

Article

Geographical Variations in Polycystic Ovarian Morphology: Comparison of India- and United States-Based Women with Polycystic Ovary Syndrome

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Abstract

Background/Objectives: Geographical differences exist in the clinical presentation of polycystic ovary syndrome (PCOS). The degree to which ovarian morphology contributes to this variability is unknown. **Methods:** This study compared ovarian ultrasound features between women with PCOS residing in two geographical regions (India and the United States) using stored de-identified ultrasound scans from 331 women with PCOS. Sonographic markers of interest included follicle number per ovary (FNPO), follicle number per cross-section (FNPS), ovarian volume (OV), ovarian area (OA), stromal area (SA), and stromal-to-ovarian area ratio (S/A). **Results:** Most participants in both regions met the accepted criteria for polycystic ovarian morphology (India 87% vs. U.S. 83%). The U.S.-based group had a higher prevalence of follicle excess (41% in U.S. vs. 29% in India; $p = 0.037$), whereas the prevalence of ovarian enlargement was similar across groups (India 37% vs. U.S. 31%, $p = 0.252$). FNPS was higher in the U.S.-based group ($p = 0.046$), while the India-based group had higher OV ($p = 0.010$). SA and S/A did not differ between groups, albeit OA was slightly larger in women with PCOS from India ($p = 0.022$). Associations between ovarian morphology and menstrual cycle length ($q = 0.16$ – 0.25), hirsutism score ($q = 0.19$ – 0.23), and total testosterone ($q = -0.33$ – 0.42) were noted in both groups ($p < 0.05$). **Conclusions:** Some variation in ovarian morphology may exist across geographic regions. However, the degree of variability is unlikely to warrant regional definitions for polycystic ovarian morphology at this time.

Keywords: polycystic ovary syndrome; ovarian morphology; follicle; ultrasound

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1. Introduction

The global burden of polycystic ovary syndrome (PCOS) is significant, affecting 10–13% of reproductive age women worldwide [1]. PCOS is characterized by a combination of three cardinal features: ovulatory dysfunction, hyperandrogenism, and polycystic ovarian morphology (PCOM). In addition to reproductive dysfunction, PCOS is accompanied by a diverse set of metabolic and psychological health complications, all of which merit early identification and intervention [1–3]. Despite the prevalence of PCOS being considered broadly similar across world regions, the prevalence and severity of PCOS

symptomology are known to vary across women from different geographical regions [4]. An improved understanding of the impact of regional influences on the presentation of PCOS is needed to refine diagnostic practices and improve screening in PCOS patients across the globe [5].

Individual studies conducted in specific countries or regions of the globe support geographical differences in both the prevalence and severity of hyperandrogenic symptoms and metabolic dysfunction among women with PCOS. For instance, women from South Asia experience significant hyperandrogenism and metabolic dysfunction [4,6–9]. Conversely, women from East Asia have lower rates of hirsutism and obesity [10,11]. Similarly, obesity rates in PCOS are lower in Mediterranean countries compared to the U.S. and Canada [12–14]. That said, few studies have directly compared symptoms across women with PCOS from different countries or geographical regions. In one notable analysis, Norwegian and Indian women were shown to have the highest prevalence of metabolic syndrome (independent of obesity), whereas Finnish and Norwegian women had the lowest prevalence of clinical and/or biochemical hyperandrogenism compared to the other regional groups [4]. Unlike the prevalence of oligo-amenorrhea which was consistent across the various countries, markers of androgen status and polycystic ovarian morphology on ultrasonography were sufficiently variable to suggest that regional considerations might be warranted to detect variable manifestations of these cardinal features across regions, races and/or ethnicities.

In the case of polycystic ovaries, the degree to which individual sonographic features might contribute to regional differences in the prevalence of PCOM remains limited. An understanding of which sonographic markers best capture ovarian dysmorphology in women with PCOS from across geographical regions would clarify the suitability of one international standard to define polycystic ovaries versus the need for regional definitions. The purpose of this study was to directly contrast ovarian morphology on ultrasonography in women with PCOS residing in two geographical regions, namely, India and the U.S. Further, the degree to which ovarian morphology reflected reproductive symptomology across regions was explored.

2. Materials and Methods

Study Population and Participant Selection: Participants in this study were retrospectively identified from de-identified research and clinical records originating from two distinct geographical regions. The two populations of interest were women with PCOS residing in India and the U.S. for which both (1) a scored ultrasound scan of the ovaries and (2) clinical data to corroborate a PCOS diagnosis were available for review. In India, data were amassed from medical records of patients attending a gynecological practice (Kar Clinic and Hospital, Odisha, India) for evaluation and treatment of reproductive disorders. From India, 178 consecutive patients of record that satisfied the criteria for PCOS (described below) between 2018 to 2021 were considered for inclusion in this study. Patients were excluded if they were (1) <18 or >38 years old ($n = 1$); (2) lacked sufficient clinical and ultrasonographic data to assess endpoints of interest ($n = 21$); (3) evaluated with transabdominal, instead of transvaginal ultrasonography ($n = 33$); (4) deemed to have poor image quality on ovarian ultrasonography ($n = 2$); or (5) not diagnosed with PCOS using international standards ($n = 2$). No women from the India cohort were using hormonal contraceptives or medications known to interfere with glucose or lipid metabolism within two months of study participation. Ultimately, 119 India-based women qualified for inclusion in the analysis. In the U.S., data were garnered from participants with PCOS that engaged in a clinical research study across three research centers in New York State (Ithaca, NY; Rochester, NY; New York, NY). Participants were initially recruited from the general population using flyers from respective studies. Data from 567 participants who

