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Impaired Flow-Mediated Dilation Before, During and After Preeclampsia: A Systematic Review and Meta-analysis

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Abstract

Endothelial dysfunction is believed to play a critical role in preeclampsia, however it is unclear whether this dysfunction precedes the pregnancy or is caused by early pathophysiological events. It is also unclear for how long vascular dysfunction may persist post-partum, and whether it represents a mechanism linking preeclampsia with future cardiovascular disease. Our objective was to determine whether women with preeclampsia have worse vascular function compared to women who did not have preeclampsia by performing systematic review and meta-analysis of studies that examined endothelial dysfunction using flow-mediated dilation (FMD). We included studies published before May 29, 2015 that examined FMD before, during and after preeclampsia. Differences in FMD between study groups were evaluated by standardized mean differences. Out of 610 abstracts identified through PubMED, EMBASE and Web of Science, 37 studies were eligible for the meta-analysis. When compared to women who did not have preeclampsia, women who had preeclampsia had lower FMD prior to the development of preeclampsia (~20–29 weeks gestation), at the time of preeclampsia, and for three years post-partum, with the estimated magnitude of the effect ranging between 0.5 and 3 standard deviations. Similar effects were observed when the analysis was limited to studies that excluded women with chronic hypertension, smokers, or both. Vascular dysfunction predates preeclampsia and may contribute to its pathogenesis. Future studies should address whether vascular changes that persist after preeclamptic pregnancies may represent a mechanistic link with the increased risk for future cardiovascular disease.

Keywords

endothelium; pregnancy; flow-mediated dilation; preeclampsia; hypertension; cardiovascular disease

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Conflict of Interest/Disclosures

The authors have nothing to disclose.

Introduction

Preeclampsia is a leading cause of maternal and fetal morbidity and mortality that affects 2–7% of pregnancies.[1, 2] This pregnancy-specific disorder is diagnosed in women presenting with new onset hypertension and proteinuria after 20 weeks gestation.[3] Effective prevention strategies are lacking and the only known cure is delivery.

While the pathophysiology of preeclampsia remains elusive; systemic endothelial dysfunction is believed to be a critical component[4] that may also link preeclampsia with future cardiovascular disease.[5] Evidence for endothelial dysfunction in preeclampsia includes reduced *in vitro* endothelium-dependent dilation of isolated vessels,[6] increased vascular reactivity in response to vasoconstrictor stimuli and elevated levels of biomarkers associated with endothelial activation and injury.[4, 7] The American Heart Association identified preeclampsia as a risk factor for cardiovascular disease and stroke later in life.[8, 9]

Flow-mediated dilation (FMD) is a well-established technique that allows researchers to examine endothelial function and assess cardiovascular risk non-invasively, even during pregnancy.[10, 11] This technique offers exciting possibilities to examine how endothelial dysfunction contributes to the pathophysiology of preeclampsia. Furthermore, FMD can also be used to determine whether endothelial dysfunction persists post-partum and may be one mechanism linking preeclampsia with future cardiovascular disease. However, studies to date offer conflicting results: some have reported lower FMD in women with preeclampsia, whereas others have not. In addition, most studies focus on narrow time periods rather than providing longitudinal data from early pregnancy to delivery and postpartum. We sought to elucidate the time course of vascular dysfunction in preeclampsia by conducting a systematic review and meta-analysis of studies examining FMD at three key time points: during pregnancy before the clinical diagnosis of preeclampsia, at the time of active disease, and months or years after pregnancy. This approach will provide insight into whether vascular dysfunction predates the onset of the maternal signs, contributes to the pathophysiology of preeclampsia, and may contribute to future cardiovascular disease in women who have had preeclampsia.

Methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews[12] and Meta-analysis of Observational Studies in Epidemiology[13] recommendations. The supplement contains detailed methodology for inclusion and exclusion criteria, diagnostic criteria, search strategy, article screening and selection, data abstraction and quality assessment, statistical analysis and missing information.

Briefly, studies identified through PubMED, EMBASE and Web of Science were stratified into one or more of the following time periods:

1. Before preeclampsia: FMD was measured in pregnant women who were followed until delivery to determine whether they developed preeclampsia. No participants had preeclampsia at the time of FMD testing (11–34 weeks).

2. At the time of active disease: FMD was measured after 20 weeks gestation, to compare FMD in pregnant women with vs. without preeclampsia at the time of the FMD test.

3. Post-partum: FMD was measured in non-pregnant women hours to years after delivery. Studies that combined preeclampsia with gestational hypertension and/or chronic hypertension in pregnancy were only eligible if data for the subset of women who developed preeclampsia could be obtained. We included observational studies and baseline data from randomized controlled trials.

