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# The relation between the serum anti-Mullerian hormone levels and follicle count in polycystic ovary syndrome

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## ABSTRACT

***Objectives.*** Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders, affecting up to 10% of reproductive-age women. Anti-Mullerian hormone (AMH) is a member of the transforming growth factor β family and has an inhibitory effect on primordial follicle recruitment in the ovary. The study aimed to investigate the importance of serum AMH levels in the different phenotypes of PCOS and find the optimal cut-off level of AMH in PCOS patients. ***Methods.*** This was a prospective clinical trial in which diagnoses of 50 PCOS patients based on Rotterdam revised criteria were compared to 50 normo-ovulatory cases. Additionally, the PCOS group was divided into 2 subgroups based on 2 or 3 Rotterdam criteria and compared to 50 normo-ovulatory cases. ***Results.*** When compared with the control group, the AMH levels of the PCOS group were significantly higher than those of the control group (6.81 ± 2.8 ng/ml vs. 3.22 ± 2.2 ng/ml, $p < 0.001$). In the subgroup analysis, the AMH levels of Group 1 and Group 2 were significantly higher than those of the control group ($p < 0.001$). The AMH cut-off value of 4.1 ng/ml was found to distinguish healthy women from PCOS patients, with 84% sensitivity and 80% specificity. ***Conclusions.*** Subgroup analyses showed higher levels of AMH in the severe PCOS group, but the difference was not statistically significant. More studies are suggested for researching the different PCOS subgroups to detect optimal AMH thresholds.

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***Keywords:*** anti-Mullerian hormone, ovarian follicles, polycystic ovary syndrome, ultrasonography

## Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders, affecting up to 10% of reproductive-age women [1]. Its prevalence varies according to the definition used and according to the reference population [2]. PCOS is responsible for many of the cases of hyperandrogenism and/or oligoanovulation.

In the last two decades, three different descriptions have been prepared for the diagnosis of PCOS. The most widely used 1990 National Institutes of Health (NIH) criteria include clinical and/or biochemical hyperandrogenism and chronic anovulation [3]. The

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2004 Rotterdam criteria suggest that PCOS should be diagnosed by two of the following three criteria: oligoanovulation, clinical or biochemical hyperandrogenism, and polycystic ovaries on ultrasound [4]. The most recent Androgen Excess and PCOS Society (AE-PCOS Society) criteria recommend that PCOS should be defined as clinical or biochemical hyperandrogenism associated with ovulatory dysfunction in the form of oligoanovulation or polycystic ovaries [5]. All three sets of criteria emphasize the exclusion of other related disorders before making a diagnosis of PCOS.

Anti-Mullerian hormone (AMH) is a product of the granulosa cells of growing follicles [6-9] and may regulate their growth and development by exerting a paracrine negative feedback effect on the recruitment of precursor (primordial) follicles [7, 10]. AMH also inhibits the sensitivity of follicles to follicle-stimulating hormone (FSH) [10, 11]. AMH levels are increased in PCOS in proportion to its clinical severity, as reflected by their number of diagnostic features [12] and the antral follicle count [8, 13]. Considerable evidence has been put forward that this increased AMH level results from the stimulatory effect of androgens on early follicular growth [11]. Besides, blood AMH levels were shown by cluster analysis to be associated with androgen levels and so have been proposed as a diagnostic marker for ovarian hyperandrogenism [14]. AMH levels are also raised in ovulatory women with a polycystic ovary [15]. There is debate about whether this increase indicates ovarian hyperandrogenism or rather indicates an enlarged oocyte pool (increased "ovarian reserve"). In the meta-analysis conducted by Pepe et al. [16], an AMH cutoff value of 4.7 ng/ml was determined to distinguish healthy women from PCOS patients. Additionally, AMH shows different PCOS phenotypes of varied severity [12, 13, 17, 18]. Koninger et al. [19] compared the diagnostic potency of AMH with sonographic views of ovaries, ovarian volume, testosterone, androstenedione, luteinizing hormone (LH), and the LH/FSH ratio for the purpose of establishing the age-dependency of AMH.

