http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v7i11.153

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Anti-mullerian Hormone as a Diagnostic Marker of Polycystic Ovarian Syndrome in a Tertiary Care Centre in Eastern India

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Abstract:
Introduction: *It has been posited that elevated AMH due to follicular excess, rather than facilitating ovulation, plays a critical role in the arrest of follicular growth that is characteristic of PCOS. Since 2003, the diagnostic criteria for PCOS particularly TVS which have problem with acceptance included an assessment of the follicular pool by specific ultrasound findings. There is support for the notion that AMH serves as a surrogate marker for the antral follicle count in the diagnosis of PCOS.*
Aims: *Anti-mullerian hormone level in the polycystic ovarian syndrome and it association with clinical parameters.*
Material and Method: *observational Cross-sectional study carried out in the department of Endocrinology and metabolism, Medical College, Kolkata from march 2017 to January 2019.Total number of study subjects were 207 out of which 138 were cases.*
Results: *The mean AMH were significantly higher in the case as compare to control group with a value of 11.15±4.6 ng/ml and 3.68±2.09 ng/ml respectively. The Spearman s rank (rho) correlation of Anti – mullerian Hormone with ovarian morphology and AMH is strongly and significantly associated with ovarian volume (r = 0.506, p<0.00) and follicular number (r= 0.0582, p <0.001) case group. ROC curve of the AMH: ROC curve was drawn to determined the cut-off of AMH in our PCOS population showed the cut-off AMH > 5.06 ng/ml with the sensitivity & specificity of 97.8% and 80.4% respectively.*
Keywords: *Anti Mullerian hormone , ovarian volume , follicular size , follicle count.*

Introduction

Polycystic ovarian syndrome (PCOS) is most common endocrine abnormality in women of reproductive age. Several studies of diverse populations have estimated its prevalence at 6% - 10%[1-3]. The first description of PCOS was given by Stein and Leventhal in 1935.They described a constellation of amenorrhea, oligomenorrhea, obesity and hirsutism in presence of polycystic ovary. The disorder has since being known as PCOS, although considerable change in its definition and known path physiology has occurred. Most patients with PCOS have metabolic abnormalities such as insulin resistance

with compensatory hyperinsulinemia, obesity, and dyslipidemia. All of these metabolic features may play a role in the development of glucose intolerance or type 2 diabetes mellitus and hypertension, thereby increasing cardiovascular diseases[4,5]. Although the cause of PCOS is still unknown, there are several hypotheses attempting to explain the primary defect; the most commonly accepted is insulin resistance. Insulin resistance in PCOS results in hyperinsulinemia with its associated diverse and complex effects on regulating lipid metabolism, protein synthesis and modulation of androgen production[6].

AMH is a dimeric glycoprotein member of the TGF family. In women, AMH is derived primarily from prenatal and early antral follicle sand has been shown in recent years to accurately reflect the follicular pool .Serum AMH has also been evaluated in women with polycystic ovary syndrome (PCOS). Women with this disorder have an increased preantral & early antral follicular pool and frequently present with oligo- or anovulation.

Since 2003, the diagnostic criteria for PCOS particularly TVS which have problem with acceptance included an assessment of the follicular pool by specific ultrasound findings(9). There is support for the notion that AMH serves as a surrogate marker for the antral follicle count in the diagnosis of PCOS(10–16), and it has been posited that elevated AMH due to follicular excess, rather than facilitating ovulation, plays a critical role in the arrest of follicular growth that is characteristic of PCOS(17,18). An association between the high circulating AMH in women with PCOS and their chronic anovulation has long been noted, and appears to be due to several mechanisms. First; AMH directly inhibits aromatase activity in human and rodent granulosa cells (19,20,21).

Aims

To evaluate the association of Anti-mullarian hormone with clinical parameters of adolescents and young women of polycystic ovary syndrome (PCOS). And the prevalence of AMH level in the patient of Poly cystic ovarian syndrome in our population.

Material and Method

This was a single centre observational Cross-sectional study carried out in the department of Endocrinology and metabolism, Medical College, Kolkata from march 2017 to January 2019

Total number of study subjects were 207 out of which 138 were cases**.** The power of study was 90%.

