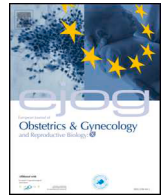


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## Arterial stiffness measurements in pregnancy as a predictive tool for hypertensive disorders of pregnancy and preeclampsia: Protocol for a systematic review and meta-analysis



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### ABSTRACT

Hypertensive disorders of pregnancy (HDPs) are a leading cause of maternal morbidity and mortality worldwide. Unfortunately, accurate early clinical screening methods for the development of these disorders are lacking. Arterial stiffness (AS) is an important hemodynamic indicator of vascular health that has shown promising results for the prediction of HDP onset. Past systematic reviews in the field have reported an increase in AS indices in women who develop HDPs and have highlighted the potential of AS measurements as a predictive tool early in pregnancy. The most recent systematic review, including papers up to 2015, assessed the differences in AS parameters between women with and without pregnancy complications. Since then, there has been a substantial influx of published research on the topic and a growing interest in the incorporation of AS measurements into clinical practice. Thus, we propose a systematic review and meta-analysis that is more inclusive to all HDP subsets and various hemodynamic indices of vascular health to provide a comprehensive overview of the current state of evidence. Specifically, we aim to evaluate these measures in women who develop HDPs compared to normotensive pregnancies to determine which measures are most associated with and/or can predict the development of HDPs. Major databases (Medline, Embase, The Cochrane Library, Web of Science, PubMed, and CINAHL), grey literature (Google Scholar) and clinical trials (clinicaltrials.gov) will be searched to identify studies that report AS and hemodynamic measurements in pregnant women with and without HDPs. No restrictions will be made on study type or year. Articles will be independently evaluated by three authors to determine eligibility based on inclusion and exclusion criteria. Methodological quality of included studies will be assessed. Pooled analyses will be conducted using a random-effects model. Publication bias and between-study heterogeneity will also be assessed. Sources of heterogeneity will be explored by sensitivity, subgroup, and/or meta-regression

**Abbreviations:** AIX, Augmentation Index; AIX75, AIX adjusted to a heart rate of 75 beats per minute; AS, Arterial stiffness; CBP, Central blood pressure; cPWV, carotid-femoral pulse wave velocity; CO, Cardiac output; CVD, Cardiovascular disease; FMD, Flow-mediated dilation; HDP, Hypertensive disorder of pregnancy; MAP, Mean arterial pressure; PrE, Preeclampsia; PWA, Pulse wave analysis; PWV, Pulse wave velocity; SEVR, subendocardial viability ratio; T1R, Time to wave reflection

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analyses. Results from this study will be shared through scientific conferences and publications in scientific journals. The analysis of potential AS and hemodynamic markers for HDP onset will help inform the development of screening guidelines and clinically relevant cut-off values of AS and hemodynamic markers for HDP risk, guiding future research. There are no applicable ethical considerations to the writing of this protocol.

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## 1. Introduction

Hypertensive disorders of pregnancy (HDPs) remain the leading causes of maternal and neonatal morbidity and mortality worldwide. HDPs include gestational hypertension, chronic hypertension, pre-eclampsia (PrE), and PrE superimposed chronic hypertension [1]. Globally, HDPs are estimated to affect as many as 10% of pregnancies, contributing up to 343,000 maternal and around 1.5 million neonatal deaths annually [2,3]. This group of disorders encompasses a range of mild to severe symptoms and can cause both acute and long-term health complications for the mother and developing fetus. While the majority of HDP-related deaths can be avoided with appropriate and timely management, early prediction remains a challenge in both low- and high-income countries [3]. Although certain maternal factors are known to be associated with HDP development, including increased body mass index, advanced maternal age, pre-existing cardiovascular diseases (CVD), among others [4], there remains a lack of effective clinical screening methods that can accurately predict the development of HDPs early in pregnancy. This is especially true for PrE, which has a particularly high level of uncertainty around its pathogenesis, diagnosis, and treatment. It is estimated that approximately 5–8% of pregnant women develop PrE, which classically manifests as new onset or worsening of hypertension and end-organ damage after the 20th week of gestation [5–7]. Given the severity and prevalence of HDPs, as well as the importance of early detection and clinical management, there is an unmet need for accurate and reliable screening tools for the prediction of HDP development.