Statistical Analysis

The supplement describes detailed statistical methods. Briefly, the primary outcome was FMD, expressed as a percent change from pre-inflation diameter. FMD methodology is highly variable; therefore we used the standardized mean difference (SMD) to examine differences between the preeclampsia and non-preeclampsia groups. This effect size measurement expresses the difference between group means in units of standard deviations. For each time period, the bias-corrected SMD (Hedges G) was estimated by pooling individual trial results using random-effects models via the DerSimonian-Laird method (Open Meta-analyst). Due to high heterogeneity in the effect sizes of included studies, confirmatory analyses were run in MetaEasy[14] using the Profile Likelihood method (data not shown). Simulation studies suggested that the Profile Likelihood method is more accurate for heterogeneous data.[15]

Results

We identified 610 potentially eligible articles. Out of 131 full text articles that were reviewed, 37 were selected for inclusion in the meta-analysis (Figure 1). This included studies that measured FMD prior to preeclampsia (n=12), at the time of preeclampsia (n=13), and post-partum (n=19). Post-partum studies were subdivided into early and late time periods, as studies were conducted at a mean or median post-partum interval of less than 3 years post-partum (n=15), or greater than 10 years post-partum (n = 4). The data supplement includes tables describing summary characteristics (Tables S1, S2, S3), diagnostic criteria for studies examining women with more severe and less severe forms of preeclampsia (Tables S4) and exclusion criteria (Tables S5, S6). The quality assessment tool and tables describing study quality and FMD protocols are available from the authors.

Prior to Preeclampsia

The 12 prospective cohort studies that were selected for the meta-analysis[16–27] included 156 pregnant women who subsequently developed preeclampsia and 947 women who did not develop preeclampsia (Tables S1, S5). Two additional studies were included in the qualitative synthesis.[28, 29]

Women who subsequently developed preeclampsia had lower FMD compared to women who did not develop preeclampsia. Six studies included multiple time points.[20, 21, 23–25] Results did not differ between analyses that included second trimester studies only (SMD: −0.84, 95% CI: −1.19, −0.50, p<0.001, Figure 2), the earliest time points from all studies

(SMD: −0.78, 95% confidence interval (CI): −1.19, −0.37, p<0.001, Figure S1, Panel A), or the latest time points from all studies (SMD: −0.83, 95% CI: −1.30, −0.37, p<0.001, Figure S1, Panel B). Results were attenuated in a sensitivity analysis of studies that excluded smokers (Earliest time points, SMD: −0.52, 95% CI: −1.02, −0.02, p=0.043).[19, 22, 23, 25, 27] Results were not different when a study that reported FMD as median (IQR)[29] was included (data not shown). The high heterogeneity for 2nd trimester studies (Figure 2) was lower in sensitivity analysis in which a study examining women with systemic autoimmune disease was excluded (SMD: −0.92, 95% CI: −1.24, −0.60, p<0.001).

At the Time of Preeclampsia

The 14 cross-sectional studies that were eligible for the meta-analysis[23, 30–41] included 333 preeclamptic women and 467 non-preeclamptic pregnant women (Tables S2, S6). Five additional studies were included in the qualitative synthesis.[42–46]

At the time of active disease, FMD was significantly lower in women who had preeclampsia (SMD: −1.41, 95% CI: −2.0, −0.83, p<0.001, Figure 3 Panel A), compared to women who did not have preeclampsia. The analysis revealed significant heterogeneity between studies (Q=130.4, p<0.001, I^2=91%). Excluding one study that observed a very large effect[33] resulted in a slight reduction in the SMD (−1.20, 95% CI: −1.70, −0.70, p<0.001) and heterogeneity (Q=80.6, p<0.001, I^2=86%). The magnitude of the overall effect was attenuated in sensitivity analyses of studies that excluded smokers (SMD: −1.30, 95% CI: −1.94, −0.66, p<0.001),[23, 30, 32, 34–36, 39–41] women with chronic hypertension (SMD: −1.15, 95% CI: −1.64, −0.66, p<0.001)[30–32, 36–40] or both (SMD: −1.30, 95% CI:−2.05, −0.55, p<0.001).[30, 32, 36, 39, 40] Selecting different time points for one study that included multiple time points[23] did not alter the results. Including a study in which FMD was reported as median (IQR) had no effect.[45]

Separate analyses were performed to examine the effects of more and less severe forms of preeclampsia (Diagnostic criteria: Table S4). FMD was significantly lower in women with less severe forms of preeclampsia[31, 34, 36, 37, 39] compared to women who had normotensive pregnancies (SMD: −0.95, 95% CI: −1.30, −0.59, p<0.001, Figure S2, Panel A). Similar results were observed in studies examining women with more severe forms of preeclampsia[31, 34, 36, 39] compared to women who had normotensive pregnancies (SMD: −1.74, 95% CI: −2.65, −0.83, p<0.001, Figure S2, Panel B).

