

Ovarian and Uterine Artery Doppler Indices in Polycystic Ovary Syndrome

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I. Introduction

Polycystic ovary syndrome (PCOS) was first reported in the modern medical literature by Stein and Leventhal who, in 1935, described seven women suffering from amenorrhea, hirsutism, and enlarged ovaries with multiple cysts.¹ PCOS is a heterogeneous pathological condition characterized by reproductive disorders and frequently associated with hyperandrogenism, obesity, hyperinsulinemia and insulin resistance.²⁻⁴ PCOS is the most common female endocrinopathy, and its frequency is about 6-8% in the reproductive period.²

The clinical presentation of PCOS varies widely. Women with PCOS often seek care for menstrual disturbances, clinical manifestations of hyperandrogenism, and infertility. Menstrual disturbances commonly observed in PCOS include oligomenorrhea, amenorrhea, and prolonged erratic menstrual bleeding.⁵ However, 30% of women with PCOS will have normal menses.⁶ Approximately 85%–90% of women with oligomenorrhea have PCOS while 30%–40% of women with amenorrhea will have PCOS.⁷ More than 80% of women presenting with symptoms of androgen excess have PCOS.⁸ Hirsutism is a common clinical presentation of hyperandrogenism occurring in up to 70% of women with PCOS.⁹ Hirsutism is evaluated using a modified Ferriman–Gallwey scoring system.¹⁰

On imaging, the current recommended diagnostic criteria at the time of review are based on a 2018 international consensus guideline¹¹ according to which, in patients >8 years post-menarche, and using a high-frequency endovaginal probe: ≥ 20 follicles per ovary, and/or ovarian volume ≥ 10 ml, ensuring no corpora lutea, cysts or dominant follicles are present.

This supersedes the initial Rotterdam criteria of 12 or more follicles and interim recommendations of 24 or 25 follicles per ovary. The presence of a single multi-follicular ovary is sufficient to provide the sonographic criterion for PCOS.¹²

Cyclic hormonal variations and subsequent ovarian and endometrial neoangiogenesis lead to significant changes in vascular patterns that can now be noninvasively evaluated with Doppler sonography. Trans-vaginal duplex and color Doppler sonography (TVU) is thus the increasingly preferred noninvasive method to assess pelvic blood flow changes and contribute to a better understanding of the underlying pathophysiology as well as better therapeutic management in a variety of disorders.¹³ Several authors¹⁴⁻¹⁶ using TVU have reported increased impedance to blood flow in the uterine arteries of patients with PCOS and have advocated the systematic use of TVU for the diagnosis of this disease, whereas others¹⁷ have found no significant change in uterine artery blood flow in these patients.

These discrepancies may be attributed to the different subgroups of PCOS subjects enrolled in these studies, especially with regard to the degree of involvement and disturbance of the hypothalamus-pituitary-ovary and/ or the hypothalamus-pituitary-adrenal cortex axis. A better knowledge of vascular patterns and changes in PCOS may allow a better understanding of its pathophysiology, especially with regard to the relative role of the exaggerated response to gonadotropin stimulation, the increased vascular resistance to uterine blood flow, and the diminished endometrial receptivity and subsequent infertility.^{13,15} Several studies have implicated impaired uterine perfusion as an important factor in implantation failure during in vitro fertilization treatments.^{14,18} Because increased uterine artery pulsatility index (PI) has been reported in infertile couples and has been linked to reduced chances of conception when using assisted reproductive techniques, pathologic uterine perfusion is suggested to contribute to the reduced success of conceiving and an increased risk of miscarriage in PCOS.¹⁹⁻²¹ Women with PCOS present significant differences in intra-ovarian and uterine artery hemodynamics compared with women with normal ovaries.^{20,21-27}

II. Materials And Methods

This study was conducted in thirty PCOS patients sent for ultrasound abdomen from the outpatient department of Obstetrics and Gynecology, Pt.B.D. Sharma PGIMS Rohtak and thirty age-matched controls sent for ultrasound abdomen from different outpatient and inpatient departments over a duration of 1.5 years.

