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Original Research Article

Effect of Right- Left Differences in Ovarian Morphology on Ultrasonographic Diagnosis of Polycystic Ovarian Syndrome

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Conflict of interest: Nil

Abstract

Aim: The aim of the present study was to assess right – left differences in ultrasonographic markers of ovarian morphology and determine the impact on the diagnosis of polycystic ovarian morphology.

Methods: The present study was conducted in the Department of Reproductive Medicine, Indira Gandhi Institute of Medical Sciences, Sheikhpura Patna for one year. Women of reproductive age (21 – 38 y) were recruited from the general population. Women with PCOS (n = 50) were identified by the combined presence of oligomenorrhea and hyperandrogenism. Women with regular cycles and no evidence of hyperandrogenism were included as controls (n = 50).

Results: Compared to controls, women with PCOS were of similar ages, but exhibited higher body mass indices, longer menstrual cycles, and higher modified hirsutism scores (All: $p < 0.01$). The proportion of women with hyperandrogenemia was greater in the PCOS group (40%) versus control group (0%) ($p < 0.01$). Mean FNPO, FNPS, and OV were higher in women with PCOS (All: $p < 0.01$). Significant correlations were detected between ovaries – both across markers and within groups. Of the three markers, FNPO showed the strongest correlation between ovaries (PCOS: $\rho = 0.74$, $p < 0.01$; Controls: $\rho = 0.58$, $p < 0.01$). FNPS and OV had moderate correlations between ovaries in women with PCOS but showed relatively weak relationships in controls.

Conclusion: In conclusion, significant intra-individual differences were observed in ultrasonographic markers of ovarian morphology among controls and women with PCOS. FNPO showed the smallest differences between ovaries. Our data may be interpreted to mean that PCOM can be reliably diagnosed in a single ovary using FNPO, but not FNPS or OV.

Keywords: polycystic ovary syndrome; ultrasonography; diagnosis.

Introduction

Polycystic ovary syndrome (PCOS), also known as the disease of Leventhal and Stein, is an endocrine and metabolic disorder that primarily effects women of reproductive age. PCOS is characterised by a wide variety of clinical symptoms related to hyperandrogenism and insulin resistance (IR). IR and compensatory hyperinsulinemia play a key role in the pathogenesis of PCOS, which may be exacerbated by concomitant obesity, which affects approximately 50% of women with PCOS (occurring in approximately 80% of obese women with PCOS and 30–40% of slender women with PCOS). Numerous women with PCOS have consistently demonstrated IR, but this is not a diagnostic criterion. [1-3] The syndrome is frequently associated with severe conditions like diabetes, cardiovascular disease, and metabolic syndrome (MetS). [4-6]

On ultrasonography, polycystic ovarian morphology (PCOM) is a well-established marker of reproductive disturbance, most commonly used to diagnose polycystic ovary syndrome (PCOS). PCOM is currently defined as an upper limit for ovarian volume (OV) and the number of follicles per ovary (FNPO) in healthy populations. [7,8]

Consequently, the diagnostic value of ovarian imaging is restricted to distinguishing between "normal" and "abnormal" morphology, without regard to the specificity, aetiology, or prospective severity of the an ovulatory condition.

Associations of follicle counts and ovarian size, with increasing androgens, gonadotropins, and intervals between menses, provide a physiological basis for the idea that features of ovarian morphology may be sufficiently different to distinguish between hyper androgenic and normo-androgenic an ovulatory conditions. [9,10] Given the numerous challenges in establishing reliable indicators of clinical hyperandrogenism and accessing high-quality, reliable androgen assays to assess biochemical hyperandrogenism in women [11,12], non-invasive morphological markers of an ovulatory conditions may help predict comorbidity risk, refine treatment recommendations, and monitor phenotypic changes over time.

Over the years, the diagnostic criteria for PCOS have been changing. The initial diagnostic criteria were established at the National Institutes of Health consensus conference. These criteria were broadened several years after describing four main PCOS phenotypes. [13] Two main features are required to diagnose PCOS: the presence of hyperandrogenism and chronic oligo-anovulation if no other disorders cause these conditions. [14] Consequently, specific ultrasound features for ovarian morphology were added to the two existing criteria, thus expanding the definition of PCOS. An ovary was considered polycystic if the ovarian volume (OV) was greater than 10 cm3 and/or the number of follicles (FNPO) measuring 2–9mm was 12 per ovary or greater. [15]

The aim of the present study was to assess right – left differences in ultrasonographic markers of ovarian morphology and determine the impact on the diagnosis of polycystic ovarian morphology.