had consecutively completed a research study from 2010 to 2022 were available for inclusion in the analysis. Participants were excluded if they were (1) <18 or >38 years old ($n = 22$); (2) using hormonal contraceptives or medications known to interfere with glucose or lipid metabolism within two months of study participation ($n = 20$); (3) lacking sufficient clinical and ultrasonographic data to assess endpoints of interest ($n = 185$); (4) evaluated with transabdominal, instead of transvaginal ultrasonography ($n = 1$); (5) evaluated outside the follicular phase or had dominant follicles in both ovaries ($n = 7$); (6) deemed to have poor image quality on ultrasonography ($n = 1$); (7) not judged to have PCOS based on international standards ($n = 102$); or (8) duplicate participants in the dataset ($n = 17$). Ultimately, 212 U.S.-based women qualified for analysis, yielding a final study sample of 331 women from both the U.S. and India.

PCOS Definition and Assessment of Clinical and Metabolic Features: Women were categorized as having PCOS according to the 2018/2023 International PCOS Guideline of two or more cardinal features: (1) ovulatory dysfunction, (2) hyperandrogenism, and (3) PCOM, in the absence of other conditions known to interfere with reproductive function [1]. Ovulatory dysfunction was based on self-reported evidence of an average menstrual cycle length > 35 days. Clinical hyperandrogenism was defined by a modified Ferriman-Gallwey score ≥ 6 [5]. Biochemical hyperandrogenism was based on increased serum concentrations of total testosterone (TT) and/or an elevated free androgen index (FAI). Different thresholds for elevated TT were used to account for variations in assay technology across sites (U.S. threshold: ≥ 61.5 ng/dL; India threshold: > 45 ng/dL). FAI was calculated as $(TT \text{ [nmol/L]} / \text{sex hormone-binding globulin [SHBG, nmol/L]} \times 100)$ and a threshold of ≥ 5 was used to define hyperandrogenism across both sites. PCOM was based on ultrasonographic assessments of follicle number per ovary (FNPO), follicle number per single slice (FNPS), and ovarian volume (OV). Thresholds to define PCOM were an FNPO of ≥ 20 , FNPS ≥ 10 , and/or an average OV ≥ 10 cm³, as judged by the average across the left and right ovaries [1]. In instances where only one ovary was visualized or a dominant follicle was present ($n = 47$), measurements made in a single or the contralateral ovary were used. Metabolic status markers included anthropometric measurements (body mass index, waist circumference, waist-to-hip ratio), vitals (blood pressure), and blood glucose levels (fasting and 2 h following ingestion of 75 g glucose). Height, weight, waist-to-hip circumference, and blood pressure were assessed using standard clinical approaches. Venous blood glucose was measured using the glucose-oxidase peroxidase method at the India site and a standard glucometer at the U.S. sites (Accu-Check Aviva, Roche Diabetes Care Inc., Indianapolis, IN, USA). Fasting lipid measures included total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides. Lipids were measured using a Siemens Dimension Xpand Chemistry Analyzer at the U.S. site and using GPO-TRINDER, CHOD-PAP, Direct HDL-C assay, and Direct LDL-C assay (all from Roche Diagnostics, Indianapolis, USA) in India. Features of the metabolic syndrome were defined as (1) central or abdominal obesity (> 88 cm), (2) high triglycerides ≥ 150 mg/dL, (3) low HDL cholesterol (< 50 mg/dL), (4) high blood pressure ($\geq 130/85$ mmHg), and (5) high fasting glucose (≥ 100 mg/dL) (18–20).

Sonographic Assessments of Ovarian Morphology: All stored ultrasound exams had been conducted using a GE Voluson ultrasound machine (E8 Expert, S6, or S10 Series) and 5–9 or 6–12 MHz endovaginal transducer (GE Healthcare, Milwaukee, WI) across both U.S. and India-based participants. Scans coincided either with the follicular phase post-natural menses (U.S.- and India-based participants), in the absence of sonographic evidence of a recent or impending ovulation (U.S.-based participants), or after a progesterone-induced bleed (India-based participants). The 3D images of the left and right ovaries were saved and exported for off-line analysis at a single site (Cornell University, Ithaca, NY). Each stored ultrasound exam file was partitioned from their native 3D file format

