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Intra-ovarian Doppler artery indices values in cases with polycystic ovarian syndrome: a case control study

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Parwin Omar Hassan [1*] Aska Faruq Jamal [2]

Abstract

Background and objective: polycystic ovarian syndrome (PCOS) is the most common female endocrine disorder during their reproductive age which results in hyperandrogenism and anovulation or oligo-ovulation. Significant changes occur in ovarian vascularization at the level of the intra ovarian arteries in PCOS patients. The objective is to assess Doppler hemodynamic changes in ovarian stromal arteries in follicular phase of the cycle in both ovaries in women with PCOS compared to normal ovulatory fertile women (control) using transvaginal Color Doppler technique, by calculating intra ovarian Doppler artery indices values: Resistive index (RI) and pulsatility index (PI) of both ovaries.

Methods: Two hundred women were included in the study. One hundred patients were diagnosed as PCOS (cases) according to Rotterdam's criteria and another one hundred were normal fertile women (controls).

Transvaginal color Doppler technique is used in examining the recruited cases and controls, Doppler indices values of intraovarian stromal arteries were measured.

Results: in the current study, the RI and PI of the ovarian stromal artery were lower in women with PCOS (cases) compared to controls. These hemodynamic changes are a predictor for the diagnosis of PCOS.

Conclusion: Doppler ultrasonography was a successful tool in assessing the hemodynamic changes in PCOS women.

Keywords: PCOS (polycystic ovarian syndrome); RI (Resistive Index); PI (Pulsatility Index); S/D (Systolic/Diastolic) ratio.

Introduction

Polycystic Ovarian Syndrome" or PCOS (is also known as polycystic ovary syndrome); it is previously known as the polycystic ovary disease (PCOD) and even before that as the "Stein – Leventhal Syndrome".

Although polycystic ovary syndrome is the most common female endocrine disorder, its etiology is still not understood.[1] It affects five to ten percent of women in child-bearing age.[2,3] About 20 to 30 percent of women in reproductive age show polycystic ovaries by Ultrasound.[4,5]

PCOS manifests with various clinical symptoms and signs including infertility (74%), irregular menstrual cycle (66%), hyperandrogenemia (48%) and obesity. The infertility and menstrual disturbance are due to Oligo-ovulation or anovulation. PCOS reported as the main cause of infertility due to anovulation which is caused by immaturity of the ovarian follicles. In female with 28 days cycle, the primordial follicles begin to grow into secondary follicles. One of these secondary follicles grows to change to mature follicle which ovulates around the mid-cycle. In PCOS, the follicle will fail to become mature Graafian follicle. As a result, numerous immature follicles, which are located in the periphery in the ovary will be seen. As a consequence of

[1] Department of Radiology, Rizgary Teaching Hospital, Ministry of Health, Erbil, Iraq.
[2] Department of Surgery, College of Medicine, Hawler Medical University, Erbil, Iraq.
Correspondence: parwin.omer777@gmail.com

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these pathological changes, the blood flow to the ovarian stromal artery will increase and vascular impedance will decrease.[6] The menstrual disturbance which is seen in PCOS includes oligomenorrhea or amenorrhea and prolonged menstrual bleeding. Clinical sign of hyperandrogenism include Hirsutism, androgenic alopecia, seborrhea and acne.[7]
Stein and Leventhal, in 1935, first described PCOS as seven women who had amenorrhea, hirsutism, and enlarged ovaries with multiple cysts.[1] The 1990 National Institutes of Health conference on PCOS recommended criteria for the diagnosis of the PCOS: hyperandrogenism and oligo ovulation. One of the criticisms of this definition was the elimination of sonographic findings of polycystic ovaries from the diagnostic panel.[8] In 2003, the Rotterdam Consensus Conference debated about the important role of 2-dimensional (2D) sonography in the assessment of PCOS and made a consensus definition for the diagnosis of polycystic ovary. In 2009, the definition had been confirmed by the Androgen Excess and PCOS Society. Consequently, the definition is included in the American College of Obstetricians and Gynecologists guidelines. So, the Rotterdam-PCOS Consensus definition requires the presence of two of the following three criteria to create the diagnosis of PCOS: 1. Oligo-ovulation and/ or anovulation. 2. Clinical and/or biochemical signs of hyperandrogenism. 3. PCOS on ultrasonography.[9]
Regarding PCOS on ultrasonography: two criteria are accepted for the definition of PCOS: ovarian volume and number of follicles. According to this definition, polycystic ovaries are present when: 1. One or both ovaries show 12 or more follicles that measure 2-9 mm in diameter. 2. The ovarian volume exceeds 10cm^3.
Just one ovary having either of these criteria is enough to diagnose polycysticovaries.[8,10] Sonographic findings, like peripheral distribution of the follicles, increased stromal echogenicity and vascularization were not involved in the criteria.[8] In spite of this, several radiologists remain unaware of the reviewed definition and remain to evaluate ovaries without expressing the volume, number of follicles in the report. As a consequence of this many women being incorrectly regarded as having polycystic ovaries.[11] Nowadays, the expanded Rotterdam criteria are generally accepted and suggested using international evidence–based guidelines.[12] Ultrasound findings for PCOS have altered – follicle number per ovary (FNPO) was changed to 20 or more (Table 1).[13]

