

META-ANALYSIS

Doppler parameters of ophthalmic artery in women with preeclampsia: A meta-analysis

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Abstract

Preeclampsia is a progressive and severe cardiovascular disorder in pregnant women. To determine the potential significance of ophthalmic Doppler parameters in preeclamptic women and to provide evidence-based hints for clinical practice and scientific investigation. We searched PubMed, Embase, Web of Science, and the Cochrane Library till July 31, 2022. Pooled standardized mean difference (SMD) with 95% confidence intervals (CIs) were calculated using the random effects model. Heterogeneity across included studies was evaluated utilizing the Q test and I^2 statistic. We identified 8 observational studies that met the inclusion criteria. The pooled SMD for peak systolic velocities (PSV) was .12 (95% CI: -.82, 1.06, $p = .8071$; $I^2 = 94%$, $p < .0001$). The overall SMD for time-averaged mean peak velocities (MV) was 1.79 (95% CI: .87, 2.71, $p = .0001$; $I^2 = 60%$, $p = .1152$). Regarding the pulsatility index (PI), the pooled SMD was -2.05 (95% CI: -3.12, -.98, $p = .0002$; $I^2 = 92%$, $p < .0001$). Overall SMD for end-diastolic velocities (EDV) was 1.11 (95% CI: .23, 1.98, $p = .0136$; $I^2 = 92%$, $p < .0001$). The pooled SMDs for resistance index (RI) and peak ratio (PR) was -.18 (95% CI: -1.90, 1.53, $p = .8333$; $I^2 = 96%$, $p < .0001$) and 1.46 (95% CI: -1.30, 4.22, $p = .2994$; $I^2 = 99%$, $p < .0001$), respectively. Publication bias was not identified. MV, PI, and EDV showed significant differences between patients with preeclampsia and non-hypertensive pregnant participants. Studies on the predictive performance of ophthalmic artery Doppler parameters are warranted.

KEYWORDS

Doppler flowmetry, meta-analysis, ophthalmic artery, preeclampsia, ultrasound

1 | INTRODUCTION

Preeclampsia is a progressive, unpredictable, and severe cardiovascular disorder characterized by hypertension and proteinuria that complicates 2% to 4% of pregnancies worldwide. There are about 46,000 maternal deaths and about 500,000 fetal and neonatal deaths

each year.^{1,2} Most preeclampsia occurs at full term, with mild and transient symptoms that disappear soon after delivery; nevertheless, 5% to 20% of women, especially those with preeclampsia before full term, develop life-threatening or fatal complications.³ Although the underlying pathophysiology of preeclampsia has not been precisely defined and may be various, a great number of studies have shown that in

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some preeclampsia patients, maternal and placental vascular dysfunction plays a role in the pathogenesis and may last to postpartum.⁴ Risk factors for preeclampsia include family history, genetic susceptibility, time of sexual cohabitation, maternal smoking, number of pregnancies, maternal age, use of in vitro fertilization, and maternal medical conditions, namely preexisting hypertension, diabetes, chronic kidney disease (CKD), and obesity.^{5,6}

The current screening model is based on the evaluation of maternal and obstetric history parameters, combined with uterine artery Doppler ultrasound and measurement of serum biomarkers, especially pregnancy-related plasma protein A (PAPP-A) and placental growth factor (PIGF).⁷ However, the accuracy of uterine artery Doppler measurement in the first or second trimester of pregnancy is limited, because it is difficult to ensure the standardization and qualification of its measurement, and the equipment is expensive.⁸ The use of plasma markers associated with angiogenic/antiangiogenic imbalance has been described in the literature as a promising tool for the early detection of PE. However, more studies are needed to define a unified quantification method and evaluate its accuracy before it is recommended in clinical practice.^{9,10} As the ophthalmic artery is a direct branch of the internal carotid artery and is similar to the small caliber intracranial artery in embryo, anatomy and function, ophthalmic artery ultrasound can be described as a noninvasive test for investigating cerebral vascular regions.^{11,12} The hemodynamic behavior of small central vessels can then be analyzed by ophthalmic artery Doppler to assist in the diagnosis of preeclampsia.¹³

The value of ophthalmic artery Doppler parameters as predictive tools for preeclampsia recently have assessed by an increased number of studies, however, the results are heterogeneous, and no clear consensus has been achieved regarding their exact role in clinical practice.^{13–25} The aim of this meta-analysis was to investigate the potential significance of ophthalmic Doppler parameters in preeclamptic women and to provide evidence-based hints for both clinical practice and scientific investigation.

