



**UNIVERSITY of
STIRLING**



**ASSOCIATION OF CENTRAL AND PERIPHERAL BLOOD PRESSURE WITH CARDIOVASCULAR
BIOMARKERS IN WOMEN WITH PREECLAMPSIA**

By

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TABLE OF CONTENTS

TABLE OF CONTENTS	ii
LIST OF TABLES.....	vii
LIST OF FIGURES	ix
LIST OF APPENDICES.....	x
DECLARATION	xii
ACKNOWLEDGEMENT.....	xiii
PUBLICATIONS	xiv
ACCRONYMS AND ABBREVIATIONS	xv
PREFACE	xvii
ABSTRACT	xvii
EXECUTIVE SUMMARY	xix
CHAPTER 1	1
1. General introduction.....	1
1.1 Epidemiology and classification of hypertensive disorders of pregnancy	1
1.2 Pathogenesis of preeclampsia	4
1.3 Angiogenic factors in preeclampsia	4
1.4 Cardiac biomarkers in pregnancy and preeclampsia	4
1.5 Peripheral brachial blood pressure	6
1.6 Central aortic blood pressure	6
1.7 Central aortic blood pressure in eclampsia	12
1.8 Statement of the problem	13
1.9 Aims of the thesis.....	15
1.10 Research questions	15
1.11 Research Objectives.....	16
1.12 Research methodology	17

1.12.1 Systematic review and meta-analysis	17
1. Search Strategy	17
2. Exposure and Comparator	17
3. Data collection and risk of bias	18
4. Statistical analysis	18
1.12.2 Experimental study	18
1. Study design	18
2. Study site	19
3. Study population	19
4. Sample size	19
5. Selection criteria	20
6. Sampling method	22
7. Study procedures	23
Proteinuria	25
Anthropometric measurements of all participants	25
Peripheral Blood pressure measurements	26
Measurement of brachial and central blood pressure using Microlife WatchBP Office Central	26
Measurement of cardiac biomarkers	28
Patient procedure for normotensive controls	28
8. Data collection instrument and variables	28
9. Data entry, checking, and analysis	30
10. Ethical considerations	31
1.12.3 Survey	32
1. Data Collection	32
2. Data Entry, Cleaning, and Analysis	32
3. Ethical considerations	33
1.13 Flowchart of studies	33
1.14 References	35
CHAPTER 2	45

2. Arterial Stiffness After 6 Weeks Postdelivery in Women with a History of Hypertensive Disorders of Pregnancy: A Systematic Review and Meta-analysis	45
Abstract.....	45
2.1 Introduction	47
2.2 Objective.....	49
2.3 Methods	49
2.4 Results	53
2.5 Discussion	78
2.6 Limitations	80
2.7 Conclusion	80
2.8 References.....	80
CHAPTER 3.....	84
3. Reliability of the Microlife WatchBP Office Central device for blood pressure measurement in hypertensive and normotensive pregnant women.....	84
Abstract.....	84
3.1 Introduction	85
3.2 Objective.....	87
3.3 Methods	87
3.4 Results	89
3.5 Discussion	94
3.6 References.....	97
CHAPTER 4.....	100
The correlation of peripheral blood pressure with central blood pressure and estimation of central blood pressure thresholds for diagnosis of hypertension during pregnancy	100
Abstract.....	100
4.1 Introduction	102
4.2 Objectives	103
4.3 Materials and Methods	103
4.4 Results	106
4.5 Discussion	121

4.6 References.....	126
CHAPTER 5.....	130
3. The relationship between central blood pressure, NT-proBNP, and hs-cTnI in women with Maternal Complications of Hypertensive Disorders of Pregnancy.....	130
Abstract.....	130
5.1 Introduction.....	132
5.2 Methods.....	134
5.3 Results.....	136
Maternal complications diagnosed in the study group.....	139
Relationship between NT-proBNP and hs-cTnI, and maternal complications in all hypertensive cases.....	139
5.4 Discussion.....	146
5.5 References.....	150
CHAPTER 6.....	155
4. Assessment of clinical practices and cardiac biomarker screening in preeclampsia: a survey of healthcare professionals.....	155
Abstract.....	155
6.1 Introduction.....	157
6.2 Methods.....	158
6.3 Results.....	160
6.4 Discussion.....	171
6.5 References.....	177
CHAPTER 7.....	180
7.1 General discussion and synthesis of the findings.....	180
7.1.1 Summary of key findings.....	181
7.1.2 Comparison with Existing Literature.....	184
7.1.3 Implications for Clinical Practice.....	189
7.1.4 Implications for Policy and Health Systems.....	190
7.2 Limitations and strengths of the study.....	194
7.3 Overall Conclusion.....	195
7.4 Recommendation and Future Directions.....	196

7.5 References.....	196
APPENDICES	200
Appendix A : Data capture sheet (study 2)	200
Correlation of central blood pressure and peripheral blood pressure with pro-BNP and troponin I - measures of future cardiovascular disease- among women with preeclampsia	200
Appendix B: Information sheet (study 2)	204
Correlation of central blood pressure and peripheral blood pressure with pro-BNP and troponin I - measures of future cardiovascular disease- among women with preeclampsia	204
Appendix C: Translated information sheet (study 2).....	205
Correlation of central blood pressure and peripheral blood pressure with pro-BNP and troponin I - measures of future cardiovascular disease- among women with preeclampsia	205
(Uxinezelelo lwegazi kwimithambo ekufuphi nentliziyo ne arterial stiffness kumanenekazi anesifo i- hypertensive disorders of pregnancy, neziphumo kumanenekazi lawo neentsana zawo)	205
Appendix D: Informed consent (study 2).....	207
Correlation of central blood pressure and peripheral blood pressure with pro-BNP and troponin I - measures of future cardiovascular disease- among women with preeclampsia	207
Appendix E: Translated informed consent (study 2)	208
Uxinezelelo lwegazi kwimithambo ekufuphi nentliziyo ne arterial stiffness kumanenekazi anesifo i- hypertensive disorders of pregnancy, neziphumo kumanenekazi lawo neentsana zawo.....	208
Appendix F: Google form (study 3).....	208
Assessment of clinical practices and cardiac biomarker screening in preeclampsia: a survey of healthcare professionals	208
Appendix G: Informed Consent form (study 3)	213
Assessment of clinical practices and cardiac biomarker screening in preeclampsia: a survey of healthcare professionals	213
Appendix H: Ethical clearances	215
Appendix I: Publications	219

LIST OF TABLES

Table 2 1. PubMed Search strategy.....	50
Table 2. 2: Data Extraction Table	55
Table 2 3: NOS for the risk of bias and quality assessment of NRSs	59
Table 2 4. NOS (adapted for cross-sectional studies) for the risk of bias and quality assessment of NRSs	60
Table 3. 1: Demographic characteristics of hypertensive cases and normotensive controls	90
Table 3. 2: Coefficient of variation (%) for Blood Pressure Parameters taken by two observers	91
Table 3. 3: Intraclass correlation coefficient and Standard error of measurement for blood pressure parameters taken by two observers.....	92
Table 3 4. Minimum detectable change for blood pressure parameters	93
Table 3 5. Inter-Observer Reliability (ICC and SEM) for Systolic and Diastolic Blood Pressure	94
Table 4. 1: General characteristics of hypertensive cases and normotensive controls in the main study	109
Table 4. 2: Sensitivity and specificity of cSBP cut-offs for prediction of central hypertension in women with HDP	110
Table 4. 3: Establishment of cSBP threshold in normotensives.....	114
Table 4. 4: Establishment of cDBP threshold in normotensives	114
Table 4. 5: Establishment of cSBP thresholds for diagnosis of severe central hypertension based on pSBP of ≥ 160 mmHg in women with severe peripheral hypertension	115
Table 4.6: Defining cDBP cut-off for severe central hypertension based on pDBP of ≥ 110 mmHg in women with severe peripheral hypertension.....	116

Table 4.7: Comparison of median pSBP and pDBP with median cSBP and cDBP among women with normal and mild peripheral hypertension as measured using Microlife WatchBP Office Central.	118
Table 4.8: Comparison of central blood pressure readings among the different phenotypes of HDP and normotensive controls.....	121
Table 5.1. General and clinical characteristics of the sample population	138
Table 5.2. Maternal complications diagnosed in the study participants	139
Table 5.3. Medial comparisons of NT-proBNP and hs-cTnI, and CBP in hypertensive cases with or without specific maternal complications	140
Table 5.4. Comparisons of PBP and CBP in hypertensive cases with or without specific maternal complications.....	142
Table 5.5: Medial comparisons of NT-proBNP and hs-cTnI in eclamptic cases with or without specific maternal complications.....	145
Table 6 1. Demographic characteristics of participants.....	160
Table 6 2. Common cardiac related complications encountered during the care of patients with preeclampsia.....	161
Table 6 3. Tests used to screen preeclamptic women for incident cardiac complications	162
Table 6 4. Measures used for prognostication	163
Table 6 5. Role of cardiac biomarkers in managing the short- and long-term prognosis of preeclampsia	166
Table 6 6. Correlation between the participants' careers, their years of experience, and the frequency of cardiac-related complications observed	170
Table 6 7. Correlation between the participants' careers, their years of experience, and their opinion on the use of cardiac biomarkers	170

LIST OF FIGURES

Figure 2 1: Flow diagram of study inclusion	54
Figure 2. 2. The pooled mean difference of the AIX (A) and PWV (B) of women with various HDP and normotensive women	63
Figure 2. 3. Funnel plot of included studies for AIX in women with HDP vs normotensive patients	64
Figure 2 4. Funnel plot of included studies for PWV in women with HDP vs normotensive patients ...	64
Figure 2.5. Pooled mean difference of the AIX of women with HDP and normotensive pregnant women, within a year or less after delivery (A), and Pooled mean difference of the AIX of women with HDP and normotensive pregnant women after one year following delivery (B)	66
Figure 2.6. Pooled mean difference of the PWV of women with HDP and normotensive pregnant women, within a year or less after delivery (A), and Pooled mean difference of the PWV of women with HDP and normotensive pregnant women after one year following delivery (B)	68
Figure 2 7. The pooled mean difference of the AIX (A), AIX@75 (B) and PWV (C) of women with preeclampsia and normotensive women	69
Figure 2.8. Funnel plot of included studies for PWV in preeclamptic vs normotensive patients. SE(Standard Error); MD (Mean difference).....	71
Figure 2 9. Pooled mean difference of the PWV of women with composite hypertensive disorders of pregnancy and normotensive pregnant women	71
Figure 2 10. Pooled mean difference of the AIX (A) and PWV (B), of women with early onset preeclampsia compared to normotensive women	73
Figure 2 11. Pooled mean difference of the AIX (A) and PWV (B), of women with late-onset preeclampsia compared to normotensive women	74
Figure 2 12. The pooled mean difference of the AIX (A) and PWV (B), of women with HDP and normotensive women in cohort studies	76

Figure 2 13. Pooled mean difference of the Alx (A) and PWV (B) of women with HDP and normotensive pregnant women in cross-sectional studies	77
Figure 4. 1: Flowchart of participant inclusion.....	108
Figure 4. 2: ROC for cSBP cut-off for prediction of central hypertension in women with HDP if 116 mmHg is chosen	113
Figure 4.3. Median pSBP among normotensive pregnant women.....	117
Figure 4. 4. Median cSBP among normotensive pregnant women	117
Figure 5 1. hs-cTnl and NT-proBNP cut-offs for prediction of maternal complications in women with hypertensive disorders of pregnancy.	143
Figure 5 2. hs-cTnl and NT-proBNP cut-offs for prediction of renal failure in women with hypertensive disorders of pregnancy.....	144
Figure 6 1. Routine review of preeclamptic patients after delivery	164
Figure 6 2. Timeline for resolution of PPCM.....	168

LIST OF APPENDICES

Appendix A : Data capture sheet (study 2.....	200
Appendix B: Information sheet (study 2)	204
Appendix C: Translated information sheet (study 2)	205
Appendix D: Informed consent (study 2)	207
Appendix E: Translated informed consent (study 2)	208

Appendix F: Google form (study 3)	208
Appendix G: Informed Consent form (study 3)	213
Appendix H: Ethical clearances	215
Appendix I: Publications	219

DECLARATION

DECLARATION

I, Xolani Bethwell Mbongozi, Student Numbers: 202600866 (Walter Sisulu University); 3139859 (University of Stirling), solemnly declare that this thesis with the title **“Association of central and peripheral blood pressure with cardiovascular biomarkers in women with preeclampsia”** is my own original work which has not been submitted at any other institution elsewhere for academic purposes. All the sources that I have used or quoted have been indicated and acknowledged by means of complete references, and any contributions from others have been specifically acknowledged in each chapter.

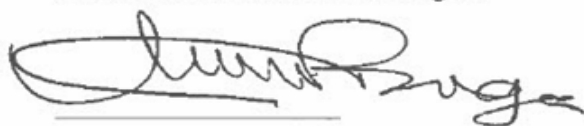


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PUBLICATIONS

Linked to chapter 2:

1. Mbongozi X, Galloway S, Hunter A and Businge CB. 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
2. Mbongozi XB, Galloway SDR, Hunter A, Milambo JP and Businge CB. Arterial Stiffness After 6 Weeks Postdelivery in Women with a History of Hypertensive Disorders of Pregnancy: A Systematic Review and Meta-analysis. *Front Med.* 2025 | doi: 10.3389/fmed.2025.1665100

Linked to chapter 3

1. Mbongozi XB, Galloway SDR, Hunter A, Businge CB and Buga GAB (2025) Reliability of the Microlife WatchBP Office Central device for blood pressure measurement in hypertensive and normotensive pregnant women. Prepared for submission to *S African Med J*.

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2. Mbongozi XB, Galloway SDR, Hunter A, Businge CB, Nanjoh M and Buga GAB. The correlation and comparison of peripheral blood pressure with central blood pressure in identifying hypertension during pregnancy. *Front Med.* 2025 Sep 3; 12:1651854. doi: 10.3389/fmed.2025.1651854.

Linked to chapter 5

1. (Abstract) Mbongozi XB, Galloway SDR, Hunter A and Businge CB. Central blood pressure, cardiac biomarkers and maternal complications in hypertensive pregnancies. *BJOG-AN International Journal of Obstetrics and Gynaecology* 131, 114-114, 2024
2. Mbongozi X, Galloway SDR, Hunter A, Nanjoh M and Businge CB. (2025). Elevated central blood pressure, NT-proBNP and hs-cTnI in women with maternal complications of hypertensive disorders of pregnancy. *Hypertension in Pregnancy.* 2025; 44(1). <https://doi.org/10.1080/10641955.2025.2524324>.

1. Mbongozi XB, Galloway SDR, Hunter A, Businge CB and Buga GAB (2025) Assessing Clinical Practices and Screening for Cardiac Complications in Preeclampsia: A Survey of Healthcare Professionals. Prepared to be submitted to J Matern Fetal Neonatal Med.

ACCRONYMS AND ABBREVIATIONS

ACOG	American College of Obstetrician and Gynaecologists
ACC	American College of Cardiology
AHA	American Heart Association
AIX	Augmentation index
AIX@75	Augmentation index adjusted for a heart rate of 75 beats per minute
ALT	Alanine aminotransferase
ANC	Antenatal clinic
AST	aspartate aminotransferase
CBP	Central blood pressure
CDBP	Central diastolic blood pressure
cfPWV	Carotid-femoral pulse wave velocity
CSBP	Central systolic blood pressure
DIC	Disseminated intravascular coagulation
FIGO	International Federation of Gynaecology and Obstetrics
HELLP	Haemolysis Elevated Liver Enzyme Low Platelet
HIV-AIDS	Human immunodeficiency virus acquired immunodeficiency syndrome

GCS	Glasgow Coma Scale
HDP	Hypertensive disorders of pregnancy
ICU	Intensive Care Unit
ISSHP	International Society for the Study of Hypertension in Pregnancy
IUFD	Intrauterine foetal death
GHPT	Gestational hypertension
HS-CTNI	Highly sensitive cardiac troponin I
LDH	Lactate dehydrogenase
NICU	Neonatal Intensive Care Unit
NMAH	Nelson Mandela Academic Hospital
NT-proBNP	N-terminal pro-brain natriuretic peptide
PDBP	Peripheral diastolic blood pressure
PE	Preeclampsia
PIGF	Placenta Like Growth Factor
PSBP	Peripheral systolic blood pressure
RCOG	Royal College of Obstetricians and Gynaecologists
SBP	Systolic blood pressure
WHO	World Health Organization

PREFACE

This thesis is structured into seven chapters. Chapter 1 covers the general introduction of the topic. Chapter 2 will cover a systematic review and meta-analysis. The results will be presented in Chapters 3, 4, 5, and 6, and the discussion and synthesis, overall conclusions and recommendations will be presented in Chapter 7. Each chapter will be concluded with its own list of references used.

The results component of this study is over four chapters presented based on publications or manuscripts in journals approved by the South African Department of Higher Education and Training (DHET) or indexed in Scopus database.

ABSTRACT

Background: Hypertensive disorders of pregnancy (HDP) are major contributors to maternal and perinatal morbidity and mortality worldwide. Traditional diagnosis of hypertension relies on peripheral blood pressure (PBP), but recent studies suggest central blood pressure (CBP) may better predict cardiovascular outcomes. Cardiac biomarkers such as N-terminal pro B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin I (hs-cTnI) are established and widely utilised biomarkers in cardiovascular risk stratification, and it is known these biomarkers are elevated in patients with HDP. However, the relationship between these cardiac biomarkers, CBP, and maternal complications of HDP remains unclear. Additionally, the current clinical use of these markers in women with HDP is not well-documented.

Aims: The aims of this thesis were to theoretically assess whether arterial stiffness in women with a history of HDP persists beyond the puerperal period. Additionally, the thesis aimed to evaluate the correlation between CBP and the PBP measured using the Microlife WatchBP Office Central, as well as the association between CBP and adverse maternal outcomes, and the association between serum levels of NT-proBNP and hs-cTnI and adverse maternal outcomes among pregnant black African women with HDP and normotensive controls. Lastly, the thesis sought to evaluate the

likelihood of clinical practitioners incorporating additional clinical diagnostic markers into the management of preeclampsia.

Methodology: This thesis had three main studies: a systematic review and meta-analysis, an experimental study, and an online survey. The systematic review followed PRISMA-P 2015 guidelines, conducting comprehensive searches across major databases to identify studies on arterial stiffness in women with HDP after delivery. Data were extracted, screened by independent reviewers, and meta-analyses were performed to compare arterial stiffness indices between women with and without HDP.

The experimental study was a cross-sectional investigation at Nelson Mandela Academic Hospital, that consecutively recruited a total of 540 participants, consisting of 270 inpatients diagnosed with HDP and an equal number of 270 normotensive pregnant inpatients. Inclusion and exclusion criteria were rigorously applied, and all procedures and measurements were conducted with meticulous attention to accuracy and adherence to clinical guidelines.

The survey targeted registrars and medical specialists in regional and tertiary maternity units, gathering insights via an online questionnaire about their experience and perspective on the use of cardiac biomarkers in women with preeclampsia. Data were statistically analysed, and ethical approvals were obtained for all components.

Results:

Women with a history of HDP showed significantly higher augmentation index and pulse wave velocity compared to normotensive controls in the systematic review. The Microlife WatchBP Office Central device demonstrated high reliability for blood pressure measurements, with coefficients of variation between 1.0–1.8% and intraclass correlation coefficients above 0.96. Peripheral and central systolic blood pressures were strongly correlated, with central systolic blood pressure (CSBP) of 116 mmHg and central diastolic blood pressure of 78 mmHg identified as diagnostic thresholds for hypertension in pregnancy. The median peripheral systolic blood pressure among eclamptic patients with mild peripheral hypertension was 138.0 mmHg (IQR: 133.0-148.0) while the CSBP level in the same group was in the severe range [145.0 mmHg (IQR: 140.0-150.0) mmHg]. Women with HDP and maternal complications had higher CBP, NT-proBNP, and hs-cTnI levels compared to those without complications. Among surveyed clinicians, 75.9% acknowledged the potential benefit of cardiac biomarkers for preeclampsia management.

Conclusion: Arterial stiffness may remain elevated in women with a history of preeclampsia, suggesting a possible increased risk of long-term cardiovascular disease. CBP, NT-proBNP, and hs-cTnI are higher in women with HDP and maternal complications, supporting their potential roles in risk stratification and monitoring. CBP may be more informative than PBP in recognizing individuals who could be at higher risk of developing eclampsia. Incorporating CBP and these biomarkers may help strengthen screening and management strategies for hypertensive pregnancy disorders.

EXECUTIVE SUMMARY

Background

HDP are a leading cause of maternal and perinatal morbidity and mortality worldwide. HDP encompasses several types, including chronic hypertension, gestational hypertension, preeclampsia, and chronic hypertension superimposed with preeclampsia. Among these, preeclampsia is associated with the greatest risk of adverse maternal and perinatal outcomes, particularly when severe features are present or when the condition develops before 34 weeks' gestation (von Dadelszen et al. 2011; Payne et al. 2014). While elevated peripheral blood pressure has long been the standard for diagnosing hypertension in both pregnancy and the general population, emerging evidence suggests that central blood pressure (CBP) may offer superior predictive value for cardiovascular outcomes.

N-terminal pro B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin I (hs-cTnI), play an important role in assessing cardiovascular risk. ProBNP is released from the left and right cardiac ventricles in response to volume expansion and pressure overload, while hs-cTnI is produced in response to damage in cardiomyocytes. In circulation, the BNP hormone is split from the inactive n-terminal part of the prohormone termed NT-proBNP by protease furin. Both NT-proBNP and hs-cTnI biomarkers may help predict peripheral perfusion and the risk of end-organ damage.

It is known that CBP and the levels of NT-proBNP and hs-cTnI are elevated in patients with HDP. However, the relationship between these cardiac biomarkers, CBP, and maternal complications of HDP remains unclear. Additionally, the current clinical use of these markers is not well-documented.

Aims of the thesis

The aims of this thesis were to theoretically assess whether arterial stiffness in women with a history of HDP persists beyond the puerperal period. Additionally, the thesis aimed to evaluate the correlation between central aortic blood pressure and the peripheral brachial blood pressure measured using the Microlife WatchBP Office Central, as well as the association between CBP and adverse maternal outcomes, and the association between serum levels of NT-proBNP and hs-cTnI and adverse maternal outcomes among pregnant black African women with HDP and normotensive controls. Lastly, the thesis sought to evaluate the likelihood of clinical practitioners incorporating additional clinical diagnostic markers into the management of preeclampsia.

Objectives of the thesis

- I. To systematically review and synthesize existing evidence to determine whether arterial stiffness remains elevated beyond six weeks postpartum in women with a history of hypertensive disorders of pregnancy.
- II. To assess the reliability of peripheral systolic and diastolic blood pressure measurements obtained using the Microlife WatchBP Office Central device in pregnant women, including those with hypertensive disorders.
- III. To evaluate the correlation and comparative use of peripheral blood pressure and central blood pressure in identifying hypertension in pregnant women, using a Microlife Office Central device; Additionally, to determine the threshold values for central systolic and diastolic blood pressure as diagnostic criteria for mild and severe central hypertension during pregnancy
- IV. To compare the levels of CBP, NT-proBNP, and hs-cTnI in women with hypertensive disorders of pregnancy who have maternal complications to those in normotensive pregnant controls
- V. To evaluate the experiences and perspectives of healthcare workers regarding the clinical assessment and usage of cardiac biomarkers in patients with preeclampsia.

Experimental approach

The initial section of this thesis presents a systematic review and meta-analysis. The main objective of this systematic review was to determine if the arterial stiffness remains elevated after six weeks post-delivery in women with a history of hypertensive disorders of pregnancy.

The second part of the thesis was a cross-sectional study evaluating the central aortic blood pressure and cardiac biomarkers among pregnant women with HDP, using a Microlife WatchBP Office Central. All blood pressure measurements were obtained using the Microlife WatchBP Office Central, a device designed to estimate both peripheral and central blood pressure. Prior to the commencement of the main cross-sectional study, an in-study pilot assessment was undertaken to determine the reliability of the blood pressure measurements obtained using the Microlife WatchBP Office Central in a pregnant population. This pilot phase involved a total of 45 participants, comprising 30 hypertensive and 15 normotensive pregnant women. During the pilot study, all measurements were performed by two trained observers under standardized conditions to ensure consistency. Each participant underwent repeat peripheral blood pressure assessments using the Microlife WatchBP Office Central device. The pilot findings demonstrated acceptable reproducibility and measurement stability, thereby supporting the use of the Microlife WatchBP Office Central device in the main study population. Following the pilot phase, the main cross-sectional study was conducted at the Nelson Mandela Academic Hospital in South Africa. The study consecutively recruited a total of 540 participants, consisting of 270 inpatients diagnosed with HDP and an equal number of 270 normotensive pregnant inpatients. The inclusion criteria for the hypertensive group encompassed all pregnant women diagnosed with any form of HDP who were at least 20 weeks of gestation. The inclusion criteria for the normotensive comparison group were limited to healthy pregnant women with singleton pregnancies and no prior diagnosis of hypertension or other medical comorbidities. The objectives of the cross-sectional study were: 1. to evaluate the correlation and comparative utility of peripheral blood pressure and central aortic blood pressure in the detection of hypertension among pregnant women. 2. to compare the levels of central aortic blood pressure and selected cardiac biomarkers in women with and without maternal complications of hypertensive disorders of pregnancy.

The final section of the thesis consists of an online survey designed to evaluate the experiences and perspectives of healthcare workers regarding the clinical assessment and application of cardiac biomarkers in patients with preeclampsia.

Results

Arterial Stiffness After 6 Weeks Postdelivery in Women with a History of Hypertensive Disorders of Pregnancy: A Systematic Review and Meta-analysis

Compared to normotensive controls, women with a history of preeclampsia had significantly elevated augmentation index (Alx) (Mean Difference [MD]: 8.57; 95% CI: 4.22–12.92) and pulse wave velocity (PWV) (MD: 0.47; 95% CI: 0.20–0.74). In subgroup analysis, early-onset preeclampsia was associated with a significantly higher PWV (MD: 1.86; 95% CI: 0.25–3.47), but not Alx (MD: 1.55; 95% CI: -0.74 – 3.84). No significant differences were found in late-onset preeclampsia.

Reliability of the Microlife WatchBP Office Central device for blood pressure measurement in hypertensive and normotensive pregnant women

Both observers demonstrated high precision, stability, and reproducibility across groups. Coefficients of variation (CVs) were low (1.0–1.8%), indicating minimal intra-observer variability. Intraclass correlation coefficients (ICCs) ranged from 0.97 to 0.99, confirming excellent reliability, while standard errors of measurement (SEMs; 0.08–0.20 mmHg) and minimal detectable changes (MDCs; 0.2–0.4 mmHg) reflected high measurement sensitivity. No statistically significant inter-observer differences were observed ($p > 0.05$), confirming consistency between observers. Inter-observer reliability during test and retest sessions was equally strong, with ICCs of 0.96–0.99 for both parameters. SEM values remained low (<0.5 mmHg), confirming negligible observer-related variability.

The correlation of peripheral blood pressure with central blood pressure and estimation of central blood pressure thresholds for diagnosis of hypertension during pregnancy

A significant positive correlation was found between peripheral systolic blood pressure (pSBP) and central systolic blood pressure (cSBP) among normotensive and hypertensive women. Among the 270 normotensive controls, the median pSBP was 114.0 (IQR:104.0-124.0) mmHg and median cSBP was 115.0 (IQR:106.0-125.0) mmHg.

The results of the receiver operator characteristic analysis indicated that a cSBP of 116 mm Hg or higher had a sensitivity of 78.5% and a specificity of 50.3% for diagnosing hypertension during pregnancy. The upper limit of central diastolic blood pressure (cDBP) in normotensive controls was calculated to be 78 mm Hg.

The median pSBP among eclamptic patients with mild peripheral hypertension was 138.0 mmHg (IQR: 133.0-148.0) while the cSBP level in the same group was in the severe range [145.0 mmHg (IQR: 140.0-150.0) mmHg]. The overall median cSBP among women with eclampsia (n=102) was 133.0 mmHg (IQR: 120.0-143.0), and the median cDBP was 73.0 mmHg (IQR: 60.0-83.0), and these were significantly higher ($p<0.0001$) than the median cSBP of 128.0 mmHg (IQR: 114.0-139) and cDBP of 71.0 mmHg (IQR: 61.0-81.0) among preeclamptic women with or without severe features, and much higher than the median cSBP of 115 mmHg (IQR:106.0-125.0) and cDBP of 61.5 mmHg (IQR: 52.0-69.0) among normotensive controls

Higher levels of central blood pressure, NT-proBNP, and hs-cTnl are associated with Maternal Complications of Hypertensive Disorders of Pregnancy

The median levels of the CBP and cardiac biomarkers were significantly higher among hypertensive participants with maternal complications (n=107/270) than those without complications (n=163/270). Specifically, the cSBP were 133 (120-142) mmHg vs 128 (109-129) mmHg ($p=0.033$) and the cDBP levels were 75 (62-86) mmHg vs 69 (56-73) mmHg ($p<0.01$) while NT-proBNP levels were 446 (145-1126) vs. 57 (21-167) pg.ml⁻¹; $p<0.0001$, and hs-cTnl levels were 12 (7-35) ng.L⁻¹ compared to 8 (3-8) ng.L⁻¹; $p<0.0001$. Only 0.7% of normotensive controls developed complications, while 39.6% of individuals with HDP experienced complications. The most common maternal complications in the HDP group included HELLP syndrome (28.9%), renal failure (10.7%), and abruptio placenta (9.6%).

Assessing Clinical Practices and Screening for Cardiac Complications in Preeclampsia: A Survey of Healthcare Professionals

The survey involved 58 participants, mainly medical officers and registrars (69%) and specialist obstetricians and gynaecologists (31%). A significant 89.8% identified pulmonary oedema as the most common cardiac-related complication in preeclampsia. For screening, 43.1% relied on clinical judgment, 10% used standardized protocols, 24.1% only screened high-risk cases, and 22.4% did no screening. Post-delivery, only 41.4% reviewed all preeclamptic patients. Additionally, 75.9% acknowledged the potential benefits of cardiac biomarkers for managing preeclampsia's short- and long-term prognosis.

Conclusion

The overall conclusion of this thesis is that arterial stiffness may remain elevated in women with a history of preeclampsia for more than six weeks postpartum, indicating a potentially increased risk for cardiovascular disease. The findings also indicate that levels of CBP, NT-pro-BNP, and Hs-cTnI are significantly elevated in Black African women experiencing various forms of HDP, particularly among those who suffer adverse maternal outcomes.

Furthermore, the thesis established the threshold values for central hypertension as a systolic BP of 116 mmHg and a diastolic BP of 78mmHg. It also reinforced the positive association between peripheral and CBP in both normotensive and hypertensive populations. Notably, the median systolic and diastolic blood pressures for both central and peripheral measurements were significantly elevated in cases of eclampsia compared to other hypertensive disorders and non-hypertensive controls. Interestingly, in women experiencing eclampsia, cSBP fell into the severe hypertension category, while their pSBP was classified as mild hypertension.

Overall, these findings suggest that measuring these CBP and cardiac biomarkers in hypertensive pregnancies might be helpful for screening and monitoring maternal complications, and that CBP measurement may be better able to distinguish between eclampsia and other types of HDP.

CHAPTER 1

1. General introduction

Pregnancy is associated with marked metabolic demand and cardiovascular changes that vary by trimester and return toward normal after delivery (Melchiorre et al. 2011; Sanghavi & Rutherford 2014). The important cardiovascular changes that occur during pregnancy include increased cardiac output and blood volume with concurrent reduction in systemic vascular resistance. Insufficient cardiovascular adaptation during pregnancy is associated with maternal and perinatal morbidity and mortality. Hypertensive disorders of pregnancy (HDP) are conditions in which cardiovascular adaptation to pregnancy is impaired (Thilaganathan 2017; Thilaganathan & Kalafat 2019; Yagel & Verlohren 2020; Kornacki et al. 2024).

1.1 Epidemiology and classification of hypertensive disorders of pregnancy

HDP are a leading cause of maternal and perinatal morbidity and mortality globally (Abalos et al. 2013). They account for approximately 14-18% of all maternal deaths globally, with an estimated 62,000-77,000 maternal deaths, and 500,000 perinatal deaths annually (Abalos et al. 2013; Brown et al. 2018; Khan et al. 2006; Say et al. 2014; Magee et al. 2022).

The classification of HDP has undergone several changes over the last two decades. Although different professional bodies in several different countries have their own classifications, the most widely used are the American College of Obstetricians and Gynecologists (ACOG) classification of 2013 which was upheld in 2019 (ACOG 2019), and the International Society for the Study of Hypertension in Pregnancy (ISSHP) classification of 2014 which was updated in 2018 and then again in 2021 (Brown et al. 2018; Magee et al. 2022) and is endorsed by FIGO (Poon et al. 2021). The 2019 South African national guidelines on HDP (Moodley et al. 2019) endorses the more comprehensive 2018 classification of the ISSHP (Brown et al. 2018).

ISSHP classifies HDP as follows:

I. Hypertension known to be present before pregnancy or identified before 20 weeks of pregnancy or persisting beyond 12 weeks postpartum:

- Chronic hypertension (essential or secondary)
- White coat hypertension
- Masked hypertension

II. Hypertension arising de novo at or after 20 weeks' gestation

- Transient gestational hypertension
- Gestational hypertension
- Preeclampsia de novo or superimposed on chronic hypertension

Preeclampsia (PE) is the hypertensive disorder of pregnancy associated with the greatest risk of maternal and perinatal morbidity and mortality, especially when associated with severe features or when it presents before 34 weeks' gestation (von Dadelszen et al. 2011; Magee et al. 2014; Payne et al. 2014; Vousden et al. 2019). Chronic hypertension and superimposed preeclampsia are also associated with increased risk of maternal and perinatal maternal outcomes (Chappell et al. 2008).

In general, hypertensive disorders affect approximately 5-10% of all pregnancies (Hutcheon et al. 2011; Jeyabalan 2013), with significant variations, ranging from 4 to 25% (Wang et al. 2021; Dzakpasu et al. 2024; Maeda et al. 2025). The incidence of PE is also variable, but the overall global incidence is estimated to be 2-8% (Duley 2009; Ahmed et al. 2014). PE is associated with increased future cardiovascular risk and other long-term complications beyond reproduction (Ahmed et al. 2014; Veerbeek et al. 2015; Ying, Catov & Ouyang 2018; Poon & Feng 2023).

The incidence of PE in low- and middle-income countries (LMICs) ranges from 1.8 to 16.7% (Belay & Wudad 2019). In Africa as a whole, the prevalence of HDP is estimated to be about 10% (Noubiap et al. 2019). Although population data are scanty, the prevalence of HDP in sub-Saharan Africa is estimated to be about 8% (Gemechu et al. 2020). The

prevalence of HDP was found to be 12.5%, and that of PE was found to be 5.8% in black South African primigravid women in Durban (Makhanya et al. 2016). An earlier study conducted in the Eastern Cape Province of South Africa reported an incidence of HDP among women delivering at Mthatha General Hospital as 4.6%, with a PE incidence of 3.0% (Buga & Lumu 1999). The higher prevalence found in women in Durban is probably because only primigravid women were included in the study, and primigravidae have a higher risk of PE disorders than other women in general.

Preeclampsia, defined as the *de novo* hypertension after 20 weeks' gestation accompanied by either proteinuria or features of maternal organ dysfunction or uteroplacental dysfunction (Braunthal & Brateanu 2019; Brown et al. 2018; Magee et al. 2022), is associated with a number of maternal and perinatal complications. In the past, preeclampsia has been classified as mild, moderate, or severe, but in recent times the use of this classification has been discouraged because the phenotype of preeclampsia can change rapidly without warning. ISSHP (Brown et al., 2018; Magee et al., 2014), ACOG (2020), and FIGO (Poon et al. 2021) recommend that preeclampsia should be classified as preeclampsia without severe features or preeclampsia with severe features. Preeclampsia with severe features also has several clinical phenotypes, which include severe hypertension, imminent eclampsia, eclampsia, stroke, pulmonary oedema, HELLP syndrome, preeclampsia with abruptio placentae, and preeclampsia with acute kidney injury, or combinations of these (Nankali et al. 2013; Sapna & Saroja 2018). Except for severe hypertension, when a diagnosis of the other phenotypes of preeclampsia with severe features is made, there is little room for expectant management. Pregnancy is usually terminated as an emergency, and such patients are often not included in pathogenetic and pathophysiological studies that require prolonged patient observation.

Women with PE are also at increased risk of developing chronic hypertension, diabetes mellitus, heart failure, stroke, end-stage renal disease, and cognitive impairment as long-term complications (Miller 2019).

1.2 Pathogenesis of preeclampsia

Although the pathogenesis of PE has not yet been fully elucidated, the placenta plays a significant role in the development of this perilous disease. The leading hypothesis is that of an inadequate placentation due to the deficient trophoblastic invasion of the uterine spiral arteries (Redman 1991; Roberts & Escudero 2012; Staff 2019). However, defective decidualization (Conrad et al. 2017; Conrad 2020; Garrido-Gomez et al. 2020), and faulty cardiovascular adaptation to pregnancy (Thilaganathan 2017; Thilaganathan & Kalafat 2019; Yagel & Verlohren 2020; Kornacki et al. 2024) are now also considered to be important contributors to the pathogenesis of preeclampsia.

Poorly invaded uterine myometrial spiral arteries exhibit resistance which results in abnormal blood flow, ischemia-reperfusion injury, and then placental oxidative stress (Burton et al. 2019). This oxidative stress provokes a cascade of events which culminates in the clinical manifestations of pre-eclampsia, as discussed in detail in the literature review below.

1.3 Angiogenic factors in preeclampsia

Several circulating biomarkers for risk stratification for PE have been studied. Among these biomarkers are angiogenic and antiangiogenic factors such as placental growth factor (PlGF) and soluble fms-like tyrosine kinase 1 receptor (Maynard et al. 2003; Allen Meeme et al. 2017). Meeme et al. (2017b) found that PlGF levels were lower, and soluble fms-like tyrosine kinase-1 (sFlt-1) levels were higher in pregnant black African women with preeclampsia when compared with normotensive controls.

1.4 Cardiac biomarkers in pregnancy and preeclampsia

Other circulating biomarkers that seem valuable among hypertensive pregnant women are NT-prohormone brain natriuretic peptide (NT-proBNP) and highly sensitive cardiac troponin I (hs-cTnI) levels (Fayers, Moodley & Naidoo 2013; Szabó et al. 2014; Sadlecki, Grabiec & Walentowicz-Sadlecka 2016; Ghomian et al. 2019; Ravichandran et al. 2019; Gencheva et al. 2021; Bacmeister et al. 2024). Natriuretic peptides exert a cardioprotective effect and inhibit cardiac re-modelling and are usually produced in increasing amounts by cardiomyocytes in response to myocardial fibre stretching, low blood pressure, and reduced cardiac output (Giannubilo et al. 2014; Sheikh et al. 2021).

Several studies have shown a significant increase in NT-proBNP in women with PE compared to normotensive pregnant women, suggesting a correlation between elevated systemic vascular resistance, left ventricular diastolic dysfunction, and depressed cardiac output in these patients. (Szabó et al. 2014; Sadlecki et al. 2016; Ghomian et al. 2019; Gencheva et al. 2021; Jacobsen et al. 2022).

Furthermore, cardiac troponins are usually released into the bloodstream by damaged cardiomyocytes, and their levels are increased in early-onset preeclampsia as well (Ravichandran et al. 2019; Muijsers et al. 2020; Dockree et al. 2021; Bacmeister et al. 2024). These biomarkers, in general, are used for diagnosing cardiomyocyte injury (Giannubilo et al. 2014; Dalal et al. 2016; Gencheva et al. 2021; Sheikh et al. 2021). A large longitudinal cohort study covering 20 years revealed that 65% of cardiovascular disorders occurred in women under 40, which is a typical age for pregnancy (Leon et al. 2019). Among these, women with one or more pregnancies affected by preeclampsia had a hazard ratio of 2.13 (1.64–2.76) for heart failure and 2.12 (1.49–2.99) for cardiovascular deaths. Given this increased risk profile among pregnant women, particularly those with a history of preeclampsia, it becomes increasingly important to identify reliable markers that can predict the likelihood of cardiac failure in this vulnerable population. Furthermore, a strong association between cardiac Troponin I and preeclampsia, both during pregnancy and many years after pregnancy, has been reported in several studies (Alma et al. 2017; Morton & Morton 2018; Ravichandran et al. 2019; Muijsers et al. 2020; Gencheva et al. 2021; Jacobsen et al. 2022; Bacmeister et al. 2024). However, these studies did not examine the relationship between NT-proBNP, hs-cTnI and central aortic blood pressure in women with different types of HDP and the maternal and perinatal outcomes.

In conclusion, the evaluation of NT-proBNP and hs-cTnI levels presents a promising avenue for enhancing the management and monitoring of HDP. Given the established associations between these biomarkers and cardiac dysfunction, as well as the increased cardiovascular risk in women with a history of preeclampsia, further research is needed to evaluate the relationship between these biomarkers and maternal and perinatal outcomes.

1.5 Peripheral brachial blood pressure

The measurement of brachial peripheral blood pressure is currently an integral part of antenatal care globally. An elevated brachial peripheral blood pressure has long been considered the hallmark of HDP, including preeclampsia. However, brachial peripheral hypertension does not necessarily correlate with maternal and perinatal outcomes, except for the increased risk of intracranial haemorrhage when there is severe peripheral hypertension (Sibai & Stella 2009).

The role of brachial blood pressure in prediction of future cardiovascular structural damage, morbidity and mortality among non-pregnant adult population is well-established in high-income countries, as well as in middle-income countries such as China and Mexico (Lewington et al. 2002; Lacey et al. 2018; Tapia-Conyer et al. 2020). Controlling brachial blood pressure can reduce the risk of cardiovascular death in individuals as well as in populations (Martínez-Ayala et al. 2023).

However, while elevated brachial peripheral blood pressure is an important factor in monitoring hypertensive disorders during pregnancy, its implications for maternal and perinatal outcomes warrant further investigation.

1.6 Central aortic blood pressure

There is accumulating evidence that the central aortic blood pressure is more independently correlated with future cardiovascular events than the brachial blood pressure (Williams et al. 2006; Roman et al. 2009; Williams et al. 2018; Cheng et al. 2019). Central aortic blood pressure has been demonstrated to have a better relationship to future cardiovascular events and mortality and is also more relevant than peripheral brachial BP in predicting target organ damage, as it represents the true load imposed on the heart, brain, kidneys, and the large arteries (Weber 2005; Roman et al. 2010; Baba, Johan & Mohan 2018; Williams et al. 2018).

Blood pressure-lowering drugs have also been shown to have substantially different effects on CBP despite a similar effect on brachial blood pressure. Beta-blockers such as atenolol are not as effective in lowering central aortic blood pressure as calcium channel blockers, angiotensin converting enzyme inhibitors, and angiotensin II receptor blockers (Williams et al. 2006; McGaughey et al. 2016), although vasodilating selective

beta-blockers such as carvedilol, labetalol, and nebivolol appear to be as effective (Kim et al. 2014; Pucci et al. 2014). This means that while the brachial pressure may appear well controlled with drugs like atenolol, the central aortic blood pressure may remain poorly uncontrolled, thus putting patients at risk of cardiovascular events. This therefore suggests that CBP targets and selection of antihypertensive drugs with beneficial effects on the CBP may be better for the management of hypertension than brachial blood pressure and drugs that do not influence CBP (Pucci et al. 2014).

Aortic pulse wave velocity and arterial stiffness, which are the earliest indication of endothelial dysfunction, are also associated with increased risk of cardiovascular events and mortality (Laurent & Boutouyrie 2020; Hametner et al. 2021).

1.6.1 Measurement of central aortic blood pressure in pregnancy

Until recently, there were only invasive methods for studying CBP, and most of the studies involved men and non-pregnant women (Williams et al. 2018). Use of applanation tonometry made it possible to measure wave reflections, arterial stiffness, and the central aortic blood pressure in the general population (Agabiti-Rosei et al. 2007; Nelson et al. 2010) and in normotensive pregnant women (Fujime et al. 2012; Khalil et al. 2009; Macedo et al. 2008). One of the noninvasive methods which uses applanation tonometry and pulse wave analysis for measuring arterial stiffness and central aortic blood pressure is the SphygmoCor device (AtCor Medical, Australia). The SphygmoCor has been validated against invasive methods of measuring central aortic blood pressure, and as a result it has become the gold standard for the non-invasive estimation of CBP. The SphygmoCor® XCEL device has recently been approved by the FDA for clinical use (ATCOR 2020).

Another method for non-invasively measuring arterial stiffness and central aortic blood pressure is the EndoPat (Itamar Medical, Israel), a device that consists of a finger plethysmograph for sensing volume changes in the digit with each arterial pulsation (Hamburg & Benjamin 2009; Meeme et al. 2017). The volume changes in the fingertip are recorded digitally as pulse amplitude that can be tracked over time.

Applanation tonometry for measuring central aortic blood pressure has been studied in normotensive pregnant women and in women with HDP (Macedo et al. 2008; Khalil et al. 2009; Fujime et al. 2012; Meeme et al. 2017; Namugowa et al. 2017). Macedo et al. (2008) carried out a study involving 193 normotensive pregnant women with singleton pregnancies at 11 to 41 weeks' gestation, and 23 non-pregnant women, and found that normal pregnant women had lower central aortic blood pressure and mean arterial blood pressure than non-pregnant controls ($96\pm 8/67\pm 7$ mmHg vs $103\pm 11/71\pm 9$ mmHg, and 81.1 ± 7.2 mmHg vs 85 ± 8.9 mmHg, respectively).

Khalil et al. (2009) studied pulse wave analysis in a prospective study involving 541 mixed ethnicity normal women with singleton pregnancies, 45 of whom were followed up longitudinally, using the SphygmoCor (Atcor Medical, West Ryde, Australia) and applanation tonometry (Millar Instruments, Houston, Texas, USA). The mean normal brachial blood pressure from 10-13 weeks' gestation to 37 weeks' gestation was 110/64 mmHg, and the mean normal central aortic blood pressure for the same period was approximately 100/64 mmHg.

Fujime et al. (2012) carried out a cross-sectional study in 830 Asian women with normal singleton pregnancies, 69 of whom had longitudinal data, from 12-36 weeks' gestation, using radial artery applanation tonometry as a non-invasive method for measuring central systolic BP (cSBP) and augmentation index. They found that the median cSBP was 103 mmHg in the first trimester, 99 mmHg at 17-27 weeks' gestation, and 105 mmHg at 34-36 weeks' gestation. The median cSBP was lowest at mid-pregnancy and gradually rose to 1st trimester levels in the 3rd trimester and postpartum. Maternal height showed a negative association with cSBP but not with bSBP. Maternal BMI showed a positive correlation with both the bSBP and cSBP. Women of ≥ 35 years had significantly higher cSBP than women < 35 years old.

The SphygmoCor device (AtCor Medical, Australia) became the gold standard for the non-invasive estimation of CBP after its validation against invasive methods, and the SphygmoCor® XCEL device has recently been approved by the FDA for clinical use (ATCOR 2020). However, because of the time and controlled environmental conditions needed for the use of the SphygmoCor, it is not suitable for routine clinical use in patients

with serious complications of preeclampsia such as eclampsia and abruptio placentae. Similarly, the EndoPat (Itamar Medical, Israel) is a costly delicate machine that requires a controlled environment and takes time to set up and is not suitable for routine clinical use.

In conclusion, the measurement of central aortic blood pressure during pregnancy has evolved with advancements in non-invasive techniques, such as applanation tonometry and the use of devices like SphygmoCor and EndoPat. These methods have been validated and shown to provide valuable insights into arterial stiffness and cardiovascular health in pregnant women. However, the practical limitations of these devices in acute clinical settings highlight the need for ongoing research and development to improve accessibility and usability in managing complications such as preeclampsia and related conditions.

1.6.2 Digital Blood Pressure Monitoring Technology and Wearables During Pregnancy

The growing integration of digital technologies into maternal healthcare is reflected in initiatives such as the digital adaptation kit for self-monitoring of blood pressure during pregnancy developed by the World Health Organization (WHO 2025). This framework provides operational guidance for incorporating digital tools into antenatal care systems to support self-monitoring of blood pressure and facilitate early detection of hypertensive disorders of pregnancy. The capacity of wearable technologies to provide continuous, ambulatory and patient-driven monitoring has therefore generated considerable interest, especially in pregnancy where repeated blood pressure assessments are required (Denu et al., 2025; Rajkumar et al., 2025).

Evidence evaluating digital and eHealth interventions in maternal and cardiovascular monitoring suggests that these technologies are generally feasible and acceptable to users, as supported by qualitative outcomes indicating that eHealth interventions are easy to use and demonstrate largely reduced health care service utilisation (Hu et al. 2025; Rajkumar et al. 2025). These findings support the broader integration of digital monitoring approaches within antenatal care models, particularly where resource constraints or geographic barriers limit access to frequent clinical review.

Recent advances in digital health technologies have expanded the possibilities for non-invasive cardiovascular monitoring. In addition to oscillometric devices such as the Microlife WatchBP Office Central, wearable technologies including smartwatches and wrist-based sensors are increasingly being explored for blood pressure monitoring (Henry et al. 2024). These devices typically use photoplethysmography and pulse wave analysis combined with machine-learning algorithms to estimate physiological parameters such as heart rate, pulse wave characteristics and, in some cases, blood pressure. However, while these advancements have significant potential to transform cardiovascular care, several challenges remain. Key among them is the need for standardized protocols and comprehensive validation studies to confirm their reliability and safety in clinical settings, especially in Black African population (Henry et al. 2024). Furthermore, the accuracy of wearable blood pressure technologies may vary depending on physiological state, calibration requirements and environmental conditions (Stergiou et al. 2018). Evidence regarding their performance in African populations remains particularly limited.

Importantly, most commercially available wearable devices estimate peripheral blood pressure rather than central aortic blood pressure. With the notable exception of the B-Pro Wristwatch (HealthSTATS, Singapore), which utilises applanation tonometry but presents its own practical and methodological limitations, central blood pressure measurement remains largely unavailable in wearable formats (Garcia-Ortiz et al. 2012). This distinction is clinically important because central aortic pressure has been shown to be more closely associated with cardiovascular outcomes than peripheral blood pressure. This highlights the need for convenient, non-invasive and validated central blood pressure devices that are suitable for use during pregnancy.

1.6.3 Oscillometric devices for measuring central aortic blood pressure

More portable, less cumbersome, non-invasive methods for measuring central aortic blood pressure and arterial stiffness have been developed. One of these is the B-Pro Wristwatch (HealthSTAT, Singapore) that derives the central aortic systolic pressure from the radial pressure waveform using an N-point moving average method (Williams et

al. 2011; Garcia-Ortiz et al. 2012). Another device is the Microlife WatchBP Office Central (Microlife, Taiwan), an oscillometric method (Cheng et al. 2013; Verberk et al. 2016). These methods are more portable and less restrictive than the SphygmoCor device and the EndoPat device, and are easier to use in the clinical setting, with the least amount of inconvenience to patients (Meeme et al. 2017; Namugowa et al. 2017). However, there is scarcity of data on the use of B-Pro Wristwatch (HealthSTAT, Singapore) and Microlife WatchBP Office Central (Microlife, Taiwan) in black African women with HDP, including preeclampsia with severe features.

The B-Pro Wristwatch (HealthSTAT, Singapore) would have been particularly convenient because it is worn on the wrist and takes the CBP and the pulse wave velocity automatically and can easily be used on an ambulatory basis without interfering with routine care of hypertensive pregnant women, including those with eclampsia. Although it has been validated for use in pregnancy, it should be used with caution in patients with confirmed preeclampsia because it appears to be less accurate (Jakes et al. 2021). In addition, the B-Pro Wristwatch appears to be easily displaced with even slight movements of the wrist and may stop measuring blood pressure. Its other disadvantage is that it cannot be used to make spot single blood pressure readings since it is programmed for 24-hour ambulatory blood pressure monitoring.

