Taiwanese Journal of Obstetrics & Gynecology 57 (2018) 499–506

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Accuracy of anti-Müllerian hormone and total follicles count to diagnose polycystic ovary syndrome in reproductive women

Thanyarat Wongwananuruk [a], Nalinee Panichyawat [a,*], Suchada Indhavivadhana [a], Manee Rattanachaiyanont [a], Surasak Angsuwathana [a], Kitirat Techatraisak [a], Busadee Pratumvinit [b], Nutchaya Sa-nga-areekul [a]

[a] Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand
[b] Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand

ARTICLE INFO

Article history:
Accepted 9 March 2018

Keywords:
Anti-Müllerian hormone
Follicles number per ovary
Ovarian volume
Polycystic ovarian morphology
Polycystic ovary syndrome

ABSTRACT

Objective: Recently, there was a new recommendation of ultrasonographic criteria to diagnosis polycystic ovary syndrome (PCOS). In addition, serum anti-Müllerian hormone (AMH) was proposed as a surrogate marker for diagnosis of PCOS, but AMH cut-off level for diagnosis of PCOS is unclear. This study aimed to investigate the accuracy of serum AMH and evaluate new ultrasonographic criteria, follicle number per ovary (FNPO) threshold ≥ 25 follicles and ovarian volume (OV) > 10 mL, for diagnosis of PCOS.

Materials and methods: A cross-sectional study was conducted. Fifty-five PCOS women and sixty-three normal ovulatory, non-hyperandrogenic women were recruited. Transvaginal or transrectal ultrasonography was performed in all participants to evaluate follicle number and OV. Serum AMH was evaluated in both study groups.

Results: The mean age of the participants was 25.1 ± 5.3 years old in PCOS group and 29.7 ± 7.2 years old in control group. Mean AMH, FNPO and OV in PCOS women were significantly higher than those in non-PCOS women. The area under the receiver-operating characteristic (ROC) curve of AMH was 0.903. The threshold of AMH at 4.7 ng/mL offered the best compromise between 80% sensitivity and 77.8% specificity. The appropriated threshold values for FNPO, follicle number per cross-section (FNPS) and OV were 15 follicles, 7 follicles and 6.5 mL, respectively. Serum AMH level was significantly positively correlated with FNPO, FNPS and OV in both PCOS and control groups. In PCOS women, serum AMH showed strongly correlation with FNPO ($r = 0.53$, $p < 0.001$) and weakly correlation with total testosterone ($r = 0.283$, $p = 0.036$).

Conclusion: Serum AMH had a good diagnostic performance for diagnosis of PCOS presenting with oligo/anovulation and hyperandrogenism. AMH threshold at 4.7 ng/mL was the best compromise level for diagnosis of PCOS. FNPO ≥15, FNPS ≥7 and OV ≥ 6.5 mL were reliable threshold for detecting polycystic ovaries in women with frank manifestation of PCOS.

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder, affecting 10% of reproductive-aged women [1]. This syndrome is associated with many long term health problems such as central obesity, metabolic syndrome, insulin resistance and diabetes mellitus [2–4]. Therefore, making diagnosis of PCOS is essential because women could be benefit from early detection of associated conditions, planning therapeutic strategies in an affected subject and prevention long term medical problems.

The diagnosis of PCOS is based on the 2003 Revised Rotterdam criteria. Ultrasonographic evidence of polycystic ovarian morphology (PCOM) which is defined as the presence of ≥12 follicles measuring 2–9 mm in diameter and/or ovarian volume (OV) > 10 mL in at least one ovary is one of the criteria [5]. However, the evidence after consensus statement of the Rotterdam criteria showed that the definition of PCOM was inappropriate. According to advancement of ultrasound technology, PCOM is frequently found in both PCOS

* Corresponding author. Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wanglang Road Bangkoknoi, Bangkok 10700, Thailand. Fax +66 24184561.
E-mail address: nalinee.pan@mahidol.ac.th (N. Panichyawat).

https://doi.org/10.1016/j.tjog.2018.06.004

women and non-PCOS women [6,7]. Previous studies reported different follicle number per ovary (FNPO) threshold to discriminate between non-PCOS and PCOS women [8,9]. In 2014, a task force report from the Androgen Excess and Polycystic Ovary Syndrome Society recommends FNPO ≥25 follicles as a new threshold for the definition of PCOM [10]. Nevertheless, ultrasonography still has many limitations, such as observer variability and ultrasound technology.

