http://www.banglajol.info/index.php/JACEDB

Original article

DOI: https://doi.org/10.3329/jacedb.v2i1.78430

Journal of Association of Clinical Endocrinologist and Diabetologist of Bangladesh
January 2023, Vol. 2, No. 1, pp. 08-13

ISSN (Online): 2959-8176
ISSN (Print): 2958-0307

Impact of combining antimullerian hormone with sonographic ovarian volume on the phenotypes of polycystic ovary syndrome

*Morshed MS[1], Banu H[2], Hasanat MA[3]

[1]Md. Shahed Morshed, Ph. D. student, Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka-1000, Bangladesh; [2]Hurjahan Banu, Medical officer, Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka-1000, Bangladesh; [3]Muhammad Abul Hasanat, Professor of Endocrinology, Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka-1000, Bangladesh

Abstract

Background: Antimullerian hormone (AMH) is a promising marker for polycystic ovarian morphology (PCOM).

Objective: To determine the usefulness of combining the AMH-PCOM criterion with ovarian volume by ultrasonography (USG-PCOM) criterion in the diagnosis and phenotype distribution in patients with polycystic ovary syndrome (PCOS).

Methods: This cross-sectional observational study included 160 newly detected PCOS patients on the basis of modified Rotterdam criteria with the same definitions of hyperandrogenism and oligo/anovulation. For PCOM, a combined-PCOM criterion by the presence of either USG-PCOM (OV >10 mL) and/or AMH-PCOM (AMH ≥3.5 ng/mL) criteria was taken. AMH was analyzed by an enzyme-linked immunosorbent assay. Clinical and biochemical features and luteinizing hormone/follicle-stimulating hormone ratio (LFR) were assessed. The association of combined-PCOM criterion with these features and phenotypes of PCOS were analyzed.

Results: USG-PCOM outperformed AMH-PCOM by missing less PCOM (0.6% vs. 5.6%). When they were combined (USG-PCOM and/or AMH-PCOM), phenotype B almost disappeared (5.0%). After removing phenotype B, there was no discordance between the criteria as well as similar metabolic features and LFR among the rest of the phenotypes (NS for all).

Conclusions: Complementing the USG-PCOM criterion, the AMH-PCOM criterion almost removed phenotype B and made the other phenotypes similar with respect to metabolic features and LFR in patients with PCOS. *[J Assoc Clin Endocrinol Diabetol Bangladesh, January 2023; 2 (1): 08-13]*

Keywords: Antimullerian hormone; Ovarian volume; Polycystic ovary syndrome

***Correspondence:** Dr. Md. Shahed Morshed, room# 1524, level# 15, Block# D, Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka-1000, Bangladesh. Cell# +88 01738-842019, Email: shahed.phd.m22@bsmmu.edu.bd

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder with debatable diagnostic criteria.[1] Among several criteria proposed by different societies, the revised 2003 Rotterdam consensus criterion is widely acceptable and requires two out of three components from oligo/anovulation (OA), clinical and/or biochemical hyperandrogenism (HA), and polycystic ovarian morphology (PCOM) by ultrasonography (USG) along with the exclusion of similar diseases. PCOM is defined by fulfillment of either ovarian volume (OV >10 mL) or follicle number per ovary (FNPO ≥12 with 2 – 9 mm in diameter) in any ovary by the Rotterdam criterion.[2] Despite the racial variation, the OV criteria remained the same. However, with the improvement of imaging technology, the FNPO criterion is changing. Despite these improvements and the precision of PCOM criteria, there are lots of limitations of USG.[3] As a result, alternative markers of PCOM have been developed. Antimullerian hormone (AMH) is one of the promising diagnostic tests for PCOS and PCOM. It correlates with both OV and FNPO. However, it needs more standardization of assay and a cut-off for accurate detection of PCOM.[4]

AMH is considered a diagnostic marker of PCOS in the differential diagnosis of ovulatory dysfunctions and ovarian reserve. It is also related to increased luteinizing hormone pulse frequency, one of the characteristics of PCOS.[5] On the other hand, PCOM usually reflects the metabolic phenotype.[6] Current diagnostic criteria do not include the altered luteinizing/follicle-stimulating hormone (LH/FSH) ratio and insulin resistance. So, combining these two (PCOM and AMH) criteria may improve the diagnosis of PCOS.[7]

Depending on the presence of at least two diagnostic components from three (OA, HA, and PCOM), there are four possible phenotypes in a patient with PCOS. The combination of all three is phenotype A, and the absence of PCOM, OA, and HA are phenotype B, C, and D respectively.[8] The impact of the combination of USG-PCOM and AMH-PCOM on phenotypes of PCOS is not widely reported especially in the Bangladeshi population. The aim of this study was to see the impact of new PCOM criteria obtained from the presence of either USG and/or AMH criteria on the phenotypes of PCOS.