(.4dv) into 2D cine-loops (.dcm) representing each of the orthogonal planes. Ultrasound images were prospectively evaluated for the following primary outcomes: (1) follicle number per ovary (FNPO), (2) ovarian volume (OV), (3) ovarian area (OA), (4) stromal area (SA), (5) stromal-to-total area (S/A), and (6) follicle number per single cross-sectional image (FNPS). The total number of 2–9 mm follicles per ovary (FNPO) was counted in a single cine-loop using a generic dicom reader software (Sante DICOM Viewer, Version 10.3.1, Santesoft LTD, Athens, Greece) equipped with a programmable grid overlay function which has been shown to improve the reliability of follicle counts in polycystic ovaries [15]. OV was calculated using the largest cross-sectional measurements in two orthogonal planes and the prolate ellipsoid formula which is considered the conventional method [16]. The cine-loop showing the largest cross-sectional view of the ovary was used to determine ovarian area (OA), stromal area (SA), stromal-to-total area (S/A), and follicle number per single cross-sectional image (FNPS) as previously described [17,18]. Briefly, OA was calculated as the average of the perpendicular measurements at the largest ovarian cross-section across both transverse and sagittal planes. SA was calculated indirectly by subtracting the total traced follicular area from the traced OA in a single frame and S/A was subsequently determined by dividing SA with traced OA. Measurements reported herein represent average values across the left and right ovaries, where appropriate. Ultrasound images were analyzed by 1 of 14 raters whose suitability to combine measures was based on performance in an internal reliability analysis with intraclass correlation coefficients (ICC) of >0.874 across measures.

Statistical analysis: Data analysis was carried out using JMP Pro 17 Statistical Software (SAS Institute, Cary, NC, USA). Normality and homogenous variances of residuals were determined using graphical methods. Continuous variables were summarized using mean and standard deviations. Categorical variables were summarized using counts and percentages. Wilcoxon rank sum tests and Pearson chi-square tests were used to assess differences across the two groups. Spearman's rho analyses determined associations between ovarian morphology markers and reproductive features. Effect sizes were quantified using Cohen's *d*. Significance was determined at $p < 0.05$.

3. Results

3.1. Clinical Characteristics of Participants

Characteristics of all study participants in both groups are reported in Table 1. The age and BMI of the participants were similar in both groups. The majority of U.S.-based participants identified as non-Hispanic or non-Latino (87%) or White (67%). The proportions of participants identifying as Black or Asian were relatively similar at 12% and 16%, respectively. The "Other" category (4%) was comprised of the participants that identified either as mixed, Pacific Islander, or Native American. Data were pooled due to the small number of participants in each category. Data on ethnicity for the India-based group were not available.

Table 1. Characteristics of the study population by geographic region.

Variable	India		U.S.		Effect Size †	p-Value
	N = 119		N = 212			
Demographics	n	Mean (SD)	n	Mean (SD)		
Age (years)	119	26.5 (3.5)	212	26.0 (5.4)	0.10	0.17
BMI (kg/m ²)	119	28.1 (5.1)	205	29.0 (8.7)	0.12	0.44
Ethnicity	n	Count (%)	n	Count (%)		
Hispanic or Latino	-	-	203	17 (8)	-	-
Not Hispanic or Latino	-	-	203	177 (87)	-	-

Race	Other	-	-	203	9 (4)	-	-
	White	-	-	205	138 (67)	-	-
	Black	-	-	205	25 (12)	-	-
	Asian	-	-	205	33 (16)	-	-
	Other	-	-	205	9 (4)	-	-
Reproductive Features		n	Count (%)	n	Count (%)		
Menstrual Irregularity		119	118 (99)	206	168 (82)	-	<0.0001
	Oligomenorrhea (36–89 days)	119	81 (68)	206	107 (52)	-	0.005
	Amenorrhea (≥90 days)	119	37 (31)	206	61 (30)	-	0.779
Hyperandrogenism		119	115 (97)	211	134 (64)	-	<0.0001
	Elevated Total Testosterone ¹	38	28 (74)	205	33 (16)	-	<0.0001
	Free Androgen Index (≥5)	-	-	202	40 (20)	-	-
	Hirsute (≥6)	114	114 (100)	205	100 (49)	-	<0.0001
Polycystic Ovarian Morphology		119	103 (87)	212	176 (83)	-	0.396
	Excess FNPO (≥20)	118	91 (77)	208	176 (85)	-	0.091
	Excess FNPS (≥10)	119	35 (29)	210	86 (41)	-	0.037
	Enlarged Ovarian Volume (≥10 cm ³)	119	44 (37)	211	65 (31)	-	0.252
PCOS Phenotype ²						-	
	Phenotype A	118	99 (84)	173	91 (53)	-	<0.0001
	Phenotype B	118	15 (13)	173	11 (6)	-	0.062
	Phenotype C	118	0 (0)	173	20 (12)	-	0.0001
	Phenotype D	118	4 (3)	173	51 (29)	-	<0.0001

Abbreviations: N, total number in group; n, number of data points available for comparison; BMI, body mass index; FNPO, follicle number per ovary; FNPS, follicle number per single section; PCO, polycystic ovary. † Cohen's *d* (absolute value shown) for continuous variables only. ¹ Elevated testosterone thresholds for India (45.0 ng/dL) and US (61.5 ng/dL). ² Phenotype was determined for those participants in which data were available for all three PCOS cardinal features. Phenotype A = ovulatory dysfunction + hyperandrogenism + polycystic ovaries. Phenotype B = ovulatory dysfunction + hyperandrogenism. Phenotype C = hyperandrogenism + polycystic ovaries. Phenotype D = ovulatory dysfunction + polycystic ovaries. Bold values indicate statistical significance ($p < 0.05$).

