ULTRASONOGRAPHIC THRESHOLD OF OVARIAN STRUCTURE IN PREMENOPAUSAL WOMEN OF DIFFERENT ETHNICITY

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ABSTRACT

The polycystic ovarian morphology (PCOM) is a generally accepted ultrasound marker for ovulatory dysfunction, is one of the criteria for polycystic ovary syndrome (PCOS) and is established based on the assessment of ovarian volume (OV) and the follicle number per ovary (FNPO), taking into account the upper normal values determined in healthy premenopausal women. However, there is a necessity for regular revision of the PCOM characteristics depending on ethnic and age characteristics.

The aim. *To develop differentiated standards for assessing the ultrasonographic ovary structure in premenopausal women of various ethnicity.*

Materials and methods. *From March 2016 to December 2019, a multicenter cross-sectional prospective study was conducted in Eastern Siberia (Irkutsk region) and in the neighboring Republic of Buryatia. The study included 1134 participants: 715 women of Caucasian origin, 312 Asian women, 107 women of mixed ethnic subpopulation.*

Results. *It has been established that for Caucasians, it is advisable to diagnose PCOM when the ovarian volume is 9 cm^3 and/or FNPO ≥ 12; for women of the Asian population – when the ovarian volume is 7 cm^3 and/or FNPO ≥ 11; for women of mixed ethnicity – when the ovarian volume is 8 cm^3 and/or FNPO ≥ 9. An important advantage of our study is that all participants were recruited from a non-selective multi-ethnic population of women with comparable socio-demographic characteristics living in the same geographical conditions.*

Conclusion. *Differentiated approach for identifying the polycystic ovarian morphology in premenopausal women of different ethnic groups requires using ethnically differentiated normative readings.*

Key words: *PCOS, polycystic morphology, follicle number per ovary, ovarian volume, pelvic ultrasound, premenopausal women, ethnicity*

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УЛЬТРАСОНОГРАФИЧЕСКИЕ НОРМАТИВЫ СТРУКТУРЫ ЯИЧНИКОВ У ЖЕНЩИН РЕПРОДУКТИВНОГО ВОЗРАСТА РАЗЛИЧНОЙ ЭТНИЧЕСКОЙ ПРИНАДЛЕЖНОСТИ

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РЕЗЮМЕ

Поликистозная структура яичников (ПКЯ) является общепризнанным ультразвуковым маркером овуляторной дисфункции, служит одним из критериев синдрома поликистозных яичников (СПКЯ) и устанавливается на основании оценки объёма яичников (ОЯ) и количества фолликулов на яичник (КФЯ) с учётом верхних нормальных значений, определяемых в здоровых популяциях женщин репродуктивного возраста. Однако отмечается необходимость регулярного пересмотра характеристик ПКЯ в зависимости от этнических и возрастных особенностей.

Цель. *Разработать дифференцированные нормативы для оценки ультрасонографической структуры яичников у женщин репродуктивного возраста различной этнической принадлежности.*

Материалы и методы. *В период с марта 2016 по декабрь 2019 г. проведено многоцентровое поперечное (кросс-секционное) проспективное исследование на территории Восточной Сибири (Иркутская область) и в сопредельной Республике Бурятия. В исследование вошли 1134 участницы: 715 женщин европеоидной принадлежности, 312 – азиатской, 107 – смешанной этнической субпопуляции.*

Результаты. *Установлено, что для европеоидов ПКЯ целесообразно диагностировать при объёме яичников 9 см^3 и/или КФЯ ≥ 12; для женщин азиатской популяции – при объёме яичников 7 см^3 и/или КФЯ ≥ 11; для женщин смешанной этнической принадлежности – при объёме 8 см^3 и/или КФЯ ≥ 9. Важным преимуществом нашего исследования является то, что все участницы были рекрутированы в неселективной мультиэтнической популяции женщин с сопоставимыми социально-демографическими характеристиками, проживающих в одинаковых географических условиях.*

Выводы. *Для дифференцированного подхода к выявлению поликистозной структуры яичников у женщин репродуктивного возраста различных этнических групп необходимо принимать этнически дифференцированные нормативные значения.*

Ключевые слова: *СПКЯ, поликистозная структура, количество фолликулов на яичник, объём яичника, УЗИ органов малого таза, женщины репродуктивного возраста, этника*

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INTRODUCTION

Polycystic ovary structure (PCOM) is a generally accepted ultrasound marker of ovulatory dysfunction and, since 2003, following the adoption of the Rotterdam Consensus [1], has served as one of the criteria for polycystic ovary syndrome (PCOS) [2–4]. Currently, PCOM is defined based on the assessment of ovarian volume (OV) and follicle number per ovary (FNPO) taking into account the upper normal values determined in healthy populations of women of reproductive age [2, 4]. The latest guidelines on the diagnosis and management of PCOS, published in 2023 [4], propose to consider the provisions adopted in Rotterdam as basic for the diagnosis of PCOS [4, 5]. However, it is noted that there is a need for regular revision of the characteristics of PCOM, taking into account ethnic and age characteristics. The following updated criteria for defining PCOM in women of reproductive age are relevant: the most effective ultrasound marker for identifying PCOM in adults with transvaginal access should be considered FNPO, while FNPO ≥ 20 in at least one ovary should be considered the threshold value for polycystic ovary structure. As an equally effective marker of PCOM, along with OV ≥ 10 ml, it is again proposed to consider follicle number per cross-section (FNPS) ≥ 10 in at least one ovary. When using old ultrasound technologies and/or transabdominal ultrasound (US) and/or when the image quality is insufficient for an accurate assessment of the follicle number in the entire ovary, the following criteria are necessary for establishing polycystic ovary structure: OV ≥ 10 ml or FNPS ≥ 10 in both ovaries. When describing the ultrasound, it is proposed to use clear standardized protocols for assessing polycystic ovary structure, including at least the following: date of the last menstruation (or phase of the cycle); characteristics of the sensor used; high-quality count of the total follicle number measuring 2–9 mm per ovary. It is mandatory to measure the ovary in three dimensions and calculate the volume of each ovary; description of other ovarian features and/or pathologies, including ovarian cysts, corpora lutea, dominant follicles (≥ 10 mm) (which should not be taken into account when calculating ovarian volume). It is recommended to rely on the contralateral ovary FNPO for the diagnosis of PCOM in the presence of a dominant follicle in the ovary being evaluated. Uterine features and/or pathologies, including endometrial thickness and structure, should not be ignored.

Ethnic differences in the number of follicles and/or ovarian volume are actively studied. Thus, in Chinese women, the sufficient criteria for defining PCOM [6] are smaller ovarian volumes and the follicle number compared to women of the European population: ≥ 6.3 cm^3 and ≥ 10 follicles, respectively. Lower values compared to the Western population were also demonstrated by Turkish women. The threshold criteria for PCOM for them are OV = 6.43 cm^3 and FNPO ≥ 8 [7]. In the population of Korean patients, the follicle number is considered a more significant criterion for polycystic disease than ovarian volume due to the smaller ovarian volume characteristic of Asian women [8].

The volume of the ovaries and the number of follicles change during a woman's reproductive period, reaching a maximum value in adolescence, with a gradual decrease in adulthood and a rapid decrease at menopause. For example, in women over 35 years of age, the prevalence of PCOM is 7.8 %, compared to 21 % in younger women [9]. Moreover, the decrease in the number of follicles occurs faster than the decrease in ovarian volume [10]. Age-related processes in women involve a decrease in the number of growing antral follicles [10].

The relevance of detecting PCOM is determined by the fact that even in women with normal menstrual function and without clinical signs of hyperandrogenism (HA), PCOM is associated with higher levels of androgens and insulin and a lower pregnancy rate [11]. However, hirsutism, ovulatory dysfunction and menstrual cycle disorders were equally present in patients with normal ovarian volume and enlarged ovaries.

The diagnostic significance of PCOM depends on age and ethnic characteristics, which requires large-scale epidemiological studies to determine the population characteristics of PCOM. Standardization of diagnostic criteria for PCOM is the key to effective diagnostics of PCOS and, accordingly, prevention of complications and concomitant diseases associated with PCOS.

THE AIM OF THE STUDY

To develop differentiated standards for assessing the ultrasonographic ovary structure in premenopausal women of various ethnicity.

HYPOTHESIS

Ultrasonographic characteristics of the ovaries vary among women depending on ethnicity and age.

MATERIALS AND METHODS

Study design and population. Subjects were recruited during a cross-sectional prospective study (ClinicalTrials.gov: NCT05194384) conducted in two large regions of Eastern Siberia (Irkutsk Region and the Republic of Buryatia) from March 2016 to December 2019 [12, 13]. The study included women of reproductive age subject to annual medical examination at their place of work. The study was conducted in accordance with the World Medical Association Declaration of Helsinki (1964) and approved by the local Ethics Committee of the Scientific Centre for Family Health and Human Reproduction Problems (Irkutsk) (protocol No. 2.1 dated February

24, 2016). Informed consent was obtained from all subjects. The study was conducted as part of the research work "Prediction of metabolic and psychoemotional disorders in women of different age groups with hyperandrogen disorders for the development of personalized approaches to prevention and treatment" (registration number 123051600030-1). The study was carried out using the equipment of the Centre for the Development of Progressive Personalized Medical Technologies of the Scientific Centre for Family Health and Human Reproduction Problems.

Inclusion criteria for the sample: age from 18 to 44 years inclusive; signing of informed consent; participant's willingness to fully comply with all study procedures; availability throughout the study period. **Exclusion criteria:** age under 18 and over 45 years; unwillingness to participate or difficulty understanding informed consent or the aims and requirements of the study; presence of factors that interfere with the participant's full compliance with the study conditions. A total of 1,490 women of reproductive age were invited to participate in the study, 92 of whom were not included in the study due to lack of informed consent. In total, 1,398 women of reproductive age were included in the study.

Hyperandrogenism was defined as hirsutism (Hs) greater than 4 (≥ 5 points) according to the cut-off values for the modified Ferriman – Gallwey visual scale (mFG) previously established by us for the entire population using 2k-cluster analysis, and/or hyperandrogenemia – with a blood serum total testosterone (tT) concentration ≥ 73.90 ng/dl and/or a free androgen index (FAI) value ≥ 6.90 for Caucasians and a blood serum tT concentration ≥ 41.03 ng/dl and/or FAI ≥ 2.92 for Asians and/or a dehydroepiandrosterone sulfate (DHEA-S) level of 355 mg/dl for the entire population (according to the cut-off values reflecting the 98th percentile concentrations of tT, DHEA-S, and FAI in the blood serum in the reference cohort). Oligomenorrhea was defined as a menstrual cycle duration < 21 or > 35 days or a menstrual frequency of less than 9 cycles per year (according to the Rotterdam Consensus recommendations) [1], and in the case of an intact menstrual cycle – a decrease in the blood serum progesterone level on days 20–24 of the cycle below 3–4 ng/ml. Primary amenorrhea was defined as the absence of menstruation during life or the failure to reach menarche by the age of 15 years or 3 years after thelarche [14]. Secondary amenorrhea was defined as the absence of previously regular menstruation for 3 months, and in the case of previously irregular menstruation – the absence of menses for 6 months.

