Serum Anti – Mullerian Hormone Level Threshold Among Infertile Filipino Women with Polycystic Ovarian Syndrome

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Objective: To determine the threshold value for anti-Müllerian hormone (AMH) in the diagnosis of polycystic ovarian syndrome (PCOS) in infertile Filipino women and to ascertain the correlation of AMH with age and body mass index of PCOS women.
Methods: A retrospective cross-sectional study was carried out on infertile Filipino women at the Center for Advanced Reproductive Medicine and Infertility from August 2015 to March 2020. The women were separated into the PCOS group and male factor infertility group. Serum AMH was analyzed with Access AMH chemiluminescent immunoassay by Beckman Coulter. The AMH threshold for the diagnosis of PCOS was computed using Youden's index.
Results: There were 585 women included in the study, 311 (53.16%) were diagnosed with PCOS by the Rotterdam criteria, while 274 (46.84%) were non PCOS women. Mean serum AMH for PCOS was 5.88 ± 3.37 ($p < 0.01$). A threshold value of serum AMH above 3.86 ng/ml was predictive of PCOS by Youden's index with a sensitivity of 67.2%, specificity of 77.7%, and correct classification rate of 72.1%. There was a negative correlation of AMH level with increasing age in both PCOS and non – PCOS group but the PCOS group had a higher AMH level. There was no correlation noted with AMH and body mass index in both groups.
Conclusion: AMH levels were higher in the PCOS women compared to those without the diagnosis. AMH threshold level could support the diagnosis of PCOS in infertile Filipino women.

Key words: Anti – Mullerian Hormone (AMH), Infertility, polycystic ovarian syndrome (PCOS), threshold

Introduction

Polycystic ovary syndrome (PCOS) accounts for 80 - 90% of anovulatory cycles[1] and 25- 30% of infertility causes[2]. It is a heterogenous, multisystem endocrinopathy that presents with a wide spectrum of clinical features such as menstrual irregularity, infertility, anovulation and metabolic disturbances with long term sequelae such as diabetes mellitus type II, cardiovascular diseases, metabolic syndrome and endometrial cancer[3]. The Rotterdam criteria is commonly used to diagnose polycystic ovarian syndrome, which must meet two out of the following criteria: oligomenorrhea and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and sonographic evidence of polycystic ovaries (polycystic ovarian morphology, PCOM) defined as presence of 12 or more follicles in each ovary, measuring 2 - 9 mm in diameter, and/or increased ovarian volume more than 10mL. Other causes of hyperandrogenism such as congenital adrenal hyperplasia, Cushing's syndrome and other androgen secreting tumors[4] must be excluded.

The diagnosis of PCOM has been disputed for various reasons: it is subjective and has a wide interobserver variability, many women with PCOS are young or adolescent and transvaginal ultrasound maybe too invasive[5] and advances in imaging have led to an artificial increase in PCOM resulting in confusion over its use as a diagnostic criterion. The threshold proposed by Christ, et al. is 28 follicles per ovary[6] which is more than twice the Rotterdam threshold. In another paper by Dewailly et al, > 19 follicles were proposed as the cut off for PCOM definition, however, this study also concluded that a serum AMH level of 35 pmol/L or 5 ng/ml is more sensitive and specific in the diagnosis of PCOS than follicle number[7].

Anti – Mullerian Hormone or AMH is a glycoprotein produced by granulosa cells of small and large pre-antral and small antral follicles that belongs to the transforming growth factor-b superfamily. It can be requested at any day of the cycle because its level is independent of the circulating gonadotropins in the body resulting in minimal intra and intercycle variability, although one of AMH's limitation is the lack of international standardized assay[8].

Due to the increased number of antral follicles, women with PCOS have a higher AMH value compared with normal women[9]. Histologically, polycystic ovaries exhibit a normal number of primordial follicles, but the number of developing follicles is doubled[10]. Therefore, circulating AMH levels in women with PCOS are two to three times higher than healthy controls[11]. As serum AMH is more stable, easily performed via blood extraction and more objective as compared to a sonologic diagnosis, some papers have proposed that it can be a biomarker for the diagnosis of polycystic ovarian syndrome.

At present there have been several cut-off levels reported of Anti – Mullerian Hormone for the diagnosis of PCOS women, however, there have been no published data for Filipino women. Since several studies have stated that AMH levels are affected by ethnic or racial disparities, it is important to determine the specific threshold level for Filipino women.

