Markers of Vascular Dysfunction After Hypertensive Disorders of Pregnancy
A Systematic Review and Meta-Analysis

Sophie Grand’Maison, Louise Pilote, Marisa Okano, Tara Landry, Natalie Dayan

Abstract—Women with prior hypertensive disorders of pregnancy (HDP) are at twice the risk of cardiovascular disease compared with women with prior normotensive pregnancy, possibly because of sustained vascular dysfunction after delivery. The aim of this systematic review and meta-analysis is to summarize evidence of vascular dysfunction at least 3 months after HDP. Articles in all languages were retrieved from principal databases. Studies included were observational, with HDP as the main exposure and measurements of vascular dysfunction via imaging modalities or serum biomarkers as the main outcome, assessed at least 3 months postpartum. We pooled results of modalities reported in >3 studies using a random effects model. Of 6109 potentially relevant studies, 72 were included that evaluated 10 imaging modalities and 11 serum biomarkers in 8702 women. There was evidence of vascular dysfunction in women post HDP compared with women with prior normal pregnancy when measured by carotid-femoral pulse wave velocity (0.64 m/s [0.17–1.11]), carotid intima–media thickness (0.025 mm [0.004–0.045]), and augmentation index (5.48% [1.58–9.37]), as well as mean levels of soluble fms-like tyrosine kinase (6.12 pg/mL [1.91–10.33]). Between-groups differences in measures of vascular dysfunction were more pronounced when assessments were performed in younger women (<40 years) or closer to the index pregnancy for almost all modalities. In conclusion, pooled data from studies evaluating vascular imaging suggest that some vascular dysfunction persists after HDP as compared with women with prior normal pregnancy. (Hypertension. 2016;68:1447–1458. DOI: 10.1161/HYPERTENSIONAHA.116.07907.) • Online Data Supplement

Key Words: biomarkers ■ endothelium ■ hypertension ■ imaging ■ preeclampsia/pregnancy ■ pregnancy and postpartum

Women who have had hypertensive disorders of pregnancy (HDP), including preeclampsia and gestational hypertension,1,2 have twice the risk of subsequent cardiovascular disease (CVD) compared with women who have had normotensive pregnancies.3,4 Furthermore, severity of HDP and fetal compromise seem most strongly associated with CVD and cardiovascular mortality.5,6

Vascular dysfunction, which could be preexisting or following HDP, including endothelial dysfunction, arterial stiffness, and subclinical atherosclerosis, has been suggested as a putative mechanism for this underlying association. Preeclampsia is a complex maternal syndrome characterized by placental hypoperfusion and subsequent widespread endothelial dysfunction because of the release of inflammatory cytokines and antiangiogenic proteins.7,8 In particular, soluble fms-like tyrosine kinase 1 (sFlt-1), an antiangiogenic protein, is elevated within the placenta and serum of preeclamptic women.9 This protein induces endothelial dysfunction by reducing the interaction of placent al growth factor (PIGF) and vascular endothelial growth factor (VEGF) with their endothelial receptors.10 An elevated ratio of sFlt-1 to PIGF has been found to be predictive of preeclampsia.11 Soluble endoglin, an important agent in vascular homeostasis,12 has also been observed at elevated levels in the serum of preeclamptic women and correlates with disease severity.13

It remains unclear whether some degree of vascular dysfunction persists in women after pregnancies complicated by HDP beyond what is captured through traditional atherosclerotic risk factors. Several vascular imaging modalities assessing function (eg, flow-mediated dilatation, pulse wave velocity, and augmentation index [AIx]) and structure (carotid intima–media thickness [cIMT]) and serum angiogenic biomarkers (eg, sFlt-1, VEGF, and PIGF) have been studied in the postpartum period. However, although some authors have reported persistent abnormalities after HDP,14–17 others have not.18–21 A 2014 meta-analysis of observational studies on nontraditional biomarkers after HDP concluded that there was evidence of endothelial dysfunction among women with a history of HDP when compared with women with previously uncomplicated
pregnancies. However, emphasis in this review was on biomarkers of unclear relevance to vascular disease (eg, serum homocysteine). Thus, the aim of the present systematic review and meta-analysis was to summarize and update evidence for vascular dysfunction at least 3 months after HDP, as measured by imaging modalities and a wide variety of relevant serum biomarkers involved in angiogenesis, thrombosis, and inflammation.

**Methods**

**Data Sources and Searches**

The following databases were searched for relevant studies: MEDLINE (via OvidSP 1946 to May 20, 2015; via PubMed 1946 to May 20, 2015); Embase Classic+Embase (via OvidSP 1947 to May 20, 2015); BIOSIS Previews (via OvidSP 1969 to 2015, Week 25); CINAHL-Plus with full text (via Ebsco, 1937 to May 20, 2015); The Cochrane Central Register of Controlled Trials (via The Cochrane Library, issue 4 of 12, April 2015). The search strategies used text words and relevant indexing to answer the following question: are HDP associated with vascular dysfunction in the postpartum period? The full MEDLINE strategy (online-only Data Supplement) was applied to all databases, with modifications to search terms as necessary. Further studies were identified in Web of Science and Scopus (16/11/2015) by examining the reference lists of included studies. Clinical Trials registries were searched to identify relevant, ongoing research. Conference proceedings from the Society of Obstetricians and Gynaecologists of Canada (http://sogc.org/) were searched from 2013 to 2014. The Medline strategy was rerun before submission (3 studies were added).

**Definitions of Exposure and Outcome**

The exposure of interest was any HDP, including preeclampsia, eclampsia, gestational hypertension, or chronic hypertension with superimposed preeclampsia according to the current guidelines. Preeclampsia was defined by a new onset of a blood pressure >140/90 mm Hg with proteinuria >0.3 g/24 h after 20 weeks of gestation, while eclampsia was the presence of seizures. Gestational hypertension was defined as a diastolic blood pressure >90 mm Hg after 20 weeks of gestation, and we also included systolic blood pressure >140 mm Hg according to the most recent guidelines. Superimposed preeclampsia was defined as preexisting hypertension with new onset proteinuria >0.3 g/24 h after 20 weeks of gestation. The majority of the included studies used normotensive pregnancy as the main comparison group. Four studies also included a control group of nulliparous women. We restricted our meta-analyses to comparisons with prior normotensive pregnancy.