Adolescents and young woman of reproductive age group between 16-40 yrs attended the in-patient and outpatient clinic of the Department of Endocrinology and metabolism in whom PCOS was diagnosed according to the Rotterdam criteria and participated by signing the consent form. Subject should had least two of the following elements

1. Hyperandrogenism (H): Modified Ferriman-Gallwey score ≥8 or serum total testosterone (TT) ≥80 ng/dL (≥2.77 nmol/L)(22).
2. Ovulatory dysfunction (O): Oligomenorrhea (cycles longer than 35 days OR less than 6 cycle in a year) or amenorrhea (no menses in the last 6 months) after a negative screening pregnancy test. In patients with regular menses, progesterone level <4 ng/mL (12.72 nmol/L) in the luteal phase of two consecutive cycle.(22)
3. Polycystic ovaries (P): 12 or more follicles of 2 to 9 mm diameter and/or increased ovarian volume (>10 mL) in at least one ovary by ultrasonography.(22)

Inclusion Criteria

Female between 16-40 age group with features of PCOS, as defined by Rotterdam criteria 2003, characterised by at least two of the following three features;

1) Oligo or anovulation
2) Clinical and/or biochemical hyperandrogenism, and
3) Ultrasound appearance of polycystic ovaries.

Exclusion Criteria

Other causes of hyperandrogenism like Cushing's syndrome, late-onset congenital adrenal hyperplasia and androgen-secreting tumours were excluded with appropriate diagnostic tests. Thyroid dysfunction,, except euthyroid on stable dose of medication for 3 month. Hyperprolactinemia, Pregnancy, OCP or any other hormonal contraception

Descriptive statistical analysis were carried out with SAS (Statistical Analysis System) Version 21.0 for windows, SPSS, Inc., Chicago, IL, US. Results on continuous measurements were presented as Mean ± SD. Results on categorical measurements are presented in Number (%). The level of Significance was assessed at 5%.*Unpaired t-test* was used to find the significant changes between the quantitative parameters between two groups i.e. PCOS and Controls. *Chi-square test* use for qualitative data to compare the test of significance difference between proportions. *Spearman correlation test* was done to find out whether any significant correlation exists between the two variables.

Results

The mean age were 22.5.0 ± 4.529 year and 23.25 ± 4.603 year in the case and control respectively & the difference was nonsignificant (table1). The most of the cases were young. (Figure1)

The mean BMI were 24.73 ± 4.364 and 22.25 ± 2.948 kg/m2 in the case and control respectively & there is significant difference in the BMI (table 1). There were 47.1%, 26.8% and 26.1% obese, overweight and lean respectively among the PCOS group while in control group the 13.0%,14.5% and 72.5% were obese ,overweight and lean subjects. The difference was statistically significant among the PCOS and control group (**p <0.001**)

There were nonsignificant difference among the Neck circumference, Waist circumference and Hip circumference among the case and control groups(table1). The was significant difference in the Waist hip ratio among the case and the control and the waist hip ratio >= 0.85 were present in 59.4% of case group as compare to 24.6% control (p <0001). There were more PCOS patients had android pattern of body fat distribution as compare to control The mean systolic and mean diastolic blood pressure were significantly higher among the cases as compare to control and The systolic blood pressure were higher in the case group as compare to control (p 0.003) and the 10.9% of case had systolic blood pressure more than >=130mmhg.

There were non-significant differences among the diastolic blood pressure among the case and the control group (p 0.23). The 7.2% of PCOS subjects had diastolic blood pressure more than 85 mug as compare to 5.8% subjects in control group.

