A comparison of Doppler measures of ovarian blood flow between women with and without ovarian dysfunction and correlations of Doppler indices with ovarian dysfunction markers: a meta-analysis

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Background: Doppler ultrasonography is used to study ovarian vascular characteristics. However, the outcomes are reported with a considerable variability in literature. Here we review the differences in Doppler ultrasound-measured ovarian blood flow indices between women with and without ovarian dysfunction and seeks correlations between Doppler measures and ovarian markers.

Methods: A literature search was conducted in electronic databases (Google Scholar, Ovid, PubMed, Science Direct, and Springer) to identify studies that used Doppler for ovarian blood flow examination and reported Doppler measures in women with and without ovarian dysfunction and/or the correlations between wDoppler indices and markers of ovarian dysfunction. After quality assessment of included studies, a meta-analysis of weighted mean differences (WMDs) between women with and without ovarian dysfunction in vascularization index (VI), flow index (FI), vascularization flow index (VFI), pulsatility index (PI) and resistance index (RI) was performed. Correlation coefficients between Doppler indices and markers of ovarian dysfunction were pooled to achieve overall estimates.

Results: A total of 27 studies [2,377 women with ovarian dysfunction and 308 controls; age 27.7 years, 95% confidence interval (CI): 26.4 to 29.1] were included. These studies were of moderate quality. The VI (WMD 9.75; P<0.0001), FI (WMD 2.73; P<0.0001), and VFI (WMD 1.29; P<0.0001) were significantly higher whereas PI (WMD −1.08; P=0.001) and RI (WMD −0.26; P<0.0001) were significantly lower in women with polycystic ovarian syndrome (PCOS) than in normal women. In women undergoing *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI), antral follicle count was positively correlated with VI (r=0.24; P=0.001), FI (r=0.42; P<0.0001), and VFI (r=0.25; P=0.002). In women with PCOS, testosterone had statistically non-significant correlations with VI (r=0.40; P=0.081), and VFI (r=0.39; P=0.063) and was inversely correlated with PI (r=−0.30; P<0.0001) and RI (r=−0.48; P<0.0001). In women with PCOS, luteinizing hormone (LH) was inversely correlated with PI (r=−0.26; P=0.086) and RI (r=−0.25; P=0.007).

Conclusions: Doppler indices are found significantly different in women with and without ovarian dysfunction and have significant correlations with markers of ovarian dysfunction. These results support the use of Doppler ultrasound to examine ovarian dysfunction. High statistical heterogeneity observed herein should be studies in future investigations.

Keywords: Doppler ultrasonography; ovarian dysfunction; blood-flow; stroma; correlation

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Introduction

Ultrasound-based diagnostics have been in use since the 1940s. Whereas conventional ultrasound can visualize two-dimensional (2D) sections, modern three-dimensional (3D) ultrasound can provide additional information such as volume and orthogonal plane metrics (1). Doppler ultrasonographic methods measure the change in ultrasound pulse when it is reflected by an object having some velocity in the beam's direction (2). Ultrasonography has an important role in reproductive medicine and assisted reproductive technologies because of its utility for several purposes including ovarian response monitoring, assessment of endometrial receptivity, transvaginal aspiration of oocytes, transcervical transfer of the embryo to the uterus, pregnancy monitoring, and fetal health assessment. It is also used to measure ovarian volume, antral follicular count (AFC), ovarian stromal blood flow, and to evaluate ovarian function after vascular embolization (3-6).

Transvaginal Doppler ultrasonography has advanced the pathophysiological understanding of blood flow dynamics in the female pelvis (7). It is a useful method of examining the blood flow through the uterus, ovaries, and even in the follicles (1). Transvaginal Doppler ultrasonography has become an important component of assisted reproduction procedures. It can assist in the examination of folliculogenesis, the selection of oocytes, and the assessment of perifollicular vascularity of the ovary that can improve implantation prospects (8,9). Doppler pulsatility index (PI) and resistance index (RI) on the day of embryo transfer may predict conception chances in women undergoing in vitro fertilization (IVF) (10).

Although 2D Doppler ultrasound can also provide information about blood flow and vascularization, its measurements are based on a single perifollicular artery. Moreover, it is insonation angle-dependent, which means that it remains problematic in organs like ovaries which contain thin and tortuous arteries. The 3D Doppler ultrasound is more efficient in measuring total vascularization and blood flow in a selected area. Power Doppler ultrasound increases the reliability of blood flow measurements because of its lower dependence on the angle of insonation. However, it represents whole blood flow from a single perifollicular vascular plane. The 3D power Doppler ultrasound is the advanced form that can account for all ovarian vessels to yield flow index (FI) which is a measure of blood flow intensity, and vascularization index (VI) which is a measure of vessel density in the whole ovary (11-13).

Approximately 15% of reproductive-aged couples are affected by infertility (https://www.who.int/health-topics/infertility#tab=tab_1). Several causes of infertility have been identified; polycystic ovarian syndrome (PCOS) being the most common as 75% of women with PCOS have anovulatory infertility (14). Use of non-invasive techniques for the detection of ovarian dysfunction by studying ovarian blood flow parameters can improve the diagnosis and prognosis. Although many studies have utilized Doppler ultrasonography for women with ovarian dysfunction, the outcomes reported have not always been consistent. For example, a study found no differences (15), but others have reported significant differences (16,17) in Doppler indices between women with and without PCOS. Some authors have found no correlation between Doppler FI or VI and antral follicles in women with infertility problems (15,18), others have found moderate to high correlations (11,16,19). Similarly, whereas good correlations are observed between PI and testosterone levels in women with PCOS by some

Highlight box

Key findings

- Women with ovarian dysfunction exhibit significantly different Doppler ultrasound indices than normal women and Doppler ultrasound indices have significant correlations with ovarian markers.

What is known and what is new?

- Doppler ultrasound is an important component of reproductive medicine and is also used to detect blood flow and vascularization abnormalities in ovaries.
- Doppler indices differ in women with and without ovarian dysfunction and corelate with disease markers.

What is the implication, and what should change now?