Methods

This was a cross-sectional observational study that consecutively included 160 newly detected PCOS patients on the basis of modified Rotterdam criteria with the exclusion of similar diseases (thyroid dysfunctions, nonclassic congenital adrenal hyperplasia, hyperprolactinemia, androgen-producing tumor, etc.), and pregnancy, lactation, as well as patients taking hormonal contraceptives, an insulin sensitizer, anti-androgen, or having other systemic diseases. The study was conducted in the Department of Endocrinology of Bangabandhu Sheikh Mujib Medical University, Bangladesh during the period from August 2014 to July 2015. We used similar definitions of OA and HA of Rotterdam criteria.[2] However, for PCOM, we used combined PCOM criteria. The presence of either USG-PCOM and/or AMH-PCOM criteria was taken as combined PCOM. As transvaginal sonography could not be done for all, we only considered OV criteria (>10 mL) to diagnose PCOM by USG (USG-PCOM).[9] We used the AMH cut-off of 3.5 ng/mL as AMH-PCOM criteria.[10] The study protocol was approved by the BSMMU's institutional review board. Informed written consent was obtained from each participant. Relevant reproductive history was taken and physical examinations were performed (height, weight, blood pressure, hirsutism, acne, and acanthosis nigricans). Body mass index (BMI) was calculated from height and weight with a value ≥25 kg/m^2 being considered obese.[11] Hirsutism was assessed by the modified Ferriman-Gallwey (mFG) method and a score of ≥8 was used as significant.[12] Fasting blood was drawn to measure total testosterone (TT), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and AMH. AMH was analyzed by an enzyme-linked immunosorbent assay, AMH GEN II ELISA kit (Beckman Coulter, Inc. USA) with an intra-assay coefficient of variation of 3.4 – 5.4% and inter-assay variation of 4.0 – 5.6%. Other hormones were measured by chemiluminescent microparticle immunoassay. A TT >46 ng/dL and a LH/FSH ratio (LFR) >2.0 were considered hyperandrogenemia and altered LFR respectively.[13,14] USG of ovaries was performed in the follicular phase of the menstrual cycle by trans-abdominal or trans-vaginal route depending on marital status.

Statistical analyses were done by SPSS software version 22.0. Qualitative data were expressed in frequency (percent, %) and quantitative data were expressed in mean±standard deviation (SD) or median (inter-quartile range IQR). For comparison between/among groups, Pearson's chi-square/Fisher's exact test for qualitative values and independent samples-t test or one-way ANOVA with post hoc Tukey or Kruskal Wallis one-way ANOVA with pairwise comparison by Dunn's test was done as appropriate. Statistical significance was set at p-values below 0.05.

Results

The characteristics of the study population with USG-PCOM and AMH-PCOM criteria are shown in Table-I. All the variables were statistically similar between the presence and absence of USG-PCOM (p=NS for all). Similarly, all the variables were also statistically similar between the presence and absence of AMH-PCOM except the percentages of hyperandrogenemia, which was statistically lower in the AMH-PCOM present group than in the absence group (present vs. absent: 50.0% vs. 75.0%, p=0.003).

The impact of AMH as a marker of PCOM is shown in Figure-1. The frequency of phenotypes A, C, and D was higher in the USG-PCOM group than in the AMH-PCOM group. On the other hand, phenotype B was higher in the AMH-PCOM group than in the USG-PCOM group. USG-PCOM missed only 0.6% and the AMH-PCOM missed 5.6% of PCOS cases. When they were combined (USG-PCOM and/or AMH-PCOM), phenotype B almost disappeared (5.0%). When phenotype B as well as absent of both USG-PCOM and AMH-PCOM criterion were removed, there was significant discordance (p=0.027). But, in post hoc analysis all the cells' adjusted residuals were within ±3. So, there was no discordance between the criteria (Table-II)

The characteristics of the study population with combined-PCOM-based phenotypes are shown in Table-III. The mFG score was significantly higher in phenotype A (p <0.001), B (p=0.001), and C (p=0.002) than phenotype D. Similarly, TT was significantly

higher in phenotype A (p=0.003) and C (p=0.001) than phenotype D. Systolic BP was significantly higher in phenotype A than phenotype B (p=0.036). Serum AMH was significantly higher in phenotype A (p=0.016), C (p=0.041), and D (p=0.015) than in phenotype B. Other characteristics were statistically similar across the spectrum of combined phenotypes (p=NS for all).

