BMJ Open

Arterial stiffness after 6 weeks postdelivery in women with a history of hypertensive disorders of pregnancy: a systematic review protocol

Xolani Mbongozi ,[1] Stuart Galloway,[1] Angus Hunter,[2] Charles Bitamazire Businge [3]

To cite: Mbongozi X, Galloway S, Hunter A, *et al*. Arterial stiffness after 6 weeks postdelivery in women with a history of hypertensive disorders of pregnancy: a systematic review protocol. *BMJ Open* 2024;**14**:e082424. doi:10.1136/bmjopen-2023-082424

► Prepublication history for this paper is available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2023-082424).

Received 22 November 2023
Accepted 22 August 2024

[1]University of Stirling, Stirling, UK
[2]Nottingham Trent University, Nottingham, UK
[3]Department of Obstetrics, Walter Sisulu University - Mthatha Campus, Mthatha, Eastern Cape, South Africa

Correspondence to
Dr Xolani Mbongozi;
x.b.mbongozi@stir.ac.uk

ABSTRACT

Introduction Hypertensive disorders of pregnancy (HDP) are one of the leading causes of maternal morbidity and mortality. The risk of developing cardiovascular diseases following HDP is high. Arterial stiffness is a prognostic indicator for cardiovascular disease in the general population, and it is elevated during pregnancy in women with HDP. No systematic reviews have been conducted to determine if arterial stiffness remains elevated beyond puerperium in these women with HDP.

Methods and analysis We will conduct a systematic literature search in the following electronic databases: Medline, PubMed, Embase, Cochrane Library, Google Scholar, Web of Science and CINAHL. The review will consider studies that investigate arterial stiffness in women who had HPD and are between 43 days and 10 years postdelivery and under 60 years of age. This systematic review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols guidelines. Estimates of mean ± SD for arterial stiffness indices (cfPWV, AIx and AIx@75) for the women in the included studies will be obtained. For studies where the estimates were reported as the median and IQR, approximate estimates of mean ± SD will be calculated by using the low and high end of the range, median and sample size. Data from the individual studies will be pooled by use of a random-effects model. The risk of bias assessment will be assessed using the Cochrane Collaboration tool and the Newcastle-Ottawa Quality Assessment Scale as appropriate. Sources of heterogeneity will be explored by sensitivity and subgroup analyses.

Ethics and dissemination No ethics approval is required as only published data will be used in this study. The research study's outcomes will be shared through scientific conferences and peer-reviewed publications.

PROSPERO registration number CRD42023461867.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol guidelines for reporting protocols of systematic reviews and meta-analysis, meeting the highest scientific quality standards.
⇒ We will conduct a comprehensive search across several databases.
⇒ The inclusion of studies only published in the English language may lead to language bias, potentially omitting studies in other languages.
⇒ The studies may have used different definitions of pregnancy-related hypertension, which could make it difficult to pool the results.

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) are one of the leading causes of maternal mortality.[1] They are associated with an increased risk of adverse perinatal and maternal outcomes, including foetal growth restriction, prematurity, obstetric haemorrhage, intracranial complications, renal failure, preterm birth, small for gestational age newborns, stillbirth and neonatal death.[1–3] These hypertensive disorders which are a worldwide burden with a prevalence of 5.2% to 8.2% in pregnancy are also associated with long-term complications, such as chronic hypertension, ischaemic heart disease and other cardiovascular diseases.[2–5]

In the general population, arterial stiffness and central blood pressure are markers of vascular health and prognostic indicators for cardiovascular disease and are targets to improve heart disease worldwide.[6–8] In pregnancy, arterial stiffness has gained attention in women with HDP. Studies have found that women with HDP have increased arterial stiffness and central blood pressure compared with normotensive pregnant women.[9–11] Arterial stiffness is related to the degree of hypertension and is a predictive marker for the development of HDP.[8] This vascular marker has been reported to be significantly higher in the first trimester of pregnancy in women who subsequently develop HDP compared with those who remain normotensive.[12 13] This finding is crucial given the need for early

detection and clinical management of HDP. However, additional research is still required to assess the accuracy of predicting HDP using arterial stiffness, and if it is high enough, preventive measures for HDP, such as aspirin usage, can be executed.[14]