Apart from using ultrasonographic criteria, serum anti-Müllerian hormone (AMH) was proposed as a surrogate marker for diagnosis of PCOS [11]. The AMH is a glycoprotein produced by the granulosa cells of preantral and antral follicles. Serum AMH concentrations increase in PCOS and significantly correspond to increase in follicle number in PCOS [11]. The previous studies showed good accuracy of AMH for PCOS diagnosis, but the cutoff value of AMH were different among studies [8,11]. The meta-analysis of AMH in diagnosing symptomatic PCOS women demonstrated 79.4% specificity and 82.8% sensitivity at cutoff value of 4.7 ng/mL [12].

The aim of the present study was to investigate the accuracy of AMH for diagnosis of PCOS. The secondary objective was to evaluate new ultrasonographic criteria of PCOM by FNPO threshold ≥25 follicles and ovarian volume >10 mL for diagnosis of PCOS in reproductive PCOS women.

Materials and methods

The cross-sectional study was conducted between April 2016 and March 2017 at Gynecologic Endocrinology Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Siriraj Hospital, Mahidol University. Ethical approval was obtained from Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University with certificate of approval (COA) number Si 229/2016. All participants were informed and written consent to participate in this study.

This study had 2 population groups: PCOS and control group. The PCOS participants were women 18–45 years of age, who diagnosed with PCOS by the Revised Rotterdam Criteria 2003 as having both 1) oligo-anovulation and 2) clinical and/or biochemical signs of hyperandrogenism, were enrolled in the study. Other etiologies, such as congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome, thyroid disease or hyperprolactinemia were assessed before diagnosis of PCOS. Oligo-anovulation was defined as menstrual interval longer than 35 days. Clinical hyperandrogenism was defined as presence of acne, hirsutism or androgenic alopecia. Acne was assessed by using the recommended criteria from Dermatological Society of Thailand in 2011 [13]. Severity of acne was graded as three levels. Mild acne was defined as presence of comedone and/or <10 papules or pustules. Moderate acne was presented as > 10 papules or pustules and/or <5 nodules. Severe acne was shown as numerous of papules or pustules or nodules. Hirsutism was evaluated by using the modified Ferriman-Gallwey scoring system (mFG), cut-off score ≥ 5 indicated hirsutism. This cut-off score was used because mFG score of 5–6 was appropriated to define hirsutism in the studies including East Asian population [14–17]. Androgenic alopecia was evaluated using Ludwig scale. Biochemical hyperandrogenemia was defined as serum total testosterone level greater than 0.8 ng/mL [18]. The control participants were healthy women aged 18–45 years old. They had to have regular menstrual cycle with interval of 21–35 days and no clinical and biochemical hyperandrogenism. The participants in both PCOS and control groups were ineligible if they had used steroid drug or hormone during the 3 months prior to enrollment and had previous history of ovarian surgery.

All participants were asked about general gynecologic history and their menstruation. They were received physical examination and evaluated signs of hyperandrogenism. Then all participants were scanned pelvic ultrasonography and taken venous blood puncture.

Ultrasonography measurements

Transvaginal or transrectal ultrasonography (TVS or TRS) was performed by one of two examiners to evaluate follicle number and ovarian volume. Control subjects were evaluated in the early follicular phase between days 2^{nd}–5^{th} of menstrual period. Women with PCOS were evaluated at anovulatory or follicular phase. Ultrasonography measurements followed the protocol as mention in literature [10,19], using an Aloga Alpha 6 with 8 MHz transvaginal transducer. Ultrasonography measurements were taken in real-time. Both ovaries were scanned from inner to outer margin in the longitudinal plane. The participant was excluded if there was a dominant follicle (≥10 mm), corpus luteum or other abnormal ovarian mass. In case of suspicious evidence of ovulation at the time of ultrasound performing, the participant was also excluded from the study. After determination of the longest axis of the ovary, the length and thickness were measured and the OV was calculated by using the formula for a prolate ellipsoid (0.5 × length × width × thickness). Follicle size was expressed as the mean of two perpendicular measurements and follicles between 2 and 9 mm were counted. For each ovary, follicle number per cross-section (FNPS) were counted in the plane of the ovary that contained maximum follicles and FNPO were counted by slow and continuous scanning of the entire ovary, from one margin to the other. The ovarian parameters were recorded from both ovaries in each participant and greater values of FNPO, FNPS, OV in each participant were used for analysis.

Reliability analysis

The participants in both PCOS group and control group were randomly selected and simultaneously evaluated by two sonographers to assess the reliability for counting FNPO and FNPS. Based on an intra-class correlation coefficient analysis from previous study, the level of inter-observer agreement for FNPO and FNPS was 0.84 and 0.94, respectively [9]. In this study, inter-observer reliability was 0.959 for FNPO and 0.945 for FNPS. Intra-observer reliability of the first operator was 0.986 and the second operator was 0.981.