Methods

This study is an analytical cross - sectional study that aimed to determine the threshold value of anti-mullerian hormone for the diagnosis of polycystic ovarian syndrome in infertile Filipino women from August 2015 to December 2020. The study was conducted at the Center for Advanced Reproductive Medicine and Infertility at St Luke's Medical Center. The study also intended to determine the demographic profile and clinical characteristics of the Filipino women included in the study and to correlate the AMH levels with age and body mass index of the study population. An age – range for patients with PCOS was also extracted from the gathered data. Upon approval of the hospital review board (RPC – 026 – 02 – 21; SL – 21031), data such as age, AMH levels, and body mass index were obtained from the center's database.

Data were extracted from two sets of women: the first group are infertile women diagnosed with polycystic ovarian syndrome through the Rotterdam criteria and the second group are those that underwent fertility treatment due to male factor (control). The age, body mass index and AMH values were retrieved from the database. The AMH levels were measured using the third generation automated Access AMH immunoassay by Beckman Coulter and reported in ng/ml. Women with incomplete data were excluded.

Statistical Analysis

After the data were extracted by the investigator from the database, all the information was manually entered into an electronic spreadsheet file; and subsequent data processing and analysis was then carried out using the software, Stata 13. Descriptive statistics such as mean, standard deviation, median and range were used for continuous variables such as age in years, baseline levels of the biomarkers, and anthropometric measurements. The frequency and percentage were then used for describing the categorical data variables such as the presence of polycystic ovary syndrome, and body-mass index category. A series of independent t-test with Welch's correction was used to compare the mean age, body-mass index, and biomarker levels between the comparison groups. The median test was performed to determine differences in the median level of AMH; and a chi-square test to compare proportion of body-mass index category (e.g. normal, overweight) between the said groups.

Box plots were also presented to show the range of AMH values between these groups.

An area under the receiver operating characteristic curve, or an AUROC, was created to examine the degree of discrimination between the actual AMH values and the presence of PCOS in the sample population. The associated plots showed the area under the curve, and yielded sensitivity and specificity – and the basis for determining the optimal cut-point to predict the occurrence of the outcome was the computed using the Youden's index and the trade-off between sensitivity, specificity and overall correct classification rate of the cut-point.

The researchers then compared different cut-off levels of the AMH for determining the presence or absence of PCOS – considering their yielded sensitivity, specificity, and overall correct classification rate. Another ROC was created to compare the area under the curve using the selected threshold value. The correlation used between a continuous variable and a dichotomous variable was computed using the Pearson's correlation coefficient between the actual AMH levels with the age in years and body mass index. Scatter plots were sub-divided to represent the pattern for those with and without PCOS. The level of significance for all sets of analysis was set at a p- value less than 0.05 using two-tailed comparisons.

Results

The clinico-demographic characteristics of the study population are presented in Table 1. A total of 585 women were included and there is an almost equal distribution between the two groups: PCOS (n=311) and non-PCOS (n=274) patients. The mean age of the patients from PCOS group was 33.77, while in the non PCOS group was 33.49. There was no difference in the age of the patients between the comparison groups whether seen as actual years (t: -0.88, df: 583, p: 0.38), or categories (X^2: 8.33, p: 0.08). There was a higher proportion of patients outside the normal body mass index classification (X^2: 11.69, p: 0.02) and a higher value of BMI (t: -1.81, df: 583, p: 0.03) in the PCOS group (24.40 + 4.36; p = 0.03) compared to the non PCOS group (23.76 + 4.06; p=0.03).

The levels of AMH are noted to be higher in women with PCOS compared to the non-PCOS women. The mean AMH for the PCOS group was 5.88 ± 3.37 ng/ml which is almost doubled from the non-PCOS group value of 3.10 ± 1.65 ng/ml (t: -12.40, df: 583, p<0.01). A similar trend is also seen in the median of the PCOS group (5.13 ng/ml) and the non-PCOS group (2.71ng/m) (z: -12.41, p<0.01). There is also a wider range of AMH values among patients with PCOS in contrast with the narrower range of AMH levels in those without PCOS as seen in Figure 1.