In the past, invasive measurement of arterial stiffness limited its widespread use. New, easy-to-use, noninvasive devices for measuring maternal arterial stiffness have been developed.[15] These new devices, which assess arterial stiffness through augmentation index (AIx) and pulse wave velocity (PWV), are designed to be convenient for daily clinical practice.[8 16] Several factors can influence the PWV. In the second and third trimesters, AIx and PWV have been shown to be lower compared with the baseline.[7] Controlling blood pressure (BP) parameters through medical treatment has also been shown to reduce PWV, whereas ageing is associated with elevated PWV and, therefore, increased risk of hypertension and cardiovascular disease in older patients.[17] However, reducing brachial arterial BP does not always correspond to equivalent reductions in central BP or arterial stiffness.[10 18] This is clinically important as arterial stiffness is a better predictor of cardiovascular disease compared with peripheral BP. Focus must therefore shift towards controlling the arterial stiffness in women with hypertension.

Numerous systematic reviews have been published with the aim of compiling available data on arterial stiffness and its association with pre-eclampsia during pregnancy.[9 19–21] However, there is still limited systematic data on arterial stiffness in women with pre-eclampsia beyond the puerperium period. For most normotensive women, pregnancy-related cardiovascular changes usually disappear within the first 6 weeks following pregnancy (puerperium).[22 23] However, pregnant patients with HDP remain at risk of developing cardiovascular complications later in life.[24] It is, therefore, worth determining if arterial stiffness remains elevated beyond puerperium in women with HDP. If elevated after 6 weeks following pregnancy, arterial stiffness status may explain the association between HDP and future cardiovascular risk; therefore, measures, such as medical treatment and lifestyle interventions, may be employed to reduce this risk.[10 18]

Objective

The objective of this systematic review is to determine if the arterial stiffness remains elevated after 6 weeks postdelivery in women with a history of HDP.

Research question

Does the arterial stiffness remain elevated after the puerperium period in women who previously had HDP?

METHODS AND ANALYSIS

This protocol is developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols 2015 guidelines.[25]

Table 1 Search strategy

Search	Search items	Hits
1	Arterial stiffness [tw] OR central blood pressure [tw] OR Pulse wave velocity [tw] OR Augmentation index [tw] OR PWV [tw] OR Aix(tw] OR AIx@75(tw]	
2	Preeclampsia [tw] OR Eclampsia(tw] OR gestational hypertension [tw] OR Hypertensive disorders of pregnancy [tw]	
3	postpartum [tw] OR after puerperium [tw]	
4	#2 AND #3	
5	#1 AND #4	

Search strategy

We will conduct a systematic literature search in the following electronic databases: Medline, PubMed, Embase, Cochrane Library, Google Scholar, Web of Science and CINAHL. We also intend to check reference lists from the included studies for any important studies missed during the database search. Before publication, we will rerun our search to capture relevant articles published after the initial search. The search strategy is shown in table 1.

Study designs

We will include randomised and non-randomised control trials, prospective and retrospective cohort studies, case-control studies and cross-sectional studies performed in humans.

Target population

The target population will include women under 60 years who are between 43 days and 10 years postdelivery.

Patient and public involvement

None for this systematic review.

The exposure

The exposure is hypertensive disease during pregnancy or within 42 days postdelivery. The hypertensive diseases will include pre-eclampsia, gestational hypertension, chronic hypertension and chronic hypertension with superimposed pre-eclampsia.[26] Pre-eclampsia is defined as persistent de novo hypertension that develops at or after 20 weeks of gestation, accompanied by either proteinuria or features of maternal organ or uteroplacental dysfunction. Features of maternal organ dysfunction include acute kidney injury (creatinine ≥ 90 µmol/L or 1 mg/dL), liver involvement (elevated alanine aminotransferase or aspartate aminotransferase > 40 IU/L) with or without right upper quadrant or epigastric abdominal pain, neurological complications (such as eclampsia, altered mental status, blindness, stroke, clonus, severe headaches and persistent visual scotomata) and haematological complications (decreased platelet count < 150 000/µL, disseminated intravascular coagulation and haemolysis). Uteroplacental dysfunction includes foetal

growth restriction, abnormal umbilical artery Doppler waveform analysis or stillbirth.[26 27] Gestational hypertension is defined as persistent de novo hypertension that develops at or after 20 weeks of gestation in the absence of features of pre-eclampsia.[26] Chronic hypertension refers to high BP predating the pregnancy or recognised at <20 weeks of gestation. Chronic hypertension with superimposed pre-eclampsia occurs when pre-eclampsia occurs in a pregnant woman who has pre-existing chronic hypertension.[26]

Comparison

We will compare the arterial stiffness biomarkers of the women who had HDPs with those who had normotensive pregnancies ≥43 days postdelivery.