The outcome of interest was any form of vascular dysfunction measured by imaging modalities and serum biomarkers. We included all imaging modalities assessing various types of vascular dysfunction: endothelial dysfunction by flow-mediated dilatation, forearm blood flow, laser doppler and endoPAT, arterial stiffness by pulse wave velocity, and AIx and subclinical atherosclerosis by cIMT. Only serum biomarkers directly linked to vascular function either alone or in association with preeclampsia were considered, including markers of angiogenesis (sFlt-1, VEGF, PIGF, and soluble endoglin), inflammation (soluble intercellular adhesion molecule-1 [sICAM-1] and soluble vascular cellular adhesion molecule-1 [sVCAM-1]), and thrombosis (endothelin, and fibronectin). We also included novel, yet promising, biomarkers (miRNA) and growth arrest-specific protein.

**Study Selection**

Publications were assessed for inclusion and quality in accordance with PRISMA guidelines (Preferred Reporting Items for Systematic Review and Meta-Analysis). Two independent reviewers (S. Grand’Maison and M. Okano) performed the study selection using specific inclusion criteria to ensure accuracy and reproducibility. The first screening was based on titles and abstracts of identified publications. All potentially relevant studies were retrieved for full-text evaluation. Both reviewers independently evaluated the full-text articles, and reasons for exclusion were recorded. Disagreement was resolved by discussion between the 2 reviewers and by a third reviewer (N. Dayan) as necessary. The inclusion criteria were human studies, observational studies with a control group, HDP (exposure), and vascular dysfunction assessed at least 3 months postpartum (to allow return to prepregnancy physiological baseline) by imaging modalities or serum biomarkers. If duplicate studies were found within the same data source, either the most recent or the most complete publication was selected.

**Data Extraction**

S. Grand’Maison and M. Okano completed data extraction for all articles that met inclusion criteria during the full-text review. Study design and details regarding exposure, including the definition provided by each study, were recorded. The following baseline characteristics of study participants were collected: number of participants in each group, mean or median age at the time of assessment, parity, mean time since the affected pregnancy, and presence of CVD risk factors at the time of the assessment (chronic hypertension, diabetes mellitus, cholesterol profile, prior history of symptomatic CVD, smoking status, and body mass index). The modalities used to assess vascular dysfunction (eg, dynamic vascular imaging or blood biomarkers) with associated mean or median values for each study population were recorded. Authors of articles with insufficient study details or incomplete reported results were contacted and allotted 3 weeks’ time for response. The characteristics of the studies included in the meta-analysis are presented in Table and of those included in the systematic review only in Table S1 in the online-only Data Supplement.

