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Original Article

Doppler analysis of ovarian stromal blood flow changes after treatment with metformin versus ethinyl estradiol-cyproterone acetate in women with polycystic ovarian syndrome: A randomized controlled trial

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ABSTRACT

Objectives. – To evaluate the effects of oral contraceptive pill (OCP) and metformin at the end of 6 months of treatment on ovarian stromal blood flow by using pulsed and color Doppler in women with PCOS.

Methods. – Women with PCOS (n = 101) fulfilling the Rotterdam criteria were enrolled and randomized to receive either OCP or metformin. OCP was administered in cycles of 28 days (21 pills containing 35 μg of ethinylestradiol plus 2 mg of cyproterone acetate followed by 7 placebo pills) for six cycles and metformin 500 mg was administered twice daily for 6 months. Clinical, anthropometric, hormonal and metabolic parameters and resistance index (RI) and pulsatility index (PI) of both ovarian stromal vessels were assessed before and after treatment.

Results. – OCP resulted in a higher reduction in serum luteinizing hormone (LH) and androgens whereas metformin resulted in significant reduction in BMI, waist circumference, and insulin resistance. There was a significant increase in RI and PI of both ovarian stromal vessels with both drugs post-treatment, however, the increase was more prominent in the OCP group. There was a significant negative correlation between changes in LH and testosterone levels with changes in PI and RI in OCP group whereas changes in serum fasting insulin levels negatively correlated with changes in PI and RI values in the Metformin group.

Conclusions. – Treatment with both OCP and metformin leads to a reduction in ovarian stromal vascularization in PCOS women perhaps through different mechanisms and this reduction is more prominent with OCP.

1. Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder characterized by menstrual irregularities, chronic oligo/anovulation, and hyperandrogenism [1]. Exaggerated androgen synthesis and secretion by ovarian theca cells appear to be the primary defect in PCOS, however, it may be triggered by coexisting obesity and insulin resistance [2]. Oral contraceptive pills (OCPs) are commonly used as first line medical therapy for treatment of menstrual disturbances and hyperandrogenism in women with PCOS, however, in some cases, it may predispose the patients to increased risk of glucose intolerance and insulin resistance [3]. Hence in this scenario, insulin sensitizers such as metformin may be used in the treatment of PCOS, which have metabolic benefits apart from improving hyperandrogenism [4,5].

The etiopathogenesis of ovarian vascular changes in PCOS is incompletely understood. Numerous studies have suggested the prime role of serum LH levels in modulating ovarian stromal vascularity [6]. Similarly, defective endothelial vasomotor function due to insulin resistance has been ascribed to anatomical and functional changes in ovary vascularity [7]. Although several studies have highlighted the presence of increased ovarian stromal blood flow and reduced resistive indices in women with PCOS

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compared to controls [8], literature has limited data regarding changes in ovarian stromal blood flow during the follow-up period of PCOS treatment. Doppler evaluation of the ovaries during treatment follow-up might give us an insight into the mechanistic aspect of the action of drugs on ovaries and might help clinicians in predicting the response to treatment.

In view of these considerations, this study was undertaken to compare the effects of treatment with commonly used OCP containing ethinyl estradiol-cyproterone acetate and metformin in women with PCOS. Special attention was paid to changes in ovarian stromal blood flow by using color Doppler and they were correlated with changes in hormonal parameters post-treatment.

2. Materials and methods

This prospective, randomized, controlled open-label, clinical trial was conducted in the department of Obstetrics and Gynecology, SCB Medical College, Cuttack, India, between August 2017 and March 2018 (ClinicalTrials.gov Identifier: NCT03236740). Our Institutional Ethical Committee approved the protocol of the study and written informed consent was obtained from all participants.

