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# Serum Anti-Mullerian Hormone as a New Marker of Polycystic Ovary Syndrome

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**Abstract:** Polycystic ovary syndrome is the most common endocrine disorder among women of reproductive age group. It is associated with number of health risks. Despite its frequency, the polycystic ovary syndrome (PCOS) is still a difficult diagnosis in Endocrinology, Gynaecology, and Reproductive medicine. Many women with PCOS have high anti-mullerian hormone concentrations; thus, this may be a useful addition to the diagnostic criteria. The aim of this study was to estimate serum Anti-Mullerian hormone in diagnosed cases of PCOS and its role in diagnosis of PCOS. This is a hospital based prospective study. Here PCOS was diagnosed according to the Rotterdam criteria. 100 women diagnosed with PCOS (according to Rotterdam criteria) were recruited into the study. Most of the patients in the current study were in the age group of 26-30 years. The optimal serum AMH cut off value for PCOS diagnosis identified in this study was 5.7 ng/ml (from meta-analysis of various studies). 100 PCOS patients have been categorised into two groups as - group a (25) = AMH level< 5.7 ng/ml and group b (75) = AMH level>5.7 ng/ml. Mean AMH level in group a was 4.56 ng/ml and in group b was 12.28 ng/ml .It was found that the difference is highly significant at 0.01 level as p< 0.01. There were no correlation between BMI and AMH levels in all study groups (r= - 0.049 ; p = 0.628 ). A significant positive correlation was seen between serum testosterone, LH and AMH levels (r = 0.858, p<0.0001 and r= 0.245, p = 0.0138 respectively ). Therefore from this study, we can propose the potential application of AMH as a diagnostic marker for PCOS.
**Keywords:** Polycystic ovary syndrome, antimullerian hormone, Rotterdam criteria, testosterone, follicle stimulating hormone.

## INTRODUCTION

Polycystic ovary syndrome is the most common endocrine disorder among women of reproductive age group [1]. The prevalence among women of fertile age is 6-10 % using the NIH criteria [2,3] and 14-17 % using the Rotterdam criteria [4,5]. It reflects multiple potential aetiologies and variable clinical presentations. Oligomenorrhoea and amenorrhoea, as signs of anovulation, and hirsutism, as a sign of hyperandrogenism, are the most common complaints of patients with PCOS.

It is highly associated with obesity, insulin resistance and abnormal lipid profile [6,7]. This insulin resistance exacerbates ovulation dysfunction in PCOS. Insulin resistance is a pathogenic characteristic feature of PCOS, particularly among obese subjects [8].

PCOS is the most common cause of infertility due to anovulation. The prevalence of infertility in PCOS women varies between 35% and 94%. A number of health risks are associated with PCOS. Problems associated with PCOS resulting in metabolic syndrome and long term sequelae include: 1. impaired glucose tolerance, 2. type 2 diabetes, 3. dyslipidemia, 4. hypertension, 5. increased cardiovascular risk, 6. increased risk of endometrial cancer.

Many PCOS women in the general population remain undiagnosed [4,10]. Moreover, obesity worsens the metabolic and endocrine profile in PCOS and obesity epidemic may lead to increased prevalence [11]. Therefore, it is important to identify women with PCOS due to the need for follow-up on short and long-term health risks.

Diagnosing PCOS is a challenge with changing criteria and different definitions. The National Institutes of health (NIH) 1990 diagnostic criteria for PCOS include oligo- and/or anovulation and clinical and/or biochemical hyperandrogenism, excluding other causes of androgen excess [12].

In 2003, the European Society for Human Reproduction/American Society of Reproduction Medicine (ESHRE/ASRM) –sponsored PCOS consensus workshop group at Rotterdam proposed that the diagnosis of PCOS should include two of the following three criteria : 1. oligo-and/or anovulation, 2. clinical and/or biochemical hyperandrogenism and 3. polycystic ovaries on ultrasound. It was proposed to include polycystic ovarian morphology (PCOM) as diagnostic criteria [13], which include an increased ovarian volume ( >10ml) and/or the presence of 12 or more follicles in each ovary measuring 2-9 mm [9].