There was a positive correlation between the presence of PCOS and the levels of the AMH (p: 0.51, CI: 0.45-0.57, p<0.01). The levels of AMH decline as the women ages, regardless of disease status but the levels of the biomarker are higher among women with PCOS than otherwise as presented in Figure 2. In Figure 3 on the other hand, there was no observed pattern for BMI and AMH levels, despite the PCOS diagnosis of the women.

Table 1. Clinico-demographic characteristics of the study population

Characteristics	Overall	Non-PCOS	PCOS	p-value
Frequency (%)	585 (100%)	274 (46.84%)	311 (53.16%)	-
Age in years	33.64 ± 3.92	33.49 ± 3.77	33.77 ± 4.05	0.38
≤30	111 (18.97%)	49 (17.88%)	62 (19.94%)	0.52
>30	474 (81.03%)	225 (82.12%)	249 (80.06%)	
Body-mass index	24.10 ± 4.23	23.76 ± 4.06	24.40 ± 4.36	0.03*
Underweight	21 (3.59%)	6 (2.19%)	15 (4.82%)	
Normal	248 (42.39%)	135 (49.27%)	113 (36.33%)	
Overweight	123 (21.03%)	54 (19.71%)	69 (22.19%)	0.02*
Obese I	149 (25.47%)	61 (22.26%)	88 (28.30%)	
Obese II	44 (7.52%)	18 (6.57%)	26 (8.36%)	
AMH level in ng/mL				
Mean ± SD	4.58 ± 3.04	3.10 ± 1.65	5.88 ± 3.37	<0.01*
Median (Range)	3.63 (1.04-22.27)	2.71 (1.04-13.20)	5.13 (1.04-22.27)	

- Independent t-test with Welch's correction, chi-square test of association, medians test