Menstrual irregularity was more prominent in India-based women compared to U.S.-based women ($p < 0.001$), with a majority having oligomenorrhea defined by cycles 36–89 days apart (proportion of oligomenorrhea in India vs. U.S., $p = 0.005$). Hyperandrogenism (both the proportion of those with elevated total testosterone and hirsutism) was also more common in the India-based group (all $p < 0.0001$). Lastly, a majority of participants in both groups met the criteria for PCOM with the U.S.-based group demonstrating a higher prevalence of follicle excess compared to the India-based group (FNPS, $p = 0.037$). With regard to clinical phenotype, a vast majority of participants in the India group met the criteria for Phenotype A (ovulatory dysfunction, hyperandrogenism + polycystic ovaries) whereas U.S.-based participants had a more heterogeneous presentation ($p < 0.0001$). A sub-group comparison of reproductive features in women with Phenotype A alone confirmed a higher prevalence of hyperandrogenemia ($p < 0.0001$) and hirsutism ($p < 0.0001$) in the India-based participants, whereas a higher prevalence of follicle excess ($p = 0.004$) was evident in the U.S.-based participants (Table 2).

Table 2. Characteristics of participants with PCOS Phenotype A in India and United States.

Variable	India		U.S.		Effect Size †	p-Value
	N = 99		N = 91			
Demographics	n	Mean (SD)	n	Mean (SD)		
Age (years)	99	26.3 (3.3)	91	25.8 (5.0)	0.12	0.22
BMI (kg/m ²)	99	27.8 (5.0)	89	29.5 (8.0)	0.26	0.46
Reproductive Features	n	Count (%)	n	Count (%)		
Menstrual Irregularity						
Oligomenorrhea (35–89 days)	99	69 (70)	91	53 (58)	-	0.100
Amenorrhea (≥90 days)	99	30 (29)	91	38 (42)	-	0.100
Hyperandrogenism						
Elevated Total Testosterone ¹	32	24 (75)	89	23 (26)	-	<0.0001
Free Androgen Index (≥5)	-	-	87	28 (32)	-	-
Hirsute (≥6)	98	98 (100)	90	64 (71)	-	<0.0001
Polycystic Ovarian Morphology						
Excess FNPO (≥20)	98	81 (83)	89	79 (89)	-	0.235
Excess FNPS (≥10)	99	34 (34)	91	50 (55)	-	0.004
Enlarged Ovarian Volume (>10 cm ³)	96	42 (44)	91	44 (48)	-	0.412

Abbreviations: N, total number in group; n, number of data points available for comparison; BMI, body mass index; FNPO, follicle number per ovary; FNPS, follicle number per single section. † Cohen's *d* (absolute value shown) for continuous variables only. ¹ Elevated testosterone thresholds for India (45.0 ng/dL) and US (61.5 ng/dL). Bold values indicate statistical significance ($p < 0.05$).

Metabolic features, including the number of those meeting the criteria for metabolic syndrome, are presented in Table 3. Participants in the India group had a higher prevalence of increased waist circumference ($p = 0.011$) and elevated waist-to-hip ratio ($p < 0.0001$). Likewise, the prevalence of elevated 2 h glucose ($p < 0.0001$), increased triglycerides ($p < 0.0001$) and LDL levels ($p = 0.004$), as well as lower HDL levels ($p < 0.0001$) were higher in the India group compared to the U.S. group. Subgroup analysis of only women with Phenotype A (Table 4) also showed increased prevalence of abnormalities in waist circumference, waist-to-hip ratio, 2 h glucose, triglycerides, and HDL within the India-based group ($p < 0.0001$).

Table 3. Metabolic features in women with PCOS based in India versus United States.

Variable	India		U.S.		Effect Size †	p-Value
	N = 119		N = 212			
	n	Mean (SD) or count (%)	n	Mean (SD) or count (%)		
Metabolic Measures						
Waist circumference (cm)	115	91.0 (11.1)	180	88.3 (20.8)	0.15	0.001
Prevalence of elevated WC (>89 cm)		60 (52)		67 (37)	-	0.011
Waist-to-hip ratio	115	0.9 (0.04)	187	0.82 (0.1)	0.96	<0.0001
Prevalence of elevated WHR (>0.85)		104 (90)		62 (33)	-	<0.0001
Fasting glucose (mg/dL)	93	95.7 (10.4)	184	93.4 (11.0)	0.21	0.030
Prevalence of elevated 0-h glucose (≥100 mg/dL)		28 (30)		51 (28)	-	0.313
2-h glucose (mg/dL)	77	142.6 (41.6)	176	96.2 (24.7)	1.51	<0.0001
Prevalence of elevated 2-h glucose (>139 mg/dL)		40 (52)		17 (10)	-	<0.0001

Systolic pressure (mmHg)	117	118.8 (9.7)	181	112.7 (15.7)	0.45	0.0002
Prevalence of elevated systolic BP (>130 mmHg)		6 (5)		20 (11)	-	0.077
Diastolic pressure (mmHg)	117	72.2 (10.9)	181	72.1 (11.8)	0.01	0.827
Prevalence of elevated diastolic BP (>85 mmHg)		11 (9)		21 (12)	-	0.549
Total Cholesterol (mg/dL)	58	178.47 (37.0)	184	173.9 (31.5)	0.14	0.279
Prevalence of elevated TC (>199 mg/dL)		15 (26)		31 (17)	-	0.127
Triglycerides (mg/dL)	59	150.2 (71.3)	184	84.1 (53.7)	1.13	<0.0001
Prevalence of elevated TG (>150 mg/dL)		28 (47)		17 (9)	-	<0.0001
HDL (mg/dL)	59	40.4 (7.9)	184	58.0 (16.3)	1.20	<0.0001
Prevalence of low HDL (<50 mg/dL)		50 (85)		62 (34)	-	<0.0001
LDL (mg/dL)	59	110.6 (28.6)	184	96.8 (26.2)	0.51	0.0004
Prevalence of elevated LDL (>99 mg/dL)		38 (64)		79 (43)	-	0.004