2.1. Subjects

One hundred and eighty-eight women with menstrual irregularities were screened for PCOS according to the Rotterdam criteria [9] and 87 women were excluded either due to not meeting the diagnostic criteria ($n = 53$), declined to participate ($n = 25$) or for other reasons ($n = 9$). The remaining 101 women aged between 18 and 35 years with PCOS were enrolled. Women were excluded if they were known to have congenital adrenal hyperplasia, pituitary insufficiency, persistent hyperprolactinemia, current or previous cardiovascular, hepatic or renal dysfunction, diabetes, if they had used ovulation induction drugs, oral hypoglycemic agents, OCPs, or anti-androgens within the last 3 months. None of the patients were either smokers or alcoholics and none were pregnant at the time of enrollment. Women with the presence of any ovarian lesion such as an ovarian cyst or follicles larger than 10 mm in diameter in either ovary were also excluded.

2.2. Study protocol (Fig. 1)

After providing informed consent, patients were randomized to receive either an anti-androgenic low-dose OCP in cycles of 28 days (21 pills containing 35 μg of ethinylestradiol plus 2 mg of cyproterone acetate followed by 7 placebo pills (Diane 35; Bayer Zydus Pharma, Maharashtra, India)), or 500 mg of metformin (Glycomet SR 500, USV, Mumbai, India) twice daily for 6 months. Women in the Metformin group were advised to use a barrier contraceptive throughout the study. All the patients were instructed to perform moderate physical activity and maintain a low carbohydrate diet throughout the trial. Simple randomization was performed using random number table. One investigator (A.S.) generated the randomization, whereas another (J.M.) enrolled the participants and another investigator (P.T.) assigned the participants to treatment groups.

At the beginning of the study, a single investigator (P.T.) performed clinical and anthropometric evaluations of all patients. A detailed clinical history was collected regarding the menstrual cycle, the onset and degree of clinical symptoms of PCOS and infertility if relevant. Each patient's body mass index (BMI) was computed using their weight and height and waist circumference was also measured. Hirsutism was evaluated using the modified Ferriman–Gallwey scale [10]. All ultrasound evaluations and analysis of blood samples for hormonal and metabolic parameters were performed within the first 5 days of the menstrual cycle.

2.3. Ultrasound evaluation

All Doppler examinations were performed using an ultrasound machine (Philips HD-7, Bothell, WA, USA) equipped with a 7 MHz transvaginal transducer to exclude the effects of circadian rhythmicity on ovarian blood flows. All patients were studied between 9:00 a.m. and 11:00 a.m. By means of color and power Doppler flow imaging, color signals were searched in the ovarian stroma away from the ovarian surface and not adjacent to the wall of a follicle. Areas of maximum color intensity, representing the greatest Doppler frequency shifts, were chosen for pulsed Doppler examination. Then, after angle correction, optimal flow velocity waveforms were chosen for analysis. The pulsatility index (PI) and resistance index (RI) were electronically calculated for each selected Doppler wave [11,12].

One investigator (A.S.) performed all the Doppler studies to avoid inter-observer variations. Moreover, this investigator was blinded to all clinical and laboratory records of PCOS women to avoid bias. For intra-observer error, there was a very good correlation of the consecutively repeated measurements for the right ($r = 0.892$) and the left ovary ($r = 0.924$), and there was no significant difference between the two repeated measurements ($p > 0.05$). Since no significant difference in Doppler parameters of right and left ovaries were observed, the mean values of all ovarian Doppler parameters were used in the statistical analysis.

2.4. Biochemical assessment

Blood samples were collected from each patient on the same day as Doppler flow analysis, in the morning hours in a fasting state. The serum concentration of luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone (TT), sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), and fasting insulin (FIN) were measured using a chemiluminescent immunoassay (Immulite 2000 Diagnostic Products Corp., Los Angeles, CA, USA). The concentrations of high-density lipoprotein cholesterol (HDL-C), triglyceride (TG) and fasting glucose (FG) levels were established by enzymatic and colorimetric methods (fully automated Humastar 600 biochemistry analyzer, Wiesbaden, Germany). Serum low-density lipoprotein cholesterol (LDL-C) levels were calculated according to the Friedewald formula [LDL-C = TC − (HDLC + (TG/5))]. A homeostasis model assessment of insulin resistance (HOMA-IR) was derived using the formula: HOMA-IR = FG (mg/dL)/18 × FIN (IU/L)/22.5.

