

AOGS MAIN RESEARCH ARTICLE

Elevated serum levels of anti-Müllerian hormone can be introduced as a new diagnostic marker for polycystic ovary syndrome

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Key words

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Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Abstract

Objective. To determine the possible role of anti-Müllerian hormone (AMH) in the diagnosis of polycystic ovary syndrome (PCOS) with a larger population of women and to evaluate its role as a new diagnostic marker. **Design.** Cross-sectional study. **Setting.** University hospital. **Population.** A total of 570 women, with PCOS ($n = 419$) and without PCOS ($n = 151$). **Methods.** Serum basal hormone; AMH, follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, and thyroid-stimulating hormone (TSH) levels were measured. Mean hormone levels were compared and the predictive value of serum AMH level was evaluated with the use of the receiver operating characteristic (ROC) curve analysis. **Results.** No statistically significant differences were found between PCOS women and control groups in terms of age, body mass index and TSH levels. Differences between mean serum, FSH, LH and estradiol levels and LH/FSH ratio were found to be statistically significant ($p < 0.001$). Mean serum AMH level was higher in PCOS women than in controls (7.34 vs. 2.24 ng/mL, $p < 0.001$). The area under the ROC curve assay yielded a satisfactory result of 0.916 (95% confidence interval 0.897–0.935, $p < 0.0001$). The best compromise between 89.8% specificity and 80% sensitivity was obtained with a cut-off value of 3.94 ng/mL for PCOS diagnosis. **Conclusions.** 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 when reliable ultrasonography data are not available or when typical clinical and laboratory findings are not available. The serum AMH level is a new and useful diagnostic tool in PCOS diagnosis.

Abbreviations: AMH, anti-Müllerian hormone; BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PCOM, polycystic ovarian morphology; PCOS, polycystic ovary syndrome; ROC, receiver operating characteristic; TSH, thyroid-stimulating hormone.

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine abnormalities among premenopausal women, yet its diagnosis remains one of the most challenging issues in endocrinology and reproductive

Key Message

There is no single established diagnostic criteria or test for polycystic ovary syndrome. The strength of our study comes from sample size with a reliable cut-off value of anti-Müllerian hormone for the diagnosis of polycystic ovary syndrome.

medicine (1). Different combinations of clinical, biological, and ultrasound criteria have been used to define and diagnose PCOS.

The National Institutes of Health criteria for PCOS require the presence of elevated androgens and menstrual irregularity but do not require the presence of polycystic ovarian morphology (PCOM) (2). The Rotterdam criteria for PCOS, issued in 2003 by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine, include oligoovulation and/or anovulation, hyperandrogenemia and/or hyperandrogenism (clinical signs of elevated androgen levels), and PCOM on ultrasound evaluation. A diagnosis of PCOS requires the presence of at least two of the three features, after other androgen-excess disorders have been excluded (3). The Androgen Excess and PCOS Society defines PCOS as the presence of hyperandrogenism (clinical and/or biochemical) and ovarian dysfunction (oligo or anovulation and/or PCOM), and the exclusion of related disorders (4). The use of ultrasound to diagnose PCOS can be problematic. The interpretation of ultrasound results may demand subjective judgments and is subject to inter-observer variability. Moreover, the vast majority of the target population are teenagers and women of reproductive age, and they may be unavailable for transvaginal ultrasound evaluation because of their virginal status or obesity. In addition to unclear diagnostic criteria, the presence of different phenotypes with PCOS further complicates the diagnosis. These diagnostic challenges emphasize the need for objective and quantitative diagnostic measures to guide clinicians through the diagnosis and treatment of PCOS.

As there are no established diagnostic criteria for PCOS, reported prevalence of the disease varies from 2.2 to 26% of premenopausal women. PCOS is the main cause of anovulatory infertility (5). The pathogenesis of PCOS remains largely unknown but it has been attributed mainly to disordered folliculogenesis causing oligo-ovulatory cycles (6) or impaired folliculogenesis with increased preantral and small antral follicle counts, which result in high anti-Müllerian hormone (AMH) levels (7).