The Microlife WatchBP Office Central (Microlife, Taiwan), on the other hand, is a liquid crystal oscillometric blood pressure monitor which can be used for measuring both the brachial peripheral blood pressure, as well as the central aortic blood pressure non-invasively (Cheng et al. 2013; Verberk et al. 2016). Its accuracy as a stand-alone CBP monitor has been validated against invasive catheter-based CBP and mercury sphygmomanometer-based PBP measurements in the general population (Stergiou et al. 2008; Cheng et al. 2013). However, reliability of Microlife WatchBP Office Central has not been evaluated among local black pregnant women, as ethnicity affects blood pressure readings (Stergiou et al. 2018; Hurrell et al. 2022). The Microlife Corporation makes reliable oscillometric blood pressure devices which have been tested in pregnant women with normal blood pressure, hypertension, as well as hypotension in low-resource settings (Nathan et al. 2015; Vousden et al. 2019; Hurrell et al. 2022). However, the reliability of Microlife WatchBP Office Central has not yet been adequately studied in

pregnant women before, as previous studies have focused primarily on the general population (Verberk et al., 2016).

Given these characteristics, the Microlife WatchBP Office Central could be a valuable tool for measuring both brachial peripheral and central aortic blood pressure in women with all phenotypes of hypertensive disorders of pregnancy. However, before it can be incorporated into the planned experimental study for this thesis, it is essential to first evaluate its reliability in Black African pregnant women. Establishing this reliability will ensure that subsequent use in the experimental study yields reproducibly and dependable data, forming a robust foundation for assessing blood pressure dynamics in this population.

1.7 Central aortic blood pressure in eclampsia

Eclampsia is a life-threatening complication of preeclampsia that accounts for majority of deaths from HDP, as already stated above. It is defined as the occurrence of generalized seizures or altered level of consciousness during pregnancy in a patient with HDP, and is often preceded by features of preeclampsia, but can also occur as the first sign of preeclampsia (Dimitriadis et al., 2023; Bartal & Sibai, 2022; Lam & Dierking, 2017). The incidence is 10-fold higher in LMICs than in high-income countries because of poor antenatal care, and perhaps because of the higher prevalence of multiple pregnancies (Duley 2009; Vousden et al. 2019). The cerebral complications of eclampsia include haemorrhage, stroke, brain oedema and acute brain herniation, and it also predisposes to epilepsy and cognitive impairment later in life (Cipolla & Kraig 2011).

There is little correlation between the severity of peripheral blood pressure and the occurrence of eclampsia. Several studies indicate that the peripheral blood pressure may be normal or only mildly elevated in up to 40% of women with eclampsia (Sibai 1990; Douglas et al. 1994). It is, however, not known how the peripheral blood pressure relates with the central aortic blood pressure in patients with eclampsia in such circumstances, as there is paucity of data in this regard.

The mechanisms involved in eclamptic seizures are poorly understood. However, vasogenic oedema appears to be the main underlying problem (Perry et al. 2020). The mechanism of vasogenic oedema is either hypertensive encephalopathy (associated with severe hypertension) or cerebral autoregulatory failure at a lower threshold (normal or mildly elevated peripheral blood pressure). It is also possible that the central aortic blood pressure, which is the pressure supplying blood directly to the brain via the carotids, could be elevated in such patients when the peripheral blood pressure is either normal or only mildly elevated. There is currently a dearth of data regarding CBP in patients with eclampsia. Studies are therefore needed to assess the role of central aortic blood pressure in eclampsia.

In conclusion, the relationship between central aortic blood pressure and eclampsia remains largely unexplored, highlighting a significant gap in current research. Understanding this relationship is crucial for improving the management and outcomes of patients affected by eclampsia, especially in regions with limited access to quality prenatal care.

1.8 Statement of the problem

Hypertensive disorders of pregnancy are a major clinical problem associated with increased maternal and perinatal morbidity and mortality worldwide. Accumulative evidence suggests that central aortic blood pressure is more closely correlated with future cardiovascular events and renal disease than peripheral blood pressure in the general non-pregnant population. This may also be true in patients with HDP in as far as maternal and perinatal outcomes are concerned. Although there is evidence that CBP and arterial stiffness measured at <14 weeks' gestation is predictive of PE (Khalil 2008; Khalil et al. 2009; Khalil et al. 2012), the effect of CBP and arterial stiffness on maternal and perinatal morbidity and mortality outcomes has not yet been adequately studied, especially among black African pregnant women. It has recently been shown that increased maternal arterial stiffness in hypertensive pregnancies is associated with intrauterine growth restriction and small-for-gestational-age neonates (Perry et al. 2020). An earlier study by Lim et al. (2015) revealed that increased maternal CBP is associated with higher blood pressures in the offspring at 3 years of age (Lim et al. 2015).

However, both studies did not evaluate all maternal outcomes of raised CBP and arterial stiffness.

It is known that the cerebrovascular complications of preeclampsia and eclampsia can occur in the presence of mild elevations of peripheral blood pressure, and even in the absence of proteinuria (Cipolla & Kraig 2011; Miller 2019). Since the blood flow to the brain is controlled by central aortic blood pressure, it is possible that under conditions when there is only mild elevation of the brachial blood pressure, the CBP may be much higher, thus accounting for the vasogenic oedema typical of eclampsia, justifying the need to know how the CBP behaves in patients with HDP and eclampsia.

While the role of angiogenic factors in the prediction of preeclampsia and its severity for clinical use is established in some high-income countries such as the United Kingdom, the tests are costly and not easily accessible in low resource settings. The levels of the cardiac biomarkers NT-proBNP and hs-cTnI are known to be elevated in patients with gestational hypertension and preeclampsia (Gencheva et al. 2021; Bacmeister et al. 2024). It has recently been suggested that these cardiac biomarkers could be used for predicting the development of preeclampsia in patients with gestational hypertension or chronic hypertension in low-resource settings, instead of using the expensive measurement of angiogenic factors (Bacmeister et al. 2024). A study to assess the value of cardiac biomarkers in HDP in low-resource settings would therefore address this need.

Arterial stiffness and central aortic blood pressure, as well as biomarkers of endothelial dysfunction, have recently been studied in pregnant black African women with PE at Nelson Mandela Academic Hospital (Meeme et al. 2017; Namugowa et al. 2019). However, these studies excluded patients with eclampsia, as well as those with preeclampsia and severe features, mainly because these patients are usually obstetric emergencies, and because the methods are time-consuming and inconvenient for seriously ill patients.

This thesis included patients with different types of HDP and compared them with normotensive pregnant controls. Women with preeclampsia and severe features such as eclampsia, HELLP syndrome, pulmonary oedema, abruptio placentae, and acute

kidney injury were specifically recruited in this thesis to assess the role of CBP and cardiac biomarkers in their outcomes. The central aortic blood pressure was assessed using the more portable Microlife WatchBP Office Central, following an evaluation of its reliability. Serum cardiac biomarkers were also measured among women with different types of HDP and normotensive controls to determine their added value in distinguishing between these types of HDP.

1.9 Aims of the thesis

The aims of this thesis were to assess whether arterial stiffness in women with a history of HDP persists beyond the puerperal period. Additionally, the thesis aimed to evaluate the correlation between central aortic blood pressure and the peripheral brachial blood pressure measured using the Microlife WatchBP Office Central, as well as association between CBP and adverse maternal outcomes, and the association between serum levels of NT-proBNP and hs-cTnI and adverse maternal outcomes among pregnant black African women with HDP and normotensive controls. Lastly, the thesis sought to evaluate the likelihood of clinical practitioners incorporating additional clinical diagnostic markers into the management of preeclampsia.

1.10 Research questions

- I. In women with a history of hypertensive disorders of pregnancy, does arterial stiffness remain elevated beyond 6 weeks postpartum compared to women with normal pregnancies?
- II. Can the Microlife WatchBP Office Central device provide reliable peripheral blood pressure measurements in pregnant women, particularly those with hypertension?
- III. What is the relationship between peripheral brachial blood pressure and central aortic blood pressure as measured using the Microlife WatchBP Office Central among black African pregnant women with HDP and normotensive controls?

- IV. What is the normal central aortic blood pressure as measured using the Microlife WatchBP Office Central and what is the threshold for central hypertension among black African pregnant women?
- V. Is there any association between the serum levels of NT-proBNP, hs-cTnI and central blood pressure and adverse maternal outcomes in pregnant women with HDP?
- VI. 5. What are the perspectives and experiences of healthcare workers in utilizing cardiac biomarkers for the clinical management of patients with preeclampsia?

1.11 Research Objectives

1.11.1 The objectives of the thesis were:

- 1. To systematically review and synthesize existing evidence to determine whether arterial stiffness remains elevated beyond six weeks postpartum in women with a history of hypertensive disorders of pregnancy.
- 2. To assess the reliability of peripheral systolic and diastolic blood pressure measurements obtained using the Microlife WatchBP Office Central device in pregnant women, including those with hypertensive disorders.
- 3. To evaluate the correlation and comparative use of peripheral blood pressure and central blood pressure in identifying hypertension in pregnant women; Additionally, to determine the threshold values for central systolic and diastolic blood pressure as diagnostic criteria for mild and severe central hypertension during pregnancy
- 4. To compare the levels of CBP, NT-proBNP, and hs-cTnI in women with hypertensive disorders of pregnancy who have maternal complications.
- 5. To evaluate the experiences and perspectives of healthcare workers regarding the clinical assessment and usage of cardiac biomarkers in patients with preeclampsia.

1.12 Research methodology

The research methodology section describes the approaches used for systematic review and meta-analysis, experimental study, and the survey.

1.12.1 Systematic review and meta-analysis

This subsection provides only a brief overview of the methodology for systematic review and meta-analysis. Full methodological details are presented in Chapter 2.

1. Search Strategy

The protocol for the systematic review and meta-analysis was developed following the Preferred Reporting Items for Systematic reviews and Meta-Analysis protocols (PRISMA-P) 2015 Guidelines (Moher et al. 2016). A comprehensive search was conducted in Medline, PubMed, Embase, Cochrane Library, Google Scholar, Web of Science, and CINAHL. The following MeSH terms for database searches were used: (“Arterial stiffness” OR “central blood pressure” OR “Pulse wave velocity” OR “Augmentation index” OR “PWV” OR “Aix” OR “Aix@75”) AND (“Preeclampsia” OR “Eclampsia” OR “Gestational hypertension” OR “Chronic hypertension” OR “Hypertensive disorders of pregnancy” OR “pregnancy induced hypertension”) AND (“After postpartum” OR “after delivery” OR “after puerperium”).

2. Exposure and Comparator

The exposure was hypertensive disease during pregnancy or within 42 days post-delivery. The hypertensive diseases included preeclampsia, gestational hypertension, chronic hypertension, and chronic hypertension with superimposed preeclampsia. The control group consisted of women under 60 years old with no history of HDP, cardiovascular diseases, renal failure, or diabetes. The review included randomized and non-randomized control trials, prospective and retrospective cohort studies, case-control studies, and cross-sectional studies performed in humans. Studies were eligible if they

reported arterial stiffness indices (cfPWV, Alx, and Alx@75) measured at least 43 days postpartum.

3. Data collection and risk of bias

Mendeley Reference Manager was used to store and manage searched items under the following headings in a separate table: Authors, publication year, title of the study, location of the study, participants ages, country, and main study findings (Elsevier 2023). Two independent reviewers screened all the titles and abstracts using the predetermined inclusion and exclusion criteria. Where consensus on eligibility could not be achieved, a third reviewer was involved in the discussion. For case-control and cohort studies, the 9-item Newcastle Ottawa Quality assessment scale or a modified version was used (Stang 2010).

4. Statistical analysis

Estimates of mean and $\pm$ SD for arterial stiffness indices (cfPWV, Alx, Alx@75) for women who had HDPs (for each subtype of HDP, as available) and normotensive women was obtained from the relevant studies. For studies that provided data on the association between these hemodynamic variables and the outcome of interest, we meta-analyzed these effect measures using a random effects model. We performed a subgroup analysis for each subtype of HDP, as available.

1.12.2 Experimental study

1. Study design

This was a cross-sectional study evaluating the central aortic blood pressure measured non-invasively using Microlife WatchBP Office Central and cardiac biomarkers among pregnant women with HDP, including those with complications, and normotensive participants, as well as assessing the relationship of these with adverse maternal outcomes.

2. Study site

The study was conducted in the Maternity Unit of Nelson Mandela Academic Hospital (NMAH), Mthatha, Eastern Cape Province. Nelson Mandela Academic Hospital is a 700-bed level III referral and teaching hospital. The maternity section of this hospital has 54 beds- 14 of these beds are in labour ward and the rest of the beds are in antenatal and in postnatal wards.

There are 21 hospitals and 18 clinics which refer patients to the maternity unit of NMAH. All patients with HDP are routinely referred to NMAH. Those with preeclampsia, chronic hypertension with superimposed preeclampsia, IUGR or abruptio placentae, imminent eclampsia, and eclampsia are routinely admitted either to the antenatal wards or to the Labour Ward High-dependency area. About 3600 deliveries are conducted at NMAH annually.

3. Study population

The study population comprised of hypertensive and high-risk normotensive pregnant women referred to NMAH during the study period. It is a standing policy that all patients with preeclampsia and severe features and high-risk normotensive pregnant women are all referred by the surrounding level 1 district hospitals to NMAH.

4. Sample size

With a catchment area estimated population of 1 862 214 (45% of the population are males and 55% are females), about 400 000 of all females in the catchment area are in the reproductive age (The Province of the Eastern Cape 2013).

The total number of deliveries at NMAH in 2021 was 3691, and the total number of women with HDP who delivered in NMAH during the same period was 1448 (unpublished departmental perinatal statistical data). Patients with HDP constituted 37% of all the pregnant women who delivered at NMAH in 2020.

Based on the above figures, using the prevalence rate of 37% for HDP among women delivering at NMAH, a power of at least 80% and confidence interval of 95%, for an in-depth analysis of perinatal and maternal outcomes, an estimated sample size for the

study was calculated to be 359, comprising of patients with HDP and normotensive pregnant women, using the formula below.

The sample size (n) was calculated according to the Cochran formula: $n = z^2 \times p \times (1 - p) / e^2$ (Pourhoseingholi et al. 2013)

$$z = 1.96, p = 0.37, e = 0.05$$

$$n = 3.84 \times 0.37 \times (1 - 0.37) / 0.0025$$

$$n = 0.8955 / 0.0025 = 358.191$$

$$n \approx 359$$

With a contingency of 10%, the final minimal sample size was 400 participants.

5. Selection criteria

All pregnant women admitted in the Maternity Ward at NMAH with HDP, as well as normotensive pregnant women, were approached and informed about the study. Those who volunteered were then asked to participate in the study. The guardians of minors below the age of 18 years, and of patients with low Glasgow Coma Scale (GCS) who could not give consent for themselves, were also be approached for consent to allow the minors and the unconscious patients to participate in the study. This was important because a number of eclamptic patients are below the age of 18 years and a number are admitted with low GCS, and it was essential that they participated in this study. Complicated HDP were characterised by any one or more of the following:

- Imminent eclampsia (blurred vision, visual scotomata, severe headache not responding to ordinary analgesia, nausea, epigastric pain, and clonus)
- Eclampsia (reported or witnessed seizures)
- HELLP syndrome
- Pulmonary oedema
- Abruption placentae
- Acute kidney injury (serum creatinine of $\geq 90 \mu\text{mol/L}$)
- Severe uncontrollable hypertension (severe hypertension that does not respond to nifedipine and labetalol, and three other oral agents).

- Severe IUGR with absent or reversed flow on Doppler studies
- Intra-uterine Foetal death (IUFD)

Inclusion criteria for patients with HDP

The inclusion criteria for patients with HDP included the following:

- Patients with singleton pregnancies and HDP who were <18 years old whose guardians give informed consent for participation in study.
- Patients with hypertensive disorders of pregnancy of any age with low GCS whose guardians gave informed consent for them to participate in the study.

Exclusion criteria for patients with HDP

- Patients with hypertensive disorders of pregnancy who declined participation in study or those who guardians do not give consent for participation in the study.
- Patients with hypertensive disorders of pregnancy who were <20 weeks' gestation.
- Patients with hypertensive disorders of pregnancy who were dire emergencies with no time to seek consent for participation in study.
- Patients with hypertensive disorders of pregnancy who withdrew consent after initial granting of consent.
- Patients with diabetes mellitus.
- Patients with cardiac disease.
- Patients with chronic renal disease.
- Patients with multiple pregnancy

Inclusion criteria for normotensive pregnant women

- Normotensive patients with singleton pregnancies who consented to participate in the study and had conditions such as placenta previa, preterm premature

rupture of membranes, preterm labour, or patients admitted for repeat elective caesarean section.

Exclusion criteria for normotensive pregnant women

- Patients with previous history of HDP.
- Patients with chronic hypertension (predating pregnancy or identified before 20 weeks of pregnancy).
- Patients with diabetes mellitus.
- Controls who developed HDP after recruitment.
- Patients with cardiac disease.
- Patients with chronic renal disease.
- Patients with multiple pregnancy
- Patients with antiphospholipid syndrome or other autoimmune disease
- Patients taking medications that can affect blood pressure.

6. Sampling method

The study recruited consecutive patients admitted with HDP as well as normotensive pregnant women who consented or for whom consent was granted and fulfilled the inclusion criteria, until the required number of participants was reached. In this study, a deliberate attempt was made to recruit a disproportionately larger number of patients with preeclampsia and severe features, as well as eclamptic patients because patients with these conditions were excluded in previous studies from NMAH because of the emergency nature of their conditions (Meme et al., 2017 and 2017; Namugowa et al. 2018; Namugowa et al. 2019). Patients were recruited within 24 hours of their admission to the labour ward. In normotensive women, peripheral blood pressure was measured again before and after delivery to ensure they remained normotensive.

7. Study procedures

Routine procedure for inpatients with HDP during the study period

On arrival at NMAH, all patients with preeclampsia without severe features who are <35 weeks' gestation were admitted to the antenatal ward until after delivery. Patients with preeclampsia and severe features or complications such as imminent eclampsia, eclampsia, HELLP syndrome, abruptio placentae, foetal distress, preterm labour, pulmonary oedema, etc, were admitted in the Labour Ward for stabilization, after which they were usually delivered as an emergency, irrespective of the gestational age. Patients who initially presented with preeclampsia without severe features who developed severe features were also transferred to the Labour Ward for stabilization and delivery. Corticosteroids in the form of betamethasone 12 mg 12 hourly (total dose 24 mg) were routinely administered to all patients either at the referring hospital or at NMAH at admission if the gestational period is <35 weeks.

Routine investigations carried out on all patients with HDP included full blood count (FBC), urea and electrolytes (U&Es), liver function tests (aspartate aminotransferase, alanine aminotransferase and lactate dehydrogenase) and non-stress test (NST) every 2-3 days, ultrasound with Doppler studies every 2 weeks or weekly if these were abnormal umbilical artery Doppler studies, and biophysical profiles when necessary. These investigations were also carried out as baseline investigations in all patients with complications of HDP who were due for termination of pregnancy and were repeated every 2-3 days postpartum. Coagulation profiles were carried out in patients with abruptio placentae and those with HELLP syndrome and repeated as necessary.

Methyldopa was routinely administered to all patients with HDP to maintain a target blood pressure of 110-130/85 mm Hg according to the ISSHP and FIGO guidelines (Brown et al. 2018; Poon et al. 2019; Magee et al. 2022). Patients with severe hypertension (SBP of ≥ 160 and/or DBP of ≥ 110 mmHg) were started on oral nifedipine at a dose of 10 mg, and this was repeated every 30 minutes for a maximum of 40-50 mg until the blood pressure was <150/100 mmHg. If this failed, then the patients were put on the second line of treatment with IV bolus doses of labetalol starting with 20 mg and doubled every 10-15 minutes until 80 mg, and the 80 mg dose was repeated until a maximum of 300 mg

was given. If the IV bolus labetalol did not successfully control the severe hypertension to <150/100 mmHg, the patient was put on labetalol infusion starting with 20 mg/hour, and the infusion dose was doubled every 30 minutes until a maximum 160 mg/hour, while monitoring the blood pressure. If this did not control the severe hypertension, then the pregnancy was terminated by caesarean section under spinal anaesthesia. In patients where control of the severe hypertension was achieved, expectant management was continued, provided there were no other complications. Anti-hypertensive maintenance treatment was continued with methyldopa to achieve the BP target of 110-130/85. For those patients who were $\geq 34^{+6}$ weeks' gestation, elective termination of pregnancy was carried out.

Magnesium sulphate was administered prophylactically to prevent seizures when there was severe hypertension or when there were complications such as imminent eclampsia, and during delivery. All patients with eclampsia were routinely given magnesium sulphate to prevent further seizures using the Pritchard regimen, while monitoring respiration, urine output and deep tendon reflexes for signs of magnesium toxicity. Magnesium sulphate was continued for up to 24 hours after delivery, or the last seizure, whichever was longer.

Most patients admitted with eclampsia were referred from level 1 hospitals and arrived having already been started on magnesium sulphate. Few patients with eclampsia had magnesium sulphate initiation at NMAH. Majority of patients received maintenance treatment.

Patients who required organ support were admitted in the Intensive Care Unit after consultation with intensivists/ anaesthetists and neuro-physicians. Premature babies and babies with low Apgar score were routinely managed by neonatologists.

Patients with preeclampsia who are ≥ 35 weeks' gestation and patients with uncomplicated chronic hypertension or gestational hypertension who were at $\geq 37^{+6}$ were admitted for baseline investigations and electively delivered within 48 hours, even if they had no severe features or complications.

For patients with preeclampsia and severe features who were not yet delivered, delivery was carried out as an emergency, either by induction of labour or emergency caesarean section based on obstetric indications.

Post-delivery, all hypertensive patients were continued on magnesium sulphate for at least 24 hours, their BP is optimised, and they remained in the hospital for at 3-5 days or until their condition was optimal. Before discharge, patients were counselled about recurrence of HDP and the long-term cardiovascular, metabolic, renal and cerebral complications. They were also advised about the need for aspirin prophylaxis in all future pregnancies, starting <16 weeks' gestation. A follow up at postnatal care clinic was done a week post-delivery where their BP was also checked and a need for continuing antihypertensives was evaluated until 12 weeks postdelivery.

Proteinuria

Random urine samples were analysed serially for protein creatinine protein ratio in all patients with HDP who tested negative for protein on urine dipstick. These were mainly patients with chronic hypertension without complications and patients with provisional diagnosis of gestational hypertension to detect conversion to preeclampsia. A spot urine protein/creatinine ratio of $\geq 0.3\text{mg/mg}$ (or $\geq 30\text{ mg/mmol}$) was regarded as significant proteinuria. A 24-hour urine protein was only carried out if the urine protein-creatinine ratio was negative, and a reading of $\geq 300\text{ mg/l}$ was regarded as significant proteinuria.

All patients with chronic HT or provisional diagnosis of GHT were also regularly evaluated for evidence of organ dysfunction, and those who developed any organ dysfunction received a diagnosis of preeclampsia with severe features.

Anthropometric measurements of all participants

a. Height

Single measurements of height were done to the nearest centimeter using a standard stadiometer, with participants wearing underclothes only, barefooted, feet together, back and heels firmly against the upright of the height scale.

b. Body weight

A digital platform weighing scale was used to measure the weights of the study participants. Participants were asked to remove any heavy clothing items and shoes and to step in the middle of the scale with feet parallel. The weight of the participant was recorded to the resolution of the scale (0.1kg).

The BMI in pregnancy was then calculated using a formula: $BMI = \text{weight (kg)} / \text{height (m}^2\text{)}$, with full appreciation of the fact that the BMI during pregnancy is not a true reflection of the non-pregnant BMI.

Peripheral Blood pressure measurements

Brachial blood pressure was measured using automated blood pressure devices that are recommended for pregnancy and preeclampsia, specifically Microlife WatchBP Home A BT or Omron HBP-1300 (Chung et al., 2009; Cao et al., 2015; Mazoteras-Pardo et al., 2023; Sharman et al., 2023). Blood pressure was automatically recorded three times at 1-minute intervals, and the average of the three readings taken as the blood pressure and documented. The conscious participant sat on a straight-back chair with the arm resting on a table at the same level as the heart. A cuff of the appropriate size for the patients was placed on the mid-arm of the dominant arm. For patients with low level of consciousness who are normally placed recumbent on the left lateral side, the cuff was placed on the right mid-arm place at the level of the heart. The device was then switched on to automatically take the brachial blood pressure and the heart rate. BP measurements with these devices were performed prior to the measurement of both the brachial pressure and the central aortic pressure using the Microlife WatchBP Office Central.

Measurement of brachial and central blood pressure using Microlife WatchBP Office Central

Before using the Microlife WatchBP Office Central for measuring the peripheral and central BP in patients with HDP and normotensive controls, an in-study pilot study was carried out to evaluate the reliability of the peripheral blood pressure measurements obtained using this device in pregnant women. It is worth noting that the reliability and validation of the Microlife WatchBP Office Central have already been established in the general population (Stergiou et al. 2008; Cheng et al. 2013). In particular, Cheng et al. (2013) demonstrated that the device provides accurate central blood pressure readings

compared with simultaneous invasive arterial measurements—the gold standard—thereby confirming its validity for non-invasive central hemodynamic assessment. However, limited data existed on its measurement reliability in pregnant women, particularly among African populations.

Fifteen normotensive pregnant women, 15 women with gestational hypertension, and 15 women with preeclampsia were involved in the in-study pilot study, as recommended by the Association of Advancement of Medical Instrumentation/European Society of Hypertension/International Organization for Standardization (Stergiou et al. 2018; Hurrell et al. 2022). Subsequently the same women were included in the main study.

The in-pilot study showed that the Microlife WatchBP Office Central device provides reliable, and reproducible blood pressure measurements in pregnant women, including those with hypertensive disorders. After the reliability evaluation exercise, the Microlife WatchBP Office Central was then used for simultaneous measurement of both the brachial blood pressure and central blood pressure in each participant. Being portable, this device was used without much inconvenience to patients. The Microlife WatchBP Office Central uses brachial pulse volume plethysmography (PVP) waveforms to determine the central blood pressure. It is designed to perform PVP at a cuff pressure of 60 mmHg. Based on the analysis of the PVP waveforms, the central systolic pressure and central pulse pressure values are automatically determined.

Before using the Microlife WatchBP Office Central, the correct size of cuff was selected for each participant (medium-large size arm cuff: 22-42 cm; extra-large: 32-52 cm) and placed over the dominant mid upper arm so that the air tube and artery mark arrow point towards the lower arm. The cuff was wrapped around the arm, making sure the lower edge of the cuff was approximately 2 cm above the elbow.

Central mode was selected for central blood pressure measurements on the preferred arm. The Microlife WatchBP Office Central device automatically took two consecutive measurements at 15 second intervals. At each measurement, the brachial blood pressure was measured first, thereafter the cuff pressure held around 60 mmHg for 30 seconds to assess the central blood pressure value. The readings of the two brachial blood pressures were automatically averaged and displayed, and the readings of the two

central blood pressure readings were also averaged and displayed after the measurement process was completed.

Patients with a low level of consciousness were placed on the recumbent left-lateral position, and the brachial and central blood pressures were measured on the right upper arm placed at the level of the heart.

The Microlife WatchBP Office Central can also measure the patient's blood pressure on both arms simultaneously, and this was used to select the arm with the higher BP values in cases where there were significant differences of >5 mmHg.

Measurement of cardiac biomarkers

At recruitment, blood samples were collected for serum NT-proBNP and hs-cTnI. A total of 10 mL of venous blood from the antecubital vein was drawn into tubes containing EDTA. The plasma was separated by centrifugation at 3500 rpm for 15 minutes at 4°C and subsequently stored at -80°C until analysis. All assays were conducted using an Alinity iSTAT automatic analyzer (Abbott, USA) in the central hospital laboratory.

Patient procedure for normotensive controls

As the normotensive controls were patients with heterogenous high-risk conditions, such as placenta previa, previous caesarean section, premature rupture of membranes, no routine procedures are reported here. However, their brachial blood pressures and central aortic blood pressures were measured using the Microlife WatchBP Office Central at the time of recruitment. Their peripheral blood pressure was taken again before and after delivery to ensure they remained normotensive. Blood samples were also taken for serum NT-proBNP and hs-cTnI at recruitment.

8. Data collection instrument and variables

A structured questionnaire (see Appendix 1) was used to collect data on all patients with HDP and controls after recruitment. For those with low GCS, aspects of the questionnaire were administered after they regained full consciousness. Other relevant information about the diagnosis, clinical course, and both maternal and perinatal outcomes were abstracted from the case files using a data collection instrument.

Study variables

- Socio-demographic variables:
 - Maternal age in years.
 - Parity.
 - Marital status categorized into married/divorced or single.
 - Education, classified into no formal education, primary, secondary and tertiary education.
 - Occupation, classified into employed and un-employed.
- Blood pressure
 - Presence and type thereof of HDP (GHT, preeclampsia, eclampsia, chronic hypertension)
 - Antihypertensives used (type, dose)
 - Magnesium sulphate use
 - Central and peripheral blood pressure levels
 - Pulse wave analysis and augmentation index
- Complications of preeclampsia if present (HELLP syndrome, AKI, pulmonary oedema, abruptio placentae, eclampsia, IUGR, IUFD)
- Antenatal care:
 - Booking status
 - Number of antenatal care visits
 - Last antenatal care visit before the current admission
 - Infectious diseases: HIV, syphilis and others
 - Chronic hypertension.
 - Foetal complications such IUGR, foetal distress and foetal death

- Intrapartum care
 - Mode of delivery
 - Gestational age at delivery
 - Magnesium sulphate (prophylactic or therapeutic)
 - Apgar score
 - Sex of baby
 - Weight of baby
- Postpartum care
 - Use of magnesium sulphate
 - Type of antihypertensive treatment
 - Postpartum complications (PPH, AKI, ICU admission, maternal or neonatal death)

9. Data entry, checking, and analysis

The data was checked for completeness and consistency before being captured using the latest IBM SPSS STATISTICS software package for Windows (IBM Inc., Chicago IL, USA). The data were summarized into proportions (%) for categorical variables, means and standard deviation (SD) for continuous variables using figures and tables. To examine the relationship between categorical variables such as types of HDP, and maternal outcomes the Chi-square test was utilized. The Student's t-test or Wilcoxon signed rank test (for non-parametric data) was employed to compare the means or medians of variables such as blood test results, age, and peripheral and central blood pressure levels. Univariate analysis with Odds ratios (OR) were computed for association between central aortic blood pressure and adverse maternal and perinatal outcomes, as well the association of the cardiac biomarkers and adverse maternal and perinatal outcomes using contingency table with 95% confidence intervals (95% CI). Multivariate logistic regression models were used to identify the independent factors associated with adverse maternal and perinatal outcomes. After adjustment for confounding factors,

multivariate OR were calculated with 95% CI. A $p < 0.05$ was considered statistically significant.

10. Ethical considerations

Ethical approval to conduct the study was obtained from the Biosafety and Ethics Committee of the Faculty of Medicine and Health Sciences, Walter Sisulu University (Certificate Number 035/2022), and from the University of Stirling (Ethics number 13813). Permission was also sought from the Provincial Department of Health and Nelson Mandela Academic Hospital Administration before the research commenced (Ethics number EC-202302-009).

Written consent was obtained from the participants, or from the parents/guardian in the case of minors and patients with low level of consciousness. All consent forms were in English and IsiXhosa, the local language. Both, the investigator, and the assistant, obtained consent from the participants or parents/guardians in layman's terms and in the language of their choice. Participants were free to opt out of the study if they chose to without any penalties or breach of care.

All collected data were stored both physically, in a locked cupboard in a locked storeroom, and electronically in a password-protected laptop for a minimum of 5 years. Only the investigator, the supervisor, and the biostatistician had access to the information. To ensure confidentiality, participants were assigned study numbers, and their names, surnames and identities were not used in the study.

1.12.3 Survey

This was a cross-sectional online survey of medical doctors in maternity units of regional and tertiary hospitals using Google Forms. The variables included demographic information, current employment status, years of experience, and the level of the healthcare facility. Other questions focused on their clinical experience and perspectives regarding the complications and management of preeclampsia, as well as the use of cardiac markers in patients with this condition.

The study population consisted of medical doctors working in the maternity units at Mthatha Regional Hospital, Nelson Mandela Academic Hospital, Cecilia Makhiwane Hospital, and Frere Hospital. All who agreed to participate and provided consent were included in the survey. Medical students and interns were excluded from the study.

1. Data Collection

There were a total of 46 medical officers and 25 medical specialists in the maternity units across these hospitals, making a total of 71 potential participants. A pre-designed online survey was distributed via email and WhatsApp to these 71 medical doctors, of whom 58 agreed to participate.

2. Data Entry, Cleaning, and Analysis

Data was extracted from the Google Form and verified for accuracy before being recorded using the latest version of IBM SPSS Statistics software for Windows (IBM Inc., Chicago, IL, USA). The data was summarized as proportions (%) and presented using figures and tables. Responses to open-ended questions were analysed thematically. The Chi-square test was employed to assess the association between categorical variables, such as career and shared perspectives. A p-value of less than 0.05 was considered statistically significant.

3. Ethical considerations

Approval to conduct the study was obtained from the Walter Sisulu University Faculty of Medicine and Health Sciences Research Ethics Committee (WSU HREC 037/2025) before the research commenced. Informed consent was secured from all participants prior to their involvement in the survey. To ensure anonymity, no names were included in the Google Forms used in the study. The research posed no risks to the participants' health or well-being.

1.13 Flowchart of studies

The thesis followed a sequential structure. A systematic review was first conducted to evaluate evidence on arterial stiffness following hypertensive disorders of pregnancy. This was followed by a reliability assessment of the Microlife WatchBP Office Central device for measuring blood pressure in pregnancy. The subsequent clinical study evaluated the relationship between peripheral and central blood pressure and the association between central blood pressure and cardiac biomarkers in women with hypertensive disorders of pregnancy. Finally, a survey of healthcare professionals assessed current clinical practices and perspectives regarding biomarker screening in preeclampsia (Figure 1.1).

Association of central and peripheral blood pressure with cardiovascular biomarkers in women with preeclampsia



STUDY 1

Systematic Review and Meta-analysis (arterial stiffness after HDP)

Method:

- PRISMA-guided systematic search; Meta-analysis of arterial stiffness indices (cfPWV, AIx, AIx@75)



STUDY 2

Reliability Study (Microlife WatchBP Office Central)

Method:

- Cross-sectional study involving 45 hypertensives and normotensive pregnant women |



STUDY 3

Central vs Peripheral BP Study (Correlation and diagnostic thresholds)

Method:

- Correlation analysis
- Determination of diagnostic thresholds using Linear regression and ROC



STUDY 4

Cardiac Biomarkers and Central blood pressure Study
(CBP, NT-proBNP and hs-cTnI in HDP complications)

Method:

- Measurement of CBP; Laboratory measurement of NT-proBNP and hs-cTnI
- Association with maternal complications of HDP

STUDY 5

Clinical Practice Survey(Management and cardiac biomarker use in preeclampsia)

Method:

- Cross-sectional survey of healthcare professionals

Figure 1.1 Flowchart of studies

1.14 References

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CHAPTER 2

2. Arterial Stiffness After 6 Weeks Postdelivery in Women with a History of Hypertensive Disorders of Pregnancy: A Systematic Review and Meta-analysis

Credit author statement

Xolani B Mbongozi led the design, methodology, conduct, analysis, interpretation, and writing of the research. Stuart DR Galloway and Angus Hunter provided supervision and contributed to review and editing. Jean-Paul Milambo was responsible for review and editing. Charles B Businge played a key role in conceptualization, supervision, and review and editing.

Abstract

Introduction: The main objective of this systematic review was to determine if the arterial stiffness remains elevated six or more weeks post-delivery in women with a history of hypertensive disorders of pregnancy.

Methods and Analysis: A comprehensive systematic literature search was conducted across multiple electronic databases, including Medline, PubMed, Embase, Cochrane Library, Google Scholar, Web of Science, and CINAHL. We included studies assessing arterial stiffness in women with a history of HDP between 43 days and 10 years postdelivery, with participants under 60 years of age. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines. We extracted data on arterial stiffness indices, including carotid-femoral pulse wave velocity (cfPWV), augmentation index (Alx), and heart rate-adjusted augmentation index (Alx@75), along with the mean $\pm$ standard deviation for each study. A random-effects model was used to pool data, and heterogeneity was explored through sensitivity and subgroup analyses. The risk of bias in the included studies was assessed using the Newcastle-Ottawa Quality Assessment Scale.

Results: Out of 121 identified articles, 12 studies involving a total of 856 women were included in the final review after eliminating duplicates and studies that did not meet the inclusion criteria.

The overall pooled data revealed a significantly elevated Alx and cfPWV among women with a history of HDP. Specifically, the mean difference (MD) in Alx was 11.63 (95% Confidence Interval (CI): [1.72 – 21.54]), and for cfPWV, the MD was 0.53 (95% CI: [0.27 – 0.78]). Notably, while Alx showed no significant change in women within one year postpartum (MD 14.85, 95% CI [-6.03 – 35.72]), an elevation was observed in those beyond one year post-delivery (MD 9.11, 95% CI [4.20 – 14.02]). cfPWV was also found to be elevated in HDP patients both within one year (MD 0.59, 95% CI [0.32 – 0.86]) and beyond one year (MD 0.45, 95% CI [0.03 – 0.88]).

In cases of early-onset preeclampsia, Alx did not show a significant increase; however, a significant increase in cfPWV was observed, with Alx having an MD of 1.55 (95% CI: -0.74 – 3.84) and cfPWV an MD of 1.86 (95% CI: 0.25 - 3.47). For late-onset preeclampsia, there was no significant difference in Alx (MD 2.44, 95% CI: -8.82 - 13.70) or cfPWV (MD 0.10, 95% CI: -0.42 - 0.62).

Conclusion: This systematic review and meta-analysis suggest that arterial stiffness may remain elevated beyond 6 weeks postpartum in women with a history of HDP. However, the findings should be interpreted with caution due to heterogeneity across studies and limited number of available studies. High-quality longitudinal studies are needed to confirm these results. In the meantime, regular cardiovascular monitoring for these women is recommended while awaiting more conclusive evidence.

PROSPERO registration number: CRD42023461

Keywords: Hypertensive disorders of pregnancy, Arterial stiffness, Cardiovascular disease, Pulse wave velocity, Augmentation index, Preeclampsia, Maternal morbidity, Postdelivery risk

2.1 Introduction

Hypertensive disorders of pregnancy (HDP), including gestational hypertension and preeclampsia, contribute significantly to maternal morbidity and mortality worldwide (Abalos et al. 2013). Research has consistently indicated that women with a history of HDP face an increased risk of long-term cardiovascular issues, such as hypertension, stroke, and heart disease (Parikh et al. 2021; Palmiero et al. 2025). One important marker of cardiovascular health is arterial stiffness, which has been observed to be elevated in women with HDP both during and after pregnancy (Torrado et al. 2015; Meeme et al. 2017). Evidence suggests that arterial stiffness and central aortic blood pressure are more closely linked to future cardiovascular events and renal complications than peripheral blood pressure in non-pregnant populations, a trend that may extend to HDP women in terms of their long-term cardiovascular outcomes.

From a physiological standpoint, the six-week mark post-delivery is noteworthy as it typically signals the stabilization of hemodynamics (Umar et al. 2012; Sanghavi & Rutherford 2014). Throughout pregnancy, women experience considerable metabolic demands and cardiovascular adaptations that differ by trimester and gradually normalize after delivery (Soma-Pillay et al. 2016). Key cardiovascular changes during pregnancy include an increase in cardiac output and blood volume, accompanied by a decrease in systemic vascular resistance (SVR). In particular, during pregnancy, elevated serum levels of progesterone and relaxin, a peptide hormone produced by the corpus luteum and placenta, facilitate systemic vasodilation (Soma-Pillay et al. 2016; Sanghavi & Rutherford 2014). This process results in a 25 to 30% reduction in SVR during pregnancy, with levels normalizing within two weeks postpartum and other vascular changes returning to normal during the six-week puerperal phase (Sanghavi & Rutherford 2014). Examining how arterial stiffness evolves after this timeframe is essential for understanding a woman's cardiovascular health trajectory and potential long-term risks.

Although studies indicate that central blood pressure and arterial stiffness measured before 14 weeks of gestation can predict preeclampsia, further evaluation is needed on their impact on future cardiovascular health (Umar et al. 2012; Sanghavi & Rutherford 2014; Meeme et al. 2017). Importantly, increased maternal arterial stiffness in hypertensive pregnancies has also been associated with intrauterine growth restriction and small-for-gestational-age infants (Perry et al. 2020). Research has also found associations between elevated maternal arterial stiffness and central blood pressure, foetal growth restriction, and small for gestational age infants, as well as increased blood pressure in offspring by the age of 3 years (Lim et al. 2012; Perry et al. 2020). However, there is limited global data on whether arterial stiffness remains elevated beyond six weeks postpartum in women who have a history of HDP.

Global research investigating this issue reveals both regional variations and consistent patterns of elevated risk. i) In United Kingdom: Research shows that women with a history of HDP face significant long-term cardiovascular risks. These include accelerated cardiovascular aging and an increased likelihood of developing various conditions such as valvular heart disease (Honigberg et al. 2019). ii) In Canada: Evidence demonstrates a strong association between HDP and persistent cardiovascular risk. Women who have experienced preeclampsia may exhibit increased arterial stiffness for up to six years postpartum (Werlang et al. 2023). This growing body of evidence suggests that arterial stiffness may remain elevated beyond puerperium, reinforcing the need for regular cardiovascular monitoring in women with a history of HDP; iii) In Asia, particularly Korea, research suggests that elevated arterial stiffness seen in women with HDP during pregnancy may return to baseline levels after delivery (Kim et al. 2020). This variation in findings emphasizes the importance of conducting a global review to understand the long-term effects of HDP on arterial health. iv) In Africa, where HDP is a major cause of maternal mortality, research on the lasting cardiovascular effects of HDP is still emerging but gradually increasing. Some studies suggest that women with a history of HDP may contend with a greater risk of cardiovascular disease; however, further

research is essential to evaluate the specific role of arterial stiffness after delivery (Meeme et al. 2017; Namugowa et al. 2017). Given the significant long-term cardiovascular risks associated with HDP, it is crucial to understand the duration of elevated arterial stiffness. This systematic review synthesized the existing literature to provide a better picture of the long-term effects of HDP on arterial health.

2.2 Objective

The objective of this systematic review was to determine if the arterial stiffness remains elevated after six weeks post-delivery in women with a history of hypertensive disorders of pregnancy.

2.3 Methods

This protocol was developed following the Preferred Reporting Items for Systematic reviews and Meta-Analysis protocols (PRISMA-P) 2015 Guidelines (Moher et al. 2016). A comprehensive search was conducted in Medline, PubMed, Embase, Cochrane Library, Google Scholar, Web of Science, and CINAHL. The following MeSH terms for database searches were used: (“Arterial stiffness” OR “central blood pressure” OR “Pulse wave velocity” OR “Augmentation index” OR “PWV” OR “Aix” OR “Alx@75”) AND (“Preeclampsia” OR “Eclampsia” OR “Gestational hypertension” OR “Chronic hypertension” OR “Hypertensive disorders of pregnancy” OR “pregnancy induced hypertension”) AND (“After postpartum” OR “after delivery” OR “after puerperium”). One example of the search strategies used is shown in Table 2.1.

Table 2 1. PubMed 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 Alx@75[tw]	21613
2	Preeclampsia [tw] OR Eclampsia[tw] OR Gestational hypertension[tw] OR Chronic hypertension[tw] OR Hypertensive disorders of pregnancy [tw] OR pregnancy-induced hypertension [tw]	69722
3	After postpartum [tw] OR after delivery [tw] OR after puerperium [tw]	21178
4	#2 AND #3	2098
5	#1 AND #4	23

The exposure

The exposure was hypertensive disease during pregnancy or within 42 days post-delivery. The hypertensive diseases included preeclampsia, gestational hypertension, chronic hypertension, and chronic hypertension with superimposed preeclampsia. Preeclampsia was 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 $\mu\text{mol/L}$ 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 $<150,000/\mu\text{L}$, disseminated intravascular coagulation, haemolysis). Uteroplacental dysfunction includes fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or stillbirth (Brown et al. 2018; Braunthal & Brateanu 2019).

Gestational hypertension was defined as persistent de novo hypertension that develops at or after 20 weeks of gestation in the absence of features of preeclampsia. Chronic hypertension referred to high blood pressure predating the pregnancy or recognized at < 20 weeks of gestation. Chronic hypertension with superimposed preeclampsia was diagnosed when preeclampsia occurred in a pregnant woman who had pre-existing chronic hypertension.

Inclusion criteria

We included randomized and non-randomized control trials, prospective and retrospective cohort studies, case-control studies, and cross-sectional studies performed in humans. The studies were included based on the following criteria:

1. Women with a history of HDP, aged under 60 years.
2. Studies reporting arterial stiffness indices (cfPWV, Alx, and Alx@75) at least 43 days postpartum.

There were no restrictions by the date of publication.

Exclusion criteria

We excluded 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 were also excluded. Studies that only assess arterial stiffness measurements during pregnancy, labour, and delivery or within 6 weeks post-partum were excluded.

Comparator

The control group consisted of women under 60 years old with no history of HDP, cardiovascular diseases, renal failure, or diabetes.

Data collection

Mendeley Reference Manager was used to store and manage searched items under the following headings in a separate table: Authors, publication year, title of the study, location of the study, participants ages, country, and main study findings (Elsevier 2023). Two independent reviewers screened all the titles and abstracts using the predetermined inclusion and exclusion criteria. We followed PRISMA-P guidelines. Records identified as potentially eligible based on title, abstract, and full texts were obtained to screen. Where consensus on eligibility could not be achieved, a third review author was involved in the discussion. When the same cohort was reported in multiple articles, the study which contains the largest sample was selected. Data from selected studies were extracted and entered into a Microsoft Excel spreadsheet.

Risk of bias

Two independent authors evaluated the methodological quality of all included studies. Where consensus on eligibility could not be achieved, a third reviewer was involved in the discussion. For case-control and cohort studies, the 9-item Newcastle Ottawa Quality assessment scale or a modified version was used (Stang 2010). Disagreements among the two authors was resolved by consultation with the other authors to reach a consensus. No studies were excluded based on the risk of bias assessment.

Potential sources of heterogeneity were first assessed using the I^2 statistic (Deeks et al. 2019). Values of 25% or less were classified as low, around 50% as moderate, and 75% or more as high. The subgroup and sensitivity analyses using RevMan 7.2.0 and NOS assessment scale were performed. Since all subgroups contained fewer than ten studies, a funnel plot was only created for those with six or more studies.

Statistical analysis

Estimates of mean and $\pm$ SD for arterial stiffness indices (cfPWV, Alx, Alx@75) for women who had HDPs (for each subtype of HDP, as available) and normotensive women was obtained from the relevant studies. For studies where the estimates were reported as the median and interquartile range, approximate estimates of mean and

$\pm$ SD were calculated using the available estimates of the median and, first quartile and third quartile. These data were summarized using a DerSimonian and Laird random-effects model (DerSimonian & Kacker 2007). A separate meta-analysis was conducted for each hemodynamic indices of interest (cfPWV, Alx, Alx@75) for the combined outcome in those who had HDPs. For studies that provided data on the association between these hemodynamic variables and the outcome of interest, we meta-analyzed these effect measures using a random effects model. We performed a subgroup analysis for each subtype of HDP, as available.

2.4 Results

Study selection

Through our literature search, we identified 121 articles. After removing 22 duplicates and excluding 70 based on title and abstract screening (see **Figure 2.1**), Twenty-nine articles remained that were eligible for full-text review. Out of these, 12 studies were included in the final review. Specifically, there were 4 cross-sectional studies, 5 cohort studies, and 3 case-control studies (**Table 2.2**). The total number of participants across the studies was 856 women with HDP and healthy women.

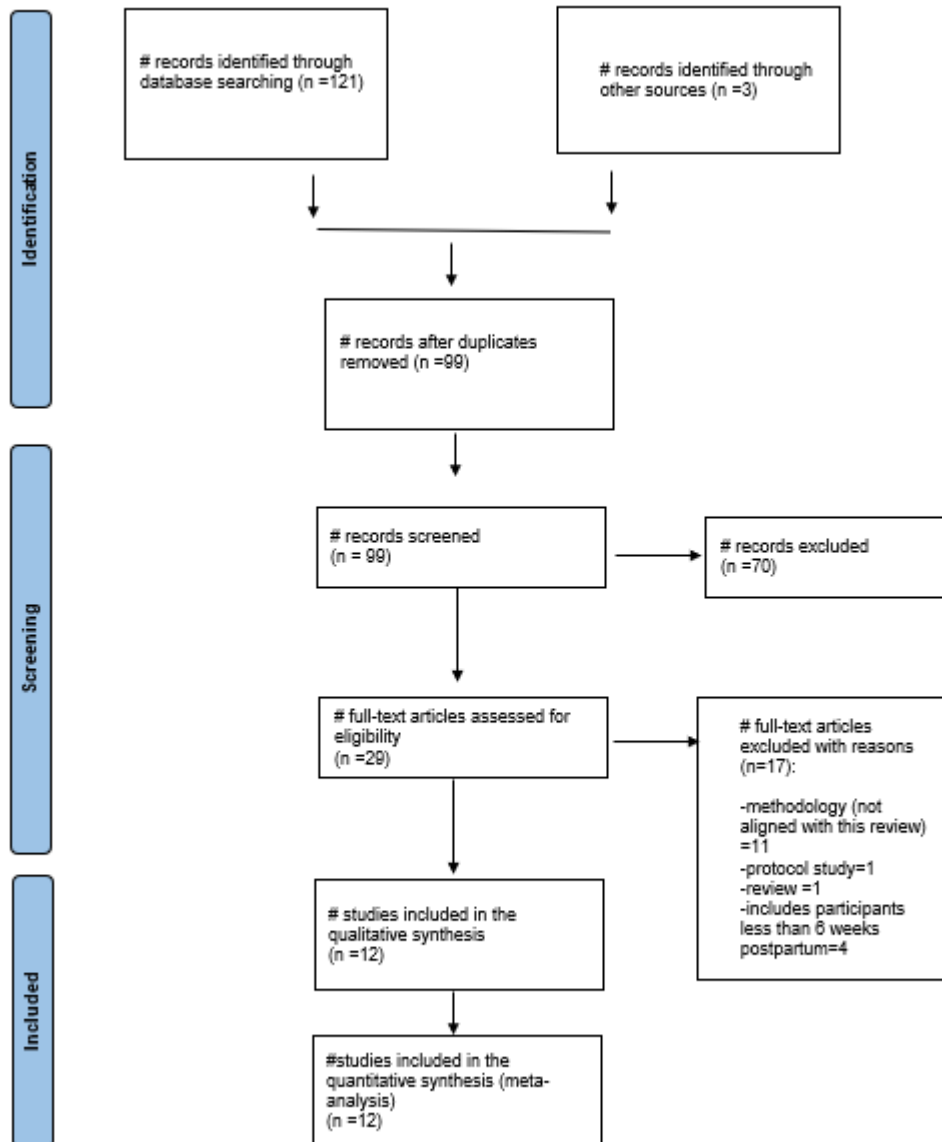


Figure 2 1: Flow diagram of study inclusion

Table 2. 2: Data Extraction Table

Study	Authors (year)	Country	Study Design	Sample Size	Population Characteristics (age, comorbidities)	Time Postpartum	Arterial Stiffness Measure (cfPWV, Alx)	Mean $\pm$ SD of Arterial Stiffness	Comparison Group	Elevated Arterial stiffness (Yes/No)	Risk of Bias Assessment (Cochrane/NOS)	Other Key Findings
1	Namugowa et al. (2017)	South Africa	case-control	30 (15 preeclampsia 15 control)	African Black; 16-40 years; no CVD	15 weeks	cfPWV, Alx	Mean: 5.9 m/s $\pm$ 0.09. 23 $\pm$ 16%	Normal pregnancy group	Yes	Low risk	Significant difference in cfPWV between HDP and normal group
2	Pàez et al. (2009)	Argentina	Cas e-control	40 (20;20)	18-33 years old; no CVD	2 years	cfPWV, Alx	Mean: 10.5 m/s $\pm$ 2.3; 37.5 $\pm$ 5.1%	Normal pregnancy group	Yes	Low risk	Significant difference in cfPWV between HDP and normal group
3	Christensen et al. (2016)	Denmark	cohort	48 (24;24)	Average 40 years old; no CVD	1 year	cfPWV, Alx	Mean: 8.03 m/s $\pm$ 0.93; 22.1 $\pm$ 9.22%	Normal pregnancy group	No	Low risk	The hypertension exposed women tended to have a higher aPWV compared to unexposed women; but the difference was not significant
4	Polónia et al. (2014)	Portugal	Cross-sectional	100 (45;55)	no CVD	10 years	cfPWV, Alx	6.7m/s $\pm$ 1.1; 25.7 $\pm$ 5.1%	Normal pregnancy group	Yes	Low risk	Significant difference in cfPWV between HDP and normal group
5	Ehrenthal et al.	United States	cohort	74 (33;41)	18 years and above; White and	1 year	cfPWV, Alx	6.2 m/s $\pm$ 1.5; 22.0 $\pm$ 13.4;	Normal pregnancy group	Yes	Low risk	Significant difference in cfPWV between

	(2014)	es of America			African Americans; no CVD or Diabetes							HDP and normal group
6	Franz et al. (2013)	Austria	cohort	74 (53;21)	Unknown	3-6 months	cfPWV, Alx	9.9 ± 1.6; -10.7 ± 21.1	Normal pregnancy group	yes	Low risk	Presence of a higher cardiovascular risk in patients after early-onset pre-eclampsia.
7.	Werlang et al. (2023)	Canada	Cross-sectional	80 (40;40)	Average 36 years; no CVD	6 months-6 years	cfPWV, Alx	6.3m/s ± 1.0; 16.2 ± 2.5%	Normal pregnancy group	yes	Low risk	Significant difference in cfPWV between HDP and normal group
8.	Robb et al. (2009)	United Kingdom	cohort	37 (22;15)	Average 30 years; no CVD	7 weeks	cfPWV,	7.3m/s ± 0.3;	Normal pregnancy group	Yes	Low risk	Significant difference in cfPWV between HDP and normal group
9	Evans et al. (2011)	United States of America	cohort	68 (18;50)	18-40 years Black and White participants ; no preexisting cardiac disease or diabetes mellitus	16 months after delivery	cfPWV	cfPWV Mean: 2.39m/s ± 0.8;	Normal pregnancy group	No	Low risk	No significant difference in Alx between HDP and normal group
10	Moe et al. (2020)	Norway	Cross-sectional	221 (126;95)	18 years and above; no CVD or renal disease	1 year after delivery	cfPWV	6.3m/s ± 2.9;	Normal pregnancy group	Yes	Low risk	Significant difference in Alx between HDP and normal group

1 1	Usselman et al. (2020)	United States of America	Cross-sectional	24(12;12)	White, Hispanic, black women; no CVD	6-24 months after delivery	cfPWV	7.1m/s $\pm$ 1.1;	Normal pregnancy group	yes	Low risk	Significant difference in Alx between HDP and normal group
1 2	Orabona et al. (2017)	Italy	Case-control	60 (30;30)	No CV risk factors, smoking, dyslipidemia, overweight, diabetes mellitus or chronic hypertension.	6 months - 4 years after delivery	cfPWV	cfPWV Mean: 8.42 m/s $\pm$ 1.92	Normal pregnancy group	yes	Low risk	Significant difference in cfPWV between HDP and normal group

Study characteristics

The included studies, conducted between 2009 and 2023, came from various countries: South Africa (1), Argentina (1), Denmark (1), Portugal (1), United States (3), Austria (1), Canada (1), the United Kingdom (1), Norway (1) and Italy (1) (see **Table 2.2**). These studies evaluated arterial stiffness, with some utilizing carotid-femoral pulse wave velocity (cfPWV) and/or augmentation index (Alx) and/or Augmentation index adjusted for heart rate (Alx@75).