Table 1 Main Ultrasound Parameters

FNPO	≥ 12 per ovary * measuring 2-9mm
FNPO	≥ 20 per ovary ** measuring
OV	> 10 ml ensuring no corpora lutea cysts, or dominant follicles are present

* -Rotterdam criteria.
**-International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018.

Other ultrasound findings that aid in the diagnosis of PCOS: follicle distribution pattern, antral follicle count, RI and PI of uterine and ovarian arteries, and ovarian stromal echogenicity.[13-15]
Although ultrasound assessment is necessary for diagnosis of PCOS, but there is no single available test to assist the diagnosis in suspected cases.[16,17] Nowadays, better sensitivity was attained with transvaginal Color Doppler Ultrasound which is widely used as a non-invasive technique to evaluate blood flow changes in the ovaries particularly in PCOS patients.[8] Intraovarian vascularization is usually not seen before days 8 of the 28-day cycle in normal women, however Doppler sonographic studies showed that ovaries of PCOS women have a greater number of vessels than that of normal ovaries in the early follicular phase that's why in patients with PCOS these vessels are seen between days 3 and day 5 of the cycle.[9] Although transvaginal ultrasound is

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considered more accurate, but it's not appropriate for adolescent girls.[13,17] The international guidelines suggest that for diagnosis of PCOS ultrasound should be used for patients after eight years have passed after their menarche.[12,13] Because at this period the body of female undergoes considerable hormonal changes which result in growth of follicles which resemble PCO appearance.[13,17] This is also suggested by other studies like Witchel et al. which suggest that ultrasound should not be used for diagnosis of PCOS during puberty.[13]

The rationale for conducting this study was to aid the diagnosis of PCOS by doppler ultrasound through measuring the doppler indices values of intra-ovarian arteries by doppler technique as it is a non-invasive, easily available and recently interesting technique.

Aim of the study

To assess Doppler hemodynamic changes in ovarian stromal arteries in follicular phase of the cycle in both ovaries in women with PCOS compared to normal ovulatory fertile women (control) using transvaginal Color Doppler technique, by calculating intra ovarian Doppler artery indices values: Resistive index and pulsatility index of both ovaries.

To compare such Doppler parameters obtained from hemodynamic changes in ovarian stromal arteries of PCOS patients between each other and comparing it to normal patients.

Methods

Study Design: This study was prospective case-control study.

Study Area: The patients were recruited from outpatient gynecological clinic at Maternity Hospital and Rizgary Hospital Erbil, Iraq.

Time of the study: 1st Feb 2021 till 1st June 2022

Ethical consideration: Ethical approval was obtained from the ethical committee of the College of Medicine/ Hawler Medical University. The data collection permission was taken from the administrators of both Maternity Hospital and Rizgary Hospital Erbil, Iraq. Each female participants were assured confidentially, and written informal consent was taken from them. Participation remained anonymous throughout the study and allowed them to withdraw through the research process.

Sample Size Sample Selection Method

Sampling: A convenience sample of two hundred patients was involved in this study. The

patients were subdivided into two groups, as it is a case-control study.

Group 1 (cases): comprised 100 obese women previously diagnosed as PCOS patients according to Rotterdam criteria.

Groups 2 (controls): comprised one hundred normal healthy fertile women, who had regular menstrual cycles ranging from 25 to 32 days.

