fatty liver etc [2–5].

Women with PCOS exhibit unfavourable cardiometabolic biomarkers during their life span. Apart from the more established biomarkers such as BMI, visceral fat, insulin resistance (IR), and dyslipidemia, which cause an increase in the prevalence of Metabolic Syndrome, growing evidence supports the concept that inflammatory cytokines which negatively affect cardiovascular health [6, 7] are disturbed in PCOS women. Infertility is also increased among patients with PCOS [8] and serum antimullerian hormone promising single marker of ovarian reserve, has emerged as a surrogate in PCOS. The relationship between AMH and markers of cardiovascular health does not appear to be straightforward; large and small studies in regular cycling women with and without infertility have reported associations between AMH and various cardiometabolic parameters, but there is a lack of clarity around potential confounding effects of age and BMI [9–15]. Thus, there remains uncertainty over the degree to which AMH may reflect underlying cardiometabolic health in regularly cycling women or even with PCOS women. It is well established through cross-sectional data that women with PCOS are at increased risks of cardiometabolic disease compared to women without [2, 3]. However, the relationship between AMH level and cardiometabolic risk factors in a PCOS population remains unclear and needs further exploring. This study was therefore conducted to compare the differences in cardiometabolic parameters between PCOS and healthy controls and understand if this forms the biological basis of cardiovascular disease later in life.

Methodology

The ICMR-PCOS Task Force conducted a comprehensive study across various regions of India, covering both rural and urban areas in six geographical zones: North, South, East, West, Northeast, and Central India, to define the prevalence of the disease from a diverse country. The study complied with the Helsinki Declaration of 1975 and received approval from the institutional ethics committees at all ten participating sites (IEC, SKIMS, 107/2016). Written informed consent was obtained from all participants, ensuring they understood the study's purpose and potential consequences. To protect against COVID-19, face masks, hand gloves, and hand sanitizer were provided to the data collection team and participants.

This multicentre study recruited apparently healthy women aged 18 to 40 years using a multistage sampling technique from randomly selected polling booths in urban and rural areas of the six zones. The inclusion criteria were: women who were permanent residents of the area for more than one year and willing to participate in the study and sign an informed consent form. Women were excluded if they were hypothyroid, or detected hyperthyroid, sub-clinical hypothyroid, after hyperprolactinemia, type 2 diabetes, exogenous Cushing syndrome, premature ovarian failure, and hypopituitarism after an initial clinical and hormonal screening. Pregnant or lactating women and those with cognitive disorders preventing them from answering the questionnaire were also excluded.

Of the 14,061 subjects approached at all participating sites, 2841 were found to be ineligible. After the preliminary screening and refusals, a pre validated questionnaire was administered to a total of 10,109 subjects confirming 201 as diagnosed PCOS prior. From this eligible cohort, 2314 that seemed probable of PCOS, were subjected to detailed evaluation, including clinical, ultrasound and hormone estimation especially serum testosterone to confirm 860 as PCOS (cases) as per Rotterdam criteria. and 1174 as healthy controls.

Participants underwent a comprehensive clinical assessment, which included recording detailed medical histories and conducting physical examinations.