**Quality Assessment**

The reviewers applied the Newcastle-Ottawa Scale to assess study quality. The quality of observational studies was determined by assignment of stars to a series of questions that assess 3 categories of biases: selection, comparability, and exposure. Based on available literature, we considered age, chronic hypertension, and diabetes mellitus as the most...
<table>
<thead>
<tr>
<th>Studies</th>
<th>Exposure (n)</th>
<th>Controls (n)</th>
<th>Age Exposed, y</th>
<th>Age Controls, y</th>
<th>Follow-Up Exposed, mo</th>
<th>Follow-Up Controls, mo</th>
<th>Modalities Used</th>
<th>Quality Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akhter et al36 (CS)</td>
<td>Severe preeclampsia (42)</td>
<td>Normotensive (44)</td>
<td>44±3</td>
<td>44±3</td>
<td>132±60</td>
<td>132±60</td>
<td>cIMT</td>
<td>9</td>
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<td>Aykas et al37 (CS)</td>
<td>Preeclampsia (25)</td>
<td>Normotensive (20)</td>
<td>…</td>
<td>…</td>
<td>At least 60</td>
<td>At least 60</td>
<td>FMD, cIMT</td>
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<tr>
<td>Blauw et al25 (CS)</td>
<td>Early-onset preeclampsia (22)</td>
<td>Normotensive (23)/never pregnant (22)</td>
<td>31±4</td>
<td>31±4/30±6</td>
<td>6.4±2.9</td>
<td>7.0±2.6</td>
<td>cIMT</td>
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<td>Blauw et al38 (CS)</td>
<td>Preeclampsia (17)</td>
<td>Normotensive (16)</td>
<td>33±5</td>
<td>34±4</td>
<td>57</td>
<td>52</td>
<td>cIMT, sICAM-1</td>
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<td>Chambers et al18 (CS)</td>
<td>Single (78)/recurrent (35) preeclampsia</td>
<td>Normotensive (48)</td>
<td>34±5/37±5</td>
<td>35±6</td>
<td>36 (median)</td>
<td>36 (median)</td>
<td>sICAM-1, FMD</td>
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<td>Collen et al39 (CS)</td>
<td>Previous preeclampsia and now normotensive (10) and now with chronic hypertension (8)</td>
<td>Previous normotensive pregnancy and still normotensive (10)</td>
<td>60±5.4/62±4.2</td>
<td>63±3.1</td>
<td>=480</td>
<td>=480</td>
<td>cPWV</td>
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<td>Collen et al40 (CS)</td>
<td>HDP (50)</td>
<td>Normotensive (55)</td>
<td>63±6</td>
<td>63±5</td>
<td>408–480</td>
<td>408–480</td>
<td>cPWV, Alx, cIMT</td>
<td>6</td>
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<tr>
<td>Drost et al41 (CC)</td>
<td>Early-onset preeclampsia (339)</td>
<td>Normotensive (332)</td>
<td>38.9±4.9</td>
<td>39.3±4.4</td>
<td>109±44</td>
<td>128±36</td>
<td>sICAM-1, sVCAM-1</td>
<td>8</td>
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<td>Ehrenthal et al42 (CS)</td>
<td>HDP (33)</td>
<td>Normotensive (41)</td>
<td>30.4</td>
<td>32.0</td>
<td>12</td>
<td>12</td>
<td>Carotid–radial PWV, Alx</td>
<td>7</td>
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<td>Elvan-Taspinar et al43 (CS)</td>
<td>Early-onset preeclampsia (44)</td>
<td>Normotensive (46)</td>
<td>32.4±4.8</td>
<td>35.1±4.1</td>
<td>13 (4–52) (mean range)</td>
<td>12 (5–6) (mean range)</td>
<td>cPWV</td>
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<td>Gaugler-Senden et al44 (CS)</td>
<td>Severe early-onset (&lt;24 wk) preeclampsia (20)</td>
<td>Normotensive (20)</td>
<td>38.8 (22.1–47.7)</td>
<td>37.7 (23.8–41.9)</td>
<td>66 (48–120)</td>
<td>70 (53–131)</td>
<td>cIMT</td>
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<td>Gaugler-Senden et al45 (CS)</td>
<td>Severe early-onset (&lt;24 wk) preeclampsia (16)</td>
<td>Normotensive (18)</td>
<td>42.9 (38.8–45.1)</td>
<td>41.6 (38.8–45.7)</td>
<td>113 (110–124)</td>
<td>116 (112–131)</td>
<td>sFlt-1, VEGF</td>
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<td>Goynumber et al46 (CS)</td>
<td>Severe preeclampsia (34)</td>
<td>Normotensive (42)</td>
<td>30.94±4.37</td>
<td>29.67±4.29</td>
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<td>19±4</td>
<td>cIMT, FMD</td>
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<td>Hamad et al47 (CS)</td>
<td>Preeclampsia (18)</td>
<td>Normotensive (17)</td>
<td>30±4</td>
<td>31±4</td>
<td>15±3</td>
<td>15±3</td>
<td>FMD, sICAM-1, sVCAM-1</td>
<td>8</td>
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<tr>
<td>Hamad et al48 (CS)</td>
<td>Preeclampsia (35)</td>
<td>Normotensive (30)</td>
<td>…</td>
<td>…</td>
<td>5</td>
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<td>FMD, PIGF, sFlt-1, VEGF, sICAM-1, sVCAM-1</td>
<td>8</td>
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<tr>
<td>Henriques et al49 (CC)</td>
<td>Gestational hypertension (30)</td>
<td>Normotensive (30)</td>
<td>42.5±8.9</td>
<td>40.1±8.7</td>
<td>182±42</td>
<td>182±42</td>
<td>FMD</td>
<td>6</td>
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<tr>
<td>Hubel et al50 (CS)</td>
<td>Preeclampsia (29)</td>
<td>Normotensive (35)</td>
<td>33.7±5.8</td>
<td>30.8±6.7</td>
<td>18±10</td>
<td>18±9</td>
<td>sFlt-1, VEGF</td>
<td>6</td>
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<td>Kvehaugen et al51 (CS)</td>
<td>Preeclampsia (26)</td>
<td>Normotensive (15)</td>
<td>37.2±4.4</td>
<td>40.5±4.2</td>
<td>77 (median)</td>
<td>84 (median)</td>
<td>sFlt-1, VEGF, PIGF, Alx, Endoglin</td>
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<td>Lampinen et al52 (CS)</td>
<td>Preeclampsia (30)</td>
<td>Normotensive (21)</td>
<td>38±6</td>
<td>36±4</td>
<td>66</td>
<td>66</td>
<td>FBF, Alx</td>
<td>5</td>
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<tr>
<td>Lampinen et al53 (CS)</td>
<td>Preeclampsia (28)</td>
<td>Normotensive (20)</td>
<td>38±6</td>
<td>36±4</td>
<td>60–72</td>
<td>60–72</td>
<td>Alx, endothelin</td>
<td>6</td>
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<tr>
<td>McDonald et al54 (CC)</td>
<td>Preeclampsia (109)</td>
<td>Normotensive (219)</td>
<td>49 (44–55)</td>
<td>49 (45–56)</td>
<td>240 (median)</td>
<td>240 (median)</td>
<td>cIMT</td>
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<td>Mersch et al55 (CS)</td>
<td>Preeclampsia (12)</td>
<td>Normotensive (12)</td>
<td>29.9±1 (SEM)</td>
<td>30.2±0.8 (SEM)</td>
<td>12±0.6</td>
<td>12±0.4</td>
<td>cIMT</td>
<td>4</td>
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<tr>
<td>Ostlund et al56 (CS)</td>
<td>Severe preeclampsia (15)</td>
<td>Normotensive (16)</td>
<td>39.4±3.6</td>
<td>41.2±3.2</td>
<td>95±40</td>
<td>79±29</td>
<td>cPWV, Alx, FMD, PIGF, sICAM-1, sVCAM-1, sFlt-1</td>
<td>7</td>
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(Continued)
important confounders to be considered. The Newcastle-Ottawa scale was selected as opposed to the Cochrane Risk of Bias Assessment Tool: for NonRandomized Studies of Interventions as we did not evaluate an intervention. No study was excluded on the basis of quality alone.

**Statistical Analysis**

Results of studies were pooled using a random effects model if there were at least 3 studies evaluating the same technique or biomarker that reported means±standard deviation (SD) or standard error of mean (SEM). Results of the meta-analyses are presented as weighted mean difference (WMD) between HDP and normotensive pregnancy with the corresponding 95% confidence interval. Heterogeneity was assessed using the I-squared (I²) method. If substantial heterogeneity was present, results were only pooled if subgroup analyses reduced heterogeneity. Predefined subgroup analyses included stratified results based on women’s age at the time of assessment (dichotomized at 40 years), the delay since the index pregnancy (dichotomized at median duration of follow-up in months for each modality), study design (cohort or case–control), type of HDP (preeclampsia, gestational hypertension, or combined), and severity of cases. For modalities examined in 10 or more studies, visual inspection of funnel plot and an Egger’s test were conducted to assess for possible publication bias. A 2-sided P value <0.05 was considered statistically significant for all analyses. Analyses were conducted using Stata, version 13 (StataCorp).