Materials and Methods

The present study was conducted in the Department of Reproductive Medicine, Indira Gandhi Institute of Medical Sciences, Sheikhpura Patna for one year. Women of reproductive age (21 – 38 y) were recruited from the patients who came to Reproductive medicine department for subfertility issues. Those with thyroid abnormalities, hyperprolactinemia, history of oophorectomy, or limited visualization of the ovaries on ultrasound were excluded from the present study. Women with PCOS (n = 50) were identified by the combined presence of oligomenorrhea and hyperandrogenism. Hyperandrogenism was defined as a modified hirsutism score ≥ 7 or serum total testosterone concentration ≥ 61.5 or ≥ 127.1 ng/dl (depending on the protocol and hormone assay used). Women with regular cycles and no evidence of hyperandrogenism were included as controls (n = 50).

Ultrasonographic Assessments

Participants were evaluated with high-resolution transvaginal ultrasonography using Mindray DC-80 USG machine with 5 – 9 or 6 – 12 MHz multi frequency transducers. Ultrasound examinations were conducted in the early follicular phase of the menstrual cycle (on day 2 or day 3). Whole ovaries were scanned from their inner to outer margins in the longitudinal plane. parameters included FNPO, FNPS, and OV. FNPO was assessed throughout each ovary by imposing a programmable grid onto the viewing window and making focused follicle counts in each grid section. FNPS and OV were obtained in the largest cross-section of each ovary. OV was calculated using the simplified formula for a prolate ellipsoid. FNPO, FNPS, and OV were tabulated for each ovary. Mean values between ovaries were calculated and rounded to the nearest whole numbers. Sided and mean values were ascribed a morphologic diagnosis based on recent international consensus guidelines or proposed thresholds for PCOM. PCOM was defined by an FNPO ≥ 20, FNPO ≥ 25, FNPS ≥ 9, or OV ≥ 10 ml. [7,8,16]

Statistical Analysis

Statistical analysis were performed with JMP Pro 12 (SAS Institute Inc., Cary, NC). The threshold for statistical significance was set at $p < 0.05$. All endpoints were non-normally distributed. Demographic and diagnostic characteristics were compared between groups using Mann-Whitney U or Fisher's Exact tests. Right – left differences in FNPO, FNPS, and OV was assessed using Wilcoxon Signed Rank tests. Correlations were considered with Spearman's rank coefficients. Differences in the probability of uni- versus bilateral PCOM were determined using McNemar's Test. Sensitivity analyses were also undertaken in the entire cohort to confirm that findings were not impacted by methodologic or physiologic factors. FNPO, FNPS, and OV were compared across sites, ultrasound machines, and maximum transducer frequencies (i.e., 9 vs. 12 MHz) using the Steel-Dwass test. Post hoc calculations revealed that the present study had 99.9% power to detect the observed intra-individual differences in FNPO, FNPS, and OV ($\alpha = 0.05$).

Results

Table 1: Demographic and diagnostic characteristics of the study participants

	PCOS (n = 50)	Control (n = 50)
Age (y)	27 (22–30)	27 (23–32)
Body mass index (kg/m2)	28.2 (23.7–38.2)	26.4 (21.5–27.2)
Menstrual cycle length (d)	68 (47–146)	29 (28–32)
Modified hirsutism score	11 (8–14)	2 (1–5)
Proportion with biochemical hyperandrogenism	20 / 100 (40%)	0 / 50 (0%)
Mean FNPO	42 (34–60)	22 (16–32)
Mean FNPS	12 (8–13)	8 (5–9)
Mean OV (ml)	10 (9–15)	8 (6–9)

Compared to controls, women with PCOS were of similar ages, but exhibited higher body mass indices, longer menstrual cycles, and higher modified hirsutism scores (All: $p < 0.01$). The proportion of women with hyperandrogenemia was greater in the PCOS group (40%) versus control group (0%) ($p < 0.01$). Mean FNPO, FNPS, and OV were higher in women with PCOS (All: $p < 0.01$).