Measurements such as body weight, height, BMI, and waist circumference were taken using standard calibrated instruments (SECA 213, Hamburg, Germany). Blood pressure was measured with an electronic device (Omron HEM7120) and the average of three readings was used as the final value for each parameter. Additionally, all participants were evaluated for biochemical and hormonal parameters. An oral glucose tolerance test was administered after an overnight fast of 10–12 h. A total of 5 mL of venous blood was collected in a fasting state between days 2 and 7 of the menstrual cycle. The blood samples were immediately processed in a cold centrifuge and separated into aliquots for hormonal and other laboratory investigations. These aliquots were shipped to the coordinating centre in a cold chain (dry ice) and stored at -80 °C until analysis. Hormone levels—including serum total T4, thyroid-stimulating hormone (TSH), total testosterone, 17-OHP, cortisol, prolactin, luteinizing hormone, follicle-stimulating hormone, E2, C-peptide, insulin, and DHEAS—along with sex hormone-binding globulin (SHBG), were quantified using electro chemiluminescent immunosorbent assays on a (Cobas e411 analyser, Roche Diagnostics, Serum Anti Mullerian Hormone was measured in all samples using the Beckman Coulter (M/S Immunotech AMH Gen II ELISA kits. This kit uses the two-site 'sandwich' assay and has an analytical sensitivity of 0.08ng/ml. This method has got a validated correlation with the automated access AMH assay. The limit of detection for Gen II was 0.18 ngm/ml and the measurement range varied between 0.16 and 29.8 ngm/ml. To ensure accuracy, standards (reagents with known concentrations) were run daily to validate the hormone analyser and calibrated as needed according to the manufacturer's guidelines. Polycystic ovaries were defined as having at least 12 follicles measuring 2–9 mm in diameter, or an ovarian volume greater than 10 ml in at least one ovary. Antral follicle counts were done using transvaginal/transabdominal transducer (for TVS: 8.5 MHz; S-6, GE 3600 Healthcare, USA) where follicles between 2 and 8 mm were measured in three planes in each ovary. All scans were done by trained persons.

Data management and statistical analysis

Data were entered into Microsoft Excel database. Mean, median and standard deviations were computed for each of the biochemical and hormonal parameters of the study participants. Statistical analysis was carried out using Stata latest version. Pearson correlation coefficient was used to test correlation. All tests were considered significant with two-tailed $p < 0.05$.

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Results

As expected, in the baseline characteristics, PCOS group had higher systolic and diastolic blood pressure, fasting blood sugar, 2 h Oral Glucose Tolerance Test(OGTT), fasting, 30 min and two hours post OGTT insulin levels than control group (Table 1). In lipid profile, PCOS group

Table 1 Comparison of cardiometabolic markers between cases and controls

Cardiometabolic characteristic	PCOS (Definite) cases	Healthy Controls	*P* value
Age (years)	27.17 ± 6.30	27.90 ± 6.18	0.3064
BMI (Kg/m^2)	24.64 ± 4.34	24.44 ± 4.18	0.3064
Waist circumference (cms)	81.42 ± 11.70	80.98 ± 12.06	0.4110
Waist-to-Height ratio	0.38 ± 0.06	0.37 ± 0.06	0.1355
Systolic blood pressure (mmHg)	116.94 ± 12.15	115.86 ± 11.80	**0.0441**
Diastolic blood pressure (mmHg)	76.07 ± 8.51	75.10 ± 7.71	**0.0077**
Plasma glucose- fasting (mg/dl)	90.00 ± 16.32	88.66 ± 16.59	**0.0725**
Post OGTT glucose- 30 min (mg/dl)	139.16 ± 32.55	137.09 ± 31.37	0.1543
Post OGTT glucose- 2 h. (mg/dl)	110.35 ± 31.46	103.76 ± 25.63	**0.0001**
Fasting plasma insulin-(mIU/ml)	18.34 ± 21.40	13.30 ± 11.78	**0.0001**
Plasma insulin-30 min. post OGTT (mIU/ml)	62.95 ± 51.01	55.87 ± 39.06	**0.0006**
Plasma insulin-2 h post OGTT (mIU/ml)	41.58 ± 36.11	34.27 ± 26.16	**0.0001**
Cholesterol(mg/dl)	166.51 ± 36.04	163.39 ± 31.55	**0.0403**
Triglycerides (mg/dl)	124.71 ± 47.09	113.51 ± 41.81	**0.0001**
HDL-C (mg/dl)	43.67 ± 8.76	49.45 ± 11.00	**0.0001**
LDL-C (mg/dl)	97.92 ± 32.94	91.28 ± 31.75	**0.0001**
HOMA-IR	4.09 ± 4.91	2.95 ± 2.81	**0.0001**
VAI	2.40 ± 1.08	1.95 ± 0.95	**0.0001**
LAP	33.55 ± 22.81	29.98 ± 20.60	**0.0003**