Anti-Müllerian hormone is secreted from granulosa cells in developing primary preantral and early antral follicles up to 6 mm in diameter, and its expression gradually decreases as the follicle develops (8). Increased AMH levels in PCOS may be caused by an increased preantral follicle count and/or increased follicular secretion. In women with PCOS, serum AMH levels correlate with other clinical features such as the duration of the cycle, mean ovarian volume, and serum testosterone and androstenedione levels (9). Thus, AMH is a potential biological marker for PCOM and PCOS, and its application could avoid the need for invasive early follicular phase ultrasound examinations (10,11).

The aim of this study was to assess the possible role of AMH as a diagnostic marker for PCOS in larger population. Moreover, the potential important effect of circulating AMH level on serum luteinizing hormone (LH) level, and the LH to follicle-stimulating hormone (FSH) ratio as a diagnostic marker for PCOS was determined.

Material and methods

Patients who were admitted to Istanbul University Cerrahpasa Faculty of Medicine Hospital, Department of Obstetrics and Gynecology, subdivision of Reproductive Endocrinology between January 2008 and August 2010 were included in this cross-sectional study. Data of 570 women (419 PCOS women, 151 non-PCOS women) younger than 40 years of age were collected. The Rotterdam 2003 criteria were used to diagnose PCOS. Women with a history of ovarian surgery, an abnormality of thyroid or prolactin hormone levels, a history of hormone therapy in the 6 months before the study, a body mass index (BMI) below 19 kg/m² or above 35 kg/m², or an FSH level higher than 12 mIU/L were excluded from the study. Socioeconomic status, medical history, parity, age, and BMI were recorded in a standardized manner. Women who met the Rotterdam criteria for PCOS diagnosis with adequate data available for the study were recruited for the PCOS group. Women who presented to our center and did not meet the Rotterdam criteria (who had none or only one of the criteria) and with adequate records were compared with the PCOS group.

Routine gynecological examination and a basic vaginal ultrasound scan on the day 3–5 of the menstrual cycle was performed. PCOM was identified by pelvic or abdominal ultrasonography and was defined as the presence of 12 or more follicles in either ovary measuring 2–9 mm in diameter, and/or increased ovarian volume of >7 mL. Transvaginal ultrasound scans of the ovaries were performed by experienced sonographers who participated in the study. Additionally, blood samples were collected early in the morning in the fasting state. Serum AMH, FSH, LH, estradiol, prolactin, and thyroid-stimulating hormone (TSH) levels were measured. AMH concentrations were measured with an enzymatically amplified two-sided immunoassay (DSL-10-14400, Active Müllerian inhibiting substance/AMH enzyme-linked immunosorbent assay kit; Diagnostic Systems Laboratories, Webster, TX, USA). The theoretical sensitivity of the method was 0.006 ng/mL, the intra-assay coefficient of variation for high values was 3.3%, and the inter-assay coefficient of variation for high values was 6.7%. Serum estradiol, LH, and FSH were measured on a Roche E-170 automated immunoassay analyzer. The between-batch coefficient of variation for these assays was 10%. Moreover, the

anthropometric parameters body mass in light clothing using electronic digital scales (Mercury, AMZ 14, Tokyo, Japan) and barefoot height with a stadiometer (G-Tech International CO LTD, Kyonggi Province, Korea) were measured and BMI was calculated using the standard formula.

The study was approved by Istanbul University Medical Ethics Committee (approval date 05 July 2012) and each participant signed an informed consent to use data from their medical history for the purposes of this cross-sectional study.

Statistical evaluation of two independent groups were performed using the Student *t*-test. The Mann–Whitney *U*-test was used for comparison of age-related subgroups. A *p*-value <0.001 was considered statistically significant. The diagnostic value of serum AMH level was evaluated by receiver operating characteristic (ROC) curve analysis. Correlation analysis was performed using the Pearson test. All statistical analyses were performed using the Statistical Package for Social Sciences software version 17 for PC (SPSS Inc., Chicago, IL, USA).