While only two studies, Ehrenthal et al. (2014) and Moe et al. (2020), examined composite HDP, other studies focused on specific types, including preeclampsia, early preeclampsia, and late-onset preeclampsia. As a result, the findings were categorized into four groups: composite HDP, preeclampsia, early preeclampsia, and late-onset preeclampsia.

Risk of bias assessment

The risk of bias was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort and case-control studies, and a modified NOS for cross-sectional studies. The assessment indicated that all studies had a low risk of bias (**Table 2.3 and Table 2.4**).

Table 2 3: NOS for the risk of bias and quality assessment of NRSs

Author Year	Selection				Comparability	Exposure	Selection		Total Score
	Adequate definition of patient cases	Representativeness of patient cases	Selection of controls	Definition of controls	Control for important or additional factors	Ascertainment of exposure	Same method of ascertainment for participants	Nonresponse rate	
Namugowa et al. 2019	*	*		*	**	*	*		7
Christensen et al. 2017	*	*		*	**	*	*	*	8
Robb et al. 2009	*	*		*	**	*	*		7
Orabona et al. 2017	*	*		*	**	*	*	*	8
Pàez et al. 2008	*	*		*	**	*	*		7
Ehrenthal et al.	*	*		*	**	*	*		7

2014									
Franz et al. 2013	*	*		*	**	*	*		7
Evans et al. 2011	*	*		*	**	**	*		8

NOS, Newcastle-Ottawa scale; NRS, non-randomized study.

Table 2 4. NOS (adapted for cross-sectional studies) for the risk of bias and quality assessment of NRSs

Author Year	Selection					Comparability	Exposure	Total score
	Representative ness of the sample	Sample size	Non- respondents	Ascertainment of the exposure (risk factor)	Control for important or additional factors	Assessment of the outcome	Statistical test	
Polonia et al. 2013	*		*	**	**	**	*	9
Werlang et al. 2023	*		*	*	**	**	*	8
Moe et al. 2020	*		*	*	*	**	*	7

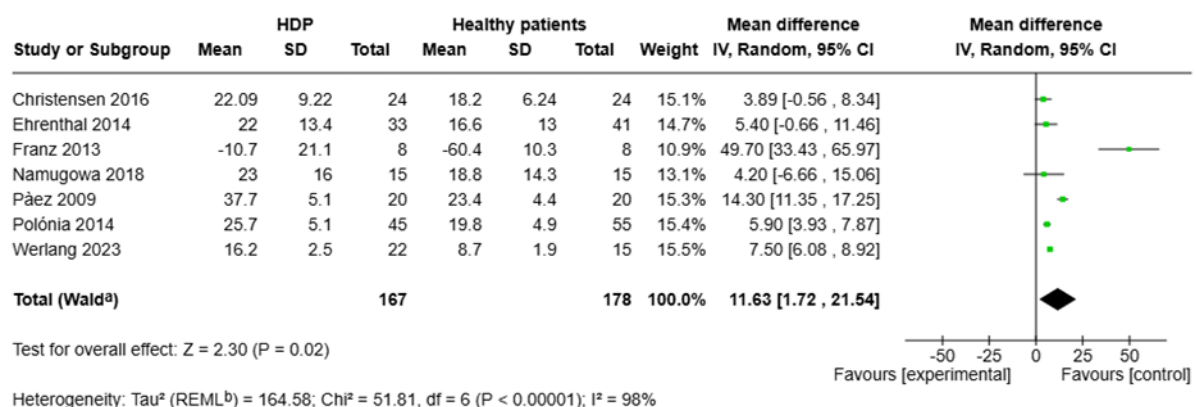
Usselman 2020	*		*	*	**	**	*	8
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NOS, Newcastle-Ottawa scale; NRS, non-randomized study.

Comparison of Augmentation Index and pulse wave velocity between women with all types of hypertensive disorders of pregnancy and normotensive women

A total of 7 studies assessed the Alx in patients with all various HDP compared to normotensive women (**Figure 2.2A**). The pooled data demonstrated a significantly elevated Alx among women with HDP, indicating a Mean difference (MD) of 11.63 and a 95% confidence interval (CI) of [1.72 – 21.54]. This analysis included 345 participants, comprising 167 women with HDP and 178 normotensive controls. The heterogeneity among the studies was high, with an I^2 value of 98%. Additionally, the analysis of funnel plots indicated the presence of publication bias, with a P value of 0.045 in the Egger's test (**Figure 2.3**).

A

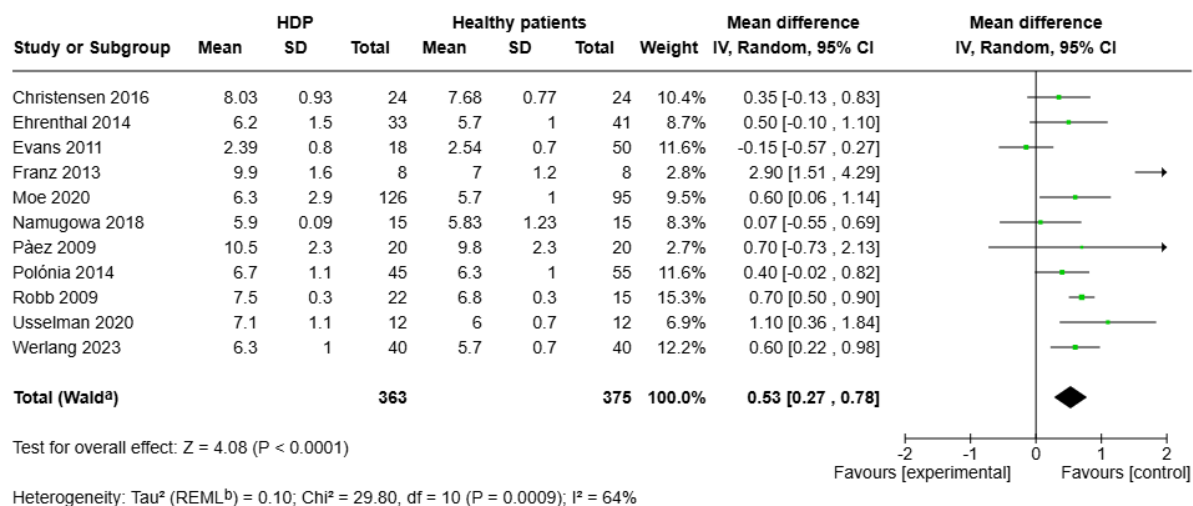


Footnotes

^aCI calculated by Wald-type method.

^b Tau^2 calculated by Restricted Maximum-Likelihood method.

B



Footnotes

^aCI calculated by Wald-type method.

^bTau² calculated by Restricted Maximum-Likelihood method.

Figure 2. 2. The pooled mean difference of the AIX (A) and PWV (B) of women with various HDP and normotensive women

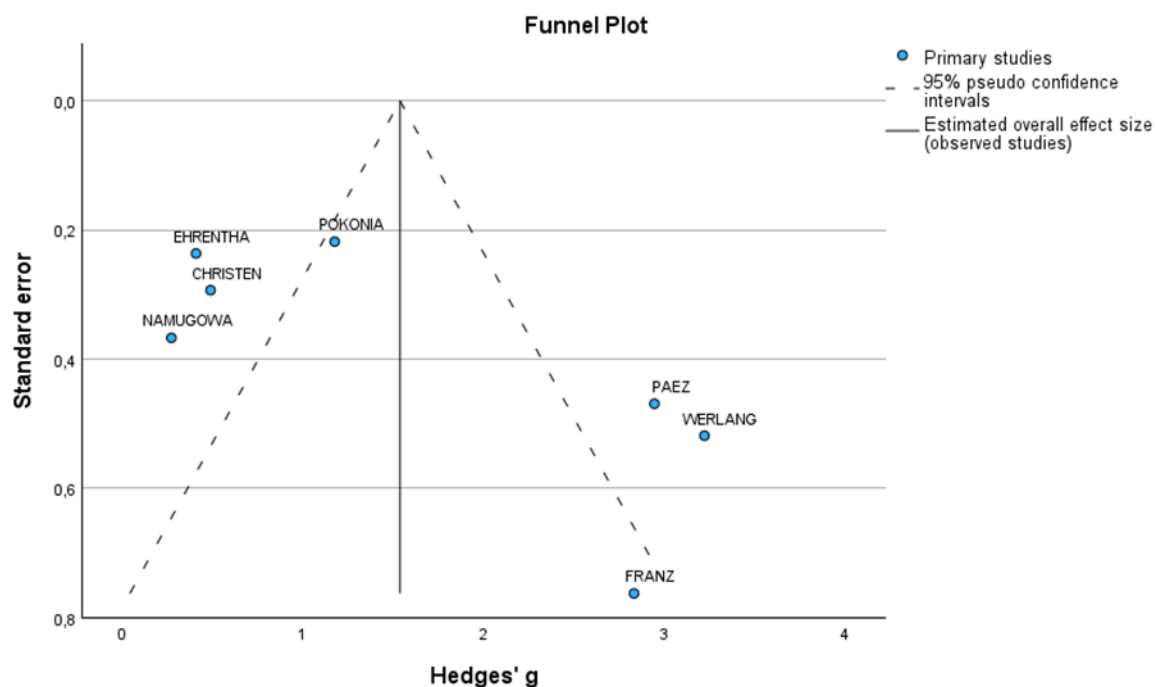


Figure 2. 3. Funnel plot of included studies for *Alx* in women with HDP vs normotensive patients

Furthermore, a total of 11 studies examined cfPWV in women with all various HDP compared to normotensive women (**Figure 2.2B**). The pooled data showed a significantly elevated cfPWV in women with HDP, with a MD of 0.53 and a 95% CI of [0.27 – 0.78]. This analysis included 738 participants, comprising 363 women with HDP and 375 normotensive controls. The studies showed moderate heterogeneity, with an I^2 value of 64%. Additionally, the analysis of funnel plots indicated the presence of publication bias, with a P value of 0.002 in the Egger's test (**Figure 2.4**).

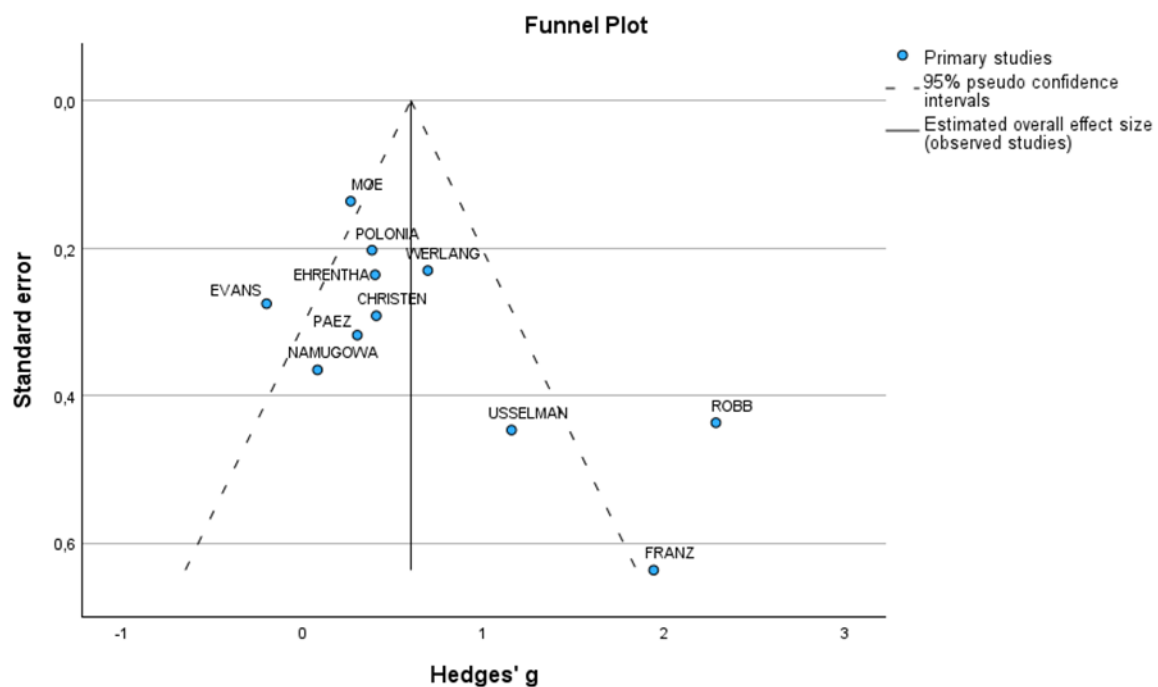


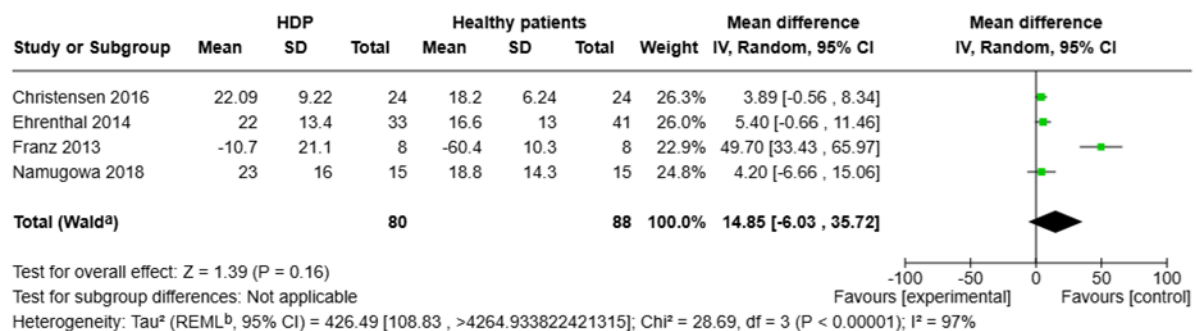
Figure 2 4. Funnel plot of included studies for *PWV* in women with HDP vs normotensive patients

Comparison of Augmentation index and pulse wave velocity between women with hypertensive disorders of pregnancy and normotensive women, within a year after delivery and after more than a year after delivery

Four studies investigated Alx in patients with HDP compared to normotensive controls within one year after delivery (see **Figure 2.5A**). The results showed no significant increase in Alx for women with HDP, reporting a MD of 14.85 and a 95% CI of [-6.03 – 35.72]. Additionally, there was high heterogeneity among these studies, with an I^2 value of 97%.

In contrast, other studies focused on Alx in patients with HDP compared to normotensive controls more than one year after delivery (see **Figure 2.5B**). The findings indicated a significant increase in Alx for women with HDP, with a MD of 9.11 and a 95% CI of [4.20 – 14.02]. The heterogeneity in these studies was also high, with an I^2 value of 94%.

A

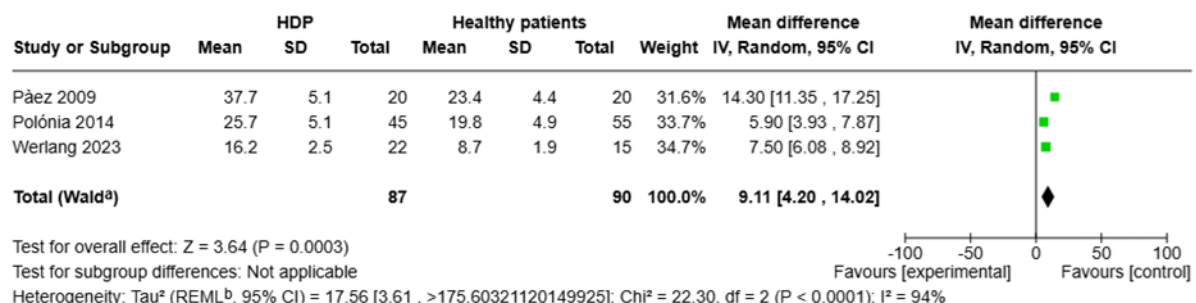


Footnotes

^aCI calculated by Wald-type method.

^b Tau^2 calculated by Restricted Maximum-Likelihood method.

B



Footnotes

^aCI calculated by Wald-type method.

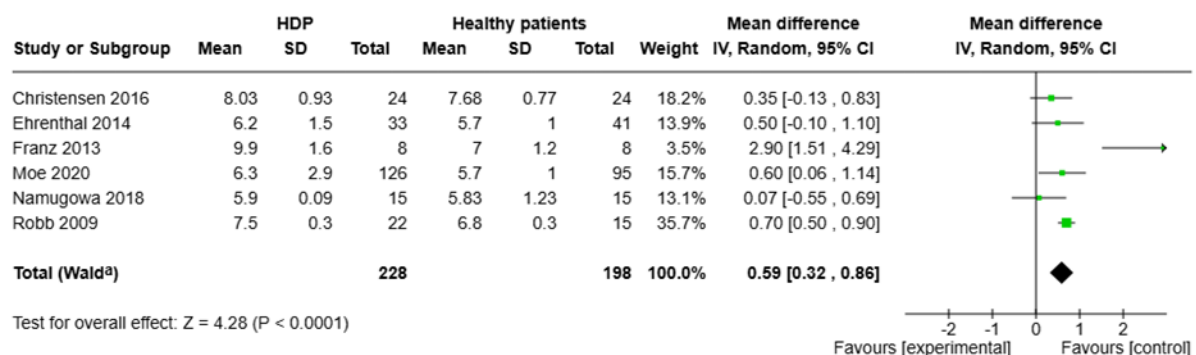
^b Tau^2 calculated by Restricted Maximum-Likelihood method.

Figure 2.5. Pooled mean difference of the AIX of women with HDP and normotensive pregnant women, within a year or less after delivery (A), and Pooled mean difference of the AIX of women with HDP and normotensive pregnant women after one year following delivery (B)

Six studies evaluated cfPWV in women with HDP compared to normotensive controls within one year after delivery (**Figure 2.6A**). The results demonstrated a significantly higher cfPWV for women with HDP, reporting an MD of 0.59 and a 95% CI of [0.32 – 0.86]. The heterogeneity among these studies was moderate, with an I^2 value of 41%.

Additionally, five studies focused on cfPWV in women with HDP compared to normotensive controls more than one year after delivery (**Figure 2.6B**). The findings also revealed a significant increase in cfPWV for women with HDP, with an MD of 0.45 and a 95% CI of [0.03 – 0.88]. Heterogeneity in these studies was also moderate, with an I^2 value of 67%.

A

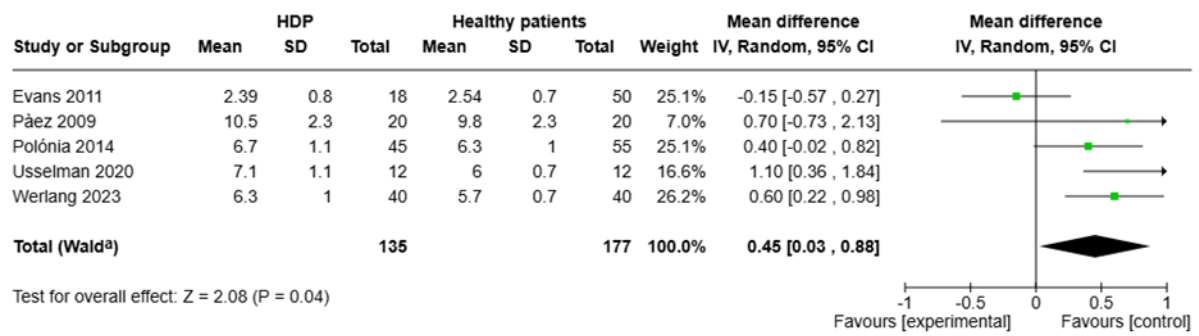


Footnotes

^aCI calculated by Wald-type method.

^b Tau^2 calculated by Restricted Maximum-Likelihood method.

B



Footnotes

^aCI calculated by Wald-type method.

^bTau² calculated by Restricted Maximum-Likelihood method.

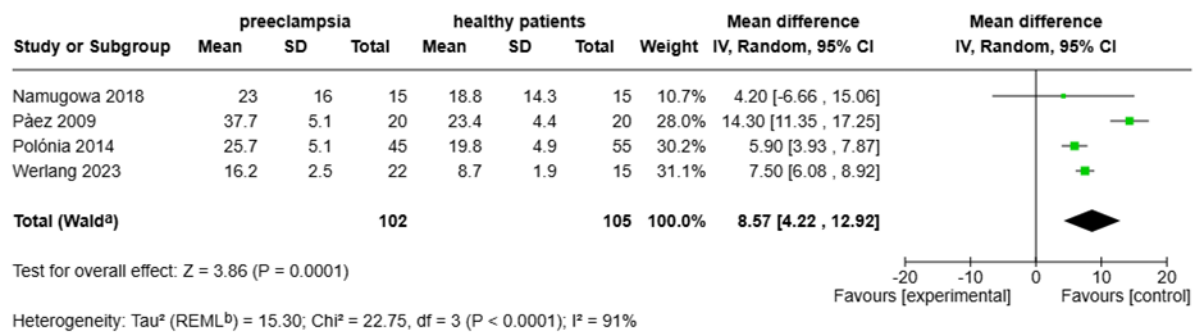
Figure 2.6. Pooled mean difference of the PWV of women with HDP and normotensive pregnant women, within a year or less after delivery (A), and Pooled mean difference of the PWV of women with HDP and normotensive pregnant women after one year following delivery (B)

Comparison of Augmentation Index and Pulse Wave Velocity in Preeclamptic versus Normotensive Women

A total of 4 studies assessed the Alx in patients with preeclampsia compared to normotensive women (**Figure 2.7A**). This pooled data demonstrated a significantly elevated Alx among women with preeclampsia, with a mean difference (MD) of 8.57 and a 95% confidence interval (CI) of [4.22 – 12.92]. The analysis included 207 participants, comprising 102 women with preeclampsia and 105 normotensive controls. The heterogeneity among the studies was high at 91%, indicating varying results across the studies. In two studies (Namugowa et al. 2017 and Werlang et al. 2023) that adjusted the Alx for heart rate (Alx@75), the Alx remained significantly elevated after the adjustment, with a MD of 7.50 and a 95% CI of [6.09 - 8.90] (**Figure 2.7B**). These two studies showed no heterogeneity.

Additionally, an examination of cfPWV across eight studies indicated a significant increase in cfPWV among women with preeclampsia, demonstrating an MD of 0.47 with a 95% CI of [0.20 - 0.74] (**Figure 2.7C**). This analysis involved 600 patients (298 preeclamptic and 302 normotensive). The studies displayed moderate heterogeneity, with an I^2 value of 62%.

A

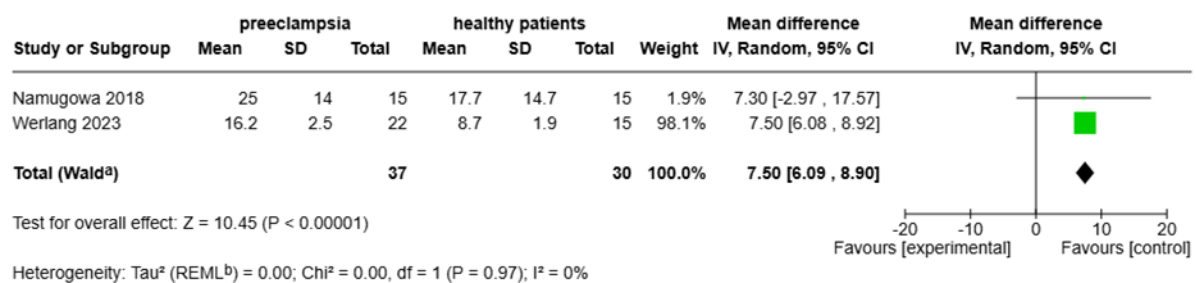


Footnotes

^aCI calculated by Wald-type method.

^b Tau^2 calculated by Restricted Maximum-Likelihood method.

B

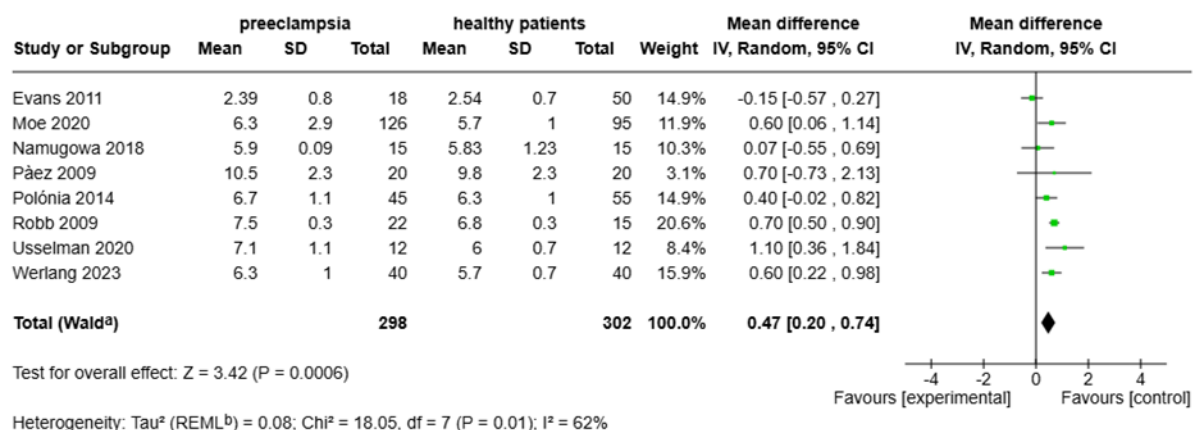


Footnotes

^aCI calculated by Wald-type method.

^b Tau^2 calculated by Restricted Maximum-Likelihood method.

C



Footnotes

^aCI calculated by Wald-type method.

^b Tau^2 calculated by Restricted Maximum-Likelihood method.

Figure 2 7. The pooled mean difference of the Alx (A), Alx@75 (B) and PWV (C) of women with preeclampsia and normotensive women

The funnel plot was generally symmetrical; however, a few studies deviated from the main axis, indicating the possibility of a small sample effect or publication bias. To further investigate potential bias, Egger's test was conducted, which showed no significant publication bias ($p = 0.144$) (**Figure 2.8**).

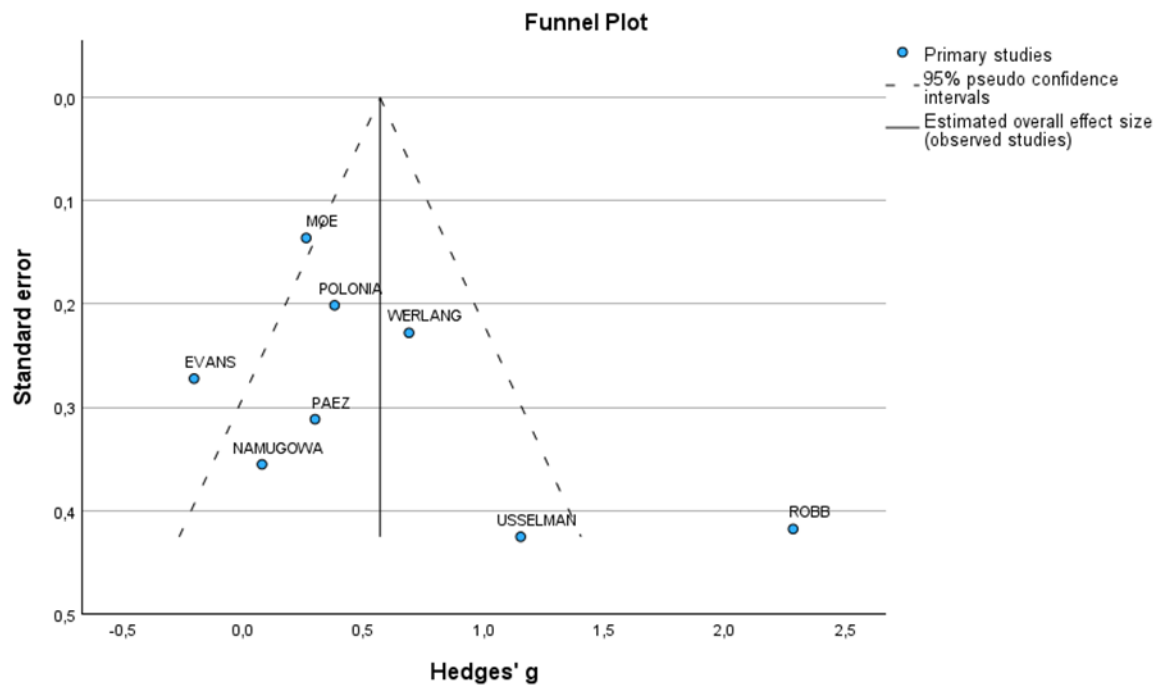


Figure 2.8. Funnel plot of included studies for PWV in preeclamptic vs normotensive patients. SE(Standard Error); MD (Mean difference)

Comparison of Augmentation Index and Pulse Wave Velocity in women with HDP versus Normotensive Women

One study focused on Alx in patients with composite HDP against normotensive controls (Ehrenthal et al. 2014) The results indicated no significant increase in Alx for women with HDP (MD 5.40, 95% CI [-0.66 – 11.46]). The heterogeneity assessment was not applicable due to the analysis being based on a single study. This analysis included a total of 74 participants, with 33 diagnosed with HDP and 41 who were normotensive. However, Alx was found to be significantly elevated after adjusting for heart rate (Alx@75) (MD 6.40, 95% CI [0.52 – 12.28]) [20].

Two studies, Ehrenthal et al. (2014) and Moe et al. (2020) analysed cfPWV in the context of HDP, reporting no significant increase in cfPWV among affected women (MD 0.35, 95% CI [-0.13 - 0.83]), with zero statistical heterogeneity noted (**Figure 2.9**). This part of the analysis comprised 305 individuals (169 with HDP and 136 normotensive controls).

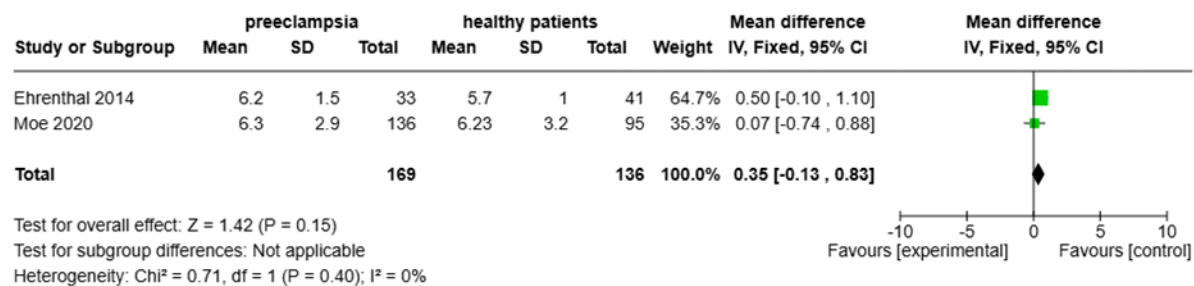


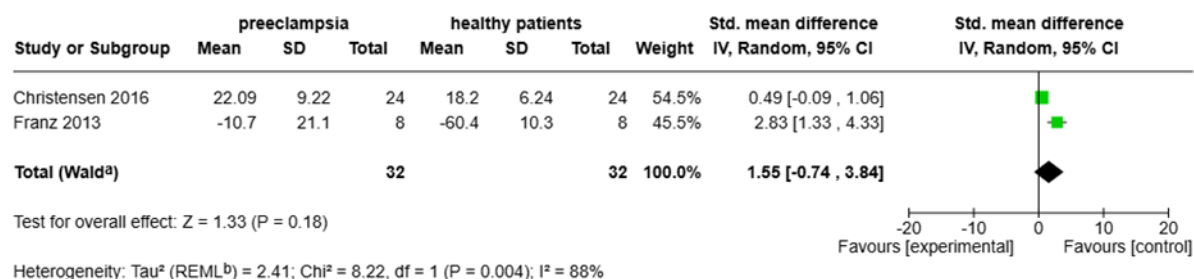
Figure 2 9. Pooled mean difference of the PWV of women with composite hypertensive disorders of pregnancy and normotensive pregnant women

Comparison of Augmentation Index and Pulse Wave Velocity among women with early onset preeclampsia and normotensive Women

In the context of early onset preeclampsia (EOP), two studies, conducted by Christensen et al. and Franz et al. (2013), evaluated the Alx and found no significant increase associated with EOP (MD 1.55, 95% CI [-0.74 – 3.84]), with a heterogeneity of 88% (**Figure 2.10A**). The studies included a total of 64 participants, comprising 32 EOP and 32 normotensive women. Orabona et al. (2017) was the only study to evaluate Alx after adjusting for heart rate, and it indicated a significant elevation in Alx following this adjustment (MD 0.94, 95% CI [2.17-3.70]).

Additionally, Christensen et al., Franz et al. (2013), and Orabona et al. (2017) also assessed cfPWV in patients with EOP. The results indicated a significant increase in cfPWV (MD 1.86, 95% CI [0.25-3.47]) and a heterogeneity of 92%. A total of 124 participants were included in these studies, consisting of 62 EOP and 62 normotensive women (**Figure 2.10B**).

A



Footnotes

^aCI calculated by Wald-type method.

^bTau² calculated by Restricted Maximum-Likelihood method.

B

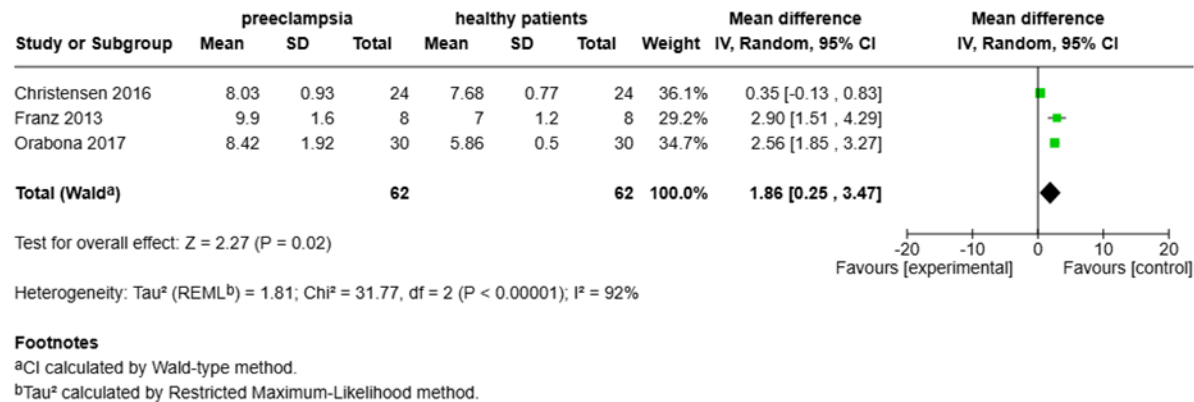


Figure 2 10. Pooled mean difference of the Alx (A) and PWV (B), of women with early onset preeclampsia compared to normotensive women

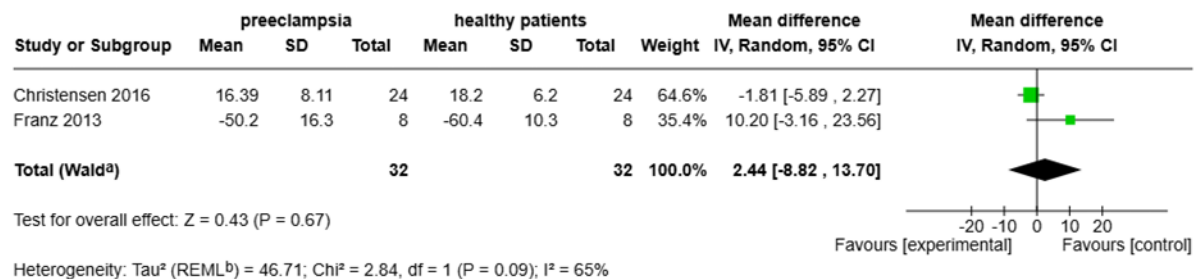
Comparison of Augmentation Index and Pulse Wave Velocity among women with late onset preeclampsia and normotensive pregnancy

Christensen et al. (2016) and Franz et al. (2013) also studied the Alx in cases of late-onset preeclampsia. Their analysis showed no significant difference (MD of 2.44, 95% confidence interval [-8.82- 13.70]) and indicated a heterogeneity of 65% (**Figure 2.11A**). This study included a total of 64 participants, comprising 32 individuals with LOP and 32 normotensive controls. However, after adjusting for heart rate, Orabona et al. (2017) found that the augmentation index was significantly higher in the LOP group (MD of 4.80, 95% confidence interval [0.60 -9.00]).

Furthermore, Christensen et al. (2016), Franz et al. (2013), and Orabona et al. (2017) also assessed cfPWV in patients with LOP. Their findings indicated no significant increase in cfPWV (MD 0.10, 95% CI [-0.42-0.62]), with a heterogeneity of 56% (**Figure 2.11B**). The total

sample size in this analysis was 124 participants, including 62 with LOP and 62 normotensive individuals.

A

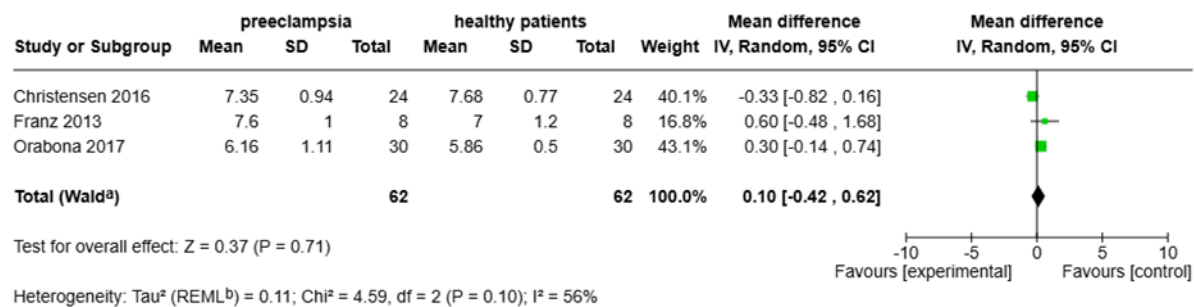


Footnotes

^aCI calculated by Wald-type method.

^b Tau^2 calculated by Restricted Maximum-Likelihood method.

B



Footnotes

^aCI calculated by Wald-type method.

^b Tau^2 calculated by Restricted Maximum-Likelihood method.

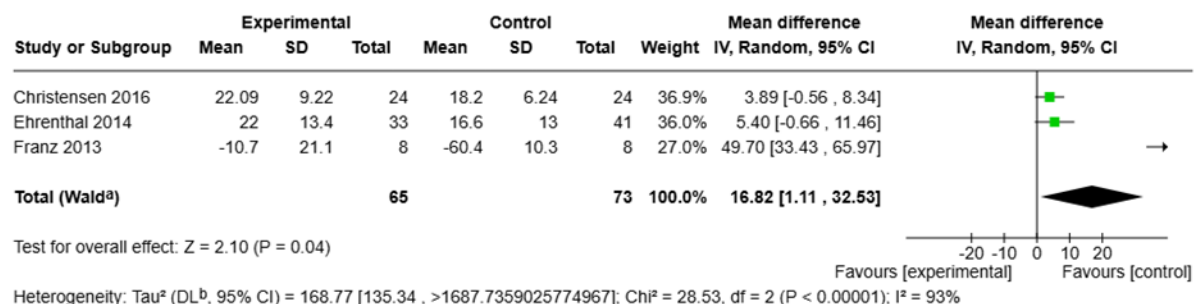
Figure 2 11. Pooled mean difference of the Alx (A) and PWV (B), of women with late-onset preeclampsia compared to normotensive women

Comparison of Augmentation Index and Pulse Wave Velocity among women with HDP and normotensive pregnancy in cohort studies

A total of three studies assessed the Alx in patients with HDP compared to normotensive women (Christensen et al. 2017; Ehrenthal et al. 2014; Franz et al. 2013) (see **Figure 2.12A**). The pooled data demonstrated a significantly elevated Alx among women with HDP, indicating a MD of 16.82 and a 95% CI of [1.11 – 12.92]. This analysis included 138 participants, comprising 65 women with HDP and 73 normotensive controls. The heterogeneity among the studies was high at 93%, suggesting varying results across the studies. In the only study that adjusted the Alx for heart rate (Alx@75), Alx remained significantly elevated after adjustment, with a MD of 6.40 and a 95% CI of [0.52 – 12.28] (Ehrenthal et al. 2014).

Furthermore, an examination of cfPWV across five studies showed no significant increase in cfPWV among women with HDP, demonstrating a MD of 0.70 with a 95% CI of [-0.10 – 1.49] (see **Figure 2.12B**). The heterogeneity was again high at 93%, and this analysis involved 243 patients (105 with HDP and 138 normotensive).

A



Footnotes

^aCI calculated by Wald-type method.

^b τ^2 calculated by DerSimonian and Laird method.

B

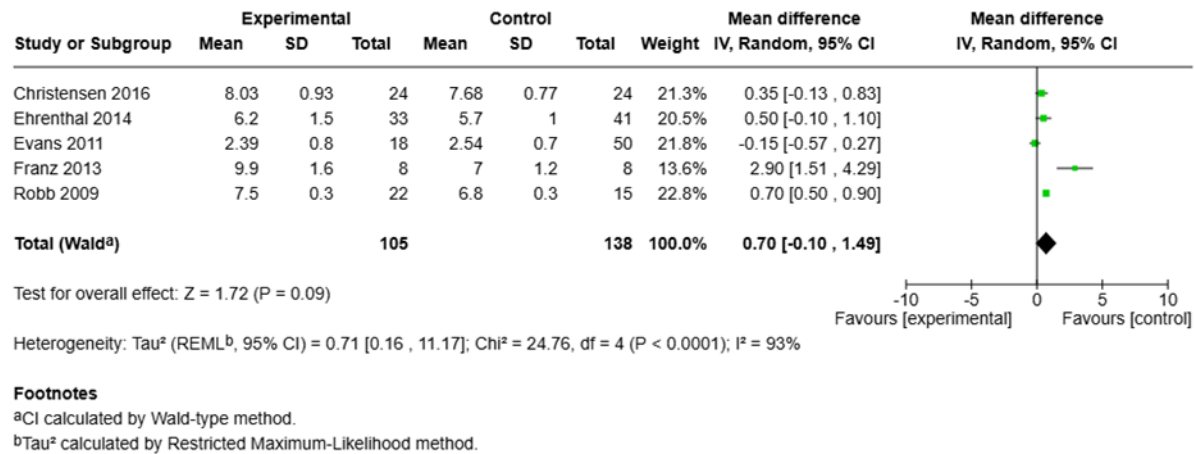


Figure 2 12. The pooled mean difference of the Alx (A) and PWV (B), of women with HDP and normotensive women in cohort studies

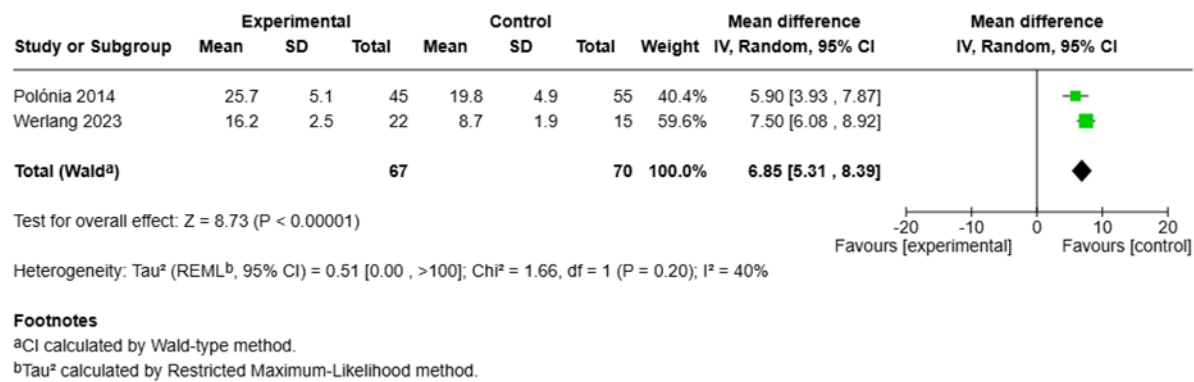
Comparison of Augmentation Index and Pulse Wave Velocity in women with HDP versus Normotensive Women in cross-sectional studies

Two studies focused on Alx in patients with HDP compared to normotensive controls (Polónia et al. 2014; Werlang et al. 2023) (see **Figure 2.13A**). The results indicated a significant increase in Alx for women with HDP, with a MD of 6.85 and a 95% CI of [5.31 – 8.39]. The heterogeneity among these studies was low at 40%. This analysis included a total of 137 participants, with 67 diagnosed with HDP and 70 who were normotensive. In one study, the Alx remained significantly elevated after adjusting for heart rate, with a MD of 7.50 and a 95% CI of [0.68 – 8.92](Werlang et al. 2023).

Four studies analysed cfPWV in the context of HDP, reporting a significant increase in cfPWV among affected women, with a MD of 0.59 and a 95% CI of [0.35 - 0.82](Polónia et al. 2014; Moe et al. 2020; Usselman et al. 2020; Werlang et al. 2023). No statistical

heterogeneity was observed in this analysis (see **Figure 2.13B**). This part of the analysis comprised 426 individuals (223 with HDP and 203 normotensive controls).

A



B

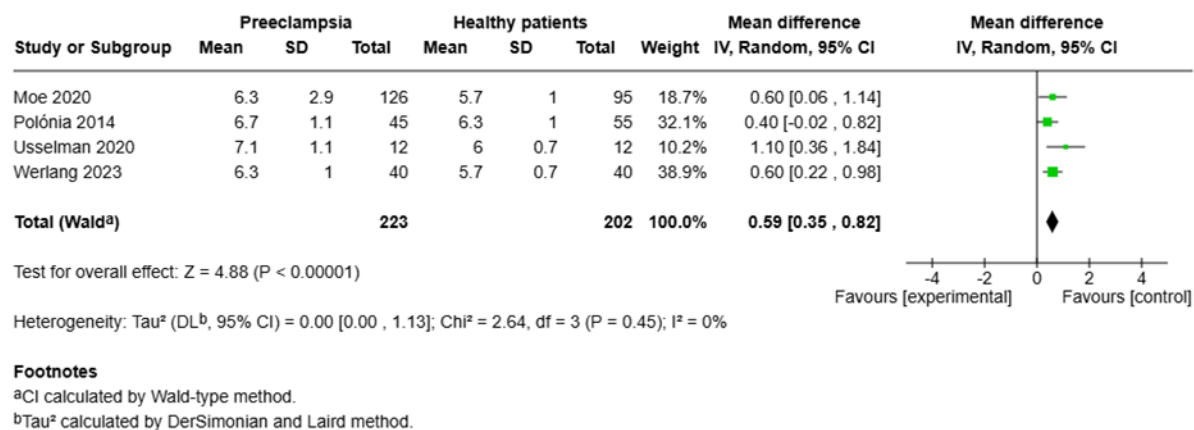


Figure 2 13. Pooled mean difference of the Alx (A) and PWV (B) of women with HDP and normotensive pregnant women in cross-sectional studies

2.5 Discussion

The systematic review presents a comprehensive analysis of the literature regarding arterial stiffness in women with previous history of HDP, particularly pre-eclampsia. Most studies revealed elevated arterial stiffness after six weeks post-delivery in women with a history of preeclampsia, suggesting ongoing vascular dysfunction that could lead to an increased cardiovascular risk lingering even years after pregnancy (Cecelja & Chowienczyk 2012). The duration of the studies ranged from seven weeks postpartum to ten years post-pregnancy, showcasing the long-term implications of preeclampsia on cardiovascular health. However, not all studies demonstrated a consistent association between HDP and increased arterial stiffness. For example, a Danish study by Christensen et al. and research by Evans et al. in the United States reported no increase in arterial stiffness as measured by PWV and Alx (Evans et al. 2011; Christensen et al. 2017). This indicates that, while a relationship may exist, its impact can vary based on the demographic and clinical characteristics of the populations studied.

The Alx, particularly after adjusting for heart rate, was found to be elevated in women with HDP (Páez et al. 2009; Polónia et al. 2014; Orabona et al. 2017; Namugowa et al. 2019; Werlang et al. 2023). This includes specific types such as composite preeclampsia and both early and late onset preeclampsia, when compared to normotensive women (Orabona et al. 2017). This suggests a considerable increase in arterial stiffness, which may indicate a heightened cardiovascular risk in this preeclampsia population. The high heterogeneity (87%) observed among the studies points to variability in results, potentially due to differences in study populations, methodologies, or measurement techniques. Additionally, a single study examining Alx@75 in women with composite HDP also reported a significant increase, although heterogeneity assessment was not applicable in this case (Ehrenthal et al. 2014). These findings reinforce the idea that women with various types of hypertensive disorders experience increased arterial stiffness, emphasizing the associated cardiovascular risk. The consistently elevated Alx in both cohort and cross-sectional studies further supports the notion that there is a significant alteration in arterial function among

women with a history of HDP. Additionally, a review of Alx findings one year after delivery indicates changes in vascular function in women with a history of HDP, suggesting a lasting cardiovascular risk. Although arterial stiffness, as indicated by Alx, may not differ significantly within the first year postpartum, long-term effects of HDP could increase arterial stiffness and potentially, cardiovascular risk. Importantly, both women in their first year after delivery and those beyond that period demonstrated a significant increase in cfPWV.