Outcomes

The outcomes are the arterial stiffness-specific and related haemodynamic indices that include cfPWV, AIx and AIx@75 at ≥43 days postpartum.

Inclusion criteria

The systematic review will encompass human studies published from inception to the date of data collection.

Inclusion in the review will require that studies have measured arterial stiffness in participants between 43 days and 10 years postpartum.

To ensure data accessibility and language homogeneity, only studies published in the English language will be considered for inclusion in this systematic review.

Exclusion criteria

We will exclude case series and 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. Studies that only assess arterial stiffness measurements during pregnancy, labour and delivery or within 6 weeks postpartum will be excluded. Additionally, due to the increase in arterial stiffness in older women, women aged 60 years and above will also be excluded from the study.[28]

Data collection

Mendeley Reference Manager will be used to store and manage searched items. Records identified as potentially eligible based on title, abstract and full texts will be obtained to screen. Two reviewers, namely, XM and CBB, will independently extract the required data from the studies and compare them in duplicate. Any disagreements between the reviewers will be resolved through a discussion with SG. AH will be involved in writing drafts and reviewing the manuscript overall.

The data to be extracted will include the following information:

- Study characteristics: author(s), journal, title, year of publication, study design and sample size.
- Study objective.
- Demographic details of the study participants, including age and the country/countries where the study participants were recruited.
- Outcome: summary data for arterial stiffness indices (cfPWV, AIx and AIx@75) for each group (women who had HDP and normotensive controls).
- Comments on the study quality for grading.
- Concluding points made by the authors of the included study. When the same cohort was reported in multiple articles, the study which contains the largest sample will be selected.

If the data of interest are not included in tables, the Results section text will be carefully read for relevant information. If an eligible study does not provide full data or further clarifications are needed, we will contact the corresponding authors to obtain data.

Risk of bias

For randomised control trials, risk of bias assessment will be performed using the Cochrane Collaboration tool for assessing risk of bias, where each paper is judged as having a high, low or unclear risk of bias.[29] For case-control and cohort studies, the nine-item Newcastle Ottawa Quality Assessment Scale or a modified version will be used.[30] No studies will be excluded based on the risk of bias assessment; however, a sensitivity analysis will be performed with studies of higher quality.

Statistical analysis

Estimates of mean ± SD for arterial stiffness indices (cfPWV, AIx and AIx@75) for women who had HDPs (and each subtype of HDP, as available) and normotensive women will be obtained from the relevant studies. For studies where the estimates were reported as the median and IQR, approximate estimates of mean ± SD will be calculated using the available estimates of the median, minimum and maximum.

These data will be summarised using a DerSimonian and Laird random-effects model.[31] A separate meta-analysis will be conducted for each haemodynamic indices of interest (cfPWV, AIx and AIx@75) for the combined outcome in those who had HDPs and for each subtype of HDP.

For studies that provide data on the association between these haemodynamic variables and the outcome of interest, we will meta-analyse these effect measures using a random effects model. For any studies that may dichotomise the haemodynamic variables in terms of high/low binary variables, we will additionally meta-analyse 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. If we are unable to analyse data using meta-analysis, a narrative synthesis will be conducted to summarise and tabulate the results.

Assessment of heterogeneity

Potential sources of heterogeneity will first be assessed using the I^2 statistic.[32]

The following subgroup and sensitivity analyses using RevMan 5.3 will be performed, where the data allow:

1. according to study design (case-control vs cohort);
2. according to study quality (minimal/low vs moderate/high);
3. according to age of the HDP offspring.

