Diagnostic Utility of Anti-mullerian hormone levels in different Phenotypes of Polycystic ovary syndrome - A Hospital based Case-Control study.

Naveen Charantimath[1], Pallavi Charantimath[2], Manjula Rangappa[3]

[1]Department of Endocrinology, [2]Department of Paediatrics, [3]Department of Community Medicine,
S. Nijalingappa Medical College and HSK Hospital & Research Center, Bagalkote, Karnataka, India

Abstract

Background: Polycystic ovary syndrome (PCOS) is considered to be a multifaceted disease with a spectrum of manifestations affecting not only women of childbearing age, but also adolescents and postmenopausal women. Anti-Müllerian hormone (AMH) is an important regulator of folliculogenesis in the ovaries. It is secreted by granulosa cells of the ovarian follicles and its serum levels are elevated two to three fold in women with PCOS in comparison with normo-ovulatory women, consistent with the increased number of small antral follicles in PCOS. Different phenotypes of PCOS which varied etiopathology, might have different impact on AMH levels, which could help in the diagnosis and management of such cases.

Objectives: To Estimate and compare the Anti-mullerian hormone levels in different phenotypes of polycystic ovary syndrome patients and healthy controls. To study the diagnostic accuracy of AMH in different Phenotypes of PCOS patients.

Materials and Methods: This Institute based case-control study was conducted in Endocrinology Department, tertiary health centre, North Karnataka from March 2022-Febraury 2023. This study includes the PCOS patients, newly diagnosed based on Rotterdam criteria and healthy controls.

Results: In the present study the common PCOS phenotype was phenotype A (40%) followed by B (30%), C (20%) and D (10%). The median AMH levels in phenotype A were significantly high (12 [6.97 IQR] ng/mL) compared to phenotype B (6.25 [0.98 IQR] ng/mL), phenotype C (4.11 [1.05 IQR] ng/mL) and phenotype D (4 [1.83 IQR] ng/mL) ($p<0.001$). Serum AMH levels were at higher range in Phenotype A and B, and also the diagnostic accuracy was maximum for Phenotype A and B, with 60.22 % and 55.56% respectively.

Conclusions: This study concludes that the AMH levels helps to understand the clinical phenotypes of PCOS and also has an implication in the management of the condition.

Key words: Polycystic ovary syndrome, Phenotypes, Anti-mullerian hormone

Introduction:

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women, presenting with several possible combinations of signs and symptoms and a range of phenotypes, which may include reproductive, endocrine, and metabolic alterations. PCOS is characterized by hypothalamic–pituitary–ovarian axis dysfunction and anovulation but, unlike other causes of ovulatory failure that feature insufficient ovarian follicle growth or suppressed gonadotropin secretion (or both), PCOS typically includes androgen excess and subtle alterations (not detected by routine tests) in serum levels of gonadotropins and estrogens. The clinical manifestations of PCOS include oligomenorrhoea, hirsutism, excessive acne and hair loss. In adolescence, it causes significant psychiatric disturbances such as anxiety and depression. PCOS is the leading cause of anovulatory infertility in women. PCOS has the potential for serious consequences, including increased risk for the development of endometrial hyperplasia and neoplasia. Furthermore, extra-reproductive manifestations of PCOS include insulin resistance (IR), metabolic syndrome (MS), and low-grade chronic inflammation[1].

Address for Correspondence:

Dr. Manjula R

Professor, Department of Community Medicine,
SNMC and HSK Hospital & Research Centre, Bagalkote, Karnataka, India.
Email: drmanjulakashinakunti@gmail.com

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in reproductive age affecting 5-10% of women, and is the leading cause of ovulatory dysfunction[2-5]. Based on the limited data, the prevalence of PCOS in India ranges from 3.7 to 22.5%[6].

Polycystic ovary syndrome (PCOS) is considered to be a multifaceted disease with a spectrum of manifestations affecting not only women of childbearing age, but also adolescents and postmenopausal women. The exact etiology and pathogenesis of PCOS are still an area of active research, although multiple hypotheses have been postulated, ranging from genetic susceptibility to environmental exposure, both *in utero* and in the postnatal life[6].

Anti-Müllerian hormone (AMH) is an important regulator of folliculogenesis in the ovaries[7]. It is secreted by granulosa cells of the ovarian follicles and its serum levels are elevated two to three fold in women with PCOS in comparison with normo-ovulatory women, consistent with the increased number of small antral follicles in PCOS[8,9]. However, it is unclear whether AMH is simply a marker which is increased in PCOS, or actually an important contributing factor to its pathophysiology.