Furthermore, pooled data from eleven studies comparing various hypertensive disorders in normotensive women, as well as data from eight studies comparing preeclampsia and normotensive women, revealed a significant increase in PMW (Páez et al. 2009; Robb et al. 2009; Evans et al. 2011; Polónia et al. 2014; Namugowa et al. 2019; Moe et al. 2020; Usselman et al. 2020; Werlang et al. 2023). However, studies on cfPWV for women with composite HDP and late onset preeclampsia showed no significant increases (Páez et al. 2009; Moher et al. 2016). This suggests that while Alx@75 is elevated, reflecting increased arterial stiffness, cfPWV might not indicate a similar degree of change, potentially highlighting that the two measurements assess different aspects of arterial function.

cfPWV directly measures the speed at which pressure waves travel through the arterial tree. A faster cfPWV indicates stiffer arteries and is more representative of large artery function. It is less influenced by peripheral changes and wave reflections from smaller arteries (Brown 1999). On the other hand, Alx measures the augmentation of pressure waves in the arteries caused by reflected waves from peripheral sites (McEniery et al. 2014; Agabiti-Rosei et al. 2007). This metric reflects not only the stiffness of the arteries but also the timing and intensity of these reflections.

Notably, the assessment of early-onset preeclampsia also revealed a significant rise in cfPWV, contrasting with late-onset preeclampsia, which showed no significant changes. This discrepancy may indicate that the early onset of preeclampsia is associated with

distinct hemodynamic changes that are absent in the later onset. Furthermore, the absence of significant mean differences in cohort studies, alongside notable findings in cross-sectional studies, suggests that cfPWV may be a more variable measure influenced by various factors present in different study designs. The contrasting results warrant further investigation to understand better the relationship between cfPWV and HDP.

2.6 Limitations

This review had a limited number of studies, which could introduce bias. Additionally, a high level of heterogeneity was observed in most group analyses. However, a low risk of bias was identified when assessments were carried out using the Newcastle-Ottawa Scale. Furthermore, the review adhered to the PRISMA-P guidelines, and a comprehensive search was performed across several databases.

2.7 Conclusion

This systematic review and meta-analysis suggest that arterial stiffness may remain elevated for more than 6 weeks postpartum in women with a history of HDP. However, the findings should be interpreted with caution due to heterogeneity across studies and limited number of available studies. High-quality longitudinal research is needed to confirm these results. In the meantime, regular cardiovascular monitoring for these women is recommended while awaiting more conclusive evidence.

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CHAPTER 3

3. Reliability of the Microlife WatchBP Office Central device for blood pressure measurement in hypertensive and normotensive pregnant women

Credit author statement

Xolani B Mbongozi contributed to conceptualization, data curation, formal analysis, and methodology, and was responsible for writing the original draft as well as reviewing and editing the manuscript. Stuart DR Galloway provided supervision and contributed to the review and editing process. Angus Hunter also offered supervision and contributed to the review and editing. Charles B. Businge participated in supervision and was involved in reviewing, and editing. Mirabel Nanjoh conducted a formal analysis. Geoffrey AB Buga was involved in methodology, supervision, and review and editing.

Abstract

Background: Accurate and reliable blood pressure measurement is essential in pregnancy, particularly for detecting hypertensive disorders, which can have serious maternal and fetal consequences. The Microlife WatchBP Office Central device has been validated for use in adults, but its reliability in pregnant populations has not been established.

Objective: To assess the reliability of peripheral systolic and diastolic blood pressure measurements obtained using the Microlife WatchBP Office Central device in pregnant women, including those with hypertensive disorders.

Methodology: A cross-sectional study was conducted involving 30 hypertensive and 15 normotensive pregnant women. The definition of HDP adhered to the classification recommendations set by the International Society for the Study of Hypertension in

Pregnancy. Repeat blood pressure measurements were taken by two trained observers using the Microlife WatchBP Office Central device. Reliability was evaluated using coefficient of variation (CV), intraclass correlation coefficient (ICC), standard error of measurement (SEM), and minimum detectable change (MDC).

Results: Both observers demonstrated high measurement precision, stability, and reproducibility across groups. CVs were low (1.0–1.8%), indicating minimal intra-observer variability. ICCs (0.97–0.99) confirmed excellent reliability, while SEMs (0.08–0.20 mmHg) and MDCs (0.2–0.4 mmHg) reflected high measurement sensitivity. No statistically significant inter-observer differences were observed ($p > 0.05$), confirming consistency between observers. Inter-observer reliability during test and retest sessions was equally strong, with ICCs of 0.96–0.99 for both parameters. SEM values remained low (<0.5 mmHg), confirming negligible observer-related variability.

Conclusion

The Microlife WatchBP Office Central device provides reliable, and reproducible blood pressure measurements in pregnant women, including those with hypertensive disorders. These findings support its use in routine clinical monitoring, enabling healthcare providers to confidently detect and manage clinically significant blood pressure changes.

Keywords: Blood pressure, pregnancy, hypertensive disorders, reliability, Microlife WatchBP Office Central, clinical monitoring.

3.1 Introduction

Measurement of blood pressure during pregnancy is an integral part of routine clinical care, as it plays a crucial role in the timely detection and management of hypertensive disorders of pregnancy (HDP), which can lead to significant morbidity and mortality for

both mothers and infants (von Dadelszen et al. 2011; Magee et al. 2022). Accurate blood pressure measurement is vital: inaccurate readings, whether they are overestimations or underestimations of true blood pressure, can lead to inappropriate clinical decisions (Whelton et al. 2018). Historically, the mercury sphygmomanometer has been considered the gold standard for blood pressure measurement (Pickering et al. 2005). However, with advances in technology, automatic oscillometric devices are increasingly utilized in clinical settings. While these devices offer convenience and ease of use, it is essential that they undergo thorough reliability evaluations, particularly in special populations such as pregnant women. It is worth noting that the reliability and validation of the Microlife WatchBP Office Central have already been established in the general population (Stergiou et al. 2008; Cheng et al. 2013). In particular, Cheng et al. (2013) demonstrated that the device provides accurate central blood pressure readings compared with simultaneous invasive arterial measurements—the gold standard—thereby confirming its validity for non-invasive central hemodynamic assessment. However, limited data exist on its measurement reliability in pregnant women, particularly among African populations.

Pregnancy is characterized by several physiological changes, including variations in blood volume, vascular resistance, and hormone levels, all of which can influence blood pressure measurements (Sanghavi & Rutherford 2014; Whelton et al. 2018). As such, these physiological adaptations necessitate specific evaluation of blood pressure monitoring devices within the pregnant population (Thilaganathan 2017; Yagel & Verlohren 2020; Kornacki et al. 2024). The Microlife WatchBP Office Central is a non-invasive oscillometric blood pressure device capable of measuring both central and peripheral blood pressure. Utilizing brachial pulse volume plethysmography (PVP), this device provides automatic measurements of blood pressure and heart rate, presenting the results on a user-friendly display. WatchBP Office Central is designed to perform PVP at a cuff pressure of 60 mmHg. Based on the analysis of the PVP waveforms, the central systolic pressure (CBP) and central pulse pressure values are automatically calculated. CBP estimations have shown

heightened significance in recent research, suggesting that they may offer superior predictive capabilities for cardiovascular risk compared to peripheral blood pressure measurements (Protogerou et al. 2009; Wang et al. 2009). Furthermore, existing studies indicate that women with HDP may experience elevated CBP relative to their normotensive counterparts (Namugowa et al. 2017).

Given that pregnancy is recognized as a unique population by the American Association for the Advancement of Medical Instrumentation, it is crucial to evaluate the reliability of the Microlife WatchBP Office Central's peripheral blood pressure measurements specifically in this group (Kollias et al. 2018). A key aspect of this assessment is quantifying measurement variability, which establishes the threshold for meaningful change and distinguishes true physiological signals from random noise. Quantifying the signal-to-noise ratio is essential to minimize the risk of Type I and Type II errors when interpreting changes in blood pressure. Although the device has been validated for the general population, confirming its reliability and variability during pregnancy is essential to ensure that any observed changes in this thesis reflect genuine physiological differences rather than coincidental measurement variation.

3.2 Objective

To assess the reliability of peripheral systolic and diastolic blood pressure measurements obtained using the Microlife WatchBP Office Central device in pregnant women, including those with hypertensive disorders.

3.3 Methods

This was a cross-sectional study conducted in the maternity unit at Nelson Mandela Academic Hospital in the Eastern Cape province of South Africa. Forty-five black African pregnant women were recruited to participate in this study. Of these 45 pregnant women, 30 were hypertensive (15 were preeclamptic, 15 had gestational hypertension), and 15 were normotensive. The definitions of hypertensive disorders of pregnancy adhered to the classification recommendations set by the International Society for the Study of

Hypertension in Pregnancy (Brown et al. 2018). Ethical approval was granted by Walter Sisulu University (ethics number 035/2022) and the Eastern Cape Department of Health ethics committees (ethics number EC-202302-009), and informed consent was obtained from all participants.

Blood pressure measurements were performed using the Microlife WatchBP Office Central by two different observers. The same device was consistently used throughout the study, and the observers were blinded to each other's measurements. A third observer oversaw the reliability assessment process. The circumference of each participant's arm was measured to ensure that the appropriate cuff size was used. Each woman underwent two consecutive blood pressure measurements, 3-5 minutes apart, from each observer. Measurements were taken using the "same arm, consecutive measurements" protocol on the left arm, which was supported at heart level (Kollias et al. 2018). The procedure was as follows:

- a) The participant was asked to relax for 5-10 minutes.
- b) The participant was positioned seated, with legs uncrossed and back supported.

The statistical analysis was performed using IBM SPSS STATISTICS software package version 31 for Windows (IBM Inc., Chicago IL, USA). Continuous data were analyzed using means and standard deviations (SD). The coefficient of variation (CV) was determined using the formula $CV = (SD/mean) \times 100$. The standard error of measurement (SEM) was calculated based on the standard deviation and the reliability coefficient. Additionally, the minimum detectable change (MDC) was computed using the formula $MDC = SEM \times 1.96$. Paired t-tests were used to compare measurements between the two observers, while independent t-tests were applied to compare values between the hypertensive and normotensive groups, with a significance level set at $p < 0.05$.

3.4 Results

3.4.1 Demographic characteristics of hypertensive cases and normotensive controls

Forty-five black African pregnant women were recruited to participate in this study. Of these 45 pregnant women, 30 were hypertensive (15 were preeclamptic, 15 had gestational hypertension), and 15 were normotensive. The mean age of the participants was 27.5 ± 7.3 years, and the mean gestational age was 35.7 ± 3.6 weeks.

There were no statistically significant differences in the age, gravidity, and parity between women with HDP and the normotensive controls ($p > 0.05$), as shown in **Table 3.1** below. However, the mean gestational age of the women with HDP (34.4 ± 3.6 weeks) was significantly lower than the mean gestational age (38.4 ± 1.5 weeks) of the normotensive controls ($p < 0.0001$). The controls had a significantly higher gestational age than the women with HDP because they were only fully recruited after delivery to ensure they remained normotensive.

As shown in **Table 3.1** below, the mean pSBP was significantly higher in women with HDP than in the normotensive controls ($p = 0.001$). Similarly, the pDBP was significantly higher among women with HDP than in the normotensive controls ($p < 0.0001$). The mean central systolic blood pressure (cSBP) of women with HDP as measured using Microlife WatchBP Office Central was also significantly higher than that of the normotensive controls ($p < 0.0001$). Although the mean central diastolic blood pressure (cDBP) of women with HDP was higher than that of the normotensive controls, this did not achieve statistical significance ($p = 0.801$).

Table 3. 1: Demographic characteristics of hypertensive cases and normotensive controls

Characteristics	Hypertensive cases (N=30)	Normotensive controls (N=15)	Total	Student's t-test p value (difference between groups)
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	
Age (years)	28.9 $\pm$ 7.6	24.9 $\pm$ 6.0	27.5 $\pm$ 7.3	0.08
Gravidity	2.3 $\pm$ 1.3	2.2 $\pm$ 1.7	2.3 $\pm$ 1.4	0.83
Parity	1.3 $\pm$ 0.9	1.4 $\pm$ 0.8	1.3 $\pm$ 0.9	0.72
Gestational age (wks)	34.4 $\pm$ 3.6	38.4 $\pm$ 1.5	35.7 $\pm$ 3.6	<0.0001
pSBP (mmHg)	135.7 $\pm$ 11.3	123.3 $\pm$ 10.6	131.6 $\pm$ 12.4	0.001
pDBP (mmHg)	82.2 $\pm$ 7.8	64.7 $\pm$ 5.4	76.4 $\pm$ 10.9	<0.0001
cSBP (mmHg)	130.1 $\pm$ 12.1	114.4 $\pm$ 12.5	124.9 $\pm$ 14.2	<0.0001
cDBP (mmHg)	71.6 $\pm$ 13.1	70.6 $\pm$ 11.2	71.3 $\pm$ 12.4	0.80

pSBP = peripheral systolic blood pressure; pDBP = peripheral diastolic blood pressure; cSBP = central systolic blood pressure; cDBP = central diastolic blood pressure; SD =standard deviation; wks = weeks.

3.4.2 Test-Retest reliability of Microlife Office Central and minimum detectable change in pregnancy

Coefficient of Variation

Overall, both pSBP and pDBP demonstrated low measurement variability across observers and participant groups, indicating high stability and reproducibility (**Table 3.2**). For observer 1, the pSBP CV was 1.1% in the hypertensive group and 1.2% in the normotensive group, reflecting excellent consistency. Observer 2 recorded pSBP CVs of 1.1% for hypertensive participants and 1.0% for normotensives, further confirming the stability of systolic measurements. A similar pattern of low variability was observed for pDBP: Observer 1 recorded CVs of 1.1% in the hypertensive group and 1.7% in normotensives, while observer 2 reported 1.6% and 1.8%, respectively. Paired t-tests showed no

statistically significant inter-observer differences for either systolic or diastolic blood pressure, highlighting the reliability of the measurements.

Table 3. 2: Coefficient of variation (%) for Blood Pressure Parameters taken by two observers

Group	Obs1 pSBP	Obs2 pSBP	Paired T-Test	Obs1 pDBP	Obs2 pDBP	Paired T-Test
			P-value			P-value
Hypertensives	1.1	1.1	0.12	1.1	1.6	0.17
Normotensives	1.2	1.0	0.23	1.7	1.8	0.17

Obs 1=Observer 1; Obs 2= Observer 2; pSBP = peripheral systolic blood pressure; pDBP = peripheral diastolic blood pressure.

The overall ICC values were exceptionally high, reflecting excellent intra-observer reliability (**Table 3.3**). In the hypertensive group, observer 1 achieved an ICC of 0.99 for pSBP and 0.99 for pDBP, whereas observer 2 demonstrated an ICC of 0.97 for pSBP and 0.99 for pDBP. In the normotensive group, observer 1 had ICC values of 0.99 for pSBP and 0.99 for pDBP. In comparison, observer 2 demonstrated ICC values of 0.99 for pSBP and 0.98 for pDBP.

Both observers demonstrated lower SEM across both blood pressure parameters and participant groups, indicating higher measurement precision (see **Table 3.3**). In the hypertensive group, observer 1 had an SEM of 0.16 for the pSBP and 0.17 for the pDBP. Observer 2 recorded SEMs of 0.16 for pSBP and 0.16 for pDBP. In the normotensive group, observer 1's SEM was 0.17 for pSBP and 0.13 for pDBP, while observer 2 showed SEMs of 0.13 for pSBP and 0.20 for pDBP.

Table 3. 3: Intraclass correlation coefficient and Standard error of measurement for blood pressure parameters taken by two observers

ICC					SEM			
Group	Obs 1		Obs 2		Obs 1		Obs 2	
	pSBP	pDBP	pSBP	pDBP	pSBP	pDBP	pSBP	pDBP
Hypertensives	0.99	0.99	0.97	0.99	0.16	0.08	0.16	0.16
Normotensives	0.99	0.99	0.99	0.98	0.17	0.13	0.13	0.20

Obs 1=Observer 1; Obs 2= Observer 2; pSBP = peripheral systolic blood pressure; pDBP = peripheral diastolic blood pressure.

Minimum Detectable Change

Overall, both observers demonstrated low MDC values across both groups and parameters, reflecting high measurement sensitivity (**Table 3.4**). Although the Microlife WatchBP Office Central device records BP to the nearest 1 mmHg, the calculated MDC values include decimals as they are derived statistically from variability estimates. In the hypertensive group, observer 1 recorded MDC values of 0.3 mmHg for both pSBP and pDBP. Observer 2 reported the same MDC values of 0.3 mmHg for pSBP and 0.2 mmHg for pDBP. In the normotensive group, observer 1 had MDC values of 0.3 mmHg for pSBP and 0.3 mmHg for pDBP, while observer 2 recorded 0.2 mmHg for pSBP and 0.4 mmHg for pDBP.

These results indicate that, for hypertensive participants, changes of up to 0.3 mmHg in both pSBP and pDBP is required to be considered significant, while for normotensive participants, changes of 0.3 mmHg for pSBP and 0.4 mmHg for pDBP represent meaningful differences.

Table 3 4. Minimum detectable change for blood pressure parameters

MDC (mmHg)					MDC (%)			
Group	Obs 1		Obs 2		Obs 1		Obs 2	
	pSBP	pDBP	pSBP	pDBP	pSBP	pDBP	pSBP	pDBP
Hypertensives	0.3	0.2	0.3	0.3	0.4	0.3	0.4	0.4
Normotensives	0.3	0.2	0.2	0.4	0.4	0.3	0.3	0.6

Obs 1=Observer 1; Obs 2= Observer 2; pSBP = peripheral systolic blood pressure; pDBP = peripheral diastolic blood pressure.

3.4.3 Inter-Observer Reliability

Inter-observer reliability between the two observers was excellent across both hypertensive and normotensive participants during both test and retest sessions (Table 3.5). For pSBP, inter-observer ICCs were 0.99 for both hypertensive and normotensive participants during the test, and 0.97 and 0.96, respectively, during the retest. For pDBP, ICCs were 0.99 in both groups during the test and 0.98 and 0.94 at retest.

The SEM analysis between observers further supported the reliability findings. During the test session, SEM values were 0.15 mmHg (hypertensive) and 0.12 mmHg (normotensive) for pSBP, and 0.10 mmHg and 0.08 mmHg for pDBP. During the retest session, SEM values were 0.38 mmHg (hypertensive) and 0.48 mmHg (normotensive) for pSBP, and 0.16 mmHg and 0.54 mmHg for pDBP, further indicating that observer-related measurement error remained minimal.

Table 3. 5: Inter-Observer Reliability (ICC and SEM) for Systolic and Diastolic Blood Pressure

Group	Parameter	Test ICC	Retest ICC	Test SEM (mmHg)	Retest SEM (mmHg)
Hypertensive	pSBP	0.99	0.97	0.15	0.38
Hypertensive	pDBP	0.99	0.98	0.10	0.16
Normotensive	pSBP	0.99	0.96	0.12	0.48
Normotensive	pDBP	0.99	0.94	0.08	0.54

ICC = Intraclass Correlation Coefficient; SEM = Standard Error of Measurement; pSBP = peripheral systolic blood pressure; pDBP = peripheral diastolic blood pressure.

3.5 Discussion

The results of this study demonstrate high reliability, precision and reproducibility of pSBP and pDBP measurements across hypertensive and normotensive participants, as assessed by two observers. Multiple reliability indices, including the coefficient of variation (CV), intraclass correlation coefficient (ICC), standard error of measurement (SEM), and minimum detectable change (MDC), clearly indicated that the Microlife WatchBP Office Central device provides reliable and dependable measurements.

The CV values for both pSBP and pDBP were consistently low across all observers and participant groups, ranging from 1.0% to 1.8%. Low CV values indicate minimal relative variability and suggest high measurement consistency (Atkinson & Nevill 1998). While data on the accepted threshold for reliable physiological measurements during pregnancy is limited, a CV value of less than 10% is generally considered acceptable (Atkinson & Nevill 1998). The CVs observed in this study fall well within this reliable threshold of less than 10%, highlighting the reproducibility of these blood pressure measurements (Atkinson & Nevill 1998)

Intra- and inter-observer reliability were both excellent. ICC values for intra-observer measurements ranged from 0.97 to 0.99, while inter-observer ICCs ranged from 0.94 to 0.99 for pDBP and 0.96 to 0.99 for pSBP, exceeding the conventional threshold of 0.90 indicative of excellent reliability (Cao et al. 2015; Koo & Li 2016). High ICC values suggest that most variability in measurements is due to true differences in participants' blood pressure rather than observer-related differences. SEM values were similarly low, ranging from 0.08 to 0.54 mmHg, reflecting minimal observer-induced error and confirming the precision of the device (Weir 2005). MDC values of 0.2–0.3 mmHg for pSBP and 0.2–0.4 mmHg for pDBP further demonstrate the sensitivity of the device in detecting clinically meaningful changes beyond measurement error (de Vet et al. 2006).

Overall, the findings of this study suggest that the Microlife WatchBP Office Central device is reliable, indicating that any significant changes in blood pressure are likely to represent genuine physiological fluctuations rather than inconsistencies related to the device or process. Consistent and repeatable blood pressure measurement is particularly crucial in pregnancy, where small fluctuations can have major clinical implications (Whelton et al. 2018). The strong reliability demonstrated here supports the device's use in both clinical management and longitudinal research involving pregnant populations. It makes it suitable for measuring blood pressure in this thesis without concern for type I or type II errors.

Our findings are consistent with existing literature regarding the reliability of blood pressure devices in clinical settings, demonstrating that many devices meet reliability standards when specifically tested in pregnant women (Bello et al. 2018; Murthy et al. 2023). A systematic review conducted by Bello et al. (2018) highlights the effectiveness of many devices in this context, noting that a considerable number met validation criteria without breaching any established protocols (Bello et al. 2018). However, the review also identified some major protocol violations in some studies, such as the inclusion of insufficient numbers of pregnant women, which resulted in inadequate comparisons

between the devices and recognized reference standards. The analysis further found that the most common minor violations were related to discrepancies in arm circumference measurements and the ranges for systolic and diastolic blood pressure. Notably, our study successfully adhered to the recommended sample size and ensured proper categorization of arm circumferences, addressing potential limitations identified in the aforementioned systematic review (Bello et al. 2018; Kollias et al. 2018).

This study also indicated that women with HDP had significantly higher mean central and peripheral systolic blood pressure when measured using the Microlife WatchBP Office Central, compared to normotensive controls. These findings align with previous research demonstrating elevated CBP in women with HDP. For example, a study by Namugowa et al. (2017) involving 85 women with preeclampsia and 112 normotensive pregnant women found increased maternal central arterial stiffness in those with preeclampsia. Similarly, Avni et al. (2010) observed significantly higher peripheral and central systolic and diastolic blood pressures across three hypertensive groups compared to normal pregnancies (Avni et al. 2010).

Although the Microlife WatchBP Central Office has been validated for use in adults and children aged 3 to 12 years, its reliability during pregnancy had not been established (Kollias et al. 2018). This study fills that gap, confirming the reliability of the Microlife WatchBP Central Office in a pregnant population and significantly enhancing the existing evidence of its clinical effectiveness. Limitations include the exclusive focus on a Black African population, which may not fully represent other racial groups. However, given the similar physiological manifestations of pregnancy and preeclampsia across races, these findings are likely generalizable to broader populations.

Conclusion

This study demonstrates that the Microlife WatchBP Office Central device provides reliable, precise, and reproducible measurements of systolic and diastolic blood pressure in

pregnant women, including those with hypertensive disorders. Low coefficients of variation, high intraclass correlation coefficients, and minimal standard errors of measurement and minimum detectable changes confirm the device's consistency across observers and participant groups. These findings indicate that the device can reliably detect physiologically meaningful changes, supporting its use in routine clinical monitoring during pregnancy.

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CHAPTER 4

The correlation of peripheral blood pressure with central blood pressure and estimation of central blood pressure thresholds for diagnosis of hypertension during pregnancy

Credit author statement

Xolani B Mbongozi contributed to the conceptualization, data curation, formal analysis, investigation, methodology, and was responsible for writing the original draft and revising the manuscript. Stuart DR Galloway provided supervision and contributed to the review of the manuscript. Angus Hunter also offered supervision and participated in the review process. Charles B Businge engaged in supervision and review. Mirabel Nanjoh was involved in the formal analysis. Geoffrey AB Buga was responsible for supervision and reviewing of the manuscript.

Abstract

Objective: The main objective of the study was to evaluate the correlation and comparative use of peripheral blood pressure and central blood pressure (CBP) in identifying hypertension among pregnant women.

Methods: A cross-sectional study was conducted at Nelson Mandela Academic Hospital from December 2022 to April 2024, involving 270 inpatients diagnosed with HDP and 270 normotensive controls in their second and third trimesters. Blood pressure measurements were obtained using the Microlife WatchBP Office Central, both at enrolment and within seven days postpartum. A linear regression equation and a receiver operating characteristic curve (ROC) analysis were used to determine the thresholds for normal, mild, and severe CBP.

Results: The ROC revealed that a central systolic blood pressure (cSBP) of 116 mm Hg or higher has a sensitivity of 78.5% and a specificity of 50.3% for diagnosing hypertension during pregnancy. Considering a normal peripheral diastolic pressure of less than 90 mm Hg, the upper limit of central diastolic blood pressure (cDBP) in normotensive controls was calculated to be 78 mm Hg. A significant positive correlation was found between pSBP and cSBP among normotensive and hypertensive women ($P < 0.05$).

The median pSBP among eclamptic patients with mild peripheral hypertension was 138.0 mmHg (IQR: 133.0-148.0) while the median cSBP level in the same group was 145.0 mmHg (IQR: 140.0-150.0) mmHg.

The overall median cSBP among women with eclampsia ($n=102$) was 133.0 mmHg (IQR: 120.0-143.0), and the median cDBP was 73.0 mmHg (IQR: 60.0-83.0), and these were significantly higher ($p < 0.0001$) than the median cSBP of 128.0 mmHg (IQR: 114.0-139) and cDBP of 71.0 mmHg (IQR: 61.0-81.0) among preeclamptic women.

Conclusion: This study established the threshold values for central hypertension as 116/78 mmHg, with severe central hypertension defined as 148/95 mmHg or more. It reinforces the positive correlation between peripheral and CBP in both normotensive and hypertensive populations. CBP may serve as a better parameter for evaluating hypertension, especially in eclampsia. Further research is warranted to confirm these findings and to explore their clinical implications.

Keywords: Pregnant Women, Eclampsia, Preeclampsia, Hypertensive Disorders of Pregnancy, Arterial stiffness, central and peripheral hypertension

4.1 Introduction

Elevated brachial blood pressure has traditionally been the main indicator for diagnosing hypertension, but with the increased availability of non-invasive central blood pressure (CBP) measuring devices, there is growing interest in using CBP for managing hypertension in non-pregnant and pregnant individuals.

The role of brachial blood pressure in prediction of future cardiovascular structural damage, morbidity and mortality among non-pregnant adult population is well-established in high-income countries (Lewington et al. 2002), as well as in middle-income countries such as China and Mexico (Lacey et al. 2018; Tapia-Conyer et al. 2020). Controlling brachial blood pressure can reduce the risk of cardiovascular death (Martinez et al. 2022). However, peripheral hypertension does not necessarily correlate with maternal and perinatal outcomes, except for the increased risk of intracranial haemorrhage when there is severe peripheral hypertension (Sibai & Stella 2009). Numerous studies suggest that CBP is superior to peripheral blood pressure (PBP) in predicting cardiovascular disease among non-pregnant patients (Roman et al. 2007; Protogerou et al. 2009; Wang et al. 2009; Alsomali et al. 2024). The superiority of CBP is likely due to central pressures exhibiting lower variability and more accurately reflecting the tension levels on major target organs such as the heart, brain, and kidneys (McEniery et al. 2005). CBP is defined as blood pressure readings taken from the aorta or common carotid arteries, primarily influenced by increased arterial stiffness and wave reflection (Cheng et al. 2019). It represents the pressure against which the heart must pump to ensure blood flow throughout the body. Evidence indicates that preeclampsia (PE) is associated with increased CBP, pulse wave velocity, and arterial stiffness (Torrado et al. 2015; Meeme et al. 2017; Namugowa et al. 2017). It is known that the cerebrovascular complications of PE and eclampsia can occur in the presence of mild elevations of PBP, and even in the absence of proteinuria. Since the blood flow to the brain is controlled by the central aortic blood pressure, it is possible that under conditions when there is only mild elevation of the brachial blood pressure, the CBP may be much higher, thus

accounting for the vasogenic oedema typical of eclampsia, justifying the need to know how the CBP behaves in patients with HDP and eclampsia.

To evaluate this hypothesis, it is essential to clearly define what constitutes mild and severe central hypertension. Current literature presents conflicting findings regarding the definition of central hypertension (Takase et al 2013; Hao et al. 2016). Notably, Cheng et al (2018) have proposed a threshold CBP of 130/90 mmHg, which generally serves as a benchmark for central hypertension in non-pregnant women (Cheng et al. 2013; Cheng et al. 2019). However, given the physiological changes that occur during pregnancy, it would be biased to apply findings from the non-pregnant population, especially those involving men (Mahendru et al. 2014). During pregnancy, physiological changes generally result in lower CBP readings compared to those in non-pregnant women and men (Macedo et al. 2008). Therefore, it is necessary to establish the CBP threshold for diagnosing central hypertension in pregnant population.

4.2 Objectives

The primary objective of this study was to evaluate the correlation and comparative use of peripheral blood pressure and central blood pressure in identifying hypertension among pregnant women. The secondary objective was to determine the threshold values for central systolic blood pressure and central diastolic blood pressure for diagnosing mild and severe central hypertension in pregnancy.

4.3 Materials and Methods

This was a cross-sectional study conducted between December 2022 and April 2024. We prospectively studied 270 inpatients diagnosed with hypertensive disorders of pregnancy (HDP) and 270 inpatient normotensive controls who were in their second and third trimesters of pregnancy. This study was conducted at Nelson Mandela Academic Hospital, South Africa, in keeping with the principles laid down in the Helsinki Declaration (World medical association 2025). Walter Sisulu University and the Nelson Mandela Academic Hospital board approved this study (ethics reference number 035/2022), and informed consent was obtained from each participant before data collection.

The definition of hypertension and of hypertensive disorders of pregnancy was based on the International Society for the Study of Hypertension in Pregnancy (Magee et al. 2022). Mild peripheral hypertension was defined as a pSBP of 110-159 mmHg and/or a pDBP of 90-109 mmHg. Severe peripheral hypertension was defined as a pSBP of 160 mmHg or higher and/or a pDBP of 110 mmHg or higher. The inclusion criteria for hypertensive patients were current hypertensive disease in pregnancy with a gestation period of ≥ 20 weeks. For controls, the inclusion criteria were a healthy normotensive singleton pregnancy in labour, those admitted for a repeat elective caesarean section at term, or women without hypertension presenting with particular conditions such as placenta previa, preterm premature rupture of membranes, or preterm labour. Participants were excluded if they were under 20 weeks pregnant, or if they opted out of participating. Additionally, individuals with diabetes mellitus, cardiac disease, chronic renal disease, antiphospholipid syndrome, or other autoimmune diseases were also excluded in the study.

Data on the presence and type of hypertensive disorders of pregnancy were collected from patient interviews and medical records using a standard data collection sheet. At enrolment and within seven days after delivery, brachial and central systolic and diastolic blood pressures were measured using the Microlife WatchBP Office Central. Participants who were initially normotensive but later developed elevated blood pressure were reclassified as hypertensive, while those with gestational hypertension who later exhibited features of PE were reclassified as having PE. Before using the Microlife WatchBP Office central, the correct size of cuff was chosen and placed over the left or right upper arm so that the artery mark arrow points towards the lower arm. The cuff was wrapped around the arm, making sure that the lower edge of the cuff was approximately 2 cm above the elbow. The WatchBP Office Central device automatically measured both brachial and central blood pressure, displaying the results on the screen once the measurement process was complete. It is important to note that while the validity and reliability of the Microlife WatchBP Office Central have been established in the general population, its peripheral blood pressure measurements had not been assessed for reliability in pregnant women (Cheng et al. 2013). To address this deficiency, a pilot study was conducted, involving three distinct groups of participants: 15

normotensive pregnant women, 15 women diagnosed with gestational hypertension, and 15 women with preeclampsia. Blood pressure measurements were taken by two trained observers using the Microlife WatchBP Office Central device. Reliability was evaluated using coefficient of variation, intraclass correlation coefficient, standard error of measurement, and minimum detectable change.

The results of the reliability assessment demonstrated that the Microlife WatchBP Office Central provided reliable and reproducible blood pressure measurements in pregnant women, including those with hypertensive disorders. Subsequently, the Microlife WatchBP Office Central was used to simultaneously measure both brachial blood pressure and central blood pressure in each participant.

Statistical analysis

Data were checked for completeness and consistency before being captured using the IBM SPSS STATISTICS software package version 31 for Windows (IBM Inc., Chicago IL, USA). Two approaches were used to try to establish the upper thresholds for normal and abnormal CBP in order to determine what constitutes central hypertension. The first approach used a linear regression equation for calculating the cSBP and cDBP from the pSBP and cDBP of normotensive controls, and a p-value of <0.05 was taken as significant. The second approach used the receiver operating curve analysis for calculating the upper threshold of normal cSBP and cDBP, together with sensitivity and specificity. The Youden's J index, sensitivity, and specificity were calculated for each blood pressure reading. Cut-off points were determined based on the index, sensitivity, specificity and clinical relevance. The outcome variable was HDP. The lower of these thresholds from these two approaches was then chosen to represent the threshold of normal and abnormal CBP.

For the rest of the study, blood pressure readings were interpreted using medians and percentiles (p25, p75) due to the skewed nature of the data. The Kruskal-Wallis H test and

the Mann-Whitney U test were employed to assess the degree of association between the continuous variables. The Wilcoxon signed-rank test was applied to compare dependent variables. A p-value of less than 0.05 was considered statistically significant.

4.4 Results

General description and socio-demographic characteristics of the sample population

A total of 550 pregnant women were initially recruited for the study. However, 10 patients were excluded due to comorbidities like diabetes, chronic renal failure, and cardiac disease (**Figure 4.1**). Ultimately, 540 pregnant women were enrolled in the study, with 270 diagnosed with HDP and 270 who were normotensive controls. Of the 270 women with HDP, 143 (53%; 95% CI: 47% - 58.9%) had preeclampsia (PE), 102 (37.8%; 95% CI: 32.1% - 43.7%) had eclampsia, 14 (5.2%; 95% CI: 3.0% - 8.3%) had chronic hypertension, and 11 (4.1%; 95% CI: 2.2% - 6.9%) had gestational hypertension. Notably, two of the eleven patients with gestational hypertension initially had normal blood pressure and were classified as controls at the time of recruitment, but subsequently developed hypertension, resulting in their reclassification. Additionally, four of the 143 preeclamptic patients initially presented with gestational hypertension but later exhibited significant proteinuria, resulting in their reclassification as preeclampsia. Of the 143 women with PE, 75 (52.4%; 95% CI: 44.3% - 60.5%) had PE with severe features (this number excludes women with eclampsia who form their own group), and 68 (47.6%; 95% CI: 39.5% - 55.7%) had PE without severe features.

The non-hypertensive controls had a median age of 28 (IQR: 24.0-33.0) years, which was significantly older than the hypertensive cases, whose median age was 25 (IQR: 20.0 -32.0) years ($p<0.0001$) (**Table 4.1**). Most participants (63.1%, $n=341$) were aged between 20 and 34 years, while a smaller group (17.2%, $n=93$) was under 20 years. Almost all participants (99.4%, $n=537$) were of African descent, with the remainder being mixed race (0.6%, $n=3$).

In terms of marital status, over three-quarters (77.2%) were single, and slightly more than a quarter (22.6%, n=122) were married.

Most participants (93.7%, n=434) attended antenatal clinics, while 34 (6.3%) did not. Statistically, antenatal clinic attendance was similar between the hypertensive and non-hypertensive groups ($p>0.05$). The median gestational age at enrolment in the study was 36 (IQR: 33.0-38.0) weeks, with the non-hypertensive controls having a significantly higher median gestational age of 38 (IQR 36.0-39.0) weeks compared to the hypertensive cases at 34 weeks (IQR 31.0-37.0; $p<0.0001$).

A significant majority of participants (86.7%, n=468) delivered via caesarean section, while the remaining 13.3% (n=72) had vaginal births. No significant differences in delivery methods were found between the two groups.

In terms of body weight classification, nearly one-third of the women (32.4%, n=175; 95% CI=28.6%-36.4%) were classified as obese, while 12.4% (n=67; 95% CI=9.8%-15.4%) were severely obese, and 0.6% (n=3; 95% CI=0.2%-1.5%) were underweight.

Overall, 28.3% (n=153; 95% CI=24.7%-32.2%) of the women in the study were HIV-positive, while the remainder tested negative. There was no significant difference in HIV prevalence between women with HDP and the normotensive controls ($p>0.05$). Most of the HIV-positive women had viral loads below detectable limits, with only 12.4% (n=19; 95% CI=7.9%-12.4%) not achieving viral suppression. Moreover, no significant differences were observed between HIV-positive women with HDP and those who were HIV-positive but normotensive regarding viral suppression ($p>0.05$).

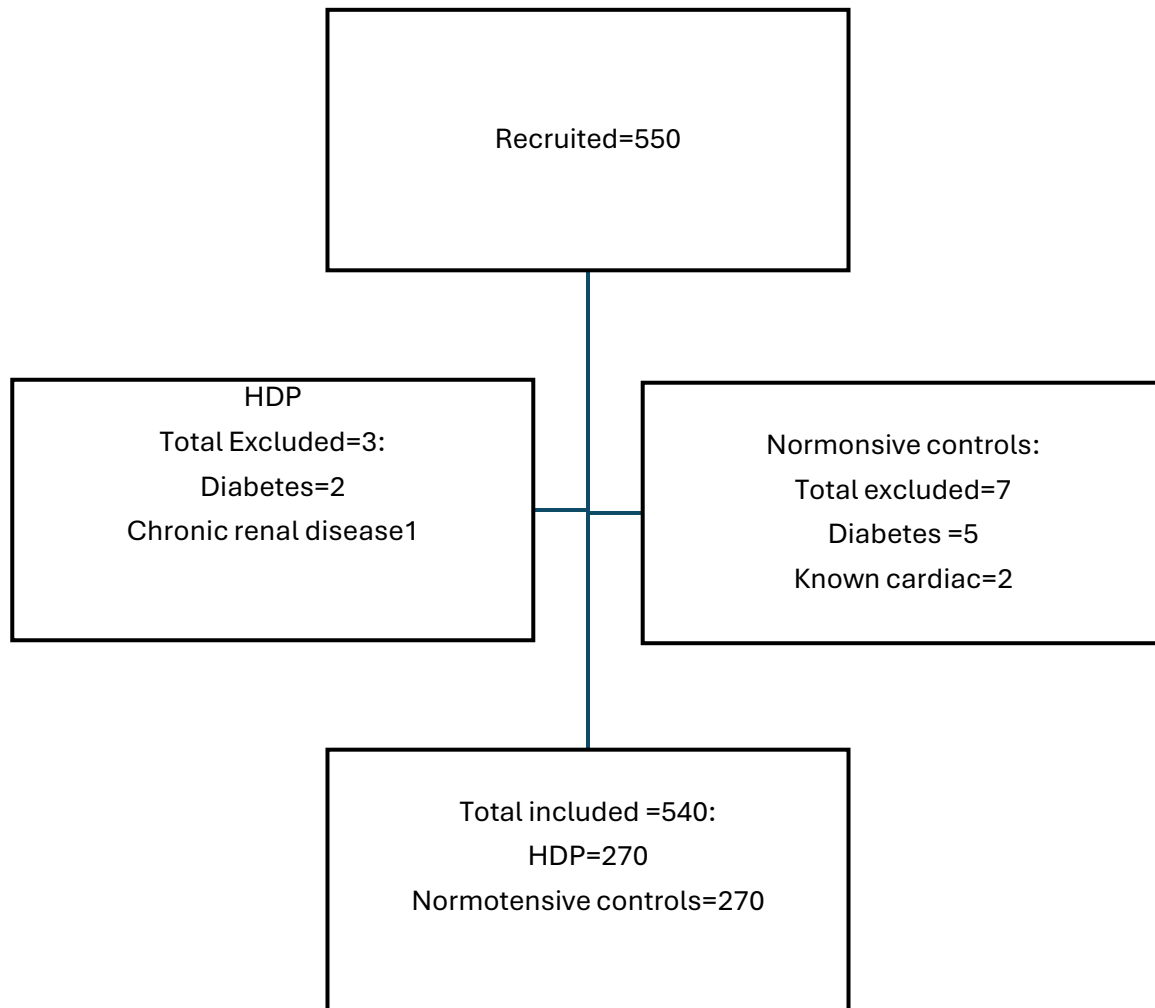


Figure 4. 1: Flowchart of participant inclusion

Table 4. 1: General characteristics of hypertensive cases and normotensive controls in the main study

Characteristics	Hypertensive cases; n= 270	Normotensive controls; n=270	Total	
	Median (IQR)	Median (IQR)	Median (IQR)	Sig.**
Age (years)	25 (20.0-32.0)	28 (24.0-33.0)	27 (21.0-33.0)	<0.0001
Body mass index (kg/m ²)	28.5 (23.9-34.3)	29.5 (25.1-35.5)	29 (24.7-34.9)	0.071
Gestational age at recruitment	34 (31.0-37.0)	38 (36.0-39.0)	36 (33.0-38.0)	<0.0001
	Number (Percentage)	Number (Percentage)	Number (Percentage)	Pearson X ² Sig.
Age group (years)				
<20 years	64 (23.7)	29 (10.7)	93 (17.2)	<0.0001
20-34 years	157 (58.1)	184 (68.1)	341 (63.1)	
≥35 years	49 (18.1)	57 (21.1)	106 (19.6)	
Ethnicity				
Black African	269 (99.6)	268 (99.2)	537 (99.4)	0.624*
Mixed race	1 (0.4)	2 (0.7)	3 (0.6)	
Marital status				
Single	210 (77.8)	207 (76.7)	417 (77.2)	0.837*
Married	60 (22.2)	62 (23.0)	122 (22.6)	
Divorced	0 (0.0)	1 (0.4)	1 (0.2)	
Level of education				
Tertiary	35 (13.0)	46 (17.0)	81 (15.0)	0.194*
Secondary	207 (76.7)	189 (70.0)	396 (73.3)	
Primary	27 (10.0)	35 (13.0)	62 (11.5)	
No formal education	1 (0.4)	0 (0.0)	1 (0.2)	
Booking status				
Booked	248 (91.9)	258 (95.6)	506 (93.7)	0.111
Not booked	22 (8.1)	12 (4.4)	34 (6.3)	
Mode of delivery				
Caesarean section	233 (86.3)	235 (87.0)	468 (86.7)	0.800
Vaginal	37 (13.7)	35 (13.0)	72 (13.3)	
Underweight (BMI <18.5)	2 (0.7)	1 (0.4)	3 (0.6)	0.196*
Normal weight (BMI 18.5-24.9)	81 (30.0)	59 (21.9)	140 (25.9)	
Overweight (BMI ≥25.0-29.9)	74 (27.4)	81 (30.0)	155 (28.7)	

Obese (BMI ≥30.0-39.9)	79 (29.3)	96 (35.6)	175 (32.4)	
Severely obese (BMI ≥40.0)	34 (12.6)	33 (12.2)	67 (12.4)	
HIV status				
Positive	66 (24.4)	87 (32.2)	153 (28.3)	0.056
Negative	204 (75.6)	183 (67.8)	387 (71.7)	
Viral suppression				
Unsuppressed (>1000 cp/mL)	10 (15.2)	9 (10.3)	19 (12.4)	0.609*
Suppressed (<1000 cp/mL)	0 (0.0)	1 (1.1)	1 (0.7)	
Less than detectable limit (<50 cp/mL)	56 (84.8)	77 (88.5)	133 (86.9)	

BMI = body mass index (kg/m²); cp/mL = copies/mL; *Fisher's Exact p-value; ** Mann-Whitney U p-value

Establishment of cSBP and cDBP thresholds for diagnosis of central hypertension

To establish the upper thresholds for normal and abnormal CBP a linear regression equation and the receiver operating curve analysis were used. The lower of these thresholds was then chosen to represent the threshold of normal and abnormal CBP. Consequently, the upper threshold of normal cSBP was found to be <116 mmHg, and that of the normal cDBP was <78 mmHg (**Table 4.2 and Figure 4.2**). CBPs above these thresholds signified central hypertension.

Table 4. 2: Sensitivity and specificity of cSBP cut-offs for prediction of central hypertension in women with HDP

Variable	Positive if Greater Than or Equal To	Sensitivity	Specificity
CSBP	59	100.0%	0.00%
	71	100.0%	0.37%
	79	100.0%	0.74%
	81	100.0%	1.11%
	84	100.0%	1.48%
	88	100.0%	1.85%
	89	100.0%	2.22%
	90	100.0%	3.33%
	91	100.0%	4.07%
	92	100.0%	4.81%

93	99.26%	5.56%
94	98.52%	6.30%
95	98.52%	7.04%
96	98.52%	7.41%
97	97.41%	8.89%
98	97.41%	10.00%
99	97.04%	11.11%
100	95.93%	12.96%
101	95.56%	13.70%
102	94.81%	15.93%
103	93.70%	16.67%
104	93.70%	18.52%
105	92.96%	21.48%
106	90.74%	24.07%
107	90.00%	25.93%
108	89.63%	28.15%
109	88.89%	31.48%
110	87.04%	32.96%
111	85.93%	35.19%
112	83.70%	37.41%
113	82.22%	40.74%
114	81.48%	43.33%
115	79.63%	46.67%
116	78.52%	50.37%
117	75.93%	54.07%
118	74.44%	55.19%
119	74.07%	58.15%
120	71.48%	60.74%
121	69.26%	62.96%
122	66.67%	64.81%
123	64.07%	67.78%
124	63.33%	69.63%
125	60.74%	73.70%
126	59.63%	77.04%
127	57.41%	78.89%
128	54.81%	80.00%
129	51.11%	84.07%
130	48.89%	86.67%
131	47.04%	87.78%
132	44.44%	90.74%
133	42.22%	92.96%
134	38.89%	93.33%
135	35.19%	95.19%
136	32.59%	96.30%
137	31.11%	96.67%
138	30.37%	97.41%

139	28.15%	97.78%
140	25.93%	98.52%
141	23.33%	98.52%
142	21.85%	99.26%
143	21.11%	99.26%
144	19.63%	99.26%
145	18.89%	99.63%
146	17.41%	99.63%
147	15.56%	99.63%
148	13.70%	99.63%
149	11.48%	99.63%
150	11.11%	99.63%
151	9.63%	99.63%
152	8.15%	99.63%
153	8.15%	100.00%
154	7.78%	100.00%
155	6.30%	100.00%
156	4.81%	100.00%
157	4.44%	100.00%
159	4.07%	100.00%
161	3.70%	100.00%
164	2.96%	100.00%
167	2.22%	100.00%
170	1.85%	100.00%
174	1.48%	100.00%
180	1.11%	100.00%
185	0.74%	100.00%
193	0.37%	100.00%
193	0.00%	100.00%

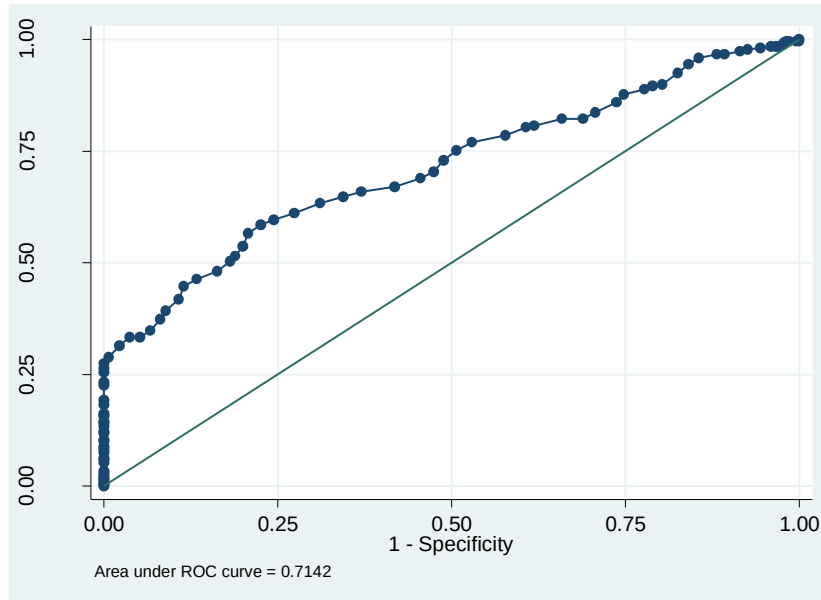


Figure 4. 2: ROC for cSBP cut-off for prediction of central hypertension in women with HDP if 116 mmHg is chosen

Receiver operating characteristics analysis for defining cSBP thresholds for diagnosis of central hypertension during pregnancy

To predict the diagnosis of central hypertension during pregnancy, the ROC analysis results indicate that a cSBP of 116 mm Hg or higher has a sensitivity of 78.5% and a specificity of 50.3%. The cSBP values utilized as predictive variables for the ROC curve were derived exclusively from the HDP group. This model demonstrated a moderate discriminatory ability, with an area under the curve (AUC) of 0.7384 (Table 4.2 and Figure 4.2).

Linear regression equation for defining the cSBP and cDBP threshold from peripheral blood pressure

Based on a normal pSBP of <140 mmHg and a diastolic pressure of <90 mmHg, the upper limit of cSBP in normotensive controls was calculated to be 130 mmHg, while the upper limit of cDBP was calculated to be 78 mmHg (see **Tables 4.3 and 4.4**) (Mark A. Brown et al. 2018a).

Table 4. 3: Establishment of cSBP threshold in normotensives

		Unstandardized Coefficients		Standardized Coefficients		
Normotensive controls (N=270)		B	Std. Error	Beta	T	p value
1	(Constant)	47.505	6.013		7.901	.000
	pSBP (mmHg)	.592	.052	.568	11.290	.000

a. All assumptions for linear regression were checked, and the values in the model met all of the assumptions. Using the simple regression formula, where, predicted cSBP = a + bx (with 'a' representing the constant, 'b' as the unstandardized coefficient for pSBP, and 'x' as any pSBP reading), if a pSBP of 139 mm Hg is chosen as a reference point for normal systolic pressure, then the upper limit of cSBP in normotensive controls = 47.505 + 0.592 (139) = 130 mmHg.

Table 4. 4: Establishment of cDBP threshold in normotensives

		Unstandardized Coefficients		Standardized Coefficients		
Normotensive (N=270)		B	Std. Error	Beta	t	Sig.
1	(Constant)	19.006	2.817		6.748	.000
	pDBP (mmHg)	.658	.043	.681	15.204	.000

a. Dependent Variable: Peripheral Diastolic Blood Pressure (mmHg). If the reference point of the pDBP in normotensive controls is taken as 89 mmHg (less than 90 mmHg), then the upper limit of cDBP in normotensive controls = 19.006+ 0.658 (89) = 77.6 or 78mm Hg

Establishment of thresholds for severe central hypertension

Linear regression equation was used to calculate the thresholds for severe central hypertension from the thresholds of severe PBP, defined as a pSBP of ≥ 160 mmHg, and/or pDBP of ≥ 110 mmHg among women with HDP who were identified to have severe peripheral hypertension (Mark A. Brown et al. 2018a). The thresholds for severe central hypertension were found to be a cSBP of ≥ 148 mmHg and/or a cDBP of ≥ 95 mmHg (See Table 4.5 and Table 4.6).