Inclusion criteria: - Cases: Women aged 20-40 years who are diagnosed cases of PCOS were enrolled. Controls: Age-matched controls who had come for ultrasound imaging due to other conditions like abdominal pain, colic, infertility, etc.

Exclusion criteria: - Follicular cyst >20mm, dominant follicle >10mm, history of pelvic surgery, local uterine and adnexal conditions, no induction of ovulation in the current cycle, any condition that may affect circulation like hypertension, cardiovascular disorders and hypotension.

Days preferred for imaging were second to the fifth day of the menstrual cycle.

Imaging technique:- Transabdominal and/or Transvaginal sonography imaging technique was used on the Siemens Ultrasound machine model available in Department of Radiodiagnosis, PGIMS Rohtak, Haryana.

Parameters recorded:- Ovarian volume, pulsatility index of each uterine and ovarian artery, resistive index of each uterine and ovarian artery.

Methodology:- Clinical, historical and hormonal data were obtained from each patient. Ultrasound and Doppler analyses were performed. Bilateral ovaries were assessed as polycystic ovary based on a 2018 international consensus guideline¹¹ or normal. Each were classified into normal or PCOS patients using Rotterdam criteria.²⁸ Blood flow waveforms were recorded and RI and PI were calculated. For uterine artery measurements, color flow images identifying the ascending branches lateral to the cervix at the level of internal os in the sagittal plane were taken. For ovarian artery measurements, color signals in ovarian stroma measuring the largest distance from the ovarian surface were recorded.

III. RESULTS

- A total of 60 people were included in the final analysis of which 30 (50.00%) were cases and remaining 30 (50.00%) were controls. Among the cases 22 (73.33%) participants presented with oligomenorrhoea, 21(70.00%) with hirsutism, 9 (30.00%) participants presented with infertility.
- Among the cases, the median right ovary volume was 13.8 (IQR 11.67- 18.15) and it was 4.0 (IQR 3.45-6.17) in controls. Among the cases, the median left ovary volume was 12.0 (IQR 10.95-14.75) and it was 4.95 (IQR 3.77- 7.7) in controls. The difference in the ovarian volume between the study groups was statistically significant (p-value < 0.001).
- The mean right uterine artery RI in cases was 0.93 ± 0.05 and it was 0.85 ± 0.04 in controls. The mean left uterine artery RI in cases was 0.92 ± 0.08 and it was 0.86 ± 0.03 in controls. The difference in the uterine artery RI between the two groups was statistically significant (p-value < 0.001).
- In cases, the median right uterine artery PI was 3.3 (IQR3.15- 3.48) and it was 2.61 (IQR 2.56-2.66) in controls. Among the cases, the median left uterine artery PI was 3.32 (IQR 3.15- 3.51) and it was 2.63 (IQR 2.59-2.66) in controls. The difference in the uterine artery PI between the study groups was statistically significant (p-value < 0.001).
- The mean right ovarian artery RI in cases was 0.58 ± 0.03 and it was 0.71 ± 0.06 in controls. The mean left ovarian artery RI in cases was 0.57 ± 0.05 and it was 0.7 ± 0.07 in controls. The difference in the ovarian artery RI between the two groups was statistically significant (p-value <0.001).
- In cases, the median right ovarian artery PI was 0.93 (IQR 0.91- 0.98) and it was 1.28 (IQR 1.22-1.32) in controls. In cases, the median left ovarian artery PI was 0.96 (IQR 0.93- 1.00) and it was 1.26 (IQR1.22-1.32) in controls. The difference in the ovarian artery PI between the study group was statistically significant (p-value <0.001).

CASE : 21 year old female presented in Medicine department with complaints of facial acne. On history she revealed irregular menses since 1 year.