Biochemical assays

In PCOS group, blood was taken in the morning at the same day of TVS or TRS performing. Hormonal assays included serum total testosterone and AMH were evaluated in both PCOS and control group. Serum assays were performed in the Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital. Serum total testosterone was measured by electrochemiluminescence immunoassay (ECLIA) using Cobas8000 c602 (Roche Diagnostic, Germany) with intra-assay coefficient of variation (CV) of 1.57%–2.26% and inter-assay CV of 2.92%–4.32%.

For serum AMH measurement, blood samples were centrifuged at room temperature within 30 min. Serum was stored at −80 °C until AMH analysis. Serum AMH was assayed by Elecsys AMH ECLIA on a Cobas e602 automated assay system (Roche Diagnostic, Germany) with intra-assay CV of 0.55%–0.86% and inter-assay CV of 0.93%–1.02%. The available range of measurement using the Elecsys AMH assay is between 0.03 and 23 ng/mL.

Sample size

The sample size was calculated based on the meta-analysis study of Iliodromiti S et al., in 2013 [12]. Serum AMH at cutoff

value of 4.7 ng/mL had sensitivity and specificity in diagnosing PCOS in the symptomatic women of 82.8% and 79.4%, respectively. The sample size calculation yielded 55 women in PCOS group and 63 women in control group.

Statistical analysis

Statistical analysis was performed with SPSS version 14. Descriptive statistics was used to describe participants' characteristics. Values are given as means and standard deviations (SD) or absolute number and percentages. Groups were compared with independent samples t-tests for normally distributed variables and by Mann–Whitney test for variables not normally distributed.

The receiver-operating characteristic (ROC) curves were constructed to evaluate the diagnostic test performance such as sensitivity, specificity of AMH and ultrasonographic ovarian parameters for diagnosis of PCOS. Sensitivity against 1-specificity was plotted at each threshold level. The area under the ROC curve (AUC) was computed to represent the probability of correctly identifying controls and patients with PCOS.

Relationships between AMH and other variables were evaluated by Pearson's correlation coefficient. The p-value < 0.05 was considered statistically significant.

Results

The numbers of participants were 55 women in PCOS group and 63 women in control group. Characteristics of the participants are presented in Table 1.

Table 2 presents the result of AMH and ovarian ultrasonographic findings. The mean AMH in PCOS women was significantly higher than non-PCOS women. After adjusting for age using regression analysis, AMH level was still significantly higher in PCOS women. All ovarian parameters (total antral follicle count, FNPO, FNPS, OV) were also statistically significant greater in PCOS group than control group.

Sensitivity, specificity of anti-Müllerian hormone and ovarian parameters for diagnosis of PCOS are presented in Table 3 and ROC curve with AUC of these parameters are shown in Fig. 1. The serum AMH had AUC of 0.903. The cut-off AMH of 4.7 ng/mL showed the best compromise between 80.0% sensitivity and 77.8% specificity. The AUC of FNPO was 0.918 and the proper level was 15 follicles in an ovary with sensitivity of 81.8% and specificity of 85.7%. The AUC of FNPS was 0.904 and the proper level was 7 follicles in the cross sectional plane of an ovary with sensitivity of 87.3% and specificity of 84.1%. Lastly, the AUC of OV was 0.872 and the proper level was 6.5 mL with sensitivity of 81.8% and specificity of 81.0%.

Correlation between AMH and other parameters affecting PCOS is presented in Table 4. AMH level was significantly positive correlated with total antral follicle count (AFC), FNPO, FNPS and OV in both PCOS and control group. Serum AMH showed high correlation with FNPO in PCOS women ($r = 0.530$, $p < 0.001$).

Additionally, example vaginal sonographs for showing how to count FNPO are demonstrated in Fig. 2. Fig. 3 presents scatter plots of AMH and sonographic parameters (total AFC, FNPO, FNPS and OV) in both PCOS and control group.

Table 1
Baseline characteristics of the participants.

Characteristic	PCOS (N = 55) (mean ± SD) or n (%)	Control (N = 63) (mean ± SD) or n (%)	p-value
Age (years)	25.1 ± 5.3	29.7 ± 7.2	<0.001
Body mass index (kg/m^2)	25.3 ± 6.3	23.5 ± 5.1	0.085
Waist circumference (cm)	81.6 ± 13.7	76.3 ± 9.8	0.016
Systolic blood pressure (mmHg)	115.0 ± 14.2	115.7 ± 10.6	0.755
Diastolic blood pressure (mmHg)	71.4 ± 12.4	74.6 ± 9.4	0.110
Parity			0.028
0	50 (90.9)	41 (65.1)	
1	3 (5.5)	10 (15.9)	
2	2 (3.6)	9 (14.3)	
3	0	3 (4.8)	
Abortion			0.279
0	53 (96.4)	56 (88.9)	
1	2 (3.6)	6 (9.5)	
2	0	1 (1.6)	
Total testosterone (ng/mL)	0.450 ± 0.172	0.180 ± 0.089	<0.001

Table 2
The result of AMH and ovarian ultrasonographic findings.