Discussion

The aim of this study was to see the impact of a new

Table-I: Characteristics of the study participants (N=160)

Variables	Present	Absent	p	Present	Absent	p
Number (%)	135 (84.37)	25 (15.63)		108 (67.50)	52 (32.50)	
Age, years	23.59±4.42	22.58±4.99	0.308	23.06±4.17	24.20±5.11	0.133
Irregular menstruation	118 (87.4)	25 (100.0)	0.077	96 (88.9)	47 (90.4)	0.796
Menstrual regulation/abortion	9 (6.7)	2 (8.0)	0.683	8 (7.4)	3 (5.8)	1.00
Subfertility	18 (13.3)	4 (16.0)	0.753	18 (16.7)	4 (7.7)	0.147
Family history of PCOS	13 (9.6)	1 (4.0)	0.699	9 (8.3)	5 (9.6)	1.00
Family history of subfertility	33 (24.4)	4 (16.0)	0.446	27 (25.0)	10 (19.2)	0.434
Family history of DM	88 (65.2)	21 (84.0)	0.100	71 (65.7)	38 (73.1)	0.372
Obesity (BMI ≥25 kg/m^2)	82 (60.7)	13 (52.0)	0.507	65 (60.2)	30 (57.7)	0.864
Acne	41 (30.4)	5 (20.0)	0.345	29 (26.9)	17 (32.7)	0.461
Acanthosis nigricans	48 (35.6)	7 (28.0)	0.503	40 (37.0)	15 (28.8)	0.375
Significant hirsutism (mFG score ≥8)	110 (81.5)	24 (96.0)	0.081	89 (82.4)	45 (86.5)	0.649
Elevated BP (≥130/85 mm-Hg)	19 (14.1)	4 (16.0)	0.761	16 (14.8)	7 (13.5)	1.00
Hyperandrogenemia (TT >46 ng/dL)	79 (58.5)	14 (56.0)	0.829	54 (50.0)	39 (75.0)	0.003
Altered LH/FSH ratio (>2.0)	36 (26.7)	10 (40.0)	0.228	30 (27.8)	16 (30.8)	0.712

Data were expressed in mean±SD or frequency (%). Within parentheses are percent over the column total
Independent samples t-test or Fisher's exact test was done