The Androgen Excess Society criteria in 2006, defined PCOS as patient demonstrating both 1 and 2: 1. Hirsutism and /or hyperandrogenemia (clinical or biochemical) and 2 oligo-anovulation and/or polycystic ovarian morphology.

Anti-Mullerian hormone is a dimeric glycoprotein and a member of the transforming growth factor β family of growth and differentiation factors [14]. It is produced by the granulosa cells of small antral follicles. Polycystic ovaries are characterised by excessive number of growing follicles. The two-to threefold increase in the number of growing follicles is reflected by a two-to threefold increase in serum AMH level, thus AMH has been proposed as a marker of PCOS.

In the ovary, AMH inhibit the recruitment of primordial follicles as well as the response of growing follicles to Follicle-Stimulating Hormone (FSH). This FSH is responsible for the follicular development leading to ovulation, so the oligo/anovulation, characteristic of PCOS, could be due to a dysfunction of FSH which may be quantitative, or qualitative or both. Thus AMH by counteracting the actions of FSH imply that the high production of AMH by polycystic ovary may have an important role in the pathophysiology of the syndrome.

## MATERIALS AND METHODS

This was a hospital based prospective study, carried out in the department of Obstetrics and Gynaecology of Gauhati Medical College and Hospital, Guwahati, a tertiary care hospital for a period of one year from 1st June, 2016 to 31st May 2017. The study groups comprised of females attending Obstetrics and Gynaecology department in Gauhati Medical College and Hospital, having clinical features of PCOS. Exclusion criteria are pregnancy, thyroid dysfunction, Cushing syndrome, hyperprolactinemia and premature ovarian failure.

Before doing the study, synopsis was submitted to the Institutional Ethical Committee (Gauhati Medical College and Hospital) and clearance was obtained for the same. 100 women who presented with oligomenorrhoea or amenorrhoea and were diagnosed with PCOS according to the European Society of Human Reproduction and Embryology (ESHRE)/American Society for Reproduction Medicine (ASRM) (Rotterdam) criteria were recruited in this study. A thorough history was taken from the cases, followed by examination and then required investigation was done. In day 2-4 of cycle, pelvic ultrasonography was performed and serum hormonal level of AMH, luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, fasting blood sugar (FBS), thyroid stimulating hormone (TSH) and prolactin were measured .

## RESULTS

Patients in the study group were in the age range of 19 to 34 years. They were divided in 4 groups, $\leq$ 20 years, 21-25 years, 26-30 years and >30 years.

In the present study, it was seen that amongst the 100 cases of PCOS maximum number of patients were in the age group of 26-30 years – 53% with mean age group of 26.6 years, standard deviation of 4.0 and 95% confidence interval is (25.76 - 27.36).

The total number of cases were categorised according to their marital status and it was seen that majority of the cases in this study were unmarried (80%).

### Distribution of cases according to their menstrual symptoms

In the present study, it was seen that maximum number of patients presented with oligomenorrhoea (79%).

**Table-1: Relation between menstrual symptom and age distribution**

| Menstrual symptom | $\leq$ 20 | 21-25 | 26-30 | >30 |
|---|---|---|---|---|
| Oligomenorrhoea | 9 | 13 | 46 | 11 |
| Amenorrhoea | 7 | 5 | 7 | 2 |
| Total | 16 | 18 | 53 | 13 |

From the table-1, it was seen that oligomenorrhoea was the common symptom in all age groups. In the present study, majority of cases has associated hirsutism (62 % of the study population)

**Distribution of cases according to BMI:**

The study population was divided into 4 groups according to their BMI . From the table-2, it was seen that maximum number of patients are overweight (74%). The mean (BMI) body mass index of the study groups is 27.6 kg/m2 (range 21.0 – 32.0 kg/m2) and a standard deviation of 2.36 , 95% confidence interval is ( 27.09 – 28.03 )