Parameter	PCOS (N = 55) (mean ± SD)	Control (N = 63) (mean ± SD)	p-value
Anti-Müllerian hormone (ng/mL)	8.347 ± 4.305	3.153 ± 1.703	<0.001
Total antral follicle count[a]	41.11 ± 17.90	17.25 ± 7.00	<0.001
Follicle number per ovary (follicles)	24.29 ± 10.33	9.97 ± 3.86	<0.001
Follicle number per cross-section (follicles)	9.95 ± 3.41	5.10 ± 1.52	<0.001
Ovarian volume (mL)	9.15 ± 3.29	4.66 ± 1.83	<0.001

[a] Total antral follicle count means sum of antral follicles count of both ovaries.

Table 3
Sensitivity, specificity of anti-Müllerian hormone and ovarian parameters for diagnosis of PCOS.

Parameters	AUC[a] (95% CI)	Threshold (ng/mL or follicles or mL)	Sensitivity (%)	Specificity (%)
Anti-Müllerian hormone	0.903 (0.851–0.956)	6.3	61.8	96.8
		5.0	76.4	81.0
		4.7	80.0	77.8
		4.2	83.6	73.0
		4.1	85.5	71.4
Follicles number per ovary	0.918 (0.866–0.970)	25.0	45.4	100.0
		17.0	76.0	95.0
		15.0	81.8	85.7
		14.0	85.5	79.4
		12.0	90.9	65.1
Follicle number per cross-section	0.904 (0.844–0.963)	12.0	38.2	100.0
		8.0	71.0	94.0
		7.0	87.3	84.1
		6.0	90.9	63.5
		5.0	94.5	31.7
Ovarian volume	0.872 (0.803–0.941)	10.0	38.2	98.4
		7.0	75.0	90.0
		6.5	81.8	81.0
		6.0	83.6	76.2
		5.5	83.6	74.6

[a] Area under the receiver-operating characteristic (ROC) curve.

Discussion

According to some disadvantages of ultrasound in diagnosis of PCOM, such as examiner-dependent, difficult in obtaining standardized measurements and obsolete PCOM criteria, many studies explored the surrogate marker to increase the accuracy for diagnosis. Serum AMH is proposed as a marker for diagnosis of PCOS. The AMH concentrations are constant throughout menstrual cycle [20]. The AMH is more sensitive and specific than follicle count as it reflects both preantral and small antral follicles. This study primarily evaluated role of AMH in diagnosis of PCOS.