2 | MATERIALS AND METHODS

2.1 | Statements

This meta-analysis was conducted based on the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.^{26–28} Data in this study was extracted from published articles, so ethnic approval and informed consent were not required.

2.2 | Literature search and study selection

We performed a comprehensive search of online databases was performed, including PubMed, Embase, Web of Science, and the Cochrane Library, from inception to July 31, 2022. We used ophthalmic artery, Doppler, ultrasound, and preeclampsia as keywords.

The titles and abstracts of the literature were screened to identify duplicates and irrelevant citations. Then the full-text review of the remaining articles was carried out for final inclusion. Moreover, we manually searched the references of included studies and reviews for potentially eligible studies. The inclusion criteria were as follows: (1) randomized controlled, prospective or retrospective cohort, case-control, cross-sectional studies; (2) participants were women with diagnosed preeclampsia, or normotensive women; (3) reported any ophthalmic artery Doppler parameter including peak systolic velocities (PSV), time-averaged mean peak velocities (MV), end-diastolic velocities (EDV), peak ratio (PR, the ratio of the first diastolic peak to the peak systolic velocity), pulsatility index [$PI = (PSV - EDV)/MV$], and resistance index [$RI = (PSV - EDV)/PSV$],^{13,17,29} decreased resistance and pulsatility indices combined with increased blood flow velocity and peak ratios suggest decreased vascular resistance; and (4) outcomes aforementioned can be calculated according to the datasets in included citations. Conference abstracts, review articles, case reports or series, animal studies, or non-English reports were excluded. Two reviewers conducted literature search, screening, and study selection independently, and resolved their disagreements through discussion.

2.3 | Data extraction and quality assessment

We extracted the name of the first author, year of publication, country, study design, the total number of participants, gestational week at the examination, ultrasound characteristics, and aforementioned Doppler parameters. We used the Cochrane risk of bias tool to assess the quality of randomized controlled trials,³⁰ and non-randomized studies were evaluated with the Newcastle-Ottawa Scale (NOS) score.³¹ In doing so, the two authors worked independently on the above and coordinated different views.

2.4 | Statistical analysis

Data analysis was performed by the R software (Version 4.0.2, Comprehensive R Archive Network) and the random effects model was used for data synthesis.³⁰ Standardized mean difference (SMD) of ophthalmic artery Doppler indices between the preeclampsia and control groups and the 95% confidence intervals (CIs) were calculated as endpoints. A positive SMD value means a higher level of Doppler indices in preeclamptic women than in normotensive women and vice versa. The Q test and I^2 statistic investigated heterogeneity across enrolled studies. I^2 values $\geq 25\%$, $\geq 50\%$, and $\geq 75\%$ were regarded as low, moderate, and high heterogeneity.³² Furthermore, meta-regression and subgroup analyses were conducted to investigate potential sources of heterogeneity. Sensitivity analysis was introduced to detect the effect of every single study on the robustness of pooled outcome.³³ Egger's test and funnel plots were used to identify potential publication bias. A p -value $< .05$ was considered as statistically significant.