**Table-2: Distribution of cases according to BMI**

| Body mass index (BMI) (Kg/m2) | No. of cases | Percentage |
|---|---|---|
| <18.5 (underweight ) | 0 | 0% |
| 18.5-24.9 (normal weight) | 14 | 14% |
| 25-29.9 ( overweight) | 74 | 74% |
| ≥ 30 (obese) | 12 | 12% |
| Total | 100 | 100% |

**Distribution of cases according to testosterone level**

The study populations were divided into 4 groups according to the different testosterone level. The table-3 show maximum number of patients in the present study has testosterone level in the range of (41 - 60)ng/dl. The mean of testosterone is 45.07 ng/dl (range 20.01– 75.10 ng/dl) and standard deviation of 15.90 .

**Table-3: Distribution of cases according to testosterone level**

| Testosterone level (ng/dl) | No. of patients | Percentage % |
|---|---|---|
| 20 – 40 | 34 | 34% |
| 41 – 60 | 40 | 40% |
| 61 – 80 | 26 | 26% |
| Total | 100 | 100% |

**Distribution of cases according to LH and FSH value**

The study population was divided according to LH value. The table-4 shows distribution of cases according to LH level with mean LH level 8.8 IU/Litre ( range 4.87 – 14.98 ) and standard deviation of 2.54 ; 95 % confidence interval is ( 8.34 – 9.35 ). The table-5 shows that the distribution of cases according to the FSH level with mean value 5.3 IU/Litre ( range 2.12 – 7.99 ) and standard deviation of 1.16, 95% confidence interval is ( 5.08 -5.54 )

**Table-4: Distribution of cases according to LH**

| LH ( IU/ litre) | No. of patients | Percentage % |
|---|---|---|
| 2.1 – 6 | 4 | 4% |
| 6.1 -10 | 65 | 65% |
| 10.1 – 15 | 31 | 31% |

**Table-5: Distribution of cases according to FDH**

| FSH value ( IU/Litre ) | No. of patients | Percentage % |
|---|---|---|
| 2.1-5 | 46 | 46 % |
| 5.1-8 | 54 | 54 % |

**Distribution of cases according to AMH**

The table-6 shows the serum AMH level in the study population. The mean value of AMH in the present study is 10.35 ng/dl (range 3.45 – 20.36) with a standard deviation of 4.92, 95% confidence interval is ( 9.37 -11.33).

**Table-6: Distribution of cases according to AMH**

| AMH level ( ng/ml) | No. of patients | Percentage |
|---|---|---|
| 2.1 – 5 | 15 | 15% |
| 5.1- 8 | 23 | 23% |
| 8.1-11 | 19 | 19% |
| 11.1- 14 | 15 | 15% |
| 14.1 -17 | 14 | 14% |
| 17.1 – 20 | 14 | 14% |

**Relation between AMH and menstrual symptoms**

In the present study, it was seen that the serum AMH level is higher in women with PCOS and amenorrhoea, compared to those with oligomenorrhoea. The mean value of AMH in those cases with oligomenorrhoea is 8.92 ng/ml (range 3.45 – 18.36 ) with standard deviation of 4.2 and in those with amenorrhoea is 15.69 ng/ml (range 7.56 – 20.36 ) with standard deviation of 3.5. The mean of AMH level differed significantly between those presenting with oligomenorrhoea or amenorrhoea (p value < 0.0001).

**Correlations of AMH concentration with Testosterone and BMI**

In the current study , serum AMH level was positively correlated to the serum testosterone level ( r = 0.864 and p < 0.0001 ). But no significant correlation was observed between (BMI) body mass index and AMH in all study groups (p = 0.628). (r= Pearson coefficient correlation)

**Correlations between serum AMH and LH level**

A significant correlation was seen between serum AMH and LH level with coefficient correlation (r = 0.245) and p = 0.0138, but no significant correlation was seen between serum AMH and FSH level with p value = 0.179. (r = Pearson coefficient correlation).

**DISCUSSION**

In this study, we investigated whether AMH estimation could be a useful diagnostic marker of PCOS. Maximum number of patients in the current study belonged to the age group of 26-30 years (53 %) with the mean age of 26.6 years. The result is quite comparable to the study done by Lin et al in 2011 with the mean age group of 27.7 years ( ± 5.8 ) [15].