Ultrasound findings were as follows(Figure1a-f): Uterus normal, endometrial thickness 4mm, bilateral ovaries were bulky with no dominant follicle and peripherally arranged follicle. Doppler analysis and findings were as follows:

R ovary volume	L ovary volume	R uterine RI	R uterine PI	L uterine RI	L uterine PI	L ovarian RI	L ovarian PI	R ovarian RI	R ovarian PI
11cc	10.7cc	0.89	3.4	0.93	3.42	0.57	0.92	0.52	0.91



Figure1a. Right ovary volume.

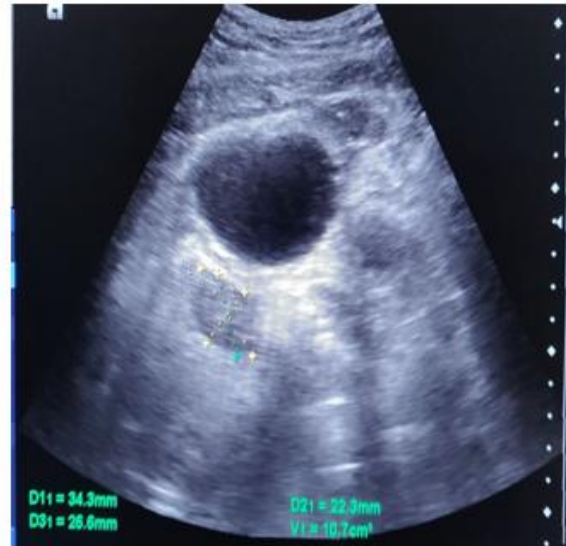


Figure1b. Left ovary volume.



Figure1c. Left ovarian RI and PI.

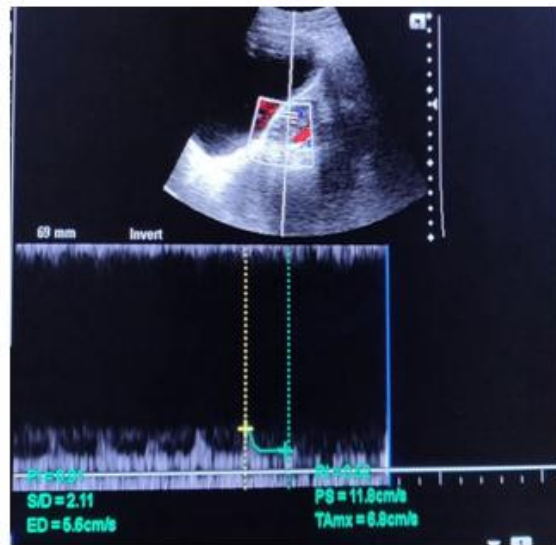


Figure1d. Right ovarian RI and PI.

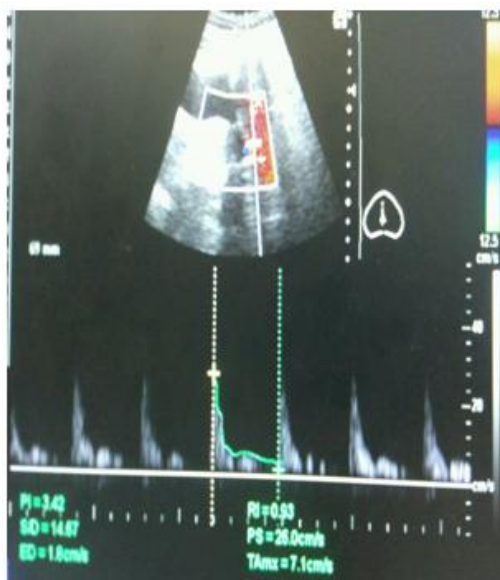


Figure1e. Left uterine RI and PI.