Table 2: Right – left differences in ultrasonographic features in controls and women with PCOS

	Right Ovary	Left Ovary	MD ± SE (95% CI)	P Value
PCOS (n = 50)				
FNPO	44 (33–69)	45 (32–54)	5 ± 5 (1, 6)	0.74
FNPS	12 (8–13)	11 (7–12)	2 ± 0 (0, 2)	0.52
OV	15 (9–17)	10 (7–14)	3 ± 3 (2, 4)	0.55
Control (n = 50)				
FNPO	25 (16–32)	27 (15–33)	0 ± 1 (−2, 2)	0.58
FNPS	5 (4–10)	7 (5–9)	0 ± 0 (−1, 1)	0.44
OV	9 (6–11)	6 (4–9)	2 ± 1 (1, 3)	0.32

Significant correlations were detected between ovaries – both across markers and within groups. Of the three markers, FNPO showed the strongest correlation between ovaries (PCOS: $\rho = 0.74$, $p < 0.01$; Controls: $\rho = 0.58$, $p < 0.01$). FNPS and OV had moderate correlations between ovaries in women with PCOS but showed relatively weak relationships in controls.

Discussion

PCOM is an ultrasonographic finding that may be present in women with ovulatory disorder and oligomenorrhea caused by hypothalamic, pituitary, and ovarian dysfunction. [17-19] PCOM can be found in multiple endocrine conditions in which follicular development is altered, resulting in antral follicle arrest. [20] PCOS phenotypes exist, including normo-androgenic and hyperandrogenic phenotypes. [7] The normo-androgenic phenotype is characterized by ovarian dysmorphology, menstrual irregularity, and reproductive and metabolic disturbance, albeit to a lesser degree than the hyperandrogenic phenotype. [21-23] Consequently, it has been hypothesised that the normo-androgenic phenotype may represent an intermediate condition that may progress to the hyperandrogenic phenotype under certain circumstances (e.g., weight gain). [24-26] Therefore, clinical differentiation between normo-androgenic and hyperandrogenic an ovulatory conditions may be useful for guiding treatment strategies aimed at both treatment and prevention to avoid progression towards hyperandrogenism.

Compared to controls, women with PCOS were of similar ages, but exhibited higher body mass indices, longer menstrual cycles, and higher modified hirsutism scores (All: $p < 0.01$). The proportion of women with hyperandrogenemia was greater in the PCOS group (40%) versus control group (0%) ($p < 0.01$). Mean FNPO, FNPS, and OV were higher in women with PCOS (All: $p < 0.01$). Significant correlations were detected between ovaries – both across markers and within groups. Of the three markers, FNPO showed the strongest correlation between ovaries (PCOS: $\rho = 0.74$, $p < 0.01$; Controls: $\rho = 0.58$, $p < 0.01$). FNPS and OV had moderate correlations between ovaries in women with PCOS but showed relatively weak relationships in controls. Previous studies have also reported weaker correlations between ovaries for OV versus FNPO[27] and suggested that size differences make PCOM more likely on the right side. [28] Atiomo and colleagues proposed that the right ovary could offer differential diagnostic potential for PCOS, as a result. [29]

There are challenges associated with the evaluation of FNPO, such as distinguishing an anechoic structure as one or two clustered follicles and re-counting previously identified follicles. In polycystic ovaries, it is especially difficult to obtain accurate counts of follicular density. [30,31] The clinical significance of intra-individual differences in follicle number must be considered. Deb et al. [32,33] have reported intra-observer and inter-method variability in counts as large as 11 follicles, indicating that mean differences 11 may be within

the margin of error. Scientists have observed that the widely accepted Rotterdam criteria can misdiagnose PCOS in women of middle age. Therefore, PCOS may be underdiagnosed in elderly women if the currently used OV (>10 cm3) and FNPO (>20) cut-offs are implemented. [34] Kim et al. lowered the cut-off values of OV and FNPO for women older than 30 years, as ovarian volume and follicle count begin to decrease at this age. [35]

Conclusion

To conclude, notable variations within individuals were noted in ultrasonographic indicators of ovarian morphology among both control subjects and women diagnosed with polycystic ovary syndrome (PCOS). The FNPO exhibited the most minimal variations among the ovaries. The data suggests that the diagnosis of PCOM in a single ovary can be reliably achieved through the use of FNPO, while FNPS or OV may not yield consistent results. It is advisable for practitioners and researchers to recognise the possibility of asymmetrical ultrasonographic indicators of ovarian morphology and employ the follicle number per ovary (FNPO) criterion to establish polycystic ovary morphology (PCOM) in cases where only one ovary is observable.