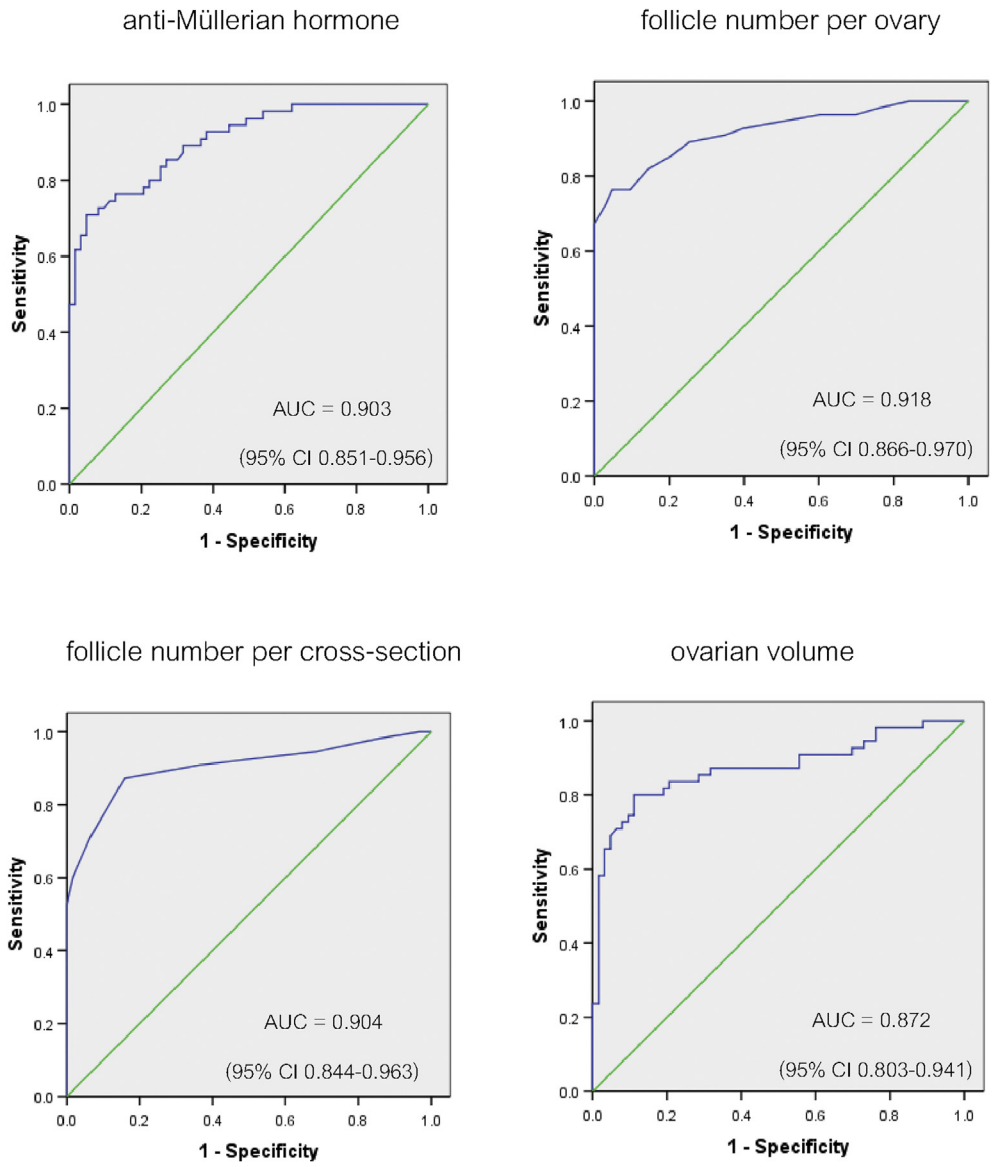

Fig. 1. Receiver-operating characteristic (ROC) curve and area under the ROC curve of AMH, FNPO, FNPS and OV.

From the result in this study, serum AMH level was significantly higher in PCOS women than non-PCOS women even after adjusting for age. Because AMH is produced from granulosa cells of preantral and small antral follicles and these follicles substantially increase in PCOS. Therefore, AMH is also increased in PCOS women [8,11,21,22]. The ability of AMH for diagnosis of PCOS was confirmed in many literature, but the threshold values of AMH differed among studies, ranging from 2.52 to 10 ng/mL [8,11,22–25]. In our study, serum AMH demonstrated a good diagnostic performance. The threshold of 4.7 ng/mL designated as the best compromise with sensitivity of 80.0% and specificity of 77.8%. Our results are consistent with the meta-analysis result that demonstrated 82.8% sensitivity and 79.4% specificity for AMH cutoff value of 4.7 ng/mL [12].

Table 4
Correlation between AMH and other parameters.

Parameter	PCOS		Control	
	r[f]	p-value	r[f]	p-value
Age	−0.164	0.233	−0.209	0.101
BMI[a]	−0.268	0.048	−0.225	0.076
Total AFC[b]	0.499	<0.001	0.672	<0.001
FNPO[c]	0.530	<0.001	0.625	<0.001
FNPS[d]	0.327	0.015	0.568	<0.001
OV[e]	0.456	<0.001	0.324	0.010
Total testosterone	0.283	0.036	0.206	0.112

[a] Body mass index.
[b] Antral follicle count.
[c] Follicle number per ovary.
[d] Follicle number per cross-section.
[e] Ovarian volume.
[f] r = Pearson correlation.

The reason for inconsistence of AMH cutoff is possibly using different AMH assay. Previous studies used manual enzyme-linked immunosorbent assays which utilized different primary antibodies against AMH and different standards and values [26,27]. At present, there are fully automated assays with lower inter-laboratory variation, the Elecsys AMH assay and the Access AMH assay [27]. Both automated assays exhibited excellent analytical performance and high degree of accordance [28]. Even if our result was consistent with the meta-analysis included the East Asian studies, all studies in the meta-analysis used the AMH manual assays which were different from our study using automated assay. To compare