- These outcomes support the use of Doppler ultrasound in the examination of ovarian dysfunction. However, high statistical heterogeneity should be studied in future investigations.

authors (20,21), others have reported weak correlations (22,23). This necessitated a systematic review of this subject that could help in understanding how efficient Doppler ultrasound is to detect ovarian dysfunction. In this study, we aimed to evaluate the strength of relationship between Doppler ultrasonographic indices and ovarian dysfunction markers. We conducted a literature search to identify studies reporting the associations between Doppler ultrasonographic indices and pathological markers of ovarian dysfunction, and further performed meta-analyses to estimate differences in Doppler indices between women with and without ovarian dysfunction and to pool correlation coefficients between Doppler indices and markers of ovarian dysfunction. Patients: PCOS/women with polycystic ovaries/women undergoing intracytoplasmic sperm injection (ICSI) or IVF; control: normal women without ovarian dysfunction; outcomes: mean differences in Doppler indices between women with and without ovarian dysfunction/correlation coefficients between Doppler indices and ovarian dysfunction markers; study design: any. We present the following article in accordance with the MOOSE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5813/rc).

Methods

Eligibility criteria

A study was included if it utilized Doppler ultrasonography to observe ovarian blood flow parameters and reported the differences in Doppler indices between women with and without ovarian dysfunction and/or the correlation between a Doppler ultrasound index and an ovarian dysfunction marker. A study was excluded for one or more of the following reasons: (I) it utilized Doppler ultrasonography to investigate the effect of a therapy or treatment; (II) it reported associational outcomes other than correlation coefficients; (III) it reported the correlation of Doppler ultrasound index with an indirect measure such as the difference between post- and pre-treatment values.

Literature search

For the acquisition of required data, a literature search was conducted in the Google Scholar, Ovid, PubMed, Science Direct, and Springer online databases. Most relevant keywords were used in logical combinations. These included Doppler ultrasound, ultrasonography, ovary, ovarian, stromal blood flow, vascularization, resistance, pulsatility, correlation, infertility, infertile, polycystic, and index. Bibliographic sections of identified research articles were also screened to supplement keyword-based searches. Two reviewers carried out literature search independently and then unified their outputs. Disagreements were resolved with mutual consultations. The literature search was restricted to research articles published in the English language before February 2022.

Statistical analysis

Demographic, anthropometric, clinical, endocrinological, and ultrasonographic data, study design and conduct features, outcome measures, and outcome data were extracted from research articles of selected studies. Two reviewers extracted data independently and then checked for accuracies. The quality of the included studies was assessed with the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).

Doppler ultrasonography measures of interest included VI, FI, vascularization flow index (VFI), PI, and RI. Meta-analyses of weighted mean differences (WMDs) in VI, FI, VFI, PI, and RI between women with and without ovarian dysfunction were performed under the random-effects model where the overall estimates were based on DerSimonian-Laird method of pooled estimates. A P value of <0.05 was considered to show a significant difference.

Correlation coefficients between Doppler ultrasonography indices and ovarian dysfunction markers or related pathological factors were converted to Fisher's z-scores and pooled under a random-effects model by deriving variance from the study sample size. The DerSimonian-Laird method was used for the meta-analyses to obtain a weighted average and its 95% confidence intervals (CIs) of z-scores which were then back-transformed to correlation coefficient for interpretation.

The I^2 index was used to estimate between-study inconsistency in the outcomes. The I^2 provides an estimate of the proportion of variance in the outcomes that cannot be attributed to sampling error alone and thus reflects actual heterogeneity in the outcomes. Stata software (Stata Corporation; College Station, TX, USA) was used for meta-analyses and graphics.

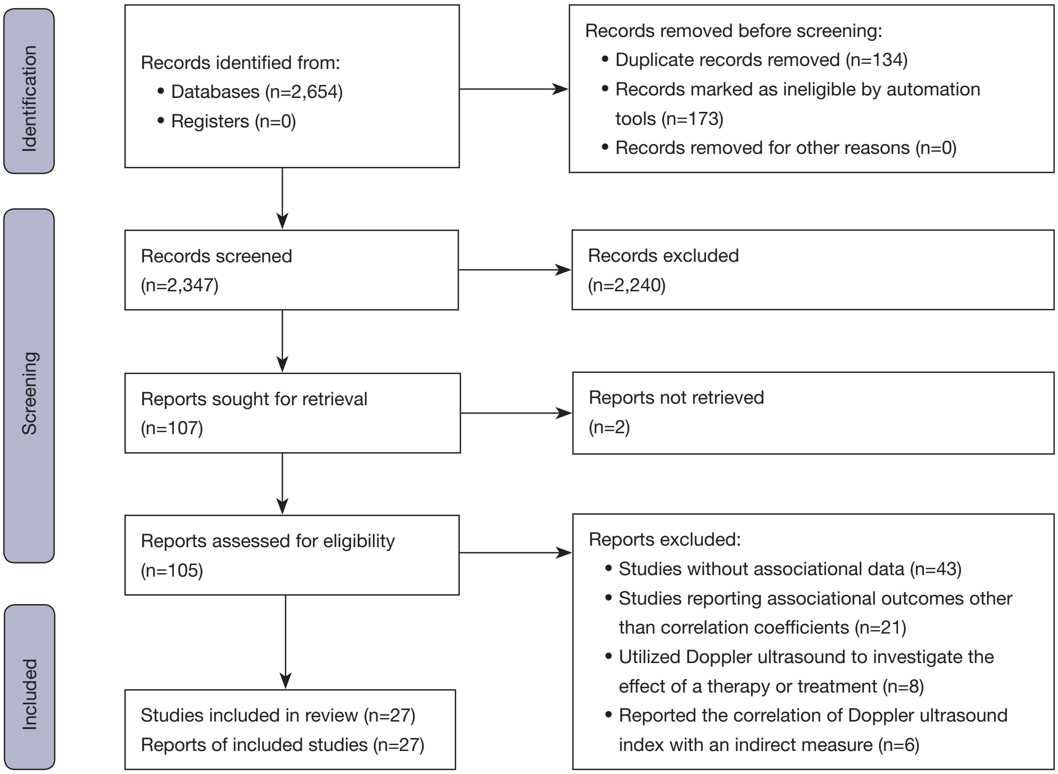

Figure 1 Flowchart of the study screening and selection process.

Results

A total of 27 studies, including studies (3,11,12) and studies (15-38), were included (*Figure 1*). These studies recruited 2,377 women including 1,512 with PCOS, 151 with polycystic ovary (PCO), and 714 women undergoing IVF/ICSI. In the meta-analysis of mean differences in Doppler indices between women with and without ovarian dysfunction, 308 normal women acted as controls. All were cross-sectional studies. Doppler examinations were performed during the early follicular phase in women with PCOS and during the mid-luteal phase in IVF/ICSI subjects.

