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Correlation of Anti-Mullerian Hormone with clinical, hormonal and ultrasonographic parameters in PCOS and normo-ovulatory women

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Abstract:
Objective:-*To compare the serum AMH levels in PCOS and normo-ovulatory women and investigate the correlation between clinical, hormonal, ultra-sonographic parameters and AMH levels in both groups.*
Method:-*A comparative cross sectional study was conducted at Pacific Medical College and Hospital, Udaipur, Rajasthan during the period 15 October 2015 to April 2016 . A total of 64 women of reproductive age (21–35 years) were recruited for study after taking informed consent and were divided into 32 Case (PCOS patients defined by the Rotterdam criteria) and 32 Control (non-PCOS patients) groups. Menstrual history, clinical manifestations of hyperandrogenism, transvaginal ultrasound assessments for ovarian follicles , and the levels of AMH, LH, FSH, and estradiol were collected.*
Results:- *Thirty-two cases and 32 controls were recruited. AMH serum levels were significantly higher in PCOS patients than in controls. The Area Under the Curve (AUC) of the serum AMH assay in PCOS patients reached a value of 0.870. With a cut-off value of 4.45 ng/ml, the serum AMH level had a sensitivity of 76.1 % and a specificity of 74.6 %. The most common phenotypes of PCOS in this study were anovulation and polycystic ovary (63.4 %). However, the mean level of AMH was highest in the phenotypes of anovulation, polycystic ovaries and hyperandrogenism (11.1 ng/ml).*
Conclusion:-*AMH can be used as an alternative diagnostic criteria for PCOS patients with a cut-off value of 4.45 ng/ml. AMH value rise when hyperandrogenism is present therefore serum AMH levels also reflect the phenotype of PCOS*
Keywords: *AMH,Diagnosis of PCOS .HA , PCOS, Prognosis of PCOS, PCO*

I. Introduction

PCOS is the most common female endocrine abnormality affects around 5-10% of female of reproductive age[1]. It is characterized by: Menstrual cycle disturbance as oligo-amenorrhea and\or anovulation, clinical and\or biochemical signs of hyperandrogenism(HA), presence of polycystic ovary (PCO) by ultrasound as an ovary with 12 or more subcapsular follicles 2-9 mm in diameter and increased ovarian stroma and volume (> 10cm3) on trans-vaginal ultrasound (The Rotterdam consensus 2004[2]. A diagnosis is made in the presence of at least two criteria, after excluding diseases associated with excessive androgen production. Based on these criteria, we were able to acknowledge four different phenotypes in PCOS: phenotype A (OA+HA+PCO); phenotype B (HA+OA), phenotype C (HA+PCO), and phenotype D (OA+ PCO) [3]. The majority of patients with PCOS also have metabolic disorders, such as insulin resistance, that result in hyperinsulinemia, obesity, and dyslipidemia [4].

AMH is also known as mullerian inhibiting substance (MIS), a homodimericglycoproteinbelongs to the Transforming Growth Factor-β superfamily, the AMH gene is located on short arm of chromosome 19[5]. In females AMH is produced only by granulose cells from preantral and small antralfollicles[6]. AMH has an inhibitory effect on the primordial follicle recruitment as well as on the responsiveness of growing follicles to follicle-stimulating hormone (FSH), suppressing the FSH-depending aromatase and,also, diminish the LH receptors, thus helping the selection of the dominant follicle[7]. AMH has been heralded as a marker of ovarian aging and reserve in humans[8]. The cause of the increased AMH production in PCOS is unknown; however, the distinctive feature of PCOS is failure of follicular maturation, despite initial recruitment, resulting in anovulation and accumulation of preantral and small antral follicles, which contribute significantly to the production of AMH[9]. Granulosa cells from anovulatory PCOs produced on average 18 times more AMH than granulosa cells from ovulatory PCOs [10], also increased concentrations may be a consequence of other factors altered in PCOS, the most obvious being androgen production. Evidence to support this comes from the studies showing that in serum, AMH has been positively correlated to androgen levels[11]. Another candidate for the cause of the increase in AMH in PCOS is insulin. Insulin has been shown to enhance gonadotrophin-stimulated

steroid production in granulosa cells and theca [12]. The level of AMH circulating in the blood is not affected by the menstrual cycle nor altered during the use of oral contraceptives, therefore it can be used as a potential biological marker for PCO or PCOS. . Weerakiet's et al. stated that AMH plasma levels can be a marker of the degree to which folliculogenesis is impaired in patients with PCOS[13].