**Results**

**Search Results and Characteristics of Included Studies**

In the initial literature search, 6109 potentially relevant studies were identified, of which 177 full-text articles were retrieved for detailed assessment (Figure 1). Sixty-five studies
Records identified through database searching (n=7378) → Additional records identified through other sources (n=3421) → Gray literature search = 15 References lists = 3406 → Records after duplicates removed (n=6109) → Abstracts and titles screened (n=6109) → Records excluded (n=5932) → Full-text articles excluded (n=105) Different outcomes = 43 Wrong or not specified timing = 12 Different exposure = 10 Duplicates = 25 Insufficient data = 4 Multiple reasons = 11 → Full-text articles assessed for eligibility (n=177) → Studies included in the meta-analysis (n=37)

and 7 abstracts with sufficient data were included in our final review: 59 case–control and 13 cohort studies for a total of 8702 women (3356 cases with HDP and 5346 controls). Thirty-seven studies were pooled in our analyses (Table). The characteristics of studies that were not pooled are presented in the Table S1.

The definitions of preeclampsia, gestational hypertension, and HDP were consistent with the guidelines of the International Society for the Study of Hypertension in Pregnancy, including the distinction between early (<34 weeks) and late (>34 weeks) preeclampsia. However, one study used an unusual definition for early preeclampsia (<24 weeks), as specified in Table.

The most frequently used modalities to assess different types of vascular dysfunction were cIMT, flow-mediated dilatation, carotid–femoral pulse wave velocity (cfPWV), AIx, sICAM-1, sVCAM-1, sFlt-1, and VEGF (Table S2), and results for these modalities were pooled if appropriate.

**Imaging Modalities of Vascular Dysfunction**

**Measures of Arterial Stiffness**

Arterial stiffness was assessed after any HDP using AIx in 1145 women (283 exposed and 862 controls) and more specifically after preeclampsia with cfPWV in 1087 women (242 exposed and 845 controls). Within these modalities, pooled results demonstrated persistence of arterial stiffness after the index pregnancy (AIx, WMD of 5.48% [1.58–9.37]; cfPWV, WMD of 0.64 m/s [0.17–1.11]; Figure 2). However, there was evidence of at least moderate heterogeneity measured by the $I^2$ method in these pooled modalities (AIx, 88.0%; cfPWV, 81.5%). We explored whether this was because of study quality, study design, or type of exposure. The heterogeneity in the AIx results seemed to be explained by study design because heterogeneity was not present in cohort studies ($I^2=0.0%$), but it was substantial in case–control studies ($I^2=91.3%$). Examining forest plots, the overall WMD for cfPWV was found to be influenced by the study by Tam et al, which was only available as an abstract. Excluding this study, heterogeneity was diminished ($I^2=0.0%$), but findings of greater arterial stiffness in women post HDP persisted. Subgroup analyses based on mean age (<40 or ≥40 years) revealed that differences in vascular dysfunction were more pronounced in younger women as measured by AIx (WMD of 6.27% [1.86–10.69] versus 3.62% [−4.55 to 11.79]) and cfPWV (WMD of 0.372 m/s [0.153–0.592] versus 0.771 m/s [0.003–1.538]). Visual inspection of a funnel plot and the Egger’s test revealed no evidence of publication bias for AIx (Figure S1).

**Measures of Subclinical Large Vessel Atherosclerosis**

Persistence of subclinical large-vessel atherosclerosis in women with HDP as compared with controls was also found. Pooled analysis of cIMT measured in 802 women (341 exposed and 461 controls) revealed an overall WMD of 0.025 mm [0.004–0.045]; Figure 2). However, there was
evidence of moderate heterogeneity (50.4%) measured by the $I^2$ method. Results of cIMT were influenced by the study by Aykas et al,37 without a readily apparent explanation: the population and definition of preeclampsia were similar, and the study was at low risk of bias. Nevertheless, pooled analyses excluding this study reduced heterogeneity ($I^2=0.0\%$) without affecting the overall WMD. Subgroup analyses based on mean age (<40 or ≥40 years) were similar as with arterial stiffness.
modalities (WMD of 0.031 mm [0.002–0.061] versus 0.009 mm [−0.012 to 0.029]). Visual inspection of a funnel plot and the Egger’s test revealed no evidence of publication bias for cIMT (Figure S2).

The magnitude of between-group differences in various measures of vascular dysfunction (cIMT, AIX, and cfPWV) diminished over time, as might be expected based on the development of traditional atherosclerotic risk factors in the control groups as they age (cIMT, WMD of 0.03 mm [0.01–0.05] before 48 months post delivery versus 0.02 mm [−0.02 to 0.07] after 48 months post delivery; AIX, WMD of 9.92% [5.92–13.92] before 60 months post delivery versus 2.69% [−1.79 to 7.17] after 60 months post delivery; cfPWV WMD of 0.63 m/s [−0.16 to 1.42] before 287 months post delivery versus 0.54 m/s [0.19–0.88] after 287 months post delivery). To test this hypothesis, we evaluated the absolute values in exposed and control women before and after the overall median follow up time (Table S3). We found that, indeed, cfPWV and cIMT increased over time (eg, with age) in the control groups. This same trend was not as apparent with AIX, but the duration of follow-up was shorter than the other marker of arterial stiffness (cfPWV).

**General Measures of Endothelial Dysfunction**

There was high heterogeneity between studies assessing endothelial dysfunction through flow-mediated dilatation, which was not reduced by our subgroup analyses. Thus, results of these studies were not pooled.

**Serum Biomarkers of Vascular Dysfunction**

**Markers of Angiogenesis**

Our included studies evaluated sFlt-1 (704 women [359 exposed and 345 controls]) and VEGF (528 women [273 cases and 255 controls]) to assess impaired angiogenesis in women with previous HDP. In pooled analyses, mean levels of sFlt-1 were modestly higher in women with previous HDP compared with women without (WMD of 6.12 pg/mL [−16.12 to 17.47] and 3.94 ng/mL [−18.04 to 25.92], respectively; Figure 3). There was moderate heterogeneity in studies assessing sICAM-1 (I²=59.0%), but not in studies measuring sVCAM-1 (I²=0.0%). As with the angiogenesis biomarkers, we were unable to account for the heterogeneity in sICAM-1 studies after evaluating the impact of study quality, study design, or type of HDP. In subgroup analyses based on maternal age and delay since pregnancy, no difference was observed with these biomarkers. There were not enough studies included to adequately assess publications bias.