Abbreviations: N, total number in group; n, number of data points available for comparison; WC, waist circumference; WHR, waist to hip ratio; BP, blood pressure; TC, total cholesterol; TG, triglycerides; HDL, high density lipoprotein; LDL, low density lipoprotein. † Cohen's *d* (absolute value shown) for continuous variables only. Bold values indicate statistical significance ($p < 0.05$).

Table 4. Metabolic features in women with PCOS Phenotype A based in India versus United States.

Variable	India		US		Effect Size †	<i>p</i> -Value
	N = 99		N = 91			
	n	Mean (SD) or count (%)	n	Mean (SD) or count (%)		
Metabolic Measures						
Waist circumference (cm)	97	90.4 (10.7)	79	89.8 (20.8)	0.04	0.125
Prevalence of elevated WC (>89 cm)		50 (52)		33 (42)	-	0.196
Waist-to-hip ratio	97	0.9 (0.04)	82	0.8 (0.1)	1.36	<0.0001
Prevalence of elevated WHR (>0.85)		88 (91)		30 (37)	-	<0.0001
Fasting glucose (mg/dL)	81	95.5 (9.7)	77	93.4 (11.1)	0.20	0.086
Prevalence of elevated 0-h glucose (≥ 100 mg/dL)		25 (31)		18 (23)	-	0.291
2-h glucose (mg/dL)	67	143.1 (41.6)	74	96.0 (23.6)	1.41	<0.0001
Prevalence of elevated 2-h glucose (≥ 140 mg/dL)		36 (54)		2 (3)	-	<0.0001
Systolic pressure (mmHg)	99	117.9 (9.3)	77	111.6 (14.0)	0.54	0.009
Prevalence of elevated systolic BP (>130 mmHg)		3 (3)		5 (6)	-	0.300
Diastolic pressure (mmHg)	99	71.4 (10.3)	77	71.3 (11.0)	0.01	0.946
Prevalence of elevated diastolic BP (>85 mmHg)		6 (6)		8 (10)	-	0.292
Total cholesterol (mg/dL)	51	177.9 (38.0)	79	177.4 (35.0)	0.01	0.760
Prevalence of elevated TC (≥ 200 mg/dL)		13 (25)		18 (23)	-	0.724
Triglycerides (mg/dL)	51	152.6 (74.0)	79	86.4 (61.8)	0.99	<0.0001
Prevalence of elevated TG (>150 mg/dL)		24 (47)		7 (9)	-	<0.0001
HDL (mg/dL)	51	40.2 (8.1)	79	56.1 (15.9)	1.19	<0.0001

Prevalence of low HDL (<50 mg/dL)		44 (86)		28 (35)	-	<0.0001
LDL (mg/dL)	51	109.6 (30.0)	79	101.2 (28.1)	0.29	0.058
Prevalence of elevated LDL (≥100 mg/dL)		31 (61)		39 (49)	-	0.202

Abbreviations: N, total number in group; n, number of data points available for comparison; WC, waist circumference; WHR, waist to hips ratio; BP, blood pressure; TC, total cholesterol; TG, triglycerides; HDL, high density lipoprotein; LDL, low density lipoprotein. † Cohen's *d* (absolute value shown) for continuous variables only. Bold values indicate statistical significance ($p < 0.05$).

3.2. Ovarian Morphology Markers

Figure 1 depicts a comparison of conventional and nonconventional markers of PCOM across India and U.S.-based participants. FNPS was higher in the U.S. group (8.2 ± 3.0 for India vs. 9.3 ± 4.0 for U.S., $p = 0.046$) while no difference in FNPO was noted between groups. By contrast, OV and OA were higher in the India group compared to the U.S. group (9.8 ± 3.9 for India vs. 8.8 ± 4.0 for U.S., $p = 0.010$ and 6.4 ± 1.8 for India vs. 6.0 ± 1.8 cm² for U.S., $p = 0.022$). Subgroup analysis of those with Phenotype A demonstrated greater follicle excess in the U.S.-based group (FNPO 36.7 ± 13.9 follicles for India vs. 47.1 ± 22.2 follicles for U.S., $p = 0.001$; FNPS 8.9 ± 2.7 follicles for India vs. 10.9 ± 3.9 follicles for U.S.; $p = 0.0002$) (Figure 2).