After completing the baseline evaluation, treatment was started on the first day of the menstrual cycle. In women with amenorrhea, after excluding pregnancy by appropriate testing, medroxyprogesterone acetate (5 mg/day) for 5 days was administered in order to induce vaginal bleeding. On the third month of follow-up, the participants were contacted to determine their compliance to drug administration and lifestyle modifications. At the end of the study, i.e. after completion of the six months of treatment, all of the clinical, anthropometric, biochemical, hormonal and Doppler parameters were measured again using the same methods and compared with the pre-treatment values.

2.5. Statistical analysis

Data are shown as the mean ± standard deviation (SD) and were analyzed using Stata 9.2 for Windows. A Kolmogorov–Smirnov test was applied to test for normality of the data. The differences between groups were tested with either an unpaired *t*-test or a Mann–Whitney *U* test and differences between pre- and post-treatment values were compared using a paired t-test or Wilcoxon test as appropriate. The relationship between ovarian stromal blood flow indices and hormonal parameters was examined by the Pearson correlation test. Statistical significance was set at $p < 0.05$.

The sample size analysis was performed using the online calculator (http://hedwig.mgh.harvard.edu/sample_size/size.html) provided by the Mallinckrodt General Clinical Research Center, Massachusetts General Hospital. The sample size was determined to produce a study power of 80% and the statistical significance was set to 95%, based on the ovarian stromal PI differences between PCOS women and controls reported by Adali et al. [13] (1.40 ± 0.63 *vs* 2.90 ± 0.20).

3. Results

The baseline characteristics of each group are presented in Table 1, showing no differences among the patients randomized to each drug ($p > 0.05$). Of the 101 recruits, only 86 (OCP: $n = 44$; metformin: $n = 42$) completed the 6-month treatment, others withdrew from the study due to side effects, moving away or unwillingness to adhere to therapy guidelines (Fig. 1). The data of those patients withdrawn from the study were excluded from the final statistical analysis.

The correlations between ovarian Doppler values and hormonal parameters are shown in Table 2. A significant negative correlation of serum LH with PI ($r = -0.532$, $p < 0.001$) and RI ($r = -0.497$, $p < 0.001$), serum TT with PI ($r = -0.486$, $p < 0.001$) and RI ($r = -0.438$, $p < 0.001$) and FIN levels with PI ($r = -0.464$, $p < 0.001$) and RI ($r = -0.428$, $p < 0.001$) were noted. Serum FSH, SHBG and DHEAS did not correlate with any Doppler parameter.

The changes in baseline characteristics of both the groups post-treatment are shown in Table 3. Significant reductions in BMI and WC were observed in the Metformin group compared to the OCP group. There was a significant improvement in the hirsutism scores in both groups, however, participants receiving OCP showed significant improvement compared to metformin recipients. The menstrual cycle duration showed a normalization trend in the Metformin group. Among the hormonal parameters, LH, TT and DHEAS decreased and SHBG increased significantly in both groups after treatment; however, the post treatment differences were more noticeable in the OCP group. Among the metabolic parameters FG, FIN and HOMA-IR decreased significantly in the Metformin group compared to the OCP group. The lipid profile showed a significant increase in HDL-C levels in both groups and a slight increase in TG levels in the OCP group. Both ovarian Doppler parameters, PI and RI, increased post treatment; however, an increase in PI values was more evident in the OCP group.