References

1. Laganà AS, Rossetti P, Buscema M, La Vignera S, Condorelli RA, Gullo G, Granese R, Triolo O. Metabolism and ovarian function in PCOS women: a therapeutic approach with inositols. International Journal of Endocrinology. 2016 Oct;2016.
2. Laganà AS, Garzon S, Casarin J, Franchi M, Ghezzi F. Inositol in polycystic ovary syndrome: restoring fertility through a pathophysiology-based approach. Trends in endocrinology & metabolism. 2018 Nov 1;29(11):768-80.
3. Paul C, Lagana AS, Maniglio P, Triolo O, Brady DM. Inositol's and other nutraceuticals' synergistic actions counteract insulin resistance in polycystic ovarian syndrome and metabolic syndrome: state-of-the-art and future perspectives. Gynecological Endocrinology. 2016 Jun 2;32(6):431-8.
4. Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. The Journal of Clinical Endocrinology & Metabolism. 2005 Apr 1;90(4):1929-35.
5. Dokras A, Bochner M, Hollinrake E, Markham S, VanVoorhis B, Jagasia DH. Screening women with polycystic ovary syndrome for metabolic syndrome. Obstetrics & Gynecology. 2005 Jul 1;106(1):131-7.
6. Ollila MM, West S, Keinänen-Kiukaanniemi S, Jokelainen J, Auvinen J, Puukka K, Ruokonen A, Järvelin MR, Tapanainen JS, Franks S, Piltonen TT. Overweight and obese but not normal weight women with PCOS are at increased risk of Type 2 diabetes mellitus—a prospective, population-based cohort study. Human Reproduction. 2017 Feb 1;32(2):423-31.
7. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, Piltonen T, Norman RJ. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Human reproduction. 2018 Sep 1;33(9):1602-18.
8. Dewailly D, Lujan ME, Carmina E, Cedars MI, Laven J, Norman RJ, Escobar-Morreale HF. Definition and significance of polycystic ovarian morphology: a task force report from the Androgen Excess and Polycystic Ovary Syndrome Society. Human reproduction update. 2014 May 1;20(3):334-52.
9. Chen MJ, Yang WS, Chen CL, Wu MY, Yang YS, Ho HN. The relationship between anti-Müllerian hormone, androgen and insulin resistance on the number of antral follicles in women with polycystic ovary syndrome. Human Reproduction. 2008 Apr 1;23(4):952-7.
10. Jonard S, Robert Y, Cortet-Rudelli C, Pigny P, Decanter C, Dewailly D. Ultrasound examination of polycystic ovaries: is it worth counting the follicles? Human reproduction. 2003 Mar 1;18(3):598-603.
11. Rosner W, Auchus RJ, Azziz R, Sluss PM, Raff H. Utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement. The Journal of Clinical Endocrinology & Metabolism. 2007 Feb 1;92(2):405-13.
12. Rosner W, Vesper H, Endocrine Society the endorsing organizations. Toward excellence in testosterone testing: a consensus statement. The Journal of Clinical Endocrinology & Metabolism. 2010 Oct 1;95(10):4542-8.
13. Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. Fertility and sterility. 2016 Jul 1;106(1):6-15.
14. Roe AH, Dokras A. The diagnosis of polycystic ovary syndrome in adolescents. Reviews in obstetrics and gynecology. 2011;4(2):45.
15. Jonard S, Robert Y, Ardaens Y, Dewailly D. Ovarian histology, morphology, and ultrasonography in the polycystic ovary syndrome. Androgen Excess Disorders in