The clinical methods of the study included a questionnaire survey, general medical and gynecological examinations. During the objective examination, the hirsute number was assessed using mFG [15] in accordance with the standardized scoring technology. During the examination by the gynecologist, all women underwent the following: assessment of the condition of the mammary glands; gynecological bimanual examination of the pelvic organs; Pap smear study.

To determine the hormone levels in each patient, blood was collected from the cubital vein on an empty stomach from 8 to 9 a.m., after a 15-minute rest (according to the generally accepted method) and taking into account the phases of the menstrual cycle, using disposable vacuum systems BD Vacutainer (Becton, Dickinson and Company, USA).

Determination of concentrations of thyroid stimulating hormone (TSH), free thyroxine (Free T4), prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), 17-OH-progesterone, sex hormone-binding globulin (SHBG) and progesterone was carried out using the competitive solid-phase enzyme immunoassay method using the Alkor-Bio test systems (Russia). The study of total tT was carried out using a liquid chromatography–mass spectrometry (LC-MS) LCMS-8060 (Shimadzu, Japan). DHEA-S in blood serum was determined using a chemiluminescent enzyme immunoassay analyzer Immulite 1000 (Siemens, USA).

Instrumental examination methods included pelvic ultrasound performed by three experienced specialists trained to perform ultrasound examinations uniformly with coefficients of variation of examination results less than 6 %, using only the Mindray M7 device (Mindray Bio-Medical Electronics Co., China) with a transvaginal probe (5.0–8.0 MHz) for sexually active subjects. Ovarian volume was calculated using the formula for an oblate ellipsoid: length × width × height × π/6 [4, 5, 16]. The number of follicles was determined by scanning each ovary from the inner to the outer edge in longitudinal section (follicle number per ovary). Follicles were measured in two planes of the ovary, and the follicle diameter was determined as the average value of two diameters (longitudinal and transverse).

Sample size calculations were carried out using the formula:

$$n = [(z_{1-\alpha})^2(P(1-P) / D^2)],$$

where n is the sample size for the study; $z_{1-\alpha} = 1.96$ (at $\alpha = 0.05$); P is the estimated prevalence of PCOS according to previously published data; D is the absolute error.

As a result, the sample size that would allow us to identify a significant diagnostic potential of the ovarian volume and follicle count values per ovary using ROC curves was at least 198 women for the entire sample.

The study data were entered and managed (report generation, data export for statistical analysis) using the REDCap information system, which is deployed on the server of Scientific Centre for Family Health and Human Reproduction Problems.

The statistical analysis methods included descriptive statistics, testing statistical hypotheses, analysis of relationships between variables, and construction of statistical models. Interval estimation of proportions and frequencies is performed by calculating 95%

confidence intervals (95% CI). To test statistical hypotheses, we used parametric Student's t-test, nonparametric Mann – Whitney test, parametric one-way analysis of variance (ANOVA, ANalysis Of VAriance) or nonparametric rank analysis of variance according to Kruskal – Wallis and median test, z-test, χ^2 criterion. The significance level is defined as 0.05. ROC analysis was used to determine the upper limit of the norm (ULN) for ultrasonographic parameters.

RESULTS

Among the overall population of women of reproductive age included in the study and who underwent a complete examination, 1134 participants had satisfactory visualization of the ovaries based on the results of ultrasonography, and we divided them in the following groups: women with a regular cycle and no signs of hyperandrogenism – group 0 (control group) ($n = 642$); a group of women with PCOS according to NIH (National Institutes of Health) criteria – participants were defined by the combination of the presence of oligomenorrhea/oligoanovulation (OA) [4, 5] and hyperandrogenism (hirsutism and/or hyperandrogenemia) [4, 5, 17] – group 11 ($n = 82$); a group with the presence of any one criterion of PCOS according to NIH (hyperandrogenemia or hirsutism or oligoanovulation) – group 11 ($n = 410$) (fig. 1).

The number of women in subgroups depending on ethnicity is presented in the diagram (fig. 1).

The main sociodemographic, anthropometric characteristics, menstrual and reproductive history of women of reproductive age by groups are presented in Tables 1 and 2.

Women with PCOS according to NIH criteria and study participants with any one symptom of PCOS were younger compared to the representatives of the control group ($p < 0.001$ and $p = 0.013$, respectively). The ethnic composition of the analyzed groups was comparable.

Women with PCOS had higher weight and waist circumference (WC) compared to women in the control group and participants with any one symptom of PCOS ($p < 0.001$ and $p = 0.018$; $p = 0.003$, and $p = 0.020$, respectively). We noted a trend towards higher blood pressure values in the group of women with two symptoms of PCOS compared to the control group ($p = 0.007$). As expected, participants with PCOS had a higher incidence of ovulatory dysfunction, hyperandrogenemia, and hirsutism compared to the group with one criterion ($p < 0.001$ for all frequencies). The mFG index was statistically significantly different in both groups compared to the control group ($p < 0.001$ for all groups), as well as between women with one and two PCOS criteria, with predictably higher values in group 11 ($p < 0.001$) (table 2).

The average age at menarche did not differ between the study groups. However, women with two symptoms of PCOS had a longer menstrual cycle length compared with both the control group ($p < 0.001$) and the group with one criterion ($p < 0.001$); however, women in group 12 also had a statistically significantly longer cycle length than the control group ($p < 0.001$). Accordingly, the frequency of cycles per year was significantly lower in the PCOS group compared with both the group with one criterion ($p < 0.001$) and the control group ($p < 0.001$), and in the group with one criterion compared with the control group ($p < 0.001$). When assessing the reproductive history (table 2), we noted a lower number of pregnancies and births in women in the groups with one and two PCOS criteria compared to the control group ($p < 0.001$ for both groups), with the lowest rate in the PCOS group. The lower frequency of pregnancy can probably also explain the lack of statistically significant differences in the frequency of ectopic and non-viable pregnancies, as well as therapeutic abortions at the request of a woman in the representatives of the groups with one and two symptoms of PCOS compared to the control group. At the same time, we noted a higher number of antenatal fetal deaths in the group of women with one criterion of PCOS compared to the group with two criteria and the control group, and a higher number of spontaneous abortions in women with two criteria of PCOS compared to the control group and the group with one criterion ($p < 0.001$). Certainly, these data confirm the negative impact of both hyperandrogenism and oligoanovulation on the reproductive function of women and justify the need for early detection, management and treatment of such patients.

There were no significant differences in the mean levels of prolactin, TSH, FSH, and 17-OH between the groups, although the participants with PCOS had slightly higher 17-OH values, which were within the normal range, compared with women with one criterion for PCOS and the control group. The representatives of the group with two criteria of PCOS demonstrated higher levels of testosterone, DHEA-S, LH/FSH ratio, FAI, and AMH and, accordingly, the lowest SHBG value compared with the control group and women with one criterion ($p < 0.001$ for all values). However, women with one criterion of PCOS similarly differed statistically significantly in these hormones from the control group ($p < 0.001$ for all values) (table 3).

As for FNPO and OV, the following main results were obtained: among the studied groups, antral follicles number and OV for both the right and left ovary were increased in the groups with hyperandrogenism. Among the groups with the presence of PCOS criteria, the highest values of antral follicles number and OV were found in the group with two criteria (table 3).

Determination of cut-off points for ovarian volume and follicle number in overall population and by ethnicity

In the next step, we evaluated the ultrasound characteristics of the ovaries of the women included in the study.

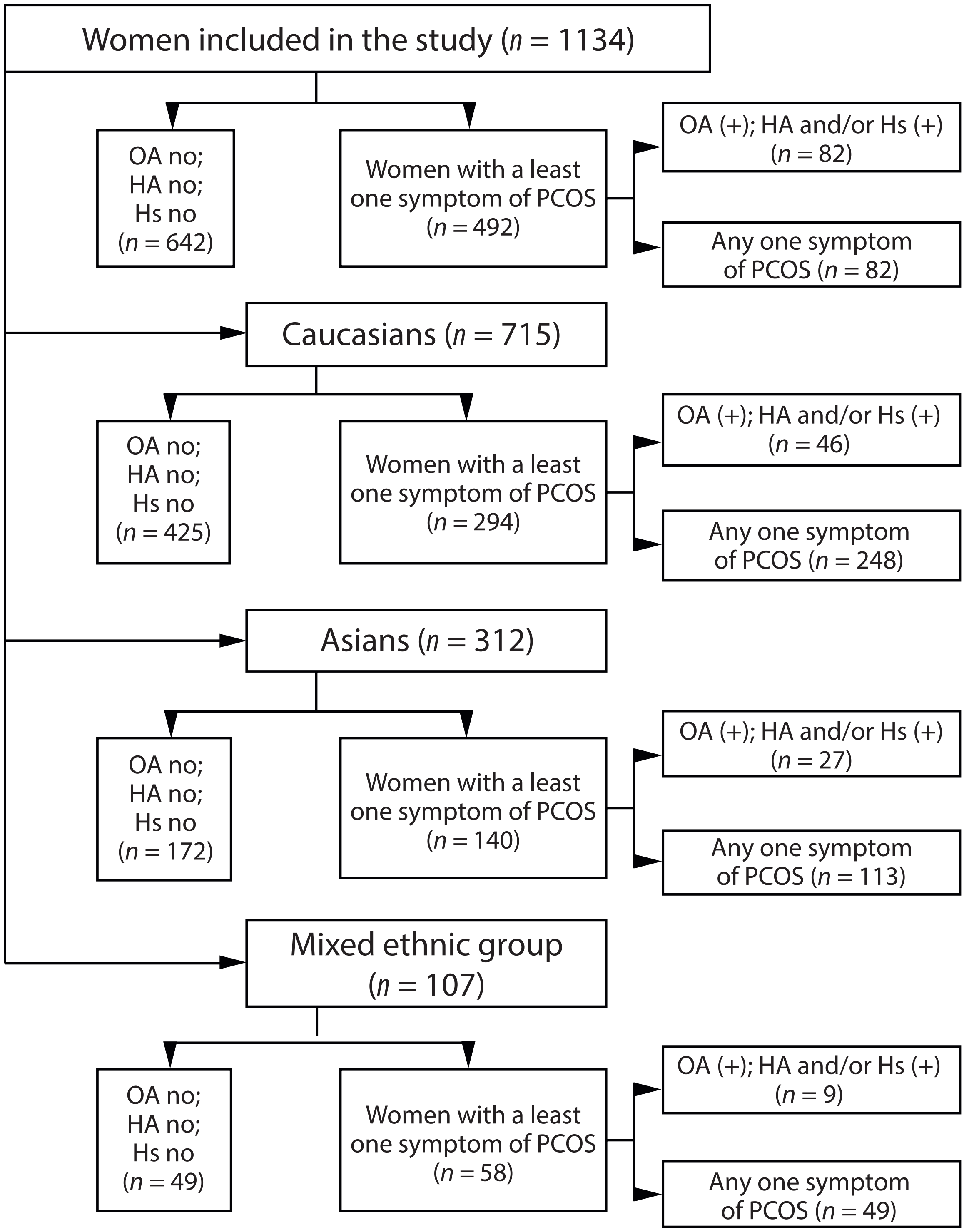

FIG. 1.
Diagram of the distribution of women into subgroups with no PCOS criteria, with one and two criteria overall, and according to ethnicity