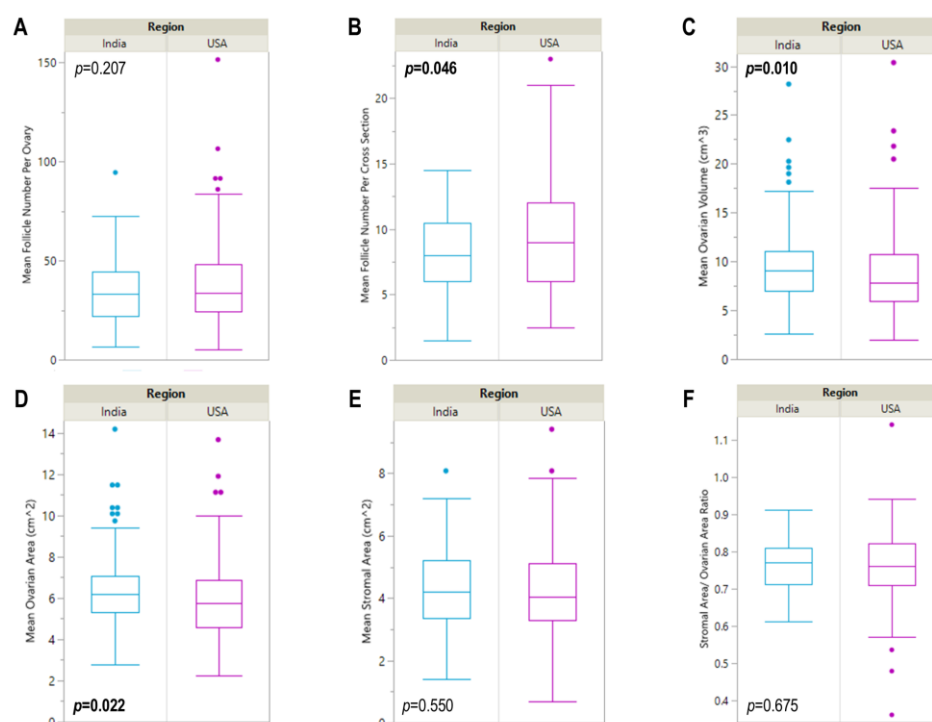


Figure 1. Comparison of conventional and nonconventional markers of polycystic ovarian morphology across India and United States-based women with PCOS. A comparison of conventional [(A) FNPO, (B) FNPS, (C) OV] and nonconventional [(D) OA, (E) SA, (F) S/A] markers in women with PCOS in India and the U.S. Box-and-whisker diagrams of conventional and unconventional markers are presented for women with PCOS in India (N = 119) and the U.S. (N = 212). Boxes represent the 25th and 75th percentile, and the horizontal band within the box represents the median. The 5th–95th percentile range is denoted by the vertical bars. *p*-values from Wilcoxon two sample *t*-tests (unadjusted comparison).

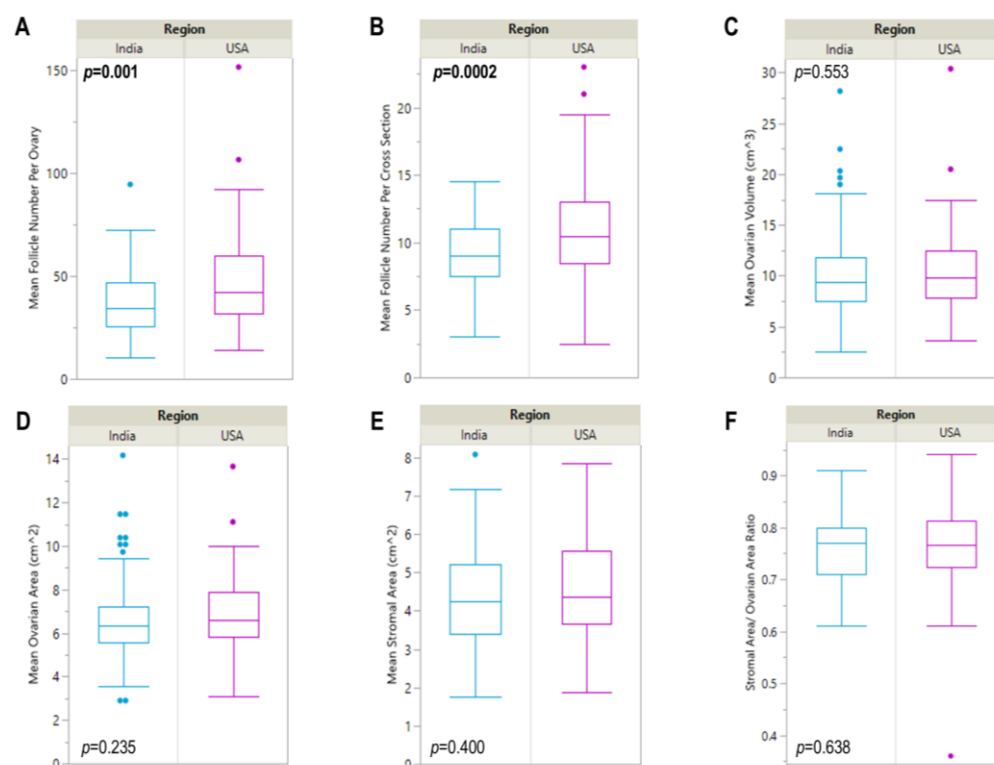


Figure 2. Comparison of conventional and nonconventional markers of polycystic ovarian morphology across India and United States-based women with PCOS Phenotype A. A comparison of conventional [(A) FNPO, (B) FNPS, (C) OV] and nonconventional [(D) OA, (E) SA, (F) S/A] markers in women with PCOS in India and the U.S. Box-and-whisker diagrams of conventional and unconventional markers are presented for women with PCOS in India (N = 99) and the U.S. (N = 91). Boxes represent the 25th and 75th percentile, and the horizontal band within the box represents the median. The 5th–95th percentile range is denoted by the vertical bars. *p*-values from Wilcoxon two sample *t*-tests.