Inclusion Criteria

Cases: Group 1women diagnosed as PCOS according to Rotterdam's criteria.

Controls: Group 2 normal fertile regular menstruating women.

Exclusion criteria

1. Presence of hypertension, diabetes, autoimmune disease, renal or hepatic disease, anemia, cardiovascular disorders or condition that affect the circulatory system.
2. Uterine malformation and endometriosis, these are regarded as local uterine or adnexal condition (excluding PCOS)
3. Any history of ovarian surgery or pathology (e.g., unilateral ovarian resection).
4. Ovarian follicular cyst > 20 mm in early follicular phase.
5. History of drug intake e.g., drug used for induction of ovulation in the current cycle or hormonal therapy for at least six months prior to the study.

After taking their consent, the included patients were submitted to:

- History which included history of age, parity and menstrual history, history of infertility, and hirsutism.
- Weight is measured in kg and height is

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measured in meters.

- BMI of each patient is calculated according to the formula:

BMI=weight in kilogram/height in meter^2

- Grey scale transvaginal Ultrasound Scan, using VOLUSON E8; GE Healthcare, USA which is equipped with 4-9 MHz transvaginal transducer in early follicular phase for estimation of:

* Ovarian volume: A volume of 10 cm^3 was chosen as the threshold volume for a polycystic ovary from the definition. For calculating ovarian volume, the simplified formula 0.5 x length x width x thickness should be used. The length and width of the ovary should be measured in the sagittal plane and the thickness should be measured in the transvers plane. In case of the existence of a follicle >10mm diameter or a corpus luteum which will lead to increased ovarian volume, ultrasound should be postponed and repeated during the beginning of the following cycle. For calculating ovarian volume in patients with amenorrhea, ultrasound can be achieved at random.[11]

* Number of follicles in each ovary is calculated.

* Diameter of the all follicles is measured.

- Color Doppler ultrasound Scan, VOLUSON E8; GE Healthcare, USA, which is equipped with IC5-9-D probe of 4-9 MHz transvaginal transducer, by using this probe in early follicular phase (day 2-4) before day 8 of the cycle, small vessels in the ovarian stroma were identified. The transvaginal Doppler ultrasound Scan used to evaluate:

Resistance index RI, Pulsatility index (PI) and Systolic / Diastolic (S/D) ratio of ovarian stromal vessels on both sides, (Figure 1 & Table 2)

The vessels which are located near a follicle were neglected as well as those vessels which are very close to surface of ovary. Setting the velocity about 20 cm/s for PSV gives maximum sensitivity 70% and specificity 75%.

Table 2 Variation in Doppler Indices in the Uterine and Ovarian Arteries during the Menstrual Cycle

	RI OVA	PI OVA	VEL OVA (cm/s)	PI UTA
Early follicular	0.65 - 0.7	1.8 - 2.2	20	1.67±0.22
Late follicular/ ovulation	0.55 - 0.6	1.0 - 1.3	40	1.89±4.0
Luteal	0.6 - 0.65	1.3 - 1.8		2.23±0.67
Non- conception	0.6 - 0.7	1.8 - 2.2		3.85±1.1
Postmenopausal	0.6 - 1.0	1.3 - 4.0		1.8±3.8