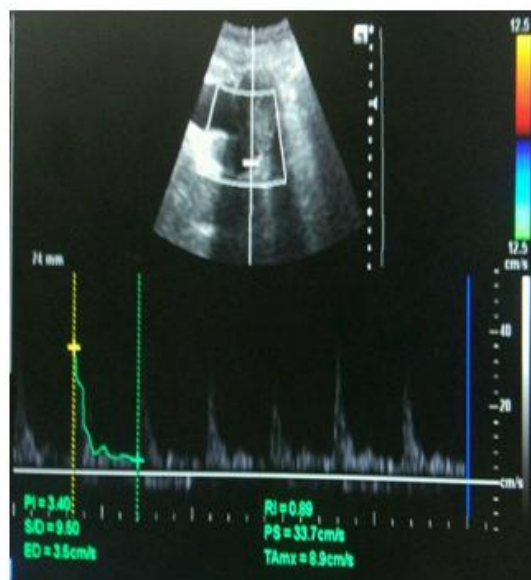


Figure1f. Right uterine RI and PI.

IV. Discussion

- Polycystic ovary syndrome is one of the most common endocrinologic disorders among fertile woman, and its etiology is still not well understood.⁷ Eighteen to twenty-five percent of healthy fertile women have the appearance of PCO, however, its importance still remains uncertain.²⁹ It is still controversial whether normal ovulatory women with the sonographic appearance of PCOs but without any other PCOS symptoms are subgroups of PCOS or normal variants only.³⁰
- In our study, ovarian volume was higher in PCOS patients compared to controls. Among the cases, the median right ovary volume was 13.8 cc and it was 4.0 cc in controls. Among the cases, the median left ovary volume was 12.0 cc and it was 4.95 cc in controls. This was in accordance with the current recommended diagnostic criteria at the time of review based on a 2018 international consensus guideline²⁰ according to which, in patients >8 years post-menarche, and using a high-frequency endovaginal probe: ≥ 20 follicles per ovary, and/or ovarian volume ≥ 10 ml, ensuring no corpora lutea, cysts or dominant follicles are present.
- Menstrual disturbances commonly observed in PCOS include oligomenorrhea, amenorrhea, and prolonged erratic menstrual bleeding.⁵ However, 30% of women with PCOS will have normal menses.⁶ In our study, among 30 PCOS women, 22 (73.33%) participants presented with oligomenorrhoea.
- More than 80% of women presenting with symptoms of androgen excess have PCOS.⁸ Hirsutism is a common clinical presentation of hyperandrogenism occurring in up to 70% of women with PCOS.⁹ Hirsutism is evaluated using a modified Ferriman–Gallwey scoring system.¹⁰ In our study, among the PCOS population 21 (70.00%) participants out of 30 presented with hirsutism.
- The prevalence of infertility in women with PCOS varies between 70 and 80%³¹, however, in our study only 9 (30.00%) out of 30 PCOS women presented with infertility.
- In this study, the PI and RI of the uterine arteries was significantly higher in patients with PCOS than in control women. The mean right uterine artery RI in cases was 0.93 ± 0.05 and it was 0.85 ± 0.04 in controls. The mean left uterine artery RI in cases was 0.92 ± 0.08 and it was 0.86 ± 0.03 in controls. In cases, the median right uterine artery PI was 3.3 and it was 2.61 in controls. Among the cases, the median left uterine artery PI was 3.32 and it was 2.63 in controls. This was in contrast to data reported in another study¹⁷, but in agreement with those reported by others^{14,24,32}, and possibly due to the lower serum estradiol levels, since this hormone increases blood flow in many tissues. In patients with PCOS, there is no increase in estradiol concentration during the preovulatory period, as normally occurs in women with ovulatory cycles³³. The hyperestrogenism of patients with PCOS is due to estrone levels originating from the peripheral conversion of hyperandrogenism. However, the biological activity of estrone is significantly lower than that of estradiol. A study of uterine artery flow showed that patients with premature ovarian failure or submitted to oophorectomy have a high degree of vascular resistance, with a profound modification of the flow pattern, followed by a marked decrease in resistance after hormonal replacement to levels observed in normal menstrual cycles.³⁴ Estrogen receptors have been identified on the walls of the uterine arteries, suggesting the occurrence of a direct effect of estrogen on vascular flow in these arteries, while progesterone did not interfere significantly with the vasodilating effect of estrogen on the uterine arteries.³⁵ In patients with PCOS, the androgens, which are vasoconstrictors, are increased and may be involved in the increase in uterine artery PI and RI, probably through the mediation of specific receptors present on the uterine wall.³⁶ Androstenedione levels have been reported to be positively correlated with mean uterine artery PI^{25,30}, and the reduction in androgen levels is associated with improved PI in these arteries.²⁶ In the present study, androgen levels were higher in patients with PCOS, but no correlation was observed between uterine artery PI and androgen (testosterone and androstenedione) or LH levels. In PCOS, the ovaries are bilaterally enlarged in 70–90% of cases³⁷⁻³⁸ and in the present study the mean ovary size was found to be larger in patients with PCOS than in normal women. However, it is known that ovary size does not indicate the severity of the disease since the rate of testosterone production is independent of the proportions of the organ.³⁹ Most of the patients with PCOS studied here presented ovaries with a peripheral cystic pattern, and the increased ovarian volume was possibly due to this frequently detected morphological pattern.⁴⁰ It has been reported that testosterone levels are better correlated with sonographic parameters in PCOS than LH.⁴¹ In this study, the patients with PCOS presented increased ovarian stroma compared to the control group, in agreement with other reports.^{29,42} The increased LH levels in PCOS may be responsible for the increased vascularization of ovarian stroma brought about by neoangiogenesis⁴³, catecholaminergic stimulation⁴⁴ and leukocyte and cytokine activation.⁴⁵ In addition, these organs have higher levels of angiogenic cytokine vascular endothelial growth factor. The increased vascularization of the ovarian stroma in women with polycystic ovaries, but without PCOS (normal plasma androgen levels and LH: FSH ratio), suggests that a higher local androgen concentration in the ovaries may be an important factor in stroma vascularization.⁴⁶
- Similar to many other studies^{23-24,26,36-37,47-48} in the literature, our study states that ovarian stromal arterial PI and RI values are lower in women with PCOS than controls. The mean right uterine artery RI in cases was 0.58 ± 0.03 and it was 0.71 ± 0.06 in controls. The mean left uterine artery RI in cases was 0.57 ± 0.05 and it was 0.7 ± 0.07 in controls. In cases, the median right ovarian artery PI was 0.93 and it was 1.28 in controls. In