**Other Modalities**

Our search strategy revealed studies evaluating other markers and techniques to measure vascular dysfunction. However, pooled analyses were not conducted either because there were 3 or fewer available studies (ie, PIGF, EndoPAT, fibronectin, soluble endoglin, miRNA, large and small artery elasticity index, growth arrest–specific protein 6, ambulatory stiffness index, CD34+–VEGF-2+, CD133–VEGF-2+; and vascular compliance) or because reported results were insufficient (laser doppler, forearm blood flow, and endothelin).

**Quality Assessment**

Quality assessment results are presented in Table and Table S1, with 53.5% (38/71) of the studies at medium risk of bias (4–6 stars) and 25.3% (18/71) at high risk (0–3 stars), which is mostly because of the inclusion of abstracts. Of the 37 pooled studies, 18 (48.6%) were at medium risk of bias.

**Discussion**

Our systematic review and meta-analysis represent the most recent and updated work summarizing the evidence for subclinical vascular dysfunction in women with prior HDP compared with women with prior normotensive pregnancies, which is a hypothesized mechanism explaining the increased risk of premature CVD in these women. We included case–control and cohort studies without language restriction and pooled studies stratified by modality to reduce potential heterogeneity. We explored reasons for heterogeneity in all pooled studies. We used a validated quality assessment tool (Newcastle-Ottawa Scale)⁴ and multiple reviewers to avoid selection bias. We summarized evidence from studies evaluating various types of vascular dysfunction through imaging modalities (arterial stiffness: cfPWV, AIX; and subclinical atherosclerosis: cIMT), as well as soluble biomarkers (angiogenesis: sFlt-1, VEGF; and inflammation: sICAM-1, sVCAM-1), in women with prior HDP. All of the pooled studies on imaging modalities demonstrated more vascular dysfunction in women with prior HDP as compared with women with prior normotensive pregnancy. In contrast, sFlt-1 was the only biomarker consistently higher in women with prior preeclampsia relative to women with recent normotensive pregnancy. Results for other biomarkers were varied and could not be pooled. To date, literature on serum biomarker involvement in angiogenesis or inflammation after HDP has been inconsistent, with reports of lower⁴¹ or higher⁴² levels in women with preeclampsia.
compared with normotensive pregnancy after a 3-month follow-up period. Our hypothesis is that serum biomarkers, which are responsible for the initial endothelial insult during pregnancy and are more expressed in placental tissue than in the endothelium, may not be detected at elevated levels after the index pregnancy. Furthermore, commercial kits might not

Figure 3. Results of weighted mean difference (WMD) between women with and without prior hypertensive disorders of pregnancy (HDP) of pooled serum biomarkers. Soluble fms-like tyrosine kinase 1 (sFlt-1, pg/mL; A); vascular endothelial growth factor (VEGF, pg/mL; B); soluble intercellular adhesion molecule-1 (sICAM-1, ng/mL; C); soluble vascular cellular adhesion molecule-1 (sVCAM-1, ng/mL; D). *Higher values of sFlt-1, sICAM-1, and sVCAM-1 mean more vascular impairment, whereas higher values of VEGF mean less vascular impairment.
be sensitive enough to measure lower levels of these circulating or protein-bound biomarkers later in life. However, the endothelial damage they caused during the index pregnancy is sustained and captured by other more sensitive vascular imaging modalities years after delivery.

Thus, we think that our pooled results of vascular imaging techniques (cfPWV, cIMT, and AIx) provide more robust evidence of vascular dysfunction after HDP. cIMT is a well-established marker of subclinical atherosclerosis. Specifically, a value of >0.6 mm has been associated with a high risk of coronary artery disease. We found a pooled WMD of 0.025 mm (0.004–0.045), which is small but may, nevertheless, indicate the beginning of large-vessel atherosclerosis in women post HDP. Furthermore, cfPWV, the gold standard measure of arterial stiffness, has been directly associated with increased risk of vascular disease and events. A recent meta-analysis demonstrated that an increase of cfPWV by 1 m/s corresponds to an adjusted risk increase of 14% in total vascular events after mean follow-up of 7.7 years. By extension, the WMD of 0.64 m/s (0.17–1.11) as demonstrated in our meta-analysis indicates greater arterial stiffness and a heightened risk of vascular disease in young women with prior HDP.

We found that the difference of vascular dysfunction between women with and without prior HDP was more pronounced in younger women. This may indicate that damage is present in early years after complicated pregnancy, which is generally a period where traditional CVD risk factors are not experienced. This difference appeared to be attenuated with time, possibly because with the development of traditional atherosclerotic risk factors, the disparity between groups becomes less evident. Other factors that change over time may also explain this observed phenomenon. For example, older women might become more aware of CVD and choose to modify their lifestyle or start medications for CVD risk factors, both of which may have influenced the results of vascular imaging techniques.

Regardless, these findings have important potential implications for management and surveillance of young women after HDP. In an effort to prevent CVD in these women, it is currently recommended that women with HDP be screened for CVD risk factors in the postpartum period. Our study results suggest that systematic measurement of vascular dysfunction with imaging modalities might be considered as part of global CVD screening among this population. The utilization of one of these imaging modalities could help to distinguish women with previous HDP at high risk (with preclinical atherosclerosis) who could benefit from a more aggressive control of CVD risk factors and specific reduction strategies even if their absolute risk of CVD is low. Furthermore, use of techniques that seem to persist regardless of age or time since delivery might be the most appropriate choices to follow high-risk women over time. Thus, future prospective studies are required to determine whether the presence of vascular dysfunction on imaging is correlated with a greater rate of vascular events and should prompt specific vascular risk reduction therapies.