Correlations between hormonal and Doppler parameter changes post treatment are presented in Table 4. We found significant negative correlations of a change in LH levels with changes in PI ($r = -0.372$, $p < 0.05$) and RI ($r = -0.593$, $p < 0.001$) values after

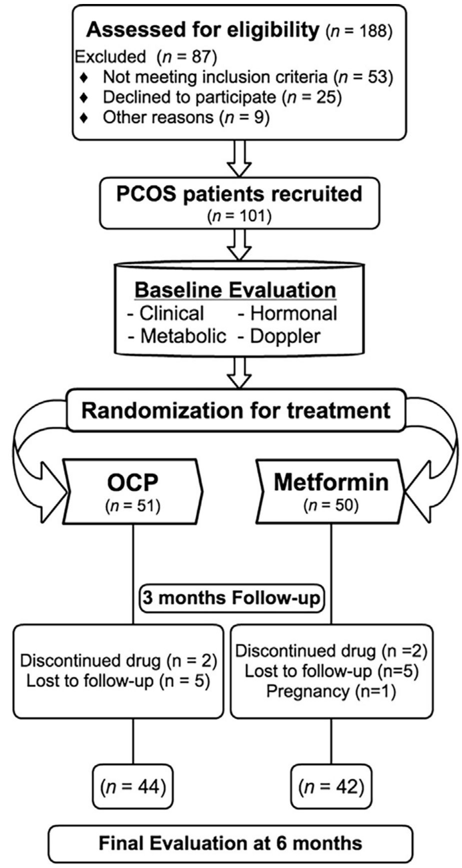

Fig. 1. Flow of the study.

Table 1
Baseline characteristics of the PCOS women in OCP and Metformin treatment groups.

	Metformin group ($n = 50$)	OCP group ($n = 51$)	p[a]
Clinical parameters			
Age	27.0 ± 5.2	26.8 ± 4.2	0.704
BMI (kg/m^2)	25.7 ± 2.6	25.6 ± 2.7	0.897
WC (cm)	87.5 ± 6.6	87.6 ± 7.1	0.976
Cycle duration	82.5 ± 16.3	85.9 ± 14.9	0.484
Hirsutism score	8 ± 2	8 ± 2	0.596
Hormonal parameters			
LH (mIU/ml)	11.2 ± 3.0	11.3 ± 2.8	0.711
FSH (mIU/ml)	6.6 ± 1.3	6.8 ± 1.3	0.39
TT (nmol/dL)	2.4 ± 0.4	2.3 ± 0.5	0.865
SHBG (nmol/L)	44.7 ± 7.5	44.6 ± 7.1	0.834
DHEAS (μg/dL)	239.4 ± 84.0	249.9 ± 77.5	0.401
Metabolic parameters			
TC (mg/dL)	170.6 ± 19.0	171.6 ± 18.5	0.682
HDL-C (mg/dL)	49.9 ± 5.7	49.2 ± 6.1	0.582
LDL-C (mg/dL)	89.7 ± 7.7	88.4 ± 8.6	0.522
TG (mg/dL)	116.5 ± 14.5	116.5 ± 15.4	0.992
FG (mg/dL)	86.9 ± 6.0	87.0 ± 7.2	0.992
FIN (mIU/L)	17.2 ± 4.5	17.4 ± 5.4	0.984
HOMA-IR	3.7 ± 1.1	3.7 ± 1.0	0.952
Ovarian Doppler parameters			
PI	1.20 ± 0.30	1.26 ± 0.33	0.596
RI	0.54 ± 0.10	0.54 ± 0.10	0.646

Data are expressed as means ± SD. BMI, body mass index; WC, waist circumference; LH, luteinizing hormone; FSH, follicle-stimulating hormone; TT, total testosterone; SHBG, sex hormone-binding globulin; DHEAS, dehydroepiandrosterone sulfate; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; FG, fasting glucose; FIN, fasting insulin; HOMA-IR, homeostatic model assessment of insulin resistance; PI, pulsatility index; RI, resistive index.

[a] An unpaired t-test or a Mann–Whitney U test was used to compare the baseline characteristics between the two treatment groups.