We will conduct funnel plots to assess the potential for publication bias where there are sufficient (>10) studies. If there are subgroup and sensitivity analyses in the process of the meta-analysis, we will conduct some post hoc analyses to explore potential high heterogeneity or publication bias.

These potential sources of heterogeneity include average participant age, per cent of nulliparous participants, race/ethnicity, average body mass index, the per cent of participants that smoke and the per cent of participants with diabetes, kidney disease and autoimmune disease, as well as other pregnancy complications, as available.

Reporting of results

The primary study topic will be determined using the aims and objectives of each included paper. A flow diagram following PRISMA-P guidelines will represent the study selection process. Two tables will list the characteristics and quality assessment of the included studies. The findings obtained from meta-analyses will be displayed using forest plots. The eligible studies we could not obtain raw data by contacting corresponding authors will be listed individually in a separate table.

DISCUSSION

HDP are a global concern due to their impact on the health of mothers and their unborn babies, particularly the long-term risk of cardiovascular disease.[1 3] The identification of biomarkers that predispose patients with HPD to a high risk of cardiovascular disease is crucial. Studies in nonpregnant patients have shown that arterial stiffness is a better predictor of future cardiovascular complications when compared with peripheral BP. In pregnancy, arterial stiffness is elevated in women with pre-eclampsia compared with normotensive women.[11] This finding could explain the association between pre-eclampsia and the elevated risk of future cardiovascular disease. This systematic review will summarise eligible studies to examine whether the arterial stiffness observed among women with HPD remains elevated beyond the puerperium period. If this turns out to be the case, it could strengthen suggestions that high arterial stiffness in hypertensive pregnant patients may relate to long-term risk of cardiovascular disease, and treatment to optimise arterial stiffness can be offered to minimise this risk. However, further reviews are necessary to determine the actual occurrence of cardiovascular diseases in women who experienced HPD and had increased arterial stiffness. The strength of this systematic review lies in being the first to investigate whether elevated arterial stiffness persists after the puerperium period in women with HDP. However, the scarcity of published literature on this topic may limit the quality of findings in this systematic review. Additionally, the included studies may differ in sample size, leading to high heterogeneity.

Acknowledgements We extend our thanks to the 'UK-SA DHET Doctoral Training Programme team' for their valuable contribution and passion towards university capacity development.

Contributors XM worked out the protocol and methods. He will participate in the selection, inclusion, quality assessment and data extraction of papers for several reviews and will perform statistical analyses. CBB advised on the original content of the review and worked on search strategy. SG and AH reviewed the manuscript and will participate in performing several test accuracy reviews and writing drafts. All authors read and approved the final manuscript. XM is the guarantor.

Funding The study is funded by the Discovery Awards Foundation (award number 66681). The funder played no part in the protocol's development.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Xolani Mbongozi http://orcid.org/0000-0001-6113-3091
Charles Bitamazire Businge http://orcid.org/0000-0002-8393-1198

REFERENCES

1 Is S. Maternal and Perinatal Outcome in Hypertensive Disorders in Pregnancy. *IGWHC* 2018;1.
2 Miller EC. Preeclampsia and Cerebrovascular Disease. *Hypertension* 2019;74:5–13.
3 Burger RJ, Delagrange H, Valkengoed IGM, *et al*. Hypertensive Disorders of Pregnancy and Cardiovascular Disease Risk Across Races and Ethnicities: A Review. *Front Cardiovasc Med* 2022. Available: https://doi.org/10.3389/fcvm.2022.933822
4 Umesawa M, Kobashi G. Epidemiology of hypertensive disorders in pregnancy: prevalence, risk factors, predictors and prognosis. *Hypertens Res* 2017;40:213–20.
5 Honigberg MC, Zekavat SM, Aragam K, *et al*. Long-Term Cardiovascular Risk in Women With Hypertension During Pregnancy. *J Am Coll Cardiol* 2019;74:2743–54.
6 Hametner B, Wassertheurer S, Mayer CC, *et al*. Aortic Pulse Wave Velocity Predicts Cardiovascular Events and Mortality in Patients Undergoing Coronary Angiography: A Comparison of Invasive Measurements and Noninvasive Estimates. *Hypertension* 2021;77:571–81.
7 Turi V, Iurciuc S, Creţu OM, *et al*. Arterial function in hypertensive pregnant women. Is arterial stiffness a marker for the outcomes in pregnancy? *Life Sci* 2021;264:118723.
8 Chirinos JA, Segers P, Hughes T, *et al*. Large-Artery Stiffness in Health and Disease: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2019;74:1237–63.
9 Hausvater A, Giannone T, Sandoval Y-HG, *et al*. The association between preeclampsia and arterial stiffness. *J Hypertens* 2012;30:17–33.
10 Protogerou A, Blacher J, Stergiou GS, *et al*. Blood Pressure Response Under Chronic Antihypertensive Drug Therapy. *J Am Coll Cardiol* 2009;53:445–51.
11 Namugowa A, Iputo J, Wandabwa J, *et al*. Comparison of arterial stiffness in preeclamptic and normotensive pregnant women from a semi-rural region of South Africa. *Clin Exp Hypertens* 2017;39:277–83.