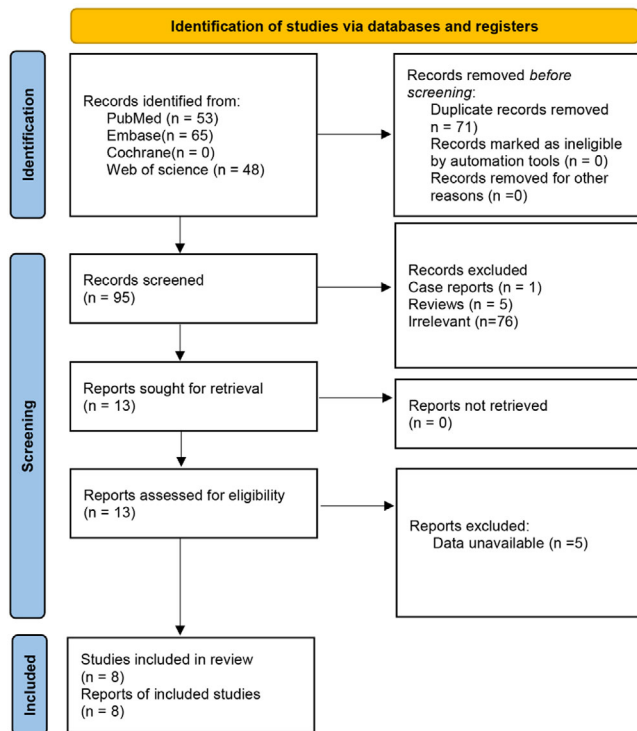


FIGURE 1 Flow chart of literature search

3 | RESULTS

3.1 | Baseline characteristics

A total of 166 citations were identified through an initial literature search. After removing 71 duplicated reports, we filtered out a further 82 studies that did not meet the inclusion criteria (5 reviews, 1 case report, and 76 irrelevant records) by browsing titles and abstracts. A full-text review of the remaining 13 articles led us to identify 8 observational studies that met the inclusion criteria, comprising 640 pregnant women with or without confirmed preeclampsia.^{13-19,25,34} Details on the literature search are displayed in Figure 1. Five case-control and 3 cross-sectional studies were enrolled. The year of publication for these citations ranged from 1995 to 2020. More information on the characteristics of the included studies is depicted in Table 1. All studies were considered low-risk bias according to the NOS scale. The results of the quality assessment for the included studies are shown in Table 1.

3.2 | Pooled outcomes on Doppler parameters

Five studies reported the outcomes on PSV. The pooled SMD for PSV was .12 (95% CI: $-0.82, 1.06, p = .8071$), and heterogeneity was statistically significant ($I^2 = 94\%, p < .0001$) (Figure 2). Two included studies reported results on MV, the overall SMD for MV was 1.79 (95% CI: $.87, 2.71, p = .0001; I^2 = 60\%, p = .1152$) (Figure 3). With regard to PI, the pooled SMD of 7 included studies was -2.05 (95% CI: $-3.12, -.98, p = .0002; I^2 = 92\%, p < .0001$) (Figure 4). Overall SMD for EDV

(5 studies) was 1.11 (95% CI: $.23, 1.98, p = .0136; I^2 = 92\%, p < .0001$) (Figure 5). The pooled SMDs for RI (7 studies) and PR (4 studies) were -0.18 (95% CI: $-1.90, 1.53, p = .8333; I^2 = 96\%, p < .0001$) and 1.46 (95% CI: $-1.30, 4.22, p = .2994; I^2 = 99\%, p < .0001$), respectively (Figures 6 and 7).

3.3 | Sensitivity analysis and publication bias

Results of sensitivity analysis revealed that the pooled effect sizes were robust after eliminating studies one after another in the meta-analysis of the Doppler parameters, including PSV, MV, EDV, PR, PI, and RI. Linear regression tests for publication bias yielded p values of .1738, .2434, .0791, .0986, and .2403 for the meta-analysis of PSV, PR, EDV, PI, and RI (Figures S1-S5). As only two included studies reported results on MV, we did not test for publication bias for this outcome.

4 | DISCUSSION

Preeclampsia is a hypertensive disorder related to pregnancy, which is the leading cause of high maternal and perinatal morbidity and mortality.^{35,36} The main pathological disorder of preeclampsia seems to be related to systemic arterial constriction, including the ocular region, whose involvement has been well elucidated.³⁷ Considering that ocular artery blood flow indirectly reflects the hemodynamic state of the intracranial vascular system, its study may help understand systemic diseases with central vascular damage, including preeclampsia.³⁸ We performed a meta-analysis to address the potential significance of ophthalmic Doppler parameters in patients with preeclampsia compared to pregnant women without preeclampsia.