Early Post-partum Period

Six prospective cohort studies,[20, 23, 32, 34, 35, 38] eight cross-sectional studies,[47–54] and one randomized controlled trial of exercise training[55] were eligible for the meta-analysis (Tables S3, S6). These studies included 429 women who had a history of preeclampsia and 470 women who did not have a history of preeclampsia. The randomized controlled trial was treated as a cross-sectional study, as only pre-randomization brachial artery FMD data were included in the meta-analysis. Two additional studies were included in the qualitative synthesis.[46, 56]

FMD was significantly lower in women with preeclampsia among studies conducted at a mean or median post-partum interval of less than 3 years (SMD: −0.90, 95% CI: −1.26,

−0.54, p < 0.001, data not shown). However, heterogeneity was high (Q = 76.9, p<0.001, I^2 = 82%). Results were not different after excluding a study[35] in which the SD for the preeclampsia group was imputed, or including a study that presented FMD as median (IQR).[56]

Whereas all studies conducted within the first 6 months post-partum were cohort studies, all studies conducted between 6 months and three years post-partum were cross-sectional. FMD was significantly lower among women with a history of preeclampsia in cohort studies conducted before 6 months post-partum (SMD:−0.44, 95% CI: −0.68, −0.20, p < 0.001, Figure 4, Panel A). This effect remain significant in sensitivity analyses of studies that excluded smokers (SMD: 0.34, 95% CI: −0.66, −0.02, p=0.035)[23, 32, 34] and studies that excluded women with chronic hypertension (SMD: 0.59, 95% CI: −0.90, −0.28, p=0.035).[20, 32, 38]

Compared to studies conducted prior to 6 months post-partum, differences in FMD were slightly larger in cross-sectional studies conducted between 6 months and 3 years post-partum (SMD: −1.25, 95% CI: −1.81, −0.69, p < 0.001). This effect remained significant in a sensitivity analysis of studies that excluded women with chronic hypertension (SMD: −1. 25, −95% CI: 1.84, −0.66, p<0.001),[47–55] smokers (SMD: −0.98, 95% CI: −1.56, −0.40, p<0.001),[35, 48–50, 52–55] or both (SMD: −1. 08, 95% CI: −1.71, 0.46, p<0.001).[48–50, 52–55]

Preeclampsia was also associated with a significant reduction in FMD among the studies that examined women with less severe[23, 34, 54] (Figure S3, Panel A) and more severe[23, 34, 48, 49, 54] (Figure S3, Panel B) forms of preeclampsia.

Late Post-partum Period

Four cross-sectional studies were eligible for the meta-analysis (Tables S3, S6).[57–60] These studies included 215 women who had preeclampsia and 164 women who did not have preeclampsia. One additional study was included in the qualitative synthesis.[61] A history of preeclampsia did not have a significant effect on FMD when assessed approximately 10 years post-partum (SMD: 0, 95% CI: −0.34, 0.34, p = 0.995, Figure 4, Panel B), although confidence intervals were wide due to the small number of studies. Heterogeneity was moderate (Q=6.9, p=0.592, I^2 = 56%). Results were not different when unpublished data[57] were excluded (SMD: −0.11, 95% CI: −0.58, 0.37, p = 0.663), or when a study that presented FMD as median (IQR)[61] was included (SMD: −0.20, 95% CI: −0.64, 0.25, p = 0.384).

All Time Periods

The high heterogeneity for some of the analyses presented in this study persisted in subgroup analyses examining the effect of cohort type, blinded FMD analysis, FMD analysis method and study quality (data not shown). Among studies conducted prior to preeclampsia, high heterogeneity was not explained by cohort type (with and without preeclampsia risk factors vs. with at least one of several risk factors). The Profile Likelihood method may provide more accurate coverage of the overall effect estimation for datasets with high heterogeneity. Confirmatory analyses using this method gave similar results to those obtained via the DerSimonian-Laird method (data not shown).