Results

Table 1 shows the characteristics of the PCOS and non-PCOS groups. The women's ages, BMI values and serum TSH levels were similar in PCOS and non-PCOS groups. The mean serum levels of FSH, LH, and estradiol, and the LH/FSH ratio were significantly higher in the PCOS group than in the non-PCOS group (*p* < 0.001, respectively). The mean serum AMH level was also significantly higher in the PCOS group than in the non-PCOS group (7.34 vs. 2.24 ng/mL, respectively; *p* < 0.001).

There was weak negative correlation between age and AMH (*r* = −0.15). Positive correlations were found

Table 1. Main clinical and hormonal features in women with PCOS and in women without PCOS.

	PCOS (<i>n</i> = 419)	Non-PCOS (<i>n</i> = 151)	<i>p</i> -value
Age (years)	25.82 ± 5.3	26.62 ± 5	NS
BMI (kg/m ²)	25.43 ± 4.6	25.4 ± 4.4	NS
AMH (ng/mL)	7.34 ± 4.05	2.24 ± 1.70	<0.001
FSH (mIU/mL)	5.18 ± 1.59	7.39 ± 3.34	<0.001
LH (mIU/mL)	5.56 ± 3.43	3.98 ± 1.63	<0.001
Estradiol (pg/mL)	40.31 ± 21.33	46.69 ± 26.23	<0.001
Prolactin (ng/mL)	18.85 ± 8.79	16.76 ± 7.96	<0.001
TSH (mIU/mL)	1.82 ± 0.97	1.82 ± 0.95	NS
LH/FSH ratio	1.104 ± 0.669	0.598 ± 0.2909	<0.001

PCOS, polycystic ovary syndrome; BMI, body mass index; AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

All values except BMI and TSH show statistically significant differences among the groups.

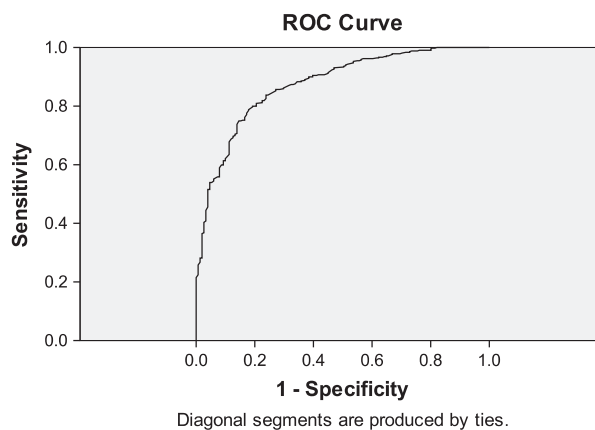


Figure 1. Receiver operating characteristic (ROC) curve for evaluating the diagnostic role of anti-Müllerian hormone on polycystic ovary syndrome. Area under curve (AUC)=0.916. Cut-off value of AMH=3.94 ng/mL (specificity 89.8% and sensitivity 80%) for PCOS diagnosis

between LH and AMH (*r* = 0.2). We could not find any correlation between androgenic hormones and AMH.

Figure 1 shows the ROC curve analysis of the serum AMH concentration for discriminating PCOS. The area under the ROC curve yielded a satisfactory result of 0.916 (95% confidence interval, 0.897–0.935; *p* < 0.0001). The best compromise between specificity (89.8%) and sensitivity (80%) for PCOS diagnosis was obtained with a cut-off value of 3.94 ng/mL. A summary of previous studies on AMH concerning its diagnostic value on PCOS is shown in Table 2. The diagnosis rates of AMH, LH, and the LH/FSH ratio for PCOS are shown in Figure 2. Patients were allocated with respect to their serum AMH levels, reported as percentiles along the *x*-axis. The rate of women diagnosed with PCOS increased gradually as the AMH value increased. A similar analysis of the serum LH levels and LH/FSH ratios resulted in poorer diagnostic values, especially for women with normal LH levels and LH/FSH ratios. In fact, at the cut-off value for AMH of 3.94 ng/mL, both the mean LH level and the mean LH/FSH ratio were at a normal level and thus were not diagnostic for PCOS.