In patients with PCOS, there is a barrier that keeps follicles from becoming the dominant follicle. In addition to the very low levels of FSH, high levels of AMH decrease the sensitivity of follicles to FSH. Thus, follicles cannot develop into a dominant follicle, which leads to an accumulation of small antral follicles 2–9 mm in diameter [14]. AMH also inhibit the activity of the aromatase enzyme, suggesting that AMH contributes to the severity of PCOS [15].A study by Dewailly et al. indicated that AMH may also be used as a surrogate marker of classical hyperandrogenism [16]. Several other studies emphasize that the concentration of AMH is associated with the severity of morphological and hormonal changes in PCOS patients. Skalba et al. found significant differences in AMH and LH in PCOS patient. AMH levels are associated with free-testosterone, androstenedione, and the free androgen index (FAI) in PCOS patients and non-PCOS patients [17].The purpose of this study was to compare serum levels of AMH in PCOS and normo-ovulatory patients and to determine the relationship of serum AMH levels with clinical parameters, hormonal levels and ultrasound features in PCOS patients.

II. Material And Methods

The present study is a hospital based prospective study. This study was carried out in the Department of Obstetrics and Gynecology, Pacific Medical College and Hospital ,Udaipur from the period of October 2015 to April 2016. The study was approved by the ethical committee. A total of 64 women of reproductive age (21–35 years) were recruited for study after taking informed consent and were divided into 32 Case (PCOS patients defined by the Rotterdam criteria) and 32 Control (non-PCOS patients) groups.Menstrual history, clinical manifestations of hyperandrogenism, transvaginal ultrasound assessments for ovarian follicles , and the levels of AMH, LH, FSH, and Estradiol were collected.

Inclusion Criteria: age between 21 and 35 years, both ovaries present, had regular ovulatory cycles (25–35 days), no endocrine abnormalities (normal prolactin, basal FSH and estradiol, and no hyperandrogenism), and normal ultrasonic ovarian morphology.
Exclusion Criteria:endometriosis, cysts, any previous ovarian operation, no adequate visualization of ovaries ontransvaginalsonography, and current hormone therapy.

Transvaginalsonography was performed for detection of the number of small follicles <10 and calculation of ovarian volume using the formula of ellipsoid (p/6 · length · width · height). Blood sampling for hormone measurement was performed in the early follicular phase (day 3–4 after the last menstrual period) both in PCOS and control women. Each participant was subjected to withdrawal of 6 mL venous blood after 8– 10 h fasting on a plain tube and centrifuged after clotting.Serum samples were separated and stored at 70 C until assayed. Serum LH and FSH levels were measured using two-site chemiluminescentimmunometric assay, Serum testosterone (19), and estradiol (20) levels were measured using electrochemiluminescence immunoassay, Serum AMH levels were measured using Enzyme-Linked Immunosorbent Assay (ELISA) with units of ng/ml. A condition of hyperandrogenemia in the subject was assessed by the Free Androgen Index (FAI), namely, testosterone levels (nmol/L) Subjects in this study were classified as having hyperandrogenemia if the FAI was >5 . Secondary data from medical records were used to obtain data on the subject's menstrual cycle, physical examination, ultrasound and laboratory

.

Data analyses were performed with Statistical Program for Social Sciences (SPSS) version . We calculated the frequency of each PCOS phenotype. Differences in age, FAI, LH-FSH ratio, LH, AMH, and FSH level were analyzed using independent t-tests for data with normal distribution and non-parametric Mann Whitney test for data that were not normally distributed. The relationship between AMH levels and PCOS phenotypes were assessed by Kruskal-Wallis test. The difference of number of follicles and ovarian volume in between PCOS and Non-PCOS was also noted .Multivariate logistic regression analyses were used to study the association between variables and PCOS. Backward selection of parameters was applied, using $P<0.05$ for entry or deletion, respectively. The area under the receiver operating characteristic curve (ROC AUC) was computed to assess the predictive accuracy of the logistic models, yielding values from 0.5 (no predictive power) to 1.0 (perfect prediction).