There were significant difference in the mean values of Fasting plasma glucose, 2 hour OGTT , fasting Insulin and HOMA-IR (homeostatic model of assessment of insulin resistance) among the case and control groups(table2) and The fasting plasma glucose were impaired in the 23.02% case as compare to 8.69% control group (p <0.0001). The 16.6% of PCOS subjects had impaired 75 gram 2 hour oral glucose tolerance test. . There were nonsignificant difference in the Total cholesterol, HDL, LDL and TGs among the case and the control groups(table2). There were significant difference among the mean serum total testosterone with a mean value of 87.68 ± 36.622 ng/dl and 33.93 ±11.36 ng/dl among the case and control group respectively(table:3). The mean Prolactin were significantly higher with the value of 11.32±5.02 ng/ml and 8.22 ± 3.21 ng/ml among case and control group respectively (table: 3). The Mean TSH were not significantly different among the case and the control groups. The mean SHBG were significantly lower in the cases as compare to control with a value of 24±15.16 nmol/l and 55.99±17.42 nmol/l respectively (table: 3). The mean AMH were significantly higher in the case as compare to control group with a value of 11.15±4.6 ng/ml and 3.68±2.09 ng/ml respectively (table: 3).

There were extremely significant differences among the modified Farriman Gallwey score, number of menstrual cycle and Acne score in the case and control groups (p<0.001). The most of the patients had mild Hirsutism with a median score of 8 in the case group while no Hirsutism in the control (table 4).

The most common pattern of the menstrual cycle was oligomenorrhea (83.33%), and the most of the PCOS had less than 6 menstrual cycle per year. The GAGS scoring was used to define the severity of Acne score. [35]. Acne were significantly higher in the PCOS group as compare to control group (<0.001).The grade 1 was the most common. The grade 1, grade 2 grade 3 and grade 4 acne were in the 38.4% , 13.8% ,0.0% and 2.2% of the PCOS as compare to the 2.9%, 1.4% , 0.00%, and 0.00% of the control . The Kendall's tau b correlation showed the positive but weak correlation between the acne severity score and AMH level in the PCOS (r 0.366, p <0.001) but there is no correlation between the AMH and Acne Score in the control group.

The trans- abdominal ultrasonography was use to diagnosed Poly cystic ovarian morphology. The mean follicular size on the day 3 of the menstrual cycle maximums size follicle of individual patient) were significantly lower in the case group as compare to control with a mean value of 6.01± 2.36 mm and 7.58 ± 2.12 mm respectively. The mean ovarian volume were significantly higher in the case group with a value of 12.43± 2.91 cc and 8.09 ± 1.73 cc among the case and control group respectively.

The mean follicular number in the single ovary were significantly higher in the cases than control group with a value of 14.9±5.32 and 0.30±0.69 respectively. The Spearman s rank (rho) correlation of Anti – mullerian Hormone with ovarian morphology and AMH is strongly and significantly associated with ovarian volume (r = 0.506, p<0.00) and follicular number (r= 0.0582, p <0.001) case group.

There was weak negative correlation between mean follicular size (r =-0.07, p=0.46) among the case and control group.

Control group also had positive correlation with ovarian volume (r=0.4, p<0.001) and follicular number (r=0.56, p <0.001). ROC curve of the AMH : ROC curve was drawn to determined the cut-off of AMH in our PCOS population showed the cut-off AMH > 5.06 ng/ml with the sensitivity & specificity of 97.8% and 80.4% respectively for detection of ovarian volume more than 10 ml.

Table 1: Clinical parameters of PCOS and control

Group Statistics			
	Group	Mean ±Std. Deviation	*p*
AGE(year)	PCOS	22.5.0 ± 4.529	0.265
	Non-PCOS	23.25 ± 4.603	
Height (cm)	PCOS	154.33 ± 4.830	0.254
	Non-PCOS	155.14 ± 4.772	
Weight (kg)	PCOS	58.44 ± 11.546	0.002
	Non-PCOS	53.52 ± 7.611	
BMI kg/m2	PCOS	24.73 ± 4.364	<0.001
	Non-PCOS	22.25 ± 2.948	
NC (cm)	PCOS	33.41± 2.706	0.069
	Non-PCOS	32.83 ± 1.534	
WC (cm)	PCOS	82.65 ± 12.025	0.062
	Non-PCOS	79.70 ± 7.297	
HC (cm)	PCOS	96.30 ± 10.534	0.232
	Non-PCOS	97.96 ± 6.307	
W/H	PCOS	0.88 ± 0.06	<0.001
	Non-PCOS	0.81 ± 0.05	
SBP(mmhg)	PCOS	117.93 ± 9.257	0.026
	Non-PCOS	114.96 ± 8.336	
DBP (mmhg)	PCOS	78.39 ± 5.520	0.013
	Non-PCOS	75.62 ± 10.320	