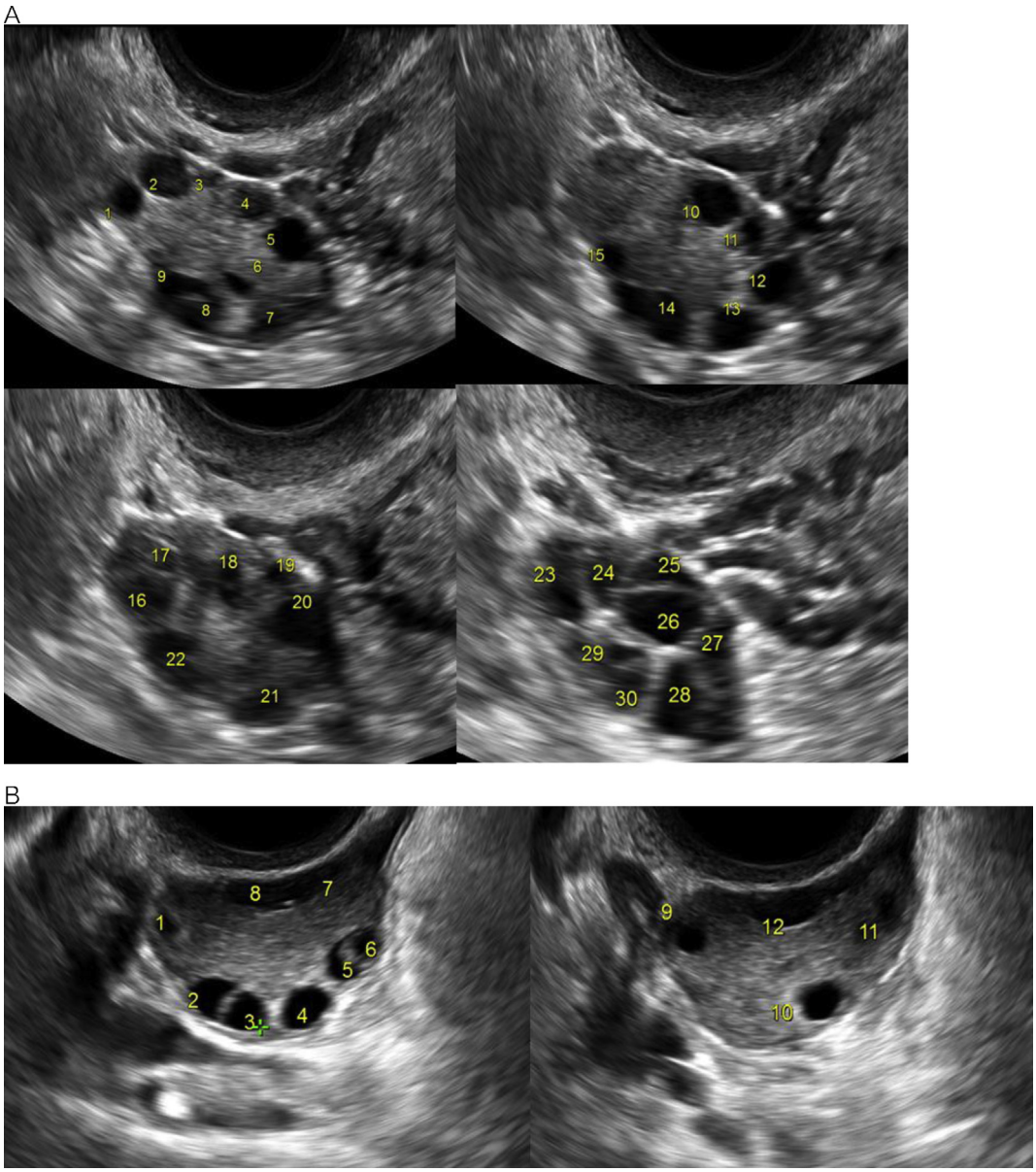

Fig. 2. Serial transvaginal ultrasound images evaluated follicle number per ovary (FNPO). Structures identified as follicles were counted and indicated by number. A. The number of follicles throughout the entire ovary in PCOS woman. B. The number of follicles throughout the entire ovary in non-PCOS woman.

with the former study that used automated Elecsys AMH ECLIA assay, AMH threshold was 5.04 ng/mL to determine PCOS status [24]. Matsuzaki T et al. reported AMH cutoff value of 7.33 ng/mL with 44.7% sensitivity and 76.8% specificity [29]. Although the same assay was used, the threshold values were still inconsistent. Another consideration for discrepancies of cutoff for AMH is the dissimilar of inclusion criteria of study participants and characteristics of recruited participants. Age of the participants was different among studies. Ethnicity also influenced the disparity of AMH values, as lower AMH in Chinese or South Asian women compared with Caucasian PCOS women [30,31]. Importantly, the different AMH assays and different population enrolled in the studies cause difficulty in comparing AMH values among studies. Thus, the consensus on AMH cut-off level for diagnosis of PCOS is unclear.