Table 4. 5: Establishment of cSBP thresholds for diagnosis of severe central hypertension based on pSBP of ≥ 160 mmHg in women with severe peripheral hypertension

		Unstandardized Coefficients		Standardized Coefficients		
Severe peripheral hypertension		B	Std. Error	Beta	t	p value
1	(Constant)	36.961	45.232		.817	.421
	pSBP (mmHg)	.696	.271	.449	2.562	.017

a. Dependent Variable: Central Systolic Blood Pressure (mmHg). If the threshold for severe pSBP is taken as 160 mmHg, then the threshold for severe cSBP = $36.961 + 0.696 (160) = 148.321$ or 148 mmHg

Table 4.6: Defining cDBP cut-off for severe central hypertension based on pDBP of ≥ 110 mmHg in women with severe peripheral hypertension

		Unstandardized Coefficients		Standardized Coefficients		
Severe peripheral hypertension		B	Std. Error	Beta	t	p value
1	(Constant)	6.512	13.149		.495	.625
	pDBP (mmHg)	.806	.126	.783	6.420	.000

a. Dependent Variable: Central Diastolic Blood Pressure (mmHg); If the threshold for severe pDBP is taken as ≥ 110 mmHg, then the threshold for severe cDBP = $6.512 + 0.806 (110) = 95.172$ or 95 mmHg

Correlation of median pSBP, cSBP, pDBP, and cDBP as measured using Microlife WatchBP Office Central among women with HDP and normotensive controls

Among the 270 normotensive controls, the median pSBP was 114.0 (IQR: 104.0 - 124.0) mmHg, and the median cSBP was 115.0 (IQR: 106.0 - 125.0) mmHg (see **Figures 4.3 and 4.4**). There was a strong positive relationship between the two measurements (Spearman rank correlation coefficient = 0.583; $p < 0.0001$) as shown in **Table 4.7**. The linear regression analysis revealed a positive correlation between pSBP and cSBP, with changes in pSBP being associated with a shift in the cSBP ($B = 0.592$; $p < 0.0001$). The difference between median pSBP and cSBP was 1.0 mmHg, but this was not statistically significant (Wilcoxon Signed Rank $p = 0.122$).

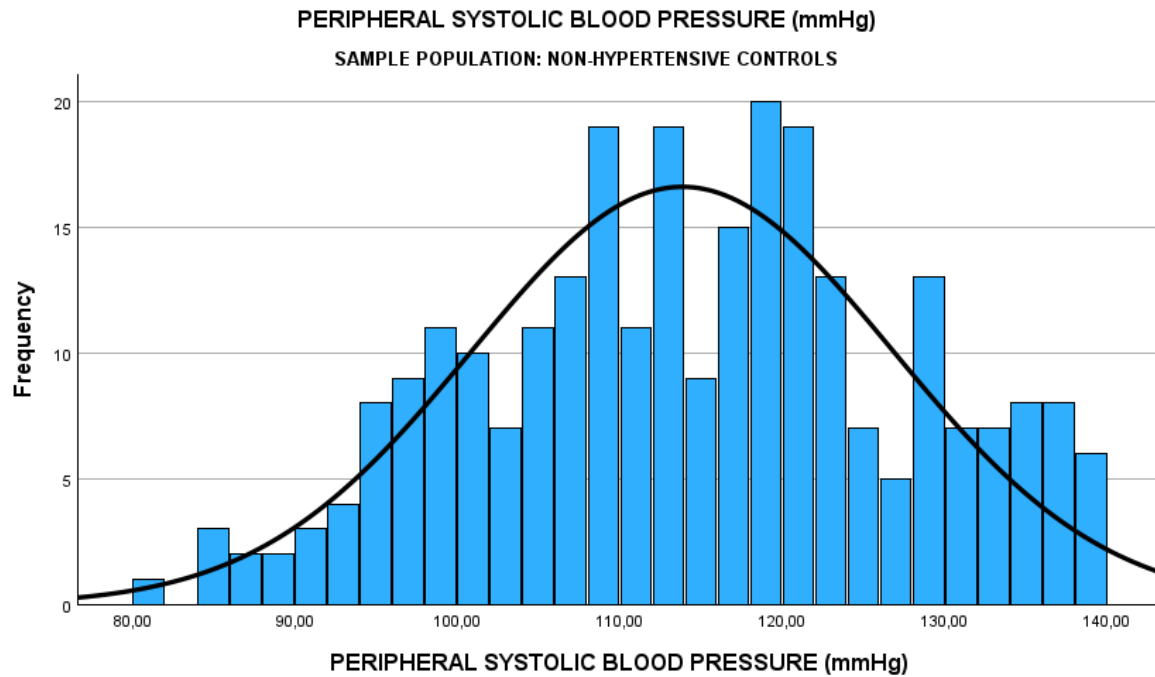


Figure 4.3. Median pSBP among normotensive pregnant women

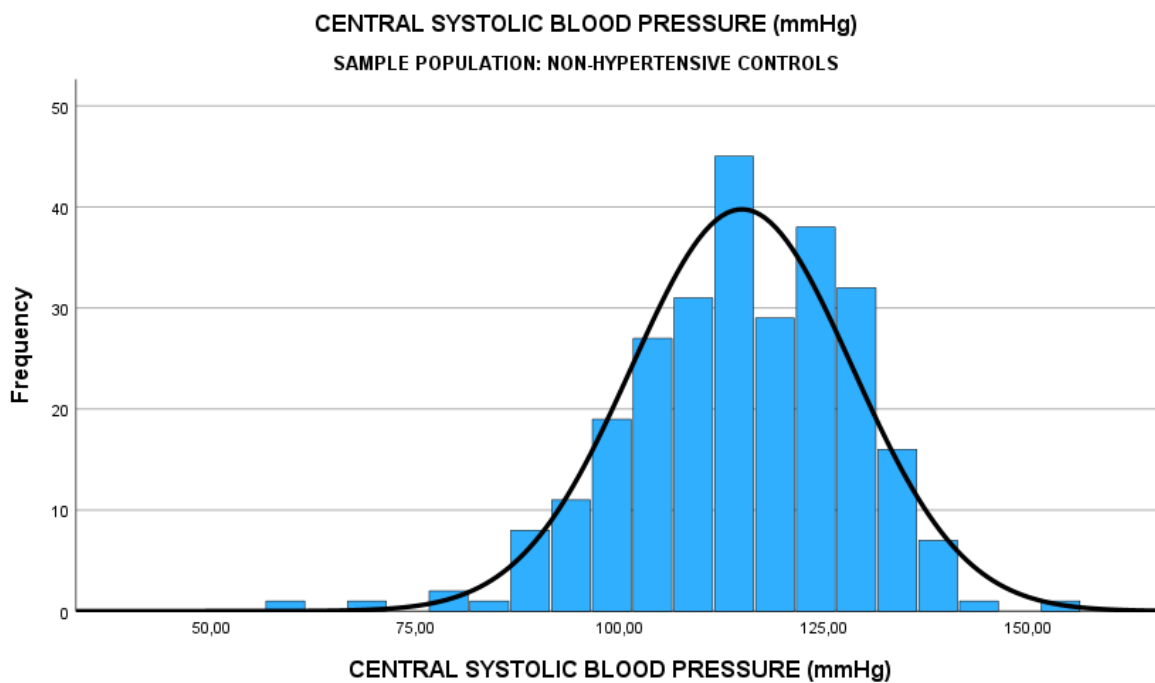


Figure 4. 4. Median cSBP among normotensive pregnant women

Table 4.7: Comparison of median pSBP and pDBP with median cSBP and cDBP among women with normal and mild peripheral hypertension as measured using Microlife WatchBP Office Central.

Hypertensive groups	cSBP median (IQR)	pSBP median (IQR)	Spearman rank	P value	cDBP median (IQR)	pDBP median (IQR)	Spearman rank	P value
Normotensive (n=270)	115.0 (106.0;125.0)	114.0 (104.0;124.0)	0.583	<0.0001	64.0 (55.0;73.0)	61.5 (52.0;69.0)	0.669	<0.0001
Mild hypertensive (n=67)	139.0 (132.0;147.0)	144.0(138.0;148.0)	0.445	<0.0001	82.0 (77.0;89.0)	91.0 (86.0;96.0) mmHg	0.596	<0.0001

Normal central blood pressure= cSBP of <116 and/or cDBP <78; mild central hypertension= cSBP of 116-147 and/or cDBP of 78-94; severe central hypertension= cSBP of ≥148 and/or cDBP of ≥95 mmHg; Mild peripheral hypertension= pSBP of 140-159 and/or cDBP of 90-109

Additionally, the median cSBP [110 (IQR: 101.0-120.0) mmHg] was less than the median pSBP [120.0 (IQR: 112.0 - 129.0) mmHg] in 119 participants (44%), the median cSBP [119.5 (111.0-128.0) mmHg] was greater than the median pSBP [109.0 (100.0-118.0) mmHg] in 146 participants (54%), and in 5 participants (1.9%), they were equal. The observed difference was not statistically significant (z based on positive ranks = -1.546; Wilcoxon Signed Rank p=0.122).

Among the 270 normotensive controls, median cDBP was 64.0 (IQR: 55.0 - 73.0) mmHg, and the median pDBP was 61.5 (IQR: 52.0- 69.0) mmHg. There was a strong positive correlation between the two measurements (Spearman rank correlation of 0.669, p<0.0001) as shown in Table 8. Linear regression analysis also revealed that there was a positive correlation between cDBP and pDBP, with changes in pDBP being significantly associated with a shift in the cDBP (B= 0.658; p<0.0001). The difference between median pDBP and cDBP was 2.5 mmHg, which was statistically significant (Wilcoxon Signed Rank p <0.0001).

Additionally, cDBP [58.0 (50.0-66.0) mmHg] was less than pDBP [68.0 (60.0-70.0) mmHg] in 159/270 participants (59%), cDBP [64.0 (IQR: 57.0-73.0) mmHg] was greater than pDBP [57.0 (IQR: 49.0-65.0) mmHg] in 98 participants (36.3%) and were equal in only 13 participants (4.8%). The observed difference was statistically significant (z based on negative ranks = -4.342; Wilcoxon Signed Rank $p < 0.0001$).

Comparison of median pSBP and median pDBP with cSBP and cDBP among women with mild peripheral hypertension as measured using Microlife WatchBP Office Central.

Among 95 women with mild peripheral hypertension the median pSBP was 144.0(138.0-148.0) mmHg while the median cSBP was 139.0 (132.0-147.0) mmHg as shown in **Table 4.7**. There was a strong positive relationship between the two measurements (Spearman rank $r = 0.445$; $p < 0.0001$). Linear regression analysis revealed a strong positive correlation between pSBP and cSBP, with changes in the pSBP being significantly associated with a shift in the cSBP ($B = 0.631$; $p < 0.0001$). The difference between the median pSBP and median cSBP was 5.0 mmHg and this was statistically significant (Wilcoxon Signed Rank $p < 0.0001$).

Additionally, among the same 95 women with mild peripheral hypertension, the median cSBP was less than the median pSBP in 69 participants, and the median cSBP was greater than the median pSBP in 24 participants, while the two were equal in 2 participants. The analysis using the Wilcoxon Signed Rank test revealed a statistically significant difference ($p < 0.0001$).

Furthermore, among the same group of women with mild peripheral hypertension, the median pDBP was 91.0 (86.0-96.0) mmHg, while the median cDBP was 82.0 (77.0-89.0) mmHg. There was a strong positive correlation between the two measurements (Spearman rank $r = 0.596$; $p < 0.0001$). Linear regression analysis revealed a strongly positive correlation between the pDBP and the cDBP, cDBP, and changes in pDBP were associated

with a shift in the cDBP ($B = 0.661$; $p < 0.0001$). The difference between the median pDBP and cDBP was 9.0 mmHg, which was statistically significant ($p < 0.0001$).

Additionally, among these women with mild peripheral hypertension, the median cDBP was less than the median pDBP in 81 participants, while in 14 participants, the median cDBP was greater than the median pDBP. The observed differences were statistically significant ($p < 0.0001$). Among the 14 participants with a higher median cDBP than the pDBP, 4 had eclampsia. The median cDBP for the 4 eclamptic patients was 108 mmHg, while their median pDBP was 93 mmHg. The difference between median cDBP and pDBP among the 4 participants was 15 mmHg and it was statistically significant (z based on positive ranks = -6.5; Wilcoxon Signed Rank $p < 0.0001$).

Twenty seven of the 102 eclamptic patients had mild peripheral hypertension, while the rest had severe peripheral hypertension. The median pSBP among eclamptic patients with mild peripheral hypertension was 138.0 mmHg (IQR: 133.0-148.0) while the cSBP level in the same group was 145.0 mmHg (IQR: 140.0-150.0) mmHg.

The overall median cSBP among women with eclampsia ($n = 102$) was 133.0 mmHg (IQR 120.0-143.0), and the median cDBP was 73.0 mmHg (IQR: 60.0-83.0), and these were significantly higher ($p < 0.0001$) than the median cSBP of 128.0 mmHg (IQR: 114.0-139) and cDBP of 71.0 mmHg (IQR: 61.0-81.0) among preeclamptic women with or without severe features, and much higher than the median cSBP of 115 mmHg (IQR: 106.0-125.0) and cDBP of 61.5 mmHg (IQR: 52.0-69.0) among normotensive controls (**Table 4.8**).

Table 4.8: Comparison of central blood pressure readings among the different phenotypes of HDP and normotensive controls

Blood pressure	Study groups						Kruskal-Wallis Sig.
	Control	A	B	C	D	E	
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	
cSBP (mmHg)	115.0 (106.0-125.0)	132.0 (122.0-143.0)	119.5 (116.0-128.0)	128.5 (114.5-142.0)	128.0 (114.0-139.0)	133.0 (120.0-143.0)	<0.0001
cDBP (mmHg)	61.5 (52.0-69.0)	71 (63.0-80.0)	65 (61.0-71.0)	69.0 (61.0-83.0)	71.0 (61.0-81.0)	73.0 (60.0-83.0)	<0.0001

A= Gestational hypertension; B= Chronic hypertension; C= Preeclampsia without severe features; D= Preeclampsia with severe features; E=Eclampsia; cSBP = central systolic blood pressure; cDBP= central diastolic blood pressure.

4.5 Discussion

The research established normal thresholds for central blood pressure (cSBP and cDBP) as 116 mmHg and 78 mmHg, respectively. Measurements equal to or above these indicate central hypertension, with a specific focus on severe central hypertension defined as a cSBP of ≥ 148 mmHg and/or a cDBP of ≥ 95 mmHg.

The findings also showed strong correlations between peripheral and central blood pressure measurements, both in normotensive controls and women with mild peripheral hypertension. For normotensive controls, the median pSBP was 114.0 mmHg, and the cSBP was 115.0 mmHg, indicating no significant difference. In women with mild peripheral hypertension, the median pSBP among eclamptic patients was 138.0 mmHg while the cSBP level in the same group was 145.0 mmHg.

The findings of this study regarding the thresholds for mild central hypertension align with the work of Chulkova et al. (2015), who noted that a cSBP of 115 mmHg in pregnant women

might indicate a risk for PE (Chulkov et al. 2015). Additionally, these results align with a study by Booysen et al. (2013), which reported a cSBP upper threshold of 112 mmHg among a cohort of 311 young Black South Africans with a median age of 31 (Booyesen et al. 2013). The similarity in our findings can be attributed to the younger demographic and shared background, as both studies focused on younger Black South Africans.

Conversely, research involving older populations has indicated higher thresholds for CBP. For example, a study with over 6,000 participants conducted by Hao et al. (2015) established a 90th percentile cutoff for cSBP at 125 mmHg for men and 126 mmHg for women. This is consistent with previous findings from Japan, where a threshold of 129 mmHg was reported (Takase et al. 2013). Additionally, Cheng et al. (2013) demonstrated through a longitudinal study involving 1,272 older participants that a central BP greater than 130/90 mmHg significantly predicts cardiovascular events over a median follow-up of 15 years (Cheng et al. 2013). While the cut-off values determined by Cheng et al. (2013) serve as important benchmarks, they may not fully apply to pregnant populations, where physiological changes result in unique cardiovascular dynamics (Mahendru et al. 2014). Moreover, aging is often associated with aortic stiffness, which leads to an earlier return of reflected waves in late systole, contributing to higher central BP levels (McEniery et al. 2005).

For severe central hypertension, our study found that among pregnant women in their third trimester with severe brachial hypertension, cSBP was ≥ 148 mmHg and cDBP was ≥ 95 mmHg. To our knowledge, this work is the first to document the threshold for severe central hypertension. However, further studies are needed to validate these findings. These thresholds are considerably lower than those of PBP (160/110 mmHg), which is expected, as central BP is generally lower than peripheral BP due to the inherent physiological differences between the two vascular systems.

One limitation in our calculations is that some normotensive controls displayed higher cSBP and/or cDBP values than their peripheral counterparts. Under typical conditions, cSBP should be lower than pSBP, with minimal variation between pDBP and cDBP. The possible explanation for this finding in our study is that, while the participants had normal PBP, their CBP may have already been abnormal.

In comparison of peripheral and central blood pressure, a positive correlation was found between pSBP and cSBP, as well as between pDBP and cDBP among normotensive pregnant women, aligning with previous findings by Fujime et al. (Fujime et al. 2012). Importantly, Fujime et al.(2012) analyzed a larger sample of 830 participants, which adds strength to their findings. Similarly, a cross-sectional study by Priyadarsini et al. (2023) involving 107 pregnant women and 53 age-matched non-pregnant women also confirmed a strong relationship between brachial systolic blood pressure and cSBP in healthy normotensive pregnant women(Priyadarsini et al. 2023).

These positive correlations could be explained physiologically by the impact of endothelial function and arterial elasticity on circulatory pressure distribution (Jacobs et al. 2016). Endothelial function plays a crucial role in regulating vascular health and blood pressure. The endothelium, which is the inner lining of blood vessels, is responsible for the synthesis and release of various substances that influence vascular tone and maintain homeostasis. One of the key roles of the endothelium is to produce nitric oxide, a potent vasodilator that helps to relax the blood vessels, improve blood flow, and reduce blood pressure (Vanhoutte et al. 2017). In the context of arterial elasticity, healthy and elastic arteries are expected to show a strong correlation between peripheral and central measurements due to their ability to efficiently transmit pressure waves generated by the heartbeat. When arteries are elastic, they can accommodate the surge of blood during systole, dampening the pressure peaks and maintaining a more stable blood flow throughout the body (Warner et al. 2008).

Additionally, several studies have demonstrated that CBP has a better relationship to future cardiovascular events and mortality and is also more relevant than peripheral brachial BP in predicting target organ damage, as it represents the true load imposed on the heart, brain, kidneys, and the large arteries (McEniery et al. 2014; Williams et al. 2018; Baba et al. 2018). Nevertheless, additional research is necessary to validate these findings, given that some authors dispute the stronger correlation between CBP and cardiovascular events (Huang et al. 2019; Lamarche et al. 2021).

In this study, the median cSBP among normotensive pregnant women was found to be 115 mmHg. This finding is consistent with the results of Turi et al. (2022), who reported a similar mean cSBP of 115 mmHg in healthy pregnant women (Turi et al. 2022). However, in our study, the cSBP value was slightly higher, though not significantly, than the pSBP value of 114 mmHg that was observed. Typically, in normotensive individuals, cSBP is expected to be lower than peripheral systolic blood pressure. This atypical finding raises the possibility that individuals with higher cSBP in this study may have an underlying increase in arterial stiffness or could be at risk of developing it. As arterial stiffness increases, systolic pressure tends to rise. This is due to the early merging of the fast-reflected wave with the forward wave (Kim & Weber, 2021). Furthermore, increased arterial stiffness damages more elastic fibres in the blood vessel walls, leading to inadequate buffering and transmission of pulsatile pressure from the heart to target organs (Laurent & Boutouyrie 2020). Such changes can ultimately result in organ damage; therefore, it's a good idea to closely monitor these patients to assess their risk of developing high blood pressure in the future.

In this study, cDBP in normotensive controls was less than pDBP in 159 participants, and it was greater than pDBP in 98 participants. This is again an unexpected finding in normotensive controls, as under physiological conditions, the cDBP should either be the same as the pDBP or less than the pDBP (Agabiti-Rosei et al. 2007). This suggests that the 98 individuals with higher cDBP may be having central diastolic hypertension or are at risk

of developing central hypertension, while their peripheral diastolic blood pressure puts them in the normal blood pressure category. Only a prospective follow-up study can test this explanation.

There is little correlation between the pBP and the occurrence of eclampsia. Several studies indicate that the blood pressure may be normal or only mildly elevated in women with eclampsia, and even with stroke (Sibai 1990; Martin et al. 2005). The present study found that the median central systolic and diastolic blood pressures, as well as pDBP, were significantly higher in cases of eclampsia compared to those with other HDP and to non-hypertensive controls. This implies that CBP measurement may be better able to distinguish between the subtypes of HDP and phenotypes of PE than PBP.

In addition, the median cSBP for women with eclampsia and mild peripheral hypertension was relatively severe. This suggests that some eclamptic patients with mild pSBP actually have a cSBP that falls into the severe range. This finding may help explain why some patients with mild peripheral hypertension experience eclampsia. This implies that the cSBP might be a better predictor of eclampsia than the pSBP. Central aortic blood pressure plays a crucial role in regulating blood flow to the brain (Cipolla & Kraig 2011). Consequently, it could be inferred that in cases of eclampsia, vasogenic oedema might occur due to elevated CBP, even when brachial blood pressure remains only slightly elevated in the affected women.

The limitation of this study is that all hypertensive patients were receiving antihypertensive treatment, which may have affected their blood pressure readings. However, patients were recruited within 24 hours of admission, a time frame during which the pharmacological treatment might not have fully taken effect.

Conclusion

This study established the threshold values for central hypertension as 116/78 mmHg, with severe central hypertension defined as 148/95 mmHg. This study also reinforces the positive correlation between peripheral and CBP in both normotensive and hypertensive populations. Notably, women with eclampsia showed higher CBP levels, with those having mild hypertension in the severe range. This may clarify why some patients with mild peripheral hypertension experience eclampsia and may thus indicate that CBP is a better predictor of eclampsia than PBP. Further research is needed to confirm these findings.

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CHAPTER 5

3. The relationship between central blood pressure, NT-proBNP, and hs-cTnI in women with Maternal Complications of Hypertensive Disorders of Pregnancy

Credit author statement

Xolani B. Mbongozi led the design, methodology, conduct, analysis, interpretation, and writing of the research. Stuart DR Galloway and Angus Hunter provided supervision and were involved in the review and editing process. Nanjoh conducted the formal analysis, while Charles B Businge also offered supervision and contributed to the review and editing of the writing.

Abstract

Objective

Central blood pressure (CBP), N-terminal pro B-type natriuretic peptide (NT-proBNP) released from the left and right cardiac ventricle in response to ventricular volume expansion and pressure overload, and high sensitivity cardiac troponin I (hs-cTnI), produced in response to cardiomyocyte damage, may predict the degree of peripheral perfusion and the risk of end organ damage. The main objective of the study was to compare the levels of CBP and these cardiac biomarkers in women with maternal complications of hypertensive disorders of pregnancy (HDP).

Methods

This was a cross-sectional study that enrolled 270 women with HDP and 270 normotensive pregnant controls. Data on socio-demographic and cardiac biomarkers, and markers of target organ damage were collected.

Results

The median levels of the CBP and cardiac biomarkers were significantly higher among hypertensive participants with maternal complications (n=107/270) than those without complications (n=163/270). Specifically, the central systolic blood pressure (CSBP) levels were 133 (120-142) mmHg vs 128 (109-129) mmHg ($p=0.033$) and the central diastolic blood pressure (CDBP) levels were 75 (62-86) mmHg vs 69 (56-73) mmHg ($p<0.01$) while NT-proBNP levels were 446 (145-1126) vs. 57 (21-167) pg.ml⁻¹; $p<0.0001$, and hs-cTnI levels were 12 (7-35) ng.L⁻¹ compared to 8 (3-8) ng.L⁻¹; $p<0.0001$.

Conclusion

In conclusion, the study found that pregnant hypertensive women with maternal complications had significantly higher median values of CSBP and CDBP, NT-proBNP, and hs-cTnI in compared to those without complications. These findings suggest that measuring these vital signs and cardiac biomarkers in hypertensive pregnancies might be helpful for screening and monitoring maternal complications.

Keywords: NT-proBNP, high sensitivity cardiac troponin I, hypertensive disorders of pregnancy, maternal complications, central blood pressure

5.1 Introduction

Central blood pressure (CBP) and cardiac biomarkers such as NT-proBNP and hs-cTnI, are among several variables studied in women with hypertensive disorders of pregnancy (HDP) (Afshani et al., 2013; Fayers et al., 2013; Sadlecki et al., 2016; Ghomian et al., 2019; Jacobsen et al., 2022; Gencheva et al., 2021; Nguyen et al., 2022). The inactive N-terminal pro B-type natriuretic peptide is co-secreted with a 32-amino acid polypeptide, B-type natriuretic peptide (BNP), from the left and right cardiac ventricle in response to ventricular volume expansion and pressure overload, while hs-cTnI is a cardiac enzyme whose levels in the circulation respond to cardiomyocyte damage (Muijsers et al. 2020; Dockree et al. 2021; Bacmeister et al. 2024). In general, both biomarkers are associated with cardiac injuries and can indicate future cardiac disease risk, and, to some degree, the severity of cardiovascular events generally used for diagnosing cardiomyocyte injury (Giannubilo et al. 2014; Dalal et al. 2016; Muijsers et al. 2020; Nguyen et al. 2022). Lam et al. (2018) demonstrated that patients with heart failure and elevated BNP are more likely to experience death and rehospitalisation compared to those with low levels (Lam & Dierking 2017).

HDP are a leading cause of maternal morbidity and mortality globally (Abalos et al. 2013). They account for approximately 14-18% of all maternal deaths globally, with an estimated 62,000-77,000 maternal deaths and 500,000 perinatal deaths annually (Khan et al. 2005; Abalos et al. 2013; Brown et al. 2018, Magee et al. 2022). Maternal complications of HDP include stroke, pulmonary oedema, Haemolysis Elevated Liver enzymes and Low Platelets (HELLP) syndrome, abruptio placentae, acute kidney injury, intensive care unit (ICU) admission, low Glasgow coma scale (GCS), and (Sapna & Saroja 2018). Studies have shown an association between preeclampsia (PE) and cardiovascular complications during pregnancy or many years after pregnancy (Bellamy et al. 2007; Miller 2019). Other long-term complications of HDP are chronic hypertension, diabetes mellitus, stroke, end-stage renal disease, and cognitive impairment (Miller 2019).

Previous studies have demonstrated a significant increase in NT-proBNP in hypertensive pregnant women compared to pregnant normotensive women (Afshani et al., 2013; Fayers et al., 2013; Sadlecki et al., 2016; Ghomian et al., 2019; Jacobsen et al., 2022; Gencheva et al., 2021; Nguyen et al., 2022). A correlation has been observed between elevated systemic vascular resistance, left ventricular diastolic dysfunction, and depression of cardiac output in preeclamptic patients, as well as elevated NT-proBNP levels (Kim & Kim, 2019; Gencheva et al., 2021; Jacobsen et al., 2022). Furthermore, a strong association between cardiac Troponin I and PE, has also been reported (Alma et al. 2017; Morton & Morton 2018; Muijsers et al. 2020; Gencheva et al. 2021; Jacobsen et al. 2022; Bacmeister et al. 2024). However, there is still insufficient data evaluating relationships between NT-proBNP, hs-cTnI, and other short-term maternal complications, other than cardiac-related complications, in women with HDP.

Evidence suggests that PE is associated with increased central aortic blood pressure, pulse wave velocity as well as elastic arterial stiffness (Torrado et al. 2015; Meeme et al. 2017; Namugowa et al. 2017). Torrado and colleagues (2015) found that CSBP was significantly higher in Caucasian women with PE compared to those with gestational hypertension (GHPT)(Torrado et al. 2015a). They further elaborated that in their study, there was no difference in PBP between those with PE and those with GHPT. The studies by Meeme et al. (2017) and Namugowa et al. (2017) focused on examining the CBP and arterial stiffness in black African women in South Africa with and without PE. They found that women with PE had higher arterial stiffness compared to normotensive women (Torrado et al. 2015; Meeme et al. 2017; Namugowa et al. 2017). However, their studies did not include women with preeclampsia with severe features such as eclampsia, imminent eclampsia, stroke, HELLP syndrome, pulmonary oedema, abruptio placentae, and acute kidney injury. Their studies also did not explore the relationship between the CBP and the maternal outcomes in women with PE. These unaddressed issues warrant further investigation. The aim of the current study was therefore to assess the levels of CBP, cardiac biomarkers proBNP and hs-cTnI in women with maternal complications of HDP. The study hypothesized that levels of CBP and

these biomarkers would be higher in women with HDP who have maternal complications compared to those without related complications.

5.2 Methods

This was a cross-sectional study evaluating the levels of CBP, NT-proBNP, and hs-cTnI in women with immediate maternal complications of HDP. The study recruited consecutively 270 inpatients with HDP and 270 inpatient normotensive controls at Nelson Mandela Academic Hospital in South Africa. The inclusion criteria for the hypertensive group encompassed all hypertensive patients who were at least 20 weeks of gestation, while the inclusion criteria for normotensive pregnant participants included healthy patients with singleton pregnancies and specific conditions such as placenta previa, preterm premature rupture of membranes, preterm labour, or patients admitted for repeat elective caesarean section at term.

Patients who were less than 20 weeks pregnant, those who were dire emergencies with no time to seek consent for participation in the study, and those who declined to participate were excluded. Patients with diabetes mellitus, cardiac disease, chronic renal disease, and antiphospholipid syndrome or other autoimmune disease were also excluded.

The cases were not matched for maternal and gestational age. This is because most patients with HDP, especially eclampsia, are younger compared to the general population, and excluding them will cause bias. According to national guidelines, patients with HDP are delivered preterm (preferably less than 35 weeks), whereas controls, such as placenta previa and previous caesarean deliveries, are delivered much later (Moodley et al. 2019).

Definitions of hypertensive disorders were made according to the International Society for the Study of Hypertension in Pregnancy classification recommendations (Brown et al. 2018):

- Chronic hypertension was defined as high blood pressure predating the pregnancy or recognized at less than 20 weeks' gestation.
- Gestational hypertension was defined as hypertension diagnosed after 20 weeks gestation, without any features of pre-eclampsia.
- Preeclampsia was defined as de novo hypertension or superimposed on chronic hypertension after 20 weeks' gestation, accompanied by proteinuria and/or other evidence of maternal end-organ dysfunction, and/or fetal growth restriction.
- Eclampsia was defined as the convulsive manifestation of the HDP.

HELLP syndrome was diagnosed when any two of the following abnormalities were present: increased Lactate dehydrogenase (LDH) (≥ 600 IU/L), increased Aspartate transaminase (AST) (≥ 70 IU/L), low platelet count ($< 100 \times 10^9/L$); and renal failure if creatinine was ≥ 90 $\mu\text{mol/L}$ (Rimaitis et al. 2019).

Data collection

These data were gathered from patient and maternity case files, using a pre-designed questionnaire. It comprised socio-demographic and clinical information, including maternal and gestational age, parity, marital status, education, presence and type of hypertensive disorders of pregnancy, maternal and foetal conditions, as well as maternal and perinatal outcomes.

Blood pressure measurements, both peripheral and central, were recorded at enrolment and within a week after delivery using the Microlife WatchBP Office Central. Before using the WatchBP Office central, the correct size of cuff was chosen and placed over the left or right upper arm so that the artery mark arrow points towards the lower arm. The cuff was wrapped around the arm, making sure that the lower edge of the cuff was approximately 2 cm above the elbow. The WatchBP Office Central device automatically measured both brachial and

central blood pressure, displaying the results on the screen once the measurement process was complete. To determine the central blood pressure, the WatchBP Office Central uses brachial pulse volume plethysmography (PVP) waveforms. It is designed to perform PVP at a cuff pressure of 60 mmHg. Based on the analysis of the PVP waveforms, the central systolic pressure and central pulse pressure values are automatically determined.

Blood samples were collected from each woman using two different types of tubes. For serum NT-proBNP, hs-cTnI, and platelet count, 10ml of venous blood from the antecubital vein was drawn into tubes containing EDTA. The plasma was separated through centrifugation at 4°C for 15 minutes at 3500 rpm and then stored at -80°C until analysis. Another 10ml of venous blood was drawn into yellow tubes containing Solution A (trisodium citrate, citric acid, and dextrose) for the measurement of creatinine, alanine transaminase (ALT), AST, and LDH. All assays, including NT-proBNP and hs-cTnI, were performed using an Alinity iSTAT analyzer (Abbott, USA).

Statistical analysis

Data were checked for completeness and consistency before being captured using the IBM SPSS STATISTICS software package version 31 for Windows (IBM Inc., Chicago IL, USA). These data were summarized into proportions (%) for categorical variables. Continuous data such as age, gestational and parity was interpreted using means and standard deviations (SD) if normally distributed or using medians, interquartile ranges, and percentiles (p25, p75) if skewed. The Chi-square test was used to delineate the degree of association between categorical variables. A $p < 0.05$ was considered statistically significant.

5.3 Results

General and clinical characteristics of the sample population

Out of the 270 hypertensive cases, 143 (53%) had preeclampsia, 102 (38%) had eclampsia, 14 (5%) had chronic hypertension, and 11 (4%) had gestational hypertension. The

demographic and clinical characteristics of the sample population are shown in **Table 5.1**. The non-hypertensive controls (median = 28 years; $p < 0.0001$) were significantly older than the hypertensive cases (median = 25 years). The majority (63.1% $n=341$) were in the 20 to 34 years age group and the minority (17.2% $n=93$) were younger than 20 years.

There was no statistical difference ($p > 0.05$) for the other demographic characteristics observed in the hypertensive cases and non-hypertensive controls. Nearly all (99.4% $n=537$) the participants were of African race, and the remaining were Multiracial (0.6% $n=3$). More than three-quarters (77.2%) were single, and slightly more than a quarter (22.6% $n=122$) were married.

Participants with HDP had a higher proportion of primigravida than the normotensive controls (44.8% Vs 11.6%, $p < 0.0001$). Most (93.7% $n=434$) of the participants attended antenatal clinics while 34 (6.3%) did not. Antenatal clinic attendance between hypertensive cases and non-hypertensive controls was comparable statistically ($p > 0.05$). The median gestational age at enrolment to the study was 36 weeks (IQR: 5). The median gestational age at recruitment was significantly higher (38 weeks IQR = 5 weeks) among non-hypertensive controls compared to hypertensive cases (34 weeks IQR = 6 weeks) ($p < 0.0001$). The majority (86.7% $n=468$) gave birth through caesarean section and the minority (13.3% $n=72$) normally. No significant difference was observed in the mode of delivery between the two groups.

Table 5.1. General and clinical characteristics of the sample population

	Hypertensive cases; n= 270	Non-hypertensive controls; n=270	Total; n=540	
Characteristics	n (%)	n (%)	n (%)	Pearson X ² Sig.
Ethnicity				
African	269 (99.6)	268 (99.2)	537 (99.4)	0.624*
Multiracial	1 (0.4)	2 (0.7)	3 (0.6)	
Marital status				
Single	210 (77.8)	207 (76.7)	417 (77.2)	0.837*
Married	60 (22.2)	62 (23.0)	122 (22.6)	
Divorced	0 (0.0)	1 (0.4)	1 (0.2)	
Gravidity				
Multigravida	149 (55.2)	209 (77.4)	358 (66.3)	<0.0001
Primigravida	121 (44.8)	61 (11.6)	182 (33.7)	
Booking status				
Booked	248 (91.9)	258 (95.6)	506 (93.7)	0.111
Not booked	22 (8.1)	12 (4.4)	34 (6.3)	
Mode of delivery				
Caesarean section	233 (86.3)	235 (87.0)	468 (86.7)	0.800
Vaginal	37 (13.7)	35 (13.0)	72 (13.3)	
Maternal complications				
Yes	107 (39.6)	2 (0.7)	109 (20.2)	<0.0001
No	163 (60.4)	268 (99.3)	431 (79.8)	
	Median (IQR)	Median (IQR)	Median (IQR)	Sig.**
Gestational age at recruitment (weeks)	34 (6)	38 (3)	36 (5)	<0.0001

*Fisher's Exact p-value; ** Mann-Whitney U p-value

Maternal complications diagnosed in the study group

More than twenty percent of all participants (109/540, 20.2%) developed complications pre- or post-delivery. Only 2 out of the 270 normotensive controls (0.7%) developed maternal complications, with both having abruptio placentae. In contrast 107/270 (39.6%) of the cases with HDP had various maternal complications with the most common being HELLP syndrome (78/270, 28.9%) renal failure (29/270, 10.7%), and abruptio placentae (26/270, 9.6%) (Table 2). Other complications included pulmonary oedema (3/270), low GCS (4/270), cerebrovascular accident, disseminated intravascular coagulopathy (n=1), or posterior reversible encephalopathic syndrome (each 1/270).

Table 5.2. Maternal complications diagnosed in the study participants

	Cases; n=107	Controls; n=2	Total; n=109
Maternal complications	n (%)	n (%)	n (%)
Abruptio placenta	24 (22.4)	2 (100.0)	26 (23.9)
HELLP syndrome	78 (72.9)	0 (0.0)	78 (71.6)
Renal failure	29 (27.1)	0 (0.0)	29 (26.6)
Pulmonary oedema	3 (2.8)	0 (0.0)	3 (2.8)
Low GCS	7 (6.5)	0 (0.0)	7 (6.4)
ICU admission	7 (6.5)	0 (0.0)	7 (6.4)

Relationship between NT-proBNP and hs-cTnl, and maternal complications in all hypertensive cases

The median levels (p25, p75) of the cardiac biomarkers and CBP were significantly higher among hypertensive participants with maternal complications (n=107/270) than those

without complications (n=163/270). Specifically, the central systolic blood pressure (CSBP) were 133 (120-142) mmHg vs 128 (109-129) mmHg (p=0.033) and the central diastolic blood pressure (CDBP) levels were 75 (62-86) mmHg vs 69 (56-73) mmHg (p<0.01) while NT-proBNP levels were 446 (145-1126) vs. 57 (21-167)) pg.ml⁻¹; p<0.0001, and hs-cTnl levels were 12 (7-35) ng.L⁻¹ compared to 8 (3-8) ng.L⁻¹; p<0.0001 (**Table 5.3**).

Table 5.3. Medial comparisons of NT-proBNP and hs-cTnl, and CBP in hypertensive cases with or without specific maternal complications

Maternal complications in hypertensive cases		Central systolic blood pressure (mmHg) Median (IQR)	Central diastolic blood pressure (mmHg) Median (IQR)	NT-proBNP (pg.ml ⁻¹) Median (IQR)	Hs-cTnl (ng.L ⁻¹) Median (IQR)
Composite maternal complications	Yes	133 (120-142)	75 (62-86)	446 (145-1126)	12 (7-35)
	No	128 (109-129)	69 (56-73)	57 (21-167)	8 (3-8)
	Sig .	0.033	0.004	<0.0001	<0.0001
Abruptio placenta	Yes	127 (119-138)	71 (56-82)	291 (85-1247)	11 (6-29)
	No	134 (123-143)	76 (63-88)	475 (151-1098)	15 (7-36)
	Sig .	0.140	0.347	0.604	0.501
HELLP syndrome	Yes	133 (119-141)	74 (64-85)	469 (145-1178)	12.5 (7-36)
	No	134 (121-147)	76 (56-87)	403 (104-783)	12 (6.5-32)
	Sig .	0.383	0.975	0.716	0.528
Renal failure	Yes	132 (120-145)	78 (66-87)	821 (434-1894)	35 (12-50)
	No	133 (120-142)	73 (61-86)	348 (85-1003)	10.5 (6-19)
	Sig .	0.922	0.570	0.002	<0.0001
Pulmonary oedema	Yes	105 (99-118)	62 (58-80)	85 (48-6943)	5 (5-48)
	No	133 (120-143)	75.5 (62-87)	451 (145-1126)	12 (7-35)
	Sig .	0.059	0.221	0.597	0.499
Low GCS	Yes	134 (123-148)	97 (73-104)	600 (262-1638)	50 (14-66)

	No	133 (120-142)	74 (61-85)	435 (145-1069)	12 (7-34)
	Sig .	0.614	0.099	0.619	0.059
ICU admission	Yes	138 (128-148)	95 (73-101)	600 (262-1638)	50 (14-66)
	No	132 (120-142)	74 (61-85)	435 (145-1069)	12 (7-34)
	Sig .	0.368	0.120	0.673	0.061

SIG.= MANN-WHITNEY

For PBP, only the PDBP was significantly higher among hypertensive participants with maternal complications when compared to those without complications [80 (65-93) vs 72(62-86) mmHg; $p=0.004$] (see Table 4). The median values indicate that NT-proBNP levels in individuals with maternal complications were above the normal range (<150 pg.ml⁻¹ for NT-proBNP), while the values for hs-cTnI were within the normal range (<30 ng.L⁻¹ for hs-cTnI). Among the participants with HDP, a significant relationship was observed between renal failure and the biomarkers (**Table 5.3**). In this hypertensive group of participants, the median hs-cTnI in cases with renal failure was significantly higher [35 (12-50) ng.L⁻¹; $p<0.0001$] compared to those without [11 (6-19) ng.L⁻¹].

The median NT-proBNP in cases with renal failure was also significantly higher [821 (434-1894) pg.ml⁻¹; $p=0.002$] compared to those without [348 (85-1003)]. The other readings of biomarkers were similar in participants with the named complications and those without them ($p>0.05$) (Table 5).

Table 5.4. Comparisons of PBP and CBP in hypertensive cases with or without specific maternal complications

Maternal complications in hypertensive cases		peripheral systolic blood pressure (mmHg) Median (IQR)	peripheral diastolic blood pressure (mmHg) Median (IQR)	Central systolic blood pressure (mmHg) Median (IQR)	Central diastolic blood pressure (mmHg) Median (IQR)
Composite maternal complications	Yes	131 (117-144)	80 (65-93)	133 (120-142)	75 (62-86)
	No	125 (113-139)	72(62-86)	128 (109-129)	69 (56-73)
	Sig .	<0.055	<0.004	0.033	0.004
Abruptio placenta	Yes	123 (112-137)	76 (65-91)	127 (119-138)	71 (56-82)
	No	133 (119-145)	82 (64-94)	134 (123-143)	76 (63-88)
	Sig .	0.59	0.428	0.140	0.347
HELLP syndrome	Yes	132 (119-144)	82 (65-93)	133 (119-141)	74 (64-85)
	No	126 (112-144)	73 (62-93)	134 (121-147)	76 (56-87)
	Sig .	0.426	0.408	0.383	0.975
Renal failure	Yes	131(117-144)	78 (67-93)	132 (120-145)	78 (66-87)
	No	131(115-144)	82 (62-93)	133 (120-142)	73 (61-86)
	Sig .	0.944	0.952	0.922	0.570
Pulmonary oedema	Yes	112 (111-112)	73 (61-76)	105 (99-118)	62 (58-80)
	No	132(118-144)	82 (65-93)	133 (120-143)	75.5 (62-87)
	Sig .	0.053	0.181	0.059	0.221
Low GCS	Yes	140 (122-173)	109 (67-121)	134 (123-148)	97 (73-104)
	No	131 (116-144)	80 (63-93)	133 (120-142)	74 (61-85)
	Sig .	0.241	0.161	0.614	0.099
ICU admission	Yes	138 (122-173)	106 (67-119)	138 (128-148)	95 (73-101)
	No	131 (116-144)	80 (63-93)	132 (120-142)	74 (61-85)

	Sig	0.246	0.177	0.368	0.120
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SIG.= Mann-Whitney

A hs-cTnI value of 8.5 ng.L⁻¹ or higher predicted maternal complications of HDP with a sensitivity of 69% and a specificity of 50% ($P < 0.001$; 95% CI 0.57-0.70; AUC=0.63), while an NT-proBNP value of 179 pg.ml⁻¹ or higher predicted maternal complications with a sensitivity of 71% and a specificity of 51% ($P < 0.001$; 95% CI 0.59-0.73; AUC=0.66) (**Figure 5.1**).

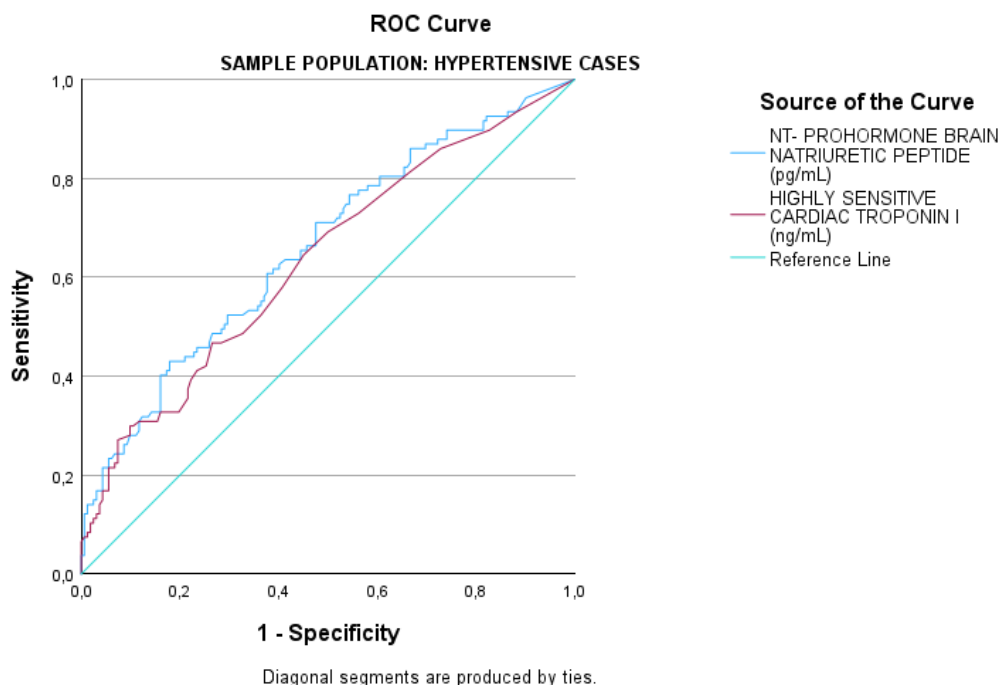


Figure 5.1. *hs-cTnI and NT-proBNP cut-offs for prediction of maternal complications in women with hypertensive disorders of pregnancy.*

A hs-cTnI value of 11 ng.L⁻¹ or higher predicted renal failure with a sensitivity of 79% and a specificity of 50% ($P < 0.001$; 95% CI 0.66-0.85; AUC=0.75), while an NT-proBNP value of 167 pg.ml⁻¹ or higher predicted renal failure with a sensitivity of 93% and a specificity of 65% ($P = 0.002$; 95% CI 0.58-0.80; AUC=0.69) (**Figure 5.2**).

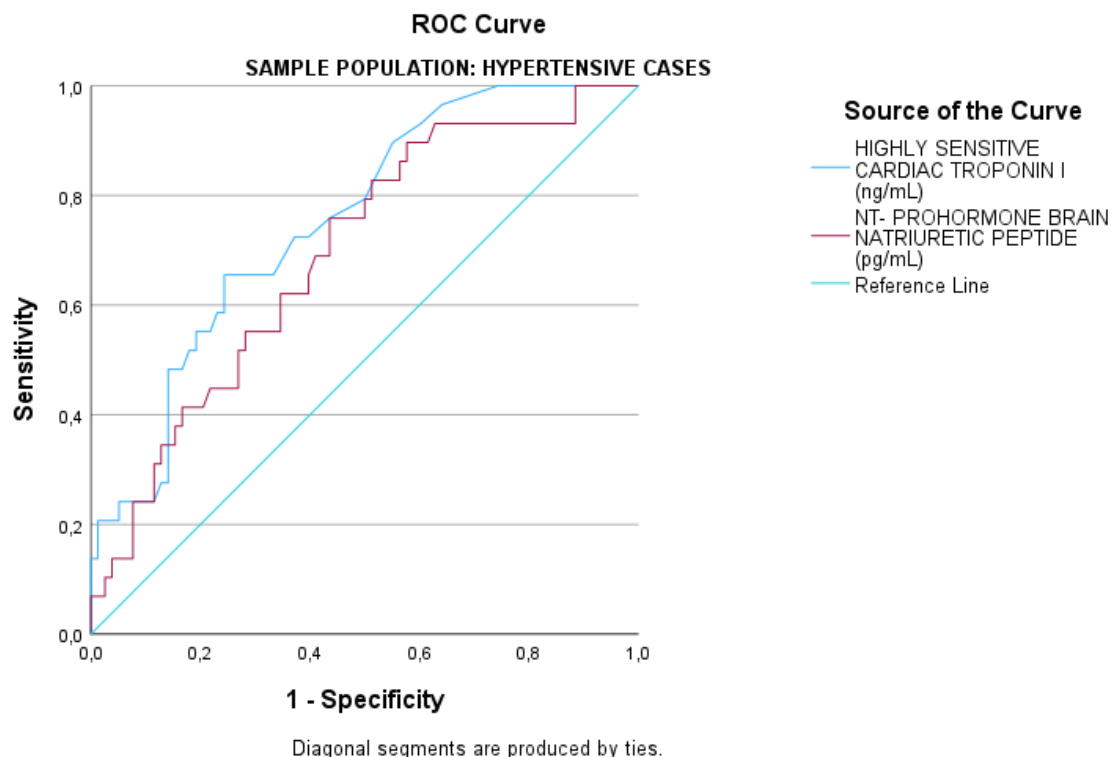


Figure 5.2. *hs-cTnI and NT-proBNP cut-offs for prediction of renal failure in women with hypertensive disorders of pregnancy.*

Relationship between NT-proBNP and maternal complications in women with preeclampsia and eclampsia

In eclamptic cases who had additional maternal complications, the NT-proBNP and the hs-cTnI were significantly higher compared to those without additional maternal complications: respectively 1030 (382 - 1894) vs. 464 (164 - 940) pg.mL⁻¹, $p=0.003$] and 33 (12 - 62) vs. 10 (5 - 25) ng.L⁻¹ $p<0.0001$ (Table 5). The cases with eclampsia who had renal failure had significantly higher hs-cTnI compared to eclamptic cases without renal failure, 46 (20 - 175) vs.21 (8 - 54) ng.L⁻¹; $p=0.036$. There was no difference in the median hs-cTnI

and NT-proBNP in eclamptic cases with and without abruptio placenta, help syndrome, pulmonary oedema, low GCS, or admission to the ICU ($p > 0.05$) (**Table 5.5**).

Table 5.5: Medial comparisons of NT-proBNP and hs-cTnI in eclamptic cases with or without specific maternal complications

Maternal complications in cases with eclampsia			Hs-cTnI Median (IQR)	NT-proBNP Median (IQR)
Composite maternal complications	Yes		33 (12 - 62)	1030 (382 - 1894)
	No		10 (5 - 25)	464 (164 - 940)
	Sig.		<0.0001	0.003
Abruptio placenta	Yes		31 (11 - 46)	1460 (403 - 1894)
	No		34 (12 - 77)	1026 (355 - 2120)
	Sig.		0.591	0.684
HELLP syndrome	Yes		34 (12 - 104)	1069 (434 - 3250)
	No		22.50 (11.50 - 48)	523 (341 - 1460)
	Sig.		0.367	0.279
Renal failure	Yes		46 (20 - 175)	1133 (434 - 3223)
	No		21 (8 - 54)	1026 (270 - 1673)
	Sig.		0.036	0.500
Pulmonary oedema	Yes		.	.
	No		33 (12 - 62)	1030 (382 - 1894)
	Sig.		-	-
Low GCS	Yes		52 (16 - 77)	877.50 (446 - 2120)
	No		29 (11 - 62)	1030 (355 - 1894)
	Sig.		0.317	0.884
ICU admission	Yes		52 (16 - 77)	877.50 (446 - 2120)
	No		29 (11 - 62)	1030 (355 - 1894)
	Sig.		0.333	0.987

SIG. = Mann-Whitney

Overall, the median NT-proBNP [246.50 (85 - 673) vs. 141.50 (45 - 381) pg.ml⁻¹; p=0.009] was significantly higher in preeclamptic cases with maternal complications compared to those without maternal complications. There was no statistically significant difference in the medians for hs-cTnl in preeclamptic cases with and without maternal complications. Upon stratified analysis, participants with PE who developed renal failure had significantly higher median hs-cTnl and NT-proBNP compared to those without renal failure, respectively 20 (10 - 46) vs. 9 (6 - 12) ng L⁻¹ p=0.001; and [619 (233 - 1894) vs. 200 (78 - 520) pg.ml⁻¹ p=0.002. There was no difference in the median hs-cTnl and NT-proBNP of preeclamptic cases with and without abruptio placenta, HELLP syndrome, low Glasgow coma scale, pulmonary oedema, and admission to the ICU (p>0.05).