TABLE 1

SOCIO-DEMOGRAPHIC CHARACTERISTICS OF WOMEN IN THE STUDY GROUPS

Variables	Group without OA, HA, Hs ($n = 642$)	NIH group ($n = 82$)	Group with any one symptom ($n = 410$)	p
	0	11	12	
Age (years), M (SD), Me (LQ; UQ)	35.12 ± 6.17 36.0 (31.0; 40.0)	31.65 ± 6.55 32.0 (26.25; 36.0)	33.67 ± 6.55 34.0 (29.0; 39.0)	**$p_u = 0.000_{0–11}$** **$p_u = 0.000_{0–12}$** **$p_u = 0.013_{11–12}$**
	Ethnic composition			
Caucasians, n/N (%)	421/642 (65.58 %)	46/82 (56.10 %)	248/410 (60.49 %)	$p_{\chi2} > 0.05$
Asians, n/N (%)	172/642 (26.79 %)	27/82 (32.93 %)	113/410 (27.56 %)	$p_{\chi2} > 0.05$
Mixed ethnicity, n/N (%)	49/642 (7.63 %)	9/82 (10.98 %)	49/410 (11.95 %)	$p_{\chi2} > 0.05$

Note. $p_{\chi2}$ – χ^2 test; p_u – Mann – Whitney test.

TABLE 2

ANTHROPOMETRIC CHARACTERISTICS, MENSTRUAL AND REPRODUCTIVE HISTORY OF PREMENOPAUSAL WOMEN

Variables	Group 0 ($n = 642$)	Group 11 ($n = 82$)	Group 12 ($n = 410$)	p
BMI (kg/m²), M (SD), Me (LQ; UQ)	25.42 ± 5.11 24.7 (21.5; 28.18)	27.78 ± 6.09 26.9 (22.82; 31.85)	26.17 ± 6.02 24.9 (21.8; 29.4)	**$p_u = 0.000_{0–11}$** $p_u = 0.175_{0–12}$ **$p_u = 0.018_{11–12}$**
Waist circumference (cm), M (SD), Me (LQ; UQ)	77.76 ± 12.02 76.0 (68.0; 85.0)	82.91 ± 14.41 82.0 (72.0; 93.0)	79.05 ± 13.83 76.0 (69.0; 86.0)	**$p_u = 0.003_{0–11}$** $p_u = 0.346_{0–12}$ **$p_u = 0.020_{11–12}$**
SBP (mm Hg), M (SD), Me (LQ; UQ)	78.43 ± 9.85 78.0 (71.0; 84.0)	80.7 ± 10.75 80.0 (74.0; 84.75)	78.65 ± 9.91 79.0 (71.25; 84.0)	$p_u = 0.109^{-11}$ $p_u = 0.424_{0–12}$ $p_u = 0.280_{11–12}$
DBP (mm Hg), M (SD), Me (LQ; UQ)	121.69 ± 13.75 121.0 (113.0; 128.0)	126.2 ± 14.78 124.0 (115.25; 135.0)	122.7 ± 13.66 122.0 (113.0; 130.0)	**$p_u = 0.007_{0–11}$** $p_u = 0.170_{0–12}$ $p_u = 0.069_{11–12}$
Oliganovulation, n/N (%)	0/642 (0.00 %)	82/82 (100 %)	208/410 (50.73 %)	**$p_{\chi2} = 0.000_{11–12}$**
Hyperandrogenemia, n/N (%)	0/642 (0.00 %)	58/82 (70.73 %)	162/410 (39.51 %)	**$p_{\chi2} = 0.000_{11–12}$**
Hirsutism, n/N (%)	0/642 (0.00 %)	38/82 (46.34 %)	52/410 (12.68 %)	**$p_{\chi2} = 0.000_{11–12}$**
Hirsutism (scores), M (SD), Me (LQ; UQ)	0.56 ± 1.01 0.0 (0.0; 1.0)	3.99 ± 3.62 4.0 (0.25; 6.0)	1.61 ± 2.51 0.0 (0.0; 2.0)	**$p_u = 0.000_{0–11}$** **$p_u = 0.000_{0–12}$** **$p_u = 0.000_{11–12}$**
Age at menarche (years), M (SD), Me (LQ; UQ)	13.3 ± 1.35 13.0 (12.0; 14.0)	13.29 ± 1.72 14.0 (12.0; 14.0)	13.2 ± 1.45 13.0 (12.0; 14.0)	$p_u = 0.843_{0–11}$ $p_u = 0.384_{0–12}$ $p_u = 0.556_{11–12}$
Duration of the menstrual cycle, M (SD), Me (LQ; UQ)	27.67 ± 2.2 28.0 (27.0; 29.0)	35.22 ± 12.49 32.0 (28.0; 38.0)	29.27 ± 5.3 28.0 (27.0; 30.0)	**$p_u = 0.000_{0–11}$** **$p_u = 0.000_{0–12}$** **$p_u = 0.000_{11–12}$**
Minimum duration of the menstrual cycle (days), M (SD), Me (LQ; UQ)	26.17 ± 2.39 26.0 (25.0; 28.0)	27.8 ± 6.5 28.0 (25.0; 30.0)	25.8 ± 4.49 27.0 (24.0; 28.0)	**$p_u = 0.001_{0–11}$** $p_u = 0.945_{0–12}$ **$p_u = 0.004_{11–12}$**
Maximum duration of the menstrual cycle (days), M (SD), Me (LQ; UQ)	29.39 ± 2.74 30.0 (28.0; 30.0)	65.95 ± 37.43 51.0 (40.0; 90.0)	40.73 ± 28.68 31.0 (28.0; 40.0)	**$p_u = 0.000_{0–11}$** **$p_u = 0.000_{0–12}$** **$p_u = 0.000_{11–12}$**

TABLE 2 (*continued*)

Number of menstrual cycles per year, M (SD), Me (LQ; UQ)	12.23 ± 1.23 12.0 (12.0; 12.0)	9.2 ± 2.56 9.0 (8.0; 11.75)	11.41 ± 1.86 12.0 (11.0; 12.0)	$\mathbf{p_u = 0.000_{0-11}}$ $\mathbf{p_u = 0.000_{0-12}}$ $\mathbf{p_u = 0.000_{11-12}}$
Pregnancies				
Number of pregnancies, M (SD), Me (LQ; UQ)	2.7 ± 2.54 2.0 (1.0; 4.0)	1.66 ± 2.48 1.0 (0.0; 2.0)	2.32 ± 2.18 2.0 (1,0; 3,0)	$\mathbf{p_u = 0.000_{0-11}}$ $\mathbf{p_u = 0.019_{0-12}}$ $\mathbf{p_u = 0.000_{11-12}}$
Number of births, M (SD), Me (LQ; UQ)	1.37 ± 1.01 1.0 (1.0; 2.0)	0.74 ± 0.89 0.0 (0.0; 1.0)	1.27 ± 1.11 1.0 (0.0; 2.0)	$\mathbf{p_u = 0.000_{0-11}}$ $\mathbf{p_u = 0.035_{0-12}}$ $\mathbf{p_u = 0.000_{11-12}}$
Number of stillbirths, M (SD), Me (LQ; UQ)	0.02 ± 0.17 0.0 (0.0; 0.0)	0.0 ± 0.0 0.0 (0.0; 0.0)	0.0 ± 0.07 0.0 (0.0; 0.0)	$p_u = 0.193_{0-11}$ $\mathbf{p_u = 0.039_{0-12}}$ $p_u = 0.529_{11-12}$
Number of self-induced miscar-riages, M (SD), Me (LQ; UQ)	0.2 ± 0.56 0.0 (0.0; 0.0)	0.07 ± 0.31 0.0 (0.0; 0.0)	0.16 ± 0.54 0.0 (0.0; 0.0)	$\mathbf{p_u = 0.000_{0-11}}$ $p_u = 0.092_{0-12}$ $p_u = 0.135_{11-12}$
Number of ectopic pregnancies, M (SD), Me (LQ; UQ)	0.04 ± 0.24 0.0 (0.0; 0.0)	0.06 ± 0.24 0.0 (0.0; 0.0)	0.04 ± 0.23 0.0 (0.0; 0.0)	$p_u = 0.275_{0-11}$ $p_u = 0.720_{0-12}$ $p_u = 0.205_{11-12}$
Number of non-viable pregnan-cies, M (SD), Me (LQ; UQ)	0.03 ± 0.22 0.0 (0.0; 0.0)	0.04 ± 0.19 0.0 (0.0; 0.0)	0.02 ± 0.15 0.0 (0.0; 0.0)	$p_u = 0.546_{0-11}$ $p_u = 0.939_{0-12}$ $p_u = 0.531_{11-12}$
Number of medical abortions, M (SD), Me (LQ; UQ)	1.06 ± 1.85; 0.0 (0.0; 2.0)	0.76 ± 1.87 0.0 (0.0; 0.75)	0.88 ± 1.41 0.0 (0.0; 1.0)	$\mathbf{p_u = 0.003_{0-11}}$ $p_u = 0.295_{0-12}$ $\mathbf{p_u = 0.016_{11-12}}$
Infertility, n/N (%)	120/633 (18.96 %)	30/82 (37.04 %)	104/404 (25.74 %)	$\mathbf{p_{\chi 2} = 0.000_{0-11}}$ $\mathbf{p_{\chi 2} = 0.018_{0-12}}$ $p_{\chi 2} = 0.071_{11-12}$

Note. $p_{\chi 2}$ – χ^2 test; p_u – Mann – Whitney test.