12 Phan K, Gomez YH, Gorgui J, *et al*. Arterial stiffness for the early prediction of pre-eclampsia compared with blood pressure, uterine artery Doppler and angiogenic biomarkers: a prospective cohort study. *BJOG* 2023;130:932–40.
13 Garg P, Jaryal AK, Kachhawa G, *et al*. Sequential profile of endothelial functions and arterial stiffness in preeclampsia during the course of pregnancy. *Pregnancy Hypertens* 2019;18:88–95.
14 Rolnik DL, Nicolaides KH, Poon LC. Prevention of preeclampsia with aspirin. *Am J Obstet Gynecol* 2022;226:S1108–19.
15 Mackenzie IS, Wilkinson IB, Cockcroft JR. Assessment of arterial stiffness in clinical practice. *QJM* 2002;95:67–74.
16 Kim HL, Kim SH. Pulse Wave Velocity in Atherosclerosis. *Front Cardiovasc Med* 2019;6:41.
17 Ungvari Z, Tarantini S, Donato AJ, *et al*. Mechanisms of Vascular Aging. *Circ Res* 2018;123:849–67.
18 WilliamsPSThomSMCruickshankKDifferential Impact of Blood Pressure–Lowering Drugs on Central Aortic Pressure and Clinical Outcomes Principal Results of the Conduit Artery Function Evaluation (CAFE) Study. *Circulation* 2006;113:1213–25. Available: https://doi.org/10.1161/CIRCULATIONAHA.105.595496
19 Forrest M, Bourgeois S, Pichette É, *et al*. Arterial stiffness measurements in pregnancy as a predictive tool for hypertensive disorders of pregnancy and preeclampsia: Protocol for a systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol X* 2022;13:100141.
20 Phan K, Schiller I, Dendukuri N, *et al*. A longitudinal analysis of arterial stiffness and wave reflection in preeclampsia: Identification of changepoints. *Metab Clin Exp* 2021;120:154794.
21 Osman MW, Nath M, Breslin E, *et al*. Association between arterial stiffness and wave reflection with subsequent development of placental-mediated diseases during pregnancy: findings of a systematic review and meta-analysis. *J Hypertens* 2018;36:1005–14.
22 Morton A. Physiological Changes and Cardiovascular Investigations in Pregnancy. *Heart Lung Circ* 2021;30:e6–15.
23 Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. *Circulation* 2014;130:1003–8.
24 Ying W, Catov JM, Ouyang P. Hypertensive Disorders of Pregnancy and Future Maternal Cardiovascular Risk. *J Am Heart Assoc* 2018;7.
25 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:148–60.
26 Brown MA, Magee LA, Kenny LC, *et al*. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens* 2018;13:291–310.
27 Braunthal S, Brateanu A. Hypertension in pregnancy: Pathophysiology and treatment. *SAGE Open Med* 2019;7:2050312119843700.
28 Vatner SF, Zhang J, Vyzas C, *et al*. Vascular Stiffness in Aging and Disease. *Front Physiol* 2021;12:762437.
29 Higgins JPT, Altman DG, Gotzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343.
30 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603–5.
31 DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. *Contemp Clin Trials* 2007;28:105–14.
32 Deeks JJ, Higgins JP, Altman DG. Analysing data and undertaking meta-analyses. 2019.