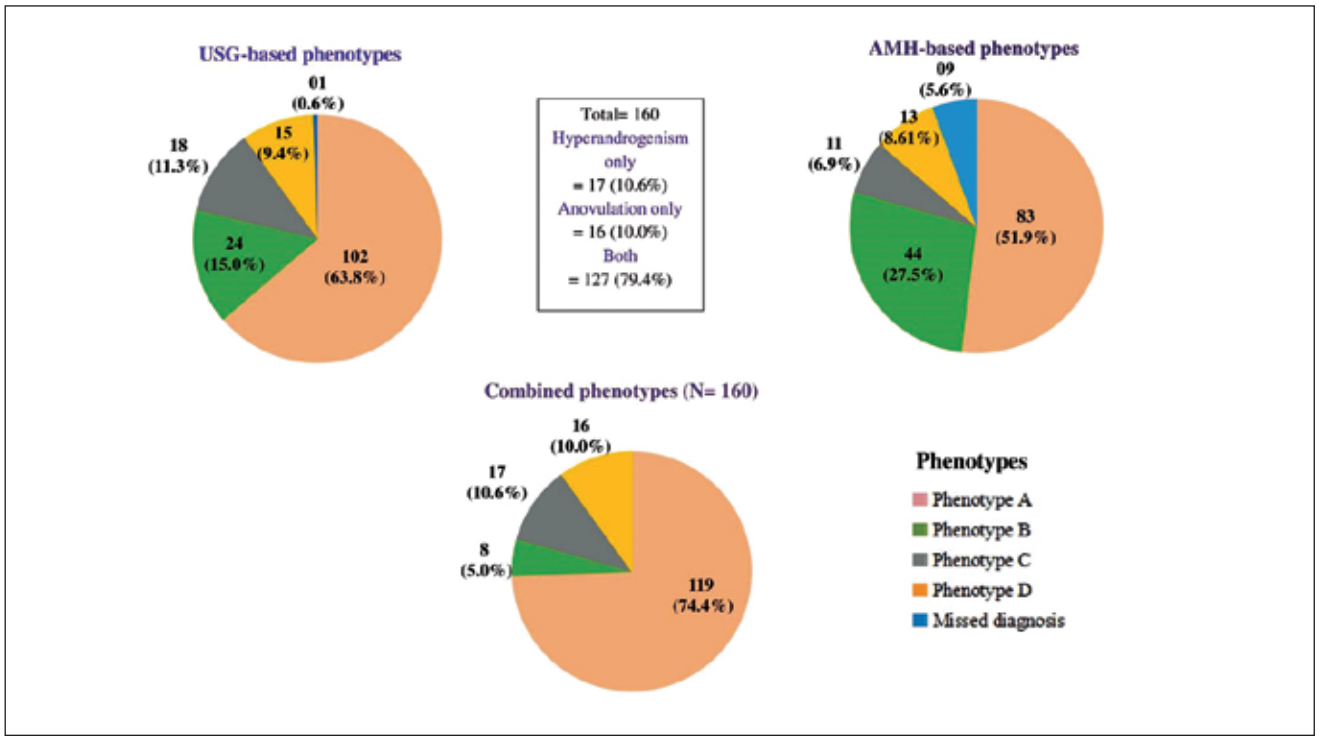

Figure 1: Phenotypic distribution according to different criteria of PCOM in the study participants (N=160)

Table-II: Concordance between USG-PCOM and AMH-PCOM with combined phenotypes of PCOS (N= 152)

Polycystic ovarian morphology	Phenotype A n= 119	Phenotype (C+D) n= 33	χ2 (df)	p
	No. (%) [adjusted residuals]			
USG+ and AMH+ criteria	53 (44.9) [-2.6]	23 (69.7) [2.6]		
USG+ and AMH- criteria	50 (42.4) [1.5]	9 (27.3) [-1.5]	7.2 (2)	0.027
USG- and AMH+ criteria	16 (13.4) [1.7]	1 (3.0) [-1.7]		

Within parentheses are percentages over the column total
*Pearson's chi-square test was done after removing phenotype B and – USG criteria – AMH criteria

combined USG-OV &/or AMH criterion on the phenotypes of PCOS. We found that the impact of the combined PCOM criterion was found mostly in phenotype B. After removing phenotype B, there was no discordance between combined phenotypes with combined PCOM. So, the combined PCOM criterion becomes an essential component to diagnose PCOS. Besides, the combined criterion also includes different manifestations of PCOS (increased LH pulse frequency, metabolic features), as this condition is largely heterogeneous, thus increasing the sensitivity of this diagnostic test.[6] The percent of phenotypes A, C, and D were higher in the USG-PCOM group than in the AMH-PCOM group. Apart from phenotype A, there is a chance of missing phenotypes C and D. The combined PCOM criterion will detect these 'mild PCOS' patients.

We found the USG-PCOM criterion better than the AMH-PCOM criterion- a similar observation to Carmina et al.[15] However, several authors found good concordance between these two criteria.[6,16,17] We also found that combining with AMH to USG-OV criteria might produce a PCOM criterion that might be an alternative to OV/FNPO criteria. Alternatively, in sonographically inconclusive cases of PCOM, AMH can help to detect more cases of PCOS.[7] On the other hand, the discordance between the two criteria may be due to individual false negative results.[6]

In this study, hyperandrogenemia was significantly higher in AMH-PCOM absent group. In combined phenotypes, systolic BP and AMH were significantly lower in phenotype B and androgenic manifestations were significantly lower in phenotype D. Phenotype D is called non-hyperandrogenic PCOS, so this feature remained the same with the phenotypes produced by the combined PCOM criteria too. On the other hand, if phenotype B is removed, then there are no significant differences in metabolic characteristics and LH/FSH ratio among the other phenotypes.