The aim of the present study was to evaluate serum AMH levels in PCOS subgroups and to compare serum AMH levels with ovarian ultrasound features and determine the optimal cut-off level of AMH in PCOS patients.

## Methods

This was a prospective clinical trial in which diagnoses of 50 PCOS patients based on Rotterdam revised criteria were compared to 50 normo-ovulatory cases. Additionally, PCOS group was divided in to 2 subgroups with inclusion of 2 or 3 Rotterdam criteria and compared to 50 normo-ovulatory cases. Thus, Group 1 involved patients with oligomenorrhea and polycystic ovarian morphology and was defined as the mild PCOS group, and Group 2 involved patients with oligomenorrhea, hyperandrogenism, and polycystic ovarian morphology, and it was defined as the severe PCOS group. The study was approved by the institutional review board of University, and all patients gave their informed consent before inclusion in this study. The study was conducted between November 2012 and May 2013. Participants were recruited from the obstetrics and gynecology polyclinics of University Medical School. Patients aged 18-35 years were taken in to the study. Weight and height were measured, and BMI was calculated as weight (kg)/height (m2). During the medical examination, patients were specifically asked about their menstrual history. Oligomenorrhea was defined as an average cycle length of more than 35 days and included women with frank amenorrhea. Clinical hyperandrogenism was defined by the presence of hirsutism (a modified Ferriman-Gallwey score over 8) and/or acne located in more than two areas as previously reported [20]. Blood samples from all the participants were collected on day 3 of the menstrual bleeding between 8:00 and 9:00 a.m. after an overnight fast. The blood samples were transferred to a central laboratory the same morning; following centrifugation at 4°C for 20 min at 3000 rpm, the serum samples were transferred into polypropylene tubes and stored at -80°C until final analysis. The patients' serum levels of FSH, LH, estradiol (E2), thyroid-stimulating hormone (TSH), prolactin, total testosterone, dihydroepiandrosteronesulphate (DHEAS), and 17-hydroxyprogesterone (17-OHP) were measured by immunoassays as described previously [20]. Serum AMH levels were assessed using the enzyme-linked immunosorbent assay human AMH ELISA kit provided by Sunred Biological Technology (China). In addition, on the third day of the cycle, the antral follicle count was performed with a General Electric Alfa Logic 3 ultrasound system with a 5 mHz transvaginal transducer by the same

physician. In virgin patients, a transabdominal transducer was used. After determination of the longest medial axis of the ovary, the length and thickness were measured and the ovarian volume was calculated as described previously [21]. For each ovary, the total number of all visible follicles smaller than 10 mm in diameter was counted by slow and continuous scanning of the entire ovary, from one margin to the other in a longitudinal cross-section. For the ovarian volume and the follicle number, the data used for statistical analysis were the mean of recorded values for the left and right ovaries. We excluded from the analysis patients with a history of ovarian surgery.

*Statistical Analysis*

The sample size calculation was based on mean AMH levels. Mean AMH levels were found to be 6.86 ± 3.13 and 2.70 ± 1.67 in each group of 30, for a total of 60 patients in a pilot study. Calculated with GPower 3.1 (http://www.gpower.hhu.de/), a power of 80% with alpha = 0.05 was calculated when comparing the two-means using Student t-test with a total sample size of 12. We extended the study until completion of the 50 patients in each group, with the aim of making subgroup analyses. SPSS v.15.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Numbers and percentages were used to express the categorical variables. Continuous variables were represented with mean and standard deviation. When the variables showed normal distribution, independent samples t-test was performed for the age, FSH and AMH. The Shapiro wilktest was used to compare the mean levels of AMH. In the case of histograms, the nonparametric Mann-Whitney U-test and Kruskal-Wallis test were used to evaluate the variables that did not fit a normal distribution. AMH levels were compared among PCOS groups using ANOVA test and subgroups analysis were performed. Correlation analysis was used to determine whether there was a statistically significant association between continuous variables and Spearman's correlation coefficient was computed. Receiver operating characteristic (ROC) curves were used to analyze the accuracy of AMH levels in predicting PCOS. According to this method, the following criteria should be met for the best test: sensitivity = 100%; false negativity = 0 (1-Specificity = 0); the area under the curve (AUC) = 1; and diagnostic value of AUC ($p$-value) < 0.05. The Youden index, which uses the point with the highest sensitivity and specificity on the ROC curve, was used to determine the cutoff values. $p$ values < 0.05 were considered statistically significant.