Arterial stiffness (AS) is a physical property of arterial walls that reflects the degree of flexibility and elasticity of the artery. AS has important functional impacts on hemodynamic health indicators, such as blood pressure and pulsatile flow with each heartbeat [8,9]. Research on AS has grown exponentially in the past two decades due to its clinical utility in predicting cardiovascular events in the general population [10–12]. Importantly, AS is known to have an independent effect from blood pressure and is thus a valuable marker of CVD risk [13,14]. Pulse wave velocity (PWV) is a major hemodynamic index of AS. PWV is a measure of the velocity of a pulse wave within a defined arterial segment, with higher values indicative of increased stiffness; PWV is considered a direct marker of AS and is most often assessed using applanation tonometry [9,15]. The gold standard measurement of AS is widely considered to be carotid-femoral PWV (cfPWV), a measure of central or aortic AS [15]. Central arterial stiffening is a hallmark of ageing and has shown a stronger association with the development of CVD compared to peripheral AS, assessed via carotid-radial, femoral-dorsal pedis, or brachial-ankle recordings, among others [16–18].

Pulse wave analysis (PWA) is performed to indirectly assess the elastic properties of the arterial wall. As the natural stiffening of arteries leads to the faster return of a pulse wave, analysis of these waveforms (by PWA) enables the estimation of central blood pressures and central hemodynamic properties [19]. Notable parameters include the augmentation index (AIx), which represents the relative magnitude of the reflected wave and is expressed as a ratio of the increment pressure of the forward and backward waveforms, with the time to wave reflection (T1R) representing the time delay in the backward waveform [9,19,20]. Because AIx can be affected by heart rate, it is often

adjusted to a heart rate of 75 beats per minute (AIx75), although there is an ongoing debate with respect to the clinical relevance of this adjustment [21]. Additionally, the central blood pressure (CBP) represents the arterial pressures at the aorta. In contrast, the mean arterial pressure (MAP) represents the average pressure throughout the arterial system and is influenced by systemic vascular resistance and cardiac output (CO) [19]. Finally, the subendocardial viability ratio (SEVR) is an index of myocardial oxygen supply and demand, which can be altered by decreased diastolic pressures caused by a faster return of the pulse wave [19]. Importantly, increased stiffness parameters can impair peripheral endothelial function, as measured by flow-mediated dilation (FMD), causing damage to organs requiring high blood flow [22]. Altogether, these parameters provide complementary information on overall vascular function and may provide insight into the complex vascular alterations in pregnancy and HDP risk.

Over the past two decades, AS measurements have shown high predictive value in determining CVD risk [10–12]. Specifically, a cfPWV of 10 m/s is considered an arbitrary cut-off for target organ damage indicating an increased risk of adverse cardiovascular events in the general population [23,24]; however, risk has been reported to significantly increase starting at a cfPWV of 7.8 m/s [12]. While reference values for cfPWV have been established in the general population [23,25], these have not been studied for men and women separately, and importantly they may not apply to pregnancy given the changes in AS that occur throughout pregnancy due to extensive hemodynamic alterations [26]. Although many studies have highlighted an association between PWV, PWA indices, CO, FMD and HDPs, there are currently no clinical reference values for these parameters that can serve to stratify risk for the development of HDPs [27–29].

A number of systematic reviews have been published that have attempted to collate published data on AS and HDPs. For example, our group conducted a systematic review in 2012, which found that cfPWV and AIx significantly increase in pregnancies at the time of PrE compared to normotensive pregnancies [30]. More recently, Osman et al. published a systematic review including studies up to March 2015 describing AS in pregnant women who developed placental-mediated diseases, including PrE [27]. Their review identified that AIx75 was significantly higher in the first trimester in women destined to develop PrE, while cfPWV was significantly higher in the second and third trimester. As technology evolves and becomes more refined, the number of publications on AS and overall vascular function in pregnancy continues to increase rapidly. For this reason, there is a need for a comprehensive review of the literature on this topic.