Table 2: Biochemical Parameters in the case and control group

	Group	Mean ±Std. Deviation	p
FPG(mg/dl)	PCOS	88.77 ±1 3.077	0.008
	Non-PCOS	83.75 ± 11.587	
75g OGTT(mg/dl) 2hr	PCOS	125.14 ± 20.238	<0.001
	Non-PCOS	102.86 ± 21.828	
Fasting .Insulin (uIU/ml)	PCOS	11.56 ±8.118	<0.001
	Non-PCOS	7.65 ± 5.625	
HOMA IR	PCOS	2.55 ± 2.026	<0.001
	Non-PCOS	1.59 ± 1.287	
HDL	PCOS	49.83 ± 8.757	0.161
	Non-PCOS	51.65 ± 8.875	
LDL	PCOS	100.78 ± 29.191	0.936
	Non-PCOS	101.12 ± 27.258	
VLDL	PCOS	47.23 ± 24.379	0.565
	Non-PCOS	46.19 ± 24.678	
TG	PCOS	169.19 ± 52.165	0.569
	Non-PCOS	164.93 ± 53.960	
T CHL	PCOS	175.83 ± 35.269	0.686
	Non-PCOS	177.87 ± 32.045	

FPG –fasting plasma glucose, 75g OGTT-75 gram oral glucose tolerance test, HOMA-IR-homeostatic model assessment-of insulin resistance, HDL-high density lipoproteins, LDL-low density lipoproteins, VLDL-very low density lipoprotien, TG-triglycerides TCHL-total cholesterol.

Table 3: Hormonal Parameters in the Case and Control Group

	Group	Mean ±SD	P
Total Testosterone (ng/dl)	CASE	87.6 ± 36.622	**<0.001**
	CONTROL	33.93 ±11.361	
TSH (mIU/ml)	CASE	2.27 ± 1.064	0.025
	CONTROL	1.91 ± 1.067	
PRL (ng/ml)	CASE	11.32 ±5.024	**<0.001**
	CONTROL	8.22 ±3.217	
AMH (ng/ml)	CASE	11.15 ± 4.604	**<0.001**
	CONTROL	3.68 ± 2.090	

Table: 4 Relation of Modified FG Score, Number of Cycle per year and Acne score

Group	PCOS	Non-PCOS	p
	Median (IQR)	Median (IQR)	
MFG. SCORE	8 (4-12)	1 (0-2)	<0.001
NO. CYCLE/YR	7 (6-8)	11 (11-12)	<0.001
ACNE SCORE	1 (0-1)	0.00	<0.001

MFG-modified ferriman gallwey score, NO.CYCLE-number of cycle

Table 5: Pattern of menstrual cycle Gr

Menstrual Cycle	PCOS	NON-PCOS	P
Normal menstrual Cycle	7.97%	85.5%	0.001
Oligomenorrhea	83.33%	14.49%	
Secondary Amenorrhea	8.69%	0.00%	

Table: 6 Ultrasonographic parameter among the PCOS and Non-PCOS Group

Group Statistics			
	Group	Mean ± Std. Deviation	p
Follicular size (mm)	PCOS	6.01 ± 2.366	<0.001
	Non-PCOS	7.58 ± 2.124	
Ovarian volume(cc)	PCOS	12.43 ± 2.91	<0.001
	Non-PCOS	8.09 ±1.732	
Follicular number	PCOS	14.90 ±5.32	<0.001
	Non-PCOS	0.30 ± 0.692	

Table 7: Spearman s rank (rho) correlation of Anti – mullerian Hormone with ovarian Morphology

Group		Variable	r	p
PCOS	AMH	Ovarian volume (cc)	0.506	<0.001
		Follicular number	0.582	<0.001
		Follicular size	-0.071	0.406
CONTROL	AMH	Ovarian volume (cc)	0.466	<0.001
		Follicular number	0.565	<0.001
		Follicular size	-0.196	0.106