## Results

Between November 7, 2012 and May 2013, a total of 100 volunteers aged 18-35 years agreed to participate in the study. As shown in Table 1, when compared with the control group, weight was significantly higher in the PCOS group ($p$ = 0.004). The body mass indexes (BMIs) of the PCOS group were higher than in the control group ($p$ < 0.001). The waist circumferences of PCOS group were significantly higher than those of the control group ($p$ = 0.002). Results of the Ferriman-Gallwey scoring were significantly higher than those in the control group ($p$ < 0.001) (Table 1). FSH, E2, and TSH levels were similar in all groups, but LH levels were higher in the PCOS group ($p$ < 0.001) (Table 2).

The AMH levels of the PCOS group (6.81 ± 2.8 ng/ml) were higher than those of the control group (3.22 ± 2.2 ng/ml), and this was statistically significant ($p$ < 0.001).

In the subgroup analysis, the AMH levels of Group 1 ( Mild PCOS Group = Polycystic Ovary + oligo/amenorrhea ) and Group 2 ( Severe PCOS = Polycystic Ovary + oligo/amenorrhea + hyperandrogenism) were significantly higher than

**Table 1.** Demographic data in PCOS and control groups.

| | PCOS (n=50) | Control (n=50) | *p* |
|---|---|---|---|
| **Age (years)** | 26.2 ± 4.89 | 29.56 ± 4.92 | < 0.001 |
| **Weight (kg)** | 67.4 (48-99) | 61.1 (49-80) [a] | 0.004 |
| **Length (m)** | 1.62 (1.53-1.75) | 1.63 (1.56-1.74) | 0.08 |
| **BMI (kg/m$^2$)** | 25.7 (18-36) | 23.9 (18-95) [a] | < 0.001 |
| **Waist circumference (cm)** | 80.5 (62-114) | 73.7 (62-114) [a] | 0.002 |
| **Ferriman-Gallwey score** | 10.34 (2-23) | 3(0-5) [a] | < 0.001 |

Data are shown mean ± standart deviation or mean (range). BMI = body mass index, PCOS = polycystic ovary syndrome. $p$ values were determined by non-parametric Mann-Whitney U test

**Table 2.** Serum AMH levels and hormonal and metabolic data in PCOS and control groups.

| | PCOS | Control | *p* |
|---|---|---|---|
| **AMH (ng/ml)** | 6.81 ± 2.8 | 3.22 ± 2.2 | < 0.001 |
| **FSH (mIU/ml)** | 5.01 ± 1.43 | 4.62 ±1.81 | 0.054 |
| **LH (mIU/ml)** | 10.64 (2.80-33) | 4.80 (2.1-32) | < 0.001 |
| **E2 (pg/ml)** | 61.74 (25-219) | 54.9 (22-173) | 0.242 |
| **PRL (mIU/ml)** | 16.07 (1.9-29) | 14.2 (6-25) | 0.08 |
| **TSH (mIU/ml)** | 1.56 (0.2-5.0) | 1.72 (0.56-3.2) | 0.075 |
| **DHEAS (mg/dl)** | 263 (96-450) | 195 (56-310) | 0.056 |
| **17-OHP (ng/ml)** | 0.90 (0.3-1.5) | 0.61 (0.01-1.4) | 0.965 |

Data are shown mean ± standart deviation or mean (range). PCOS = polycystic ovary syndrome, AMH = anti-Mullerian hormone, FSH = follicle-stimulating hormone, LH = luteinizing hormone, E2 = estradiol, PRL = prolactin, TSH = thyroid-stimulating hormone, DHEAS = dihydroepiandrosteronesulphate, 17-OHP = 17-hydroxyprogesterone. *p* values were determined by the Shapiro wilk test.

those of the control group (6.68 ± 2.8, 6.88 ± 2.9, and 3.22 ± 2.2 ng/ml, respectively; $p < 0.001$). The AMH levels of Group 2 were higher than those of Group 1, but this wasn't statistically significant ($p = 1.0$).