had lower HDL-C and higher LDL-C levels. Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), visceral adiposity index (VAI), lipid accumulation product were significantly higher in PCOS group (Fig. 1). There were significant statistical differences regarding weight, waist circumference, systolic BP and diastolic BP ($P < 0.05$). While comparing lipid profile levels, there were no statistical significant differences between the PCOS phenotypes A, B, C, and D regarding triglyceride levels. However, the levels of total cholesterol and LDL-C were highest in phenotype D. HDL-C cholesterol in phenotype C was significantly higher comparing to the three other groups. The index HOMA-*IR* that assesses beta-cell function was statistically higher in the groups A (4.73 ± 6.2) and LAP was highest in phenotype C (36 ± 22.8) in comparison to other groups ($P < 0.05$). However, VAI did not show any statistical significance (Table 2).

When AMH was correlated with various cardio-metabolic indices in women with PCOS, significant positive correlation was found with BMI, waist circumference, triglycerides and VLDL levels (Table 3). While correlating AMH with cardio-metabolic indices in different phenotypes, PCOS phenotype A, C, and D suggested a significant positive correlation with BMI, waist circumference, post -prandial blood sugar at 30 min and VLDL, while phenotype B correlated only with BMI and VLDL levels(Table 4).

Discussion

PCOS is probably the most prevalent endocrinological disorder affecting females and is the most common cause of menstrual disturbance during reproductive age.

The mean age of the patient in PCOS group our study was 27.17 ± 6.30 years. Similar findings were found in the study reported in Nepal by Vaidya A et al. and Rajbanshi I et al. [14, 15]. PCOS is reported to be more prevalent in younger ages (< 35) than among older women, which can be attributed to a physiological decline of the follicular cohort [2].

In our study, the mean systolic blood pressure was 116.94 ± 12.15 mmHg and diastolic blood pressure was 76.07 ± 8.51 mmHg. Our findings are comparable to findings in the study done by Mellembakken et al. in which the mean systolic blood pressure was 118 ± 9.6 mmHg in women with PCOS compared to 110 ± 7.56 mmHg in controls and diastolic BP was 74 ± 7 mmHg vs. 70 ± 5.5 mmHg ($p < 0.001$) [16]. The mechanism underlying the increased prevalence of hypertension in PCOS has been linked to several factors such as hyperinsulinemia, hyperandrogenemia, and obesity [17].

Abnormal glucose was demonstrated in of the PCOS participants. Parameters like fasting blood sugar, 2 h OGTT were deranged in cases in comparison to control group. The insulin level at fasting, 30 min and 2 h of OGTT is significantly higher in PCOS group than control group. In some previous studies, no differences in fasting blood glucose levels were identified between the PCOS phenotypes and the control groups [18], while another study showed higher blood glucose levels in cases compared with control subjects [19]. The present study also showed that 2-h postprandial serum insulin levels were significantly higher in cases, which is in agreement with the results reported by Chae et al. [21]. This may suggest that postprandial hyperinsulinemia plays an important role in HA and ovarian function in women with PCOS.