The average age of these women was 27.7 years (95% CI: 26.4 to 29.1) and the average body mass index (BMI) was 25.2 kg/m^2 (95% CI: 23.8 to 26.6). The important characteristics of the included studies are displayed in Table S1. The quality of the included studies was moderate in general. An assessment of the quality of included studies is presented in Table S2.

The VI [WMD 9.75 (95% CI: 6.17, 13.32); P<0.0001], FI [WMD 2.73 (95% CI: 2.26, 3.2); P<0.0001], and VFI [WMD 1.29 (95% CI: 0.81, 1.76); P<0.0001] were significantly higher in women with PCOS than in normal women, whereas the PI [WMD −1.08 (95% CI: −1.71, −0.44); P=0.001] and RI [WMD −0.26 (95% CI: −0.39, −0.13); P<0.0001] were significantly lower in women with PCOS in comparison with normal women (*Figure 2*). I^2 values were high in this meta-analysis.

In IVF/ICSI subjects, the antral follicle count (AFC) was significantly positively correlated with VI [r=0.24 (95% CI: 0.12, 0.37); P=0.001], FI [r=0.42 (95% CI: 0.18, 0.67); P<0.0001], and VFI [r=0.25 (95% CI: 0.09, 0.41); P=0.002] but AFC was not significantly correlated with either PI [r=−0.004 (95% CI: −0.15, 0.14); P=0.963] or RI [r=0.06 (95% CI: −0.20, 0.32); P=0.670] (*Figure 3*). I^2 values were moderate to high in this meta-analysis.

In women with PCOS, the testosterone levels had statistically non-significant positive correlation with VI [r=0.40 (95% CI: −0.05, 0.85); P=0.081], and VFI [r=0.39 (95% CI: −0.02, 0.80); P=0.063] and was inversely correlated with both PI [r=−0.30 (95% CI: −0.39, −0.21); P<0.0001] and RI [r=−0.48 (95% CI: −0.60, −0.36); P<0.0001]. I^2 values were moderate to high in this meta-analysis (*Figure 4*). Dehydroepiandrosterone levels were

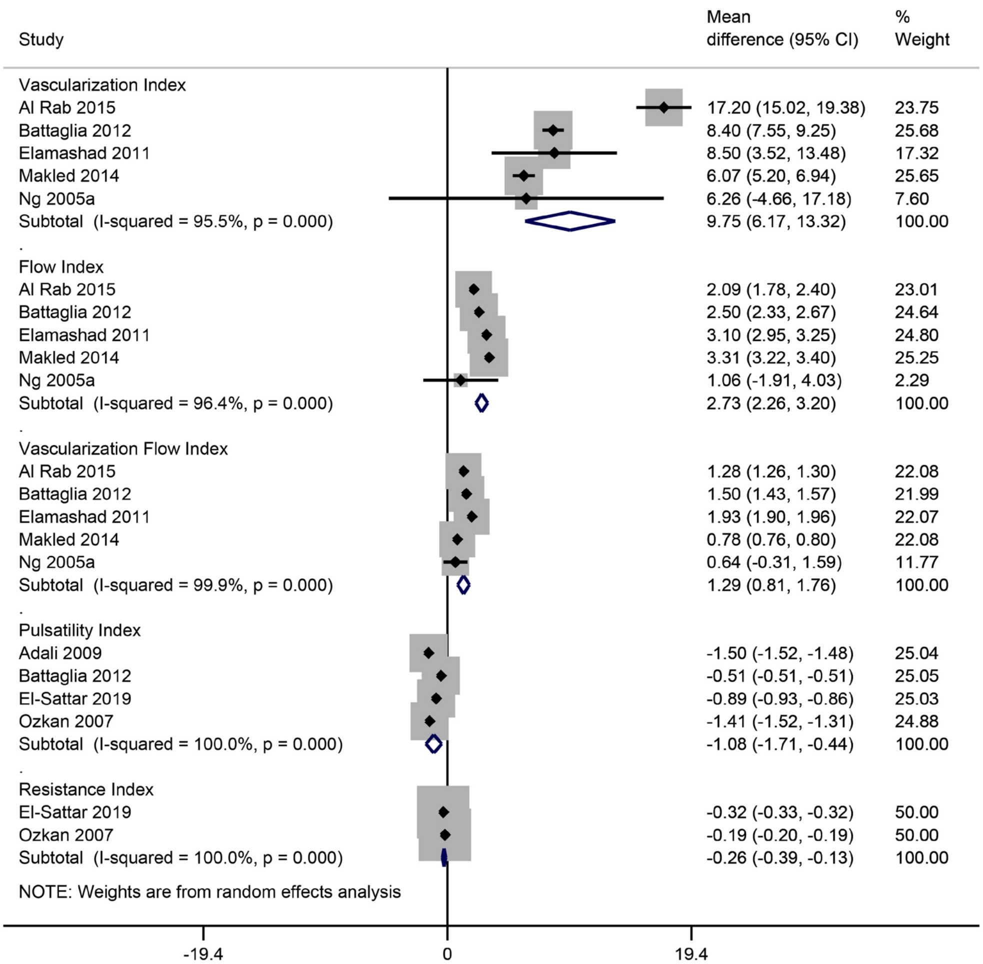

Figure 2 Forest graph showing the outcomes of the meta-analysis of WMDs in Doppler ultrasonography indices between PCOS patients and healthy controls. CI, confidence interval; WMDs, weighted mean differences; PCOS, polycystic ovarian syndrome.

also inversely correlated with PI [r=−0.24 (95% CI: −0.46 to −0.02); P=0.032] (Figure S1).

In women with PCOS, the luteinizing hormone (LH) levels were inversely correlated with PI [r=−0.26 (95% CI: −0.55, 0.04); P=0.086] and RI [r=−0.25 (95% CI: −0.43, −0.07); P=0.007] (Figure S2). Anti-Mullerian hormone (AMH) levels were positively correlated with VI, FI, and VFI in women with PCOS (*Table 1*).

Ovarian volume was not significantly correlated with any of the Doppler ultrasonography indices, although in general, it was positively correlated with VI, FI, and VFI, and was negatively correlated with PI and RI (Figure S3). Hirsutism score [r=−0.38 (95% CI: −0.56, −0.20); P<0.0001] and homeostasis model assessment-estimated insulin resistance [r=−0.21 (95% CI: −0.34, −0.08); P=0.001] were negatively correlated with PI. Age had no significant correlation with any Doppler index. The BMI was inversely correlated with PI but had no significant correlation with any other Doppler index (*Table 1*).