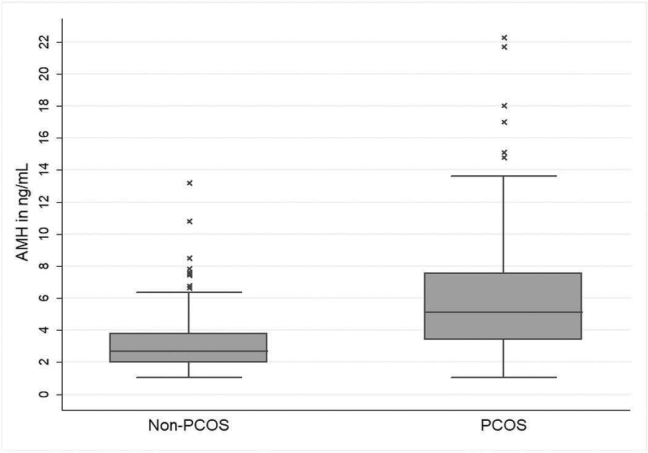

Figure 1. Box-plot of AMH levels and PCOS status

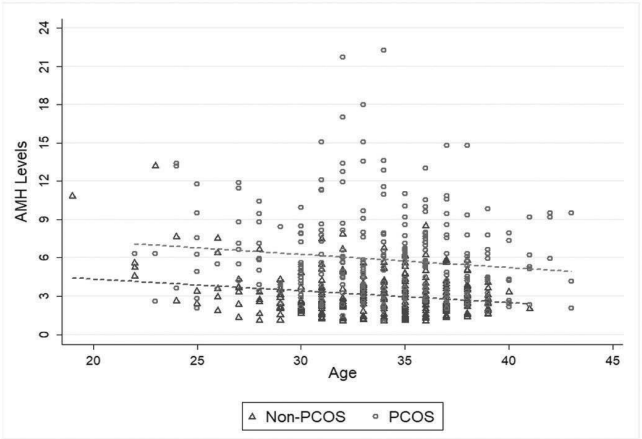

Figure 2. Two-way scatter plot of PCOS status, actual AMH levels and age

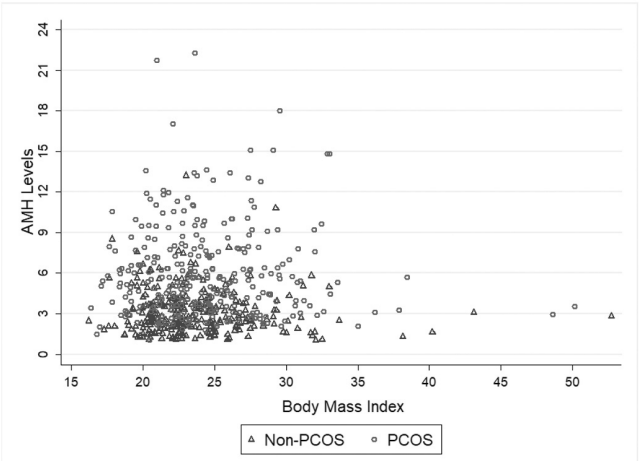

Figure 3. Two-way scatter plot of PCOS status, actual AMH levels and BMI

A receiver operating characteristic (ROC) curve for determining the presence of PCOS (or non-PCOS) from the serum levels of the AMH (Figure 4) showed an acceptable degree of discrimination (AUC: 0.80, CI: 0.76-0.83, SE: 0.02). The cut-point for discriminating the presence or absence of PCOS using the actual levels of the anti-Mullerian hormone was determined using the Youden's index – which was 3.86 mg/dL.

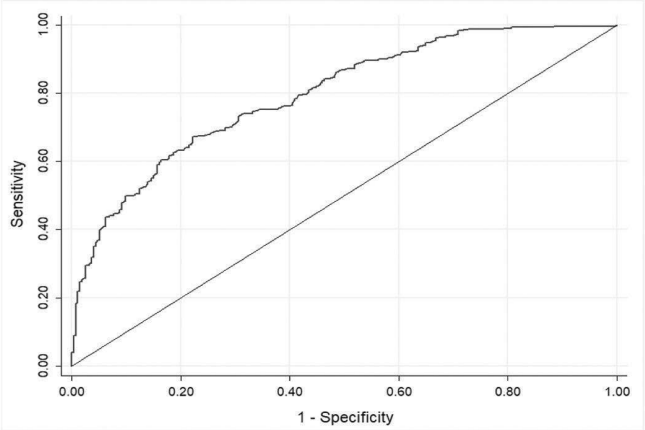

Figure 4. ROC curve for actual AMH levels and PCOS status

Other than the Youden's cut-point, there were two cut-points computed that were considered. A lower and a higher cut-point from the optimal cut-point determined before, to examine changes in the specificity, sensitivity and correction classification rate in the sample population. The > 3.04 cut-point has a higher sensitivity, would accrue a higher number of possible PCOS patients, while the cut-point > 4.15 nanogram per milliliter had better specificity, and would have lesser yield of potential PCOS patients. The receiver operating characteristic (ROC) curve of the values is presented in Figure 5.

The diagnostic characteristics of the different cut-points for AMH in determining the presence of PCOS is presented in Table 4. The mark at 3.86 ng/mL had the highest proportion of correctly classified patients, hence this was chosen as the cut off for determining patients who have PCOS.

Discussion

The use of AMH as a diagnostic tool for PCOS has been proposed as a more objective tool

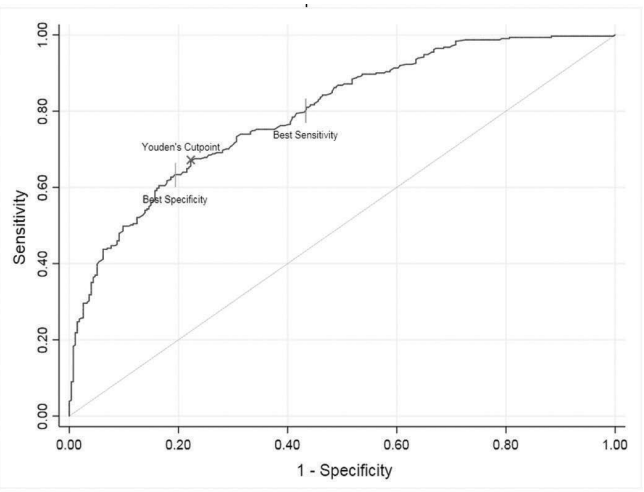

Figure 5. ROC curve for determined cut-point for AMH levels and PCOS status

compared to the measurement of polycystic ovarian morphology by ultrasound. The groups of the study population showed similarly aged women in both PCOS (33.77 ± 4.05; p=0.38) and non- PCOS women (33.49 ± 3.77; p=0.38). The result of the study showed a higher AMH mean (5.88 ± 3.37 ng/ml; p<0.01) and median (5.13 ng/ml; range: 1.04-22.27) in PCOS patients compared to the control (3.10 ± 1.65ng/ml and 2.71 ng/ml; range: 1.04-13.20 respectively), which is attributed to the higher number of preantral and small antral follicles of PCOS women[12,13]. A two to three times higher levels of AMH were reported in PCOS women compared to non-PCOS women[14,15,16].