A total of five case-control studies and three cross-sectional studies were appraised as eligible for this meta-analysis following a systematic search and selection of citations. The pooled SMD for PSV was insignificant. Of note, the PSV values of included studies were heterogeneous. The underlying causes for this inconsistency were indeterminate according to the data extracted from the included studies; more covariates are warranted to elucidate the contradiction. Only two included studies reported outcomes on MV, and pooled effect size showed that the MV value in the preeclampsia group was statistically higher than that in the non-hypertensive group.

Moreover, regarding EDV, the overall difference between preeclamptic and non-hypertensive women was 1.11 ($p < .0001$), which indicated that preeclampsia was associated with a higher level of EDV. Madina et al. compared the mean values of the resistive index of the ophthalmic arteries in patients with preeclampsia and normotensive individuals, and results manifested that the mean RI was higher in normotensive participants than that in preeclamptic women (.70 vs. .63).¹⁸ However, this significant difference was not observed in this meta-analysis. PI and PR of the ocular artery are considered the best indicators to reflect the vascularization of the eye.³⁸ Nevertheless, the

TABLE 1 Characteristics and quality assessment of included studies

Author	Year	Country	Study design	Number of participants	Gestational week at examination	Ultrasound characteristics	Reported outcomes	NOS score
Hata	1995	Japan	Case control	27	>32	Patients were studied once with color Doppler flow imaging and pulsed Doppler ultrasonography after 32 weeks gestation.	PSV, MV, EDV, PI	7
Takata	2002	Japan	Case control	84	>32	An Aloka SSD-2200 scanner with a 3.5-MHz transabdominal probe (Aloka Ltd., Tokyo, Japan) was used.	PSV, MV, EDV, PI, RI, PR	8
Ayaz	2003	Turkey	Case control	60	>32	Ultrasound examination was performed using a 10 MHz linear transducer.	PI and RI	8
de Oliveira	2013	Brazil	cross-sectional	349	>20	All scans were performed using Nemio (Toshiba Medical Systems Co, Ltd, Tokyo, Japan) and Sonoace X8 (Samsung Medison Co, Ltd, Seoul, Korea) high-resolution equipment with a 7.5-MHz linear transducer and a 50 Hz wall filter setting; the Doppler sample volume was adjusted at 2 to 3 mm.	RI, PI, PR	8
Diniz	2008	Brazil	Cross-sectional	91	30.7 ± 5.0	Orbital vascular Doppler was performed using an electronic linear probe in a frequency ranging from 7–10 MHz.	PSV, EDV, PI, RI, PR	7
Olatunji	2015	Nigeria	Case control	82	NR	Transorbital triplex ultrasound scan with a 7–10 MHz multifrequency linear transducer was used.	PSV, PI EDV, RI	8
Madina	2020	Pakistan	Cross-sectional	60	Second or third trimester.	The ultrasound machine used in the study (Toshiba Xerio) was equipped with a linear probe of 7–14 MHz for ophthalmic artery examination.	RI	8
Onwudiegwu	2020	Nigeria	Case control	143	NR	Ocular color and pulsed-wave Doppler ultrasound examination of the ophthalmic artery was done on all participants using the LOQIC P5 GE ultrasound scanner (General Electric Healthcare, South Korea) with a 5–14 MHz linear transducer.	PI, RI, PSV, PR, EDV	7

Abbreviations: EDV, end-diastolic velocities; MV, time-averaged mean peak velocities; NOS, Newcastle-Ottawa Scale; NR, not reported; PI, pulsatility index; PR, peak ratio; PSV, peak systolic velocities; RI, resistance index.