Discussion

This meta-analysis found that Doppler blood flow indices are significantly different in women with and without ovarian dysfunction and have significant correlations with ovarian dysfunction markers. The VI, FI, and VFI were higher, but PI and RI were lower in women with PCOS than in normal women. Positive correlations were found between AFC and VI, FI, or VFI in the IVF/ICSI cases. In women with PCOS, testosterone and dehydroepiandrosterone levels correlated positively with VI, FI, and VFI and correlated negatively with PI and RI.

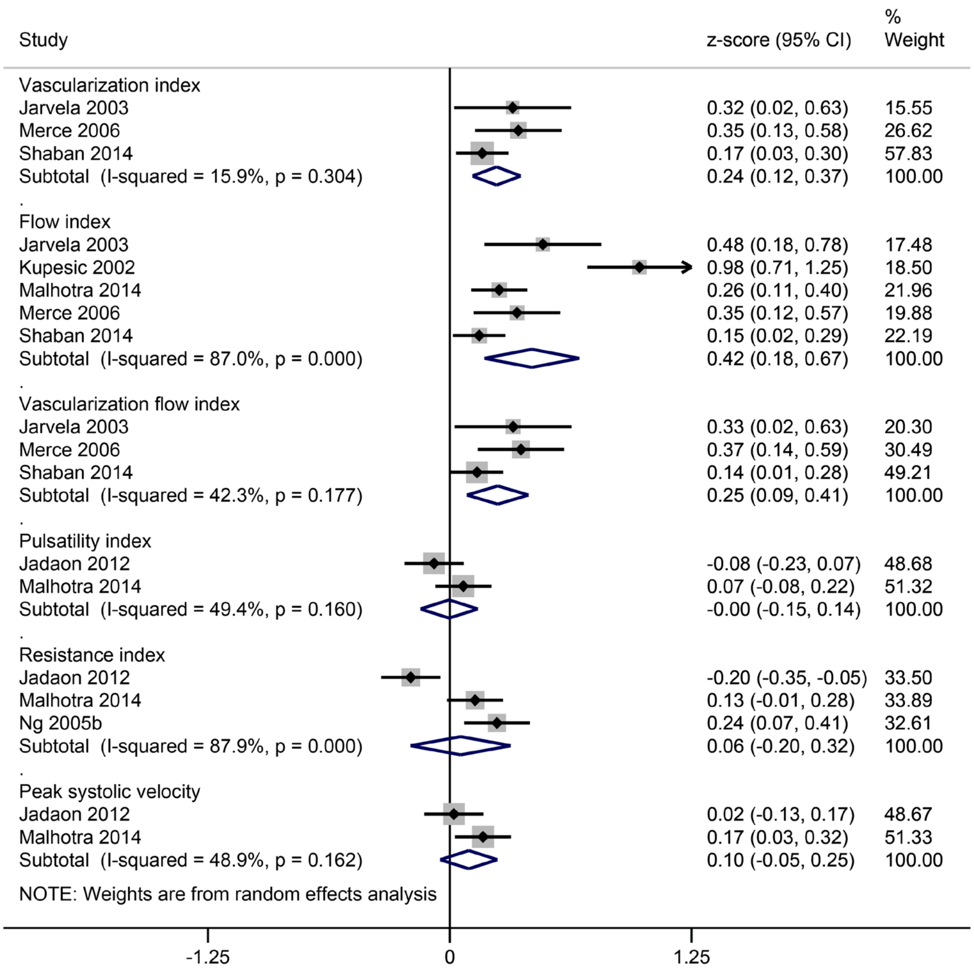

Figure 3 Forest graph showing the pooled z-scores of the correlations between antral follicle count and Doppler ultrasonography indices in women undergoing IVF/ICSI. CI, confidence interval; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection.

In general, androgens were found to correlate positively with FI, VI, and VFI, but negatively with PI and RI in women with PCOS in the present study. In women with normal menstrual cycles, testosterone correlates with retrieved oocytes (39,40). Many studies have found that 3D Doppler ultrasonographic blood flow indices are different in women with PCOS and normal women (16,17,27,41,42). It is suggested that increased ovarian blood flow in PCOS patients, which is also observed in normal ovaries, may affect, or may be affected by androgen levels directly or indirectly (29). Less data were available to study the correlation between estradiol and Doppler indices in the present study. Kupesic *et al.* (19) found a strong positive correlation (r=0.793) between the estradiol levels and FI in women undergoing IVF. Battaglia *et al.* (25) and Carmina *et al.* (29) found significant negative correlations (r=−0.33 and −0.38, respectively) between estradiol levels and PI in PCOS patients.

Among the included studies, Kupesic *et al.* (19) found a stronger negative correlation (r=−0.67) between follicle stimulating hormone (FSH) and FI in infertile women with normal FSH levels who underwent IVF procedures. Al-Rab *et al.* (16) found no correlation between FSH and either FI or VI in PCOS patients. Outside this meta-analysis, Wu *et al.* (43) found strong negative correlations between FSH and ovarian volume, antral follicle count, peak flow velocity and end-diastolic peak velocity in infertile women. We found fewer studies to report the correlations between AMH and Doppler ultrasonography measures. Elmashad *et al.* (17) and Kamal *et al.* (33) found significant positive