The proposed systematic review will generate a comprehensive overview of the current body of evidence in AS and related hemodynamic measurements with respect to HDPs. We aim to assess the various AS and hemodynamic changes that occur among women who develop HDPs compared to normotensive pregnancies. Specifically, we will focus on studies that include the vascular function measurements mentioned above, including PWV, PWA indices, FMD and CO. With the addition of a meta-analysis to the systematic review, we aim to examine how these indices change throughout normotensive and hypertensive pregnancies, to determine which, and at what timepoint(s), these measurements are most associated with and/or could be used as a predictive tool for the development of HDPs. Finally, we will assess if clinically relevant

reference values for HDP risk can be extrapolated from the current body of literature.

## 2. Methods and design

### 2.1. Registration

This protocol was written in adherence with the “Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols” (PRISMA-P) guidelines [31] and is registered with the PROSPERO International Prospective Register of Systematic Reviews (CRD42021238685) [32].

### 2.2. Study eligibility

Eligible studies must meet the following criteria:

#### 2.2.1. Study designs

We will include randomized and non-randomized control trials, prospective and retrospective cohort studies, case-control studies, and cross-sectional studies performed in humans. We will exclude case series/reports, cost-benefit analyses, and qualitative research, as well as reviews, newspapers, books, conference abstracts, theses, commentaries, letters, editorials, and unpublished data. Animal and *in vitro* studies will also be excluded.

#### 2.2.2. Population

We will include studies that recruited women with singleton pregnancies. Studies must include either women who developed HDPs during or after pregnancy, women with normotensive pregnancies, or both, and must explicitly report these outcomes. HDPs include gestational hypertension, chronic hypertension, PrE, and PrE superimposed chronic hypertension [1]. Gestational hypertension is defined as the onset of hypertension (systolic > 140 mmHg and diastolic > 90 mmHg) after 20 weeks of pregnancy without the onset of proteinuria. Chronic hypertension is defined as hypertension diagnosed before 20 weeks of pregnancy without the onset of proteinuria [33]. While chronic hypertension is diagnosed before or early in pregnancy, these patients are still susceptible to worsening hypertension or PrE and will therefore be included, in accordance with the HDP classification of International Society for the Study of Hypertension in Pregnancy [1] and the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy [34]. PrE is defined as the onset of hypertension coupled with one or more of the following: proteinuria, maternal organ dysfunction or hematological involvement, and/or uteroplacental dysfunction, including fetal growth restriction or abnormal uteroplacental blood flow from doppler ultrasounds [1]. As the diagnostic criteria for PrE have evolved over time, we will consider the PrE diagnostic criteria as defined at the time of study publication. Finally, chronic hypertension with superimposed PrE occurs when PrE occurs in the context of pre-existing chronic hypertension [33]. No exclusions will be made based on methods of conception. There will be no restrictions based on participant age, race, or ethnicity. Due to limited reporting in certain studies, we will make no exclusions based on other comorbidities or pregnancy complications.

#### 2.2.3. Exposure

We will include studies that evaluate AS-specific and related hemodynamic indices during pregnancy and postpartum, if applicable. Selected studies must report at least one of the indices mentioned above (PWV, AIx, AIx75, T1R, CBP, MAP, SEVR, FMD, CO) to be eligible. Studies reporting PWV measurements must specify whether this is a central arterial measurement (cfPWV) or peripheral artery measurement to be included. We will exclude studies that only assess uterine measurements and the state of the fetus, as well as

studies that only include AS measurements pre-pregnancy, postpartum, or solely during labor or delivery. Considering the heterogeneity among studies in acquiring the data, we will make no restrictions based on the timing, frequency, or acquisition method for these measurements. We will evaluate these hemodynamic indices at each trimester of pregnancy, if available.

#### 2.2.4. Comparator

We will compare the hemodynamic indices (as listed above) among women who develop HDPs versus normotensive pregnancies.