Table 2
Pearson correlation coefficients between parameters of ovarian blood flow with hormonal parameters in PCOS women ($n = 101$).

	LH	FSH	TT	SHBG	DHEAS	FIN
PI	−0.532**	−0.146	−0.486**	0.029	0.136	−0.479**
RI	−0.497**	−0.118	−0.438**	0.002	0.117	−0.428**

LH, luteinizing hormone; FSH, follicle-stimulating hormone; TT, total testosterone; SHBG, sex hormone-binding globulin; DHEAS, dehydroepiandrosterone sulfate; FIN, fasting insulin; PI, pulsatility index; RI, resistive index.

* $p < 0.05$.

** $p < 0.001$.

Table 3
Changes in clinical, hormonal, metabolic and ovarian Doppler parameters of PCOS women submitted to treatment with OCP or metformin for 6 months.

Parameters	Metformin group			OCP group			p^b
	Pre-treatment (n = 42)	Post-treatment (n = 42)	p^a	Pre-treatment (n = 44)	Post-treatment (n = 44)	p^a	
Clinical parameters							
BMI (kg/m²)	25.7 ± 2.7	24.6 ± 1.6	<**0.001**	25.6 ± 2.8	25.8 ± 2.8	0.085	**0.038**
WC (cm)	87.4 ± 6.9	84.4 ± 4.2	<**0.001**	87.7 ± 7.4	87.9 ± 7.4	0.067	**0.026**
Cycle duration	84.4 ± 14.7	39.9 ± 10.2	<**0.001**	84.4 ± 13.3	33.8 ± 6.9	<**0.001**	**0.002**
Hirsutism	8 ± 2	7 ± 2	<**0.001**	8 ± 3	5 ± 2	<**0.001**	<**0.001**
Hormonal parameters							
LH (mIU/ml)	11.2 ± 3.1	9.40 ± 2.4	<**0.001**	11.5 ± 2.8	8.4 ± 1.4	<**0.001**	**0.008**
FSH (mIU/ml)	6.6 ± 1.3	6.5 ± 1.0	0.968	6.7 ± 1.4	6.8 ± 1.2	0.053	0.39
TT (ng/dL)	2.3 ± 0.5	1.8 ± 0.4	<**0.001**	2.4 ± 0.5	1.6 ± 0.3	<**0.001**	**0.005**
SHBG (nmol/L)	45.3 ± 7.2	79.6 ± 14.8	<**0.001**	44.5 ± 7.4	94.5 ± 19.3	<**0.001**	<**0.001**
DHEAS (μg/dL)	236.0 ± 84.1	163.5 ± 54.5	<**0.001**	244.8 ± 73.5	126.4 ± 32.7	<**0.001**	<**0.001**
Metabolic parameters							
TC (mg/dL)	169.7 ± 19.2	169.0 ± 18.2	0.803	171.1 ± 18.4	174.1 ± 19.3	0.07	0.194
HDL-C (mg/dL)	49.9 ± 5.9	53.6 ± 4.1	<**0.001**	49.3 ± 6.4	53.2 ± 4.1	<**0.001**	0.535
LDL-C (mg/dL)	89.3 ± 7.6	89.4 ± 7.6	0.114	88.9 ± 8.5	89.3 ± 8.4	0.147	0.779
TG (mg/dL)	116.6 ± 13.3	117.5 ± 13.9	0.064	117.3 ± 15.4	118.5 ± 15.4	**0.005**	0.667
FG (mg/dL)	86.9 ± 6.0	85.5 ± 5.5	**0.002**	86.5 ± 7.2	87.6 ± 6.0	0.165	0.084
FIN (IU/dL)	17.2 ± 5.3	11.8 ± 3.9	<**0.001**	17.3 ± 4.5	17.0 ± 3.9	0.904	<**0.001**
HOMA-IR	3.5 ± 1.2	2.5 ± 0.8	<**0.001**	3.7 ± 1.0	3.7 ± 0.9	0.881	<**0.001**
Ovarian Doppler parameters							
PI	1.21 ± 0.31	1.88 ± 0.38	<**0.001**	1.24 ± 0.35	2.09 ± 0.51	<**0.001**	**0.041**
RI	0.54 ± 0.11	0.72 ± 0.13	<**0.001**	0.53 ± 0.11	0.77 ± 0.11	<**0.001**	0.07