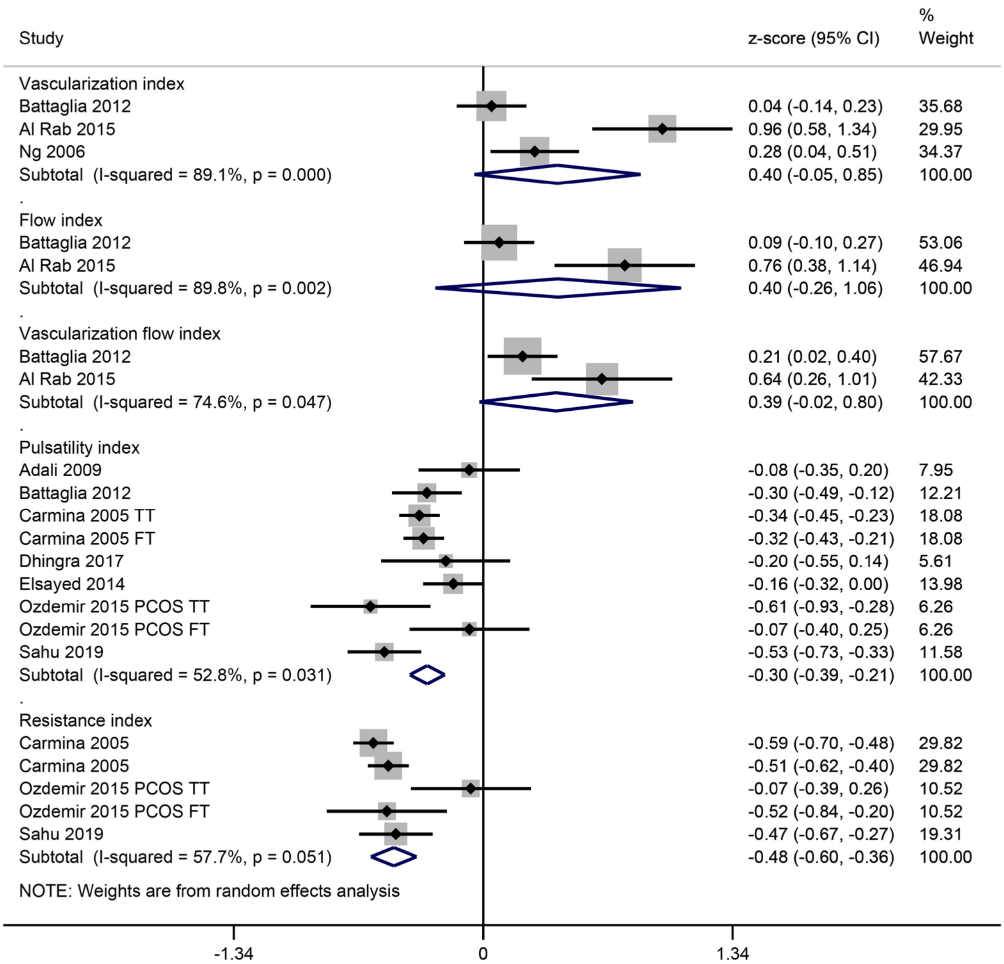

Figure 4 Forest graph showing the pooled z-scores of the correlations between testosterone and Doppler ultrasonography indices in women with PCOS. CI, confidence interval; TT, total testosterone; FT, free testosterone; PCOS, polycystic ovarian syndrome.

Table 1 Pooled correlation coefficients and their 95% CIs of Doppler ultrasound indices with other covariates

Covariate	FI	VI	VFI	PI	RI
Ovarian volume	0.224 [−0.118, 0.518]; P=0.196; I^2=90%; n=5	0.107 [−0.104, 0.308]; P=0.320; I^2=65%; n=4	0.080 [−0.172, 0.322]; P=0.539; I^2=76%; n=4	−0.160 [−0.358, 0.060]; P=0.157; I^2=74%; n=3	−0.184 [−0.424, 0.082]; P=0.174; I^2=68%; n=2
AMH	0.71 [0.56, 0.86]; P<0.0001; I^2=0%; n=2	0.61 [0.46, 0.76]; P=0.00001; I^2= 0%; n=2	0.45 [0.10, 0.79]; P=0.011; I^2=78%; n=2		
Age	−0.264 [−0.612, 0.169]; P=0.230; I^2=89%; n=4	−0.122 [−0.397, 0.171]; P=0.414; I^2=76%; n=4	−0.059 [−0.400, 0.297]; P=0.752; I^2=75%; n=3	0.001 [−0.121, 0.122]; P=0.991; I^2=0%; n=2	−0.017 [−0.233, 0.201]; P=0.882; I^2=61%; n=2
BMI	−0.200 [−0.559, 0.221]; P=0.353; I^2=91%; n=5	−0.360 [−0.766, 0.251]; P=0.244; I^2=94%; n=3	−0.262 [−0.720, 0.354]; P=0.41; I^2=91%; n=3	−0.114 [−0.216, −0.012]; P=0.029; I^2=0%; n=4	−0.056 [−0.205, 0.096]; P=0.468; I^2=0%; n=2

CI, confidence interval; FI, flow index; VI, vascularization index; VFI, vascularization flow index; PI, pulsatility index; RI, resistance index; AMH, anti-Mullerian hormone; BMI, body mass index.

correlations between AMH levels and VI and FI in women with PCOS. Several studies of infertile women have reported that serum AMH levels correlate positively with AFC whereas FSH levels correlate negatively with AFC (44-46). It is thought that an increased ovarian stromal blood flow is due to increased expression of vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF) which may cause AMH to increase secondary to androgen secretion (17). Among the included studies of the present review, Adali *et al.* (22) reported an inverse correlation between IGF and PI (r=−0.46; P<0.01) and Al-Rab *et al.* (16) found positive correlations between VEGF and VI (r=0.694; P<0.001), FI (r=0.662; P<0.001), and VFI (r=0.614; P<0.001).

Several measures of 3D Doppler ultrasonography are reported to predict the outcomes of assisted reproductive technologies. The FI is one such measure to predict the outcomes of IVF (12,19). Ovarian stromal FI was reported to predict the number of oocytes retrieved and the pregnancy rate when total ovarian volume was positively associated with oocytes retrieved, fertilization rate, and pregnancy rate in IVF subjects (47). The number of follicles, VI, and FI are found to predict the quality of embryo on the day of transfer during IVF/ICSI procedures (12). Higher FI, VI, and VFI are observed among pregnant than in non-pregnant women after IVF/ICSI procedures (12,48). In the present study, AFC was significantly positively correlated with VI, FI, and VFI but was not significantly correlated with PI or RI in IVF/ICSI cases. Data were insufficient for the meta-analyses of PCOS patients. Al-Rab *et al.* (16) found positive but non-significant correlations between total AFC and VI (r=0.42; P=0.124), FI (r=0.37; P=0.167) and VFI (r=0.19; P=0.457) and Battaglia *et al.* (25) found an inverse correlation between subcapsular follicles and PI (r=−0.30; P<0.05). However, Ng *et al.* (15) found no correlation between total AFC and either VI, FI, or VFI.

Doppler ultrasonography of ovarian stromal vascularization provides additional support for the diagnosis of PCOS or PCO (27,36,38). Doppler ultrasonographic studies demonstrate that blood flow is increased during the early stages of the follicular phase and reaches a peak at ovulation among women with spontaneous cycles but this pattern is altered in pathological conditions (49). It is suggested that 3D Doppler ultrasonography can help in individualizing treatment for women with a smaller number of antral follicles, smaller ovarian volume, and lower ovarian vascularization, who can be considered for initial higher doses of gonadotropins and longer treatment schedule (46). In comparison with 2D Doppler ultrasonography, 3D Doppler ultrasonography is more expensive, but it has several uses to study ovarian dysfunction such as follicular count, echogenicity of total ovary/stroma, ovarian volume, and blood flow (27).