Our study contributes to the knowledge gained from the recent meta-analysis by Visser et al on CVD biomarkers after HDP. In our study, we included more biomarkers directly linked to vascular function because our hypothesis was that global endothelial dysfunction results in accelerated vascular aging and persistent dysfunction years after delivery. Additional studies on fibronectin, sICAM-1, sVCAM-1, endothelin, VEGF, and sFlt-1 are featured in our meta-analysis because our search strategy included a supplemental database (BIOSIS Previews), as well as references of the included articles. The complete search strategy of the meta-analysis by Visser et al was not available in the full text of the article or the supplemental material; thus, we were unable to directly compare the MeSH and non-MeSH terms used. Our meta-analysis, to our knowledge, is the first to pool results of vascular dysfunction measured by validated imaging modalities, which most closely reflected the vascular endothelium function and structure.

We restricted our review to studies that assessed vascular dysfunction at least 3 months postpartum to allow time to return to prepregnancy physiology. We wanted to answer the question whether events occurring during pregnancy resulted in accelerated vascular aging beyond the immediate postpartum period. The delay since pregnancy varied significantly between the studies (range 3–480 months), suggesting that damage persists well beyond the immediate postpartum period in most cases and is unlikely to completely regress spontaneously. Large-scale prospective studies would better address the trajectory of vascular dysfunction after HDP to eventually assess whether vascular dysfunction is present prepartum in these women.

Limitations

Our review has several limitations. First, there was substantial heterogeneity in some of our results that could not be explained by the age of women at the time of assessment, study design, or time elapsed since the index pregnancy. Thus, the pooled results for those modalities should be interpreted with caution. However, heterogeneity for other results has been explained by study design (AIx) or by the results of one specific study (cIMT and cfPWV). Second, the duration of follow-up since the index pregnancy was reported in various ways and precluded preplanned subgroup analyses to address whether a longer or shorter delay affected the heterogeneity of some of our pooled results. However, by estimating the median duration of follow-up in months for each modality, we were able to show that for studies assessing cIMT and AIx, the difference between both groups was more pronounced in the earlier period after the index pregnancy. This finding corroborates the results of our subgroup analyses based on age because it shows that women have more vascular dysfunction near the index pregnancy when they usually are younger and have a less important burden of traditional CVD risk factors. The definitions of HDP, preeclampsia, and gestational hypertension were mainly uniform; however, studies published after 2014 may have used slightly different definitions of preeclampsia owing to the release of new guidelines on HDP, which added systolic blood pressure >140 mm Hg to diastolic blood pressure of >90 mm Hg as a diagnosis criteria. Because studies were conducted during and after pregnancy, it is unclear whether vascular dysfunction was already present prepartum, contributing to the development of HDP. However, studies evaluating vascular function in young women before
and throughout pregnancy until the development of CVD many years later do not exist. Longitudinal prospective cohort studies beginning in the prepregnancy phase would be laborious but informative on the trajectory between HDP and CVD. In addition, our review did not include cardiac echocardiography because our focus was on vascular impairment. A future systematic review on this topic would contribute to our understanding of overall cardiac function after HDP. Moreover, to completely evaluate the confounding effect of traditional atherosclerotic risk factors on the vascular dysfunction measurements, an individual patient analysis would be preferable, but could not be done with available data. Finally, owing to small numbers of studies for some modalities, mostly for biomarkers, we were unable to assess for publication bias. Thus, it remains possible that unpublished studies exist, which could have led us to overestimate the presence of vascular dysfunction post HDP with imaging modalities or underestimate it with biomarkers.

Despite these limitations, we think that our results complement previous findings and provide further evidence for vascular dysfunction after HDP. Risk stratification of women after HDP using vascular imaging modalities in addition to atherosclerotic factors might identify subgroup who would benefit from aggressive risk reduction approaches.

**Perspectives**

This systematic review and meta-analysis demonstrated the presence of vascular dysfunction in women with previous HDP when compared with women with previous normotensive pregnancies. Vascular imaging techniques seem to be useful tools in identifying women with vascular dysfunction in the postpartum period after HDP. In contrast, serum biomarkers measured after HDP appeared not as sensitive to accurately measure underlying dynamic endothelial damage. The use of vascular imaging modalities in the postpartum period might help further define an at-risk group to be targeted for more aggressive risk factor modification.

**Sources of Funding**

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**Disclosures**

None.

**References**

DG. Arterial stiffness and wave reflection 1


What Is New?

• This study summarizes evidence for measurable subclinical vascular dysfunction, including vascular imaging techniques and soluble fms-like tyrosine kinase 1, months to years after pregnancies complicated by hypertensive disorders of pregnancy.

• Vascular imaging techniques seem to be useful tools to distinguish women at risk for vascular disease in the postpartum period after hypertensive disorders of pregnancy.

What Is Relevant?

• There is uncertainty regarding the mechanism of increased cardiovascular disease in women who have had hypertensive disorders of pregnancy.

• This study provides further evidence for vascular dysfunction after initial hypertensive injury. Further, the optimal method of screening women after hypertensive disorders of pregnancy is not known.

Novelty and Significance

• Results of this study suggest that use of vascular imaging techniques might further define an at-risk population in the postpartum period to be targeted for assessment of more aggressive risk factor modification.

Summary

Vascular dysfunction is present in women after hypertensive disorders of pregnancy. It is currently recommended that women with a history of complicated pregnancy be screened for cardiovascular risk factors in the postpartum period. Risk stratification of women after these pregnancy complications using vascular imaging modalities in addition to measurement of usual atherosclerotic factors might identify subgroup who would benefit from aggressive risk reduction approaches.
Markers of Vascular Dysfunction After Hypertensive Disorders of Pregnancy: A Systematic Review and Meta-Analysis
Sophie Grand'Maison, Louise Pilote, Marisa Okano, Tara Landry and Natalie Dayan

Hypertension. 2016;68:1447-1458; originally published online October 17, 2016; doi: 10.1161/HYPERTENSIONAHA.116.07907

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MARKERS OF VASCULAR DYSFUNCTION AFTER HYPERTENSIVE DISORDERS OF PREGNANCY: A SYSTEMATIC REVIEW AND META-ANALYSIS
SUPPLEMENTAL MATERIAL

Short title: Pregnancy Complications And Vascular Dysfunction

Sophie Grand’Maison, MD MSc candidate,\textsuperscript{1,2} Louise Pilote, MD MPH PhD, \textsuperscript{1,2,3} Marisa Okano, MScPH,\textsuperscript{1} Tara Landry MLIS,\textsuperscript{4} Natalie Dayan, MD MSc.\textsuperscript{2,3}
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\textsuperscript{4} Medical Library, McGill University Health Centre, Montreal, Quebec, Canada.