5.4 Discussion

This study included a total of 540 participants, consisting of 270 individuals with hypertension and 270 non-hypertensive controls. Among the participants with hypertension, 39.6% experienced maternal complications, with HELLP syndrome being the most common complication reported. Women with complications related to HDP presented with higher levels of both diastolic and systolic central blood pressure. Additionally, those with complications had significantly elevated levels of NT-proBNP and hs-cTnl. Hypertensive patients who also had renal failure showed even higher levels of NT-proBNP and hs-cTnl compared to those without renal failure.

These study results are consistent with existing literature which has shown increased levels of NT-proBNP in women with HDP, and a correlation between these cardiac biomarkers and maternal complications in patients with HDP (Bakacak et al. 2016; Nguyen et al., 2022; Verma, Malik & Bansal 2022). Hamad et al. (2009) observed impaired diastolic left ventricular function and increased levels of NT-proBNP in pregnancies complicated by PE (477 (152) ngL⁻¹ vs 46 (6) ng.L⁻¹; p <0.0001), especially early-onset PE (1243 (583) ng.L⁻¹ vs 254 (57) ngL⁻¹, p=0.005) (Hamad et al., 2009). Fustaret et al. (2012) also evaluated the correlation

between NT-ProBNP in normotensive pregnant women and women with HDP, finding that NT-ProBNP significantly correlated with lactic dehydrogenase and platelets, which are markers for HELLP syndrome, and cardiac failure [31]. The current study did not find a significant association between NT-proBNP and HELLP syndrome but found that hypertensive patients with renal failure had significantly higher NT-proBNP levels compared to those who did not have renal failure. This finding aligns with the established phenomenon that NT-proBNP clearance occurs exclusively in the kidneys, as well-documented in patients with chronic renal failure (Charmetant et al., 2019). Therefore, impairment in the renal system may result in higher levels of NT-proBNP.

The current study did not find an association between pulmonary edema and NT-proBNP levels, which differs from the results of other studies. For instance, Kumari et al. (2017) reported a significant association of serum NT-proBNP levels with pulmonary edema [997 (642.92 to 1351.08) pg.ml⁻¹ (p=0.049)] (Kumari et al. 2017) Additionally, Kim et al. (2020) conducted a study with 124 preeclamptic patients and found that NT-proBNP levels were significantly higher in women with pulmonary oedema (H. M. Kim, Choo & Seong 2020). Their findings are consistent with a cross-sectional study of 30 women with severe PE conducted by Hafiz et al. (2021), which also found an association between NT-proBNP and pulmonary edema [33]. Further studies are necessary to understand the differences between the current study's findings and those of other studies.

In the study by Hafiz et al., a significant association was also found between NT-proBNP and HELLP syndrome in preeclamptic patients, which contradicts the findings of the present [33]. Hafiz et al. included only 35 participants with hypertension, while the present study involved a larger sample size, which may explain the discrepancies between the two studies. Conversely, a study by Kumari et al., which included 45 hypertensive women and 45 normotensive women, aligns with the results of the current study, revealing no association between NT-proBNP and HELLP syndrome in pregnant women with hypertensive conditions (Kumari et al., 2017).

In addition to NT-proBNP, the current study also found elevated levels of hs-cTnI in women with maternal complications of HDP compared to those without maternal complications. This observation is in line with previous research indicating a potential association between hs-cTnI and PE (Pergialiotis et al. 2016)(Morton & Morton 2018). However, there is a lack of studies specifically examining the relationship between hs-cTnI and maternal complications of HDP. It's worth noting that, similar to the findings for NT-proBNP among pregnant women with hypertension, those who experienced renal failure had significantly higher levels of hs-cTnI. This finding is consistent with existing literature indicating that cardiac biomarkers are filtered through the glomerular filtration barrier, and a decrease in glomerular filtration can impact their levels (Ren et al. 2021).

The current study indicates that both diastolic and systolic central blood pressure are higher in women with maternal complications of HDP. Previous studies have mainly focused on the relationship between central blood pressure and HDP, rather than examining the association between central blood pressure and maternal complications (Meeme et al. 2017;Torrado et al. 2015; Namugowa et al. 2017). These studies have consistently demonstrated that CBP is elevated in women with HDP compared to those without HDP. CBP is known to be a reliable indicator of target organ damage, which may explain the association between central blood pressure and maternal complications of HDP in the current study, as these complications are largely associated with target organs (Jeon et al. 2021).

In non-pregnant patients, CBP has been shown to be a good predictor of complications in certain target organs, such as cardiovascular events (myocardial infarction, coronary heart disease, sudden death, congestive heart failure, and stroke) and renal failure (Roman et al. 2007;Xiao et al. 2020). However, unlike other studies that have established a correlation between CBP and the decline in renal function, the current study did not find significantly different levels of CBP between women with renal failure and those without (Kumari et al. 2017; Charmetant et al. 2019; Kim & Kim 2019). This may be attributed to the fact that the other studies primarily involved non-pregnant patients with chronic kidney disease rather

than acute cases, and it also included some male participants. For example, Xiao et al. (2020) conducted a study with 1426 non-pregnant participants who were followed for a median of 4.8 years to assess the prognostic significance of various blood pressure measurements for renal function decline and early chronic kidney disease (Xiao et al., 2020). Their study revealed that central pulse pressure emerged as an independent predictor of renal function decline. Their findings are consistent with the earlier community-based population study by Fan et al. (2016), which evaluated 3153 participants and found that central SBP was a stronger predictor compared with peripheral SBP for kidney function decline (Fan et al., 2016). Ohno et al. (2016) also highlighted the association between CBP and kidney function (Ohno et al., 2016). They proposed a vicious cycle between chronic kidney disease (CKD) and CBP, indicating that abnormalities in central hemodynamics can hasten the progression of CKD by potentially causing renal ischemia and glomerular hypertension.

The current study found that the CSBP was significantly higher in women with maternal complications of HDP compared to women without complications of HDP. However, the peripheral systolic blood pressure did not show a significant difference. This may imply that CSBP may be better associated with complications of HDP compared to PSBP. This finding is consistent with the findings in the general population, where CBP is a better predictor of cerebrovascular accidents compared to peripheral blood pressure. For example, Matsumoto et al. conducted a study that found higher CSBP and central pulse pressure, but not brachial blood pressure, to be significantly associated with white matter hyperintensity volume (Matsumoto et al., 2020). Han et al. also investigated the association between CBP and long-term prognosis in patients with Embolic Stroke of Undetermined Source (ESUS) and found that CBP parameters were independently associated with unfavourable outcomes, including major adverse cardiovascular events, stroke recurrence, and mortality (Han et al., 2023). However, while the current study observed elevated CBP in relation to all maternal complications, it did not find any association between cerebrovascular events and CBP. This could be due to the short interval of exposure to high CBP in pregnant women

compared to long-term exposure in the aforementioned studies. A long-term follow-up of patients in our study might be needed to address this controversial finding.

Limited data exists on relationships between CBP, hs-cTnI, and NT-proBNP, and maternal complications in women with HPD, so this study offers valuable insights. However, the study had some limitations. One limitation is that the follow-up period was limited to seven days after delivery, potentially missing complications that may have occurred later. However, this may be mitigated by the fact that most immediate complications of HDP occur during the antenatal and immediate postpartum periods, which is seven days after delivery. Another limitation is that cases and controls were not matched for maternal and gestational age, which could introduce statistical bias.

In conclusion, the study found that pregnant women with hypertension and maternal complications had significantly higher levels of CBP and cardiac biomarkers NT-proBNP and hs-cTnI compared to those without complications. These cardiac biomarkers were particularly elevated in women with renal failure. The findings may suggest that women with maternal complications of HDP during pregnancy may be at higher risk of developing chronic cardiovascular problems. Additionally, measuring these biomarkers in hypertensive pregnancies could help in screening and monitoring maternal complications, especially renal failure, and CSBP may be more effective than PSBP in screening for maternal complications of HDP.

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CHAPTER 6

4. Assessment of clinical practices and cardiac biomarker screening in preeclampsia: a survey of healthcare professionals

Credit author statement

Xolani B. Mbongozi led the design, methodology, conduct, analysis, interpretation, and writing of the research. Stuart DR Galloway played a key role in conceptualization and supervision, in addition to contributing to the review and editing. Angus Hunter provided supervision and methodology insights, as well as review and editing. Geoffrey AB Buga and Charles B. Businge also contributed through supervision, reviewing and editing.

Abstract

Introduction:

Preeclampsia (PE) is associated with increased risk of peripartum cardiomyopathy and long-term cardiovascular complications. Cardiac biomarkers like brain natriuretic peptide (BNP) and troponin I may help assess cardiac function in pregnant women with PE. However, the extent to which healthcare professionals utilize these biomarkers for evaluating women with PE is not well-documented.

Objective:

This study aimed to evaluate the experiences and perspectives of healthcare workers regarding the clinical assessment and usage of cardiac biomarkers in patients with preeclampsia.

Methods:

A cross-sectional online survey was distributed to medical doctors working in maternity units at five hospitals. Participants were recruited through direct outreach, and only qualified medical officers, registrars, and medical specialists were included. The data were analysed using IBM SPSS Statistics software, and descriptive statistics were calculated. A p-value of less than 0.05 was considered statistically significant.

Results:

The survey included 58 participants, primarily consisting of medical officers and registrars (69%) and specialist obstetricians and gynaecologists (31%), who had varying levels of clinical experience. Notably, 89.76% of respondents identified pulmonary oedema as the most common cardiac-related complication associated with preeclampsia. When it came to screening for cardiac diseases in preeclamptic women, 43.1% of participants relied on clinical judgment, while only 10% utilized standardized protocols. Additionally, 24.1% screened only high-risk cases, and 22.4% reported conducting no screening at all. In terms of post-delivery management, only 41.4% of participants performed reviews on all patients with preeclampsia. However, a significant majority, 75.9%, recognized the potential role of cardiac biomarkers in managing both the short- and long-term prognosis of preeclampsia, highlighting various advantages of integrating these biomarkers into clinical practice.

Conclusion:

A significant number of participants support the integration of cardiac biomarkers in the management and prognosis of preeclampsia. This reflects a positive shift toward adopting new practices in clinical care. However, only a small percentage of healthcare workers are currently following screening protocols and reviewing all post-delivery patients with preeclampsia. This highlights an urgent need to educate and encourage healthcare workers on the importance of enhanced monitoring for cardiovascular issues in this high-risk population.

6.1 Introduction

Research has demonstrated that cardiac markers, including BNP and troponin I, are markedly elevated in women experiencing hypertensive disorders of pregnancy (HDP) (Gencheva et al. 2021; Sheikh et al. 2021; Bacmeister et al. 2024). Findings in the previous chapter (Chapter 5) indicate that pregnant women with HDP who encounter maternal complications exhibit significantly higher levels of these cardiac biomarkers compared to those without complications. This suggests a potential role for these biomarkers in screening and monitoring maternal health conditions.

PE, the most prevalent type of HDP, is a multisystemic disorder characterized by elevated blood pressure that arises at or after the twentieth week of gestation, accompanied by either proteinuria or symptoms indicative of organ dysfunction. This condition results from inadequate cardiovascular adaptation to the physiological changes of pregnancy (Kornacki et al., 2024; Thilaganathan & Kalafat 2019; Yagel & Verlohren 2020; Brown et al. 2018). Despite extensive research, the precise pathogenesis of PE remains elusive.

Key cardiovascular adaptations during pregnancy involve increased cardiac output and blood volume alongside a decrease in systemic vascular resistance. When these adaptations fall short, various maternal and perinatal complications may arise (Melchiorre et al. 2011). Given that the exact pathogenesis of preeclampsia is not fully understood, it is vital for healthcare professionals to be equipped with knowledge on screening, prevention and management strategies to mitigate both maternal and perinatal morbidity and mortality associated with this condition.

Effective prevention of preeclampsia relies significantly on early detection, rigorous monitoring, and prompt intervention (Moodley et al. 2018). One promising preventive approach is the administration of low-dose aspirin, which has been shown to lower the risk

of preterm or early-onset PE (Chaemsaihong et al. 2022). Predicting the likelihood of developing PE requires a systematic approach to antenatal care, which emphasizes regular blood pressure monitoring (Moodley et al. 2018). The FIGO guidelines advocate for all pregnant women to undergo screening for preterm PE early in pregnancy using a combined first-trimester test, incorporating assessments of maternal risk factors in conjunction with specific biomarkers (Poon et al. 2012). Nevertheless, current screening methods fall short in reliably predicting complications in women already diagnosed with preeclampsia. Current literature suggests that regular blood tests, including full blood count, urea and electrolytes, and liver function tests, are essential for monitoring women with PE (Brown et al., 2018; Moodley et al., 2018). Furthermore, biomarkers such as BNP and troponin I, traditionally used to diagnose cardiac muscle injury, are increasingly being validated for their potential in assessing hypertensive pregnant women (Bacmeister et al. 2024; Gencheva et al. 2021; Ghomian et al. 2019; Ravichandran et al. 2019; Sadlecki et al. 2016; Dalal et al. 2016; Gencheva et al. 2021; Sheikh et al. 2021). These biomarkers are essential not only as potential screening tools for preeclampsia but also as critical indicators of cardiac injury.

This study aimed to connect the findings from previous chapters about the potential role of cardiac biomarkers in managing preeclampsia with the clinical experiences and perspectives of healthcare professionals regarding the use of these markers in women affected by this obstetric condition. The hypothesis was that healthcare professionals' awareness and integration of cardiac biomarkers, such as BNP and troponin I, in the clinical management of preeclampsia are insufficient, contributing to inadequate screening and monitoring for cardiovascular complications in women diagnosed with this condition.

6.2 Methods

This was a cross-sectional online survey of medical doctors in maternity units of regional and tertiary hospitals using Google Forms. The variables included demographic

information, current employment status, years of experience, and the level of the healthcare facility. Other questions focused on their clinical experience and perspectives regarding the complications and management of preeclampsia, as well as the use of cardiac markers in patients with this condition.

The study population consisted of medical doctors working in the maternity units at Mthatha Regional Hospital, Nelson Mandela Academic Hospital, Cecilia Makhiwane Hospital, and Frere Hospital. All who agreed to participate and provided consent were included in the survey. Medical students and interns were excluded from the study.

Data Collection

There were a total of 46 medical officers and 25 medical specialists in the maternity units across these hospitals, making a total of 71 potential participants. A pre-designed online survey was distributed via email and WhatsApp to these 71 medical doctors, of whom 58 agreed to participate.

Data Entry, Cleaning, and Analysis

Data was extracted from the Google Form and verified for accuracy before being recorded using the latest version of IBM SPSS Statistics software for Windows (IBM Inc., Chicago, IL, USA). The data was summarized as proportions (%) and presented using figures and tables. Responses to open-ended questions were analysed thematically. The Chi-square test was employed to assess the association between categorical variables, such as career and shared perspectives. A p-value of less than 0.05 was considered statistically significant.

Ethical considerations

Approval to conduct the study was obtained from the Walter Sisulu University Faculty of Medicine and Health Sciences Research Ethics Committee (WSU HREC 037/2025) before the research commenced. Informed consent was secured from all participants prior to their involvement in the survey. To ensure anonymity, no names were included in the Google Forms used in the study. The research posed no risks to the participants' health or well-being.

6.3 Results

Demographics

The survey involved 58 participants, comprising 40 medical officers and registrars (69%) and 18 specialist obstetricians and gynaecologists (31%) (**Table 6.1**). Experience levels varied, with 37.9% (22/58) having 1-5 years of clinical practice, 32.8% (19/58) over 10 years, 27.6% (16/58) between 6-10 years, and 1.7% (1/58) with less than 1 year (post community-service) in clinical practice. More than 72% (42/58) worked in a tertiary institution, and the remaining 27% (16/58) at regional hospitals (Table 6.1).

Table 6.1. Demographic characteristics of participants

	Demographic	Frequency (%)
Career	Medical officers and registrars	40 (69)
	Medical specialist	18 (31)
Working experience	Less than 1 year	1 (1.7)
	1-5 years	22 (37.9)
	6-10 years	16 (27.6)
	More than 10 years	19 (32.8)
Level of health facility	Regional hospitals	16 (27.6)
	Tertiary	42 (72.4)

General experience and perspectives of healthcare workers on peripartum cardiomyopathy (PPCM) in women with preeclampsia

A majority of participants [77.6% (45/58)] occasionally encountered preeclamptic women suffering from left ventricular dysfunction or PPCM, while 13.8% (8/58) reported these cases as rare, and 8.6% (5/58) stated they frequently encountered them. The most frequently encountered cardiac-related complication by the participants during clinical care for patients with preeclampsia was pulmonary oedema, reported by 89.7% (51/58). This was followed by maternal and perinatal deaths, each reported by 5.2% (3/58) (**Table 6.2**).

Table 6.2: Common cardiac-related complications encountered during the care of patients with preeclampsia

Cardiac complication	Frequency (%)
Pulmonary oedema	52(89.7)
Maternal death	3 (5.2)
Perinatal death	3(5.2)
Total	58 (100)

Based on their experience, 50.0% (29/58) observed that cardiac complications from preeclampsia generally present postpartum, whereas 34.5% (20/58) indicated an antenatal presentation, and 15.5% (9/58) referred to intrapartum occurrences. When assessing the prognosis of PPCM, 56.9% (33/58) of participants indicated a moderate recovery outlook, while 29.3% (17/58) said it was good, and 13.8% (8/58) noted a high maternal mortality risk.

Methods for screening, long-term monitoring, and prognosis of cardiac-related complications in women with preeclampsia

Regarding routine screening for incidental cardiac complications in preeclamptic patients, 43.1% (25/58) base their screening on clinical judgment, some respondents (6/58, 10.3%) employ standardized protocols, 24.1% (14/58) screen only high-risk cases, and another 22.4% (13/58) do not conduct any screening at all.

In terms of methods used for screening for incidental cardiac complications in women with preeclampsia, 44.8% (26/58) use echocardiography, while 27.6% (16/58) rely on cardiac markers such as Pro-BNP and troponin. Additionally, 15.5% (9/58) do not use any tests, 10.3% (6/58) employ ECG, while one respondent (1.7%) did not specify the tests used for screening (**Table 6.3**).

Table 6 3: Tests used to screen preeclamptic women for incident cardiac complications

Tests	Frequency (%)
Echocardiography	26 (44.8)
Cardiac Biomarkers	16 (27.6)
No screening test used	9 (15.5)
Not specified	1 (1.7)
ECG	6 (10.3)
Total	57 (100)

For monitoring long-term complications of preeclampsia, 42 of 58 participants (72.4%) conducted regular blood pressure monitoring predominantly. Eight participants (14.1%) undertook comprehensive cardiovascular risk assessments, 5 (8.6%) undertook echocardiograms, 2 (3.4%) reported urinalysis and electrolyte (U&Es) results, one (1.7%) performed cardiac biomarker assessments, while one (1.7%) did not report any routine long-term monitoring.

The vast majority (84.5%; n = 49) reported using echocardiograms for follow-up and prognostication of patients with preeclampsia complicated by left ventricular dysfunction or PPCM. Other methods reported included clinical examination (6/58, 10.3%), cardiac biomarkers (1/59, 1.7%), and 3.4% (2/58) not employing any measures (**Table 6.4**).

Table 6.4. Measures used for prognostication

Measures	Frequency (%)
Echocardiogram	49 (84.5)
Clinical examination	6 (10.3)
None	2 (3.4)
Cardiac biomarkers	1 (1.7)
Total	58 (100)

Post-delivery, 24 participants (41.4%) indicated that they review all preeclamptic patients, whereas 16 (27.6%) only review those with complications, and 12 (20.7%) approach reviews on a case-by-case basis. Notably, 10.3% (6/58) reported that routine post-delivery reviews were not standard practice at their institutions (**Figure 6.1**).

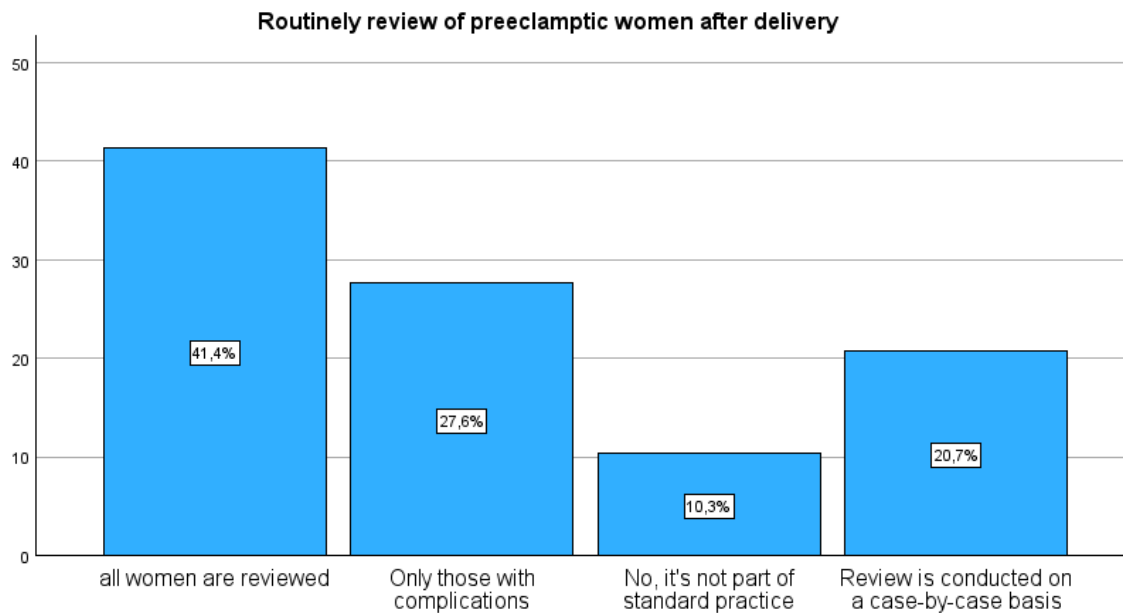


Figure 6.1. Routine review of preeclamptic patients after delivery

Role for cardiac biomarkers in managing the short- and long-term prognosis of preeclampsia

More than three-quarters of participants (44/58, 75.9%) believed that cardiac biomarkers play a role in managing the short- and long-term prognosis of preeclampsia, while 24.1% (14/58) disagreed.

Regarding the benefits of integrating cardiac biomarkers, several key advantages were noted by the 44 participants who supported the use of cardiac markers (see **Table 6.5**). Specifically, 52% (23/44) emphasized the critical role these biomarkers play in the screening and diagnosis of cardiac diseases.

“It assists with making a diagnosis of peripartum cardiomyopathy.” SPE31

“Cardiac biomarkers will help in the screening of patients and therefore we may diagnose patients with cardiac disease early.” REG32

Additionally, 25% (11/44) highlighted their value in predicting outcomes for patients with cardiac diseases.

“This would help the clinician to prognosticate the patient.” REG07

“It helps in prognosis of the patient and preconception management in the next pregnancy.” SPE28

Furthermore, 4.5% (2/44) mentioned that these biomarkers could assist in both monitoring and management roles.

“It helps with monitoring and management of the patient.” REG 35

“Cardiac biomarkers will facilitate the monitoring and management of the condition, as well as provide guidance on the long-term effects of ventricular dysfunction.” REG42

Another 4.5% (2/44) indicated that they could help differentiate between cardiogenic and non-cardiogenic causes of pulmonary oedema.

“Helps differentiate between pulmonary oedema secondary to preeclampsia alone, or with cardiac complications.” REG23

“They help in assisting to determine the cardiac properties of the patient and distinguish between cardiogenic and non-cardiogenic pulmonary oedema.” REG46

Lastly, 9.1% (4/44) recognized the potential of these biomarkers for predicting or screening for preeclampsia in future pregnancies.

“For screening of preeclampsia in subsequent pregnancies.” REG20

“Cardiac biomarkers are elevated in preeclampsia and heart failure, and they may also help detect patients at risk of developing hypertensive disorder in long run.” REG37

Conversely, 14 participants who expressed scepticism about the use of cardiac biomarkers raised several concerns (**Table 6.5**). One participant pointed out the lengthy turnaround

times for test results, while 57.1% (8/14) questioned the evidence supporting the effectiveness of these biomarkers in screening for complications related to preeclampsia.

“Reason is we spend very short time with patients, results turnaround time is very long, by the time we get results, we no longer have contact with the patient.” SPE57

Additionally, 4/14 (28.6%) noted that the use of these biomarkers is not common practice at their institutions, while one participant (1/14, 7.1%) cited the cost of the cardiac biomarkers as a potential barrier to their implementation.

“Not enough supporting evidence.” REG40

“Not aware of any scientific evidence for it in preeclampsia without cardiac complications.” SPE44

“The biomarkers are cost implicated, can’t be generalised in our institution because the volume of patients we receive may be costly to do to all of them.” SPE28

Table 6.5. Role of cardiac biomarkers in managing the short- and long-term prognosis of preeclampsia

Affirmed role of cardiac biomarkers	Response	Number (n)	Percentage (%)
	Role in screening and diagnosis of cardiac diseases	23	52.3
	Role in prognostication of cardiac diseases	11	25

	Role in both monitoring and management of cardiac diseases	2	4.5
	Useful in predicting or screening for preeclampsia in future pregnancies	4	9.1
	could help differentiate between cardiogenic and non-cardiogenic causes of pulmonary oedema	2	4.5
	Not sure	2	4.5
	Total	44	100
No role of biomarkers	Response	n	%
	lengthy turnaround time of cardiac biomarkers	1	7.1
	Lack of evidence in support of Cardiac markers in women with preeclampsia	8	57.1
	not a standard practice at their institutions	4	28.6
	Cardiac biomarkers are costly	1	7.1
	Total	14	100

Treatment, follow-up, resolution and long-term complications of PPCM

The later survey questions received responses from 51 participants. When asked about treatment options for patients diagnosed with PPCM, 60.0% (30/51) recommended diuretics as the initial treatment. Other treatment recommendations included angiotensin-converting-enzyme inhibitors (23/51, 56.0%), digoxin (14/51 28%), beta-blockers (12.51, 24.0%), and bromocriptine (6/51, 12,0%). When it comes to follow-up care for patients with PPCM, 37.3% (19/51) of these participants typically conduct monthly check-ups, while 29.4% (15/51) opt for bi-weekly follow-ups, 23.5% (12/51) adhere to weekly sessions, and 9.8% (5/51) see patients after several months.

Regarding the timeline for resolution of PPCM, 51.0% (26/51) of participants believe it typically resolves within 1 to 6 months after birth, 35.3% (18/51) think it resolves after more than 6 months, 11.8% (6/51) perceive resolution within a month, and 2.0% (1/51) believed it resolves within a week (**Figure 6.2**).

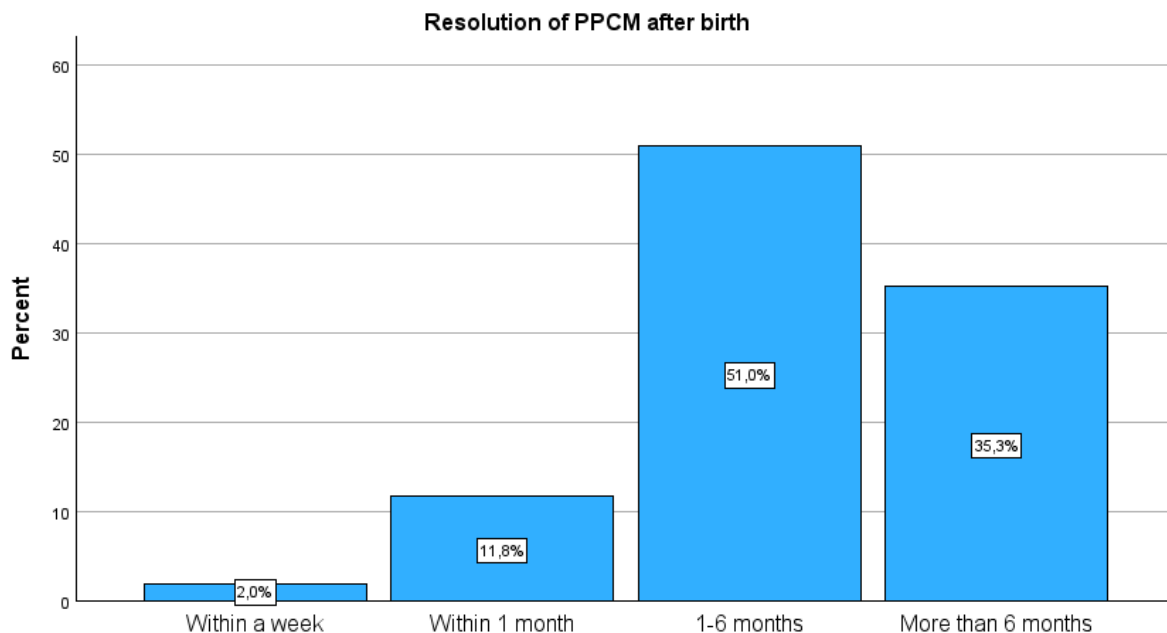


Figure 6.2. Timeline for resolution of PPCM

Some participants reported more than one long-term complication of PPCM that they believe is more common. Out of 88 responses, 38 (43.2%) identified heart failure as the most common long-term complication of PPCM. Meanwhile, 34 responses (38.6%) mentioned the recurrence of PPCM as the most frequent issue. Additionally, 15 replies (17.0%) pointed to psychological impacts, while only one (1.1%) indicated that death is the most common outcome.

There was no correlation between the participants' careers (as medical officers or specialists), their years of experience, and the frequency of cardiac-related complications observed ($p > 0.05$) (**Table 6.6**). Additionally, the participants' careers and years of experience did not influence their opinions on the use of cardiac biomarkers in managing preeclampsia or in assessing short-term and long-term prognosis ($p > 0.05$). However, the level of the healthcare facility did show a correlation with the likelihood of using cardiac markers (**Table 6.7**). Specifically, a significantly higher number of participants from tertiary institutions recognized the importance of cardiac biomarkers in the management and prognosis of preeclampsia ($p = 0.043$).

Table 6.6. Correlation between the participants' careers, their years of experience, and the frequency of cardiac-related complications observed

Variable	Cardiac-related complication			P value
	Pulmonary Oedema	Maternal Death	Perinatal Death	Pearson Chi-Square
	n (%)	n (%)	n(%)	
Career				
Medical officer	35(67.3)	3 (100.0)	2(66.7)	0.491
Medical specialist	17 (32.7)	0(0)	1(33.3)	
Years of experience				
less than 1 year	1 (1.9)	0 (0)	0(0)	0.142
1-5 years	20 (38.5)	0(0)	2(66.7)	
6-10 years	13 (25.0)	3 (100.0)	0(0)	
more than 10 years	18 (34.6)	0(0)	1(33.3)	
Level of health care facility				
Regional Hospital	14 (26.9)	1 (33.3)	1(33.3)	0.946
Tertiary Hospital	38 (73.1)	2(66.7)	2(66.7)	

Table 6.7. Correlation between the participants' careers, their years of experience, and their opinion on the use of cardiac biomarkers

Variable	Recommend use of cardiac biomarkers		P value
	Yes	No	
	n (%)	n (%)	
Career			
Medical officer	32 (72.7)	8 (57.1)	0.327*
Medical specialist	12 (27.3)	6 (42.9)	
Years of experience			

less than 1 year	1 (2.3)	0 (0)	0.533**
1-5 years	16 (36.4)	6 (42.9)	
6-10 years	14 (31.8)	2 (14.3)	
more than 10 years	13 (29.9)	6 (42.9)	
Level of health care facility			
Regional Hospital	9 (20.5)	7 (50.0)	0.043**
Tertiary Hospital	35 (79.5)	7 (50.0)	

*Fischer exact test, **Pearson Chi-Square

6.4 Discussion

The survey results provide valuable insights into the demographics, experiences, and clinical practices of healthcare professionals regarding cardiac complications associated with preeclampsia. Among 58 healthcare professionals surveyed, 77.6% reported encountering preeclamptic women with either left ventricular dysfunction or PPCM. The most frequently observed cardiac complication was pulmonary oedema, which was present in 89.7% of cases. However, routine screening for these complications revealed that only 10.3% of medical doctors in maternity wards followed standardized screening protocols. After delivery, 41.4% of healthcare professionals reviewed all preeclamptic patients, while others either focused on those with complications or assessed them on an individual basis. In terms of long-term care, 72.2% performed regular blood pressure monitoring, and a significant majority (75.9%) recognized the importance of cardiac biomarkers in managing the prognosis of preeclampsia.

The cohort primarily consisted of medical officers and registrars, making up just over two-thirds of the participants, while approximately one-third were specialists. This distribution reflects trends observed in other studies and is consistent with real-life practices in

regional and tertiary institutions (Atluri et al. 2023; Richards et al. 2020). The predominance of professionals with both 1-5 years and over 10 years of experience indicates a mix of new and seasoned practitioners, thus contributing to a range of perspectives on clinical practices. Notably, the majority of participants hailed from tertiary institutions. Being situated in higher-level care environments likely affords them enhanced access to resources, which could significantly impact their strategies for managing preeclampsia and its associated complications (Atluri et al. 2023). This notion is particularly evident in the survey results, where a significantly greater proportion of participants from tertiary institutions acknowledged the critical role of cardiac biomarkers in both the management and prognostic assessment of preeclampsia. These findings highlight the value of advanced training and resources available in these settings, which can enhance clinical decision-making and improve patient outcomes.

The data surrounding routine screening for cardiac complications in patients with preeclampsia in this study reveal a concerning trend: only 10.3% of medical doctors working in maternity adhered to standardized screening protocols, while more than 70% relied solely on routine blood pressure monitoring to assess long-term complications. This statistic highlights a significant gap in proactive measures aimed at monitoring a population that is already classified as high-risk for cardiac disease (Wu et al. 2017). The literature emphasizes that adherence to locally adapted guidelines is vital not only for reducing adverse outcomes in pregnant women but also for mitigating cardiovascular disease complications in the broader population (Moodley et al. 2018; Teo & Rafiq 2021). Therefore, the need for consistent application of these guidelines is of utmost importance.

Among the various methods of screening for cardiac-related complications in women with preeclampsia, echocardiography emerged as the most utilized technique, underscoring its significance in clinical practice. This method's ability to provide detailed insights into cardiac function and structural abnormalities is invaluable, particularly in a population at

increased risk for cardiovascular issues. The prominence of echocardiography aligns with findings from Celermajer et al. (2012), which illustrate the substantial importance of this diagnostic tool in the early detection of cardiac diseases. This is especially evident when echocardiography is contrasted with solely clinical examinations, which might miss subtle yet important cardiac changes, potentially causing serious complications (Celermajer et al. 2012). Given that preeclamptic patients are at an elevated risk of cardiovascular issues later in life, the early detection of cardiac anomalies through echocardiography can facilitate timely interventions and better health outcomes. This holds especially true for preeclamptic patients with pulmonary oedema. Literature indicates that a significant proportion of them have underlying cardiac disease (Dennis & Solnordal 2012; Nagaraj & Meganathan 2019).

It is alarming that a considerable proportion of healthcare providers reported not utilizing any screening tests for cardiac complications in preeclamptic patients, which raises questions about the overall management strategies in place for these patients. This gap in screening practices highlights the urgent need for enhanced education on established guidelines, risk stratification measures, and clinical practices that are crucial in managing preeclamptic patients effectively.

Some participants noted the inclusion of cardiac biomarkers in their screening protocols, while others advocate for their use in prognostics. This aligns with the current literature that supports the use of these biomarkers for cardiac risk assessment (Regitz-Zagrosek et al. 2018). Biomarkers such as microalbuminuria, C-reactive protein, and brain natriuretic peptide are particularly recommended for evaluating cardiovascular risk, especially in high-risk populations (Nakamura et al. 2005). Additionally, a systematic review by Singh et al. highlights the significant role of NT-proBNP in not only evaluating but also in predicting adverse outcomes in heart failure (Singh et al. 2024). The practical application of these biomarkers holds potential to enhance cardiovascular care and improve patient outcomes.

Post-delivery review practices exhibit varied approaches, with only 41.4% of patients with preeclampsia being reviewed. This finding is worrying, since preeclampsia is associated with several complications soon after delivery and later on in life (Poon et al. 2021). A post-delivery checkup is vital for the early detection of these complications.

Regular blood pressure monitoring was the most common long-term monitoring practice, reflecting an awareness of the significance of hypertension in the long-term health of these participants (Brown et al. 2021). Women with preeclampsia during pregnancy are at increased risk of developing chronic hypertension and other cardiovascular complications, and therefore, blood pressure monitoring in these patients is crucial (Regitz-Zagrosek et al. 2018; Williams et al. 2018; Giorgione, Cauldwell & Thilaganathan 2023; Palmiero et al. 2025). However, it is worth noting that regular blood pressure measurements typically refer to peripheral readings. While this method is commonly used to assess hypertension during pregnancy, it may not fully capture central hemodynamic changes. Findings from earlier chapters of this thesis indicate that pregnant women with hypertension and maternal complications have significantly higher central blood pressure compared to those without complications. These findings suggest that monitoring central blood pressure could be valuable for screening and managing maternal complications in hypertensive pregnancies. Incorporating central blood pressure monitoring into routine clinical practice could enhance the identification of at-risk individuals and potentially improve long-term outcomes for women who have experienced hypertensive disorders during pregnancy.

Cardiac disease-related complications in the context of patients with preeclampsia can manifest both in the short and long term. Pulmonary oedema was the most frequently reported immediate cardiac-related complication in our survey, observed by 86% of participants. This finding aligns with existing literature that emphasizes the severity and frequency of pulmonary oedema in preeclamptic patients, reinforcing its clinical significance (Dennis & Solnordal 2012; Vaught et al. 2018; Nagaraj & Meganathan 2019). A retrospective review involving clinical data from 182 patients diagnosed with PPCM

supports this observation about the rate of immediate complications of cardiac disease in pregnant women (Goland et al. 2009). In this retrospective review of 182 patients, 46 experienced major adverse events, with 17 requiring intensive care for severe pulmonary oedema. Some suffered cardiac arrest or arrhythmias, and tragically, 13 did not survive, highlighting the serious risks of PPCM.

Our survey also revealed that cardiac complications typically manifest in the postpartum period. This aligns with the significant physiological changes that occur during and after pregnancy, especially in preeclampsia, such as alterations in blood volume, reduced oncotic pressure, and increased cardiovascular strain (Giorgione et al. 2023). These factors can contribute to the development of pulmonary oedema and its sequelae in these women (Giorgione et al. 2023).

When considering long-term complications of PPCM, a significant majority (43.2%) of survey participants identified heart failure as the most common long-term complication. This is in line with findings from other studies and suggests a substantial burden on both the healthcare system and the patients, as heart failure can lead to ongoing medical management and a decrease in quality of life (Sliwa et al. 2010; Sliwa et al. 2011; McNamara et al. 2015). Furthermore, about two-thirds of those surveyed indicated that recurrence of PPCM is a frequent concern, highlighting the chronic nature of this condition and the ongoing risk for affected women. These findings align with previous research, such as Elkayam's review on risks in subsequent pregnancies for women with a history of PPCM (Elkayam 2014). Elkayam concluded that women who have previously experienced PPCM face an increased risk of relapse in subsequent pregnancies, emphasizing the need for careful monitoring and management in this population (Elkayam 2014).

Interestingly, psychological impacts emerged as a significant issue for some of the participants (17.0%), indicating that the repercussions of PPCM extend beyond physical health. The emotional and mental health challenges faced by women after experiencing

such a serious cardiac event cannot be overlooked, and addressing these needs is crucial for holistic patient care.

The findings of our survey reveal a range of perceptions regarding the prognosis of PPCM. Notably, a majority of participants expressed a moderately positive outlook for recovery. This cautious optimism aligns with studies in which many healthcare professionals have observed significant recovery among PPCM patients (McNamara et al. 2015; Moulig et al. 2019). Specifically, a follow-up study by Moulig et al. tracked PPCM patients for five years, revealing an average ejection fraction (EF) of 27% at the initial assessment. Remarkably, this improved to 50% after one year, with 72% of patients achieving full cardiac recovery by the five-year mark (Moulig et al. 2019). Similarly, a prospective study conducted by McNamara et al. also reported a recovery rate of 72%, which was noted one year after delivery (McNamara et al. 2015).

In managing patients diagnosed with PPCM, the majority of healthcare professionals in this study recommend initiating treatment with diuretics, a suggestion that aligns with current clinical practice guidelines emphasizing the need to address fluid overload to enhance symptoms and overall condition (Sliwa et al. 2010). Beyond diuretics, other treatment options suggested by these healthcare workers include angiotensin-converting enzyme inhibitors, digoxin, beta-blockers, and bromocriptine. The inclusion of bromocriptine represents a growing understanding of its role in PPCM management, as emerging research indicates that it may lead to substantial improvements in heart function and survival rates among affected individuals (Arrigo et al. 2017; Trongtorsak et al. 2022). This comprehensive approach acknowledges evolving treatment trends and the importance of tailoring interventions to optimize patient outcomes

Lastly, support for the incorporation of cardiac biomarkers in the management and short- and long-term prognosis of preeclampsia signals a positive trend toward adopting emerging standards in clinical practice (Clerico et al. 2024; Regitz-Zagrosek et al. 2018).

Several studies have demonstrated an association between cardiac biomarkers, such as NT-proBNP and Troponin I, and preeclampsia (Afshani et al. 2013; Fayers et al. 2013; Sadlecki et al. 2016; Ghomian et al. 2019; Jacobsen et al. 2022; Gencheva et al. 2021; Nguyen et al. 2022). A correlation has been observed between elevated systemic vascular resistance, left ventricular diastolic dysfunction, and reduced cardiac output in preeclamptic patients, along with elevated levels of NT-proBNP (Kim & Kim 2019; Gencheva et al. 2021; Jacobsen et al. 2022). Our recent study reported in chapter 5 observed that pregnant women with hypertensive complications had significantly higher levels of NT-proBNP and hs-cTnI than those without, suggesting that these cardiac biomarkers may be useful for screening and monitoring maternal complications (Mbongozi et al. 2025).

Conclusion

In conclusion, a significant number of participants support the integration of cardiac biomarkers in the management and prognosis of preeclampsia. This reflects a positive shift toward adopting new practices in clinical care. However, only a small percentage of healthcare workers are currently following screening protocols and reviewing all post-delivery patients with preeclampsia. This highlights an urgent need to educate and encourage healthcare workers on the importance of enhanced monitoring for cardiovascular issues in this high-risk population.

6.5 References

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CHAPTER 7

7.1 General discussion and synthesis of the findings

This thesis comprised interconnected studies that collectively examined the relationships between cardiac CBP, specifically NT-proBNP and hs-cTnI, and maternal outcomes in women with HDP, with a particular focus on Black African women in South Africa.

Additionally, a survey of healthcare professionals was conducted to evaluate clinical practices and perspectives regarding the assessment and use of cardiac biomarkers in patients with preeclampsia. The findings of this thesis collectively demonstrate that HDP are associated with significant alterations in vascular function, central hemodynamics, and cardiac biomarkers. When considered together, the studies included in this thesis provide an integrated perspective on the maternal morbidity associated with HDP and highlight opportunities to improve clinical risk assessment in affected women, while also revealing current gaps and potential acceptance among clinicians regarding the use of additional diagnostic markers in the management of preeclampsia.

The thesis included the following components:

1. A systematic review aimed at determining whether arterial stiffness remains elevated six weeks after delivery in women with a history of hypertensive disorders of pregnancy.
2. An in-study pilot assessing the reliability of the Microlife WatchBP Office Central device for measuring blood pressure in both hypertensive and normotensive pregnant women.
3. A clinical observational study, which covers the following aspects:

- a. Evaluation of the correlation between central blood pressure and peripheral blood pressure, coupled with establishing the thresholds for normal, mild and severe central hypertension,
 - b. The relationship between elevated central blood pressure, NT-proBNP and hs-cTnI in women with maternal complications of hypertensive disorders of pregnancy, and
4. A survey that aimed to evaluate the perspectives and experiences of healthcare workers on the inclusion of cardiac biomarkers in screening for cardiac complications in women with preeclampsia.

7.1.1 Summary of key findings

A meta-analysis was conducted to examine arterial stiffness in women with a history of hypertensive disorders during pregnancy. The meta-analysis found that arterial stiffness, an indicator of central blood pressure, as measured by Alx and PWV, remains significantly elevated beyond six weeks postpartum in women with a history of HDP compared to normotensive controls. Specifically, the pooled mean difference in Alx was 11.63 (95% CI: 1.72–21.54), and in PWV was 0.53 (95% CI: 0.27–0.78).

Following the systematic review, an in-study pilot study was conducted to assess the reliability of peripheral systolic and diastolic blood pressure measurements obtained using the Microlife WatchBP Office Central device in pregnant women, including those with hypertensive disorders. The reliability study (Chapter 3) confirmed that the Microlife WatchBP Office Central device provides excellent reliability for measuring peripheral blood pressure in pregnant women, including those with hypertensive disorders. Coefficients of variation were low (1.0–1.8%), intraclass correlation coefficients exceeded 0.96, and minimal detectable changes ranged from 0.2–0.4 mmHg. These findings established that the device could be used with confidence in the main clinical study.

In the main study, a strong positive correlation was observed between the cSBP and pSBP, as well as between the cDBP and pDBP, among normotensive pregnant controls, as measured using the Microlife WatchBP Office Central. The median pSBP among the 270 normotensive controls was 114 mmHg (IQR: 104.0-124.0) mmHg, and the median cSBP was 115.0 mmHg (IQR: 106.0-125.0). Out of the 270 normotensive controls, 146 had higher cSBP than the overall mean of 115 mmHg, and their median cSBP was 119.5 mmHg (IQR:111.0-128.0). Interestingly, the median cDBP for these patients remained normal at 64.0 (IQR: 55.0 - 73.0) mmHg. This is a curious finding because the cSBP is supposed to be lower than the pSBP in normotensive women. This suggests that although they had normal peripheral blood pressures, some of these women may already be having central hypertension if the threshold for central hypertension is taken as a cSBP of >115 mmHg, or they are at risk of developing central hypertension. While an elevated cSBP with normal central diastolic pressures may suggest early central hypertension, it could also represent an acute stress response rather than an indication of underlying vascular changes. Only longitudinal follow-up of these patients could test the outcomes of these women.

After establishing that there was a good correlation between the pSBP and pDBP and the cSBP and cDBP, receiver operating characteristics and linear regression analysis were used to establish the thresholds for central hypertension among black African pregnant women. These thresholds for central hypertension were found to be a cSBP of ≥ 116 mmHg and a cDBP of ≥ 78 mmHg, with an AUC of 0.7384, a sensitivity of 78.5%, and a specificity of 50.3%. This means that the thresholds for normal cSBP and cDBP should be ≤ 115 mmHg and ≤ 77 mmHg, respectively.

A linear regression equation was used to derive the thresholds for severe central hypertension among Black African women, as a cSBP of ≥ 148 mmHg and a cDBP of ≥ 95 mmHg. This means that the range for mild central hypertension should be a systolic blood pressure (SBP) of 116-147 mmHg, and the corresponding figures for the diastolic blood pressure (DBP) should be 78-94 mmHg. A search of current literature revealed no other studies that have established thresholds for severe central hypertension. The current

research reported in this thesis, therefore, seems to be the first to establish such thresholds.

The overall median cSBP and cDBP among women with eclampsia were significantly higher among preeclamptic women with or without severe features, and normotensive controls. This implies that the central blood pressure increases with the phenotype of preeclampsia, being highest in eclamptic patients, further implying that central blood pressure measurement may be better able to distinguish between the subtypes of HDP and phenotypes of preeclampsia than peripheral blood pressure.

The median pSBP among eclamptic patients with mild peripheral hypertension was 138.0 mmHg (IQR: 133.0-148.0) while the cSBP level in the same group was 145.0 mmHg (IQR: 140.0-150.0) mmHg. This finding suggests that in some eclamptic patients with mild pSBP, the cSBP is in the severe range. Overall, the median cSBP and median cDBP, respectively, among hypertensive women with maternal complications were significantly higher ($p = 0.004$) than the median cSBP and median cDBP of women without composite maternal adverse outcomes. This suggests that central hypertension may be a better indicator of composite adverse maternal outcomes.

The biomarker study demonstrated that women with HDP who developed maternal complications had significantly higher levels of cSBP (133 vs 128 mmHg), cDBP (75 vs 69 mmHg), NT-proBNP (446 vs 57 pg/mL), and hs-cTnI (12 vs 8 ng/L) compared to those without complications. These biomarkers were particularly elevated in women with renal failure, where NT-proBNP levels were nearly three times higher (821 vs 348 pg/mL) and hs-cTnI levels were more than three times higher (35 vs 11 ng/L) than in hypertensive women without renal failure.

Although the overall median serum levels of NT-proBNP in women with HDP were higher than the upper limit of normal of <150 pg/mL, none of these women were at risk of heart

failure because heart failure is only likely when the NT-proBNP concentration is ≥ 2000.0 pg/mL, and less likely when the levels are < 400 pg/mL (Welsh et al. 2022; Birrell et al. 2024; Mouzarou et al. 2025).

The median serum hs-cTnI levels in women with eclampsia were significantly higher than those in women with other phenotypes of HDP, although these levels did not exceed the upper limit of normal, which is < 30 ng/L. These levels, although not indicative of heart failure, are predictive of cardiac failure in the future (Welsh et al. 2022; Birrell et al. 2024; Mouzarou et al. 2025). The levels of NT-proBNP in preeclamptic women with severe features were higher than in the preeclamptic women without severe features, but lower than those with eclampsia, clearly indicating that the levels of NT-proBNP increase with the severity of HDP, as also (Dockree et al. 2021; Nguyen et al. 2022; Sarma & Scott 2023; Clerico et al. 2024; Bacmeister et al. 2024)l. 2024; Bacmeister et al. 2024).

Finally, a post-study survey was conducted among medical officers and specialists in the maternity units of regional and tertiary hospitals. The survey aimed to assess healthcare workers' perspectives and experiences regarding the use of cardiac biomarkers for screening cardiac complications in women with preeclampsia. Results demonstrated strong support among clinicians for integrating biomarkers such as BNP and Troponin I into the management and prognosis of preeclampsia, indicating a promising shift in clinical practice. However, the survey also revealed that only 41.4% of clinicians review all preeclamptic patients after delivery and only 10.3% of them follow standardised protocols for screening cardiac complications in preeclamptic women

7.1.2 Comparison with Existing Literature

The findings of this thesis are broadly consistent with, and meaningfully extend, the existing literature in several important respects.

Arterial stiffness as a marker of persistent vascular dysfunction

The systematic review and meta-analysis presented in Chapter 2 found that arterial stiffness, as measured by Alx and PWV, may remain significantly elevated beyond six weeks postpartum in women with a history of HDP compared with women who had normotensive pregnancies.