TABLE 3

HORMONAL CHARACTERISTICS OF PREMENOPAUSAL WOMEN AND DATA OF PELVIC ULTRASOUND

Variables	Group without OA, HA, Hs (*n* = 642)	NIH group (*n* = 82)	Group with any one symptom (*n* = 410)	*p*
	0	11	12	
TSH (mIU/ml), M (SD); Me (LQ; UQ)	372.01 ± 256.99 314.5 (221.0; 445.5)	403.91 ± 315.13 319.0 (239.5; 467.0)	393.92 ± 251.01 329.0 (235.0; 483.0)	$p_u = 0.807_{0-11}$ $p_u = 0.065_{0-12}$ $p_u = 0.869_{11-12}$
PRL (mU/l), M (SD); Me (LQ; UQ)	1.73 ± 1.2 1.5 (1.1; 2.1)	1.75 ± 1.05 1.6 (1.0; 2.28)	1.94 ± 1.95 1.5 (1.1; 2.2)	$p_u = 0.756_{0-11}$ $p_u = 0.340_{0-12}$ $p_u = 0.826_{11-12}$
LH (mIU/ml), M (SD); Me (LQ; UQ)	8.03 ± 10.89 5.3 (3.2; 7.9)	12.94 ± 13.06 8.5 (5.28; 16.95)	10.06 ± 12.31 6.0 (3.7; 10.85)	$\mathbf{p_u = 0.000_{0-11}}$ $\mathbf{p_u = 0.000_{0-12}}$ $\mathbf{p_u = 0.000_{11-12}}$
FSH (mIU/l), M (SD); Me (LQ; UQ)	7.02 ± 8.25 5.4 (3.8; 7.3)	6.91 ± 5.07 6.15 (4.32; 7.7)	9.34 ± 5.9 5.5 (3.9; 7.52)	$p_u = 0.100_{0-11}$ $p_u = 0.260_{0-12}$ $p_u = 0.289_{11-12}$
LH/FSH ratio, M (SD); Me (LQ; UQ)	1.24 ± 1.12 0.93 (0.66; 1.5)	1.91 ± 1.31 1.61 (1.02; 2.38)	1.4 ± 1.07 1.04 (0.67; 1.83)	$\mathbf{p_u = 0.000_{0-11}}$ $\mathbf{p_u = 0.022_{0-12}}$ $\mathbf{p_u = 0.000_{11-12}}$

TABLE 3 (*continued*)

Testosterone (g/dl), M (SD); Me (LQ; UQ)	247.03 ± 132.3 246.38 (153.5; 326.87)	571.09 ± 659.06 432.47 (306.46; 609.6)	403.15 ± 384.43 298.2 (209.63; 434.57)	**$p_u = 0.000_{0–11}$** **$p_u = 0.000_{0–12}$** **$p_u = 0.000_{11–12}$**
SHBG, M (SD); Me (LQ; UQ)	82.86 ± 54.5 67.45 (43.7; 105.65)	60.08 ± 43.87 44.3 (29.72; 75.4)	76.32 ± 52.78 64.8 (38.1; 98.9)	**$p_u = 0.000_{0–11}$** **$p_u = 0.027_{0–12}$** **$p_u = 0.003_{11–12}$**
FAI, M (SD); Me (LQ; UQ)	1.41 ± 1.09 1.16 (0.63; 1.92)	4.52 ± 4.92 3.36 (1.82; 5.36)	3.1 ± 6.78 1.65 (0.94; 3.5)	**$p_u = 0.000_{0–11}$** **$p_u = 0.000_{0–12}$** **$p_u = 0.000_{11–12}$**
DHEA-S (mg/dl), M (SD); Me (LQ; UQ)	158.59 ± 65.38 150.0 (110.5; 200.0)	244.67 ± 109.9 233.0 (168.75; 316.25)	190.59 ± 98.33 170.0 (118.0; 240.0)	**$p_u = 0.000_{0–11}$** **$p_u = 0.000_{0–12}$** **$p_u = 0.000_{11–12}$**
17-OH-progesterone, M (SD); Me (LQ; UQ)	5.5 ± 3.35 5.2 (2.48; 7.7)	6.01 ± 3.18 5.6 (4.3; 6.9)	5.83 ± 4.78 4.9 (2.9; 6.9)	$p_u = 0.222_{0–11}$ $p_u = 0.912_{0–12}$ $p_u = 0.107_{11–12}$
AMH, M (SD); Me (LQ; UQ)	2.78 ± 2.45 2.1 (1.0; 4.0)	6.58 ± 5.51 5.3 (2.65; 8.12)	4.66 ± 4.74 3.2 (1.7; 6.1)	**$p_u = 0.000_{0–11}$** **$p_u = 0.000_{0–12}$** **$p_u = 0.001_{11–12}$**
Ultrasound characteristics of the ovaries *All ovaries*				
OV	6.36 ± 2.57 5.93 (4.71; 7.46)	9.66 ± 5.43 8.82 (5.96; 11.40)	7.35 ± 3.73 6.53 (4.83; 9.09)	**$p_u = 0.000_{0–11}$** **$p_u = 0.000_{0–12}$** **$p_u = 0.001_{11–12}$**
FNPO	6.74 ± 2.83 6.00 (5.00; 8.00)	10.92 ± 4.97 12.00 (7.00; 13.5)	7.97 ± 3.70 7.00 (5.00; 10.00)	**$p_u = 0.000_{0–11}$** **$p_u = 0.000_{0–12}$** **$p_u = 0.001_{11–12}$**
Left ovaries				
OV	8.12 ± 9.0 6.34 (4.92; 8.57)	10.25 ± 8.67 8.68 (6.02; 11.69)	8.33 ± 6.75 6.9 (5.0; 9.7)	**$p_u = 0.000_{0–11}$** **$p_u = 0.000_{0–12}$** **$p_u = 0.001_{11–12}$**
FNPO	6.4 ± 2.65 6.0 (5.0; 8.0)	10.44 ± 5.31 10.0 (7.0; 13.0)	7.26 ± 3.38 7.0 (5.0; 9.25)	**$p_u = 0.000_{0–11}$** **$p_u = 0.000_{0–12}$** **$p_u = 0.000_{11–12}$**
Right ovaries				
OV	9.06 ± 23.65 6.72 (5.23; 8.84)	11.23 ± 7.15 9.74 (6.67; 12.55)	8.98 ± 8.19 7.46 (5.34; 10.54)	**$p_u = 0,000_{0–11}$** **$p_u = 0,005_{0–12}$** **$p_u = 0,000_{11–12}$**
FNPO	6.68 ± 2.79 6.0 (5.0; 8.0)	10.77 ± 4.8 12.0 (7.0; 14.0)	7.66 ± 3.84 7.0 (5.0; 10.0)	**$p_u = 0.000_{0–11}$** **$p_u = 0.000_{0–12}$** **$p_u = 0.000_{11–12}$**

Note. p_u – Mann – Whitney test.

The exclusion criterion for an ovary was the presence of a mass, cyst, or follicle of 10 mm or more in diameter detected during the ultrasound scan performed in this study. A total of 1665 ovaries that met the inclusion criteria were ultimately included in the analysis. In the control group, 927 ovaries were evaluated (group 0 in the diagram); in the group with at least one PCOS criterion (group 12 in the diagram), 597 ovaries were evaluated; in women with two PCOS criteria (group 11), 132 ovaries were evaluated (fig. 2). In women of Caucasian ethnicity, 1024 ovaries met the inclusion criteria, in Asian women, 458 ovaries, and in the mixed ethnicity group, 174 ovaries met the inclusion criteria. Next, the cut-off points (upper normal values) for ovarian volume and follicle number were determined to classify women without symptoms of PCOS with the group of participants demonstrating single criteria of PCOS and with women with PCOS both in general and taking into account their ethnicity. To clarify the upper normal values for ovarian volume and of antral follicles number per ovary in women with any one criterion of PCOS, the following subgroups were identified when stratifying by ethnic groups. The overall population is group 0/12, which included 1052 participants, the average age was 34.4 ± 6.35 years, the number of ovaries in this group was 1524. Group 0c/12c – Caucasians (*n* = 669, number of ovaries – 953), the average age was 34.4 ± 6.4 years. Group 0a/12a – Asians (*n* = 285, number of ovaries – 412), average age 33.8 ± 6.7 years. Group 0m/12m – participants of mixed ethnicity (*n* = 98, number of ovaries – 159), average age 32.1 ± 7.3 years (fig. 2).

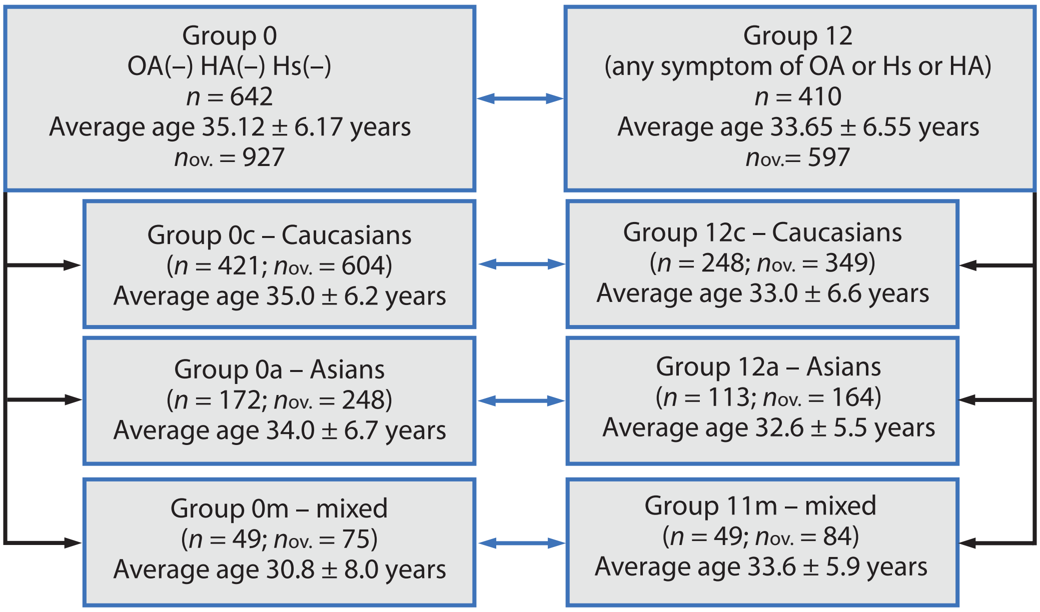

FIG. 2.
Inclusion diagram of study participants to determine cut-off points for ovarian volume and follicle number when classifying patients into groups 0–12 overall and by ethnicity

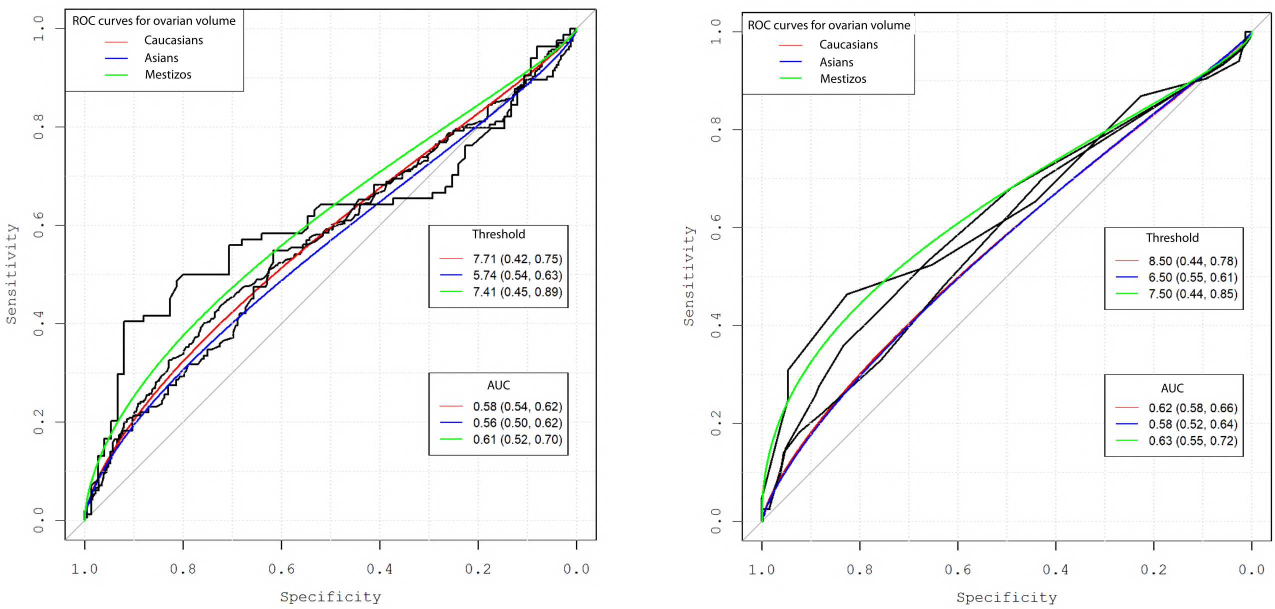

FIG. 3.
ROC-curves for ovarian volume and antral follicles number per ovary for premenopausal women (group 0/group 12 (any one sign of PCOS according to NIH criteria (hyperandrogenism/oligoanovulation)) for overall population, Caucasian women, Asian women, and women of mixed ethnicity