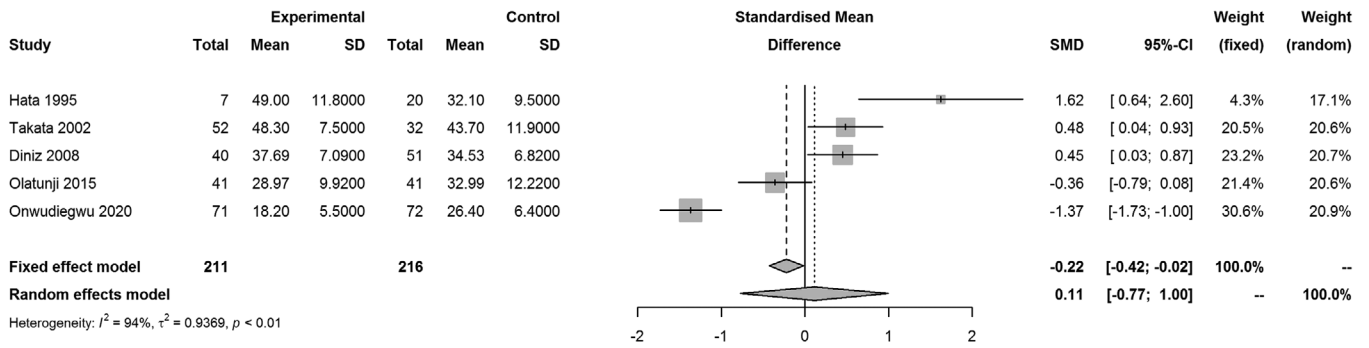


FIGURE 2 Forest plot of peak systolic velocities (PSV) in included studies. PSV did not differ among preeclamptic (experimental) and normotensive women (control)

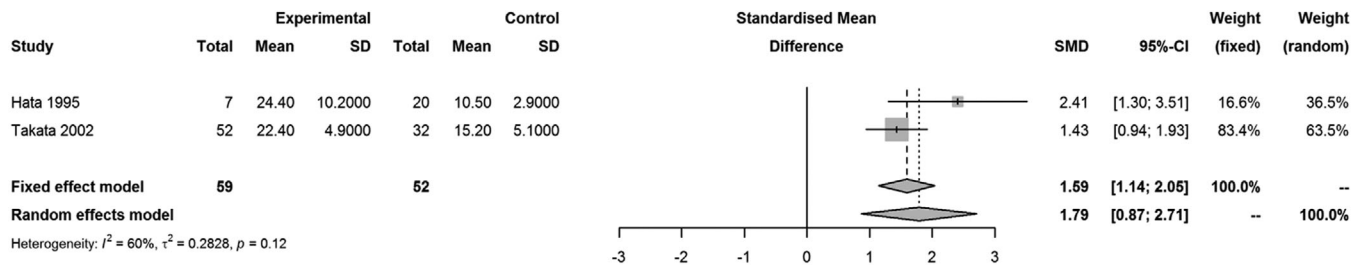


FIGURE 3 Forest plot of time-averaged mean peak velocities (MV) in included studies. MV was higher in preeclamptic women (experimental) than that in normotensive women (control)

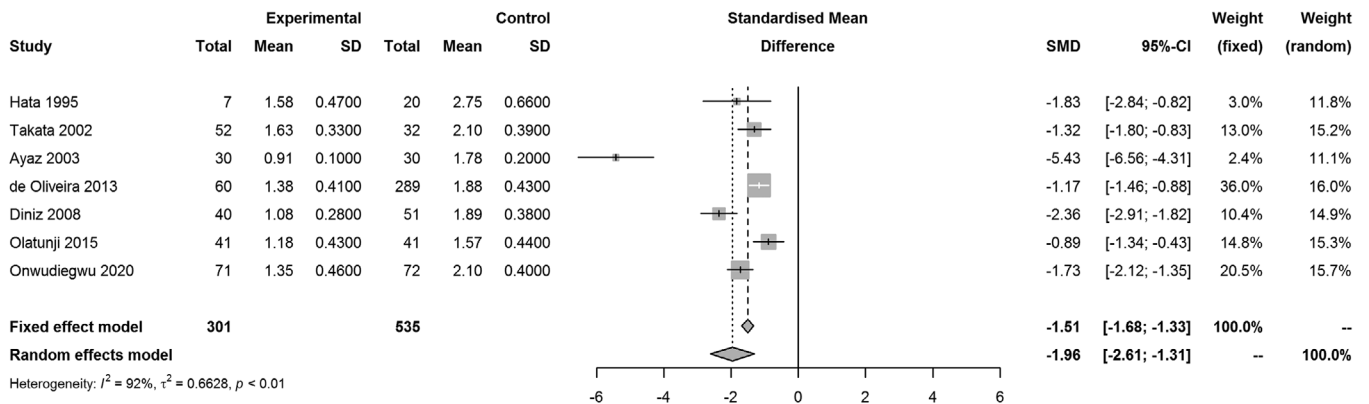


FIGURE 4 Forest plot of pulsatility index (PI) in included studies. PI was lower in preeclamptic women (experimental) than that in normotensive women (control)