Women: Polycystic Ovary Syndrome and Other Disorders. 2007:183-93.
16. Balen AH, Laven JS, Tan SL, Dewailly D. Ultrasound assessment of the polycystic ovary: international consensus definitions. Human reproduction update. 2003 Nov 1;9(6):505-14.
17. Laven JSE, Imani B, Eijkemans MJC, Fauser BCJM. New approach to polycystic ovary syndrome and other forms of anovulatory infertility. Obstet Gynecol Surv. 2002;57(11) :755–67.
18. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004;81(1):19–25.
19. Mikhael S, Punjala-Patel A, Gavrilova-Jordan L. Hypothalamic-Pituitary-Ovarian Axis Disorders Impacting Female Fertility. Biomedicines. 2019;7(1):5.
20. Pigny P, Merlen E, Robert Y, Cortet-Rudelli C, Decanter C, Jonard S, Dewailly D. Elevated serum level of anti-mullerian hormone in patients with polycystic ovary syndrome: relationship to the ovarian follicle excess and to the follicular arrest. The Journal of Clinical Endocrinology & Metabolism. 2003 Dec 1;88(12):5957-62.
21. Welt CK, Gudmundsson JA, Arason G, Adams J, Palsdottir H, Gudlaugsdottir G, Ingadottir G, Crowley WF. Characterizing discrete subsets of polycystic ovary syndrome as defined by the Rotterdam criteria: the impact of weight on phenotype and metabolic features. The Journal of Clinical Endocrinology & Metabolism. 2006 Dec 1;91(12):4842-8.
22. Barber TM, Wass JA, McCarthy MI, Franks S. Metabolic characteristics of women with polycystic ovaries and oligo-amenorrhoea but normal androgen levels: implications for the management of polycystic ovary syndrome. Clinical endocrinology. 2007 Apr;66(4):513-7.
23. Carmina E, Chu MC, Longo RA, Rini GB, Lobo RA. Phenotypic variation in hyperandrogenic women influences the findings of abnormal metabolic and cardiovascular risk parameters. The Journal of Clinical Endocrinology & Metabolism. 2005 May 1;90(5):2545-9.
24. Daan NM, Louwers YV, Koster MP, Eijkemans MJ, de Rijke YB, Lentjes EW, Fauser BC, Laven JS. Cardiovascular and metabolic profiles amongst different polycystic ovary syndrome phenotypes: who is really at risk? Fertility and sterility. 2014 Nov 1;102(5):1444-51.
25. Huddleston HG, Quinn MM, Kao CN, Lenhart N, Rosen MP, Cedars MI. Women with polycystic ovary syndrome demonstrate worsening markers of cardiovascular risk over the short-term despite declining hyperandrogenaemia: Results of a longitudinal study with community controls. Clinical Endocrinology. 2017 Dec;87(6):775-82.
26. Broekmans FJ, Knauff EA, Valkenburg O, Laven JS, Eijkemans MJ, Fauser BC. PCOS according to the Rotterdam consensus criteria: change in prevalence among WHO-II anovulation and association with metabolic factors. BJOG: An International Journal of Obstetrics & Gynaecology. 2006 Oct;113(10): 1210-7.
27. Deb S, Kannamannadiar J, Campbell BK, Clewes JS, Raine-Fenning NJ. The interovarian variation in three-dimensional ultrasound markers of ovarian reserve in women undergoing baseline investigation for subfertility. Fertility and sterility. 2011 Feb 1;95(2):667-72.
28. Korsholm AS, Hvidman HW, Bentzen JG, Nyboe Andersen A, Birch Petersen K. Left–right differences in ovarian volume and antral follicle count in 1423 women of reproductive age. Gynecological Endocrinology. 2017 Apr 3;33(4):320-3.
29. Atiomo WU, Pearson S, Shaw S, Prentice A, Dubbins P. Ultrasound criteria in the diagnosis of polycystic ovary syndrome (PCOS). Ultrasound in medicine & biology. 2000 Jul 1;26(6):977-80.
30. Lujan ME, Chizen DR, Peppin AK, Kriegler S, Leswick DA, Bloski TG, Pierson RA. Improving inter-observer variability in the evaluation of ultrasonographic features of polycystic ovaries. Reproductive Biology and Endocrinology. 2008 Dec; 6:1-1.
31. Lujan ME, Chizen DR, Peppin AK, Dhir A, Pierson RA. Assessment of ultrasonographic features of polycystic ovaries is associated with modest levels of inter-observer agreement. Journal of Ovarian Research. 2009 Dec; 2:1-9.
32. Deb S, Campbell BK, Clewes JS, Raine-Fenning NJ. Quantitative analysis of antral follicle number and size: a comparison of two-dimensional and automated three-dimensional ultrasound techniques. Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2010 Mar;35(3):354-60.
33. Deb S, Jayaprakasan K, Campbell BK, Clewes JS, Johnson IR, Raine-Fenning NJ. Intraobserver and interobserver reliability of automated antral follicle counts made using three-dimensional ultrasound and SonoAVC. Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2009 Apr;33(4):477-83.

34. Carmina E, Campagna AM, Fruzzetti F, Lobo RA. AMH measurement versus ovarian ultrasound in the diagnosis of polycystic ovary syndrome in different phenotypes. Endocrine Practice. 2016 Mar 1;22(3):287-93.

35. Kim JJ, Hwang KR, Chae SJ, Yoon SH, Choi YM. Impact of the newly recommended antral follicle count cutoff for polycystic ovary in adult women with polycystic ovary syndrome. Human Reproduction. 2020 Mar 27;35(3):652-9.