Corresponding author: Natalie Dayan, 1001 Boulevard Decarie D05.5846 Montreal, Quebec, Canada H3A 3J1. Telephone: 514-934-1934 #32967. Fax: 514-843-1676. natalie.dayan@mcgill.ca
**Supplemental text: Medline Search Strategy**

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3. limit 2 to yr="1970 - 2004"
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5. 3 and 4
6. Pregnancy Complications, Cardiovascular/
7. limit 6 to yr="1970 - 2004"
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9. (eclamp* or preclamp* or preeclamp*).tw,kf.
10. (EPH adj3 (complex* or gestosis or toxemia* or toxaemia*)).tw,kf.
11. (PIH or PPEP).tw,kf.
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22. Cardiovascular Diseases/
23. Vascular Diseases/
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26. blood flow velocity/
27. Carotid Intima-Media Thickness/
28. Laser-Doppler Flowmetry/
29. Pulse Wave Analysis/
30. exp echocardiography/
31. exp Ultrasonography, Doppler/
32. vascular stiffness/
33. elasticity/
34. limit 33 to yr="1990 - 2011"
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40. (pulse wave adj2 (analys* or velocit*)).tw,kf.
41. augment* inde*.tw,kf.
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Control Groups/
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61 58 not (59 or 60)
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63 61 not 62
64 limit 63 to "review articles"
65 limit 63 to systematic reviews
66 63 not (64 or 65)
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68 limit 67 to yr="1990 -Current"
Supplemental References:


35. Murphy MSQ, Smith GN. Pre-eclampsia is associated with early postpartum endothelial dysfunction as measured by laser doppler flowmetry and iontophoresis. *Reproductive Sciences*. 2014;1:123A.
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<td>Preeclampsia (10)</td>
<td>Normotensive pregnancy (10)</td>
<td>46 (40-49)</td>
<td>45 (43-48)</td>
<td>264 (192-276)</td>
<td>246 (216-288)</td>
</tr>
<tr>
<td>Sattar,</td>
<td></td>
<td></td>
<td>Preeclampsia</td>
<td>Normotensive</td>
<td>43 (40-44) (43-47)</td>
<td>At least 226</td>
<td>At least 226</td>
<td>sICAM-1</td>
</tr>
<tr>
<td>Year</td>
<td>Study</td>
<td>Type</td>
<td>Disease</td>
<td>Normotensive</td>
<td>Other</td>
<td>Measurement</td>
<td>Value 1</td>
<td>Value 2</td>
</tr>
<tr>
<td>------</td>
<td>-------</td>
<td>------</td>
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<td>--------------</td>
<td>-------</td>
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<tr>
<td>2003</td>
<td>Souwer, 2011</td>
<td>(CS)</td>
<td>Pregnancy</td>
<td>Normotensive</td>
<td>Early onset preeclampsia</td>
<td>sVCAM-1</td>
<td>33±5</td>
<td>34±4</td>
</tr>
<tr>
<td>2010</td>
<td>Spaanderman, 2000</td>
<td>(CS)</td>
<td>Normotensive pregnancy</td>
<td>Other</td>
<td>Preeclampsia and thrombophilia, and chronic hypertension, and no other disease</td>
<td>Vascular compliance</td>
<td>29±4 / 33±4</td>
<td>31±2</td>
</tr>
<tr>
<td>2010</td>
<td>Spaan, 2010</td>
<td>(CS)</td>
<td>Normotensive pregnancy</td>
<td>Other</td>
<td>Preeclampsia and no other disease</td>
<td>Laser doppler</td>
<td>49±3.9</td>
<td>49.8±3.9</td>
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<tr>
<td>2012</td>
<td>Tyldum, 2012</td>
<td>(CS)</td>
<td>Normotensive pregnancy</td>
<td>Other</td>
<td>Preeclampsia</td>
<td>FMD</td>
<td>29±5</td>
<td>27±4</td>
</tr>
<tr>
<td>2008</td>
<td>Van Rijn, 2008</td>
<td>(CS)</td>
<td>Normotensive pregnancy</td>
<td>Other</td>
<td>Early onset preeclampsia</td>
<td>sICAM-1</td>
<td>-</td>
<td>-</td>
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<tr>
<td>2015</td>
<td>Christensen, 2015</td>
<td>(CC)</td>
<td>Normotensive pregnancy</td>
<td>Other</td>
<td>Preeclampsia</td>
<td>PWV, AIx, cIMT</td>
<td>-</td>
<td>-</td>
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<tr>
<td>2010</td>
<td>Lazdam, 2010</td>
<td>(CS)</td>
<td>Normotensive pregnancy</td>
<td>Other</td>
<td>Preeclampsia</td>
<td>cIMT,</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>2012&lt;sup&gt;34&lt;/sup&gt; (CS)</td>
<td>Pregnancy (90)</td>
<td>PWV, Alx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
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<td></td>
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<tr>
<td>Murphy, 2014&lt;sup&gt;35&lt;/sup&gt; (CS)</td>
<td>Preeclampsia (10)</td>
<td>Normotensive pregnancy (40)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>32.1±6.1</td>
<td>30.4±4.2</td>
<td>7±0.7</td>
<td>6±0.9</td>
<td>Laser doppler</td>
<td>0</td>
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</tbody>
</table>

* Results are presented as mean +/-SD or median (IQR) if not specified otherwise
**The sample size for each group represents the number of patients not lost to follow-up