3.3. Associations of Ovarian Morphology with Reproductive Features

The relationships between reproductive markers and ovarian morphology are depicted in Table 5. FNPO, FNPS, OV, and OA were positively associated with menstrual cycle length, hirsutism score, and/or total testosterone concentrations within the U.S.-based cohort ($p < 0.05$). S/A was also positively associated with menstrual cycle length ($p = 0.020$) in the U.S.-based group. In the India-based group, positive associations were observed between OV and OA with hirsutism scores ($p < 0.05$) whereas a negative association was found between S/A and total testosterone. On subgroup analysis involving only those meeting the criteria for Phenotype A (Table 6), FNPO ($p = 0.003$), OV ($p = 0.007$) and OA ($p = 0.011$) remained positively associated with total testosterone in U.S.-based participants. Likewise, associations emerged between FNPO ($p = 0.018$), FNPS ($p = 0.018$), OV ($p = 0.028$), OA ($p = 0.027$) and SA ($p = 0.021$) with total testosterone concentrations and/or menstrual cycle length in the India-based group.

Table 5. Associations between ovarian morphology and reproductive markers by geographic location.

Reproductive Markers	FNPO		FNPS		OV		OA		SA		S/A	
	India	U.S.	India	U.S.	India	U.S.	India	U.S.	India	U.S.	India	U.S.
Menstrual cycle length (d)	−0.01	+0.23	+0.01	+0.15	+0.12	+0.21	+0.13	+0.25	+0.16	+0.12	−0.11	+0.16
Ferriman-Gall- wey hirsutism score	+0.10	+0.23	+0.01	+0.13	+0.19	+0.27	+0.19	+0.23	+0.18	+0.09	+0.13	+0.01
Total testosterone (ng/dL)	+0.24	+0.36	+0.32	+0.28	+0.04	+0.34	+0.06	+0.33	−0.11	+0.14	−0.33	−0.09

Presented as Spearman correlation coefficients. Bold values reflect a significant correlation: $p < 0.05$. Abbreviations: FNPO, follicle number per ovary; FNPS, follicle number per single section; OV, ovarian volume; SA, stromal area; S/A, stromal to ovarian area ratio.

Table 6. Associations between ovarian morphology and reproductive markers in women with PCOS Phenotype A by geographic location.

Reproductive Markers	FNPO		FNPS		OV		OA		SA		S/A	
	India	U.S.	India	U.S.	India	U.S.	India	U.S.	India	U.S.	India	U.S.
Menstrual cycle length (d)	+0.05	+0.10	+0.05	−0.06	+0.22	+0.08	+0.23	+0.08	+0.22	−0.04	−0.14	+0.16
Ferriman-Gall- wey hirsutism score	−0.02	+0.11	−0.11	+0.09	+0.12	+0.15	+0.11	+0.13	+0.15	−0.00	+0.15	−0.09
Total testosterone (ng/dL)	+0.42	+0.31	+0.41	+0.16	+0.16	+0.28	+0.17	+0.27	+0.05	+0.20	−0.31	+0.04

Presented as Spearman correlation coefficients. Bold values reflect a significant correlation: $p < 0.05$. Abbreviations: FNPO, follicle number per ovary; FNPS, follicle number per single section; OV, ovarian volume; SA, stromal area; S/A, stromal to ovarian area ratio.

4. Discussion

This study aimed to directly contrast the ovarian morphology of women with PCOS residing in two distinct geographical regions. We had hypothesized differences in ovarian morphology between populations due to variations in follicle counts and ovarian size reported in prior research [19–21]. In addition, we posited that the strength of relationships between ovarian morphology and PCOS symptomology might differ owing to a more severe clinical profile in Indian women with PCOS compared to that of their U.S.-based counterpart [4]. Contrary to our expectations, our findings unveiled largely similarities in ovarian ultrasound features between the India- and U.S.-based groups. While we noted minor discrepancies in follicle populations and ovarian size across groups, these differences would be expected to have marginal clinical significance for current diagnostic practices.

Polycystic ovaries on ultrasonography are an accepted cardinal feature of PCOS [1,5]. The International Evidence-based Guideline for PCOS preferentially defines PCOM by follicle excess as evidenced by an FNPO ≥ 20 , with FNPS ≥ 10 and OV ≥ 10 cm³ as alternatives due to their inferior diagnostic accuracy [1]. The utility of these singular criteria to define PCOM across regions is uncertain. In the case of India-based populations, one study showed that an FNPO ≥ 12 and an OV ≥ 6.15 cm³ had the best diagnostic accuracy

for PCOS in women from this region [19]. These thresholds are substantially lower than those reported in U.S.-based studies [22,23] and do not agree with current international standards. In this study, we showed that follicle counts were consistently higher in US-based women with PCOS, aligning with recent reports of higher follicle counts in Caucasian women compared to Asian women [24]. Similarly, we noted that ovarian size was larger in the India-based group, albeit this difference became less pronounced when focusing solely on women exhibiting more frank manifestations of PCOS (Phenotype A). Participants from both regions had similar age and body mass index, and thus, these factors are unlikely to have contributed to the observed morphological differences between groups. Morphological differences may have been driven by ethnic variations in follicle reserve dynamics [25] and/or global variability in menopausal timelines [26,27]. We did not have access to stored biological specimens across both groups and were unable to directly measure biochemical markers of ovarian function (i.e., total testosterone and anti-Müllerian hormone) that could have provided functional evidence to corroborate the relevance of this morphological variation. That said, we acknowledge that the observed differences between groups for markers of follicle excess (FNPO: 4.5 follicles; FNPS: 1.1 follicles) and ovarian enlargement (1 cm^3) were small and likely clinically insignificant, particularly for diagnosis and screening.