Discussion

Diagnosis of PCOS requires objective and quantitative diagnostic criteria to guide clinicians through the diagnosis and treatment of PCOS. The present study investigated the serum level of AMH as a diagnostic marker for PCOS and showed that the serum AMH levels in women with PCOS were two to three times higher than the levels in women without PCOS (*p* < 0.001) (Table 1). All women in the study were considered to be of reproductive age.

Table 2. Summary of previous studies and our study on AMH for its diagnostic value in PCOS.

References	Year	Study design	Number of patients	Mean AMH values (ng/mL)	Cut-off value of AMH (ng/mL)
Siow <i>et al.</i>	2005	Prospective	31 ^a	4.1	
Pigny <i>et al.</i>	2006	Prospective	73 ^a	11.42	8.4
Wachs <i>et al.</i>	2007	Prospective	16 ^b	7.2	
Dewailly <i>et al.</i>	2010	Retrospective	270 ^a	7.88	
Hart <i>et al.</i>	2010	Prospective	64 ^a	3.08	4.2
Park <i>et al.</i>	2010	Prospective	153 ^a	5.28	
Li <i>et al.</i>	2010	Retrospective	47 ^a	9.85	8
Skalba <i>et al.</i>	2011	Retrospective	87 ^a	10.2	
Woo <i>et al.</i>	2012	Retrospective	140 ^a	11.58	
Present study (Sahmay <i>et al.</i>)	2013	Retrospective	419 ^a	7.34	3.94

AMH, anti-Müllerian hormone; PCOS, polycystic ovary syndrome.

Differences on cut-off values may be associated with inadequate numbers of women or different patient selection criteria.

^aNumber of women with PCOS diagnosis based on the Rotterdam 2003 criteria.

^bPresence of hyperandrogenism and polycystic ovarian morphology are stated as PCOS criteria.

Based on the ROC curve analysis of the serum AMH level in the present study, a cut-off value of 3.94 ng/mL was chosen (Figure 1). Several studies have reported increased serum AMH levels in women with PCOS compared with controls, and the role of AMH as a diagnostic marker has been evaluated in previous studies

(Table 2) (10,12–18). However, both mean serum AMH levels and suggested cut-off values for AMH were inconsistent among the studies, probably because of differences in sample size, sample selection criteria, and specified PCOS phenotypes among the studies. The results of the present study are compatible with previous results only in terms of an elevated serum AMH level in women with PCOS. Our suggestion for a cut-off value of serum AMH for the diagnosis of PCOS is a more reliable diagnostic criterion, given that the population size was larger in the present study than in previous studies.

Pigny *et al.* (12) evaluated serum AMH levels in the diagnosis of PCOS; they reported a satisfactory specificity of 92% but a low sensitivity of 67% with an AMH cut-off of 8.4 ng/mL (60 µmol/L) and a mean serum AMH of 11.42 ng/mL (81.6 µmol/L). Both the mean AMH and AMH cut-off values were higher than the values in the present study, possibly due to their small patient population (12).

Li *et al.* (13) reported that serum AMH levels were elevated in adolescent young adult Chinese women with PCOS, but the serum AMH measurements offered a relatively poor diagnostic power, with a sensitivity of 61.7% and a specificity of 70% at a cut-off of 8 ng/mL. They suggested that the low specificity and sensitivity in their study was attributable to the lower prevalence of hyperandrogenism, obesity, and insulin resistance in their cohort owing to racial differences.

Hart *et al.* (10) found the most effective cut-off value of AMH to be 4.2 ng/mL (30 µmol/L), which is close to our findings.