The presence of high statistical heterogeneity representing between-study inconsistency in the outcomes and less availability of data for some covariates were important limitations of the present study. Sources of heterogeneity could not be traced because of the less availability of related data. Variabilities in patient characteristics and methodologies might have a role in high I^2 values. Insufficient correlation data for some variables such as FSH, FSH/LH ratio, and estradiol precluded us to perform meta-analyses for these important variables. Data were also insufficient to pool the correlations between Doppler ultrasound indices and IGF or VEGF.

Conclusions

Doppler ultrasonographic indices are found significantly different in women with ovarian dysfunction from those of normal women. Doppler indices have significant correlations with the number of antral follicles, testosterone, dehydroepiandrosterone, LH, and AMH. Available data also shows that hirsutism and insulin resistance have correlations with PI. These results support the use of Doppler ultrasonography for the examination of ovarian blood flow abnormalities. Keeping in view the statistical heterogeneity in the outcomes and less availability of data for some endpoints, further studies are needed to refine the outcomes of the present study.

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Footnote

Reporting Checklist: The authors have completed the MOOSE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5813/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5813/coif). The authors have no conflicts of interest to declare.

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Supplementary

Table S1 Important characteristics of the included studies

Study	N	Condition	Age (years)	BMI (kg/m^2)	DHEAS (µg/dL)	AND (nmol/L)	Testosterone (nmol/L)	FSH (IU/mL)	LH (IU/mL)	LH/FSH ratio	AMH (ng/mL)	Hirsutism score	FI	VI	VFI	PI	RI	Ovarian volume (mL)	AFC/OC
Adali 2009	55	PCOS	23.7±3	27.4±4.7	201±83		TT 2±1.14	–	–	2.24±0.6	–	10.5±4.6	–	–	–	1.4±0.63	–	10.6±3.6	
Al-Rab 2015	30	PCOS	30.5±1.4	29.1±1.2	135±12	–	2.8±0.2	4.3±1.2	11.4±1.4	2.65±0.3	–	–	57.4±4.6	4.29±1.8	2.1±0.5	–	–	18.9±1.7cm3	22±2.5
Battaglia 1998a	34	PCO	24±2	23.5±4.5	–	15±2.6	2.3±1	3.7±1	12.3±4	3.3±0.5	–	13	–	–	–	–	–	13±4.6	11.8±3.1
Battaglia 1998b	30	PCOS	24.3±4.1	25.1±2.8	–	13±0.8	2±0.2	5±0.6	10.5±3.7	3±0.6	–	23±4	–	–	–	0.7±0.4	–	11.3±1	14±0.7 SC
Battaglia 1999	30	PCOS	23.5±1.8	–	–	14±12	0.55±0.45	3.6±1.9	13±2.5	3.7±0.3	–	–	–	–	–	–	–	11.6±1.8	11.6 ±2 SC
Battaglia 2012	112	PCOS	26.2±4.6	20.8±2	–	13.1±3.7	1.6±0.5	–	–	–	–	13.4±4.1	35.5%±5%	4.2%±2.5%	2.3%±1.5%	–	–	12.6±3.5	
Bostanci 2013	20	PCOS	25.7±3.1	23.9±1.5	280±97	4.73±1.4	TT 0.92±0.6, FT 6.96±2.5	5.5±2.1	–	–	–	8.7±1.8	–	–	–	–	–		
Carmina 2005	326	PCOS	25.8±0.5	28.9±0.6	155.6±11.5	–	3.1±0.2	–	13.8±1	2.4±0.3	–	–	–	–	–	–	–	12.2±1cm^3	
Dhingra 2017	35	PCOS	23.3±3.3	–	66.3±25.9	–	1.41±0.71	7.4±5.3	9.5±7.1	1.39±0.8	–	7.9±1.7	–	–	–	0.96±0.19	–	11.8±1.4	11.7±2.4
Elmashad 2011	23	PCOS	28.8±3.1	29.2±2.6	–	–	4.2±0.4	4.2±1.3	11.7±1.3	2.8±0.4	7.4±4.6	–	52.4±4.3	4.8±1.3	2.9±0.43	–	–	13.8±2.1	29±2.4
El-Sattar 2019	49	PCOS	27.5±2.7	27±2.5	–	–	–	5.14±1	7.4±1.5	–	–	–	–	–	–	1.7±0.8	0.83±0.7		
Elsayed 2014	150	PCOS	24±3.3	28±3.4	233±71	–	2.96±0.57	5.7±1.1	9.9±2.9	–	3.2±1.7	–	–	–	–	0.95±0.21	–	10.8±2.7cm^3	
Jadaon 2012	168	IVF	30.4±5.4	26.2±6.3	–	–	–	6.9±2.4	5.1±2.4	1.72±1.1	–	–	–	–	–	0.94±0.26	0.58±0.09	9.1±4	8.5±5.5
Jarvela 2003	45	IVF	36±3.6	–	–	–	–	6.7±2	4±2	0.7±0.4	–	–	–	–	–	–	–		12±6
Kamal 2018	80	PCOS	28.2±5	28±1.5	–	12±2	11.7±4.3	3.34±1	9.9±4.7	2.9±0.8	8.3±2.2	–	27±1.3	1.88±0.37	1.34±0.29	–	–	14±2	19.6±4
Kupesic 2002	56	IVF	34.1±5.1	21.3±1	–	–	–	7.2±.3	–	–	–	–	12.6±0.6	–	–	–	–	8.23±1.3	9.43±3.5
Makled 2014	60	PCOS	25.5±2.1	31.2±4.8	–	–	FT 0.96±0.26	8.7±2.5	10.7±2.7	1.26±0.3	–	8.5±3.4	32.7%±4.4%	4.7%±1.37%	1.54%±0.69%	–	–	8.8±1.7	
Malhotra 2014	254	PCOS	31.3±3.9	24.8±3.5	–	–	–	6.4±2.1	5.4±3.3	–	4.3±3	–	–	–	–	0.7±0.5	0.4±0.3		6.5±4
Merce 2006	80	IVF/ICSI	34±3.5	–	–	–	–	–	–	–	–	–	64.2±9.2	21.2±9.5	7.6±3.5	–	–	57±21	13.1±6.3
Ng 2005a	32	PCOS	31±4	23±4.5	–	–	–	5.1±2.3	6.1±5.2	–	–	–	29.3%±3.9%	3.80%±6.2%	0.7%±2%	–	–	21±8 tot	38.5±14
Ng 2005b	136	IVF	34.5±2.5	20.9±2.2	–	–	–	6.3±1	–	–	–	–	–	–	–	–	–		9±2.5
Ng 2006	71	PCO/S	32±3	23.5±3	–	–	–	–	–	–	–	–	29.3%±3%	3%±4%	0.7%±1.5%	–	–	17.7±6.2	33±9.5
Ozdemir 2015	40	PCOS	22.3±5.1	24.4±3	323±112	–	TT 1.6±0.49, FT 9.5±3.8	6.6	12.5±4.2	1.89±1.1	–	11.1±4.2	–	–	–	0.89±0.07	0.48±0.05	11.4±4.8	
Ozdemir 2015	40	PCO	22.7±5.9	22.5±3.5	242±83	–	TT 0.87±0.35, FT 6.3±2.2	6.9	6±2.1	1.12±0.7	–	6±2	–	–	–	1.3±0.27	0.82±0.11	4.9±2.4	
Ozkan 2007	43	PCOS	21.4±1.9	23.5±4.7	260±118	–	TT 3.3±1.84	–	–	1.45±0.7	–	13.4±5	–	–	–	–	–		
Pascual 2008	38	PCO	27±5.7	23.3±3.7	–	–	–	–	–	–	–	–	–	–	–	–	–		
Sahu 2019	101	PCOS	27±4.8	25.7±2.7	245±81	–	TT 2.4±0.5	6.7	11.3	–	–	8±2	–	–	–	1.23±0.32	0.54±0.1		
Shaban 2014	212	IVF/ICSI	31.7±4.3	24.1±2.4	–	–	–	7.2	6.17	–	–	–	25%±3%	3.5%±1.5%	1.5%±0.7%	–	–		8.28±1.5