Discussion

Our objective was to perform a meta-analysis of the studies that measured FMD before, during or after preeclampsia in order to assess the role of vascular dysfunction in preeclampsia, and its potential contribution to cardiovascular disease after preeclamptic pregnancies. The data showed that women who had preeclampsia, when compared to women who did not have preeclampsia, had lower FMD prior to the clinical diagnosis of preeclampsia (~20–29 weeks gestation), at the time of preeclampsia, and for three years post-partum. Sensitivity analyses showed similar results when the analysis was limited to studies that excluded smokers, women with chronic hypertension, or both. Significantly lower FMD was observed among women with less severe and more severe forms of preeclampsia, both at the time of disease and within the first three years post-partum. These results are consistent with the hypothesis that vascular dysfunction precedes the onset of disease in women with preeclampsia risk factors. They also suggest that vascular dysfunction may contribute to the pathophysiology of preeclampsia. Persistent vascular changes after preeclamptic pregnancies may represent a mechanistic link with increased risk for future cardiovascular disease in these women.

While FMD is a vascular function test, it is also an established method of evaluating future cardiovascular disease risk in research studies. Low brachial artery FMD predicts cardiovascular event risk in healthy populations and in patients with cardiovascular disease.[62–65] A recent meta-analysis concluded that for every 1% increase in brachial artery FMD, the relative risk of cardiovascular events was 0.87 (95% confidence interval 0.83 to 0.91).[11] Lower FMD In the preeclampsia group was a consistent finding across studies and time periods, despite differences in study designs, patient populations and FMD protocols. The high heterogeneity in some analyses was explained by variations in the magnitude of the effect, rather than the direction.

While most studies conducted at the time of preeclampsia and post-partum excluded women with co-morbidities (i.e. chronic hypertension, diabetes, cardiovascular or renal disease), studies conducted prior to pregnancy included women with a variety of risk factors and co-morbidities. Studies that reported lower FMD in women with a history of preeclampsia recruited women with at least one preeclampsia risk factor,[16, 18–20] enriched their sample with women who had at least one preeclampsia risk factor,[23] or enrolled women with a normal vs. abnormal uterine artery Doppler velocimetry test in mid-pregnancy.[17, 26] Four studies found no differences in FMD between women who developed preeclampsia, compared to women who did not have preeclampsia. Two of these studies did not select or enrich their samples with women who had preeclampsia risk factors.[22, 27] The other two studies enrolled women with a single risk factor (long duration Type 1 diabetes,[21] systemic autoimmune disease[24]). These high-risk women may have had endothelial dysfunction[66, 67] prior to pregnancy. Additional studies conducted prior to conception and in early pregnancy are needed to determine whether the vascular dysfunction observed prior to preeclampsia is due to pre-existing maternal risk factors, or is attributable to early stages in the disease process.

There are several possible explanations for the finding that vascular dysfunction in women with preeclampsia does not resolve during the first three years post-partum. Women who have had preeclampsia may have persistent endothelial dysfunction due to risk factors that pre-dated the pregnancy. Alternatively, preeclampsia could also worsen other cardiovascular risk factors, increasing a women's risk of future hypertension and cardiovascular disease. Finally, preeclampsia may cause lasting damage to the heart and vasculature. If preeclampsia causes lasting damage that contributes to future cardiovascular disease, then treatment goals may need to be adjusted to prevent or mitigate this damage.

Unexpectedly, a small number of studies suggest that lower FMD in women with a history of preeclampsia was no longer apparent by 10 years post-partum. These results should be interpreted with caution, as they are based on a four studies and include fewer women that studies conducted at other time periods. A meta-analysis published in 2005 found that while FMD was related to cardiovascular risk factors in low risk populations, no association was observed in medium and high risk populations.[68] The authors postulated that FMD may not reflect endothelial dysfunction accurately in high-risk patients with stiffer brachial arteries. These findings suggest that the lack of a relationship between FMD and preeclampsia at 10 years post-partum could be related to an increase in their cardiovascular burden. However, a second meta-analysis conducted in 2013 reported that FMD was predictive of future cardiovascular events in both asymptomatic and diseased populations.[69] While this meta-analysis focused on FMD, other vascular function tests or markers may yield different results. This meta-analysis sets the stage for future studies aiming to understand the trajectory of and mechanisms regulating changes in vascular health beyond three years post-partum. Finally, studies that report two additional measurements that are derived from the FMD test, LFMC and the shear stimulus for FMD, are needed. Combining these three measurements may provide additional insight into the nature and location of vascular dysfunction.[10]

This meta-analysis highlights several limitations of the current literature, which include:

- Publication bias: All papers were small observational studies. Negative studies may not have been published. Mitigation strategy: We included abstracts and unpublished data.
- Referral bias: Patients with pre-existing conditions or severe forms of preeclampsia may be over-represented, as most studies were conducted at tertiary care or teaching hospitals. Mitigation strategy: Most studies conducted at the time of preeclampsia or post-partum excluded women with co-morbidities.
- Non-representative samples in studies conducted prior to preeclampsia: Most studies conducted prior to preeclampsia exclusively enrolled or enriched their sample with women with co-morbidities or risk factors. Recent guidelines outlined the problems with this approach.[70]
- Pre-existing risk factors: Current guidelines recommend that studies focusing on prediction, prevention, treatment or mechanisms of preeclampsia account for obesity, smoking and fetal sex.[70] Many studies reported a higher average BMI in the preeclampsia group, which may contribute to vascular dysfunction prior to

conception. Future studies should clarify the relative contributions of pre-existing maternal risk factors, vs. damage caused by preeclampsia, to vascular dysfunction in women with preeclampsia. No studies examined the relationship between FMD and fetal sex. Mitigation Strategy: Sensitivity analyses of studies that excluded smokers yielded similar results.

- FMD methodology: Most studies used older protocols, in which differences in FMD may be an artifact of the time selected for post-release diameter measurement.[71, 72] Percent FMD may underestimate FMD in large arteries and overestimate FMD in small arteries.[73] Recently proposed allometric scaling techniques may address this problem, however they are heavily debated in the FMD literature.[74–76] No studies examined allometrically-scaled FMD.

When compared to women who did not develop preeclampsia, women with pre-existing risk factors who later developed preeclampsia had lower FMD prior to the clinical diagnosis of disease (~20–29 weeks gestation). Women with preeclampsia also had lower FMD at the time of preeclampsia and within the first three years post-partum. Similar results were observed when the analysis was limited to studies that excluded women with chronic hypertension, smokers, or both. A few studies suggested that lower FMD in women with a history of preeclampsia was no longer evident by 10 years post-partum, however more research is needed.

Perspectives

This results of this meta-analysis are consistent with the hypothesis that vascular dysfunction may contribute to the pathophysiology of preeclampsia and does not resolve in the first three years post-partum. Further studies should determine whether women without pre-existing risk factors have vascular dysfunction prior to developing preeclampsia, and clarify whether vascular dysfunction persists beyond three years post-partum in women with a history of preeclampsia. These studies will set the stage for novel cardiovascular risk markers and early prevention and treatment strategies for women who have had preeclampsia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and Significance

What is New?

When compared to women who did not have preeclampsia, women who had preeclampsia had lower FMD prior to the clinical diagnosis of preeclampsia, at the time of diagnosis and for three years post-partum.

What is Relevant?

Women with a history of preeclampsia have underlying endothelial dysfunction, as measured by FMD. This may translate into elevated cardiovascular risk later in life.

Summary

A meta-analysis of studies of FMD in preeclampsia indicates that endothelial dysfunction may be mechanistically related to both the pathophysiology preeclampsia and to elevated future cardiovascular disease risk in the affected women.