TABLE 4

CUT-OFF POINTS FOR OVARIAN VOLUME AND FOLLICLE NUMBER WHEN CLASSIFYING THE PATIENTS INTO GROUPS OVERALL AND BY ETHNICITY (GROUP 0/GROUP 12 (ANY ONE SIGN OF PCOS ACCORDING TO NIH CRITERIA (HYPERANDROGENISM/ OLIGOANOVULATION))

Parameters	Cut-off point	95% CI for cut-off points	AUC	95% CI for AUC	Sensitivity	Specificity	PSPR	PSNR
				Ovarian volume				
All ethnic groups	7.55	(6.83; 8.75)	0.57	(0.54; 0.60)	0.39	0.77	0.11	0.54
Caucasians	7.71	(6.95; 9.79)	0.58	(0.54; 0.62)	0.42	0.75	0.14	0.51
Asians	5.74	(5.19; 9.36)	0.56	(0.50; 0.62)	0.54	0.63	0.24	0.35
Mixed ethnicity	7.41	(6.04; 7.47)	0.61	(0.52; 0.70)	0.45	0.89	0.11	0.67
				Antral follicles number per ovary				
All ethnic groups	8.50	(6.50; 9.50)	0.60	(0.57; 0.63)	0.39	0.80	0.09	0.61
Caucasians	8.50	(6.50; 9.50)	0.62	(0.58; 0.66)	0.44	0.78	0.12	0.56
Asians	6.50	(5.50; 10.50)	0.58	(0.52; 0.64)	0.55	0.61	0.23	0.36
Mixed ethnicity	7.50	(7.50; 8.50)	0.63	(0.55; 0.72)	0.44	0.85	0.14	0.57

Note. PSPR – prognostic significance of a positive result; PSNR – prognostic significance of a negative result.

ROC-analysis was performed on the data set obtained in the groups of women presented in figure 3. The threshold values and diagnostic efficiency of the OV and antral follicles number per ovary are presented in table 4.

Determination of cut-off points for ovarian volume and follicle number when classifying the patients into groups 0–12 of women of Caucasian, Asian, and mixed ethnicity aged less than 35 years and aged 35 years and older inclusive

To clarify the cut-off values for OV and antral follicles number per ovary in women with any one criterion of PCOS, the following subgroups were identified when stratifying the patients by ethnic groups and age. The overall population is the 0/12 group, which included 1052 participants, the average age was 34.4 ± 6.35 years, the number of ovaries was 1524; then, depending on age, the women were divided into participants aged 18–34 years and 35–44 years. As a result, the distribution by groups is as follows: group 0a1/12a1 – 496 participants, the average age was 28.91 ± 3.84 years, 726 ovaries were subject to assessment; Group $0c_{a1}/12c_{a1}$ – Caucasians aged 18–34 years (n = 324, number of ovaries – 466), average age 28.94 ± 3.85 years; Group $0a_{1a}/12a_{1a}$ – Asians aged (n = 122, number of ovaries – 177), average age 28.84 ± 3.95 years; Group $0m_{1a}/12m_{1a}$ – participants of mixed ethnicity (n = 50, number of ovaries – 83), average age 28.88 ± 4.06 years (fig. 4).

Women aged 35–44 years were distributed as follows: group $0_{a2}/12_{a2}$ – 556 women, average age 39.59 ± 3.03 years, 798 ovaries; group $0c_{a2}/12c_{a2}$ – Caucasians aged 18–34 years (n = 345, number of ovaries – 487), average age 39.56 ± 3.08 years; group $0a_{a2}/12a_{a2}$ – Asians aged 35–44 years (n = 163, number of ovaries – 235), average age 39.69 ± 2.92 years; group $0c_{a2}/12c_{a2}$ – women of mixed ethnicity (n = 48, number of ovaries – 76), average age 39.42 ± 3.07 years (fig. 4).

Next, ROC analysis was performed on the data set obtained in the groups presented in figure 3. The threshold values and diagnostic efficiency of the OV and antral follicles number per ovary are presented in table 4.

The threshold values for OV in women with one criterion of PCOS were: for all ethnic groups – 7.55 cm^3; for Caucasians – 7.74 cm^3; for Asians – 5.74 cm^3; for representatives of mixed ethnicity – 7.41 cm^3. The area under the curve (AUC) for ovarian volume was 0.57, 0.58, 0.56 and 0.61, respectively. The threshold values for antral follicles number per ovary in women with one criterion of PCOS were: for all ethnic groups – 8.50; for Caucasians – 8.50; for Asians – 6.50; for representatives of mixed ethnicity – 7.50. The AUC of antral follicles number per ovary was 0.60, 0.62, 0.58 and 0.63, respectively (table 3).

The cut-off values for OV in women with any one PCOS criterion, taking into account age for all ethnic groups, for participants aged 18–34 years were 7.48 cm^3 (AUC = 0.63), which was statistically significantly higher than the cut-off levels for women aged 35–44 years (4.63 cm^3; AUC = 0.53; $p < 0.05$) (table 5). For Caucasians in the age group of 18–34 years, this value was 8.02 cm^3 (AUC = 0.62), which was statistically significantly higher than the cut-off levels for women aged 35–44 years (5.22 cm^3; AUC = 0.535; $p < 0.05$) (table 5).

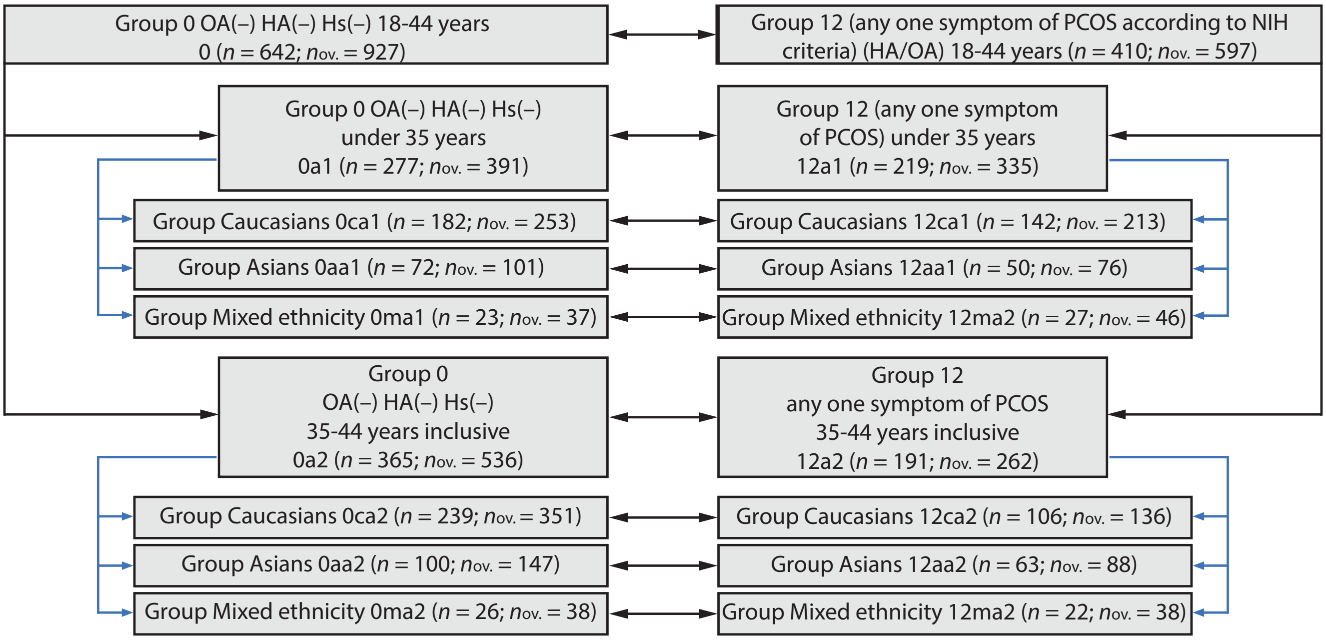

FIG. 4.
Inclusion diagram of study participants to determine cut-off points for ovarian volume and follicle number when classifying patients into groups 0–12 overall, by age and by ethnicity

TABLE 5

CUT-OFF POINTS FOR OVARIAN VOLUME AND FOLLICLE NUMBER WHEN CLASSIFYING PATIENTS UNDER 35 YEARS OF AGE AND 35–44 YEARS OF AGE INTO GROUPS 0–12

Parameters	Cut-off point	95% CI for cut-off points	AUC	95% CI for AUC	Sensitivity	Specificity	PSPR	PSNR
Ovarian volume								
All ethnic groups under 35 years of age, 0/12a1 (*n* = 726)	7.48	(6.19; 9.13)	0.63	(0.59; 0.67)	0.53	0.69	0.22	0.40
All ethnic groups 35-44 years of age, 0/12a2 (*n* = 798)	4.63	(3.02; 5.42)	0.53	(0.49; 0.58)	0.40	0.72	0.27	0.23
Caucasians under 35 years of age, 0/12a1 (*n* = 466)	8.05	(6.33; 9.76)	0.62	(0.57; 0.67)	0.52	0.71	0.21	0.42
Caucasians 35-44 years of age, 0/12a2 (*n* = 487)	5.22	(3.65; 6.27)	0.55	(0.49; 0.61)	0.49	0.65	0.29	0.26
Asians under 35 years of age, 0/12a1 (*n* = 177)	5.30	(5.04; 9.53)	0.64	(0.55; 0.72)	0.78	0.51	0.49	0.19
Asians 35-44 years of age, 0/12a2 (*n* = 235)	4.73	(3.09; 6.18)	0.62	(0.54; 0.70)	0.26	0.87	0.21	0.18
Mixed ethnicity under 35 years of age, 0/12a1 (*n* = 83)	7.30	(5.56; 8.63)	0.66	(0.54; 0.78)	0.57	0.84	0.21	0.52
Mixed ethnicity 35-44 years of age, 0/12a2 (*n* = 76)	6.83	(5.79; 8.63)	0.62	(0.50; 0.73)	0.37	0.95	0.09	0.71