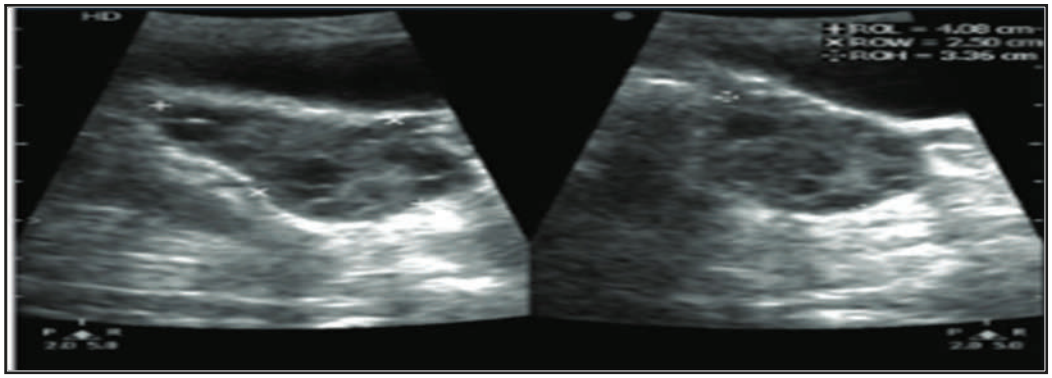

Figure 1 Ovarian Volume Measurement

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Statistical analysis

Data were collected by specially designed questionnaire and entered into Excel sheet. The Statistical Package for Social Sciences (SPSS, version 25) was used for data analysis. Chi square test of association was used to compare proportions of the two study groups. Fisher's exact test was used when the expected frequency (value) was less than 5 of more than 20% of the cells of the table. Student's t test for two independent samples (unpaired t test) was used to compare two means. A *P* value of ≤ 0.05 was considered as statistically significant. Pearson's correlation coefficient tested all intraovarian arterial indices to find the correlation between different parameters.

Results

Two hundred women were included in the study, 100 had PCOS and the other 100 women had no PCOS (control). The mean age (SD) of the whole sample was 30.1 (4.8) years. The age range was 20-44 years, and the median was 29 years. The mean age of women of the PCOS group (31.1 years) was significantly (*P* = 0.002) higher than that of the control (29.1 years) as presented in Table 3 which shows that higher proportion of women in the PCOS group (than the control) were aged 30 or more years, but the difference in the age distribution was close to the level of significance (*P* = 0.057). It is evident in Table 3 that the majority (96%) of the women of the PCOS group were obese, while none of the controls were obese (*P* <0.001). The same is for hirsutism, the rate was 96% in PCOS group vs. 0% in the control (*P* <0.001). The majority (92%) of the women in the PCOS group had menstrual disorders compared with 0% in the control group (*P* <0.001) (Table 3).

Table 3 Basic Characteristics Detected by Ultrasound in Cases and Controls by Average and Mean

	PCOS No. (%)	Control No. (%)	Total No. (%)	*P value*
Age (years)				
20-24	6 (6.0)	8 (8.0)	14 (7.0)	
25-29	41 (41.0)	56 (56.0)	97 (48.5)	
30-34	28 (28.0)	25 (25.0)	53 (26.5)	
35-39	16 (16.0)	9 (9.0)	25 (12.5)	
40-44	9 (9.0)	2 (2.0)	11 (5.5)	0.057**
Mean (SD)	31.1 (5.2)	29.1 (4.1)	30.1 (4.8)	0.002†
BMI (Kg/m^2)				
< 25	2 (2.0)	47 (47.0)	49 (24.5)	
25-29	2 (2.0)	53 (53.0)	55 (27.5)	
≥ 30	96 (96.0)	0 (0.0)	96 (48.0)	< 0.001**
Mean (SD)	36.3 (3.8)	25.3 (1.9)	30.8 (6.3)	< 0.001†
Hirsutism				
Yes	96 (96.0)	0 (0.0)	96 (48.0)	
No	4 (4.0)	100 (100.0)	104 (52.0)	< 0.001**
Menstrual status				
Regular menstruation	3 (3.0)	100 (100.0)	103 (51.5)	
Menstrual disorder	92 (92.0)	0 (0.0)	92 (46.0)	
Amenorrhea	5 (5.0)	0 (0.0)	5 (2.5)	< 0.001*
Total	100 (100.0)	100 (100.0)	200 9100.0)	

*By Fisher's exact test. **By Chi square test. †By t test for two independent samples

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All the women of the PCOS group had high right ovarian volume, compared with 0% in the control group (*P* <0.001). The mean of the right ovarian volume (12.82 cm^3) was significantly (*P* <0.001) higher than that of the control group (7.61 cm^3). Nearly the same pattern is observed in the left ovarian volume, where it is evident in Table 4 that only one woman in the PCOS group had normal left ovarian volume while all the women of the control group had normal left ovarian volume (*P* <0.001). Regarding the number of follicles, all the women with PCOS had a follicle number of ≥ 12, whether in the right or left side, while none of the controls had ≥ 12 follicles (*P* <0.001) (Table 4, Figure 1, Figure 2).