III. Results

In this study, 32 subjects diagnosed with PCOS based on Rotterdam criteria and 32 controls. All variables compared between these groups are shown in Table 1. The median age in the PCOS group was significantly lower than controls. There were also statistically significant differences between the PCOS and the control group in median/ mean AMH, LH, and FSH levels. The mean estradiol levels were comparable in both groups.

Table 1 The differences of hormonal levels ,ageand ultrasonographic data between PCOS and non-PCOS patients

Variables	PCOS(n=32)	Non- PCOS (n=32)	p value
Age(years)	28.55+3.93	32.86+3.89	0.008 [a]
AMH(ng/ml)	9.53+5.11	3.50+1.95	<0.001[a]
LH (IU/L)	11.41+8.12	3.37 (1.20-11.20)	<0.001[b]
FSH(IU/L)	5.40+1.47	6.29(1.70-17.20)	<0.001[b]
Estradiol(pg/ml)	37.00(5.42-191.00)	42.50(12.00-179.00)	0.051[b]
No.of follicles <10mm	21.3+ 7.3	7.5+3.4	<0.001
Ovarian Volume(mm3)	28.7+6.7	7.8+1.6	<0.001

[a]Non parametric Mann Whitey test, significant at the level of <0.05
[b]Independent t-test, significant at the level of <0.05

We used the ROC curve to investigate the diagnostic potential of AMH level. The AUC of AMH level was 0.870 (95 % CI 0.81–0.92) and optimal AMH cut-off level was 4.45 ng/ml, yielding 76.1 % sensitivity and 74.6 % specificity. AMH also provided the highest sensitivity and specificity compared to other variables (Fig. 1). After determining the cut-off value for AMH level, we found the odds ratios of AMH level was 9.35 (95 % CI 4.36–20.07) (Table 2).

Table 2 : Odds ratio of each variable

Variables	PCOS(n%)	Non-PCOS(n%)	P value	OR (CI 95%)
AMH(ng/ml)				
>4.45	20(38)	13(12.7)	<0.001	9.35 (4.36-20.07)
<4.45	12(12)	19(37.3)		
Age (years)				
>30	22(29.6)	15(24.6)	0.312	1.49 (0.77-2.89)
<30	10(20.4)	17(25.4)		
FSH(IU/L)				
>5.85	21(33.6)	12(15.9)	<0.001	5.41 (2.42-12.10)
<5.85	11(14.2)	20(36.3)		
LH(IU/L)				
>5.39	22(31.0)	11(18.6)	<0.002	3.33 (1.54-7.21)
<5.39	10(16.8)	21(33.6)		

OR (odds ratio) , CI (Confidence Interval)
Based on logistic regression, variables that can be used as a diagnostic tools in PCOS patients were AMH, LH and FSH serum level.

The most frequent PCOS phenotypes in this study was phenotype D (OA+PCO) (63.4 %). Women with PCOS phenotype A (OA+HA+PCO) had the highest AMH level (11.1 ng/ml), and it was significantly higher compared to AMH level in phenotype D. (Table 3).

Table 3 : AMH levels of the four groups based on PCOS related phenotypes

Phenotype	Oligo-/anovulation	Hyperandrogenism	Polycystic Ovary	Frequency (%)	AMH(ng/ml)
A	+	+	+	31.6	11.1+5.6
B	+	+	--	1.8	11.2(6.0-17)
C	--	+	+	3.2	8.50+ 2.72
D	+	--	+	63.4	6.1(3-16.9)

IV. Discussion

In our study, the average age of PCOS patients was significantly younger than non-PCOS patients (p=0.008). This finding is consistent with studies by Rousseau et al. [18] and Johnstone et al. [19], who both reported that the proportion of women with PCO decreased with age [19]. This can be caused by a decrease in the number of antral follicles throughout the reproductive years that occurs in normal women, a phenomenon that also applies to patients with PCOS [20]. Murphy et al. also reported that half of the women diagnosed with PCOS an average age of30years, no longer exhibited these phenotypes 8 years later [21].