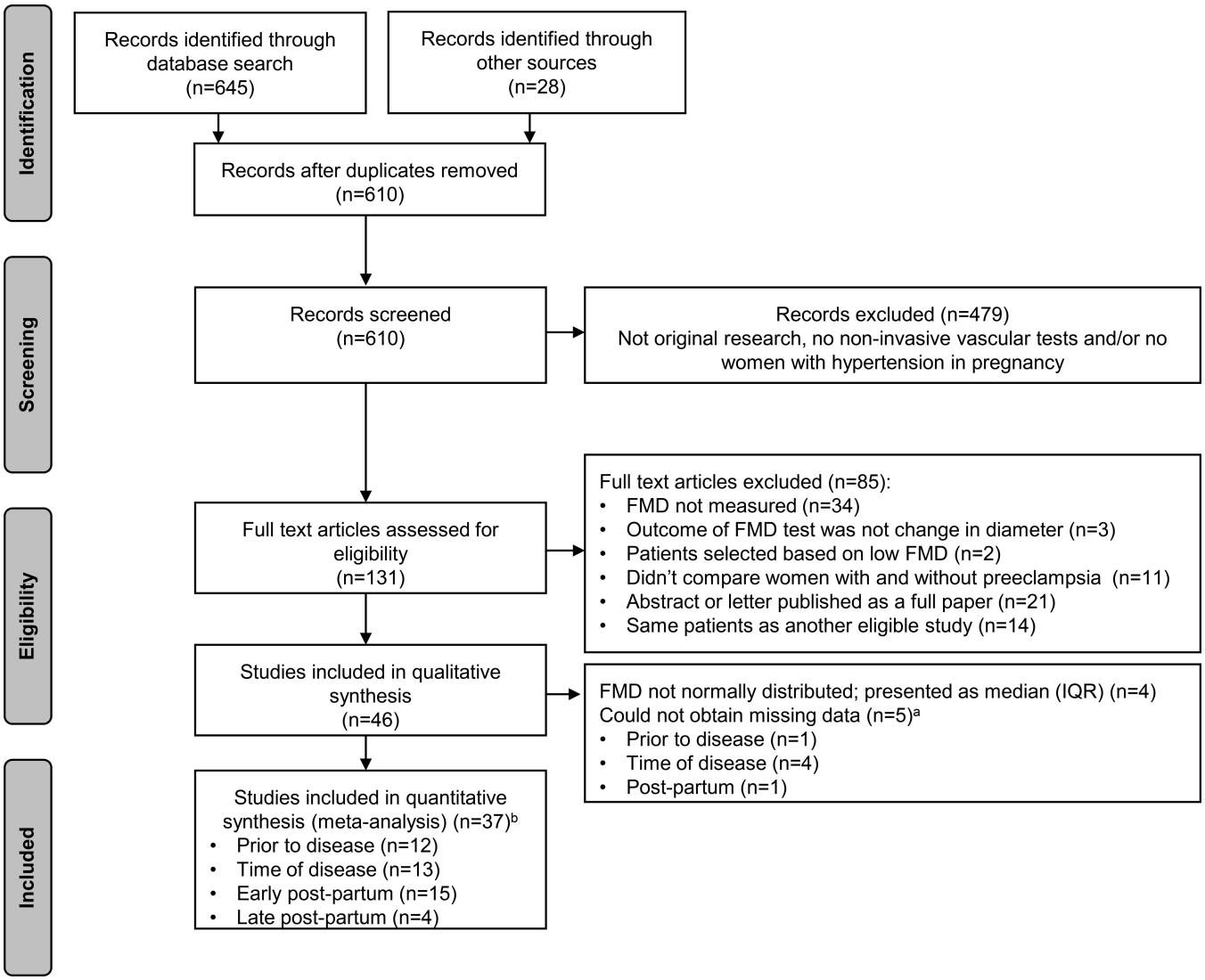

Figure 1.

Study Flow Chart

[a]One study obtained measurements at the time of disease and post-partum

[b]One study obtained measurements at 3 time points. Five studies obtained measurements at two time points.