Data are expressed as means ± SD. Bold values represent statistically significant *p*-values. BMI, body mass index; WC, waist circumference; LH, luteinizing hormone; FSH, follicle-stimulating hormone; TT, total testosterone; SHBG, sex hormone-binding globulin; DHEAS, dehydroepiandrosterone sulfate; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; FG, fasting glucose; FIN, fasting insulin; HOMA-IR, homeostatic model assessment of insulin resistance; PI, pulsatility index; RI, resistive index.

[a] A paired *t*-test or a Wilcoxon signed-rank test was used for comparison of baseline and post-treatment changes within the treatment groups.

[b] An unpaired *t*-test or a Mann–Whitney *U* test was used for comparison of post-treatment changes between OCP and the Metformin group.

Table 4
Pearson correlation coefficients between changes in ovarian Doppler indices and hormonal parameters in PCOS women post-treatment.

	OCP group (n = 44)		Metformin group (n = 42)	
	Δ-PI	Δ-RI	Δ-PI	Δ-RI
Δ-LH	**−0.372***	**−0.593****	−0.292	−0.279
Δ-FSH	0.116	−0.195	−0.226	−0.299
Δ-TT	−0.158	**−0.557****	−0.232	−0.213
Δ-SHBG	**0.319***	0.268	−0.05	−0.153
Δ-DHEAS	−0.275	0.201	0.025	0.196
Δ-FIN	0.022	0.269	**−0.442****	**−0.473****

Δ indicates difference between post-treatment and baseline value. Bold values represent statistically significant *p*-values. LH, luteinizing hormone; FSH, follicle-stimulating hormone; TT, total testosterone; SHBG, sex hormone-binding globulin; DHEAS, dehydroepiandrosterone sulfate; FIN, fasting insulin; PI, pulsatility index; RI, resistive index.

* $p < 0.05$.

** $p < 0.001$.

OCP treatment. Similarly, changes in serum levels of TT showed a significant negative correlation with a change in RI ($r = -0.557$, $p < 0.001$), and SHBG showed a significant positive correlation with changes in PI ($r = 0.319$, $p < 0.05$) after OCP treatment. Only a change in serum FIN levels correlated with changes in PI ($r = -0.442$, $p < 0.001$) and RI ($r = -0.473$, $p < 0.001$) values in the Metformin treatment group. Though a negative correlation was seen between changes in serum levels of LH and TT with Doppler parameters PI and RI, it did not reach statistical significance.

4. Discussion

To the best of our knowledge, this is the first randomized controlled study, which comparatively evaluated the effects of OCP and metformin therapy-related changes on ovarian blood flow in women with PCOS. We found a marked decrease in ovarian stromal vascularity that correlated with a decline in serum LH and androgen levels after OCP treatment. Similarly, decreasing stromal vascularity after metformin correlated with an improvement of insulin resistance.

Doppler imaging is an effective and non-invasive method for the assessment of blood flow in the ovarian stroma in PCOS patients [11]. In agreement with most studies, we found significantly lower PI and RI values of ovarian blood flows and elevated serum levels of LH, androgens and FIN in women with PCOS compared to the normal reference ranges [13–15]. We found ovarian stromal artery PI and RI to be inversely correlated with serum LH and TT levels in patients with PCOS. We also found a significant inverse correlation between serum fasting insulin and increased vascularity of the ovarian stroma in patients with PCOS. However, few studies contradict our findings, which found similar basal ovarian stromal blood flow between women with PCOS and the controls or did not find any predictive value of stromal flow [16,17].