#### 2.2.5. Outcomes

Prediction of HDP development.

#### 2.2.6. Timing

There will be no restrictions by the date of publication.

#### 2.2.7. Setting

There will be no restrictions on the type of setting.

#### 2.2.8. Language

Eligible studies will be limited to articles published in English or French.

### 2.3. Data sources

Major electronic databases, including Medline, Embase, The Cochrane Library, Web of Science, PubMed, and CINAHL, will be searched, in addition to grey literature, via Google Scholar, and clinical trials registered to clinicaltrials.gov. A Librarian at our institution (LH) helped design the search strategy and compiled the results to ensure a comprehensive and inclusive examination of the available literature. A detailed sample of our search strategy for Medline can be found in [Supplementary File 1](#). We will manually search the reference lists of relevant articles generated by our search, as well as the articles that cited them. Before publication, we will re-run our search to capture relevant articles published after the initial search.

### 2.4. Study records

#### 2.4.1. Data management

Studies generated by our search will be uploaded to Rayyan, an online screening and data extraction software that supports citation screening and full-text review for multiple collaborators [35]. All duplicate studies will be removed before uploading.

#### 2.4.2. Selection process

Two rounds of screening will take place among reviewers MF, SB, and AKD. Reviewers will independently screen articles to determine if each meets the outlined criteria. In the first round, each study's title and abstract will be screened independently to identify potential studies to include for in-depth screening, excluding any studies that all reviewers judge to be ineligible. The second round of screening will involve a full-text review and detailed examination of study procedures by reviewing authors MF and SB to determine final eligibility. In both rounds, journal titles and author names will be hidden to eliminate potential biases. Disagreements between reviewers following any stage of the screening process will be presented to the other authors, who will independently review and make the final decision. If additional information about a given study is required, the article's corresponding author (and potentially the first author) will be contacted by email. If authors do not respond within four weeks of initial contact, a follow-up email will be sent. If authors do not respond after four weeks of the second contact and necessary information is missing, the study will not be included in the analysis.

**Table 1**  
Data items to be extracted.

Data Item	Details to be extracted
Study characteristics	Study title, complete author list, year of publication, journal, funding source, type of publication, language (English or French), study period, geographical setting
Population characteristics	Number of participants, average age, average body mass index, race/ethnicity demographics, percent of primigravida patients, percent of patients with comorbidities (including diabetes, gestational diabetes, kidney disease, and autoimmune disease), or other pregnancy complications, as available.
Study design	Type of study, study design, inclusion criteria, exclusion criteria, comparisons, methods, outcome measures
Measurements	All available AS and hemodynamic measurements will be recorded, including cfPWV, peripheral PWV, Alx, Alx75, T1R, FMD, CBP, MAP, SEVR, and CO. When available, these data will be stratified by trimester.
Outcomes of interest	Number of women with HDP and normotensive women, as well as the type of HDP (gestational hypertension, chronic hypertension, PrE, and PrE superimposed chronic hypertension)

cfPWV = carotid femoral pulse wave velocity; PWV = pulse wave velocity; Alx = augmentation index; Alx75 = augmentation index adjusted to 75 beats per minute; T1R = time to wave reflection; FMD = flow-mediated dilation; CBP = central blood pressure; MAP = mean arterial pressure; SEVR = subendocardial viability ratio; CO = cardiac output; HDP = hypertensive disorder of pregnancy; PrE = preeclampsia.

#### 2.4.3. Data collection process

Data from selected studies will be extracted and entered into a Microsoft Excel spreadsheet. Reviewing authors (MF and SB) will independently enter the following information: study characteristics, population characteristics, study design, measurements, and the outcomes of interest. Data will be preferentially extracted from results tables in the included articles. If the data of interest are not included in tables, the results section text will be carefully read for relevant information. If further information or clarifications are needed, the article's corresponding author will be contacted using the same strategy as previously mentioned.

#### 2.4.4. Data items

Data items that will be extracted from each included study are presented in Table 1.