Currently, PCOM is a cornerstone of PCOS diagnosis according the Revised Rotterdam criteria. The threshold $\geq$12 follicles per ovary have been questioned, as PCOM was also commonly detected in many ovulatory non-hyperandrogenic women [6,7]. New recommendation for PCOM definition as having $\geq$25 FNPO was proposed [10]. In this study, FNPO was a good diagnostic ultrasound criterion in reproductive Thai PCOS women. However, the recommended cutoff of 25 follicles had inferior diagnostic efficacy in this study with 45.4% sensitivity and 100% specificity. The appropriate FNPO threshold for our population should be 15 follicles, with sensitivity of 81.3% and specificity of 85.7%. In previous study, Lujan ME et al. suggested FNPO threshold of 26 follicles [9] and Dewailly D et al. suggested FNPO threshold of 19 follicles [8]. In Chinese population, AUC for FNPO to diagnose PCOS was 0.911 at threshold of 12 FNPO (85.2% sensitivity, 92.6% specificity) [32].

The ovarian volume (OV) showed slightly lower sensitivity and specificity than FNPO. The OV had an optimal threshold at 6.5 mL with 81.8% sensitivity and 81% specificity in our population. This threshold was lower than mentioned threshold in the revised Rotterdam criteria and recently in a task force report [10,19].