Figure: 1

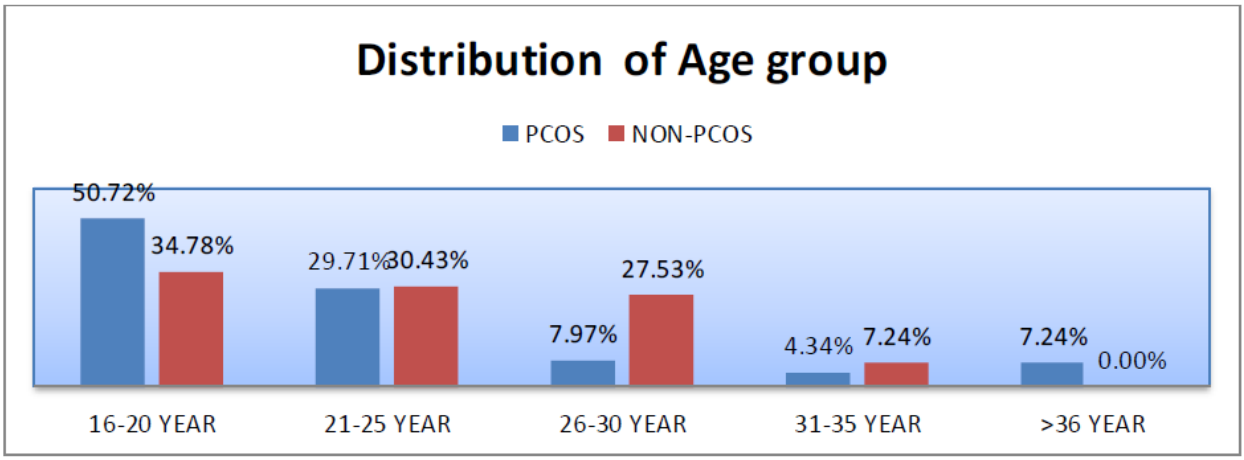
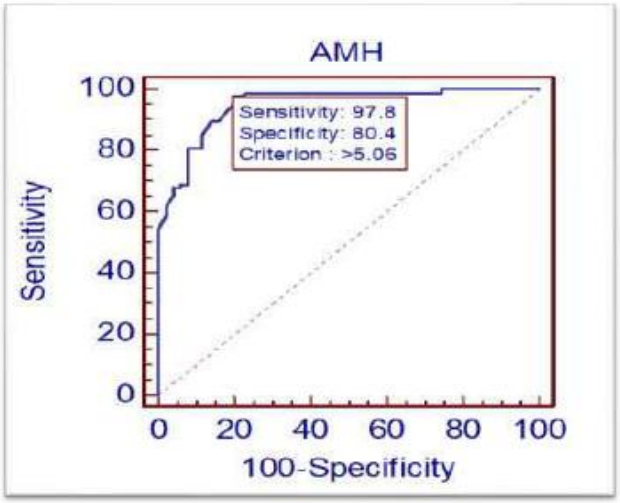


Figure 2

ROC curve of the AMH : ROC curve was drawn to determined the cut-off of AMH in our PCOS population showed the cut-off AMH > 5.06 ng/ml with the sensitivity & specificity of 97.8% and 80.4% respectively.



Discussion

The present study evaluated the association of the Anti-Mullerian Hormone with the ovarian morphology & clinical parameters in the Polycystic ovarian syndrome. Recent 2004 revised Rotterdam consensus criteria defines poly cystic ovarian morphology (PCOM) as follicular number per ovary (FNPO) threshold of ≥12 follicles measuring 2–9 mm in diameter (mean of both ovaries) with or without ovarian volume (OV) of ≥10 mL. Ovarian volume is calculated by the formula as 0.526 ×lengths × width × thickness .The Rotterdam criteria was used to diagnose the cases of PCOS in the present study.

The most patients were of the younger age (mean age -22.5 yr) & 80.43 % patients were less than 26 year of age. There were no-significant differences in the age among the case and control groups. The oligomenorrhea and secondary amenorrhea were present in the **83.33**% and **8.69%** of the PCOS. The prevalence of infertility could not be evaluated because most of the PCOS patient were unmarried (47%). In the various studies the prevalence of oligomenorrhea in PCOS varies from **40%-90%.**[23-26]

The difference in the menstrual irregularities in the different part of the world may be due to different ethnicity, environmental factors and the difference in the life style.