cases, the median left ovarian artery PI was 0.96 and it was 1.26 in controls. The lower PI and RI values are possible indicators of the increased number and dilatation of ovarian stromal vessels in PCOS.⁴⁹ Experimental studies have shown that insulin and Insulin-like Growth Factor stimulate the angiogenesis and vasodilatation in the ovarian tissue. The exact mechanism of this effect could not have been explained yet, but vascular smooth muscle relaxation, endothelial activation and IGF receptor stimulation may be possible theories.⁵⁰ Studies have shown that blood IGF levels are significantly increased in PCOS. There are also studies which reported negative correlations between blood IGF levels and ovarian stromal artery PI values.⁵⁰ Insulin-like Growth Factor 1 has an important role in steroidogenesis and follicular development, and it is also thought to be associated with the follicular development disorders in PCOS.⁵¹ Increased levels of serum androgens in PCOS, particularly DHEAS, have vasoconstrictive effects, and there are studies showing that this can cause increased resistance against uterine blood flow.⁵² On the other hand, high levels of local androgens in PCOS cause an increase in ovarian stromal vascularity.⁴⁷

- Women with PCOS were compared to healthy women in a case-control study performed by Jarville et al using 3-D technology, and no difference was found in ovarian vascularities between the two groups unlike our study and many others in the literature. But this finding must be evaluated carefully because of the small sampling size.⁵³

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