Owing to the phenotypic heterogeneity of PCOS, when a patient is diagnosed with PCOS, an additional brief description of the specific PCOS criteria that she meets would help the patient and the healthcare professionals involved in her care to understand the health consequences of such a diagnosis, thereby facilitating her peace of mind and her correct long-term medical management. In essence, this improvement in diagnostic information might be accomplished by identifying the individual's particular PCOS phenotype as recommended by the 2012 Evidence Based Methodology Workshop on Polycystic Ovary Syndrome[10].

Phenotypes of polycystic ovary syndrome[10]

- Phenotype A - Hyperandrogenism and ovulatory dysfunction.
- Phenotype B - Hyperandrogenism and polycystic ovarian morphology.
- Phenotype C - Oligo-ovulation and polycystic ovarian morphology.
- Phenotype D - Hyperandrogenism, oligo-ovulation and polycystic ovarian morphology.

However, it is the usual practice to include even more detailed descriptionsin the clinical reports of the patients, differentiating between clinical and biochemical androgen excess and giving information on the specific metabolic alterations experienced by each particular patient[11].

Objectives: To Estimate and compare the Anti-mullerian hormone levels in different phenotypes of polycystic ovary syndrome patients and healthy controls. To study the diagnostic accuracy of AMH in different Phenotypes of PCOS patients.

Materials and Methods.

Institutional Ethical clearance was obtained. This Institute based case-control study was conducted in Endocrinology Department, tertiary health centre, North Karnataka from March 2022-Febraury 2023.

Data collection procedures: Informed consent was obtained from the study subjects. All the eligible women presenting with clinically suspected PCOS and diagnosed based on Rotterdam 2013 criteria[12], during the study period were enrolled and 60 apparently healthy females were selected as controls.

Inclusion criteria: Cases: Clinically newly diagnosed PCOS cases based on Rotterdam criteria,[12] two out of three criteria are required for the diagnosis of PCOS: oligo- or anovulation, clinical or biochemical hyperandrogenism and/or polycystic ovaries on ultrasound. **Controls**: Apparently healthy females without endometriosis, cysts, or other ovarian gynecological disorders; had regular menstrual cycles (26–35days); did not have endocrine abnormalities and had morphologically normal ovaries according to ultrasound referred to Department of Endocrinology.

Exclusion criteria: Non-classical Congenital adrenal hyperplasia, Cushing's syndrome, thyroid dysfunction, hyperprolactinemia, and androgen-producing tumors patients. Patients at presentation are receiving medications that could alter the endocrine and metabolic parameters under investigation for the above disorders.

Predesigned proforma was used for collecting and documenting the data. Women were interviewed for demographic data such as age and clinical presentation were noted along with detailed medical and obstetric history. Following which patients were subjected to physical examination. The selected women were examined for anthropometry, vitals, systemic examination and clinical signs including acne, acanthosis nigricans, skin tag and hirsutism. Further these women underwent the following investigations. Under aseptic precautions blood samples were taken and sent to laboratory. The patients were evaluated for following biochemical variables using Snibe Maglumi 1000 autoanalyser

- Fasting Blood Sugars (OGTT) and Fasting Insulin
- Serum Testosterone (8am Fasting)
- Free Testosterone (if necessary)

- SHBG (if necessary)
- Serum DHEAS.
- 17 hydroxyl progesterone (if necessary)
- Free androgen index (FAI): total testosterone *100/ SHBG
- Serum TSH
- Serum Prolactin
- Fasting Lipid Profile - Triglycerides, total cholesterol, High density lipoprotein, low density lipoprotein.
- Imaging - USG pelvis

Estimation of Anti-Mullerian hormone

A total of 8 ml was withdrawn and put equally in 2 plain vials on day 2–3 of menses or after withdrawal bleeding. Samples were then centrifuged at 3000 rpm in centrifugation machine at the biochemistry laboratory for serum analysis. Analysis for AMH levels was done using Serolisa Human AMH elisa Kit.

ELISA for the quantitative measurement of human AMH level in serum or plasma (Ref KT-804)[13].

Diagnosis of PCOS

A comprehensive clinical history was obtained from all the participants. Physical examination Patients were classified as PCOS cases and controls according to the inclusion and exclusion criteria mentioned above.