We found significantly higher serum AMH levels in PCOS women compared to the controls. The OR of serum AMH level was 9.35 (95 % CI 4.36–20.07), meaning that patients with higher AMH levels >4.45 ng/ml have 9.35 times higher possibility to suffer from PCOS compared to patients with low AMH. This finding has consistently been reported in numerous studies . This increase is due to increased synthesis and secretion of AMH by polycystic ovaries [22]. Pellat et al. reported that AMH production increases approximately 75 times higher in each polycystic ovarian granulosa cell [23]. This finding is supported by Catteau-Jonard et al., who found increased mRNA expression of AMH in ovarian granulosa cells [24]. Elevated serum AMH levels in PCOS patients may also be caused by disturbances imfolliculogenesis, resulting in the accumulation of excessive pre-antral and small antral follicles [25]. Cessation of antral follicle development toward the dominant follicle is due to suppression of aromatase activity by AMH and by lower follicle sensitivity to FSH [26, 27]

FSH level was significantly lower in PCOS patients when compared to controls (p<0.001) . According to Pellat et al., FSH does not have an effect on AMH production and mRNA expression of AMH in granulosa cells, but there is a significant reduction (up to 30 %) in AMH after FSH administration in PCOS patients . The reason for this reduction is yet to be investigated. LH levels in PCOS patients are also significantly higher when compared to non-PCOS patients (p<0.001) Pigny et al. stated that there was an apparent correlation between AMH and LH because they found that LH was elevated in patients with PCOS who also had very high AMH levels [21,23].Laven et al. stated that significant relationships between serum AMH levels and increasing testosterone, LH levels, and increased number of follicles and ovarian volume on ultrasound examination [28].

Measurement of serum AMH levels as a diagnostic modality of PCOS turned out to have a high sensitivity and specificity. The AUC of the serum AMH assay in PCOS patients reached a value of 0.870 (95 % CI 0.81–0.92). Optimal specificity and sensitivity were achieved at the cutoff level of 4.45 ng/mL.

This study showed that AMH could be used as an alternative diagnostic tool in PCOS patients. Pigny et al. found that the specificity and sensitivity of serum AMH measurement reached 92 and 67 %, respectively [29]. Lin et al. obtained the cutoff AMH level of 7.3 ng/mL, giving 76 % specificity 76 % and 70 % sensitivity to predict PCOS [30]. We obtained a cutoff value of 4.45 ng/mL, lower than the findings of Lin et al [29].

The highest AMH levels were obtained in phenotype A, which was 11.1 ng/ml. Average levels of AMH in the phenotype A were significantly higher than in phenotype D (p= 0.01). It has been reported that concentrations of serum AMH correlate with the severity of symptoms [31]. Ovulatory PCOS patients had lower AMH levels compared to anovulatory PCOS patients [31, 32]. Increased androgen levels have also been related with the increased production of AMH in PCOS patients [11]. PCOS phenotypes with hyperandrogenism have higher risk of metabolic or cardiovascular disease, the highest risk being foundin phenotype A and B [33]. As

explained before, serum AMH levels were also higher in these phenotypes. In our study, sample size was relatively small for each group, hence the large confidence interval of our results.

V. Conclusion

In conclusion, the present study has demonstrated higher serum AMH levels in PCOS group than in controls. The study showed that AMH levels can be used as diagnostic and prognostic modalities in PCOS patients. We propose a logistic regression model probability of PCOS based on AMH, FSH, and LH levels. The most frequent PCOS phenotype in Indian women is phenotype D (OA+PCO). AMH value rise when hyperandrogenism is present therefore serum AMH levels also reflect the phenotype of PCOS. The highest average AMH level was observed in phenotype A (OA+HA+PCO). It could be speculated that hyperandrogenism may contribute to increased number of small antral follicles leading to increased AMH secretion in PCOS patients. Assessment of AMH levels before and after the treatment of hyperandrogenism should be recommended in the plan of management of PCOS.

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Conflict of interest

The authors declare no conflict of interest.

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None

Recommendations

1. Since serum AMH levels correlate well with antral follicle count the measurement of AMH could be used as a tool to diagnose PCOS and to evaluate treatment efficacy.
2. Studies are needed to determine the cutoff of AMH for diagnosis of PCOS

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