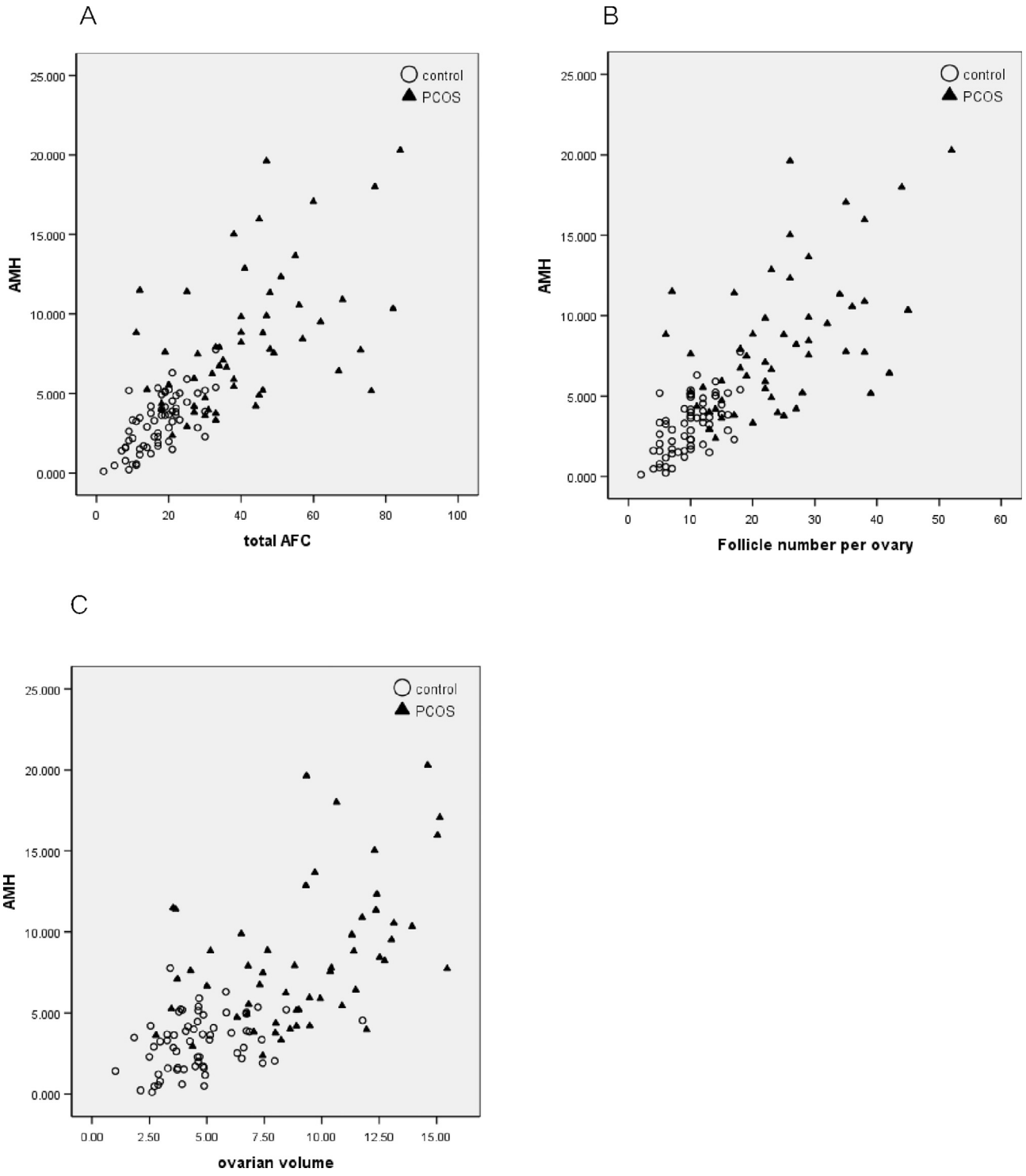

Fig. 3. Relationship between serum AMH levels and ultrasonographic parameters.

However, our results were similar to the findings of previous studies that had OV threshold of 7 mL with sensitivity of 87% and specificity of 89% [8] and OV cutoff value of 7.9 mL in Chinese PCOS women with 78% sensitivity and 85.6% specificity [32]. The appropriate threshold of FNPS in this study was 7 follicles, compared with previous suggested threshold of 9 follicles [9]. Nevertheless, the task force report stated that insufficient data to recommend FNPS threshold to define PCOM and using FNPS or OV in case of inadequate ultrasound technology for FNPO counting [10].

The main reasons for discrepancies of cutoff for PCOM are probably the difference in recruited participants, ultrasonography technology used and counting follicles methods. In women with PCOS, the mean OV and FNPO appear to be affected by ethnicity, lower values in Asian populations [32] and higher values in European and USA populations [8,9]. Mean OV in Asian populations tends to lower than the Rotterdam criteria. Another concern is characteristic of participants. European and USA populations have a tendency to have higher BMI, greater waist circumference and more

hyperandrogenism. These characteristics might be one of the differences of ovarian parameter values. Due to diverge of follicle number and OV between ethnic groups, PCOM probably use different criteria. Further studies are needed to evaluate these values.

In the aspect of correlation between AMH and other factors, AMH was positively correlated with AFC, FNPO and OV in both PCOS and non-PCOS women. These correlation results were consistently with earlier findings [8,21–24]. In this study, AMH was negatively correlated with age but without significant. Testosterone level was significant higher in PCOS women than non-PCOS women [8,22]. Additionally, testosterone had weakly correlation with AMH, but reach significant in only PCOS group as previously report [23].

The strength of the study is that neither the control nor PCOS participants were screened for PCOM prior recruitment because of the need to avoid using of any questionable ultrasound criterion of PCOM. This study is a pioneered report of AMH level in Thai PCOS and comparing with ovarian morphology. Notably, AMH indicated as having a good performance for diagnosis of PCOS in this study. The advantages of AMH are less subjective, independent of examiner skills or ultrasound machine and lastly, automated AMH assays demonstrate good analytical performance with less inter- and intra-laboratory variability. AMH could be replaced or be an alternative criteria for diagnosis of PCOS in the future which will increase accuracy and reliable in making diagnosis.

Main limitation is significant difference in age of the included population. Generally, AMH level and follicle numbers were different between ages. Subjects evaluated were recruited from only one outpatient clinic of a tertiary care hospital and thus do not represent the general population. Future prospective studies with age-matched control for identifying appropriated AMH and FNPO threshold could be benefit.

Conclusion

Serum AMH has a good diagnostic performance for diagnosis of PCOS women presenting with oligo/anovulation and hyperandrogenism. The AMH threshold of 4.7 ng/mL is the best compromised level for diagnosis of PCOS in our population. Serum AMH might be superior to ultrasonographic features of ovarian morphology, as the latter is dependent on quality of the ultrasound machines and the operator skill. The FNPO $\geq$15 follicles per an ovary, FNPS $\geq$7 follicles per a cross sectional plane and OV $\geq$ 6.5 mL are reliable threshold for detecting polycystic ovaries in women with full manifestation of PCOS. However, international threshold of AMH should be established before including in the criteria of PCOS diagnosis. Further study including diverse phenotypic PCOS population cohort to confirm the most suitability threshold should be conducted.

Conflict of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgement

The author would like to thank Miss Chongdee Dangrat from Gynaecologic Endocrinology unit, Department of Obstetrics and Gynaecology and Miss Sujitra Wangchaijaroenkit from Department of Clinical Pathology, Siriraj Hospital for their assistance in laboratory procedures. Moreover, the author would like to be grateful for Miss Julaporn Pooliam from Clinical Epidemiology Unit, Faculty of Medicine Siriraj Hospital, Mahidol University for assistance in statistical analyses.

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