The mean AMH level of the non – PCOS group of this study is 3.10 ± 1.65 ng/mL. This value is higher compared to the mean AMH level of a paper by Novero et al[17] measuring AMH levels in infertile Filipino women without PCOS which was reported to be 2.32 +/- 1.90 ng/mL. The higher mean AMH of non-PCOS group in this paper is attributed to the fact that these women are from male factor infertility only and women diagnosed with premature ovarian failure, advanced maternal age were excluded.

It is well established and reported in multiple studies that there is a negative correlation between the AMH level and age.[18,19,20,21] A similar observation is also noted in this study regardless of the diagnosis of PCOS with both groups showing decreasing levels of AMH as age increases, but it is noted that PCOS women have a higher AMH levels compared to control (Figure 2). As previously mentioned, AMH level is inversely proportional to increasing age, hence an age range was made (Table 3). The interquartile range of AMH for PCOS is 3.39 – 7.56 ng/ml. Analysis of the table showed a generally decreasing mean AMH levels.

There have been different reports regarding the effect of body mass index on AMH levels. Some studies reported a negative correlation of BMI and AMH among women more than or equal to 35 years old[22,23] suggesting that the lower AMH concentration in obese women compared to age-matched women of normal BMI suggest that the decrease maybe due to physiological issues related to obesity.[24] In another published paper, elevated BMI correlates negatively with AMH in Caucasian women but not in African-American, Hispanic or Asian[25]. In a paper by Simões- Pereira[26] (n = 951 women), BMI does not seem to affect AMH levels and that concerns on infertility in overweight and obese women maybe due to follicular development or oocyte maturation. The latter study's conclusion is similar to the findings of this study revealing no association between body mass index and AMH levels regardless of the diagnosis of PCOS (Figure 3). The BMI of both groups in this study is almost similar, with the PCOS group's mean BMI of 24.40 ± 4.36; p = 0.03, while for the non-PCOS group, the mean BMI is 23.76 ± 4.06; p = 0.03. This may

Table 3. Distribution of serum AMH level and age category among PCOS patients

Age Category	Freq. (%)	Mean	Percentiles of AMH level (ng/mL)						
			5th	10th	25th	50th	75th	90th	95th
21-25	13 (4.18%)	6.96 ± 3.94	2.07	2.63	3.63	6.35	9.51	13.20	13.39
26-30	49 (15.76%)	5.94 ± 2.42	2.90	3.28	4.08	5.51	7.23	9.94	10.42
31-35	137 (44.05%)	6.12 ± 3.94	2.22	2.33	3.23	5.06	7.65	11.55	13.60
36-40	101 (32.48%)	5.35 ± 2.86	2.35	2.51	3.09	4.46	7.21	9.64	10.55
>40	11 (3.54%)	6.24 ± 2.79	2.07	2.33	4.19	5.93	9.21	9.51	9.51
Total	311	5.88 ± 3.37	2.25	2.51	3.39	5.13	7.56	10.42	12.73

be due to the population of women in this study which are infertile couples ongoing work – up or treatment. These couples have been well advised by their physicians that lifestyle modification with diet and exercise will increase the chances of successful outcome, hence the similar mean BMI between PCOS and non-PCOS.

A receiver operating characteristic (ROC) curve for determining the presence of PCOS from the serum AMH levels showed an acceptable degree of discrimination (AUC: 0.80, CI: 0.76-0.83, SE: 0.02) as shown in Figure 4. The cut-off AMH level of 3.86 ng/mL for the diagnosis of PCOS was computed using the Youden's index, with a sensitivity of 67.2%, specificity of 77.7%, correct classification rate 72.1%, AUC: 0.72. The cut off was then compared to 2 points within the curve with the best sensitivity and best specificity (Figure 5, Table 4). Choosing a lower cut off value for AMH, 3.04 ng/ml, will improve the sensitivity (81%) but will result in a lower specificity (56.6%) and correct classification rate (69.6%), while a higher cut off value of 4.15 ng/ml will result in a higher specificity (80.7%) but will give a lower sensitivity (63.3%) and correct classification rate (71.5%). Hence the researchers decided to select the value computed using the Youden's index as the threshold.