In 2012, Eilertsen *et al*. [16] reported the mean BMI of PCOS patients as 27.8 kg/m2, similarly we also found the mean BMI of the study populations in the present study as 27.6 kg/m2 .

It was seen that maximum number of patients in the present study has testosterone level in the range of (41 -60) ng/dl - 40 %, with the mean testosterone level of the 45.1 ng/dl and a standard deviation of 15.9. The result is quit comparable to the study done by Pigny *et al.* with mean testosterone level of 45 ng/dl (17).

Homburg *et al*. [18], in 2013 reported mean AMH value of 10.86 ng/ml which is very much comparable to the findings of present study with mean AMH level of 10.35 ng/ml. To determine AMH as diagnostic criteria of PCOS, the reference values of AMH used in this study were from the mean cut-off value obtained from meta-analysis of various studies i.e 5.7 ng/ml.

On the basis of the reference value of AMH i.e 5.7 ng/ml , 100 PCOS patients have been categorised into two groups as - group a (25) = AMH level< 5.7 ng/ml and group b (75) = AMH level>5.7 ng/ml. Mean AMH level in group a was 4.56 ng/ml and in group b was 12.28 ng/ml . Unpaired student's t-test was used to test whether the difference is statistically significant or not. It was found that the difference is highly significant at 0.01 level as p< 0.01.

| Category | Mean A.M.H | SD | d.f | t-value | Significance |
|---|---|---|---|---|---|
| Group a(n=25) | 4.56 | 0.77 | 98 | 9.221** | p<0.01 (Highly significant) |
| Group b(n=75) | 12.28 | 4.15 | | | |

(d.f.→ degrees of freedom; **→ Highly significant; *→ significant; The critical value or p-value for 25+75-2=98 d.f. at 0.05 is 1.99 and at 0.01 is 2.63 respectively.).Unpaired Student's t-test has been applied. Significance was set at p < 0.01 andp < 0.05.

Lastly, in the present study we showed, a significant positive correlation between AMH and testosterone (r = 0.858 and p value < 0.0001). But there was no correlations between BMI and AMH levels (p =

0.628). This is similar to S. Cassar *et al*, who also reported that testosterone had a moderate to strong correlation with AMH (r =0.426, p < 0.001), but AMH levels did not correlate with BMI ( p = 0.3) [19]. Also according to Pigny *et al*. AMH was positively related to serum testosterone level with r = 0.360 and p value is < 0.003 [17].

In the present study, a positive correlation was seen between AMH and LH concentration with r = 0.245 and p value is 0.0138. This result is similar to Homburg *et al*. study which shows a positive correlation between AMH and LH level. (r =0.321, p= 0.01) [18]. In addition, a positive correlation between AMH and LH serum concentrations in PCOS has been reported by Carlsen *et al.* and Rosenfield *et al*..

We also showed that the serum AMH level is higher in women with PCOS and amenorrhoea, compared to those with oligomenorrhoea. The mean value of AMH in those cases with oligomenorrhoea is 8.93 ng/ml with standard deviation of 4.2 and in those with amenorrhoea is 15.69 ng/ml with standard deviation of 3.5. The mean of AMH level differed significantly between those presenting with oligomenorrhoea or amenorrhoea (p value < 0.0001 ).

Our results agree with those of La Marca *et al*. [20] study, showing that AMH is higher in amenorrheic compared with oligomenorrheic women with PCOS, which could indicate a role for AMH in the pathogenesis of PCOS-related anovulation. Also according to Pigny *et al*. who found significantly higher serum levels of AMH in women with PCOS and amenorrhoea compared with those with oligomenorrhoea[17].

## CONCLUSION

Thus from the above study, it was seen that serum AMH measurement is very valuable in the diagnosis of PCOS women. The serum AMH level in women with hyperandrogenism or oligo-anovulation could indicate the diagnosis of PCOS in conditions where reliable ultrasonography data not available or if ultrasonography cannot be done.

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