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Anti-mullerian hormone as an emerging promising marker in the prognosis of PCOS

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ABSTRACT

Aims: To correlation of AMH with clinical, hormonal and ultrasound findings; and determine the role of AMH as prognostic marker.

Methods: This was a prospective cross sectional study on women attending Gynaecology outpatient department of Medial College and Hospital, Kolkata, from January 2018 to June 2019. Study comprised of 70 newly diagnosed cases of PCOS using Rotterdam criteria 2003. Clinical history included menstrual complaint, hirsutism and weight gain; examination included BMI and Ferriman -Gallwey score; and investigations included FBS, 2hr PPBS, TSH, Prolactin, total testosterone, LH, AMH level and pelvic USG before starting intervention and same parameters were rechecked after 3 months of treatment completion.

Results: A total of 70 PCOS patients were included in a study conducted within 1 year time period. The most common Phenotype in our study is Phenotype A (O+H+P) which was almost 85.71%, followed by Phenotype B (O+H) 7.14% and the least we got Phenotype C (H+P) that is 2.86%. There was statistically significant ($p<0.05$) decrease in AMH level following treatment of PCOS (before treatment mean AMH level was 9.63 ± 4.42 and after treatment the level was 5.81 ± 2.77).

Conclusions: The most frequent PCOS phenotype in Indian women is A (O+H+P). Therapy in PCOS women with raised AMH reduces the AMH levels. Measurement of serum AMH provides a high specificity and sensitivity by which it can act as a prognostic marker for PCOS.

Keywords: anti-mullerian hormone, hyperandrogenism, oligomenorrhoea, polycystic ovarian syndrome, rotterdam criteria

INTRODUCTION

PCOS is the most common heterogeneous, multisystem endocrinopathy in women of reproductive age with prevalence of 8-13%.¹ Rotterdam criteria 2003 is gold standard for diagnosing PCOS which includes any two of the following three features: oligo/anovulation (O), clinical and/or biochemical hyperandrogenism (H) and polycystic ovaries on ultrasound (P) with ≥ 12 follicles with a diameter of 2-9mm or when ovarian volume is $>10\text{ml}$.^{2,3} This generates four types of phenotypes in PCOS as type-A/classical (O+H+P), type-B/normal morphology (O+H), type-C/ovulatory (H+P) and type-D/normoandrogenic (O+P).⁴

Anti-mullerian hormone is a member of transforming growth factor beta (TGF- β) produced by granulosa cells

and its level correlates with number of antral follicles which are 2-9 mm in size. The secretion of AMH from polycystic ovary is 75 times higher than a size-matched granulosa cell of normal ovary. AMH is important regulator of folliculogenesis⁵ and its serum level are elevated 2-3 fold in PCOS women. AMH also inhibits the activity of aromatase suggesting that AMH contributes to the severity of PCOS.⁶

The controversy regarding diagnosing PCOS still continues due to complexity of presentation. Feature which should be considered essential for its diagnosis is still a dilemma. Due to limitations associated with existing Rotterdam criteria new tool AMH can be used as potential objective, quantitative and promising marker in prognosis of PCOS. Very few such studies have been reported from India, and therefore this study was undertaken.

METHODS

The present study was a hospital based single centre prospective cross sectional study using complete enumeration method. The study was conducted between January 2018 to June 2019 in the outpatient department of Obstetrics and Gynaecology at Medical College and Hospital, Kolkata. A total of 70 diagnosed cases of PCOS as per Rotterdam criteria were enrolled in the study after institutional ethics approval and consent from the study subjects. Women with history of previous ovarian surgery, exposure to cytotoxic drugs or radiation therapy, pregnant female, history of infertility and with intake of COC in past three months were excluded from the study.

On admission, clinical history (weight gain, menstrual complaint and hirsutism) physical examination (BMI, Ferriman Gallwey score) and investigations (sugar, serum testosterone, serum anti-mullerian hormone and, lipid profile and trans-abdominal sonography) were performed for all the women to diagnose Polycystic ovarian morphology. Patients were treated with either lifestyle modification and hormonal therapy (progesterone or oral contraceptive pills) or with Metformin. After 3 months of treatment same investigations were repeated. Oligomenorrhoea was taken as fewer than eight menstrual cycles during previous 12 months or menstrual interval of more than 35 days. Clinical hyperandrogenism was defined as Ferriman-Gallwey score⁷ of more than eight and biochemical hyperandrogenism defined as serum testosterone level of >80ng/dl. Polycystic ovarian morphology was diagnosed when either ovary on ultrasound had more than 12 follicles with a diameter of 2-9mm or when ovarian volume was more than 10cumm. Results of the above laboratory investigations and imaging studies were recorded along with clinical data of the patient in proforma. Patients were classified in different phenotype according to Rotterdam criteria.

Data were entered in MS Excel and statistical analysis was done using Statistical package for Social Sciences (SPSS) version 13. Quantitative variables were compared using paired t test. The unpaired t-test was used to demonstrate the correlation between AMH, PCOS and PCOS variables. Alfa error was set at 0.05.

RESULTS

The mean age of patients was 21.54 years out of 70 cases enrolled and the mean BMI 27.04 kg/m² with 45 patients (64.29%) having BMI \geq 25. There was statistically significant difference in AMH level by BMI before and after treatment. [Table-1]

Table-1: Co-relation of AMH levels with BMI before and after treatment

BMI (kg/m ²)	AMH (ng/ml)		p-value
	Before	After	
18-22.9	9.57 \pm 4.93	6.07 \pm 3.38	0.0806
23-24.9	11.16 \pm 5.31	5.67 \pm 2.54	0.0017
>25	10.28 \pm 3.81	5.49 \pm 2.69	<0.0001

In the present study Phenotype A was found to be the most common presentation (n=60, 85.71%) followed by Phenotype B [Table-2].