AASI: ambulatory arterial stiffness index; Alx: augmentation index; CC: Cohort; CS: Case-control; cIMT: carotid intima-media thickness; CVD: Cardiovascular disease; FBF: Forearm blood flow; FMD: Flow mediated dilatation; GDM: Gestational diabetes; HDP: Hypertensive Disorders of Pregnancy; miRNA: microRNA; PAT: peripheral arterial tone; PIGF: placental growth factor; PWV: pulse wave velocity; sICAM-1: soluble intercellular adhesion molecule-1; SLE: Systemic lupus erythematos; sVCAM-1: soluble vascular cellular adhesion molecule-1; SEM: standard error of mean; VEGF: vascular endothelial growth factor.
<table>
<thead>
<tr>
<th>Modalities</th>
<th>Number of studies</th>
<th>Type of Vascular Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid intima-media thickness (cIMT)</td>
<td>16 (10)</td>
<td>Subclinical atherosclerosis (large vessels)</td>
</tr>
<tr>
<td>Flow-mediated dilatation (FMD)</td>
<td>17 (13)</td>
<td>Endothelial dysfunction (small vessels)</td>
</tr>
<tr>
<td>Pulse wave velocity (PWV)</td>
<td>13 (7)</td>
<td>Arterial stiffness (small vessels)</td>
</tr>
<tr>
<td>Augmentation index (Alx)</td>
<td>11 (10)</td>
<td>Arterial stiffness (small vessels)</td>
</tr>
<tr>
<td>Laser doppler</td>
<td>4</td>
<td>Endothelial dysfunction (small vessels)</td>
</tr>
<tr>
<td>Forearm blood flow (FBF)</td>
<td>5</td>
<td>Endothelial dysfunction (small vessels)</td>
</tr>
<tr>
<td>Peripheral arterial tone (PAT)</td>
<td>2</td>
<td>Endothelial dysfunction (small vessels)</td>
</tr>
<tr>
<td>Vascular compliance</td>
<td>2</td>
<td>Vascular compliance (large vessels)</td>
</tr>
<tr>
<td>Ambulatory stiffness index</td>
<td>1</td>
<td>Arterial stiffness (small vessels)</td>
</tr>
<tr>
<td>Large and small artery elasticity index</td>
<td>1</td>
<td>Vascular compliance (large and small vessels)</td>
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</table>

**BIOMARKERS**

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Number of studies</th>
<th>Type of Vascular Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soluble intercellular adhesion molecule (sICAM-1)</td>
<td>11 (5)</td>
<td>Inflammation</td>
</tr>
<tr>
<td>Soluble vascular cellular adhesion molecule (sVCAM-1)</td>
<td>10 (5)</td>
<td>Inflammation</td>
</tr>
<tr>
<td>Soluble fms-like tyrosine kinase-1 (sFlt-1)</td>
<td>8 (7)</td>
<td>Angiogenesis</td>
</tr>
<tr>
<td>Vascular endothelial growth factor (VEGF)</td>
<td>6 (3)</td>
<td>Angiogenesis</td>
</tr>
<tr>
<td>Endothelin</td>
<td>4</td>
<td>Thrombosis</td>
</tr>
<tr>
<td>Placental growth factor (PIGF)</td>
<td>4</td>
<td>Angiogenesis</td>
</tr>
<tr>
<td>Fibronectin</td>
<td>3</td>
<td>Thrombosis</td>
</tr>
<tr>
<td>Endoglin</td>
<td>1</td>
<td>Angiogenesis</td>
</tr>
<tr>
<td>microRNA</td>
<td>1</td>
<td>Posttranscriptional regulation of gene expression</td>
</tr>
<tr>
<td>Growth arrest specific protein 6</td>
<td>1</td>
<td>Angiogenesis</td>
</tr>
<tr>
<td>CD33+VEGR1+, CD34+VEGR2+</td>
<td>1</td>
<td>Angiogenesis</td>
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</table>

Some studies assessed more than 1 modality. Modalities in bold font have been pooled. Numbers in parentheses correspond to the number of studies included in the meta-analysis.
## Table S3: Absolute Values and Weight Mean Differences Stratified on Median Duration of Follow-up

<table>
<thead>
<tr>
<th>Metric</th>
<th>Median follow-up (months)</th>
<th>N &lt; median follow-up</th>
<th>Mean value for exposed</th>
<th>Mean value for controls</th>
<th>WMD &lt; median follow-up</th>
<th>N &gt; median follow-up</th>
<th>Mean value for exposed</th>
<th>Mean value for controls</th>
<th>WMD &gt; median follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>cIMT (mm)</td>
<td>198</td>
<td>0.57</td>
<td>0.54</td>
<td>0.03 [0.01 to 0.05]</td>
<td>604</td>
<td>0.64</td>
<td>0.60</td>
<td>0.02 [-0.02 to 0.07]</td>
<td></td>
</tr>
<tr>
<td>AIx (%)</td>
<td>173</td>
<td>23.02</td>
<td>11.84</td>
<td>9.92 [5.92 to 13.92]</td>
<td>972</td>
<td>19.92</td>
<td>17.27</td>
<td>2.69 [-1.79 to 7.17]</td>
<td></td>
</tr>
<tr>
<td>cfPWV (m/s)</td>
<td>854</td>
<td>7.64</td>
<td>7.02</td>
<td>0.63 [-0.16 to 1.42]</td>
<td>233</td>
<td>7.75</td>
<td>7.08</td>
<td>0.54 [0.19 to 0.88]</td>
<td></td>
</tr>
<tr>
<td>sFlt-1</td>
<td>145</td>
<td>207.1</td>
<td>133.93</td>
<td>10.44 [1.38 to 19.51]</td>
<td>559</td>
<td>140.66</td>
<td>133.13</td>
<td>3.23 [-0.18 to 6.23]</td>
<td></td>
</tr>
</tbody>
</table>
Figure S1: Funnel Plot of Studies Assessing Augmentation Index
Figure S2: Funnel Plot of Studies Assessing Carotid Intima-Media Thickness