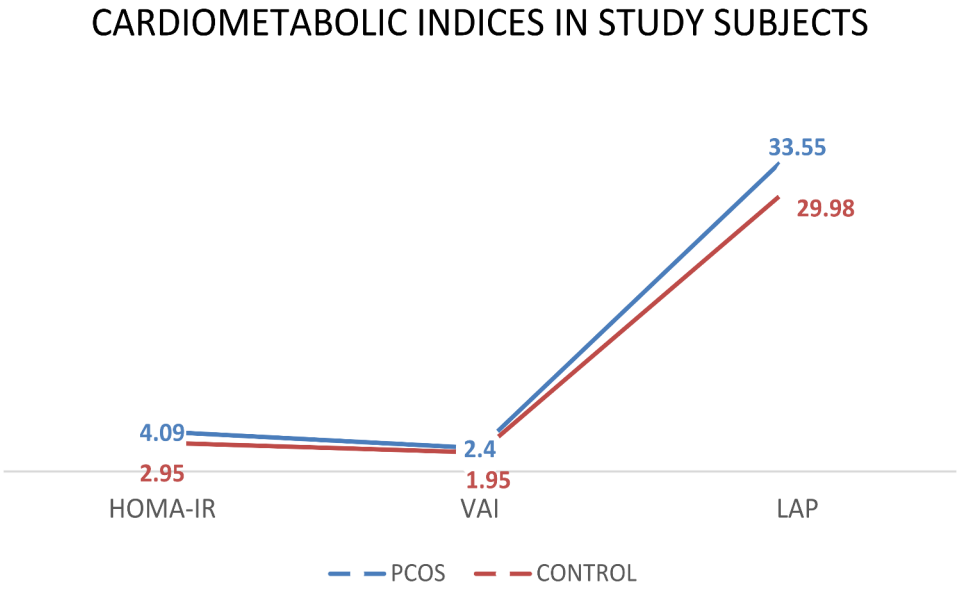

Fig. 1 Cardiometabolic Indices of PCOS

Table 2 Comparison of clinical, metabolic and hormonal profile of various PCOS phenotypes

	A (*n* = 156)	B (*n* = 119)	C (*n* = 310)	D (*n* = 187)	*p*
Weight (kg)	57.02 ± 10.23	57.9 ± 11.99	59.9 ± 10.78	58.5 ± 10.68	**0.042**
Waist to height ratio	0.37 ± 0.06	0.38 ± 0.07	0.38 ± 0.07	0.38 ± 0.06	0.168
BMI(Kg/m^2)	24.02 ± 4.07	24.6 ± 4.55	24.7 ± 4.33	24.6 ± 4.13	0.429
Waist circumference (cms)	79.6 ± 10.59	79.9 ± 12.2	82.5 ± 11.56	79.8 ± 11.59	**0.013**
SBP (mmHg)	115.9 ± 11.94	114.7 ± 13.11	117.7 ± 11.5	119.04 ± 13.04	**0.008**
DBP (mmHg)	74.9 ± 8.76	76.7 ± 7.94	77.7 ± 7.76	72.8 ± 9.23	**< 0.001**
Blood glucose (fasting) (mg/dl)	89.5 ± 11.04	88.41 ± 14.35	91.1 ± 18.69	88.7 ± 12.3	0.257
Blood glucose (30 min) (mg/dl)	140.1 ± 28.6	150.1 ± 28.62	137.2 ± 32.56	132.9 ± 32.18	**< 0.001**
Blood glucose (120 min) (mg/dl)	110.5 ± 29.56	121.2 ± 30.75	109.04 ± 30.03	105.3 ± 27.56	**< 0.001**
Insulin (fasting) (mIU/ml)	21.1 ± 27.42	17.5 ± 19.22	15.3 ± 13.58	17.2 ± 21.38	**0.032**
Insulin (30 min) (mIU/ml)	74.3 ± 66.35	70.5 ± 51.87	54.8 ± 35.03	52.7 ± 43.04	**< 0.001**
Insulin (120 min) (mIU/ml)	50.4 ± 46.39	44.7 ± 32.42	35.3 ± 27.44	35.7 ± 32.88	**< 0.001**
AMH(ng/ml)	7.3 ± 5.26	7.18 ± 5.26	7.28 ± 5.18	7.53 ± 5.53	0.432
SHBG(nmol/l)	56.4 ± 35.6	54.2 ± 38.3	58.1 ± 32.4	54.2 ± 29.6	0.561
17-OHP(ng/ml)	1.1 ± 2.72	0.6 ± 0.40	0.5 ± 0.42	1.4 ± 1.22	**< 0.001**
Serum Triglycerides (mg/dl)	122.2 ± 49.89	119.1 ± 49.3	128.8 ± 47.2	123.6 ± 46.5	0.219
Serum Cholesterol (mg/dl)	160.1 ± 33.3	169.2 ± 33.5	169.5 ± 36.3	169.5 ± 40.2	**0.043**
LDL (mg/dl)	94.1 ± 23.05	98.7 ± 24.28	96.6 ± 21.95	103.9 ± 36.56	**0.037**
HDL (mg/dl)	43.6 ± 9.32	41.9 ± 8.54	44.6 ± 8.29	44.2 ± 9.55	**0.037**
HOMA-IR	4.73 ± 6.2	3.69 ± 3.9	3.43 ± 3.1	3.80 ± 4.8	**0.029**
VAI	2.38 ± 1.29	2.36 ± 1.26	2.43 ± 1.01	2.29 ± 0.99	0.626
LAP	30.6 ± 21.3	29.5 ± 22	36 ± 22.8	31.2 ± 21.9	**0.008**