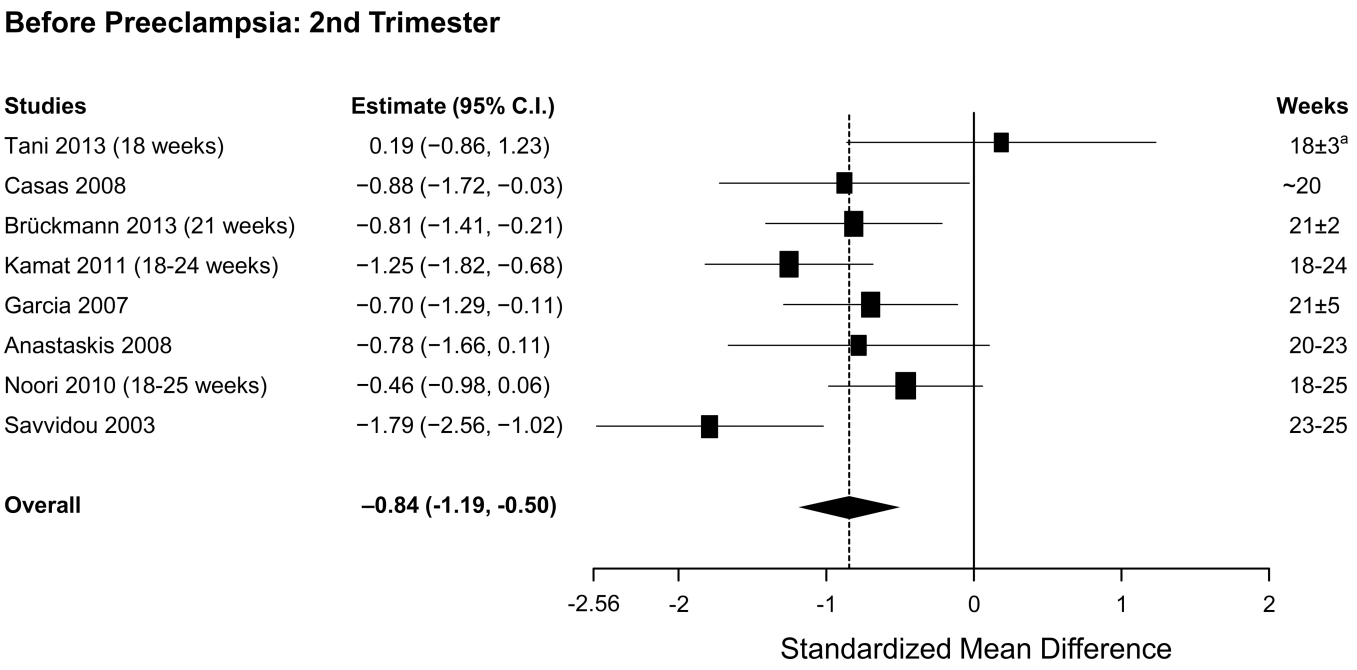

Figure 2.

Standardized Mean Difference in FMD Among Studies Conducted Before the Clinical Diagnosis of Preeclampsia

[a]All participants had systemic autoimmune disease

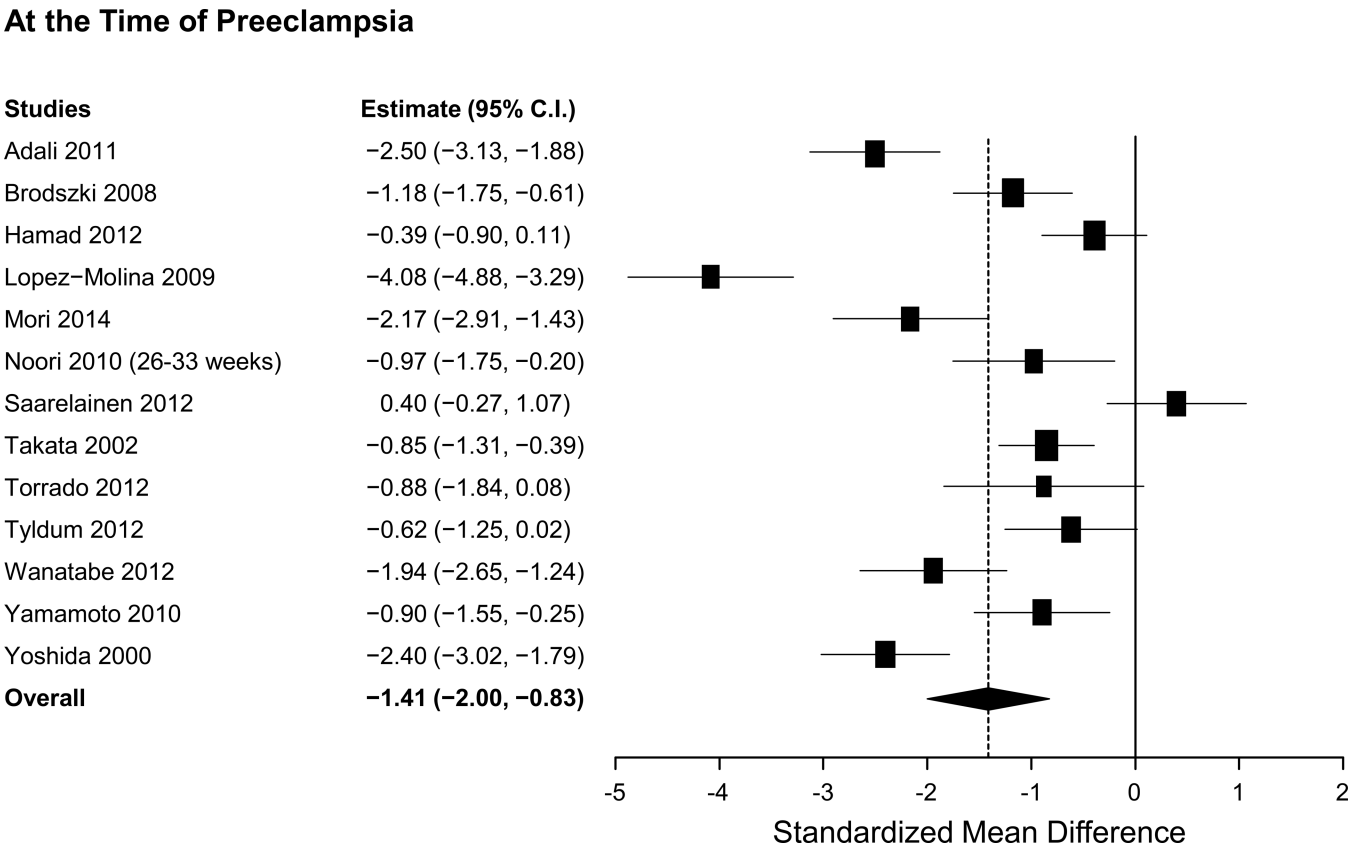

Figure 3.
Standardized Mean Difference in FMD Among Studies Conducted At the Time of Preeclampsia