Table 4 Ovarian measurements

	PCOS	**Control**	**Total**	
	No. (%)	**No. (%)**	**No. (%)**	***P value***
Right ovarian volume (cm^3)				
Normal	0 (0.0)	100 (100.0)	100 (50.0)	
High	100 (100.0)	0 (0.0)	100 (50.0)	< 0.001**
Mean (SD)	12.82 (1.59)	7.61 (1.22)		< 0.001†
Left ovarian volume (cm^3)				
Normal	1 (1.0)	100 (100.0)	101 (50.5)	
High	99 (99.0)	0 (0.0)	99 (49.5)	< 0.001**
Mean (SD)	12.67 (1.81)	7.49 (1.04)		< 0.001†
No. of right ovarian follicles				
< 12	0 (0.0)	100 (100.0)	100 (50.0)	
≥ 12	100 (100.0)	0 (0.0)	100 (50.0)	< 0.001**
Mean (SD)	21.59 (7.04)	7.29 (1.04)		< 0.001†
No. of left ovarian follicles				
< 12	0 (0.0)	100 (100.0)	100 (50.0)	
≥ 12	100 (100.0)	0 (0.0)	100 (50.0)	< 0.001**
Mean (SD)	21.11 (6.36)	7.09 (0.89)		< 0.001†
Total	100 (100.0)	100 (100.0)	200 (100.0)	

†By unpaired t test. **By Chi square test.

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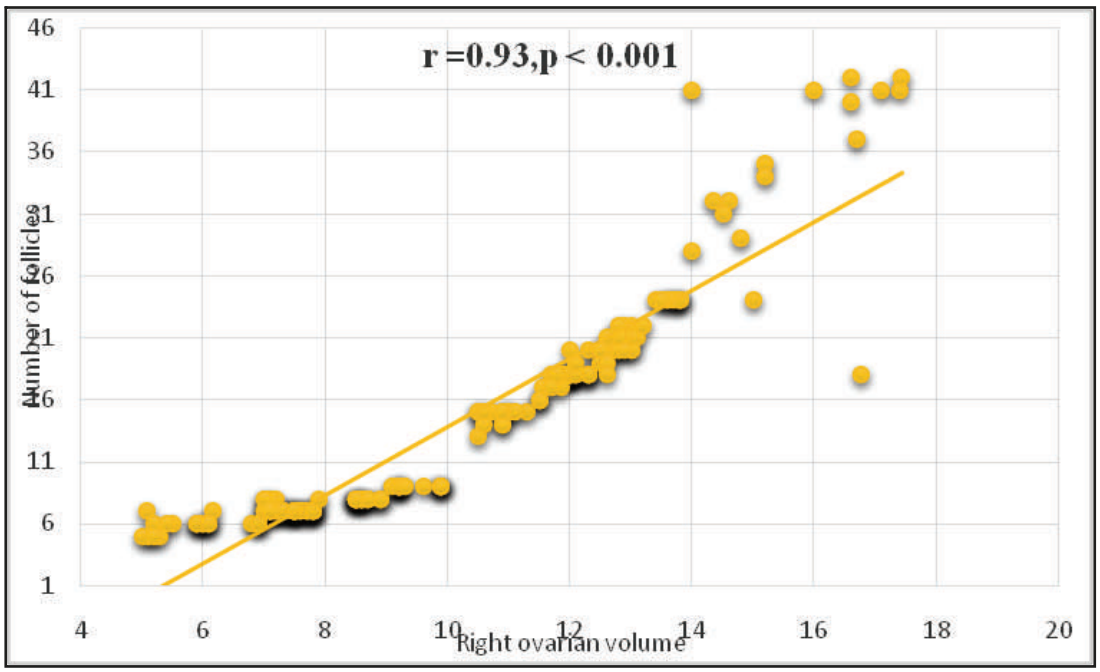

Figure 2 Shows correlation between right ovarian volume and number of follicles.