Table 3 Correlation of cardiometabolic markers with AMH in cases

AMH	*r*	*P*
BMI (Kg/m^2)	0.37966	**< 0.001**
Waist circumference (cms)	0.02088	**< 0.001**
Plasma glucose- fasting (mg/dl)	0.0342	0.2849
Post OGTT glucose- 30 min (mg/dl)	0.0081	0.7984
Post OGTT glucose- 2 h. (mg/dl)	0.0154	0.6290
Fasting plasma insulin-(mIU/ml)	0.0250	0.4346
Plasma insulin-30 min. post OGTT (mIU/ml)	0.0086	0.7866
Plasma insulin-2 h post OGTT (mIU/ml)	0.0078	0.8059
Cholesterol (mg/dl)	0.0236	0.4599
Triglycerides (mg/dl)	0.0655	**0.0405**
HDL (mg/dl)	0.0130	0.6841
VLDL (mg/dl)	0.0970	**0.0023**
LDL (mg/dl)	0.01	**0.8604**

Chae et al. also reported that there were no differences in HOMA-IR scores among the PCOS phenotypes, although there were significant differences between PCOS group and the control group, which is also in accordance with our results [20].

In this community-based study, with appropriate sample size, we found that lipid abnormalities among women with PCOS were more prevalent when compared to a healthy population. In agreement with these findings, a similar pattern of dyslipidemia has been described in women with PCOS [21–23]. Further, Wild et al. in a meta-analysis, reported that women with PCOS have higher LDL-C and non-HDL-C, regardless of BMI [24].

There is strong evidence that shows an association of higher triglycerides levels with IR, altered glucose tolerance and increased cardiovascular risk in the future [25].

Some bodies of literature support the association between PCOS, obesity, IR and metabolic disorders [26, 27]. The adiposity indicators of VAI and LAP include both anthropometric, and lipid parameters and have been proposed as valuable indicators of visceral adipose function [28]. They are known to reliably predict IR, metabolic syndrome, cardiovascular events and all-cause mortality in non-diabetic patients. Our study showed that both VAI and LAP values in women with PCOS, particularly in severe phenotypes of PCOS, are significantly higher than in healthy women. However, since both VAI and LAP are indicators based on TG, we hypothesized that a higher level of these indicators might highly correlate with higher level of TG in severe phenotypes of PCOS. Some studies supported these findings that showed the higher values of VAI and LAP among women with PCOS compared to non-PCOS counterparts [29–31].

While comparing the various phenotypes, fasting blood sugar was not statistically significant whereas blood sugar levels at 30 min and 120 min after OGTT with 75 g glucose were lowest in phenotype D. Similar findings were there in a study conducted by Zhang et al. [32] when AMH was correlated with various cardiometabolic

Table 4 Correlation of AMH with various other cardiometabolic indices in different phenotypes of cases (PCOS)