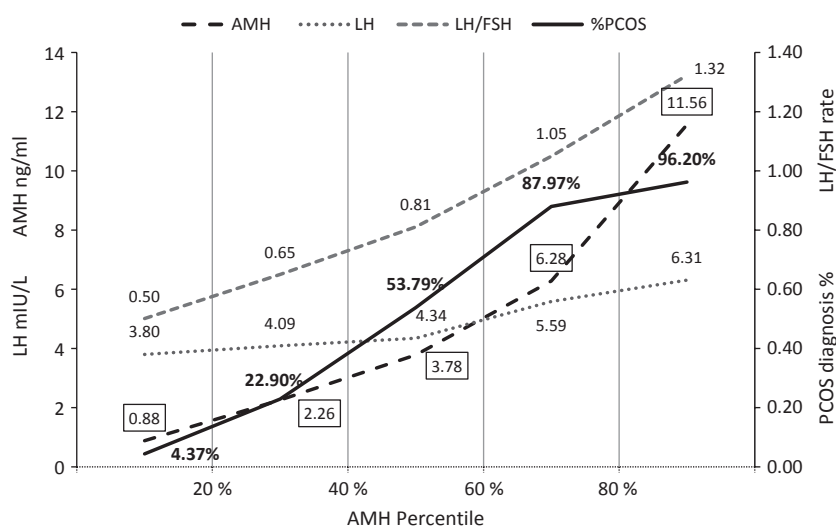


Figure 2. Diagnostic rates of serum anti-Müllerian hormone (AMH) and luteinizing hormone (LH) levels and LH/FSH ratio on polycystic ovary syndrome (PCOS). Almost 80% of the patients diagnosed with PCOS according to Rotterdam criteria, had serum LH levels and LH/FSH ratios within normal limits against high levels of AMH. Thus AMH level seems to be important diagnostic value for PCOS in patients with low or normal serum LH levels and LH/FSH ratios. Total 570 patients, 419 PCOS and 151 nonPCOS.

In the present study, the rate of PCOS diagnosis gradually increased as the serum AMH and LH values and the LH/FSH ratio increased (Figure 2). However, compared with the serum LH level and LH/FSH ratio, the serum AMH level is obviously a stronger diagnostic marker, as 80% of the women with PCOS had serum LH levels and LH/FSH ratios within normal limits. The role of the LH/FSH ratio in identifying women with PCOS remains controversial because measuring gonadotrophin levels in women with PCOS has produced variable results under different conditions (19,20). For example, the levels of LH and FSH varied depending upon whether investigators used single, pooled or frequent samples, and according to the cycle day used for the controls (21). Our findings suggest that the diagnostic criteria for PCOS remains unclear, particularly in women with low LH levels and normal LH/FSH ratios. Nevertheless, the AMH level has an important diagnostic value for PCOS in women with low or normal serum LH levels and LH/FSH ratios, and may challenge the need for ultrasound examinations in the diagnosis of PCOS.

Anti-Müllerian hormone is potentially a biologic marker for PCOM and PCOS that minimizes the need for ultrasound examination. These benefits may be particularly useful in an adolescent and reproductive age population because ovarian evaluation by vaginal ultrasonography may not be possible due to virginal status. In addition to this, the imaging quality of abdominal ultrasound is often impaired by obesity, which occasionally occurs in PCOS women (12,22). Additional studies are warranted to confirm the use of AMH as a prognostic marker of the extent of ovarian dysfunction in PCOS women. Since PCOS is a specific risk factor for ovarian hyperstimulation syndrome in controlled ovarian hyperstimulation (23), AMH level has been shown to be useful in determining the appropriate gonadotrophin dose and is used clinically for this purpose (23,24). It can also predict the response to treatment modalities used to improve metabolic parameters in PCOS women (25,26).

In conclusion, the present study suggests that the serum AMH level is a valuable diagnostic marker for PCOS. The serum AMH level in women with hyperandrogenism, oligoovulation or anovulation could indicate the presence of PCOS when reliable ultrasonographic data are not available or when there are no typical clinical and laboratory findings. AMH values possess a higher diagnostic value in PCOS women with low serum LH levels and low LH/FSH ratio.

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