Table-2: Phenotypic classification of PCOS (n=70)

Phenotype	O	H	P	N	%
A	+	+	+	60	85.71
B	+	+	-	5	7.14
C	-	+	+	2	2.86
D	+	-	+	3	4.29

Phenotype C showed significantly higher AMH level compared to other phenotypes and the change in AMH level after treatment was significantly different in phenotype A of PCOS [Table-3].

Table-3: Correlation of AMH of four phenotypes of PCOS before and after treatment

BMI (kg/m ²)	AMH (ng/ml)		p-value
	Before	After	
A	9.602 \pm 4.42	5.81 \pm 2.65	<0.0001
B	8.95 \pm 2.704	5.55 \pm 3.74	0.1037
C	14.6 \pm 4.2	8.43 \pm 2.33	0.2109
D	7.95 \pm 4.62	4.44 \pm 3.41	0.3507

AMH= Anti-Mullerian Hormone

There is significant change in ovarian volume, antral follicle count, testosterone level and anti-mullerian hormone level in PCOS after treatment. [Table-4]

Table-4: Ultrasound and hormonal changes in PCOS before and after treatment (n=70)

Parameters	Mean \pm SD		p-value
	Before	After	
Ovarian volume	13.60 \pm 3.83	9.35 \pm 2.35	<0.0001
AFC	14.64 \pm 3.38	8.3 \pm 2.11	<0.0001
Testosterone	79.40 \pm 16.28	67.88 \pm 13.16	<0.0001
AMH	9.63 \pm 4.42	5.81 \pm 2.77	<0.0001

AFC=Antral follicle count

In women with PCOS, AMH levels had a positive linear relationship with combined antral follicle count and this correlation was statistically significant. It signifies that AMH levels are increased in PCOS subjects with high antral follicular count and vice versa. [Figure-1]

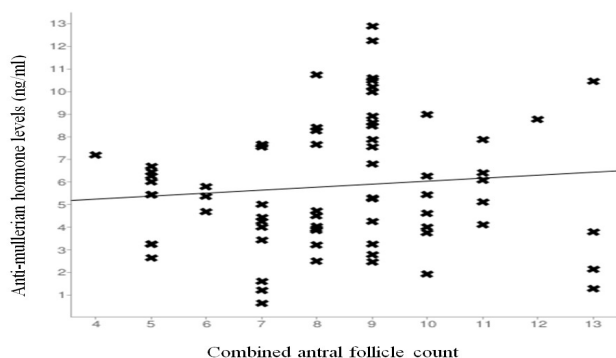


Figure-1: Scatter plot comparison of anti-mullerian hormone levels (ng/ml) and combined antral follicle count (n=70)

DISCUSSION

In this study, the average age of PCOS patients was significantly younger. This finding is consistent with studies by Rousseau et al⁸ and Johnstone et al.⁹ This is because of decrease in number of antral follicles with age.¹⁰

The mean BMI of PCOS patients belong to obese group. Various studies like Ashraf et al¹ and Balen et al¹² finding is consistent with findings of the present study. The most frequent PCOS phenotype in our study was Phenotype A (O+H+P), as much as 63.4%. This finding is consistent with study in Greece by Moghetti et al.¹³

The highest AMH levels were obtained in Phenotype C, which was 14.6 ± 4.62 ng/ml. It has been reported that concentrations of serum AMH correlate with the severity of symptoms.¹⁴ Increased androgen levels have also been related with the increases production of AMH in PCOS patients. PCOS phenotypes with hyperandrogenism have higher risk of metabolic or cardiovascular disease.¹⁵

The cause of increased AMH levels in PCOS patients is still inconclusive. Pellatt et al reported that AMH production increase approximately 75 times higher in each polycystic ovarian granulosa cell.¹⁶ Elevated serum AMH level in PCOS patients may also be caused by disturbances in folliculogenesis resulting in accumulation of excessive preantral and small antral follicle cessation of antral follicle development toward dominant follicle is due to suppression of aromatase activity by AMH. Laven et al stated that significant relationship between serum AMH levels and increase testosterone, LH levels and increase number of follicles and ovarian volume on ultrasound examination.^{17,18}

In subject with PCOS, AMH levels had a positive linear relationship with combined antral follicular count and this correlation was statistically significant. This is supported by the study Dewailly et al.¹⁹ Based on these findings, if ultrasound cannot provide accurate data, the AMH levels may be used to

replace number of follicles as a diagnostic criteria.²⁰ In addition, measurement of serum AMH levels may also be used as an indicator of PCOS patient's response to therapeutic approaches.²¹

CONCLUSION

The most frequent PCOS phenotype in Indian women is Phenotype A (O+H+P). AMH value rise when hyperandrogenism is present, therefore serum AMH levels also reflect phenotype of PCOS. The highest average AMH level was observed in photype A (O+H+P).

In PCOS there was a marked increase in serum AMH levels which is of great diagnostic value. Anovulation in PCOS is where the AMH appears to have a majority inhibitory role by interfering with during folliculogenesis AMH may be of value in differential diagnosis of oligomenorrhoea and it reflects the future of revision of the criteria for the diagnosis of PCOS.

Measurement of AMH can provide a high specificity and sensitivity by which it can act as a marker for PCOS. In situation where accurate ultrasonography data are not available AMH can be proposed that in the diagnostic criterion for PCOS than the follicular count.

This can aid in the recoiling the Rotterdam consensus and others definition for PCOS. Thus, the AMH level could be an emerging promising marker in the prognosis of PCOS for the women of reproductive age group.

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