#### 2.4.5. Risk of bias

Reviewing authors (MF and SB) will independently evaluate the methodological quality of all included studies. For randomized control trials, risk of bias assessment will be performed using the Cochrane Collaboration Tool for Assessing Risk of Bias, wherein each paper is judged as having a high, low, or unclear risk of bias [36]. For case-control and cohort studies, the 9-item Newcastle Ottawa Quality Assessment scale or a modified version will be used [37]. Disagreements among the two authors will be resolved by consultation with the other authors to reach a consensus. No studies will be excluded based on the risk of bias assessment; however, a sensitivity analysis will be performed with studies of higher quality.

### 2.5. Statistical analysis

The mean, standard deviation, and number of patients for each of the hemodynamic indices at each trimester for women with HDPs (and each subtype of HDP, as available) and normotensive women will be extracted from the full texts of the identified studies. The data will be summarized using a DerSimonian and Laird random-effects model [38]. A separate meta-analysis will be conducted for each hemodynamic variable of interest (cfPWV, peripheral PWV, Alx, Alx75, T1R, FMD, CBP, MAP, SEVR, and CO) for (1) the combined outcome of HDPs, and (2) for each subtype of HDP, as available, and in particular for PrE. For each hemodynamic variable, the effect size will be estimated using the standardized mean difference and pooled by a random-effects model. For studies that provide data on the association between these hemodynamic variables and the outcome of interest, we will meta-analyze these effect measures using a random effects model as previously described. For any studies that may dichotomize the hemodynamic variables in terms of high/low binary variables, we will additionally meta-analyze the sensitivity and specificity of these variables using the bivariate mixed effects regression model. We will perform a subgroup analysis for each subtype of HDP, as available. As done

by Osman et al. [27], we will also perform a subgroup analysis of effect measures at each trimester of pregnancy.

Potential sources of heterogeneity will first be assessed using the  $I^2$  statistic [39] and further explored with a combination of subgroup analysis and meta-regression using the random-effects model. If there is substantial variation between studies, we will investigate the potential source of this heterogeneity using subgroup analysis for dichotomous or categorical variables of interest and meta-regression for continuous variables of interest. These potential sources of heterogeneity include average participant age, percent of nulliparous participants, race/ethnicity, average body mass index, the percent of participants that smoke, and the percent of participants with diabetes, kidney disease, autoimmune disease, as well as other pregnancy complications, as available. To establish reference values for a healthy pregnant population, we will meta-analyze the previously published hemodynamic values (by trimester if available) in women with healthy, uncomplicated pregnancies and without risk factors, to get an overall mean estimate of the average normal hemodynamic values in this healthy pregnant population.

All statistical analyses will be conducted using STATA/SE, version 13 (Stata Corp LP, College Station, Texas, USA).

#### 2.5.1. Meta-bias(es)

We will assess small study effects and publication bias visually using funnel plots and quantitatively using Begg's and Egger's statistical tests, if there are at least nine studies available.  $P < 0.05$  will be considered evidence of small-study effects.

#### 2.5.2. Confidence in cumulative estimate

We will use the Grading of Recommendations Assessment, Development and Evaluation Working Group criteria to assess the quality and strength of the identified evidence.

### 2.6. Patient and public involvement

There will be no involvement of patients or the public in the design, conduct, and reporting; however, there will be involvement in the dissemination of our work.

## 3. Discussion

HDPs remain one of the leading complications of pregnancy worldwide [2,40]. The optimization of health care to prevent and treat women with HDPs continues to be a top priority on the global health agenda [41]. The early prediction of these disorders is essential to ensuring that women at risk are appropriately monitored to prevent and treat the development of serious complications. Current national and international clinical guidelines for the prediction of HDP risk involve the combined assessment of various maternal risk factors, placental biomarkers, and uterine artery doppler indices [1,42–44]. However, the

predictive accuracy of these markers in the first trimester remains limited due to high variability in detection rates and false positives early in pregnancy [45]. There is growing interest in using AS measurements as a predictive tool in early pregnancy due to their ability to detect changes in vessel hemodynamics characteristics of normotensive versus non-normotensive pregnancies.