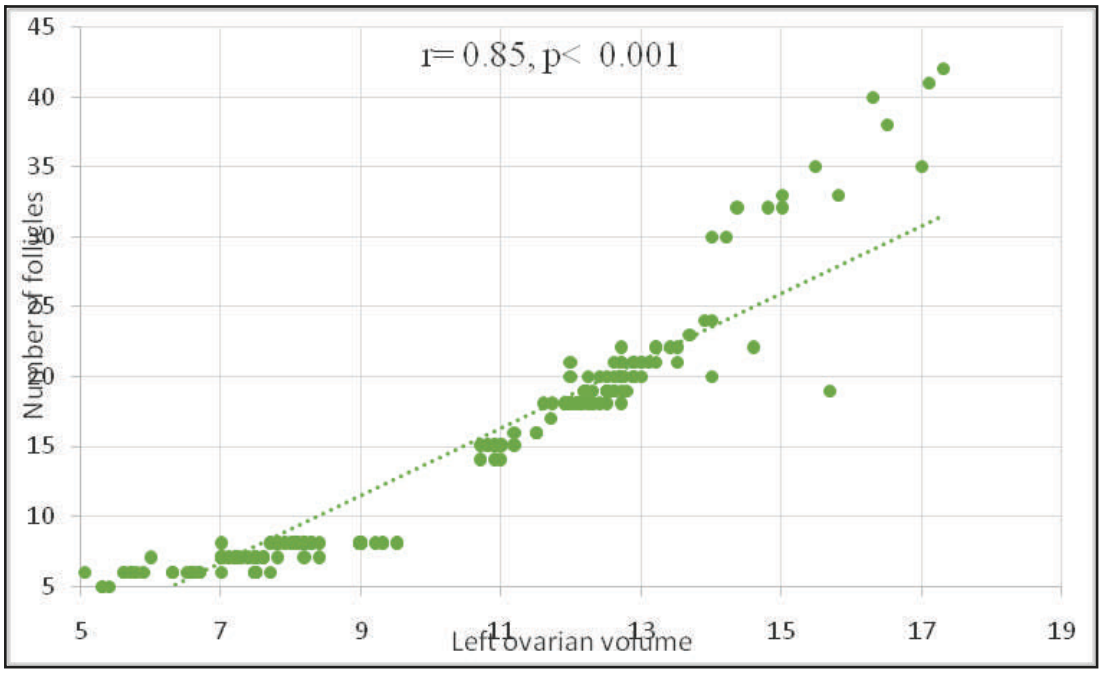

Figure 3 Correlation between left ovarian volume and number of follicles. A positive and significant correlation was detected between them

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It is evident in Table 5 that around two thirds of the women with PCOS had low RI, whether in the right or left side compared with one third (32%) of the women in the control group (*P* <0.001). The means of the RI were significantly lower in the PCOS group than the control (*P* = 0.040 in the right side and *P* = 0.018 in the left side). The majority of the women with PCOS had low PI whether in the right side (80%) or in the left side (82%) compared with 26% and 21% respectively in the control group (*P* <0.001). The means of PI were also significantly lower in PCOS compared with the control (*P* < 0.001). The mean of the right systolic/diastolic ratio in the PCOS (2.76) was significantly (*P* = 0.002) less than that of the control (3.39). The mean of the left systolic/diastolic ratio was also significantly less (*P* = 0.001) than that of the control (2.68 vs. 3.12) as presented in Table 5, Figure 4 and Figure 5

Table 5 Doppler ovarian artery indices

	PCOS No. (%)	Control No. (%)	Total No. (%)	*P* value
Right RI				
Low (<0.65)	64 (64.0)	35 (35.0)	99 (49.5)	
Normal (0.65-0.7)	36 (36.0)	65 (65.0)	101 (50.5)	< 0.001**
Mean (SD)	0.64 (0.05)	0.66 (0.10)		0.040†
Left RI				
Low (<0.65)	65 (65.0)	35 (35.0)	100 (50.0)	
Normal (0.65-0.7)	35 (35.0)	64 (64.0)	99 (49.5)	
High (≥ 1)	0 (0.0)	1 (1.0)	1 (0.5)	< 0.001*
Mean (SD)	0.64 (0.05)	0.66 (0.09)		0.018†
Right PI				
Low (<1.8)	80 (80.0)	26 (26.0)	106 (53.0)	
Normal (1.8-2.2)	20 (20.0)	74 (74.0)	94 (47.0)	< 0.001**
Mean (SD)	1.09 (0.25)	1.85 (0.53)		< 0.001†
Left PI				
Low (<1.8)	82 (82.0)	21 (21.0)	103 (51.5)	
Normal (1.8-2.2)	18 (18.0)	79 (79.0)	97 (48.5)	< 0.001**
Mean (SD)	1.05 (0.14)	1.8 (0.47)		< 0.001†
Right Systolic/diastolic ratio Mean (SD)	2.76 (0.44)	3.39 (1.95)		0.002†
Left Systolic/diastolic ratio Mean (SD)	2.68 (0.32)	3.12 (1.25)		0.001†
Total	100 (100.0)	100 (100.0)	200 (100.0)	

†By unpaired t test. *By Fisher's exact test. **By Chi square test.