More participants in the India-based group possessed all three cardinal features of PCOS, consistent with previous reports [4,7,28,29]. In contrast, the U.S.-based participants were more heterogeneous, consisting of a majority of Phenotype A followed by Phenotype D (ovulatory dysfunction, polycystic ovaries and no hyperandrogenism), consistent with representation on both sides of the PCOS severity spectrum. These differences are likely due to the study design. The India-based group was garnered from patients presenting to a reproductive health clinic seeking evaluation and/or care for PCOS and/or infertility. By contrast, data from the U.S.-based group captured individuals within the community who had self-presented for participation in a research study on reproductive health and/or PCOS pathophysiology. Therefore, it is likely that a clinic-based population in India would have exhibited a more severe clinical presentation compared to those volunteering from the general population wherein non-androgenic and ovulatory forms of PCOS were more common. Given the design bias, we performed a subgroup analysis comparing only women with Phenotype A. Clinical hyperandrogenism remained more prevalent in those from India, consistent with studies showing higher androgen levels in South Asian populations compared to other geographic regions [4,30–32], possibly influenced by genetic factors specific to South Asian populations [33–35]. Likewise, the degree of metabolic disturbance was consistently higher in the India-based group, aligning with previous reports that Indian women with PCOS demonstrate a more hyperandrogenic variant of PCOS with overt metabolic dysfunction [2,3,36,37].

In this study, we analyzed stored ultrasound images for both geographic groups using standardized approaches for conventional and non-conventional markers of PCOM [15]. While nonconventional markers, such as stromal measures, lack evidence for PCOS diagnosis globally [22], they may reflect symptom severity [18,38,39]. To our knowledge, our data represent the first report of these measures in an India-based population and support similarities in stromal characteristics across geographic groups. Accordingly, we noted that measures of follicle excess, ovarian enlargement and stromal characteristics had largely positive associations with menstrual cycle irregularity, hirsutism score, and/or total serum testosterone. While this analysis was largely exploratory, the findings support ovarian morphology as a biomarker of reproductive dysfunction in PCOS across geographic regions. Likewise, the rarity of the non-PCOM Phenotype B in either group further underscores the significance of PCOM to the clinical presentation of PCOS.

This study is novel in directly and comprehensively contrasting ovarian sonographic markers in women with PCOS across geographical locations. In addition, we examined the potential for variations in the relationships between ovarian morphology and reproductive disturbance across regions. We had access to raw images for both populations and used standardized image analysis approaches to ensure rigor and reproducibility. However, our study has limitations. As mentioned, participants were garnered from different settings and variations in symptomology between groups may relate to a higher likelihood of severe clinical manifestations presenting to a clinical practice rather than a research setting. Unlike our primary outcomes of ovarian morphology where standardized measurements were prospectively made, we were limited in that some clinical and biochemical endpoints were evaluated with different rubrics and assays across sites. The inability to pool measures across groups restricted the analyses to subgroup and qualitative comparisons. Given the retrospective nature of the study, data for the clinical and metabolic secondary endpoints of interest were not consistently available, thereby impacting the sample sizes for certain analyses. As such, we recognize that the associations identified within this study should be considered exploratory. Although all ultrasound scans were performed in the follicular phase, scans were conducted either post-natural menses or after a progesterone-induced bleed. We are unaware of any recent data documenting a differential impact of exogenous versus endogenous progesterone on ovarian morphology. However, we acknowledge that assessments following a progesterone-induced bleed were more likely in the India-based group.

5. Conclusions

In summary, geographic differences are known to exist in the clinical presentation of PCOS. However, variations in ovarian morphology may not be sufficient to warrant regional definitions for polycystic ovaries on ultrasonography at this time. Ovarian dysmorphology reflected the severity of reproductive symptomology in both regions consistent with the ovary being a helpful biomarker of PCOS. Ultimately, prospective studies involving women with and without PCOS across geographic regions are needed to directly address the utility of regional-specific criteria for PCOM.

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Abbreviations

The following abbreviations are used in this manuscript:

PCOS	Polycystic Ovary Syndrome
PCOM	Polycystic Ovarian Morphology
FNPO	Follicle Number Per Ovary
FNPS	Follicle Number Per Cross-Section
OV	Ovarian Volume
OA	Ovarian Area
SA	Stromal Area
S/A	Stromal-to-Ovarian Area Ratio
TT	Total Testosterone
FAI	Free Androgen Index
SHBG	Sex Hormone-Binding Globulin
BMI	Body Mass Index
HDL	High-Density Lipoprotein
LDL	Low-Density Lipoprotein
ICC	Intraclass Correlation Coefficient
3D	Three-Dimensional
2D	Two-Dimensional

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