Patients were classified into four PCOS phenotypes as below[12,14].

	Phenotype A	Phenotype B	Phenotype C	Phenotype D
Hyperandrogenism and hirsutism	Present	Present	Present	Absent
Ovulatory dysfunction	Present	Present	Absent	Present
Polycystic ovarian morphology	Present	Absent	Present	Present

Statistical Analysis

The data was analyzed using statistical software SPSS version 20.0.Continuous variables were presented as mean±standard deviation (SD) or median and interquartile (IQR) range and analyzed for normality by the Shapiro-Wilk test. Categorical variables were compared using the Chi-square or Fisher's exact testwhile continuous variables were compared using Mann-Whitney U tests. The continuous data pertaining to different PCOS phenotypes was compared usingKruskal Wallis test. To determine cut off value of AMH in predicting PCOS was bydetermined by receiver operating characteristic curve, sensitivity, specificity,positive predictive value (PPV) negative predictive value (NPV), All tests were two tailed and a p-value of less than 0.05 was considered significant.

Results

Table 1: Distribution of study subjects according to Phenotypes of PCOS.

PCOS Phenotypes	Distribution	
	Number	Percentage
Phenotype A (Classic PCOS)	24	40.00
Phenotype B (Non PCO PCOS)	18	30.00
Phenotype C (Ovulatory PCOS)	12	20.00
Phenotype D (Non hyperandrogenic PCOS)	6	10.00
Total	60	100.00

In the present study the common PCOS phenotype was phenotype A (40%) followed by B (30%), C (20%) and D (10%). (Table 1)

Table 2: Comparison of AMH in PCOS phenotypes

PCOS phenotypes	n	AMH (ng/mL)	
		Median	IQR
Phenotype A (Classic PCOS)	24	12.00	6.97
Phenotype B (Non PCO PCOS)	18	6.25	0.98
Phenotype C (Ovulatory PCOS)	12	4.11	1.05
Phenotype D (Non hyperandrogenic PCOS)	6	4.00	1.83
Controls	60	2.03	1.02

p < 0.001;

The median AMH levels in phenotype A were significantly high (12 [6.97 IQR] ng/mL) compared to phenotype B (6.25 [0.98 IQR] ng/mL), phenotype C (4.11 [1.05 IQR] ng/mL) and phenotype D (4 [1.83 IQR] ng/mL) (p<0.001). (Table 2)

Table 3: Comparison of PCOS clinical profile in different phenotypes

Parameters	Type A (n=24)		Type B (n=18)		Type C (n=12)		Type D (n=6)		p value
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	
Age (Years)	19.00	5.75	18.50	5.25	25.50	5.75	19.00	5.75	0.686
No. of cycles per year	8.00	5.00	7.00	2.50	11.00	1.00	7.50	2.75	<0.001
Length of cycle (days)	90.00	30.00	90.00	33.75	34.00	14.00	90.00	11.25	<0.001
Age at menarche (Years)	13.00	2.00	13.00	2.00	12.00	1.75	12.50	3.00	0.913
Hirsuitism (FG score)	6.00	2.00	6.00	4.00	6.00	3.00	1.50	4.00	0.002
Height (Cms)	154.50	10.75	151.50	8.25	152.50	8.50	151.00	8.25	0.434
Weight (Kg)	69.00	24.00	61.00	21.91	67.00	15.50	56.00	14.75	0.279
Body mass index (Kg/m2)	27.35	5.87	26.65	8.40	28.75	5.58	25.60	6.53	0.749
Waist circumference(cm)	88.00	27.25	86.00	9.25	87.50	14.00	85.00	22.00	0.743
Waist hip ratio	0.90	0.07	0.90	0.11	0.91	0.09	0.84	0.14	0.619
Pulse rate (/Minute)	84.00	7.00	82.00	4.00	81.00	8.00	83.00	8.00	0.385
Systolic blood pressure (mm Hg)	112.00	12.00	110.00	10.25	110.00	9.50	111.00	13.50	0.193
Diastolic blood pressure (mm Hg)	80.00	17.50	80.00	10.00	80.00	11.00	80.00	3.00	0.952

It was observed that there was altered PCOS profile in clinical (Median and Inter-quartile range) across different phenotypes. Difference in Number of menstrual cycles, Length of Menstrual cycles and Hirsutism was found to be statistically highly significant (<0.001) (Table 3)