The AUC was calculated for AMH levels. According to the ROC curves, the estimated AUC for AMH levels was 0.88 for detecting PCOS in patients ($p < 0.001$). We found an AMH cut-off value of 4.1 ng/ml to distinguish healthy women from PCOS patients, with 84% sensitivity and 80% specificity (Figure 1).

There was no relation between AMH levels and ovarian stromal thickness ($p = 0.866$) or ovarian volume ($p = 0.797$). A positive correlation was found between follicle numbers and AMH levels ($p < 0.001$) (Table 3).

## Discussion

AMH has an important role in folliculogenesis. Increased serum levels of AMH have been defined in patients with PCOS [8]. The highest expression of AMH is found in preantral and small antral follicles

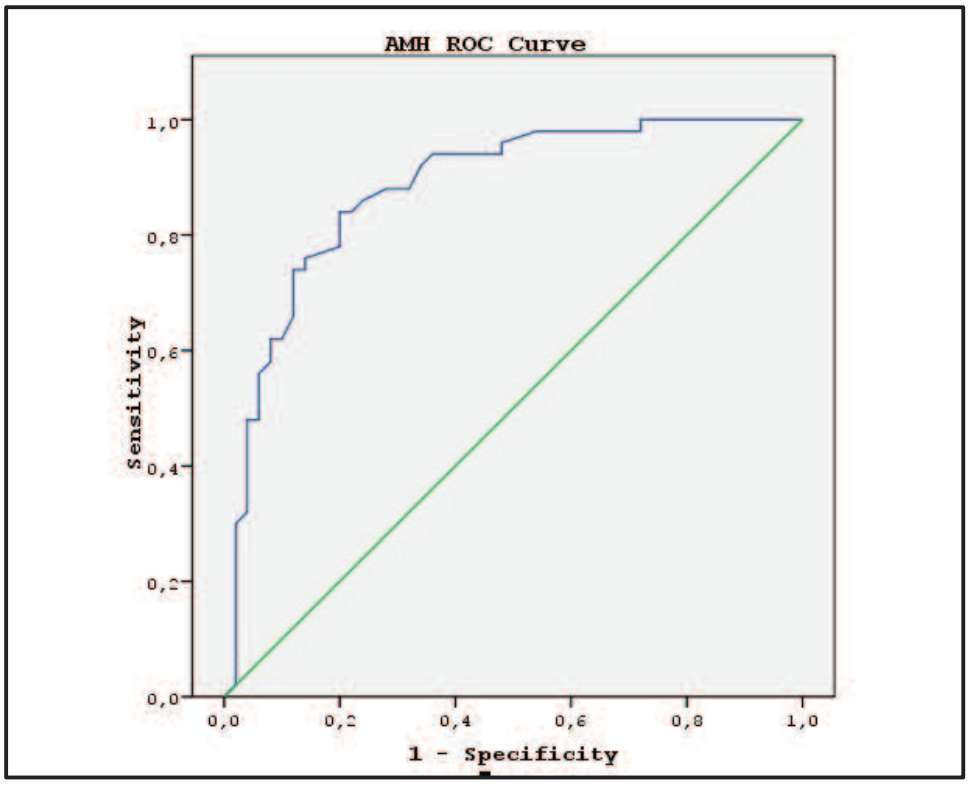


**Figure 1.** Anti-Mullerian lomone level ROC curve ($p < 0.001$).

**Table 3.** The correlation coefficients (*r*) and levels of significance (*p*) between anti-Mullerian homone and mean ovarian volume, mean stromal thickness and mean number of follicles

| | *r* | *p* |
|---|---|---|
| **Mean ovarian volume** | 0.037 | 0.797 |
| **Mean stromal thickness** | 0.024 | 0.866 |
| **Mean number of follicles** | 0.562 | < 0.001 |

[22]. AMH has a negative role in follicular recruitment and causes follicular atresia [23]. Also, AMH reduces the sensitivity of preantral and antral follicles to FSH [24]. According to many studies, serum AMH levels have shown a greater increase in PCOS patients than in normo-ovulatuory women [25].