Experimental studies have found that an elevated LH level is associated with hyperplasia of ovarian thecal and stromal cells and may be responsible for the increased ovarian androgen production by theca cells [18]. This androgen overproduction leads to increased stromal vascularization. Insulin also promotes angiogenesis and vasodilatation in ovarian stromal tissue through various mechanisms such as activation of vascular endothelium, IGF receptor stimulation, and relaxation of the vascular smooth muscle. Testosterone may also affect ovarian perfusion indirectly by association with additional parameters, such as insulin resistance [7].

Consistent with previous reports, results from this clinical trial showed that OCP is a more efficient way of treating hyperandrogenism and the restoration of regular menstrual cycles, whereas metformin is more effective in improving insulin resistance and decreasing BMI and WC [19]. We found the PI and RI of the ovary to be increased compared to baseline values after both OCP and metformin therapy. These findings suggest that the decrease in the ovarian stromal blood flow after treatment may be regarded as a positive result. The decrease in stromal blood flow was more prominent in the OCP group, which can be explained by the greater suppression of LH by treatment with OCP rather than metformin. We also mentioned a dramatic fall in ovarian blood flow in parallel with LH and testosterone levels with OCP treatment, whereas there was a fall in ovarian blood flow in parallel with serum FIN levels with metformin treatment. This finding might suggest a differential mechanism of action of both drugs on hormonal parameters, which lead to a reduction in ovarian vascularity.

To date, a limited number of studies have assessed the effects of the various drugs/interventions used in the treatment of PCOS on ovarian stromal vascularity. Okyay et al. evaluated the effects of 3 months treatment with OCP on ovarian stromal blood flow in both PCOS women and controls and found a significant reduction in vascularity, especially in women with PCOS [20]. Similarly, another study evaluated the effect of metformin on ovarian 3D power Doppler indices and found improvement in ovarian stromal blood flow and hormonal profiles in normal weight PCOS women [21]. PSV was correlated with HOMA-IR values both before and after treatment with metformin. Recently, Giampaolino et al. compared the ovarian Doppler indices before and after transvaginal hydrolaparoscopy ovarian drilling, an alternative to ovarian drilling in clomifene citrate resistant PCOS women, and found a significant reduction in ovarian vascularity after the procedure [22].

However, our study is not free from limitations. The first limitation is the non-inclusion of another placebo group of women with PCOS, which could have helped to interpret the findings in a more scientific way, but this was avoided due to ethical considerations. Second, we did not evaluate ovulation rates so could not establish the association of hormonal and Doppler changes in women who ovulated. We evaluated the changes over a relatively short duration of treatment and since PCOS is a chronic disorder it may require long-term treatment as well as a follow-up to ascertain whether the changes are persistent even after stopping treatment.

In conclusion, our observations demonstrated that both OCP and metformin therapy decreased ovarian vascularization in PCOS women and this decrease was especially noticeable in women treated with OCP. They may suggest that both of these drugs perhaps act through different mechanisms in the ovary and lead to a differential reduction in the ovarian vasculature. This further emphasizes the potential of ovarian Doppler measurements in predicting the treatment response in PCOS women. However, we believe that further research with a larger sample size is needed to determine the associations of changes in ovarian Doppler parameters with the occurrence of ovulation and future pregnancy outcomes.

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Declarations of interest

None.

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Glossary

Δ: Difference between pre and post-treatment
BMI: Body mass index
WC: Waist circumference
LH: Luteinizing hormone
FSH: Follicle-stimulating hormone
TT: Total testosterone
SHBG: Sex hormone-binding globulin
DHEAS: Dehydroepiandrosterone sulfate
TC: Total cholesterol
LDL-C: Low-density lipoprotein cholesterol
HDL-C: High-density lipoprotein cholesterol
TG: Triglyceride
FG: Fasting glucose
FIN: Fasting insulin
PI: Pulsatility index
RI: Resistive index
HOMA-IR: Homeostatic model assessment of insulin resistance