Table 4: Comparison of PCOS biochemical profile in different phenotypes

Parameters	Type A (n=24)		Type B (n=18)		Type C (n=12)		Type D (n=6)		p value
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	
Antimullerian hormone (ng/ml)	12.00	6.97	6.25	0.98	4.11	1.07	4.00	1.83	<0.001
Fasting blood sugar (mg/dL)	94.00	25.75	81.00	25.75	87.50	24.00	84.00	19.25	0.186
Oral glucose tolerance test (2hrs)	132.00	46.00	102.50	29.75	111.50	17.00	112.00	36.00	0.004
Fasting insulin (microU/ml)	32.00	15.19	13.00	12.90	12.00	6.42	6.25	6.75	<0.001
HOMA IR	6.92	4.69	2.53	3.08	2.33	2.02	1.41	1.65	<0.001
McAuley index	31.27	15.47	12.26	12.80	11.25	6.44	5.52	6.43	<0.001
Serum Testosterone (Fasting) ng/dl	67.33	45.04	58.50	15.35	54.00	15.18	33.00	11.24	<0.001
Serum Testosterone (nmol/l)	2.34	1.56	2.03	0.53	1.87	0.53	1.15	0.39	<0.001
SHBG(nmol/L)	18.42	10.28	33.10	29.92	21.19	15.68	23.75	30.96	0.317
Free androgen index (FAI)	13.56	11.08	7.67	8.02	9.88	6.53	4.84	5.64	0.007
Serum TSH (microU/ml)	4.37	3.39	3.58	3.38	3.10	1.71	2.08	2.53	0.194
Serum Prolactin (ng/ml)	13.00	9.47	8.00	5.27	7.50	7.25	9.00	4.75	0.053
Total cholesterol (mg/dL)	190.00	50.25	184.50	62.00	207.00	86.00	170.00	73.00	0.690
High density lipoprotein (mg/dL)	43.00	11.00	41.50	10.75	51.00	21.50	43.00	5.75	0.516
Low density lipoprotein (mg/dL)	105.00	36.00	106.50	48.25	102.00	51.50	93.00	70.50	0.984
Triglyderides (mg/dL)	194.00	47.50	165.00	44.25	161.50	87.00	170.50	72.00	0.290
Triglycerides (mmol/L)	10.78	2.64	9.17	2.46	8.97	4.83	9.47	4.00	0.290

It was observed that there was altered PCOS profile in biochemical parameters (Median and Inter-quartile range) across different phenotypes. Difference in AMH, OGTT, Fasting Insulin, HOMA IR, Mc Auley index, Serum testosterone, Free androgen index were found to be statistically highly significant (<0.001) (Table 4)

Table 5: Diagnostic validity of AMH levels (cutoff 3.59) in Different Phenotypes.

Phenotypes	AMH (>3.59 ng/mL)	Sensitivity	Specificity	Positive Predictive value	Negative Predictive value	Diagnostic Accuracy
A	24	88.89%	48.48%	41.38%	91.43%	60.22%
B	18	100%	44.44%	31.03%	100%	55.56%
C	11	91.67%	39.74%	18.97%	96.88%	46.67
D	2	66.67%	35.71%	6.90%	93.75%	37.78%

In the present study, the diagnostic potential of AMH were determined by ROC curve and ROC curve yielded with a cut off value of 3.59 ng/mL for AMH with maximum sensitivity (95%) and specificity (96.66%) and AUC of 0.988 (SE=0.008; p<0.001; 95% CI=0.972 to 1.000).

In the present study PCOS phenotype A was diagnosed in 24 cases. Of them, all of women had AMH levels of ≥ 3.59 ng/mL (100%). The accuracy of AMH with cut-off value of ≥ 3.59 ng/mL showed DA of 60.22% with sensitivity of 88.89%, specificity of 48.48%, PPV of 41.38%, NPV of 91.43%.

PCOS phenotype B was diagnosed in 18 cases. Of them, all of women had AMH levels (100%). The accuracy of AMH with cut-off value of ≥ 3.59 ng/mL showed DA of 55.56% with sensitivity of 100%, specificity of 44.44%, PPV of 31.03%, NPV of 100%.

In Type C, The accuracy of AMH showed DA of 46.67% with sensitivity of 91.67%, specificity of 39.74%, PPV of 18.97%, NPV of 96.88%. In them, most of women had AMH levels of ≥ 3.59 ng/mL (66.67%).