Table III: Characteristics of the study population with the combined PCOM phenotypes (N=160)

Variables	Phenotype A	Phenotype B	Phenotype C	Phenotype D	p	Post hoc significance
Number (%)	119 (74.4)	8 (5.0)	17 (10.6)	16 (10.0)		
Age, years	23.35±4.57	22.94±6.20	24.71±4.04	22.56±4.57	0.572*	-
BMI, kg/m^2	26.35±5.33	25.60±3.83	26.10±3.93	25.82±3.55	0.957*	-
WC, cm	85.83±11.60	86.75±7.65	85.53±10.43	85.0±10.48	0.986*	-
Acne	36 (30.3)	1 (12.5)	6 (35.3)	3 (18.8)	0.614¥	-
Acanthosis nigricans	41 (34.5)	3 (37.5)	7 (41.2)	4 (25.0)	0.810¥	-
mFG score	10.40±4.21	11.0±4.21	9.18±3.70	4.06±1.95	<0.001*	(A=B=C) >D
Systolic BP, mm-Hg	109.96±11.51	99.38±7.76	102.94±6.86	107.50±7.75	0.006*	(A>B)=C=D
Diastolic BP, mm-Hg	76.76±8.94	70.0±7.56	73.53±6.06	79.38±7.72	0.038*	A=B=C=D
Total testosterone ng/dL	59.20 (34.50, 94.50)	61.05 (35.88, 90.55)	65.40 (32.20, 89.20)	30.50 (19.75, 44.33)	0.005*	(A>D<C)=B
S. LH, IU/L	5.56 (4.0, 9.93)	8.96 (3.46, 13.38)	5.23 (3.44, 7.82)	5.39 (3.03 13.80)	0.588*	-
LH/FSH ratio	1.28 (0.79, 2.12)	1.78 (0.66, 3.09)	1.15 (1.03, 1.64)	1.20 (0.67, 3.20)	0.867*	-
S. AMH, ng/mL	7.19±4.88	2.0±1.0	7.39±4.89	8.17±4.21	0.019*	(A=C=D)>B

Data were expressed in mean±SD or median (IQR) for quantitative and frequency (%) for qualitative variables as appropriate
Within parentheses are percentages over the column total for qualitative variables
*One-way ANOVA (post hoc Tukey test), ǂKruskal Wallis one way ANOVA (post hoc Dunn's test), and ¥Pearson's chi-square/Fisher's exact test was done as appropriate

While FNPO is usually a better representative of hyperandrogenism, we could not report it due to its limitations by the requirement of transvaginal USG with the higher frequency of USG probe.[18]

Conclusion

In conclusion, AMH can complement USG in the diagnosis of PCOM with the disappearance of phenotype B of PCOS. Combining these two methods make the other phenotypes statistically similar with respect to metabolic features and LH/FSH ratio, thus complementing these two other important non-diagnostic phenotypes also. It requires an age-specific and population-based study to determine the optimal cut-off of serum AMH for the better application of this AMH-PCOM criterion.

Acknowledgements

We acknowledge the patients and their attendants to take part in the study. The hospital authority is also acknowledged for generous support.

Conflict Of Interest

The authors have no conflicts of interest to disclose

Financial Disclosure

The author(s) received no specific funding for this work.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Ethical approval for the study was obtained from the Institutional Review Board, BSMMU. The written informed consent was obtained from all study participants. All methods were performed in accordance with the relevant guidelines and regulations.

How to cite this article: Morshed MS, Banu H, Hasanat MA. Impact of combining Antimullerian hormone with sonographic ovarian volume on the phenotypes of polycystic ovary syndrome J Assoc Clin Endocrinol Diabetol Bangladesh, 2023; 2(1): 08-13