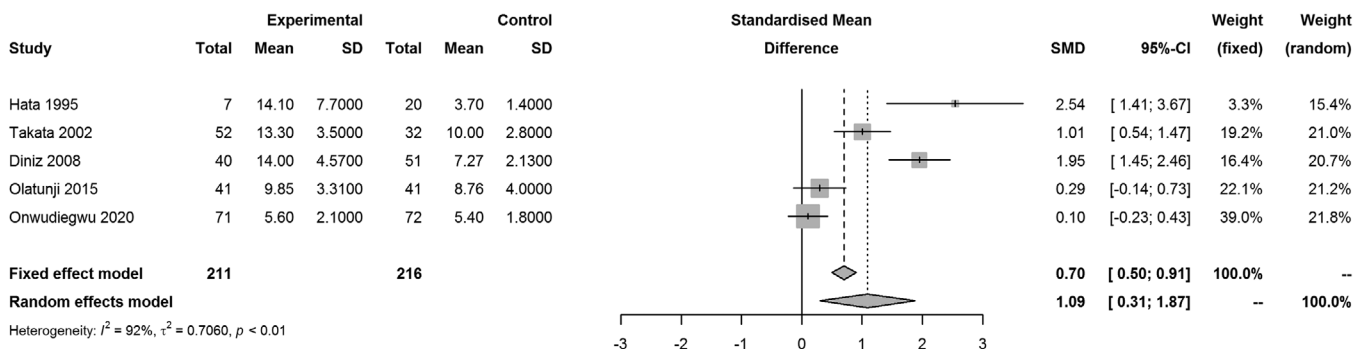


FIGURE 5 Forest plot of end-diastolic velocities (EDV) in included studies. EDV was higher in preeclamptic women (experimental) than that in normotensive women (control)

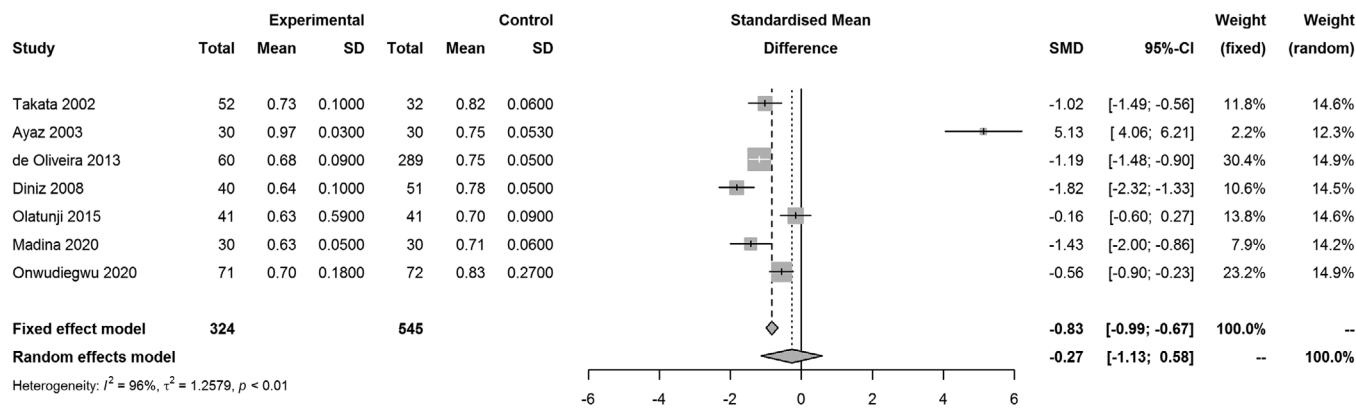


FIGURE 6 Forest plot of resistance index (RI) in included studies. RI did not differ among preeclamptic (experimental) and normotensive women (control)