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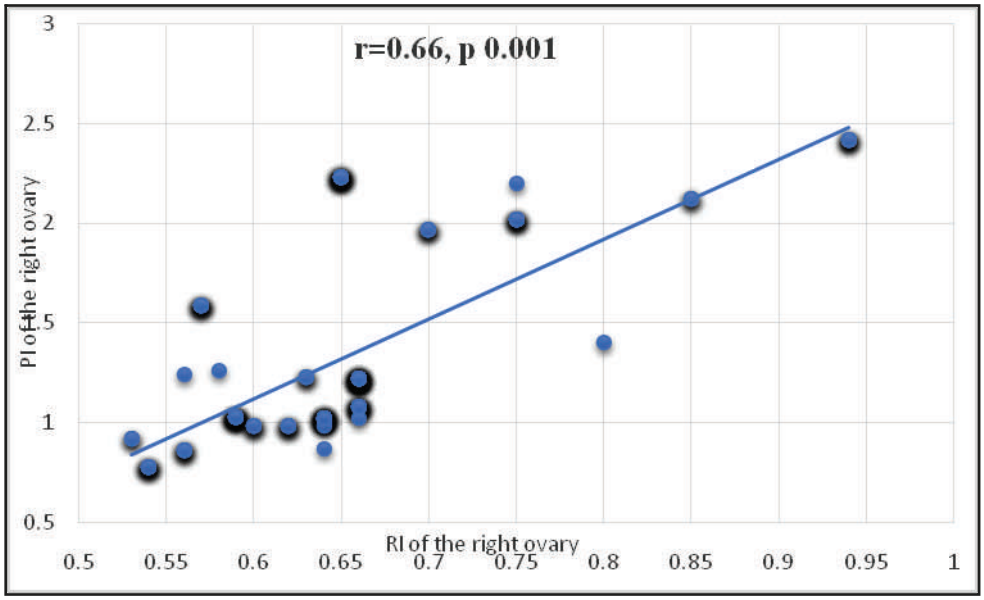

Figure 4 Correlation between RI and PI of the right ovary.
A positive correlation showed between RI and PI of the right ovary.

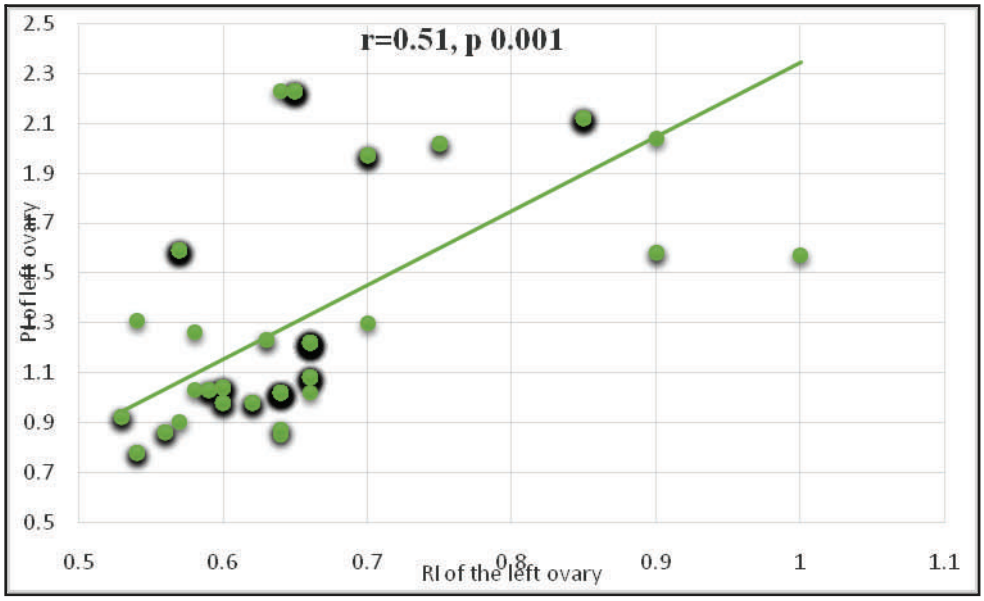

Figure 5 Correlation of RI with PI of the left ovary.
A positive correlation showed between RI and PI of the left ovary.