Publication History

Received on: 7 October 2022

Accepted on: 26 December 2022

Published on: 1 January 2023

References

1. Louwers YV, Laven JSE. Characteristics of polycystic ovary syndrome throughout life. Ther Adv Reprod Health 2020;14:2633494120911038. DOI: 10.1177/2633494120911038.
2. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004;81(1):19-25. DOI: 10.1016/ j.fertnstert.2003.10.004.
3. Lujan ME, Jarrett BY, Brooks ED, Reines JK, Peppin AK, Muhn N, et al. Updated ultrasound criteria for polycystic ovary syndrome: reliable thresholds for elevated follicle population and ovarian volume. Hum Reprod 2013;28(5):1361-8. DOI: 10.1093/humrep/det062.
4. Mahran A. The relationship between Anti-mullerian hormone and the clinical, biochemical and sonographic parameters in women with polycystic ovarian syndrome. Middle East Fert Soc J 2016;21(1):11-5. DOI: 10.1016/j. mefs.2015.06.003.
5. Capuzzo M, La Marca A. Use of AMH in the Differential diagnosis of anovulatory disorders including PCOS. Front Endocrinol (Lausanne) 2021;11:616766. DOI: 10.3389/fendo.2020.616766.
6. Fraissinet A, Robin G, Pigny P, Lefebvre T, Catteau-Jonard S, Dewailly D. Use of the serum anti-Müllerian hormone assay as a surrogate for polycystic ovarian morphology: impact on diagnosis and phenotypic classification of polycystic ovary syndrome. Hum Reprod 2017;32(8):1716-22. DOI: 10.1093/humrep/dex239.
7. Banu H, Morshed MS, Tuqan S, Akhtar N, Hasanat MA. Role of Antimullerian hormone in the diagnosis of sonographically inconclusive polycystic ovary syndrome. Bangabandhu Sheikh Mujib Med Univ J 2022;15(2):65-9. DOI: 10.3329/bsmmuj.v15i2.60856.
8. National Institute of Health. Final report: Evidence-based methodology workshop on polycystic ovary syndrome, December 3–5, 2012. Available at: file:///F:/Society/Guidelines/NIH-2012.pdf.
9. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran Let al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Hum Reprod 2018;33(9):1602-18. DOI: 10.1093/humrep/dey256.
10. Sadiqa-Tuqan, Hasanat MA, Marufa-Mustari, Hurjahan-Banu, Nazma-Akhtar, Fariduddin M. Anti-müllerian hormone is found raised in polycystic ovarian syndrome. Ame Res J Endocrinol. 2017;1(1):1–8.
11. World Health Organization. Regional Office for the Western Pacific. The Asia-Pacific perspective: redefining obesity and its treatment. Sydney: Health Communications Australia. 2000. Available at: https://apps.who.int/iris/handle/10665/206936.
12. Escobar-Morreale HF, Carmina E, Dewailly D, Gambineri A, Kelestimur F, Moghetti P, et al. Epidemiology, diagnosis and management of hirsutism: A consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society. Hum Reprod Update 2012;18:146-70. DOI: 10.1093/humupd/dmr042.
13. Braunstein GD, Reitz RE, Buch A, Schnell D, Caulfield MP. Testosterone reference ranges in normally cycling healthy premenopausal women. J Sex Med 2011;8(10):2924-34. DOI: 10.1111/j.1743-6109.2011.02380.x.
14. Alnakash AH, Al-Tae'e NK. Polycystic ovarian syndrome: the correlation between the LH/FSH ratio and disease manifestations. Middle East Fertil Soc J 2007;12(1):35–40.
15. Carmina E, Campagna AM, Fruzzetti F, Lobo RA. AMH measurement versus ovarian ultrasound in the diagnosis of polycystic ovary syndrome in different phenotypes. Endocr Pract 2016;22(3):287-93. DOI: 10.4158/EP15903.OR.
16. Dewailly D, Gronier H, Poncelet E, Robin G, Leroy M, Pigny P, et al. Diagnosis of polycystic ovary syndrome (PCOS): revisiting the threshold values of follicle count on ultrasound and of the serum AMH level for the definition of polycystic ovaries.

Hum Reprod 2011;26(11):3123-9. DOI: 10.1093/humrep/der297.
17. Iliodromiti S, Salje B, Dewailly D, Fairburn C, Fanchin R, Fleming R, et al. Non-equivalence of anti-Müllerian hormone automated assays-clinical implications for use as a companion diagnostic for individualised gonadotrophin dosing. Hum Reprod 2017;32(8):1710-5. DOI: 10.1093/humrep/dex219.
18. Bell RJ, Islam RM, Skiba MA, Herbert D, Martinez Garcia A, Davis SR. Substituting serum anti-Müllerian hormone for polycystic ovary morphology increases the number of women diagnosed with polycystic ovary syndrome: A community-based cross-sectional study. Hum Reprod 2021;37(1):109-18. DOI: 10.1093/humrep/deab232.