Although at present, international guidelines do not recommend using AMH as an alternative for the detection of PCOM or as a single diagnostic test for PCOS[27], the international committees recognize that AMH assays may become more accurate in the detection of PCOM due to improved standardization of assays and established cut off levels with large scale validation in populations of different ages and ethnicities such as the one performed by Dietz de Loos[28], serum AMH cut-off of 3.5 ng/mL was determined and achieved 85.9% sensitivity and specificity. After analyzing the validation cohort, the cut-off achieved 82.4% (95% CI 78.6–85.8) sensitivity and 89.8% (95% CI 86.8–92.3) specificity, with an AUC of 94.0% (95% CI 92.6–95.5).

A systematic review by Iliodromiti proposed that AMH is a useful first line investigation in the identification of women with PCOS for a cut off value of 4.7ng/ml and a sensitivity of 82.8% and specificity of 79.4%[29]. The threshold of 3.86 ng/mL for the diagnosis of PCOS of the current study is compared with threshold levels from different countries seen in Table 5. The cut - off value of this paper is higher than the ones reported by Eilersten[30] in Norway (2.8 ng/ml), Saxena[31] in India(3.44 ng/ml), Chao[32] in Taiwan (3.5 ng/ml) and Ahmed[33] in Saudi Arabia (3.19 ng/ml), but lower than the ones reported by Yue[34] in China (8.16ng/ml and 5.89ng/ml), Wiweko[35] in Indonesia (4.45 ng/ml), Dewailly7 in France (4.9 ng/ml) and Homburg[36] in United Kingdom (6.72 ng/ml). These can be attributed to ethnical variation between the women between the studies. Another explanation for the wide range of AMH levels may be due to dissimilarity in the machines used. The papers mentioned measured AMH using Diagnostic Systems Laboratories, ELISA kit by Immunoconcept bio-detect, Immunotech – Beckman Coulter, and Union Immune analyzer, while the current paper used Access immunoassay by Beckmann Coulter. A similar study measuring AMH by Access immunoassay was performed by Kakkad [37] in India reporting a 3.75 ng/ml threshold for the diagnosis of PCOS. This latest paper presents the closest value to the one reported by this paper.

Limitations and Recommendation

The main restriction of the study is its cross-sectional design. A larger multi-center prospective study will verify the AMH threshold value for PCOS, relationship of AMH levels with increasing age and

Table 4. Summary of diagnostic parameters for AMH levels.

Diagnostic Criteria	AMH ≥3.04	AMH ≥3.86	AMH ≥4.15
Sensitivity	81% (76.2-85.2%)	67.2% (61.7-72.4%)	63.3% (57.7-68.7%)
Specificity	56.6% (50.5-62.5%)	77.7% (72.3-82.5%)	80.7% (75.5-85.2%)
Correct Classification Rate	69.6% (65.7-73.3%)	72.1% (68.3-75.7%)	71.5% (67.6-75.08%)
Area under the Curve	0.69 (0.65-0.72)	0.72 (0.69-0.76)	0.72 (0.68-0.76)

- Area under the curve receiver operating characteristic curve analysis, Youden's index computation

Table 5. Summary of AMH Threshold values for PCOS from different papers

Author	Year	Country	AMH threshold for PCOS (ng/ml)
Eilersten	2012	Norway	2.8
Ahmed	2019	Saudi Arabia	3.19
Saxena	2018	India	3.44
Chao	2011	Taiwan	3.5
Kakkad	2020	India	3.75
Wiweko	2014	Indonesia	4.45
Dewailly	2011	France	4.9
Homburg	2013	United Kingdom	6.72
Yue	2018	China	8.16 (20 – 29 yo) 5.89 (30 – 39 yo)
Yu	2021	Philippines	3.86

body mass index. Other factors that can potentially influence AMH levels such as environmental background, socio-economic status, history of smoking, and the presence of other diseases were not characterized in this paper. A validation of this study is also recommended.

Conclusion

The results of this study confirm that AMH levels are higher in PCOS women compared to women without the disease. The study also reiterates the negative correlation of AMH with age regardless of the diagnosis of PCOS. The threshold level of AMH for PCOS reported in this study could serve to assist in the diagnosis of PCOS in Filipino women, however we do not recommend the use of AMH as the sole basis for the diagnosis.

Disclosure of interest

The authors have no conflicts of interest to declare.

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