In normotensive pregnancies, rapid hemodynamic adaptations ensure adequate uteroplacental perfusion for optimal fetal development [46]. Early in the first trimester, the maternal cardiovascular system undergoes a complex series of vascular and hematological changes to accommodate the required blood volume expansion and other metabolic demands of pregnancy. These changes include systemic vasodilation, decreased vascular resistance, and increased vascular compliance, CO, and plasma volume [46,47]. Altogether, these vascular alterations characteristically present as a U-shaped curve in blood pressures, cfPWV, and wave reflection, reaching the lowest point in the second trimester [46,48]. As the pregnancy progresses, the demands of the developing fetus increase. Failure to accommodate these necessary adaptations may result in the onset of clinical complications later in pregnancy. Indeed, it has been suggested that pregnancy essentially acts as a 'stress test' that unmasks underlying vascular dysfunction and CVD risk [49,50].

These increased vascular demands may be key to the early identification of potential complications in women with underlying HDP risk. Specifically, impaired vascular responses are observed in hypertensive pregnancies; rather than the U-shaped curve observed in normotensive pregnancies, HDPs exhibit a greater and continuous increase in blood pressures, cfPWV, and wave reflection across gestation [51]. Moreover, AS is significantly higher in women with HDPs compared to normotensive pregnancies and further increases with disease severity [52]. In recent studies, we and others have demonstrated that AS measurements can detect altered hemodynamic responses in the first trimester of pregnancy in women who subsequently develop HDPs [53–58]. PWA parameters, CO, and FMD are also outcomes of interest in our study as they provide complementary information regarding overall vascular function and have been reported to be associated with HDPs. For instance, Osman et al. and Hausvater et al. reported associations between increased AIx75 in the first trimester, and AIx, respectively, with PrE [27,30]. Moreover, as AS technology rapidly evolves, studies are beginning to report more AS-related parameters, such as T1R, CBP, MAP, SEVR, and CO, providing novel information regarding the hemodynamic alterations throughout pregnancy. Furthermore, FMD has been reported to be associated with the development of HDPs [29,59,60]. FMD represents peripheral endothelial function, which can be greatly impacted by increased pulsatile load caused by alterations in AS [22,56]. It is of interest to evaluate whether the assessment of large artery stiffness, wave reflection, or endothelial function can better identify those women destined to develop HDPs.

The proposed systematic review and meta-analysis will serve to summarize the available literature in the field and provide a comprehensive overview and analysis of the association between AS, associated vascular measurements, and the development of HDPs [27,30]. To our knowledge, this will be the first meta-analysis to systematically compare multiple major AS indices in women with all HDP types to normotensive pregnancies by trimester. To establish whether variations in participant data influence our meta-analysis, we will investigate potential sources of heterogeneity by exploring a variety of common modifiable and non-modifiable risk factors, including maternal age, obesity, nulliparity and diabetes, among others [4]. By designing an inclusive search strategy evaluating a variety of AS, wave reflection and vascular parameters, this study may uncover novel information related to the complex vascular changes that occur in normotensive and hypertensive pregnancies. By analyzing these data, we hope to determine which, and at what timepoint(s), these measures are most associated with and/or can predict the

development of HDPs. Measurement of AS during pregnancy could represent an accurate non-invasive predictive tool for identifying and characterizing hemodynamic changes associated with HDP risk.

### 3.1. Ethics and dissemination

Results from this study will be shared through presentations at scientific conferences and publications in scientific journals. This study's findings could help generate clinical guidelines for HDP screening, as well as guide future research in the field.

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### Conflict of interest

The authors declare no conflicts of interest in the writing of this manuscript.

### Acknowledgments

None.

### Consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Author Agreement & Submission Declarations

The authors agree to the submission of this manuscript and confirm that this submission is original, has not been previously published and is not being considered for publication elsewhere. The authors confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but who are not listed.

### Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.eurox.2022.100141](https://doi.org/10.1016/j.eurox.2022.100141).

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