The accuracy of AMH with cut-off value of ≥ 3.59 ng/mL among Phenotype D showed DA of 37.78% with sensitivity of 66.67%, specificity of 35.71%, PPV of 6.90%, NPV of 93.75%. (Table 5)

Discussion

Polycystic ovary syndrome is the common endocrinopathy in reproductive age affecting 5 to 10% of women. It is the leading cause of ovulatory dysfunction[2-5]. According to the Rotterdam 2003 consensus, two out of three criteria are required for the diagnosis of PCOS: oligo- or anovulation, clinical or biochemical hyperandrogenism and/or polycystic ovaries on ultrasound[12]. A total of 90 participants that is, 60 patients with PCOS (Cases) and 30 apparently healthy females (Controls) were studied. The selected women were evaluated for obesity, AMH, blood sugar levels, insulin resistance and lipids. In the present study, the diagnostic potential of AMH were determined by ROC curve and ROC curve yielded with a cut off value of 3.59 ng/mL for AMH with maximum sensitivity (95%) and specificity (96.66%) and AUC of 0.988 (SE=0.008; p<0.001; 95% CI=0.972 to 1.000).

Based on the cut-off of value ≥ 3.59 ng/mL, significantly higher number of women with PCOS had AMH levels of ≥ 3.59 ng/mL (95%). The accuracy of AMH with cut-off value of ≥ 3.59 ng/mL in the diagnosis of overall PCOS showed higher DA (95.96%), sensitivity (95%), specificity (96.67%), PPV (98.28%) and NPV (90.63%). The PLR was very high (28.50) with minimum NLR (0.50) and higher RR that is 29.48 (95% CI=4.29 to 202.58). Although the higher accuracy observed for overall PCOS and PCOS phenotype A, which was not observed in other phenotypes that is, phenotype B, C and D which can be explained by the smaller subset of women with phenotype B (n=18), C (n=12) and D (n=6) and prompt further studies with adequate sample size with PCOS phenotypes.

The higher accuracy of AMH observed in the present study for the diagnosis of PCOS strongly corroborates with a recent study by Saxena U. et al[15]. (2018) who reported the best diagnostic potential of AMH at cut-off of 3.44 ng/ml with sensitivity and specificity of 77.78% and of 68.89%, respectively which is similar to the present study. In another Indian study by Saikumar P. et al[16]. (2013) a cut-off of 3.34 ng/mL yielded higher sensitivity and specificity of 98% and 93%, respectively which was also consistent with the present study. The AMH cut-off value noted in the present study was also in congruence with previous studies by Wiweko B et al[17].

Few studies reported higher sensitivity and specificity but at a higher cut-off of 7.82 ng/ml and 7.3 ng/ml, respectively.[18,19,20] In contrast Dewailly D et al.[21] (2011) observed a higher sensitivity and specificity of 92% and 97%, respectively, at a cut-off of 4.9 ng/ml and concluded that AMH not only reflects AFC but also the degree of hyperandrogenism making AMH a better marker than follicle numbers per ovary. However, Homburg R. et al.[22] (2013) reported a high specificity of 98.2% but a low sensitivity of 60% of AMH at cut-off of 6.7 ng/mL. Li Y et al.[20] (2012) reported a low sensitivity and specificity of AMH of 62% and 65%, respectively, at a cut-off of 3.92 ng/ml with higher AMH in patients having hyperandrogenism. Higher cut-off of 4.7 ng/ml with sensitivity of 79.4% and specificity of 82.8% was reported in a metanalysis by Iliodromiti S. et al.[23] (2013). Some studies have reported that there was

increased AMH levels in Phenotype A which is similar to our study. AMH with a cut-off value of 3.59 ng/mL in highly accurate in discriminating PCOS among the women presenting with features of PCOS. [24,25,26] There is significant strong linear relationship between AMH with hyperandrogenism as well as insulin resistance in women with PCOS. It significantly varies with PCOS phenotypes. Phenotype A having the highest levels followed by phenotype B while phenotypes C & D have similar lower levels. There is significant strong linear relationship between AMH with hyperandrogenism as well as insulin resistance in women with PCOS. Further, women with PCOS are at significant risk of developing insulin resistance, diabetes mellitus and dyslipidemia.

Conclusion: This study helps us to understand that the AMH levels helps to understand the clinical phenotypes of PCOS and also has an implication in the management of the condition. The AMH levels were higher in Phenotypes A and B and it correlates with the clinical severity of PCOS.

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