	Phenotype A		Phenotype B		Phenotype C		Phenotype D	
	r	*P*	r	*p*	r	*p*	R	*P*
BMI (Kg/m^2)	0.3772	**0.0045**	0.2160	**0.0014**	0.3056	**0.0073**	0.4155	**<0.001**
WC (cms)	0.2586	**0.0566**	0.0772	0.2576	0.1815	0.1166	0.2107	**0.0215**
BG (Fasting) (mg/dl)	0.1447	0.2920	-0.0106	0.8767	0.0670	0.5651	0.0291	0.7534
BG PP 30 (mg/dl)	0.3464	**0.0096**	-0.0221	0.7462	0.2995	**0.0086**	0.0932	0.3132
BG PP120 (mg/dl)	0.2256	0.0977	-0.0031	0.9639	0.2107	0.0677	0.0555	0.5490
INSULIN(F) (mIU/ml)	0.1422	0.3003	0.0548	0.4218	0.1235	0.2879	0.0599	0.5178
INSULIN30 (mIU/ml)	0.2061	0.1311	0.1174	0.0845	0.1596	0.1686	0.0796	0.3894
INSULIN120 (mIU/ml)	0.1355	0.3240	0.0710	0.2980	0.0891	0.4442	0.0264	0.7759
CHOLESTROL (mg/dl)	0.0311	0.8216	0.0115	0.8665	0.0504	0.6652	0.1403	0,1281
HDL (mg/dl)	-0.0061	0.9648	0.0145	0.8317	-0.0954	0.4124	0.1134	0.2194
TG (mg/dl)	0.1837	0.1794	0.1294	0.0570	0.1340	0.2484	0.1154	0.2114
VLDL (mg/dl)	0.2882	**0.0329**	0.1753	**0.0097**	0.2231	0.0527	0.1931	**0.0354**

indices, significant positive correlation was found with BMI, waist circumference, triglycerides and VLDL levels.

In National Health and Nutrition Examination Survey, Anti-Müllerian Hormone Levels and Cardiometabolic Disturbances by Weight Status Among Men in the 1999 to 2004 were studied, AMH was associated with specific cardiometabolic risk factors, including WC, diabetes status, and insulin resistance, in overweight and obese US men [33]. Also, in a recent study, it was observed that serum AMH level is associated with HOMA-IR, triglycerides, HDL-C, and adiponectin levels, and hence it may be used as a potential cardiometabolic risk marker in women with PCOS [34]. However on the contrary, it was seen in a recent Indian study that AMH levels do not correlate with components of metabolic syndrome so it may not be useful as an indicator of cardiovascular risk, insulin resistance, or MS in PCOS [35].

In a similar study very recently, menstrual cycle length, serum testosterone, fasting total cholesterol levels, and follicle number per ovary had positive correlation with serum AMH levels ($P<0.05$) and interpreted high serum AMH levels in PCOS are associated with worse clinical, endocrinological, and metabolic parameters. These levels may be used to counsel patients regarding treatment response, help in individualized management and prediction of reproductive and long-term metabolic outcomes [13].

This is the first study of its kind among Indian PCOS women which may shed light on differences in phenotypes and their correlation with AMH with a large sample size. There is variation in the AMH assay method used in previous studies with most studies using the Diagnostic Systems Lab (DSL) assay and only few studies using the more accurate Gen II ELISA as used in our study. The limitations of our study were that the study population consisted of all types of PCOS women (both fertile and sub-fertile), and did not include the adolescent PCOS.

Conclusion

There is controversy in literature on correlation of hormonal and metabolic.

parameters in different phenotypic groups. A positive correlation between serum AMH and BMI, waist circumference, triglycerides and VLDL levels could be established in Indian PCOS women, however no significant correlation was found with other insulin resistance markers. Further larger prospective studies are needed to conclusively establish the metabolic and hormonal patterns across the PCOS phenotypic spectrum.

Abbreviations

AMH	Anti-mullerian hormone
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
LAP	Lipid accumulation product
OGTT	Oral glucose tolerance test
PCOS	Polycystic ovary syndrome
VAI	Visceral adiposity index

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Author contributions
NM, MAG, SK, TK wrote the main manuscript text. NM, MAG, RR, SA, PKJ, RS, SC, PKB recruited patients and ran thee project and KI prepared stats. MAG procured fund for the entire project. All authors reviewed the manuscript.

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Data availability
Data shall be provided on a considerable request to corresponding author.

Declarations

Ethics approval
Ethics approval was taken from all the respective sites with SKIMS being the coordinating centre(IEC, SKIMS, 107/2016).

Consent for publication
All the subjects provided a written informed consent.

Competing interests
The authors declare no competing interests.

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