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Discussion

Two hundred women were included in the study, 100 had PCOS and the other 100 women had no PCOS (control).

Age: The mean age (SD) of the whole sample was 30.1 (4.8) years. The age range was 20-44 years, and the median was 29 years. The mean age of women of the PCOS group (31.1 years) was significantly (*P* = 0.002) higher than that of the control (29.1 years) which shows that higher proportion of women in the PCOS group (than the control) were aged 30 or more years, but the difference in the age distribution was close to the level of significance (*P* =0.057).

BMI: Obese women are more prone to menstrual disturbance and infertility than normal weight women.[18]Regarding the mean BMI, there was significant increase in mean BMI in cases in comparison to control. In current study, the mean BMI of cases was 36.3±3.8 and for controls was 25.3±1.9. The result was in agreement with a study done by Sarhan A M, et al,[19] in Egypt; Dwivedi S, et al [18], in India; Younesi L, et al,[4] in Iran; Fetouh and Mohamed,[9] in Egypt; and Bostanci, et al,[20] in Turkey.

Ovarian Volume: According to Rotterdam's consensus criteria, the increased ovarian volume of more than 10 ml was one of the ultrasound criteria for diagnosis of PCOS. In current study, the mean ovarian volume for cases and controls was (12.82± 1.58 vs 7.60± 1.22) for the right ovary and (12.66± 1.8vs7.48±1.04) for the left ovary respectively. Our result was in line with Rotterdam's criteria. This agrees with studies done by Sarhan A M, et al [19], in Egypt; Younesi L, et al,[4] in Iran; Dwivedi S, et al,[18] in India; and Fetouh and Mohamed [9] in Egypt with several other studies showed that women with PCOS have enlarged ovaries than controls.[3, 21-24]

RI: This study like numerous previous studies showed that the doppler indices values of the ovarian stromal artery are lower in PCOS patients possibly related to the engorgement and dilatation of ovarian blood vessels which is consequently result in increased vascularity and thus increase in PSV and EDV which result in lower values of RI, PI, and S/D ratio.[15]

In the current study the RI for the right and left ovary was lower in cases compared to controls and the mean RI were considerably lower in PCOS groups than controls in both ovaries.

This was in agreement with Pureha G and Magu S,[1] in India; Sarhan A M, et al,[19] in Egypt; Younesi L, et al,[4] in Iran; Fetouh and Mohamed [9] in Egypt; Bano A, et al,[25] in Pakistan; and Bostanci, et al,[20] in Turkey.

PI: The pulsatility index of the ovarian stromal artery for the right and left ovary was lower in cases compared to controls and the mean PI were significantly lower in PCOS groups than controls in both sides. This was in agreement with Pureha G and Magu S[1] in India; Sarhan A M, et al,[19] in Egypt; Younesi L, et al, [4] in Iran; Fetouh and Mohamed [9] in Egypt; Bano A, et al,[25] in Pakistan; and Bostanci, et al, [20] in Turkey.

S/D ratio: S/D ratio was considerably lower in cases compared to control. The mean of the right S/D ratio in the PCOS (2.76) was significantly less than that of the control. The mean of the left S/D ratio in the PCOS (2.68 vs 3.12) was significantly less than that of the control. This was in agreement with Fetouh and Mohamed [9] in Egypt.

Conclusion

Doppler sonography was a successful tool in giving evidence about the pathophysiological and hemodynamic deviations in cases of PCOS. Ovarian stromal artery Doppler study show a considerable role in the pathophysiology of this disease. Patients with PCOS on color Doppler ultrasound reveal low RI and PI of the ovarian stromal artery. So, we can aid the diagnosis of PCOS by measuring and calculating these indices values. Therefore, the average RI of ovarian stromal arteries on both sides were statistically analyzed. In the statistical analysis, there was

a significant difference between the Doppler indexes in these two groups.

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Competing interests

The authors declare that they have no competing interests.

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