TABLE 5 (*continued*)

Antral follicles number per ovary								
All ethnic groups under 35 years of age, 0/12a1 (*n* = 726)	9.50	(7.50; 10.50)	0.63	(0.58; 0.67)	0.48	0.75	0.16	0.51
All ethnic groups 35-44 years of age, 0/12a2 (*n* = 798)	6.50	(6.50; 10.50)	0.52	(0.48; 0.57)	0.38	0.72	0.12	0.49
Caucasians under 35 years of age, 0/12a1 (*n* = 466)	9.50	(8.50; 11.50)	0.63	(0.58; 0.68)	0.53	0.72	0.20	0.45
Caucasians 35-44 years of age, 0/12a2 (*n* = 487)	6.50	(6.50; 10.50)	0.52	(0.45; 0.58)	0.43	0.68	0.16	0.44
Asians under 35 years of age, 0/12a1 (*n* = 177)	9.50	(5.50; 10.50)	0.60	(0.52; 0.69)	0.37	0.86	0.09	0.66
Asians 35-44 years of age, 0/12a2 (*n* = 235)	5.50	(1.0; 0.45)	0.59	(0.51; 0.67)	0.56	0.59	0.27	0.31
Mixed ethnicity under 35 years of age, 0/12a1 (*n* = 83)	7.50	(7.50; 8.50)	0.68	(0.57; 0.80)	0.57	0.86	0.25	0.49
Mixed ethnicity 35-44 years of age, 0/12a2 (*n* = 76)	7.50	(7.50; 8.50)	0.64	(0.53; 0.75)	0.34	0.87	0.07	0.69

Determination of cut-off points for ovarian volume and follicle count when classifying the patients into groups 0–11 overall and by ethnicity

To clarify the upper normal values for OV and antral follicles number per ovary in women with two signs of PCOS according to the NIH criteria, the following subgroups were identified when stratifying by ethnic groups. The overall population is group 0/11, which included 724 participants, the average age was 33.1 ± 7.2 years, the number of ovaries was 1059. Group 0c/11c – Caucasians (*n* = 467, the number of ovaries was 675), the average age was 34.8 ± 6.9 years. Group 0a/11a – Asians (*n* = 199, the number of ovaries was 294), the average age was 32.1 ± 6.9 years. Group 0m/11m – women of mixed ethnicity (*n* = 58, the number of ovaries was 90), the average age was 32.9 ± 8.3 years (fig. 5).

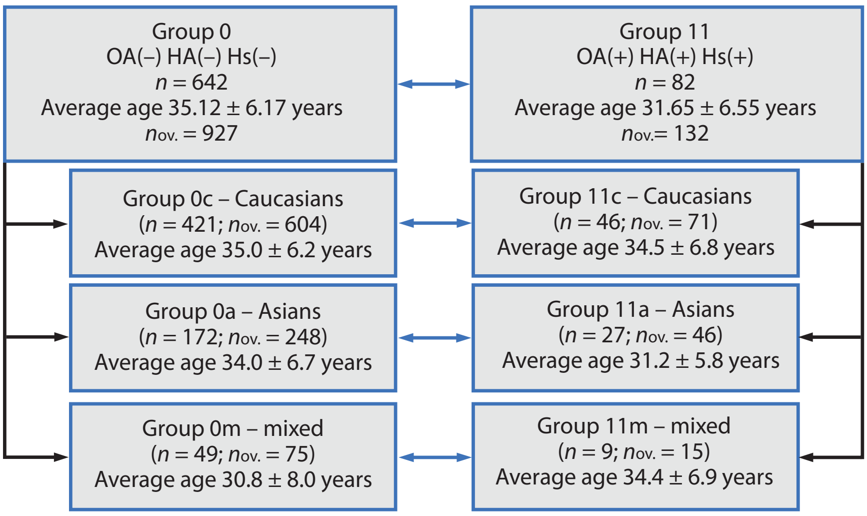

FIG. 5.
Inclusion diagram of study participants to determine cut-off points for ovarian volume and follicle number when classifying patients into groups 0–11 overall and by ethnicity

ROC-analysis was performed on the data set obtained in the groups presented in figure 6. The threshold values and diagnostic efficiency of OV and antral follicles number per ovary are presented in table 6.

The threshold values for OV in women with two PCOS criteria were: for all ethnic groups – 8.11 cm^3; for Caucasians – 8.4 cm^3; for Asians – 6.56 cm^3; for representatives of mixed ethnicity – 7.11 cm^3. The AUC

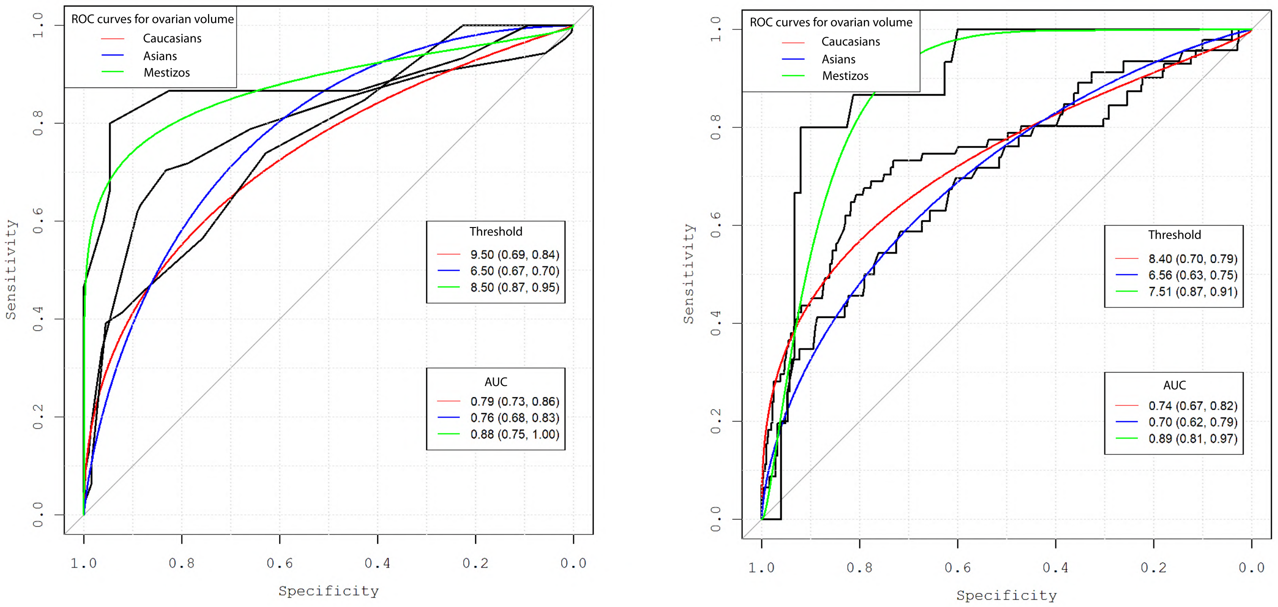

FIG. 6.
ROC-curves for ovarian volume and antral follicles number per ovary for premenopausal women (group 0/group 11 (PCOS according to NIH criteria (hyperandrogenism/oligoanovulation)) for overall population, Caucasian women, Asian women, and women of mixed ethnicity

TABLE 6

CUT-OFF POINTS FOR OVARIAN VOLUME AND FOLLICLE NUMBER WHEN CLASSIFYING PATIENTS INTO GROUPS OVERALL AND BY ETHNICITY (GROUP 0/GROUP 11 (PCOS ACCORDING TO NIH CRITERIA (HYPERANDROGENISM/OLIGOANOVULATION))

Parameters	Cut-off point	95% CI for cut-off points	AUC	95% CI for AUC	Sensitivity	Specificity	PSPR	PSNR
	Ovarian volume							
All ethnic groups	8.11	(7.62; 8.66)	0.73	(0.67; 0.78)	0.62	0.80	0.15	0.61
Caucasians	8.40	(7.61; 8.81)	0.74	(0.67; 0.82)	0.70	0.79	0.18	0.59
Asians	6.56	(4.71; 9.37)	0.70	(0.62; 0.79)	0.63	0.75	0.20	0.51
Mixed ethnicity	7.51	(5.73; 8.57)	0.89	(0.81; 0.97)	0.87	0.91	0.17	0.73
	Antral follicles number per ovary							
All ethnic groups	9.50	(7.50; 10.50)	0.78	(0.73; 0.82)	0.61	0.86	0.12	0.70
Caucasians	9.50	(8.50; 11.50)	0.79	(0.73; 0.86)	0.69	0.84	0.15	0.65
Asians	6.50	(6.50; 11.00)	0.76	(0.68; 0.83)	0.67	0.70	0.29	0.40
Mixed ethnicity	8.50	(7.50; 9.00)	0.88	(0.75; 1.00)	0.87	0.95	0.15	0.78

Note. PSPR – prognostic significance of a positive result; PSNR – prognostic significance of a negative result.

for ovarian volume was 0.73, 0.74, 0.71 and 0.89, respectively. The threshold values for antral follicles number per ovary in women with one PCOS criterion were: for all ethnic groups – 9.50; for Caucasians – 9.50; for Asians – 6.50; for representatives of mixed ethnicity – 8.50. The AUC of antral follicles number per ovary was 0.78, 0.79, 0.76 and 0.88, respectively (table 6). Considering the high values of sensitivity and specificity for the threshold levels of OV and antral follicles number per ovary both in the overall population and depending on ethnicity, we can conclude that the diagnostic ability of the studied variables is satisfactory.

Determination of cut-off points for ovarian volume and follicle count when classifying the female patients aged less than 35 years and aged 35 years and older inclusive (group 0-11)

At the next stage, to determine the upper normal values for OV and antral follicles number per ovary in women with two signs of PCOS according to the NIH criteria, the following subgroups were identified when stratified the patients by ethnic groups and age. The overall population is group 0/11, which included 724 participants, the average age was 34.72 ± 6.30 years, $n_{ov.}$ = 1059. The women were then divided depending on age into participants aged 18–34 years (B1) and 35–44 years (B2). Taking into account the age, the following groups were ultimately formed. Group $0_{a1}/11_{a1}$ included 329 participants, average age 28.96 ± 3.93 years, $n_{ov.}$ = 480. Group $0c_{a1}/11c_{a1}$ included Caucasians aged 18–34 years (*n* = 212; n_{ov} = 302), average age 28.83 ± 3.94 years. Group $0a_{a1}/11a_{a1}$ included Asians aged (*n* = 87; $n_{ov.}$ = 128), average age 29.55 ± 3.68 years. Group $0m_{a1}/11m_{a1}$ included individuals of mixed ethnicity (n = 30; $n_{ov.}$ = 50), average age 28.17 ± 4.49 years (fig. 7).