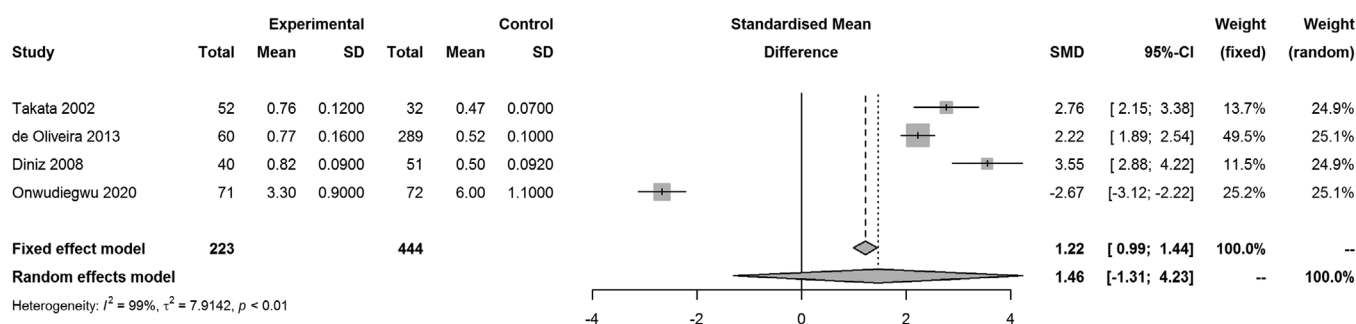


FIGURE 7 Forest plot of peak ratio (PR) in included studies. PR did not differ among preeclamptic (experimental) and normotensive women (control)

pooled SMDs for PI were statistically significant, while PR was statistically insignificant; the primary cause may be attributed to heterogeneity across component records, either meta-regression or subgroup analysis was performed due to limited covariates extracted and limited number of studies in each subgroup. Moreover, evaluation results for linear regression tests demonstrated nonsignificant publication bias in enrolled studies. The sensitivity analysis results did not suggest that any of the studies significantly contributed to the overall effect sizes.

Although we adopted a comprehensive approach concerning literature search, study selection, data extraction, and quality assessment, this meta-analysis still has several limitations. First, The outcomes were synthesized on the study level because we could not obtain individual patient data in included studies. Second, we conducted no meta-regression or subgroup analysis due to the limited number of covariates available in this study and the small number of studies in each potential subgroup. Third, there were insufficient data to analyse the effect of ophthalmic arterial Doppler on assessing the severity of pre-eclampsia at different stages. Fourth, Pooled results of this work may provide evidence for the choice of ophthalmic artery Doppler parameters in detecting preeclampsia. Diagnostic studies are needed to investigate the accuracy, sensitivity, and specificity of these Doppler parameters.

When considered separately, no Doppler variable can provide a firm and clear explanation of the underlying mechanism.³⁸ There are few published works on Doppler study of the orbital vessels, particularly the ophthalmic artery, to evaluate their accuracy in predicting preeclampsia. More well-performed prospective studies in earlier stages of pregnancy are necessary to explore this possibility.

5 | CONCLUSION

In this meta-analysis, MV, PI, and EDV manifested significant differences between patients with preeclampsia and non-hypertensive pregnant participants. Studies on the efficacy of the combined utility of these ophthalmic artery Doppler parameters and their predictive performance are needed to provide more reliable and robust evidence for clinical practice and scientific investigation.

AUTHOR CONTRIBUTIONS

Conceptualization: Xinxin Dai. Methodology: Xinxin Dai. Formal analysis and investigation: Xinxin Dai and Li Kang. Writing – original draft preparation: Xinxin Dai. Writing – review and editing: Xinxin Dai and Huiyu Ge. Supervision: Huiyu Ge.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

PATIENT CONSENT STATEMENT

Not Applicable.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not Applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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