These findings are supported by previous studies demonstrating that women with a history of preeclampsia exhibit greater arterial stiffness than those with normotensive pregnancies ((Cecelja & Chowienczyk, 2012; Namugowa et al. 2019). However, global evidence regarding whether this vascular dysfunction persists beyond six weeks postpartum in women with prior HDP has remained limited. Studies addressing this question have reported mixed results, with most demonstrating sustained increases in arterial stiffness, while others found no persistent effect (Honigberg et al. 2019; Kim & Kim, 2019; Werlang et al. 2023). The findings of the systematic review in this thesis, which suggest that arterial stiffness may remain elevated after HDP, reinforce concerns that women with prior HDP may carry a greater long-term cardiovascular risk burden. These results indicate that hypertensive pregnancy is not merely a transient obstetric complication, but rather a marker of persistent vascular dysfunction that may extend well beyond the postpartum period. This evidence adds to the growing recognition of HDP as an important predictor of future cardiovascular disease (Leon et al. 2019; Williams et al. 2021)

Given these findings, incorporating measures such as cfPWV and Alx into routine postpartum care may facilitate earlier risk stratification and intervention in this high-risk population. Regular assessment of arterial stiffness could help identify women at increased risk of hypertension, atherosclerosis, and other cardiovascular conditions

before overt clinical disease develops (Cheng et al. 2019; Williams et al. 2021). Accordingly, integration of these measures into standard postpartum cardiovascular screening warrants consideration.

Central blood pressure: reliability, thresholds, and clinical utility

The pilot study demonstrated that the Microlife WatchBP Office Central provided consistent and reproducible blood pressure measurements in pregnant women, including those with hypertensive disorders. Earlier non-invasive methods for estimating central blood pressure in pregnancy primarily relied on applanation tonometry, including devices such as the SphygmoCor (AtCor Medical, Australia) (Fujime et al. 2012; Khalil et al. 2008; Macedo et al. 2008; Namugowa et al. 2017), and the EndoPAT (Itamar, Israel) (Meeme et al. 2017).

These devices, which had previously been used to assess central haemodynamics in pregnant women at the same institution where this study was conducted (Meeme et al. 2017; Namugowa et al. 2017), are relatively bulky, time-consuming, and require controlled testing environments, limiting their suitability for routine clinical use. By contrast, the Microlife WatchBP Office Central is an oscillometric device that non-invasively estimates central blood pressure and has been validated against invasive central blood pressure measurements (Cheng et al. 2013; Verberk et al. 2015). However, because its reliability for peripheral blood pressure measurement had not previously been evaluated in Black African pregnant women, an in-study pilot was undertaken. Based on the findings of this thesis, together with prior validation studies, the device appears capable of providing reliable and reproducible measurements of both peripheral and central blood pressures in pregnancy.

The threshold study (Chapter 4) established that $\text{cSBP} \geq 116 \text{ mmHg}$ and/or $\text{cDBP} \geq 78 \text{ mmHg}$ define central hypertension in pregnancy, with severe central hypertension defined as $\text{cSBP} \geq 148 \text{ mmHg}$ and/or $\text{cDBP} \geq 95 \text{ mmHg}$. To our knowledge, this is the first study to propose thresholds for severe central hypertension in pregnancy. The study also demonstrated a strong positive correlation between peripheral and central blood pressures in both normotensive and hypertensive women. The thresholds for central hypertension identified in Chapter 4 are lower than those proposed for non-pregnant populations (typically 130/90 mmHg) (Cheng et al. 2019). This difference is physiologically plausible, given the lower systemic vascular resistance characteristic of normal pregnancy (Macedo et al. 2008; Mahendru et al. 2014). These findings are consistent with Chulkov et al. (2015), who reported that a cSBP of 115 mmHg in pregnancy may indicate increased risk for preeclampsia, and with Booysen et al. (2013), who identified an upper cSBP threshold of 112 mmHg in young Black South Africans. The thresholds for severe central hypertension ($\text{cSBP} \geq 148 \text{ mmHg}$ and/or $\text{cDBP} \geq 95 \text{ mmHg}$), however, have not previously been reported. In summary, this thesis confirms the reliability of the Microlife WatchBP Office Central for non-invasive blood pressure measurement in pregnant women. By identifying pregnancy-specific thresholds for central hypertension, the research offers valuable clinical guidance and supports the use of central blood pressure monitoring in routine antenatal care to improve outcomes for mothers and babies.

Eclampsia and central blood pressure

The observation that women with eclampsia and only mild peripheral hypertension had severe central hypertension (Chapter 4) addresses an important gap in the literature. Previous studies have shown that up to 40% of women with eclampsia may present with only mild or even normal peripheral blood pressure, yet the haemodynamic basis of this paradox has remained poorly understood (Douglas et al. 1994; Sibai, 1990). In our cohort, women with mild peripheral systolic hypertension (median pSBP 138 mmHg) demonstrated central systolic pressures within the severe range (median cSBP 145

mmHg). Because central blood pressure more directly influences cerebral perfusion pressure than brachial pressure, these findings suggest that the true cerebrovascular load may be substantially underestimated when clinical assessment relies solely on peripheral measurements. This provides a plausible explanation for why eclamptic seizures may occur in women whose brachial blood pressure appears only modestly elevated. The findings are consistent with the vasogenic oedema hypothesis of eclampsia, which proposes that abrupt increases in cerebral perfusion pressure overwhelm autoregulatory mechanisms, resulting in endothelial dysfunction, blood–brain barrier disruption, and cerebral oedema (Cipolla & Kraig, 2011).

Collectively, these findings suggest that central blood pressure may be a more clinically relevant marker of seizure risk than peripheral blood pressure in some women with HDP. Incorporating CBP assessment into obstetric care could therefore improve identification of women at imminent risk of eclampsia, particularly those who may otherwise appear low risk on the basis of brachial blood pressure alone.

Cardiac biomarkers reflect disease severity

The observation that NT-proBNP and hs-cTnI concentrations were elevated in women with HDP (Chapter 5) is consistent with previous studies (Bacmeister et al. 2024; Gencheva et al. 2021; Ghomian et al. 2019; Hamad et al. 2009). This thesis advances existing knowledge by specifically examining how these cardiac biomarkers relate to a spectrum of maternal complications in HDP. Notably, although elevated biomarker levels were observed across composite complications, the greatest increases occurred in women who developed renal failure. NT-proBNP concentrations were nearly threefold higher, and hs-cTnI concentrations more than threefold higher, compared with hypertensive pregnant women without renal impairment. This novel association has not previously been emphasised in the literature

and carries important clinical implications. Elevated NT-proBNP and hs-cTnI may serve as useful adjunctive markers for identifying women with HDP who are at increased risk of renal complications, thereby enabling earlier recognition and more targeted surveillance of this particularly high-risk group.

7.1.3 Implications for Clinical Practice

The findings of this thesis have several practical implications for clinicians managing women with HDP.

Central blood pressure measurement should be considered in women with HDP

The finding that eclamptic women with only mild peripheral hypertension had severe central hypertension (Chapter 4) suggests that reliance on PBP alone may underestimate haemodynamic burden. In addition, the observation that CSBP may be more effective than PSBP in screening for maternal complications of HDP supports the potential clinical value of central blood pressure assessment.

Furthermore, the Microlife WatchBP Office Central device was shown to be reliable (Chapter 3), and its portability and relative ease of use in clinical settings make it a practical option for central blood pressure estimation. Although it is more expensive than standard automated blood pressure monitors, its use may be justified in selected high-risk patients where more accurate haemodynamic assessment could improve risk stratification and management.

Cardiac biomarkers may help identify women with maternal complications, particularly those at risk of renal involvement.

The finding that NT-proBNP and hs-cTnI were markedly elevated in women with HDP and renal failure (Chapter 5) suggests that these biomarkers may have utility in identifying women who require closer monitoring. A hs-cTnI value of 11 ng/L or higher predicted renal failure with a sensitivity of 79% and a specificity of 50% (AUC=0.75), while an NT-proBNP value of 167 pg/mL or higher predicted renal failure with a sensitivity of 93% and a specificity of 65% (AUC=0.69). These cut-offs may assist clinicians in risk stratification.

Structured postpartum follow-up should be standard care

The systematic review (Chapter 2) demonstrated that arterial stiffness remains elevated beyond six weeks postpartum in women with a history of HDP, indicating persistent cardiovascular risk. The clinician survey (Chapter 6) revealed that only 41.4% of clinicians review all preeclamptic patients post-delivery. Structured postpartum cardiovascular assessment, including blood pressure monitoring, cardiovascular risk counselling, and lifestyle modification advice such as dietary modification, exercise, and smoking cessation, should be established as standard care for all women with a history of HDP.

7.1.4 Implications for Policy and Health Systems

The findings of this thesis also have implications for health policymakers and health system managers.

Cost implications and Targeted implementation of central blood pressure monitoring at higher levels of care

Implementation of central haemodynamic monitoring and cardiac biomarkers is feasible and potentially cost-effective. The pilot study demonstrated that the Microlife WatchBP Office Central device provides reliable and reproducible blood pressure measurements in pregnant women, including those with hypertensive disorders. Unlike earlier central haemodynamic monitoring technologies, this device is portable, relatively affordable, and easy to use in routine clinical settings. These features make it a practical option for estimating central blood pressure in real-world clinical practice.

From a policy perspective, tertiary and regional obstetric centres managing high-risk pregnancies should consider phased adoption of these oscillometric devices capable of estimating central blood pressure. Targeted implementation would allow health systems to balance the higher acquisition costs of central monitoring devices with the potential clinical benefits of improved cardiovascular risk stratification and earlier intervention.

Although more expensive than standard automated blood pressure monitors, the cost of these devices should be considered in relation to the potential benefits of improved risk identification. Early recognition of patients at risk of severe complications may facilitate timely intervention, reducing the need for costly emergency care, intensive management, and even maternal deaths—particularly given that HDP remain leading causes of maternal and perinatal morbidity and mortality worldwide.

From a policy perspective, the cost of implementation can be considered at different levels of the health system. If central haemodynamic monitoring devices were introduced across approximately 100 antenatal clinics in the Eastern Cape, assuming one device per clinic at an estimated cost of R15,800 (≈\$860), the total capital investment would be approximately R1.58 million (≈\$86,000). While this represents a substantial upfront investment, it provides a useful upper-bound estimate for province-wide implementation.

A more pragmatic and immediately feasible strategy would be targeted implementation at higher levels of care. Equipping all 8 regional and tertiary hospitals in the Eastern Cape province with 1–2 devices each would require a total investment of approximately R126,400–R252,800 (≈\$6,900–\$13,800), representing a small fraction of the cost of full primary care rollout. This phased approach allows for initial deployment in high-risk settings, where the burden of severe disease is greatest, and the potential clinical benefit is maximised.

Importantly, the costs of implementation should be viewed in relation to the financial burden of severe maternal complications. The management of a single high-risk pregnancy complicated by severe disease often requires intensive care support. In a South African central hospital, the cost of intensive care has been estimated at approximately R22,870 per patient day, with mean admission costs ranging from R157,883 to R245,087 depending on case complexity (Mahomed & Mahomed 2019). These figures highlight that even short ICU stays represent a substantial financial burden on the health system. When combined with additional costs such as high-dependency care, emergency caesarean delivery, blood transfusion, and management of complications such as stroke, the total cost per severe case may be considerable.

Preventing even a small number of such severe cases could offset a substantial proportion of the implementation costs. For example, averting 10–20 severe cases annually—particularly those requiring ICU admission—could translate into estimated savings of approximately R1.6 million to R4.9 million per year (≈\$87,000–\$267,000), based on South African ICU cost data (Mahomed & Mahomed 2019). From a cost–benefit perspective, these projected savings are comparable to—or may exceed—the initial capital investment required for implementation, suggesting that even modest reductions in severe morbidity could render this strategy cost-saving within a short time horizon. Notably, even preventing 1–2 ICU admissions could offset the cost of implementing devices at all regional and tertiary hospitals.

Taken together, these findings support a policy approach that promotes targeted implementation, clinician training, and integration of oscillometric central blood pressure monitoring and cardiac biomarkers within maternal care protocols. Such strategies could improve early detection of severe disease, optimise clinical decision-making, and ultimately help reduce the maternal and perinatal morbidity and mortality associated with hypertensive disorders of pregnancy.

Integration of cardiac biomarker assessment into obstetric protocols

NT-proBNP and high-sensitivity troponin I testing, at approximate costs of \$15–\$25 (≈R275–R460) and \$10–\$20 (≈R185–R370) respectively, represent relatively low-cost adjuncts. As these biomarkers are already widely available in hospital laboratories, their incorporation into obstetric care requires minimal additional infrastructure. They may serve as useful adjunctive tools in the assessment of pregnant patients with suspected complications of preeclampsia. Notably, clinician survey findings from this thesis indicate favourable attitudes toward their adoption, supporting the feasibility of integration into routine practice. Their integration into obstetric protocols for women with severe preeclampsia or suspected peripartum cardiomyopathy could improve early detection of cardiac involvement. National and institutional guidelines should be updated to include recommendations for cardiac biomarker assessment in selected high-risk patients.

Development of standardised screening protocols

The clinician survey (Chapter 6) revealed that only 10.3% of clinicians follow standardised protocols for screening cardiac complications in preeclamptic women. National and institutional guidelines should be updated to include recommendations for central blood

pressure monitoring and cardiac biomarker assessment in selected high-risk patients. The development and dissemination of such protocols, accompanied by clinician education, could improve the consistency and quality of care.

Establishment of structured postpartum cardiovascular follow-up programmes

Given the persistent elevation of arterial stiffness documented in Chapter 2 and the increased long-term cardiovascular risk associated with HDP (Leon et al. 2019; Wu et al. 2017), health systems should consider establishing dedicated postpartum cardiovascular clinics for women with a history of preeclampsia. Such programmes could provide structured blood pressure monitoring, cardiovascular risk assessment, and lifestyle counselling, potentially reducing long-term cardiovascular morbidity.

7.2 Limitations and strengths of the study

The strength of this study lies in its prospective inclusion of patients with preeclampsia featuring severe features and those with eclampsia, groups that are often excluded from prospective studies due to the emergency nature of their conditions. This study specifically recruited a larger number of these patients to encompass the full spectrum of HDP. To the best of our knowledge, there are no other studies in recent literature that include as many eclamptic cases and focus on central blood pressure.

However, the clinical observational study does have limitations. One of the limitations is that the follow-up period was limited to seven days after delivery, potentially missing complications that may have occurred later. However, this may be mitigated by the fact that most immediate complications of HDP occur during the antenatal and immediate

postpartum periods, which is seven days after delivery. Second, the study was conducted exclusively in a Black African population, which may limit generalizability to other racial groups. Nevertheless, the physiological aspects of pregnancy and preeclampsia tend to present similarly across different races, which may address some concerns regarding the generalizability of the findings.

7.3 Overall Conclusion

The overall conclusion of this thesis is that arterial stiffness may remain elevated in women with a history of preeclampsia for more than six weeks postpartum, indicating a potentially increased risk for cardiovascular disease. Additionally, the Microlife WatchBP Office Central device demonstrated reliable and reproducible blood pressure measurements in pregnant women, including those with hypertensive disorders. Furthermore, the thesis established the threshold values for central hypertension as systolic blood pressure of 116 mmHg or higher and/or diastolic blood pressure of 78 mmHg or higher, with severe central hypertension defined as a systolic blood pressure of 148 mmHg or higher and/or diastolic blood pressure of 95 mmHg or higher.

Additionally, the thesis confirms a strong positive correlation between peripheral and CBP in both normotensive and hypertensive populations. It indicates that severe central hypertension is associated with a higher rate of maternal complications compared to mild central hypertension. In contrast, no significant association was found between composite maternal outcomes and the severity of peripheral blood pressure. The thesis further suggests that CBP may be a superior parameter for evaluating hypertension, particularly in cases of eclampsia. Overall, this suggests that CBP should be prioritized when identifying patients at risk for complications related to HDP and should be included in the routine care of pregnant women. Moreover, the thesis highlights that elevated levels of CBP, NT-proBNP, and hs-cTnI were significantly present in Black African women with HDP, particularly among those experiencing adverse maternal outcomes. Notably, women with renal failure

exhibited even greater increases in these biomarkers compared to those without renal complications. Lastly, a substantial number of participants expressed support for incorporating cardiac biomarkers in the management and prognosis of preeclampsia, reflecting a positive trend towards adopting innovative practices in clinical care.

7.4 Recommendation and Future Directions

Clinicians and policy-makers should consider incorporating measurements of central blood pressure, NT-proBNP, and hs-cTnI into their evaluations to enhance early detection, management, and intervention for women experiencing maternal and perinatal complications related to HDP, particularly those with renal complications.

Future research could focus on interventions targeting these biomarkers and central blood pressure to assess their impact on improving outcomes. Additionally, expanding studies to include larger and more diverse populations will enhance the generalizability of these findings and contribute to the development of clinical guidelines. It would also be of interest to longitudinally evaluate CBP in patients with gestational hypertension and determine whether central blood pressure monitoring can predict the development of preeclampsia or eclampsia in these patients. The ability to predict severe disease easily would assist clinicians in managing such patients effectively.

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APPENDICES

Appendix A : Data capture sheet (study 2

Correlation of central blood pressure and peripheral blood pressure with pro-BNP and troponin I - measures of future cardiovascular disease- among women with preeclampsia

STUDY NUMBER

History

1. Age
2. Ethnicity (please tick)
 - a. African b. Coloured c. White d. Asian
3. Marital status (please tick)
 - a. Married b. single c. divorced d. other (please specify)
4. Highest Level of education (please tick)
 1. None (No formal education) 2. Primary
 3. Secondary 4. Tertiary
5. Address
.....
6. Occupation of woman (please tick)
 - a. Unemployed b. Employed c. Other(specify).....
7. If married, is the spouse employed? Yes=1/No=2.....
8. Parity: Gravida..... Para..... +.....
9. Booking
 - a) a. Booked [] b. Unbooked []

- b) Gestational age at booking.....
- c) No of subsequent antenatal visits.....
- d) Date of last antenatal visit.....

10. Was she suffering from any medical illnesses before pregnancy?

- a) Diabetes Yes=1/No=2.....
- b) Hypertension Yes=1/No=2.....
- c) Other Yes=1/No=2..... (if yes please specify)

.....

11. For a participant with HDP,

1.1. Type of HDP (gestational HPT, preeclampsia, eclampsia, chronic hypertension)

.....

1.2. is she on medication? Yes=1/No=2.....

I. When was she started on the medication?.....

II. State the medication (with dosage) she is using:

.....

12. State any medical condition identified during this pregnancy (other than HDP)

.....

13. Is she on any Medical treatment (other than antihypertensives)?

Yes=1/No=2.....

(If yes please specify)

.....

14. Past obstetric history

Pregnancy and year	Mode of delivery	Weight at birth	Any complications	Outcome (stillbirth/alive)
1.				

2.				
3.				
4.				
5.				
6.				

At recruitment

15. Gestational age.....

16. Bp..... pulse temp..... proteinuria.....

17. Central blood pressure

18. Pulse wave analysis

19. augmentation index.....

20. Height..... WeightBMI.....

Intrapartum

21. Magnesium sulphate Yes=1/No=2.....

If yes, prophylactic or therapeutic?.....

22. Bp..... pulse temp..... proteinuria.....

23. Mode of delivery (please tick)

i) Vaginal delivery

ii) Caesarean Section (indication).....

iii) Instrumental vaginal delivery

24. Retroplacental clot Yes=1/No=2.....

Postpartum care

25. Neonate

- i) Birth weight.....Sex.....
- ii) Any structural abnormalities
(specify).....
- iii) Outcome (alive/stillbirth)
if stillbirth, fresh or macerated.....
if alive, Apgar score: 1 min.....5 min.....10 min.....

26. Use of magnesium sulphate Yes=1/No=2.....

27. Type of antihypertensive treatment.....

28. Bp..... pulse temp..... proteinuria.....

29. Central blood pressure

30. Pulse wave analysis

31. augmentation index.....

Perinatal complications (tick if present)

1.IUGR 2. Foetal distress 3. Foetal death 4. Other (please specify)

Maternal complications (tick if present)

1. Renal failure 2. Pulmonary oedema 3. CVA 4. Cerebral oedema 5. PRES 6. DIC
7. Abruptio Placentae 8. DIC 9. HELLP syndrome 10. ICU admission 11. Other
(please specify)

Investigations

1. Hb.....Platelet count.....Urea.....Creatinine.....AST.....ALT.....
LDH.....

Appendix B: Information sheet (study 2)

Correlation of central blood pressure and peripheral blood pressure with pro-BNP and troponin I - measures of future cardiovascular disease- among women with preeclampsia

You have been invited to participate in a research experiment titled “correlation of central blood pressure and peripheral blood pressure with pro-BNP and troponin I - measures of future cardiovascular disease- among women with preeclampsia.” This study is being conducted by Dr Xolani Mbongozi in the Department of Obstetrics and Gynaecology, Walter Sisulu University. We would like you to read and then sign the consent form, indicating that you understand your rights as a participant. For any questions, please contact Dr Xolani Mbongozi at 0735524763.

Purpose and procedure

The purpose of this study is to evaluate the central blood pressure and arterial stiffness non-invasively in women with hypertensive disorders of pregnancy to determine whether these vary with the severity of the condition, and how they relate to maternal and perinatal outcomes. If you agree to participate in this study, you will be asked to complete a questionnaire. After the questionnaire phase, the actual procedure will involve your arm being cuffed and occluded for 2 minutes. The occlusion feels a bit uncomfortable, but it only lasts for 2 minutes. After this, about 5mls of blood will be drawn from your arm to be taken to the laboratory for examination. The prick will be a bit painful but only lasts for a few seconds.

Risks

There is no risk on you in participating in the research apart from slight discomfort.

Benefits

There is no direct benefit to the participants in the study, but the results of the study may benefit others in future.

Confidentiality

Only the primary researcher and his supervisors will have the confidence of the data.

Right to withdraw or decline to participate

Your participation is voluntary, and you may choose to withdraw at any time of the study without any consequences.

Appendix C: Translated information sheet (study 2)

Correlation of central blood pressure and peripheral blood pressure with pro-BNP and troponin I - measures of future cardiovascular disease- among women with preeclampsia

(Uxinezelelo lwegazi kwimithambo ekufuphi nentliziyo ne arterial stiffness kumanenekazi anesifo i-hypertensive disorders of pregnancy, neziphumo kumanenekazi lawo neentsana zawo)

Isimemo sokuthatha inxaxheba kuphando

Uyamenywa ukuba uthathe inxaxheba kuphando olusihloko esithi “uxinezelelo lwegazi kwimithambo ekufuphi nentliziyo ne arterial stiffness kumanenekazi anesifo i-hypertensive disorders of pregnancy, neziphumo kumanenekazi lawo neentsana zawo”. Oluphando luqhutywa ngu Gqirha uXolani Mbongozi phantsi ko Prof Buga kwisebe le obstetrics and Gynaecology, Walter Sisulu university. Siyakuthanda ukuba ufunde uthi wakugqiba utyikitye kule mpepha-mvume ngelithi uyawaqonda amalungelo akho njenga nomthabathi

nxaxheba. Ukuba unemibuzo, qhakamshelana no Gqirha uXolani Mbongozi ku 0735524763.

Injongo nenqubo

Injongo yesisifundo kukuphanda uxinezelelo lwegazi kwimithambo ekufuphi nentliziyo ne arterial stiffness kumanenekazi ane hypertensive disorders of pregnancy, sifuna ukuqonda ukuba ezizinto ziyatshintsha na ngokuya isimo sesigulo siba maxongo, nokuba zizalana njani neziphumo komama nentsana zabo.

Xa uvuma ukungenela koluphando uza kubuzwa imibuzo. Emva kwemibuzo uzakumfaxazwa engalweni kangangemizuzu emibini. Ukumfaxangwa oku akumandanga kodwa iba yimizuzu emibini kuphela. Emva koko uyakutsalwa igazi elizakuya kuxilongwa e-laboratory. Kuyakuthi kubebuhlungu imizuzwana nje xa kutsalwa igazi.

Iziphene

Ngaphandle nje kongungaphatheki kamandana okuncinci ngenxa yokumfaxazwa akukho ngozi eza noluphando.

Iinzuzo

Akukho nzuzo efumaneka kuba thabathi nxaxheba kolu phando kodwa iziphumo zoluphando zinokuba yinzuzo kwabanye abantu kwilixa elizayo.

Imfihlelo

linkcukacha ezifunyenweyo kolu phando ziyakubayimfihlo, ziyakwaziwa ngu mphandi nabamphetheyo kuphela.

Ilungelo lokurhoxa okanye ukwala ukuthatha inxaxheba

Inxaxheba yakho koluphando ingokuthanda kwakho. Uvumelekile ukuba uyeke nanini na uthanda, isigqibo sakho asiyi kubangela ukuba uphulukane namalungelo akho.

Appendix D: Informed consent (study 2)

Correlation of central blood pressure and peripheral blood pressure with pro-BNP and troponin I - measures of future cardiovascular disease- among women with preeclampsia

I have had the opportunity to ask questions concerning any and all aspects of the project and my questions have been answered. I understand that participation is voluntary and that I may withdraw my consent at any time without prejudice to me. Confidentiality of records concerning my involvement in this project will be maintained in an appropriate manner. When required by law, the records of this research may be reviewed by applicable government agencies. A copy of this written consent has been given to me and I understand that if I have any questions concerning this research, I can contact the investigator stated above or the supervising faculty member at Walter Sisulu University

Signature of the participant

Date

Appendix E: Translated informed consent (study 2)

Uxinezelelo lwegazi kwimithambo ekufuphi nentliziyo ne arterial stiffness kumanenekazi anesifo i-hypertensive disorders of pregnancy, neziphumo kumanenekazi lawo neentsana zawo

Isivumelwano

Ndilifumene ithuba lokubuza ngako konke, imibuzo yam iphendulwe. Ndinolwazi ngokuthatha inxaxheba ngokuzithandela, ndivumelekile u kuyeka xa ndithanda. Inkcukacha zam zakugcinwa ziyimfihlo kwaye zigcinwe ngesiphatho. Umthetho unokucela ukuba oluphando lujonwe nguceba ojongene nezifundo zophando.

Iphepha elibhaliweyo ngoluphando ndiyifumene, kwaye ukuba ndinemibuzo ngoluphando ndiya kuyibhekisa kumphandi e Walter Sisulu University.

Isayini yomthathi nxaxheba

Ngomhlawe

Appendix F: Google form (study 3)

Assessment of clinical practices and cardiac biomarker screening in preeclampsia: a survey of healthcare professionals

Demographic data

1. Career

☐-general medical officer/Registrar

☐Medical specialist

2. How many years of experience do you have as a medical doctor (excluding internship)?

- ☐ Less than 1 year
- ☐ 1-5 years
- ☐ 6-10 years
- ☐ More than 10 years

3. What is the name of your hospital?

4. What level of healthcare facility do you work in?

- ☐ Regional Hospital
- ☐ Tertiary Hospital

Experience and perspectives

1. What are the common cardiac-related complications you have encountered during the care of patients with preeclampsia?

.....

2. What is the prognosis of patients with Peripartum cardiomyopathy (PPCM) during pregnancy and postpartum?

- A. Good recovery
- B. Moderate recovery
- C. High maternal mortality

3. In your experience, when do the cardiac complications of preeclampsia tend to present: antenatally, intrapartum, or postpartum?

- A. Primarily antenatally

- B. Mostly intrapartum

- C. Commonly postpartum

4. Do you routinely screen preeclamptic patients for incident cardiac complications?

- A. Yes, with standardized protocols

- B. Yes, but only in high-risk cases

- C. No, we don't screen routinely

- D. Screening is done based on clinical judgment

5. At your institution, what tests are used to screen preeclamptic women for incident cardiac complications? (you can tick more than one)

- A. Regular ECG monitoring

- B. Echocardiography

- C. Cardiac biomarkers eg ProBNP, Troponin and others

- D. none

- E. Other (please specific)

6. At your institution, do you routinely review preeclamptic women after delivery?

- A. Yes, all women are reviewed

- B. Yes, but only those with complications

- C. No, it's not part of our standard practice

- D. Review is conducted on a case-by-case basis

7.(If your answer to Q6 is yes) What specific screening for short-term and long-term complications of preeclampsia is carried out upon review?

- A. Follow-up echocardiograms
- B. Assessment of cardiac biomarkers
- C. Comprehensive cardiovascular risk assessment
- D. Regular blood pressure monitoring
- E. Other

8. What role do ECG, cardiac echo, and BNP, NTproBNP, and cardiac troponin have in the management of women with preeclampsia at your institution?

- A. Standard part of the assessment process
- B. Used primarily for symptomatic patients
- C. Limited role; not routinely used

9. How often do you get preeclamptic women complicated with left ventricular dysfunction or peripartum cardiomyopathy?

- A. Rarely
- B. Occasionally, in a small percentage
- C. Commonly, in many cases

10. At your institution, what follow-up and prognostic measures do you use in the management of patients with preeclampsia who develop left ventricular dysfunction or PPCM?

- A. None
- B. Echocardiogram

- C. Clinical examination

- D. Cardiac biomarkers

11. In your opinion, is there any role of using cardiac biomarkers in the management, short-term, or long-term prognosis of preeclampsia (and why)?

- A. Yes

- B. No

12. What initial treatments do you recommend for patients diagnosed with PPCM? (Select all that apply)

A. Beta-blockers

B. ACE inhibitors

C. Diuretics

D. Anticoagulants

E. Other: _____

13. What is the typical frequency of follow-up appointments for your PPCM patients?

a) Weekly

b) Bi-weekly

c) Monthly

d) Every few months

14. On average, how soon after birth do you think PPCM typically resolve?

a) Within a week

b) Within 1 month

c) 1-6 months

d) More than 6 months

15. What are the common long-term complications you observe in PPCM patients? (Select all that apply)

a) Heart failure

b) Recurrence of PPCM

c) Psychological impacts

d) Other: _____

Appendix G: Informed Consent form (study 3)

Assessment of clinical practices and cardiac biomarker screening in preeclampsia: a survey of healthcare professionals

We would like to invite you to complete a survey online.

We would like to hear your thoughts and experiences regarding the inclusion of cardiac biomarkers in the screening process for cardiac complications in women with preeclampsia.

Participation in this research is voluntary, and your identity will be kept anonymous. Neither your name nor the name of your institution will be captured.

The questionnaire will take ten to fifteen minutes to fill in.

Target audience:

Medical officers and medical specialists who work in maternity unit at Mthatha regional Hospital and Nelson Mandela Academic hospital.

Consent:

I have read the information on the proposed study and was given adequate time to rethink the issue. The aim of the study is sufficiently clear to me. I have not been pressured to participate in any way.

I understand that participation in this Study is completely voluntary and that I may withdraw from it at any time and without supplying reasons.

I know this Study has been approved by the Walter Sisulu University Health Sciences Research Ethics Committee (Ethics number 037/2025). I am fully aware that the results of this Study will be used for scientific purposes and may be published. I agree to this, provided my privacy is guaranteed.

I hereby give consent to participate in this Study

☐ I agree, in this case please PROCEED to the next question

☐ I don't agree- in this case do NOT proceed

Appendix H: Ethical clearances



FACULTY OF HEALTH SCIENCES
POSTGRADUATE EDUCATION, TRAINING, RESEARCH AND ETHICS UNIT

**HUMAN RESEARCH COMMITTEE
CLEARANCE CERTIFICATE**

PROTOCOL NUMBER : 035/2022

PROJECT : CENTRAL BLOOD PRESSURE AND ARTERIAL STIFFNESS IN WOMEN WITH
HYPERTENSIVE DISORDERS OF PREGNANCY AND MATERNAL AND
PERINATAL OUTCOMES

AMENDED TITLE : CORRELATION OF CENTRAL BLOOD PRESSURE AND PERIPHERAL BLOOD
PRESSURE WITH PRO-BNP AND TROPONIN I - MEASURES OF FUTURE
CARDIOVASCULAR DISEASE- AMONG WOMEN WITH PREECLAMPSIA

INVESTIGATOR(S) : DR XOLANI B MBONGOZI

DEPARTMENT : OBSTETRICS & GYNAECOLOGY

DECISION OF THE COMMITTEE : APPROVED

DATE OF APPROVAL : 17 OCTOBER 2022

DURATION : 1 YEAR (17 OCTOBER 2022 TO 16 OCTOBER 2023)

CONDITIONS : NONE

N.B You are required to provide the committee with a progress or outcome report of the research after every 6 months and/ or 1 year. The committee expects a report on any changes in the protocol as well as any untoward events that may occur at any time during the study not later than 7 days of knowing as the investigator/s.


PROF EJ NDEBIA, PhD
CHAIRPERSON

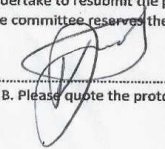
WALTER SISULU UNIVERSITY
ACADEMIC HEALTH SERVICE COMPLEX OF THE
EASTERN CAPE
POSTGRADUATE EDUCATION AND TRAINING
FACULTY OF HEALTH SCIENCES
WALTER SISULU UNIVERSITY
P/BAG X 1, WSU, 5117, E.C
TEL: (047) 502 2100 / FAX: (047) 502 2101

18.10.22
DATE

DECLARATION OF INVESTIGATOR(S)

(To be completed in duplicate and one copy returned to the Research Officer at Office AB 02 GF 03 Administration Building, Sisson Street Campus, Fort Gale, Mthatha, WSU)

I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Research Ethics Committee. I/We agree to a completion of a 6-monthly/ yearly progress report. The committee reserves the right to withdraw approval in the event that there are serious ethical violations.

 (Signature)
N. B. Please quote the protocol number in all enquiries.

18/10/2022 (Date)

21/04/2023

Dear Xolani

Ethics Application Form : [Blood pressure and cardiac damage risk markers among women with preeclampsia 13813](#)

Thank you for your submission of the above ethics application.

The ethical approaches of this project have been approved and you can now proceed with your project.

Please note that should any of your proposal change, a further amendment submission will be necessary.

If you have any further queries, please do not hesitate to contact the Panel by email to ethics@stir.ac.uk

Yours sincerely,

NHS, Invasive or Clinical Research

WALTER SISULU UNIVERSITY HEALTH SCIENCES RESEARCH ETHICS COMMITTEE
(NHREC Reg. number REC-120209-020)

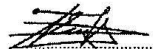
Ethics Approval Number	WSU HREC 037/2025									
Project Title	Perspectives and Experiences of Healthcare Workers on the Inclusion of Cardiac Biomarkers in Screening for Cardiac Complications in Women with Preeclampsia									
Principal Researcher/ Investigator	Xolani Mbongozi					Co-investigator: Charles Businge				
Supervisor/s	N/A									
Collaborator/s	N/A									
Department	Obstetrics & Gynaecology									
Faculty	Medicine & Health Sciences									
Type of Risk	Low									
Nature of the Project	Undergrad	Hons	Masters	Doctoral	Departmental	X	Clinical Trial	External Researcher		
Ethics Approval Commencement Date	16 APRIL 2025					Expiry Date	15 APRIL 2026			

Walter Sisulu University Health Research Ethics Committee (WSU HREC) hereby grants ethical approval for 1 year in respect of the undertakings submitted by the research project mentioned above. The researcher needs to submit to the HREC the gatekeeper/s' approval letters and certificate of registration of the study with the National Health Research Database before data collection.

Conditions:

- The certificate is valid for 1 year.
- The Principal Investigator/s is/ are required to provide the committee with a progress or outcome report of the research after every 1 year, 1 month before the expiry of the ethics clearance and the due date is **15 MARCH 2026**.
- Please submit study closure report should the study be completed within approval period as final submission; and if the study continues beyond approval, please submit a progress report and request for extension of ethics clearance.
- The approval is strictly for the submitted proposal, any changes/amendments in the protocol must first be submitted and approved by the HREC as well as any adverse events or deviations that may occur at any time during the study must be submitted not later than 7 days of knowing as the investigator/s.
- The committee expects a report on any changes in the protocol as well as any untoward events that may occur at any time during the study not later than 7 days of knowing as the investigator/s.
- As indicated in the Protection of Personal Information Act 04 of 2013 (POPIA), researchers have a legal duty to protect participants' personal information that they process. They must ensure privacy and security for all personal information process through research. They need to explicitly define the lawful purpose of collecting personal information and the duration that they are going to keep it. Collected personal information must be de-identified and destroyed when it is no longer in use. Participants should always give their consent and be informed that should they decide to leave the research they will not be disadvantaged at any point.
- The investigator must submit a copy of the Site/ Gatekeeper permission to the HREC before commencing data collection.**
- The HREC must be informed immediately of discontinuation of the study and state the reasons.

The WSU HREC wishes you well with your study.


PROF EJ NDEBIA
WSU HREC Chairperson
Date: 16 APRIL 2025

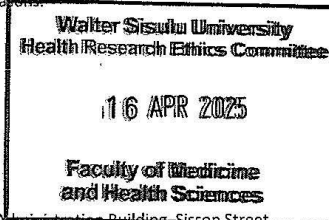
DECLARATION OF INVESTIGATOR(S)

(To be completed in duplicate and one copy returned to the Research Officer at Office AB 02 GF 03 Administration Building, Sirson Street Campus, Fort Gale, Mthatha, WSU)

I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the WSU Research Ethics Committee. I/We agree to a completion of a yearly progress/ final report. The committee reserves the right to withdraw approval in the event that there are serious ethical violations.

..... (Signature)

N. B. Please quote the protocol number in all enquiries.



Enquiries: Yvonne Gixela

TEL: 043 605 4540/4518

Email: ncebagixela22@gmail.com

Date: 15 February 2023

**CORRELATION OF CENTRAL BLOOD PRESSURE AND PERIPHERAL BLOOD
PRESSURE WITH PRO-BNP AND TROPONIN I - MEASURES OF FUTURE
CARDIOVASCULAR DISEASE- AMONG WOMEN WITH PREECLAMPSIA.
(EC_202302_009)**

Dear Dr. X.B. Mbongozi

The department would like to inform you that your application for the above mentioned research topic has been approved based on the following conditions:

1. During your study, you will follow the submitted protocol with ethical approval and can only deviate from it after having a written approval from the Ethics Research Committee.
2. You are advised to ensure, observe and respect the rights and culture of your research participants and maintain confidentiality of their identities and shall remove or not collect any information which can be used to link the participants.
3. The Department of Health expects you to provide a progress update on your study every 3 months (from date you received this letter) in writing.
4. At the end of your study, you will be expected to send a full written report with your findings and implementable recommendations to the Eastern Cape Health Research Committee secretariat. You may also be invited to the department to come and present your research findings with your implementable recommendations.
5. Your results on the Eastern Cape will not be presented anywhere unless you have shared them with the Department of Health as indicated above.

Your compliance in this regard will be highly appreciated.



SECRETARIAT: EASTERN CAPE HEALTH RESEARCH COMMITTEE

TOGETHER, MOVING THE HEALTH SYSTEM FORWARD



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

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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 $\pm$ SD for arterial stiffness indices (cPWV, Alx and Alx@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 $\pm$ 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.

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

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.

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

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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 post-delivery 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 $\mu\text{mol/L}$ 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 $\pm$ 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 $\pm$ 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.¹³ 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.

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Charles Bitamazire Businge <http://orcid.org/0000-0002-8393-1198>

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Elevated central blood pressure, NT-proBNP and hs-cTnI in women with maternal complications of hypertensive disorders of pregnancy

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ABSTRACT

Objective: The main objective of the study was to compare the levels of CBP and these cardiac biomarkers in women with maternal complications of hypertensive disorders of pregnancy (HDP).

Methods: This was a cross-sectional study that enrolled 270 women with HDP and 270 normotensive pregnant controls. Data on basic characteristics and incidence of maternal complications were collected among the two groups. Additionally, information on cardiac biomarkers and CBP was gathered from the women with HDP, to compare the levels of these biomarkers with maternal complications experience by this group.

Results: Non-hypertensive controls were significantly older than hypertensive cases and had a higher median gestational age at recruitment compared to hypertensive cases. The median levels of CBP and cardiac biomarkers were significantly higher among hypertensive participants with maternal complications ($n = 107/270$) than those without complications ($n = 163/270$). Specifically, central systolic blood pressure (CSBP) was 133 (120–142) mmHg vs 128 (109–129) mmHg ($p = 0.033$) and central diastolic blood pressure (CDBP) was 75 (62–86) mmHg vs 69 (56–73) mmHg ($p < 0.01$), while NT-proBNP was 446 (145–1126) vs. 57 (21–167) pg.mL⁻¹; $p < 0.0001$, and hs-cTnI was 12 (7–35) ng.L⁻¹ compared to 8 (3–8) ng.L⁻¹; $p < 0.0001$, in cases v. controls, respectively.

Conclusion: In conclusion, the study found that pregnant hypertensive women with maternal complications had significantly higher median values of CSBP and CDBP, NT-proBNP, and hs-cTnI in compared to those without complications. These findings suggest that measuring these vital signs and cardiac biomarkers in hypertensive pregnancies might be helpful for screening and monitoring maternal complications.

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Introduction

Central blood pressure (CBP) and cardiac biomarkers such as NT-proBNP and hs-cTnI, are among several variables that have been studied in women with hypertensive disorders of pregnancy (HDP) (1–5). The inactive N-terminal pro B-type natriuretic peptide is co-secreted with a 32-amino acid polypeptide, B-type natriuretic peptide (BNP), from the left and right cardiac ventricle in response to ventricular volume expansion and pressure overload, while hs-cTnI is a cardiac enzyme whose levels in the circulation respond to cardiomyocyte damage (6–8). In general, both biomarkers are associated with cardiac injuries and can indicate future cardiac disease risk, and, to some degree, the severity of cardiovascular events generally used for diagnosing cardiomyocyte

injury (6,9–11). Lam et al. (2018) demonstrated that patients with heart failure and elevated BNP are more likely to experience death and rehospitalisation compared to those with low levels (12).

HDP are a leading cause of maternal morbidity and mortality globally (13). They account for approximately 14–18% of all maternal deaths globally, with an estimated 62,000–77,000 maternal deaths, and 500,000 perinatal deaths annually (13–15). Maternal complications of HDP include stroke, pulmonary edema, Haemolysis Elevated Liver enzymes and Low Platelets (HELLP) syndrome, abruptio placentae, acute kidney injury, intensive care unit (ICU) admission, low Glasgow coma scale (GCS), and others (16,17). Studies have shown an association between preeclampsia (PE) and cardiovascular complications during pregnancy or many years after pregnancy

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(18,19). Other long-term complications of HDP are chronic hypertension, diabetes mellitus, stroke, end-stage renal disease, and cognitive impairment (19).

Hypertension can negatively affect pregnancy outcomes in women with advanced pregnancies and those undergoing assisted reproductive technologies (ART) such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) (20). Research has shown that even a slight increase in blood pressure among normotensive women undergoing IVF/ICSI is associated with a reduced live birth rate. A recent study involving 73,462 patients demonstrated that elevated systolic blood pressure (SBP) in normotensive women has a significant impact on live birth outcomes during these procedures (21). These findings are consistent with earlier research by Chen et al., which showed that both (SBP) and diastolic blood pressure (DBP) were lower in a group of 1,487 women who achieved successful outcomes after fresh embryo transfers following IVF/ICSI compared to those who did not have live births (22). Previous studies have demonstrated a significant increase in NT-proBNP in hypertensive pregnant women compared to pregnant normotensive women (1,3,4,11,23–25). A correlation between elevated systemic vascular resistance, left ventricular diastolic dysfunction, and depression of cardiac output in preeclamptic patients and elevated NT-proBNP levels has been observed ((24–26). A strong association between cardiac Troponin I and PE, has also been reported (6,8,24,25,27,28). However, there is still insufficient data evaluating relationships between NT-proBNP, hs-cTnI, and other short-term maternal complications, other than cardiac-related complications, in women with HDP.

Evidence suggests that PE is associated with increased central aortic blood pressure, pulse wave velocity as well as elastic arterial stiffness (5,29,30). Torrado and colleagues (2015) found that CSBP was significantly higher in Caucasian women with PE compared to those with gestational hypertension (GHPT) (29). They further elaborated that in their study there was no difference in PBP in those with PE compared to those with GHPT. The studies by Meeme et al. (2017) and Namugowa et al. (2017) focused on examining the CBP and arterial stiffness in black African women in South Africa with and without PE. They found that women with PE had higher arterial stiffness compared to normotensive women (5,30). However, their studies did not include women with preeclampsia with severe features such as eclampsia, imminent eclampsia, stroke, HELLP syndrome, pulmonary edema, abruptio placentae and acute kidney injury. Their studies also did not explore

the relationship between the CBP and the maternal outcomes in women with PE. These unaddressed issues warrant further investigation. The aim of the current study was therefore to assess the levels of CBP, cardiac biomarkers proBNP and hs-cTnI in women with maternal complications of HDP. The study hypothesized that levels of CBP and these biomarkers would be higher in women with HDP who have maternal complications compared to those without related complications.

Methods

This was a prospective cross-sectional study evaluating the levels of CBP, NT-proBNP and hs-cTnI, in women with immediate maternal complications of HDP. A total of 540 participants were enrolled, comprising 270 inpatient women with HDP and 270 inpatient normotensive pregnant women in the maternity ward at Nelson Mandela Academic Hospital in South Africa. Data on basic characteristics and incidence of maternal complications were collected among the two groups. Additionally, information on cardiac biomarkers and CBP was gathered from the women with HDP, to compare the levels of these biomarkers with maternal complications experience by this group. All participants were followed up for up to seven days after delivery to identify maternal complications and rule out normotensive patients developing hypertension.

The inclusion criteria for the hypertensive group encompassed all hypertensive patients who were at least 20 weeks gestation, while the inclusion criteria for normotensive pregnant participants included healthy patients with singleton pregnancies and specific conditions such as placenta previa, preterm premature rupture of membranes, preterm labor, or patients admitted for repeat elective cesarean section at term.

Patients who were less than 20 weeks gestation, those who were dire emergencies with no time to seek consent for participation in the study and those who declined to participate, were excluded. Patients with diabetes mellitus, cardiac disease, chronic renal disease, and antiphospholipid syndrome or other autoimmune disease were also excluded.

The cases were not matched for maternal and gestational age. This is because most patients with HDP, especially eclampsia, are younger compared to the general population, and excluding them will cause bias. According to national guidelines, patients with HDP are delivered preterm (preferably less than 35 weeks), whereas controls such as placenta previa and previous cesarean deliveries are delivered much later (31).

Definitions of hypertensive disorders were made according to the International Society for the Study of Hypertension in Pregnancy classification recommendations (32):

- Chronic hypertension was defined as high blood pressure predating the pregnancy or recognized at less than 20 weeks' gestation.
- Gestational hypertension was defined as hypertension diagnosed after 20 weeks gestation, without any features of pre-eclampsia.
- Preeclampsia was defined as de novo hypertension or superimposed on chronic hypertension after 20 weeks' gestation, accompanied by proteinuria and/or other evidence of maternal end-organ dysfunction, and/or fetal growth restriction.
- Eclampsia was defined as the convulsive manifestation of the HDP.

HELLP syndrome was diagnosed when any two of the following abnormalities were present: increased Lactate dehydrogenase (LDH) (≥ 600 IU/L), increased Aspartate transaminase (AST) (≥ 70 IU/L), low platelet count ($< 100 \times 10^9/L$); and renal failure if creatinine was ≥ 90 $\mu\text{mol/L}$ (28,33).

Data collection

These data were gathered from patient and maternity case files, using a pre-designed questionnaire. It comprised socio-demographic and clinical information, including maternal and gestational age, parity, marital status, education, presence and type of hypertensive disorders of pregnancy, maternal and fetal conditions, as well as maternal and perinatal outcomes.

Blood pressure measurements, both peripheral and central, were recorded at enrollment and within a week after delivery using the Microlife WatchBP Office Central. Before using the WatchBP Office central, the correct size of cuff was chosen and placed over the left or right upper arm so that the artery mark arrow point toward the lower arm. The cuff was wrapped around the arm, making sure that the lower edge of the cuff was approximately 2 cm above the elbow. The WatchBP Office Central device automatically measured both brachial and central blood pressure, displaying the results on the screen once the measurement process was complete. To determine the central blood pressure, the WatchBP Office Central uses brachial pulse volume plethysmography (PVP) waveforms. It is designed to perform PVP at a cuff pressure of 60 mmHg. Based on the analysis of

the PVP waveforms, the central systolic pressure and central pulse pressure values are automatically determined.

Blood samples were collected from each woman using two different types of tubes. For serum NT-proBNP, hs-cTnI, and platelet count, 10 ml of venous blood from the antecubital vein was drawn into tubes containing EDTA. The plasma was separated through centrifugation at 4°C for 15 minutes at 3500 rpm and then stored at -80°C until analysis. Another 10 ml of venous blood was drawn into yellow tubes containing Solution A (trisodium citrate, citric acid, and dextrose) for the measurement of creatinine, alanine transaminase (ALT), AST, and LDH. All assays, including NT-proBNP and hs-cTnI, were performed using an Alinity iSTAT analyzer (Abbott, USA).

Statistical analysis

Data were checked for completeness and consistency before being captured using the IBM SPSS STATISTICS software package version 29 for Windows (IBM Inc., Chicago IL, USA). These data were summarized into proportions (%) for categorical variables. Continuous data such as age, gestational and parity was interpreted using means and standard deviations (SD) if normally distributed or using medians, interquartile ranges, and percentiles (p25, p75) if skewed. The Chi-square test was used to delineate the degree of association between categorical variables. A $p < 0.05$ was considered statistically significant.

Results

General and clinical characteristics of the sample population

Out of the 270 hypertensive cases, 143 (53%) had preeclampsia, 102 (38%) had eclampsia, 14 (5%) had chronic hypertension, and 11 (4%) had gestational hypertension.

Two out of the eleven patients with gestational hypertension initially had normal blood pressure at recruitment but later developed hypertension during labor and were reassigned as gestational hypertension instead of normotensive controls.

The demographic and clinical characteristics of the sample population are shown in Table 1. The non-hypertensive controls (median = 28 years; $p < 0.0001$) were significantly older than the hypertensive cases (median = 25 years). The majority (63.1% $n = 341$) were in the 20 to 34 years age group and the minority (17.2% $n = 93$) were younger than 20 years.

Table 1. General and clinical characteristics of the sample population.

Characteristics	Hypertensive cases; <i>n</i> = 270 <i>n</i> (%)	Non-hypertensive controls; <i>n</i> = 270 <i>n</i> (%)	Total; <i>n</i> = 540 <i>n</i> (%)	Pearson χ^2 Sig.
Ethnicity				
African	269 (99.6)	268 (99.2)	537 (99.4)	0.624*
Multiracial	1 (0.4)	2 (0.7)	3 (0.6)	
Marital status				
Single	210 (77.8)	207 (76.7)	417 (77.2)	0.837*
Married	60 (22.2)	62 (23.0)	122 (22.6)	
Divorced	0 (0.0)	1 (0.4)	1 (0.2)	
Gravidity				
Multigravida	149 (55.2)	209 (77.4)	358 (66.3)	<0.0001
Primigravida	121 (44.8)	61 (11.6)	182 (33.7)	
Booking status				
Booked	248 (91.9)	258 (95.6)	506 (93.7)	0.111
Not booked	22 (8.1)	12 (4.4)	34 (6.3)	
Mode of delivery				
Caesarean section	233 (86.3)	235 (87.0)	468 (86.7)	0.800
Vaginal	37 (13.7)	35 (13.0)	72 (13.3)	
Maternal complications				
Yes	107 (39.6)	2 (0.7)	109 (20.2)	<0.0001
No	163 (60.4)	268 (99.3)	431 (79.8)	
	Median (IQR)	Median (IQR)	Median (IQR)	Sig.**
Gestational age at recruitment (weeks)	34 (6)	38 (3)	36 (5)	<0.0001

*Fisher's Exact *p*-value; ** Mann-Whitney *U* *p*-value.

There was no statistical difference ($p > 0.05$) for the other demographic characteristics observed in the hypertensive cases and non-hypertensive controls. Nearly all (99.4% $n = 537$) the participants were of African race, and the remaining were Multiracial (0.6% $n = 3$). More than three-quarters (77.2%) were single, and slightly more than a quarter (22.6% $n = 122$) were married.

Participants with HDP had a higher proportion of primigravida than the normotensive controls (44.8% Vs 11.6%, $p < 0.0001$). Most (93.7% $n = 434$) of the participants attended antenatal clinics while 34 (6.3%) did not. Antenatal clinic attendance between hypertensive cases and non-hypertensive controls was comparable statistically ($p > 0.05$). The median gestational age at enrollment to the study was 36 weeks (IQR: 5). The median gestational age at recruitment was significantly higher (38 weeks IQR = 5 weeks) among non-hypertensive controls compared to hypertensive cases (34 weeks IQR = 6 weeks) ($p < 0.0001$). The majority (86.7% $n = 468$) gave birth through cesarean section and the minority (13.3% $n = 72$) normally. No significant difference was observed in the mode of delivery between the two groups.