Women aged 35–44 years were distributed as follows: group $0_{a2}/11_{a2}$ – 395 participants, average age 39.52 ± 4.04 years, n_{ov} = 579; group $0c_{a2}/11c_{a2}$ – Caucasians aged 18–34 years (*n* = 255; $n_{ov.}$ = 373), average age 39.49 ± 3.08 years; group $0a_{a2}/11a_{a2}$ – Asians aged (*n* = 112; n_{ov} = 166), average age 39.44 ± 3.01 years; group $0m_{a2}/11m_{a2}$ – individuals of mixed ethnicity (*n* = 28; $n_{ov.}$ = 40), average age 40.14 ± 2.85 years (Fig. 7).

The threshold values for OV in women with two criteria of PCOS, taking into account age for all ethnic groups were: for participants aged 18–34 years – 8.39 cm^3 (AUC = 0.77); for women aged 35–44 years – 8.43 cm^3 (AUC = 0.58); for Caucasians in the age group 18–34 years – 8.57 cm^3 (AUC = 0.80); in the group of women aged 35–44 years – 8.51 cm^3 (AUC = 0.80) (table 7).

For Asian women aged 18–34 years, the threshold for ovarian volume was determined as 6.52 cm^3 (AUC = 0.75), for the age group 35–44 years – 6.75 cm^3 (AUC = 0.72). For 18–34-year-old participants in the mixed group, the threshold was 7.50 cm^3 (AUC = 0.86), for the age group 35–44 years – 7.50 cm^3 (AUC = 0.87) (table 7). We noted the absence of statistically significant differences in ovarian volume in women aged 18–34 and 35–44 years in all ethnic groups.

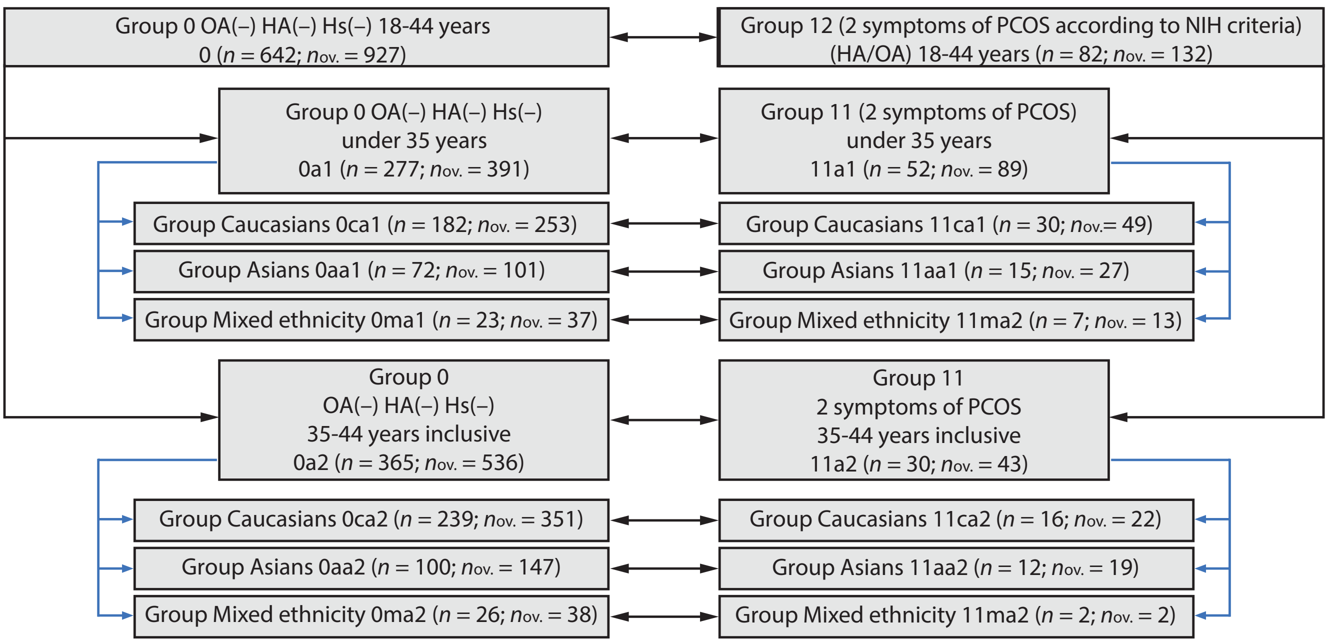

FIG. 7.
Inclusion diagram of study participants to determine cut-off points for ovarian volume and follicle number when categorized into groups 0–11 overall, by age and by ethnicity

TABLE 7

CUT-OFF POINTS FOR OVARIAN VOLUME AND FOLLICLE NUMBER WHEN CLASSIFYING PATIENTS UNDER 35 YEARS OF AGE AND 35–44 YEARS OF AGE INTO GROUPS 0–11

Parameters	Cut-off point	95% CI for cut-off points	AUC	95% CI for AUC	Sensitivity	Specificity	PSPR	PSNR
				Ovarian volume				
All ethnic groups under 35 years of age, 0/11a1 (*n* = 815)	8.39	(7.58; 9.04)	0.77	(0.71; 0.82)	0.73	0.76	0.24	0.51
All ethnic groups 35-44 years of age, 0/11a2 (*n* = 579)	8.43	(4.58; 10.62)	0.58	(0.49; 0.68)	0.40	0.87	0.05	0.75
Caucasians under 35 years of age, 0/11a1c (*n* = 302)	8.57	(7.58; 9.06)	0.80	(0.72; 0.87)	0.84	0.74	0.29	0.48
Caucasians 35-44 years of age, 0/11a2c (*n* = 373)	8.51	(7.58; 9.17)	0.80	(0.73; 0.87)	0.41	0.87	0.06	0.75
Asians under 35 years of age, 0/12a1(*n* = 128)	6.52	(5.23; 9.53)	0.75	(0.64; 0.85)	0.78	0.67	0.35	0.37
Asians 35-44 years of age, 0/11a2a (*n* = 166)	6.85	(5.34; 9.50)	0.72	(0.62; 0.82)	0.84	0.42	0.54	0.15
Mixed ethnicity under 35 years of age, 0/11a1m (*n* = 50)	7.51	(5.73; 8.57)	0.86	(0.75; 0.97)	0.92	0.84	0.30	0.57
Mixed ethnicity 35-44 years of age, 0/11a2m (*n* = 40)	7.50	(5.73; 8.57)	0.87	(0.77; 0.97)	1.00	0.71	0.35	0.46
				Antral follicles number per ovary				
All ethnic groups under 35 years of age, 0/11a1 (*n* = 815)	10.50	(8.50;11.50)	0.82	(0.77; 0.87)	0.73	0.85	0.19	0.63
All ethnic groups 35-44 years of age, 0/11a2 (*n* = 579)	6.50	(6.50; 9.50)	0.65	(0.55; 0.74)	0.58	0.72	0.73	0.49
Caucasians under 35 years of age, 0/11a1c (*n* = 302)	11.50	(9.50; 11.50)	0.84	(0.77; 0.90)	0.82	0.82	0.23	0.59
Caucasians 35-44 years of age, 0/11a2c (*n* = 373)	11.50	(9.50; 11.50)	0.84	(0.78; 0.90)	0.59	0.79	0.13	0.62
Asians under 35 years of age, 0/12a1 (*n* = 128)	10.50	(7.50; 11.00)	0.76	(0.65; 0.87)	0.63	0.91	0.11	0.75

TABLE 7 (*continued*)

Asians 35-44 years of age, 0/11a2a (*n* = 166)	6.50	(6.50; 11.00)	0.76	(0.68; 0.83)	0.67	0.70	0.29	0.40
Mixed ethnicity under 35 years of age, 0/11a1m (*n* = 50)	8.50	(7.50; 10.00)	0.96	(0.92; 1.00)	1.00	0.92	0.30	0.64
Mixed ethnicity 35-44 years of age, 0/11a2m (*n* = 40)	8.50	(7.50; 11.00)	0.96	(0.92; 1.00)	1.00	0.45	0.4	0.27

DISCUSSION

In our study, cut-off points for OV and antral follicles number per ovary were determined using pairwise comparisons of three groups: 1) women with regular cycles and no signs of hyperandrogenism versus 2) study participants with oligomenorrhea/olianovulation [4, 5] and hyperandrogenism (hirsutism and/or hyperandrogenemia) [4, 5, 17], the combination of which allows the diagnosis of PCOS without assessment of ovarian ultrasonographic characteristics, or 3) women with either oligoanovulation or any one sign of hyperandrogenism.

According to our data, for differentiation of the 1st and 2nd comparison groups in Caucasians, the best compromise between sensitivity and specificity was achieved with a diagnostic threshold for OV ≥ 9 cm^3, which did not depend on age (8.57 cm^3 and 8.51 cm^3 in the younger and older age groups, respectively) and was slightly lower compared to the results of previous studies presented by E. Carmina et al. [18], D. Dewailly et al. [19] and M.E. Lujan et al. [20], where the ULN was 10 cm^3.

For Asian women, the upper normal value for ovary that we determined also did not differ statistically significantly depending on age. Thus, at the age of 18–34 years, the ULN for ovary was determined as 6.52 cm^3, and for the age group of 35–44 years – 6.75 cm^3, which is consistent with the data obtained previously in Korean patients with PCOS [8], who had the right ovary volume of 6.4 cm^3, the left – 6.7 ml [8], as well as in Chinese women [21]: the ULN values for ovary were 6.3 cm^3 [22] and 7 cm^3 [23]. A lower OV in women of the Asian population with PCOS compared to Caucasians has been mentioned previously [24–26].

When comparing patients with two criteria for PCOS and a control group of Caucasian ethnicity, high values of sensitivity and specificity were determined at a threshold level of FNPO ≥ 12, while D. Dewailly et al. [19] and M.E. Lujan et al. [20] on a similar sample proposed an ULN for FNPO at a level of ≥ 19 and ≥ 26, respectively. The authors substantiated their results by the high sensitivity of modern ultrasound devices and assumed that the use of a lower threshold for assessing FNPO would lead to overdiagnosis of PCOM in young women with a high ovarian reserve.

Our study demonstrated the high performance of FNPO as a marker of PCOM in women of the Asian subpopulation. The best compromise between sensitivity and specificity was achieved with a threshold for FNPO ≥ 11, which is consistent with the results of estimating the ULN for FNPO in Asian women obtained by other researchers: ≥ 10 [22], > 11.25 for young women under 35 years old and > 10.75 for the older age group [27].

For women of mixed ethnicity, according to the results of our study, the ULN for OV was ≥ 8 cm^3, and for FNPO ≥ 9. The data obtained are unique, since similar studies have not been previously conducted in populations of women of mixed (Caucasian-Asian) ethnicity.

The obtained values can be explained by the contingent included in the study (a small number of young women aged 18–25 years) with an average age of participants in the 18–35 group of 28.83 ± 3.94 years. It is known that the period of the most rapid loss of follicles in both women with PCOS and those without PCOS occurs between the ages of 18 and 30 years [28].