Values after ± sign are standard deviations of preceding values. Values after ± sign are standard deviations of preceding values. BMI, body mass index; DHEAS, dehydroepiandrosterone; AND, androstenedione; FSH, follicle stimulating hormone; LH, luteinizing hormone; AMH, anti-Mullerian hormone; FI, flow index; VI, vascularization index; VFI, vascularization flow index; PI, pulsatility index; RI, resistance index; AFC/OR, antral follicle count/oocyte retrieved; PCOS, polycystic ovarian syndrome; TT, total testosterone; PCO, polycystic ovary; FT, free testosterone; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; SC, subcapsular.

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Table S2 Quality assessment of the included studies with NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Criteria	Adali 2009	Al-Rab 2015	Battaglia 1998a	Battaglia 1998b	Battaglia 1999	Battaglia 2012	Bostanci 2013	Carmina 2005	Dhingra 2017	Elmashad 2011	El-Sattar 2019	Elsayed 2014	Jadaon 2012	Jarvela 2003	Kamal 2018	Kupesic 2002	Makled 2014	Malhotra 2014	Merce 2006	Ng 2005a	Ng 2005b	Ng 2006	Ozdemir 2015	Ozkan 2007	Pascual 2008	Sahu 2019	Shaban 2014
1. Was the research question or objective in this paper clearly stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Was the study population clearly specified and defined?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3. Was the participation rate of eligible persons at least 50%?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
4. Were all subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5. Was a sample size justification, power description, or variance and effect estimates provided?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	N	Y	N	N	N	N	N	N	N	Y	N	N	N	N	Y	N	Y	N	N	N	N	N	N	N	N	Y	N
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
10. Was the exposure(s) assessed more than once over time?	N	Y	N	N	N	N	N	N	N	Y	N	N	N	N	Y	N	Y	N	N	N	N	N	N	N	N	Y	N
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
12. Were the outcome assessors blinded to the exposure status of participants?	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	Y	N	N	Y	N
13. Was loss to follow-up after baseline 20% or less?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

NIH, National Institutes of Health; Y, yes; NA, not applicable; N, no.

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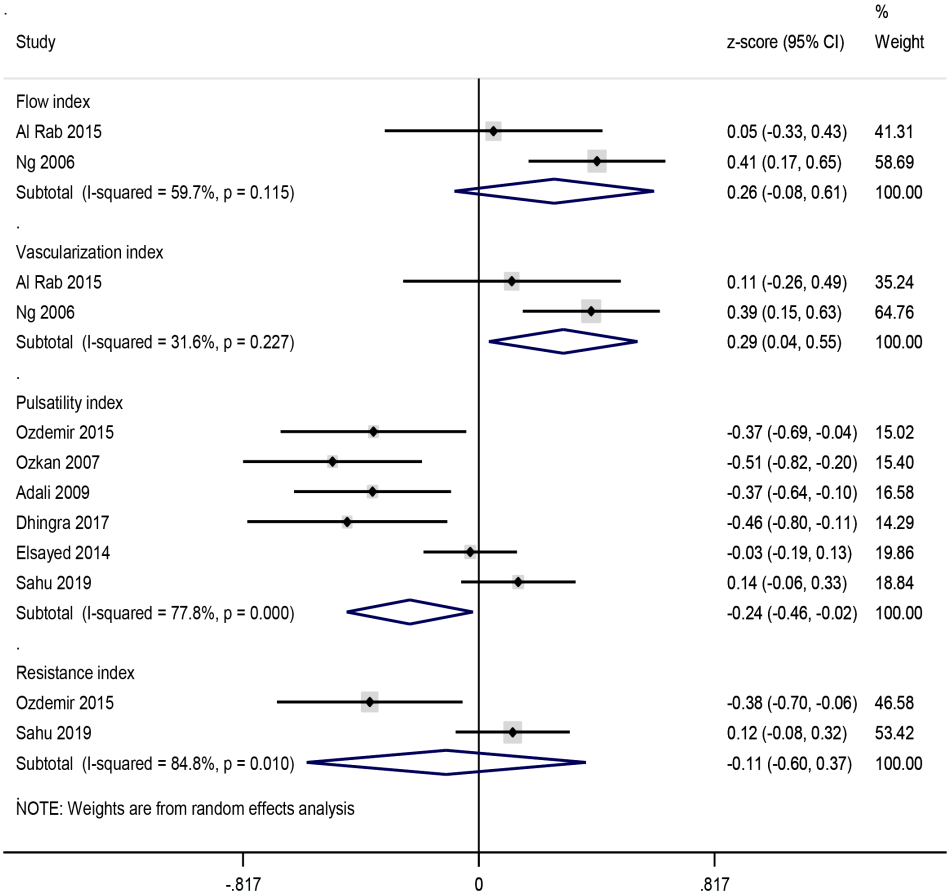

Figure S1 Forest graph showing the pooled z-scores of the correlations between dehydroepiandrosterone and Doppler ultrasonography indices. CI, confidence interval.