In the present studies, differences in AMH levels between different PCOS subgroups were evaluated and checked; the results included additional features involved in the pathogenesis of PCOS, for example, androgens, gonadotropins, and sonographic parameters. Next to sonographic parameters and androgens, which were used in the streaming of PCOS patients, patients with severe PCOS also showed higher levels of AMH and LH and higher LH/FSH ratios than did patients with mild PCOS and controls. AMH appears one of the single best and useful parameters to determine different degrees of PCOS at the group level [12, 13, 18, 19]. Similar results were found in our study: the AMH levels of the PCOS group was higher than those of the control group; this was statistically significant ($p < 0.001$).

AMH and the antral follicle count demonstrated comparable diagnostic potential for the indication of severe and mild PCOS in recent studies. It is known that the antral follicle count is strongly associated with AMH, as proven by several studies also in our analyses [26, 27]. AMH levels seem to be more appropriate for reflecting PCOS severity at the group level, but not necessarily in PCOS diagnosis, as shown by the diagnostic potency of AMH and antral follicle count in the studies [19]. Piouka *et al.* [12] demonstrated that, conversely to AMH levels, the antral follicle count did not differ significantly between severe and mild PCOS subgroups; however, AMH levels differed significantly. As indicated by Dewailly *et al.* [13] higher sensitivity and specificity in the diagnosis of severe PCOS were found for AMH compared to follicle numbers, qualifying AMH as a potential alternate marker for antral follicle count in PCOS diagnosis. As a result, AMH and antral follicle count both are appropriate diagnostic tools for determining PCOS severity. On the other hand, the ovarian volume demonstrated substantially lower diagnostic potency compared to antral follicle count [19]. In our study, the AMH levels of Group 2 were higher than those of Group 1, but the subgroup difference in AMH levels wasn't statistically significant. This may be due to the insufficient number of patients in the subgroups.

Dewailly *et al.* [13] analyzed a population with severe PCOS and detected a threshold of 5 ng/ml for the diagnosis of severe PCOS. Köninger et al. [19] found the optimal threshold of AMH for both mild and severe PCOS to be 3.5 ng/ml, with 84% sensitivity and 89% specificity for severe PCOS and 71% sensitivity and 89% specificity for mild PCOS. In our study, in the ROC analyses of AMH, the estimated AUC was found to be 0.88. We found the optimal AMH cut-off value to be 4.1 ng/ml to distinguish healthy women from PCOS patients, with 84% sensitivity and 80% specificity.

In de Vet *et al.*'s study [28], the number of small-growing follicles which show ovarian reserve in ovaries decreased with advancing age, and showed a relationship between the reduced stock of primordial follicles and the number of follicles that were little developed. Women < 25 years of age had higher serum AMH concentrations than those aged 35 years and above, and when women were tracked for a period of 1-7 years, there was a decrease in serum AMH levels, with levels becoming undetectable when menopause was reached [29]. Similarly, in our study, a statistically significant positive correlation was found between the average number of ovarian follicles and AMH levels ($p < 0.001$).

*The Limitations of the Study*

Our study limitations are the number of the subgroups may be more thus we could assess the PCOS severity at the group level better. Nevertheless the complete data set was from a single center and the same physician performed all the ultrasonographic procedures. Thus, this could better accomplish interobserver discrepancies.

## Conclusions

Studies analyzing PCOS have noticed that AMH serum levels provide suitable results for detecting PCOS severity at the group level. AMH serum levels in PCOS patients shows similar results to AFC in the diagnosis of PCOS cases. Furthermore, for the detection of mild PCOS, AMH seems to be the most definitive diagnostic tool next to sonographic views. In patients where vaginal examination is not possible or in patients without hyperandrogenemia, AMH may be utilized as a believable alternate parameter in PCOS diagnosis. More studies are suggested for further research into the diagnostic potency of AMH, considering different PCOS subgroups to detect optimal AMH thresholds.

*Conflict of interest*

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

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