Strengths of the study. Overall, given the high sensitivity and specificity values for the ovarian volume and antral follicles number cut-off levels which we determined both in the overall population and depending on ethnicity, we can conclude that the diagnostic ability of the studied variables is satisfactory. An important advantage of our study is that all participants were recruited from a non-selective multiethnic population of women with comparable socio-demographic characteristics and living in the same geographic conditions [12, 29]. We consider the population of Eastern Siberia as an ideal model for studying the characteristics of PCOM in Caucasians and Asians using ethnically dependent normative ranges of androgens [30].

Another advantage is that testosterone measurement for the diagnosis of hyperandrogenemia in our study was performed using the HPLC-MS/MS method [31], while our previously developed population-specific standards for assessing hirsutism were used.

Limitations of the study. In our study, the examination of patients was carried out using mid-range ultrasound equipment. At the same time, mid-range ultrasound devices are the most frequently used equipment in practical healthcare and our data are as close as possible to the realities of routine medical practice.

CONCLUSION

For a differentiated approach to identifying PCOM in women of reproductive age of different ethnic groups, it is necessary to take into account the normative values we have developed: thus, in Caucasians, it is advisable to diagnose PCOM with an ovarian volume of 9 cm^3 and/or FNPO ≥ 12; in women of the Asian population, an ovarian volume of 7 cm^3 and/or FNPO ≥ 11 is diagnostically significant, and for women of mixed ethnicity – 8 cm^3 and/or ≥ 9, respectively. When assessing age aspects, we noted the absence of statistically significant differences in the upper normal values of OV and FNPO in women aged 18–34 and 35–44 years in all ethnic groups.

Conflicts of interest

No potential conflict of interest relevant to this article reported.

REFERENCES

1. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod*. 2004; 19(1): 41-47. doi: 10.1093/humrep/deh098

2. Dewailly D, Alebić M, Duhamel A, Stojanović N. Using cluster analysis to identify a homogeneous subpopulation of women with polycystic ovarian morphology in a population of non-hyperandrogenic women with regular menstrual cycles. *Hum Reprod*. 2014; 29(11): 2536-2543. doi: 10.1093/humrep/deu242

3. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al. Recommendations from the international evidence-based guideline forthe assessment and management of polycystic ovary syndrome. *Clin Endocrinol (Oxf)*. 2018; 89(3): 251-268. doi: 10.1111/cen.13795

4. Teede HJ, Tay CT, Laven J, Dokras A, Moran LJ, Piltonen TT, et al. Recommendations from the 2023 international evidencebased guideline for the assessment and management ofpolycystic ovary syndrome. *Fertil Steril*. 2023; 120(4): 767-793. doi: 10.1016/j.fertnstert.2023.07.025

5. Teede HJ, Norman RJ, Garad RM. A new evidence-based guideline for assessment and management of polycystic ovary syndrome. *Med J Aust*. 2019; 210(6): 285-285.e1. doi: 10.5694/mja2.50053

6. Chen X, Yang D, Mo Y, Li L, Chen Y, Huang Y. Prevalence of polycystic ovary syndrome in unselected women from southern China. *Eur J Obstet Gynecol Reprod Biol*. 2008; 139(1): 59-64. doi: 10.1016/j.ejogrb.2007.12.018

7. Köşüş N, Köşüş A, Turhan N, Kamalak Z. Do threshold values of ovarian volume and follicle number for diagnosing polycystic ovarian syndrome in Turkish women differ from western countries? *Eur J Obstet Gynecol Reprod Biol*. 2011; 154(2): 177-181. doi: 10.1016/j.ejogrb.2010.10.007

8. Han YS, Lee AR, Song HK, Choi JI, Kim JH, Kim MR, et al. Ovarian volume inKorean women withpolycystic ovary syndrome and its related factors. *J Menopausal Med*. 2017; 23(1): 25-31. doi: 10.6118/jmm.2017.23.1.25

9. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: The complete task force report. *Fertil Steril*. 2009; 91(2): 456-488. doi: 10.1016/j.fertnstert.2008.06.035

10. Hsu MI. Changes in the PCOS phenotype with age. *Steroids*. 2013; 78(8): 761-766. doi: 10.1016/j.steroids.2013.04.005

11. Adams JM, Taylor AE, Crowley WF, Hall JE. Polycystic ovarian morphology with regular ovulatory cycles: Insights into the pathophysiology of polycystic ovarian syndrome. *J Clin Endocrinol Metab*. 2004; 89(9): 4343-4350. doi: 10.1210/jc.2003-031600

12. Suturina L, Lizneva D, Danusevich I, Lazareva L, Belenkaya L, Nadeliaeva Ia, et al. The design, methodology, and recruitment rate forthe Eastern Siberia PCOS Epidemiology&Phenotype (ES-PEP) Study. Proceedings ofthe 41st Annual Meeting oftheAndrogen Excess and PCOS Society (Lorne, Victoria, Australia, 10–12.11.2016). 2016: 76.

13. Atalyan VV, Kolesnikova LI, Kolesnikov SI, Grjibovski AM, Suturina LV. Research electronic data capture (REDCap) for building and managing databases for population-based biomedical studies. *Human Ecology*. 2019. 2019; 26(2): 52-59. (In Russ.). [Аталян А.В., Колесникова Л.И., Колесников С.И., Гржибовский А.М., Сутурина Л.В. Информационная система REDCap для сбора и хранения данных популяционных биомедицинских исследований. *Экология человека*. 2019; 2: 52-59]. doi: 10.33396/1728-0869-2019-2-52-59

14. Klein DA, Paradise SL, Reeder RM. Amenorrhea: Asystematic approach to diagnosis and management. *Am Fam Physician*. 2019; 100(1): 39-48.

15. Yildiz BO, Bolour S, Woods K, Moore A, Azziz R. Visually scoring hirsutism. *Hum Reprod Update*. 2010; 16(1): 51-64. doi: 10.1093/humupd/dmp024

16. Rao P, Bhide P. Controversies in the diagnosis ofpolycystic ovary syndrome. *Ther Adv Reprod Health*. 2020; 14: 2633494120913032. doi: 10.1177/2633494120913032

17. Zawadski JK, Dunaif A. *Diagnostic criteria for polycystic ovary syndrome: Towards a rational approach, polycystic ovary syndrome*. In: Dunaif A, Dunaif

AGJ, Haseltine F (eds). Polycystic ovary syndrome. Boston: Blackwell Scientific; 1992: 377-384.

18. Carmina E, Campagna AM, Fruzzetti F, Lobo RA. AMH measurement versus ovarian ultrasound in the diagnosis of polycystic ovary syndrome indifferent phenotypes. *Endocr Pract*. 2016; 22(3): 287-293. doi: 10.4158/EP15903.OR

19. 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 ofthe serum AMH level forthe definition of polycystic ovaries. *Hum Reprod*. 2011; 26(11): 3123-3129. doi: 10.1093/humrep/der297

20. Lujan ME, Jarrett BY, Brooks ED, Reines JK, Peppin AK, MuhnN, et al. Updated ultrasound criteria for polycystic ovary syndrome: reliable thresholds for elevated follicle population andovarian volume. *Hum Reprod*. 2013; 28(5): 1361-1368. doi: 10.1093/humrep/det062

21. Le NSV, Le MT, Nguyen ND, Tran NQT, Nguyen QHV, Cao TN. A cross-sectional study on potential ovarian volume and related factors in women with polycystic ovary syndrome from infertile couples. *Int J Womens Health*. 2021; 13: 793-801. doi: 10.2147/IJWH.S329082

22. Chen Y, Li L, Chen X, Zhang Q, Wang W, Li Y, et al. Ovarian volume and follicle number in the diagnosis of polycystic ovary syndrome in Chinese women. *Ultrasound Obstet Gynecol*. 2008; 32(5): 700-703. doi: 10.1002/uog.5393

23. Jonard S, Robert Y, Dewailly D. Revisiting the ovarian volume as a diagnostic criterion for polycystic ovaries. *Hum Reprod*. 2005; 20(10): 2893-2898. doi: 10.1093/humrep/dei159

24. Wongwananuruk T, Panichyawat N, Indhavivadhana S, Rattanachaiyanont M, Angsuwathana S, Techatraisak K, et al. Accuracy of anti-Müllerian hormone and total follicles count to diagnose polycystic ovary syndrome in reproductive women. *Taiwan J Obstet Gynecol*. 2018; 57(4): 499-506. doi: 10.1016/j.tjog.2018.06.004

25. Welt CK, Gudmundsson JA, Arason G, Adams J, Palsdottir H, Gudlaugsdottir G, et al. Characterizing discrete subsets of polycystic ovary syndrome as defined by the Rotterdam criteria: The impact of weight on phenotype and metabolic features. *J Clin Endocrinol Metab*. 2006; 91(12): 4842-4848. doi: 10.1210/jc.2006-1327

26. Dewailly D. Diagnostic criteria for PCOS: Is there a need for a rethink? *Best Pract Res Clin Obstet Gynaecol*. 2016; 37: 5-11. doi: 10.1016/j.bpobgyn.2016.03.009

27. Lie Fong S, Laven JSE, Duhamel A, Dewailly D. Polycystic ovarian morphology and the diagnosis of polycystic ovary syndrome: Redefining threshold levels for follicle count and serum anti-Müllerian hormone using cluster analysis. *Hum Reprod*. 2017; 32(8): 1723-1731. doi: 10.1093/humrep/dex226

28. Wiser A, Shalom-Paz E, Hyman JH, Sokal-Arnon T, Bantan N, Holzer H, et al. Age-related normogram for antral follicle count in women with polycystic ovary syndrome. *Reprod Biomed Online*. 2013; 27(4): 414-418. doi: 10.1016/j.rbmo.2013.06.016

29. Suturina L. *The epidemiology of polycystic ovary syndrome*. In: Kovacs GT, Fauser B, Legro RS (eds). Polycystic ovary syndrome; 3rd ed. Cambridge, UK: Cambridge University Press; 2022: 21-28.

30. Suturina L, LiznevaD, AtalyanA, Lazareva L, Belskikh A, Bairova T, et al. Establishing normative values to determine the prevalence ofbiochemical hyperandrogenism inpremenopausal women of different ethnicities from Eastern Siberia. *Diagnostics (Basel)*. 2022; 13(1): 33. doi: 10.3390/diagnostics13010033

31. Suturina LV, Belskikh AV, Sholokhov LF, Rashidova MA, Danusevich IN, Lazareva LM, et al. The experience in the development and validation of method for testosterone measurement in blood serum of premenopausal women using HPLC-MS/MS. *Acta biomedica scientifica*. 2022; 7(6): 92-101. (In Russ.). [Сутурина Л.В., Бельских А.В., Шолохов Л.Ф., Рашидова М.А., Данусевич И.Н., Лазарева Л.М., и др. Опыт разработки и валидации метода определения тестостерона в сыворотке крови женщин репродуктивного возраста с использованием высокоэффективной жидкостной обращённо-фазовой хроматографии с тандемной масс-селективной детекцией аналита. *Acta Biomedica Scientifica*. 2022; 7(6): 92-101]. doi: 10.29413/ABS.2022-7.6.9

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