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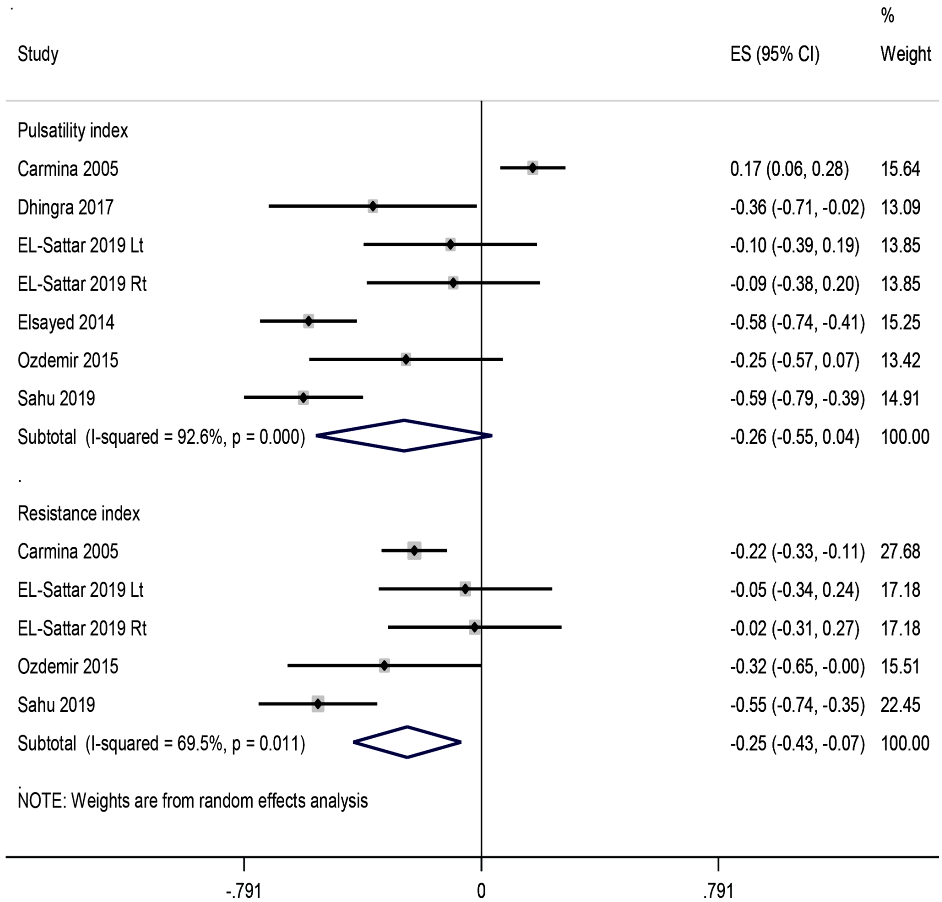

Figure S2 Forest graph showing the pooled z-scores of the correlations between LH and Doppler ultrasonography indices. ES, effect size (z-score); CI, confidence interval; Lt, left; Rt, right; LH, luteinizing hormone.

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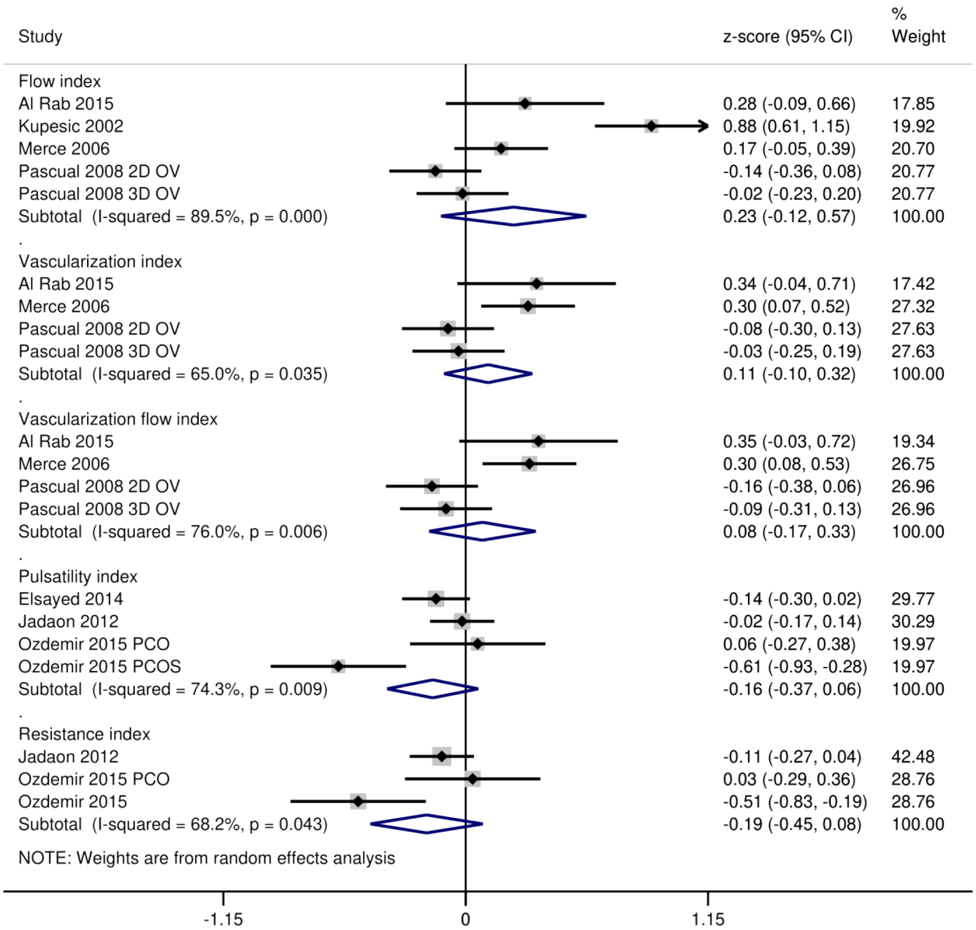

Figure S3 Forest graph showing the pooled z-scores of the correlations between ovarian volume and Doppler ultrasonography indices. CI, confidence interval; 2D, two-dimensional; OV, ovarian volume; 3D, three-dimensional; PCO, polycystic ovary; PCOS, polycystic ovarian syndrome.

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