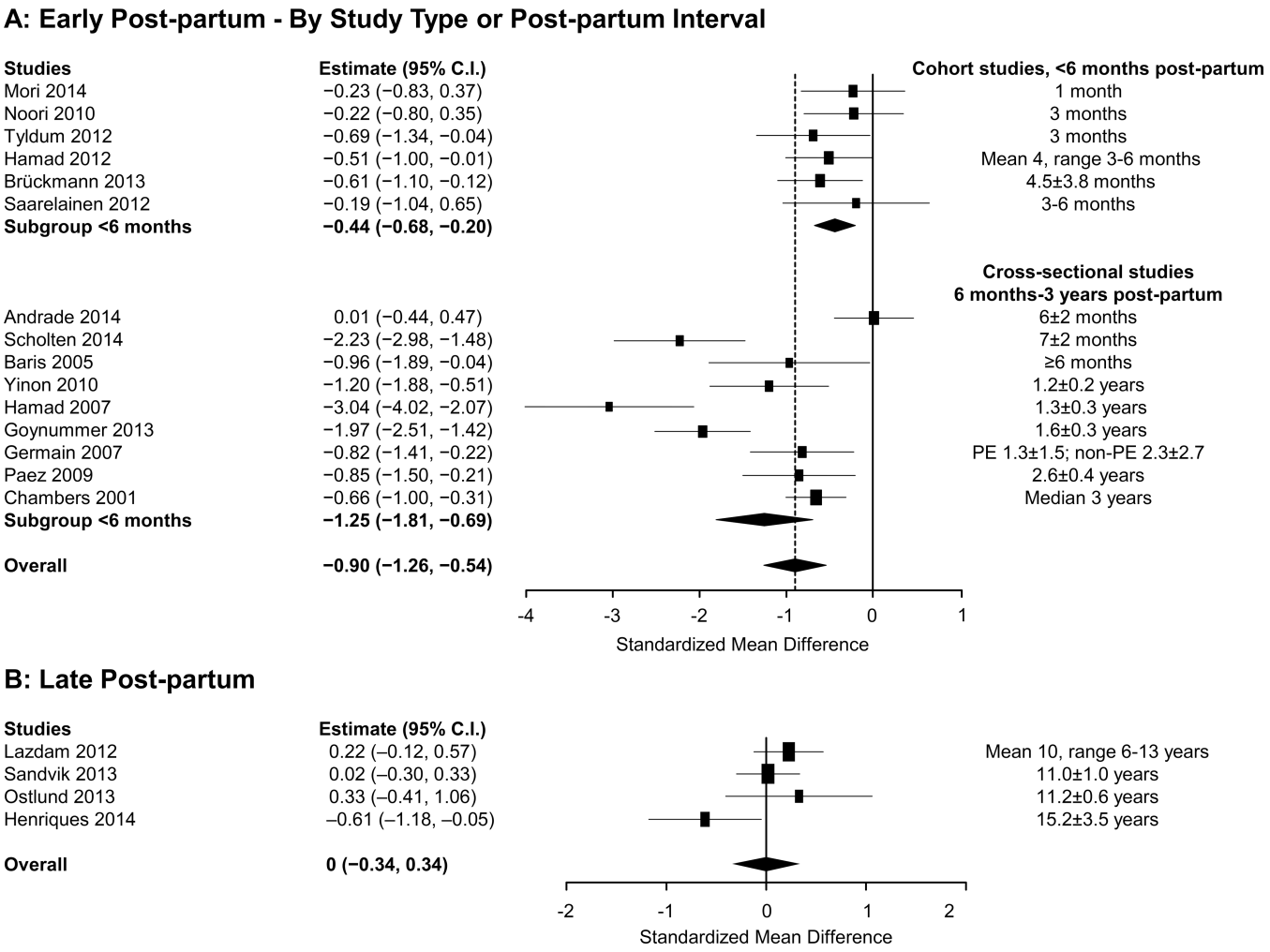

Figure 4.

Standardized Mean Difference in FMD Among Studies Conducted After Preeclampsia