The severity of hirsutism was defined as per the modified Ferriman gallwey score (MFG). The hirsutism was present in **61.6%** of cases and **0.00%** in controls. Mild Hirsutism was the most common pattern **(39.10%)**

The prevalence of hirsutism in PCOS varies from **3%-80%** in the different part of world.[27-28] The variable prevalence of hirsutism may be due to differential susceptibility of pilosebaceous unit to the androgens across the different ethnic group.

The most of the patients had mild acne **(40%)** & only **16%** of PCOS had moderate to severe acne.

The different studies have shown 17%-22% prevalence of acne.[29,30]. It may be due to difference in ethnicity. The Anti-mullerian hormone was significantly higher in the PCOS patients as compare to the control (**11.34± 4.62 vs 3.86±2.21 ng/ml <p<0.001**).

The result of our study were similar to Dolfing et al who found significantly higher AMH level

(**11.1 ± 3.0** ng/mL vs. **3.3 ± 1.8** ng/mL, P < **0.01**) in the PCOS.[31]

The various studies (Fallat et al. in 1997 , Cook et al., Pigny et al.) conducted all over the world showed eleveted level of AMH in PCOS.[31,32]

In our study AMH had strongly positive and significant correlation with the mean follicular number of each ovary and the mean ovarian volume but had weak negative correlation with follicular size.

Our results were similar to van Rooij et al.& Fanchin et al who found significant positive correlation (r =0.77, p<0.01) between AMH & Follicular count. The Piouka et al. and Dolfing et al also similarly found that the AMH level was positively correlated to the mean ovarian volume {(r = 0.178, P = 0.007). (r = 0.75, P <0.0001)[1].

In the present study of elevated serum AMH in both cases and controls with regard to ovarian volume and follicular number can be explained by the fact that serum AMH is produced by the granulosa cells of follicles from the time of follicle growth initiation.[33]

AMH serum level has been reported to be closely correlated with small antral follicle number in both healthy women and women with PCOS[18]

Disrupted folliculogenesis resulting in the arrest of follicular growth and excess accumulation of small antral follicles may increase serum AMH level in women with PCOS.

In present study the **cut-off value of** anti-Mullerian hormone to diagnose polycystic ovary syndrome by ROC curve analysis was **5.06** ng/ml with the sensivity and specificity of **97.8%** and **80.4%** respectively.

Different studies have showed different cut-off varied from 4.7 -10.5 ng/ml with different sensitivity & specificity.[34]

Conclusion

PCOS women had higher BMI, truncal obesity, insulin resistance, impaired glucose tolerance and metabolic syndrome .The mild hirsutism was the most common pattern of the hirsutism. Anti-Mullerian Hormone value was higher in the PCOS. The greater number of small antral follicle is associated with higher serum AMH value. The ovarian volume more than 10 ml associated with higher serum AMH level. Hence as a diagnostic marker, AMH measurement has been found to offer a relatively high sensitivity & specificity (97.5% and 80.4%, respectively) for PCOS .with a cutt off value of 5.0 ng/ml. Thus in situations where accurate ultrasound data are not available or where there is lack of adequate quality of equipment used for sinology. AMH could be used instead of the Polycystic ovarian morphology as a diagnostic criterion for PCOS.

Limitation of the study

Our study population had the potential for bias since participants were recruited based on self reported concerns over PCOS not from population survey. It would be expected that those with the most concerns over PCOS would be selected for evaluation (ie Frank PCOS).

The most of the population were unmarried so the prevalence of infertility could not be assessed.

The metabolic and clinical manifestation may be less common due to the younger population in the study.

In this study the ratio of the case and control was not as per the standards. So the findings of this study may not be applicable to the general population.

So, in the future the longitudinal and prospective study may address the causal relationship

Acknowledgment

We are very thankful to the whole team of the department of biochemistry and statistician Mr Kinghshuk B for their support.

Conflict of interest: None

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