Maternal complications diagnosed in the study group

More than twenty percent of all participants (109/540, 20.2%) developed complications pre- or post-delivery. Only 2 out of the 270 normotensive controls (0.7%) developed maternal complications with both having abruptio placenta. In contrast 107/270 (39.6%) of the

cases with HDP had various maternal complications with the most common being HELLP syndrome (78/270, 28.9%) renal failure (29/270, 10.7%), and abruptio placental (26/270, 9.6%) (Table 2). Other complications included pulmonary edema (3/270), low GCS (4/270), cerebrovascular accident, disseminated intravascular coagulopathy ($n = 1$), or posterior reversible encephalopathic syndrome (each 1/270). Multiple regression analysis indicated that maternal age and parity were not associated with maternal complications (Table 3). Only gestational age at recruitment showed an independent association with maternal complications. Specifically, as gestation progressed in weeks, the odds of experiencing maternal complications decreased by 17.4% (Table 4). However, when using Integrated Discrimination Improvement (IDI) predictive model, inclusion of gestational age, CBP and PBP did not increase the risk prediction of maternal complications in women with HDP. In this group, NT-proBNP was the most effective predictor of maternal complication risk, followed closely by hs-cTnI.

Table 2. Maternal complications diagnosed in the study participants.

	Cases; <i>n</i> = 107 <i>n</i> (%)	Controls; <i>n</i> = 2 <i>n</i> (%)	Total; <i>n</i> = 109 <i>n</i> (%)
Maternal complications	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
Abruptio placenta	24 (22.4)	2 (100.0)	26 (23.9)
HELLP syndrome	78 (72.9)	0 (0.0)	78 (71.6)
Renal failure	29 (27.1)	0 (0.0)	29 (26.6)
Pulmonary edema	3 (2.8)	0 (0.0)	3 (2.8)
Low GCS	7 (6.5)	0 (0.0)	7 (6.4)
ICU admission	7 (6.5)	0 (0.0)	7 (6.4)

Table 3. Multiple regression analysis examining the relationship between maternal complications and factors such as age, parity, gestational age, BMI, and HIV status.

	No maternal complications	Yes-Maternal complications	p-value
Age(years)	28.0 (22.0–33.0)	25.0 (19.0–30.0)	0.002
Parity	1.0 (0.0–2.0)	0.0 (0.0–2.0)	<0.0001
Gestational age at recruitment	37.0 (34.0–38.0)	33.0 (29.0–36.0)	<0.0001
Body Mass Index (kg/m ²)	29.4 (25.0–35.1)	27.8 (23.8–33.3)	0.086
HIV status			
Positive	125 (29.0)	28 (25.7)	0.571
Negative	306 (71.0)	81 (74.3)	

Table 4. Relationship between maternal complications and gestational age.

	B	S.E.	Wald	p-value	OR (95%CI)
Age(years)	–0.016	0.022	0.509	0.475	0.985 (0.943–1.028)
Parity	–0.172	0.126	1.861	0.172	0.842 (0.657–1.078)
Gestational age at recruitment	–0.191	0.027	48.664	<0.0001	0.826 (0.783–0.872)
Constant	5.818	1.046	30.926	<0.000	336.259

The serum concentrations of hs-cTnI and NT-proBNP in women with different types of HDP

Women with eclampsia had significantly higher median serum hs-cTnI levels (15.5 ng.L^{–1}; 7.0–44.0) and log-transformed hs-cTnI levels (1.19 ng.L^{–1}; 0.85–1.64) than women with other phenotypes of HDP ($p < 0.0001$), as shown in Table 5. Similarly, women with eclampsia had significantly higher median serum NT-proBNP levels (577.5 pg.mL^{–1}; 236.0–1175.0) and log-transformed NT-proBNP (2.76 pg.mL^{–1}; 2.37–3.07) compared to women with other phenotypes of HDP ($p < 0.0001$), as shown in Table 5. The levels of serum NT-proBNP in women with eclampsia were well above the upper normal limit of 150 pg.mL^{–1}.

Relationship between PBP, CBP, NT-proBNP and hs-cTnI, and maternal complications in all hypertensive cases

The median levels (p25, p75) of the cardiac biomarkers and CBP were significantly higher among hypertensive participants with maternal complications ($n = 107/270$) than those without complications ($n = 163/270$). Specifically, the central systolic blood pressure

(CSBP) were 133 (120–142) mmHg vs 128 (109–129) mmHg ($p = 0.033$) and the central diastolic blood pressure (CDBP) levels were 75 (62–86) mmHg vs 69 (56–73) mmHg ($p < 0.01$) while NT-proBNP levels were 446 (145–1126) vs. 57 (21–167) pg.mL^{–1}; $p < 0.0001$, and hs-cTnI levels were 12 (7–35) ng.L^{–1} compared to 8 (3–8) ng.L^{–1}; $p < 0.0001$ (Table 6). For PBP, only the PDBP was significantly higher among hypertensive participants with maternal complications when compared to those without complications [80 (65–93) vs 72(62–86) mmHg; $p = 0.004$] (see Table 4). The median values indicate that NT-proBNP levels in individuals with maternal complications were above the normal range (<150 pg.mL^{–1} for NT-proBNP), while the values for hs-cTnI were within the normal range (<30 ng.L^{–1} for hs-cTnI). Among the participants with HDP, a significant relationship was observed between renal failure and the biomarkers (Table 6). In this hypertensive group of participants, the median hs-cTnI in cases with renal failure was significantly higher [35 (12–50) ng.L^{–1}; $p < 0.0001$] compared to those without [11 (6–19) ng.L^{–1}].

The median NT-proBNP in cases with renal failure was also significantly higher [821 (434–1894) pg.mL^{–1}; $p = 0.002$] compared to those without [348 (85–1003)].

Table 5. Serum levels of hs-cTnI and Nt-proBNP in women with the different types of HDP.

	GESTATIONAL HYPERTENSION ($n = 11$)	CHRONIC HYPERTENSION ($n = 14$)	PREECLAMPSIA ($n = 68$)	ECLAMPSIA ($n = 102$)	p-value*
Hs-cTnI (ng.L ^{–1})	Median (IQR) 6.0 (5.0–9.0)	Median (IQR) 5.5 (4.0–8.0)	Median (IQR) 10.0 (6.0–15.0)	Median (IQR) 15.5 (7.0–44.0)	<0.001
NT-proBNP (pg.mL ^{–1})	53.0 (18.0–217.0)	44.5 (11.0–188.0)	180.0 (68.0–508.0)	577.5 (236.0–1175.0)	<0.001
Log transformed NT-proBNP (pg/mL)	1.72 (1.26–2.34)	1.65 (1.04–2.27)	2.26 (1.83–2.71)	2.76 (2.37–3.07)	<0.001
Log transformed Hs-cTnI (ng/L)	0.78 (0.70–0.95)	0.74 (0.60–0.90)	1.00 (0.78–1.18)	1.19 (0.85–1.64)	<0.001

*Kruskal-Wallis.

Table 6. Maternal complications in hypertensive cases: medial comparisons of PBP, CBP, NT-proBNP, and hs-cTnI.

		Peripheral systolic blood pressure (mmHg) Median (IQR)	Peripheral diastolic blood pressure (mmHg) Median (IQR)	Central systolic blood pressure (mmHg) Median (IQR)	Central diastolic blood pressure (mmHg) Median (IQR)	NT-proBNP (pg.mL ⁻¹) Median (IQR)	Hs-cTnI (ng.L ⁻¹) Median (IQR)
Composite maternal complications	Yes (n = 107)	131 (117–144)	80 (65–93)	133 (120–142)	75 (62–86)	446 (145–1155)	8(5–16)
	No (n = 163)	125 (113–139)	72(62–86)	128 (109–129)	69 (56–73)	187 (46–513)	12 (7–36)
Abruptio placentae	P	0.055	<0.004	0.033	0.004	<0.0001	<0.0001
	Yes (n = 24)	123 (112–137)	76 (65–91)	127 (119–138)	71 (56–82)	291 (140–1460)	11(7–31)
HELLP syndrome	No (n = 83)	133 (119–145)	82 (64–94)	134 (123–143)	76 (63–88)	475 (145–1126)	15(7–36)
	P	0.59	0.428	0.140	0.347	0.604	0.501
HELLP syndrome	Yes (n = 78)	132 (119–144)	82 (65–93)	133 (119–141)	74 (64–85)	469 (145–1178)	13(7–36)
	No (n = 29)	126 (112–144)	73 (62–93)	134 (121–147)	76 (56–87)	403 (200–821)	12(7–35)
Renal failure	P	0.426	0.408	0.383	0.975	0.716	0.528
	Yes (n = 29)	131(117–144)	78 (67–93)	132 (120–145)	78 (66–87)	821 (434–1894)	35 (12–50)
Pulmonary edema	No (n = 78)	131(115–144)	82 (62–93)	133 (120–142)	73 (61–86)	348 (109–1013)	11(6–19)
	P	0.944	0.952	0.922	0.570	0.002	<0.0001
Pulmonary edema	Yes (n = 3)	112 (111–112)	73 (61–76)	105 (99–118)	62 (58–80)	85 (11–13801)	5(5–91)
	No (n = 104)	132(118–144)	82 (65–93)	133 (120–143)	75.5 (62–87)	451 (157–1141)	12(7–36)
Low GCS	P	0.053	0.181	0.059	0.221	0.597	0.499
	Yes (n = 7)	140 (122–173)	109 (67–121)	134 (123–148)	97 (73–104)	600 (77–2120)	50 (11–77)
ICU admission	No (n = 100)	131 (116–144)	80 (63–93)	133 (120–142)	74 (61–85)	435 (151–1098)	12(7–5)
	P	0.241	0.161	0.614	0.099	0.619	0.059
ICU admission	Yes (n = 7)	138 (122–173)	106 (67–119)	138 (128–148)	95 (73–101)	600 (77–2120)	50 (11–77)
	No (n = 100)	131 (116–144)	80 (63–93)	132 (120–142)	74 (61–85)	435 (151–1098)	12(7–35)
	P	0.246	0.177	0.368	0.120	0.673	0.061

SIG.= MANN-WHITNEY.

The other readings of biomarkers were similar in participants with the named complications and those without them ($p > 0.05$).

A hs-cTnI value of 8.5 ng.L⁻¹ or higher predicted maternal complications of HDP with a sensitivity of 69% and a specificity of 50% ($p < 0.001$; 95% CI 0.57–0.70; AUC = 0.63), while an NT-proBNP value of 179 pg.mL⁻¹ or higher predicted maternal complications with a sensitivity of 71% and a specificity of 51% ($p < 0.001$; 95% CI 0.59–0.73; AUC = 0.66) (Table 7 and Table 8). A combination of NT-proBNP, hs-cTnI, and CBP (AUC: 68%; $p < 0.0001$) demonstrated a superior ability to distinguish between participants with and without maternal complications compared to NT-proBNP alone (AUC: 66 %; $p < 0.0001$). (Figure 1 and 2).

A hs-cTnI value of 11 ng.L⁻¹ or higher predicted renal failure with a sensitivity of 79% and a specificity of 50% ($p < 0.001$; 95% CI 0.66–0.85; AUC = 0.75), while an NT-proBNP value of 167

pg.mL⁻¹ or higher predicted renal failure with a sensitivity of 93% and a specificity of 65% ($p = 0.002$; 95% CI 0.58–0.80; AUC = 0.69) (Figure 3).

Relationship between CBP, NT-proBNP and hs-cTnI and maternal complications in women with eclampsia and preeclampsia

Eclamptic women with composite maternal complications had significantly higher median cSBP (138 mmHg; 124–148; $p = 0.010$) and cDBP (79 mmHg; 67–95; $p = 0.001$) compared to those without such complications (cSBP:128 mmHg; 117–136); (69 mmHg; 58–77). The median cSBP and cDBP in eclamptic women with specific maternal complications such as abruptio placentae, HELLP syndrome, pulmonary edema, low Glasgow coma scale, ICU admission did not differ significantly from those women without the specific maternal complications (all p values > 0.05), as shown in Table 5.

Table 7: Coordinates of the ROC Curve for Highly Sensitive Cardiac Troponin I (ng/ml)

Test Result Variable	Positive if Greater Than or Equal To	Sensitivity	1 - Specificity
Highly Sensitive Cardiac Troponin I (ng/ml)	2.000	1.000	1.000
	3.500	.935	.883
	4.500	.897	.822
	5.500	.860	.724
	6.500	.813	.663
	7.500	.729	.558
	8.500	.692	.497
	9.500	.645	.448
	10.500	.579	.405
	11.500	.523	.362
	12.500	.486	.325
	13.500	.467	.282
	14.500	.467	.264
	15.500	.421	.252
	16.500	.411	.233
	17.500	.393	.221
	18.500	.374	.215
	19.500	.355	.215
	20.500	.336	.202
	21.500	.327	.196
	22.500	.327	.178
	23.500	.327	.166
	24.500	.327	.160
	25.500	.308	.153
	26.500	.308	.141
	27.500	.308	.135
	28.500	.308	.117
	29.500	.299	.104
	30.500	.299	.098
	32.000	.290	.098
	33.500	.280	.098
	34.500	.271	.074
	35.500	.252	.074
	37.000	.234	.074
	39.500	.224	.074
	41.500	.224	.067
	43.000	.215	.067

Additionally, in eclamptic cases who had additional maternal complications, the NT-proBNP and the hs-cTnI were significantly higher compared to those without additional maternal complications: respectively 1030 (382–1894) vs. 464 (164–940) pg.mL^{-1} , $p = 0.003$] and 33 (12–62) vs. 10 (5–25) ng.L^{-1} $p < 0.0001$ (Table 9). The cases with eclampsia who had renal failure had significantly higher hs-cTnI compared to eclamptic cases without renal failure 46 (20–175) vs. 21 (8–54) ng.L^{-1} ; $p = 0.036$. There was no difference in the median hs-cTnI and NT-proBNP in eclamptic cases with and without abruptio placenta, help syndrome, pulmonary edema, low GCS, or admission to the ICU ($p > 0.05$) (Table 9).

Table 8: Coordinates of the ROC Curve for NT-Prohormone Brain Natriuretic Peptide

Test Result Variable	Positive if Greater Than or Equal To	Sensitivity	1 - Specificity
NT-Prohormone Brain Natriuretic Peptide (pg/mL)	9.000	1.000	1.000
	10.500	.963	.896
	11.500	.944	.883
	13.000	.935	.877
	14.500	.935	.871
	15.500	.935	.859
	17.000	.925	.859
	18.500	.925	.847
	19.500	.925	.840
	21.000	.925	.834
	22.500	.925	.828
	23.500	.925	.816
	24.500	.916	.816
	25.500	.916	.810
	27.500	.897	.810
	30.000	.897	.804
	31.500	.897	.791
	34.000	.897	.779
	37.000	.897	.773
	40.000	.897	.761
	44.000	.897	.755
	46.500	.897	.748
	47.500	.897	.736
	50.000	.879	.736
	52.500	.879	.730
	54.500	.879	.718
	56.500	.869	.718
	58.000	.869	.712
	59.500	.869	.706
	61.000	.869	.699
	65.000	.869	.693
	69.000	.860	.693
	70.500	.860	.687
	71.500	.860	.681

Overall, the median NT-proBNP [246.50 (85–673) vs. 141.50 (45–381) pg.mL^{-1} ; $p = 0.009$] were significantly higher in preeclamptic cases with maternal complications compared to those without maternal complications. There was no statistically significant difference in the medians for hs-cTnI, in preeclamptic cases with and without maternal complication.

Upon stratified analysis, participants with PE who developed renal failure had significantly higher median hs-cTnI and NT-proBNP compared to those without renal failure, respectively 20 (10–46) vs. 9 (6–12) ng.L^{-1} $p = 0.001$; and [619 (233–1894) vs. 200 (78–520) pg.mL^{-1} $p = 0.002$. There was no difference in the median hs-cTnI and NT-proBNP of preeclamptic cases with and without abruptio placenta, HELLP syndrome, low Glasgow coma scale, pulmonary edema, and admission to the ICU ($p > 0.05$).

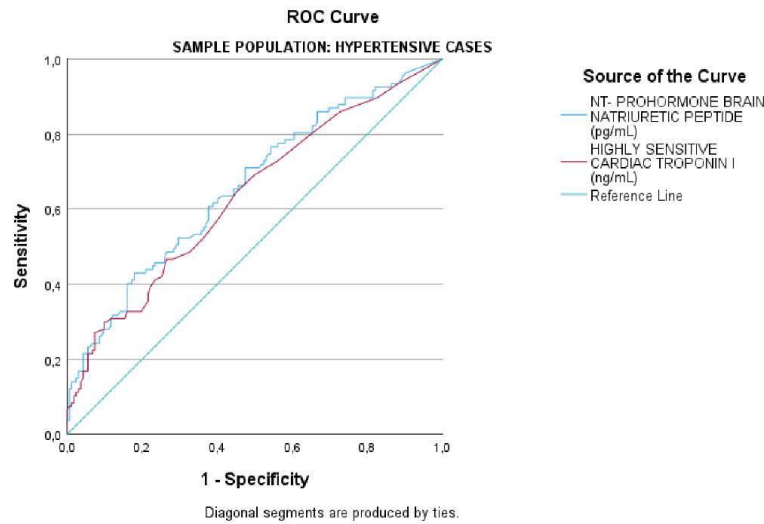


Figure 1. ROC curve analysis of hs-cTnI and Nt-proBNP in women with maternal complications of hypertensive disorders of pregnancy.

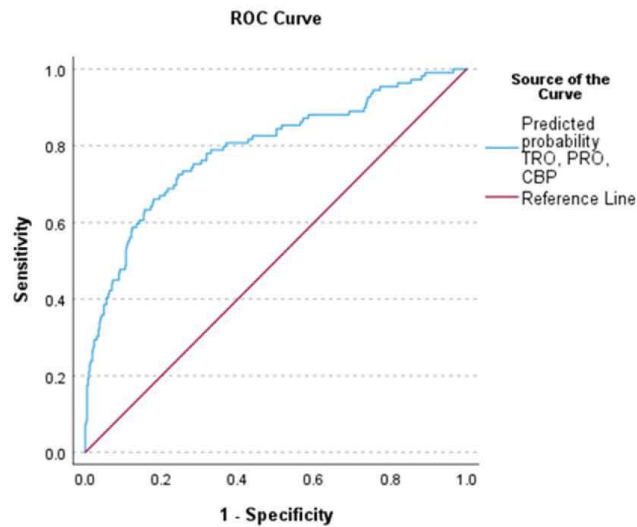


Figure 2. ROC curve analysis of the combined biomarkers hs-cTnI, NT-proBNP, and CBP in women with hypertensive disorders of pregnancy. TRO= hs-cTnI; PRO= NT-proBNP; CBP=Central blood pressure.

Discussion

This study included a total of 540 participants, consisting of 270 individuals with hypertension and 270 non-hypertensive controls.

The control group of non-hypertensive participants was significantly older and had a higher median gestational age at recruitment compared to those with

hypertensive conditions. Typically, preeclampsia and eclampsia affect younger women and often lead to early delivery, which likely influenced the median maternal and gestational age of women with HDP in this study (15,34). As a result, the median age of hypertensive participants in this study was 25 years, with most falling within the age range of 25 to 35

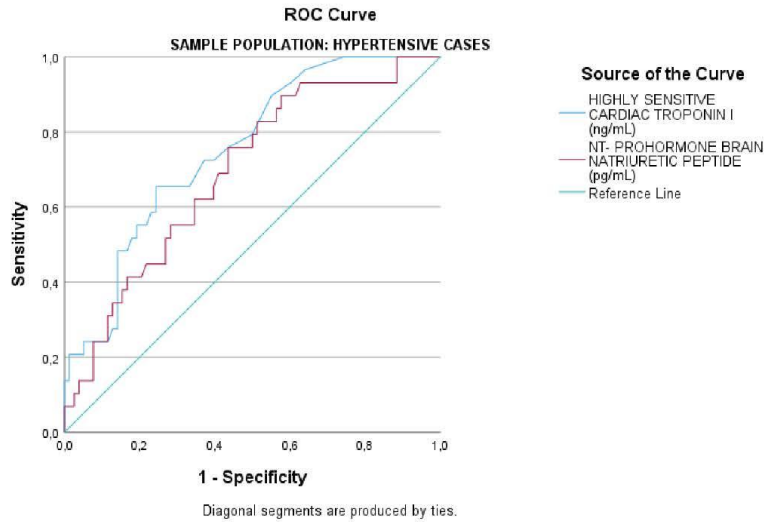


Figure 3. ROC curve analysis of hs-cTnI and Nt-proBNP in hypertensive pregnant women with renal failure.

Table 9. Maternal complications in cases with eclampsia: medial comparisons of CBP, NT-proBNP, and hs-cTnI.

		cSBP	cDBP	NT-proBNP	hs-cTnI
		Median (IQR) mmHg	Median (IQR) mmHg	Median (IQR)	Median (IQR)
Composite maternal complications	Yes (<i>n</i> = 45)	138 (124–148)	79 (67–95)	1030 (382–1894)	33 (12–62)
	No (<i>n</i> = 57)	128 (117–136)	69 (58–77)	464 (164–940)	10 (5–25)
	<i>P</i>	0.010	0.001	0.003	<0.0001
Abruptio placenta	Yes (<i>n</i> = 6)	140.5 (120–150)	83 (79–86)	1460 (403–1894)	31 (11–46)
	No (<i>n</i> = 39)	138 (124–148)	77 (64–95)	1026 (355–2120)	34 (12–77)
	<i>P</i>	0.858	0.660	0.684	0.591
HELLP syndrome	Yes (<i>n</i> = 33)	134 (122–148)	79 (64–95)	1069 (434–3250)	34 (12–104)
	No (<i>n</i> = 12)	144.5 (134.5–152.0)	84 (72–92)	523 (341–1460)	22.50 (11.50–48)
	<i>P</i>	0.156	0.621	0.279	0.367
Acute kidney injury	Yes (<i>n</i> = 14)	139 (120–154)	82 (70–93)	1133 (434–3223)	46 (20–175)
	No (<i>n</i> = 31)	138 (124–148)	77 (64–97)	1026 (270–1673)	21 (8–54)
	<i>P</i>	0.883	0.951	0.500	0.036
Pulmonary edema	Yes (<i>n</i> = 0)	-	-	-	-
	No (<i>n</i> = 45)	138 (124–148)	79 (67–95)	1030 (382–1894)	33 (12–62)
	<i>P</i>	-	-	-	-
Low GCS	Yes (<i>n</i> = 6)	137 (124–155)	100.5 (74–104)	877.50 (446–2120)	52 (16–77)
	No (<i>n</i> = 39)	138 (122–148)	79 (64–89)	1030 (355–1894)	29 (11–62)
	<i>P</i>	0.637	0.123	0.884	0.317
ICU admission	Yes (<i>n</i> = 6)	139 (134–155)	96 (74–104)	877.50 (446–2120)	52 (16–77)
	No (<i>n</i> = 39)	138 (122–148)	79 (64–89)	1030 (355–1894)	29 (11–62)
	<i>P</i>	0.442	0.170	0.987	0.333

p value (Mann-Whitney).

years. This distribution is of interest, as previous research offers a mixed narrative regarding the association between maternal age and the risk of HDP. While some studies suggest that women in the 25–35 age bracket may be at higher risk, others indicate heightened risks in those older than 35 or younger than 25 (35–37). These discrepancies highlight the

complexity of the relationships between age and HDP, possibly reflecting varying demographic, environmental, and healthcare-related factors influencing these outcomes.

Among the participants with hypertension, 39.6% experienced maternal complications, with HELLP syndrome being the most common complication

reported. Women with complications related to HDP presented with higher levels of both diastolic and systolic central blood pressure. Additionally, those with complications had significantly elevated levels of NT-proBNP and hs-cTnI. Hypertensive patients who also had renal failure showed even higher levels of NT-proBNP and hs-cTnI compared to those without renal failure.

These study results are consistent with existing literature which has shown increased levels of NT-proBNP in women with HDP, and a correlation between these cardiac biomarkers and maternal complications in patients with HDP ((11,38,39). Hamad et al. (2009) observed impaired diastolic left ventricular function and increased levels of NT-proBNP in pregnancies complicated by PE (477 (152) ng.L⁻¹ vs 46 (6) ng.L⁻¹; $p < 0.0001$), especially early-onset PE (1243 (583) ng.L⁻¹ vs 254 (57) ng.L⁻¹, $p = 0.005$) (40). Fustaret et al. (2012) also evaluated the correlation between NT-ProBNP in normotensive pregnant women and women with HDP, finding that NT-ProBNP significantly correlated with lactic dehydrogenase and platelets, which are markers for HELLP syndrome, and cardiac failure (31). The current study did not find a significant association between NT-proBNP and HELLP syndrome but found that hypertensive patients with renal failure had significantly higher NT-proBNP levels compared to those who did not have renal failure. This finding aligns with the established phenomenon that NT-proBNP clearance exclusively occurs in the kidneys, which is well-documented in patients with chronic renal failure (41). Therefore, an impairment in the renal system may result in higher levels of NT-proBNP.

The current study did not find any association between pulmonary edema and NT-proBNP levels, which is different from the results of other studies. For instance, Kumari et al. (2017) reported a significant association of serum NT-proBNP levels with pulmonary edema [997 (642.92 to 1351.08) pg.mL⁻¹ ($p = 0.049$)] (42). Additionally, Kim et al. (2020) conducted a study with 124 preeclamptic patients and found that NT-proBNP levels were significantly higher in women with pulmonary edema (43). Their findings are consistent with a cross-sectional study of 30 women with severe PE conducted by Hafiz et al. (2021), in which an association between NT-proBNP and pulmonary edema was also found (33). Further studies are necessary to understand the differences between our findings and those of other studies.

In the study by Hafiz et al., a significant association was also found between NT-proBNP and HELLP syndrome in preeclamptic patients, which contradicts our

findings (33). Hafiz et al. included only 35 participants with hypertension, while our study involved a larger sample size, which may explain the discrepancies between the two studies. Conversely, a study by Kumari et al., which included 45 hypertensive women and 45 normotensive women, aligns with our results, revealing no association between NT-proBNP and HELLP syndrome in pregnant women with hypertensive conditions (42).

In addition to NT-proBNP, our study also found elevated levels of hs-cTnI in women with maternal complications of HDP compared to those without maternal complications. This observation is in line with previous research indicating a potential association between hs-cTnI and PE (28,44). However, there is a lack of studies specifically examining the relationship between hs-cTnI and maternal complications of HDP. It's worth noting that, similar to the findings for NT-proBNP among pregnant women with hypertension, those who experienced renal failure had significantly higher levels of hs-cTnI. This finding is consistent with existing literature indicating that cardiac biomarkers are filtered through the glomerular filtration barrier, and a decrease in glomerular filtration can impact their levels (45).

The current study indicates that both diastolic and systolic central blood pressure are higher in women with maternal complications of HDP. Previous studies have mainly focused on the relationship between central blood pressure and HDP, rather than examining the association between central blood pressure and maternal complications (5,29,30). These studies have consistently demonstrated that CBP is elevated in women with HDP compared to those without HDP. CBP is known to be a reliable indicator of target organ damage, which may explain the association between central blood pressure and maternal complications of HDP in the current study, as these complications are largely associated with target organs (46).

In non-pregnant patients, CBP has been shown to be a good predictor of complications in certain target organs, such as cardiovascular events (myocardial infarction, coronary heart disease, sudden death, congestive heart failure, and stroke) and renal failure (47,48). However, unlike other studies that have established a correlation between CBP and the decline in renal function, the current study did not find significantly different levels of CBP between women with renal failure and those without (40–42). This may be attributed to the fact that the other studies primarily involved non-pregnant patients with chronic kidney disease rather than acute cases, and it also included some male participants. For example, Xiao et al.

(2020) conducted a study with 1426 non-pregnant participants who were followed for a median of 4.8 years to assess the prognostic significance of various blood pressure measurements for renal function decline and early chronic kidney disease (48). Their study showed that central pulse pressure emerged as an independent predictor of the decline in renal function. Their findings are consistent with the earlier community-based population study by Fan et al. (2016), which evaluated 3153 participants and found that central SBP was a stronger predictor compared with peripheral SBP for kidney function decline (49). Ohno et al. (2016) also highlighted the association between CBP and kidney function (50). They proposed a vicious cycle between chronic kidney disease (CKD) and CBP, indicating that abnormalities in central hemodynamics can hasten the progression of CKD by potentially causing renal ischemia and glomerular hypertension.

The current study found that the CSBP was significantly higher in women with maternal complications of HDP compared to women without complications of HDP. However, the peripheral systolic blood pressure did not show a significant difference. This may imply that CSBP may be better associated with complications of HDP compared to PSBP. This finding is consistent with the findings in the general population, where CBP is a better predictor of cerebrovascular accidents compared to peripheral blood pressure. For example, Matsumoto et al. conducted a study that found that higher CSBP and central pulse pressure, but not brachial blood pressure, were significantly associated with white matter hyperintensity volume (51). Han et al. also investigated the association between CBP and long-term prognosis in patients with Embolic Stroke of Undetermined Source (ESUS) and found that CBP parameters were independently associated with unfavorable outcomes, including major adverse cardiovascular events, stroke recurrence, and mortality (52). However, while the current study observed elevated CBP in relation to all maternal complications, it did not find any association between cerebrovascular events and CBP. This could be due to the short interval of exposure to high CBP in pregnant women compared to long-term exposure in the aforementioned studies. A long-term follow-up of patients in our study might be needed to address this controversial finding.

Limited data exists on relationships between CBP, hs-cTnI and NT-proBNP, and maternal complications in women with HPD, so this study offers valuable insights. However, the study had some limitations. One limitation is that the follow-up period was only up to seven days after delivery, potentially missing

complications that could have occurred later. However, this may be mitigated by the fact that most immediate complications of HDP occur during the antenatal and immediate postpartum periods, which is seven days after delivery. Another limitation is that cases and controls were not matched for maternal and gestational age, which could introduce statistical bias.

In conclusion, the study found that pregnant women with hypertension and maternal complications had significantly higher levels of CBP, and cardiac biomarkers NT-proBNP and hs-cTnI compared to those without complications. These cardiac biomarkers were particularly elevated in women with renal failure. The findings may suggest that women with maternal complications of HDP during pregnancy may be at higher risk of developing chronic cardiovascular problems. Additionally, measuring these biomarkers in hypertensive pregnancies could help in screening and monitoring maternal complications, especially renal failure, and CSBP may be more effective than PSBP in screening for maternal complications of HDP.

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Author contributions

CRedit: Mirabel Nanjoh: Formal analysis.

Disclosure statement

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Ethics approval

Approval to perform the study was obtained from Faculty of Health Sciences research and ethics at Walter Sisulu University. The approval number is 035/2022.

Data availability statement

The datasets used during the current study are available from the corresponding authors on reasonable requests.

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Correlation of peripheral blood pressure with central blood pressure and estimation of central blood pressure thresholds for diagnosis of hypertension during pregnancy

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Objective: The main objective of the study was to evaluate the correlation and comparative use of peripheral blood pressure and central blood pressure (CBP) in identifying hypertension among pregnant women.

Methods: A cross-sectional study was conducted at Nelson Mandela Academic Hospital from December 2022 to April 2024, involving 270 inpatients diagnosed with hypertensive disorders of pregnancy (HDP) and 270 normotensive controls in their second and third trimesters. Blood pressure measurements were obtained using the Microlife WatchBP Office Central, both at enrolment and within 7 days postpartum. A linear regression equation and a receiver operating characteristic curve (ROC) analysis were used to determine the thresholds for normal, mild, and severe CBP.

Results: The ROC revealed that a central systolic blood pressure (cSBP) of 116 mm Hg or higher has a sensitivity of 78.5% and a specificity of 50.3% for diagnosing hypertension during pregnancy. Considering a normal peripheral diastolic pressure of less than 90 mm Hg, the upper limit of central diastolic blood pressure (cDBP) in normotensive controls was calculated to be 78 mm Hg. A significant positive correlation was found between peripheral systolic blood pressure (pSBP) and cSBP among normotensive and hypertensive women ($p < 0.05$). The median pSBP among patients with eclampsia with mild peripheral hypertension was 138.0 mmHg (IQR: 133.0–148.0) while the cSBP level in the same group was 145.0 mmHg (IQR: 140.0–150.0) mmHg. The overall median cSBP among women with eclampsia ($n = 102$) was 133.0 mmHg (IQR: 120.0–143.0), and the median cDBP was 73.0 mmHg (IQR: 60.0–83.0), and these were significantly higher ($p < 0.0001$) than the median cSBP of 128.0 mmHg (IQR: 114.0–139) and cDBP of 71.0 mmHg (IQR: 61.0–81.0) among preeclamptic women.

Conclusion: This study established the threshold values for central hypertension as 116/78 mmHg, with severe central hypertension defined as 148/95 mmHg or more. It reinforces the positive correlation between peripheral and CBP in both normotensive and hypertensive populations. CBP may serve as a better

parameter for evaluating hypertension, especially in eclampsia. Further research is warranted to confirm these findings and to explore their clinical implications.

KEYWORDS

pregnant women, eclampsia, preeclampsia, hypertensive disorders of pregnancy, arterial stiffness, central and peripheral hypertension

Introduction

Elevated brachial blood pressure has traditionally been the main indicator for diagnosing hypertension, but with the increased availability of non-invasive central blood pressure (CBP) measuring devices, there is growing interest in using CBP for managing hypertension in non-pregnant and pregnant individuals.

The role of brachial blood pressure in the prediction of future cardiovascular structural damage, morbidity, and mortality among non-pregnant adult population is well-established in high-income countries (1), as well as in middle-income countries, such as China and Mexico (2, 3). Controlling brachial blood pressure can reduce the risk of cardiovascular death (4). However, peripheral hypertension does not necessarily correlate with maternal and perinatal outcomes, except for the increased risk of intracranial hemorrhage when there is severe peripheral hypertension (5). Numerous studies suggest that CBP is superior to peripheral blood pressure (PBP) in predicting cardiovascular disease among non-pregnant patients (6–9). The superiority of CBP is likely due to central pressures exhibiting lower variability and more accurately reflecting the tension levels on major target organs such as the heart, brain, and kidneys (10). CBP is defined as blood pressure readings taken from the aorta or common carotid arteries, primarily influenced by increased arterial stiffness and wave reflection (11). It represents the pressure against which the heart must pump to ensure blood flow throughout the body. Evidence indicates that preeclampsia (PE) is associated with increased CBP, pulse wave velocity, and arterial stiffness (12–14). It is known that the cerebrovascular complications of PE and eclampsia can occur in the presence of mild elevations of PBP and even in the absence of proteinuria (15, 16). Since the blood flow to the brain is controlled by the central aortic blood pressure, it is possible that under conditions when there is only mild elevation of the brachial blood pressure, the CBP may be much higher, thus accounting for the vasogenic oedema typical of eclampsia, justifying the need to know how the CBP behaves in patients with HDP and eclampsia.

To evaluate this hypothesis, it is essential to clearly define what constitutes mild and severe central hypertension. Current literature presents conflicting findings regarding the definition of central hypertension (17, 18). Notably, Cheng et al. have proposed a threshold CBP of 130/90 mmHg, which generally serves as a benchmark for central hypertension in non-pregnant women (11, 19). However, given the physiological changes that occur during pregnancy, it would be biased to apply findings from the non-pregnant population, especially those involving men (20). During pregnancy, physiological changes generally result in lower CBP readings compared with those in non-pregnant women and men (21). Therefore, it is necessary to establish the CBP threshold for diagnosing central hypertension in the pregnant population.

Objectives

The primary objective of this study was to evaluate the correlation and comparative use of PBP and CBP in identifying hypertension among pregnant women. The secondary objective was to determine the threshold values for central systolic blood pressure (cSBP) and central diastolic blood pressure (cDBP) for diagnosing mild and severe central hypertension in pregnancy.

Materials and methods

This was a cross-sectional study conducted between December 2022 and April 2024. We prospectively studied 270 inpatients diagnosed with hypertensive disorders of pregnancy (HDP) and 270 inpatient normotensive controls who were in their second and third trimesters of pregnancy. This study was conducted at the Nelson Mandela Academic Hospital, South Africa, in keeping with the principles laid down in the Helsinki Declaration (22). Walter Sisulu University and the Nelson Mandela Academic Hospital board approved this study (ethics reference number 035/2022), and informed consent was obtained from each participant before data collection.

The definitions of hypertension and HDP were based on the International Society for the Study of Hypertension in Pregnancy (23). Mild peripheral hypertension was defined as a pSBP of 110–159 mmHg and/or a pDBP of 90–109 mmHg. Severe peripheral hypertension was defined as a pSBP of 160 mmHg or higher and/or a pDBP of 110 mmHg or higher. The inclusion criteria for hypertensive patients were current hypertensive disease in pregnancy with a gestation period of ≥ 20 weeks. For controls, the inclusion criteria were a healthy normotensive singleton pregnancy in labor, those admitted for a repeat elective caesarean section at term, or women without hypertension presenting with particular conditions such as placenta previa, preterm premature rupture of membranes, or preterm labour. Participants were excluded if they were under 20 weeks pregnant or if they opted out of participation. Additionally, individuals with diabetes mellitus, cardiac disease, chronic renal disease, antiphospholipid syndrome, or other autoimmune diseases were also excluded from the study.

Data on the presence and type of HDP were collected from patient interviews and medical records using a standard data collection sheet. At enrolment and within 7 days after delivery, brachial and central systolic and diastolic blood pressures were measured using the Microlife WatchBP Office Central. Participants who were initially normotensive but later developed elevated blood pressure were reclassified as hypertensive, while those with gestational hypertension who later exhibited features of PE were reclassified as having PE. Before using the Microlife WatchBP Office central, the correct size of cuff was chosen and placed over the left or right upper arm so that the artery mark arrow points toward the lower arm. The cuff was

wrapped around the arm, making sure that the lower edge of the cuff was approximately 2 cm above the elbow. The WatchBP Office Central device automatically measured both brachial and CBP, displaying the results on the screen once the measurement process was complete.

It is important to note that while the validity and reliability of the Microlife WatchBP Office Central have been established in the general population, its PBP measurement component lacked validation for pregnancy use (19). To address this deficiency, a pilot study was conducted involving three distinct groups of participants: 15 normotensive pregnant women, 15 women diagnosed with gestational hypertension, and 15 women with PE. Initially, PBP was measured using the pregnancy-validated Microlife WatchBP Home BT, followed by measurements with the Microlife WatchBP Office Central.

The validation process adhered to the guidelines set forth by the Association for the Advancement of Medical Instrumentation, the European Society of Hypertension, and the International Organization for Standardization (24, 25).

The results of the validation exercise demonstrated a strong correlation between the pregnancy-validated Microlife WatchBP Home BT and the Microlife WatchBP Office Central (refer to Tables 1, 2). Subsequently, the Microlife WatchBP Office Central was used to simultaneously measure both brachial blood pressure and CBP in each participant.

Statistical analysis

Data were checked for completeness and consistency before being captured using the IBM SPSS STATISTICS software package version 29 for Windows (IBM Inc., Chicago IL, USA). Two approaches were used to try to establish the upper thresholds for normal and abnormal CBP to determine what constitutes central hypertension. The first approach used a linear regression equation for calculating the cSBP and cDBP from the pSBP and cDBP of normotensive controls, and a p -value of <0.05 was taken as significant. The second approach used the receiver operating curve analysis for calculating the upper threshold of normal cSBP and cDBP, together with sensitivity and specificity. The Youden's J index, sensitivity, and specificity were calculated for each blood pressure reading. Cut-off points were determined based on the index, sensitivity, specificity, and clinical

relevance. The outcome variable was HDP. The lower of these thresholds from these two approaches was then chosen to represent the threshold of normal and abnormal CBP.

For the rest of the study, blood pressure readings were interpreted using medians and percentiles (p25, p75) due to the skewed nature of the data. The Kruskal–Wallis H test and the Mann–Whitney U test were employed to assess the degree of association between the continuous variables. The Wilcoxon signed-rank test was applied to compare dependent variables. A p -value of less than 0.05 was considered statistically significant.

Results

General description and socio-demographic characteristics of the sample population

A total of 550 pregnant women were initially recruited for the study. However, 10 patients were excluded due to comorbidities like diabetes, chronic renal failure, and cardiac disease (Figure 1). Ultimately, 540 pregnant women were enrolled in the study, with 270 diagnosed with HDP and 270 who were normotensive controls. Of the 270 women with HDP, 143 (53%; 95% CI: 47–58.9%) had PE, 102 (37.8%; 95% CI: 32.1–43.7%) had eclampsia, 14 (5.2%; 95% CI: 3.0–8.3%) had chronic hypertension, and 11 (4.1%; 95% CI: 2.2–6.9%) had gestational hypertension. Notably, two of the eleven patients with gestational hypertension initially had normal blood pressure and were classified as controls at the time of recruitment, but subsequently developed hypertension, resulting in their reclassification. Additionally, four of the 143 preeclamptic patients initially presented with gestational hypertension but later exhibited significant proteinuria, resulting in their reclassification as PE. Of the 143 women with PE, 75 (52.4%; 95% CI: 44.3–60.5%) had PE with severe features (this number excludes women with eclampsia who form their own group) and 68 (47.6%; 95% CI: 39.5–55.7%) had PE without severe features.

The non-hypertensive controls had a median age of 28 (IQR: 24.0–33.0) years, which was significantly older than the hypertensive cases, whose median age was 25 (IQR: 20.0–32.0) years ($p < 0.0001$) (Table 3). Most participants (63.1%, $n = 341$)

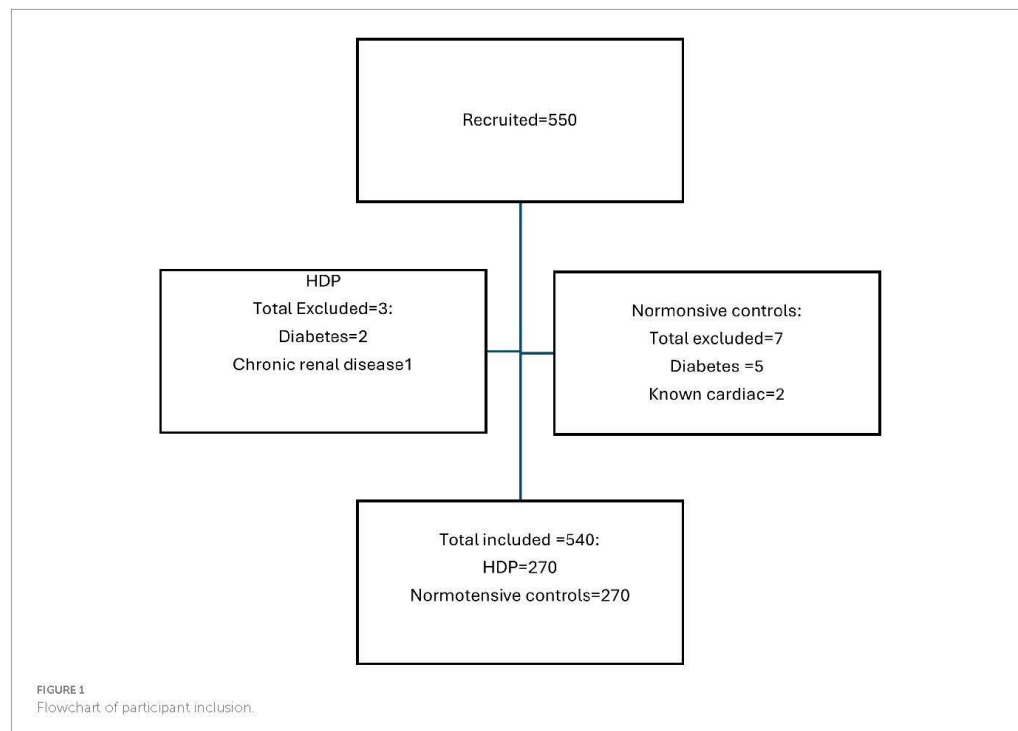
TABLE 1 Demographic characteristics of hypertensive cases and normotensive controls in the pilot study.

Characteristics	Hypertensive cases ($N = 30$)	Normotensive controls ($N = 15$)	Total	Student's t -test p value
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	
Age (years)	28.9 $\pm$ 7.6	24.9 $\pm$ 6.0	27.5 $\pm$ 7.3	0.082
Gravidity	2.3 $\pm$ 1.3	2.2 $\pm$ 1.7	2.3 $\pm$ 1.4	0.825
Parity	1.3 $\pm$ 0.9	1.4 $\pm$ 0.8	1.3 $\pm$ 0.9	0.715
Gestational age (wks)	34.4 $\pm$ 3.6	38.4 $\pm$ 1.5	35.7 $\pm$ 3.6	<0.0001
pSBP (mmHg)	135.7 $\pm$ 11.3	123.3 $\pm$ 10.6	131.6 $\pm$ 12.4	0.001
pDBP (mmHg)	79.7 $\pm$ 10.8	64.3 $\pm$ 13.1	74.6 $\pm$ 13.6	<0.0001
cSBP (mmHg)	130.1 $\pm$ 12.1	114.4 $\pm$ 12.5	124.9 $\pm$ 14.2	<0.0001
cDBP (mmHg)	71.6 $\pm$ 13.1	70.6 $\pm$ 11.2	71.3 $\pm$ 12.4	0.801

pSBP, peripheral systolic blood pressure; pDBP, peripheral diastolic blood pressure; cSBP, central systolic blood pressure; cDBP, central diastolic blood pressure; SD, standard deviation; wks, weeks.

TABLE 2 The absolute differences in systolic and diastolic pressures, categorized as 0–5, 0–10, and 0–15 mmHg, between the two measuring devices.

Blood pressure differences	Blood pressure categories	<i>n</i> ; <i>N</i> = 45	% (95%CI)	Mean $\pm$ SD
Absolute SBP differences	0–5 mmHg	39	86.7	2.5 $\pm$ 1.5
	0–10 mmHg	44	97.8	3.0 $\pm$ 1.9
	0–15 mmHg	45	100.0	3.1 $\pm$ 2.2
Absolute DBP differences	0–5 mmHg	37	82.2	2.4 $\pm$ 1.4
	0–10 mmHg	43	95.5	3.0 $\pm$ 2.1
	0–15 mmHg	45	100.0	3.5 $\pm$ 3.1



were aged between 20 and 34 years, while a smaller group (17.2%, $n = 93$) was under 20 years. Almost all participants (99.4%, $n = 537$) were of African descent, with the remainder being mixed race (0.6%, $n = 3$). In terms of marital status, over three-quarters (77.2%) were single and slightly more than a quarter (22.6%, $n = 122$) were married.

Most participants (93.7%, $n = 434$) attended antenatal clinics, while 34 (6.3%) did not. Statistically, antenatal clinic attendance was similar between the hypertensive and non-hypertensive groups ($p > 0.05$). The median gestational age at enrolment in the study was 36 (IQR: 33.0–38.0) weeks, with the non-hypertensive controls having a significantly higher median gestational age of 38 (IQR 36.0–39.0) weeks compared with the hypertensive cases at 34 weeks (IQR 31.0–37.0; $p < 0.0001$).

A significant majority of participants (86.7%, $n = 468$) delivered via caesarean section, while the remaining 13.3% ($n = 72$) had vaginal

births. No significant differences in delivery methods were found between the two groups.

In terms of body weight classification, nearly one-third of the women (32.4%, $n = 175$; 95% CI = 28.6–36.4%) were classified as obese, while 12.4% ($n = 67$; 95% CI = 9.8–15.4%) were severely obese, and 0.6% ($n = 3$; 95% CI = 0.2–1.5%) were underweight.

Overall, 28.3% ($n = 153$; 95% CI = 24.7–32.2%) of the women in the study were HIV-positive, while the remainder tested negative. There was no significant difference in HIV prevalence between women with HDP and the normotensive controls ($p > 0.05$). Most of the positive for HIV women had viral loads below detectable limits, with only 12.4% ($n = 19$; 95% CI = 7.9–12.4%) not achieving viral suppression. Moreover, no significant differences were observed between HIV-positive women with HDP and those who were HIV-positive but normotensive regarding viral suppression ($p > 0.05$).

TABLE 3 General characteristics of hypertensives cases and normotensive controls in the main study.

Characteristics	Hypertensive cases; <i>n</i> = 270	Normotensive controls; <i>n</i> = 270	Total	Sig.**
Numerical parameters	Median (IQR)	Median (IQR)	Median (IQR)	<i>p</i> -values
Age (years)	25 (20.0–32.0)	28 (24.0–33.0)	27 (21.0–33.0)	<0.0001
Body mass index (kg/m ²)	28.5 (23.9–34.3)	29.5 (25.1–35.5)	29 (24.7–34.9)	0.071
Gestational age at recruitment	34 (31.0–37.0)	38 (36.0–39.0)	36 (33.0–38.0)	<0.0001
Categorical values	Number (percentage)	Number (percentage)	Number (percentage)	Pearson χ^2 Sig.
Age group (years)				
<20 years	64 (23.7)	29 (10.7)	93 (17.2)	<0.0001
20–34 years	157 (58.1)	184 (68.1)	341 (63.1)	
≥35 years	49 (18.1)	57 (21.1)	106 (19.6)	
Ethnicity				
Black African	269 (99.6)	268 (99.2)	537 (99.4)	0.624*
Mixed race	1 (0.4)	2 (0.7)	3 (0.6)	
Marital status				
Single	210 (77.8)	207 (76.7)	417 (77.2)	0.837*
Married	60 (22.2)	62 (23.0)	122 (22.6)	
Divorced	0 (0.0)	1 (0.4)	1 (0.2)	
Level of education				
Tertiary	35 (13.0)	46 (17.0)	81 (15.0)	0.194*
Secondary	207 (76.7)	189 (70.0)	396 (73.3)	
Primary	27 (10.0)	35 (13.0)	62 (11.5)	
No formal education	1 (0.4)	0 (0.0)	1 (0.2)	
Booking status				
Booked	248 (91.9)	258 (95.6)	506 (93.7)	0.111
Not booked	22 (8.1)	12 (4.4)	34 (6.3)	
Mode of delivery				
Caesarean section	233 (86.3)	235 (87.0)	468 (86.7)	0.800
Vaginal	37 (13.7)	35 (13.0)	72 (13.3)	
Underweight (BMI < 18.5)	2 (0.7)	1 (0.4)	3 (0.6)	0.196*
Normal weight (BMI 18.5–24.9)	81 (30.0)	59 (21.9)	140 (25.9)	
Overweight (BMI ≥ 25.0–29.9)	74 (27.4)	81 (30.0)	155 (28.7)	
Obese (BMI ≥ 30.0–39.9)	79 (29.3)	96 (35.6)	175 (32.4)	
Severely obese (BMI ≥ 40.0)	34 (12.6)	33 (12.2)	67 (12.4)	
HIV status				
Positive	66 (24.4)	87 (32.2)	153 (28.3)	0.056
Negative	204 (75.6)	183 (67.8)	387 (71.7)	
Viral suppression				
Unsuppressed (>1,000 cp/mL)	10 (15.2)	9 (10.3)	19 (12.4)	0.609*
Suppressed (<1,000 cp/mL)	0 (0.0)	1 (1.1)	1 (0.7)	
Less than detectable limit (<50 cp/mL)	56 (84.8)	77 (88.5)	133 (86.9)	

BMI, body mass index (kg/m²); cp/mL, copies/mL; *Fisher's exact *p*-value; ** Mann–Whitney U *p*-value.

Establishment of cSBP and cDBP thresholds for diagnosis of central hypertension

To establish the upper thresholds for normal and abnormal CBP, a linear regression equation and the receiver operating curve analysis were used. The lower of these thresholds was then chosen to represent the threshold of normal and abnormal CBP. Consequently, the upper threshold of normal cSBP was found to be <116 mmHg and that of the normal cDBP was <78 mmHg (Table 4 and Figure 2). CBPs above these thresholds signified central hypertension.

ROC analysis for defining cSBP thresholds for diagnosis of central hypertension during pregnancy

To predict the diagnosis of central hypertension during pregnancy, the ROC analysis results indicate that a cSBP of 116 mm Hg or higher has a sensitivity of 78.5% and a specificity of 50.3%. The cSBP values utilized

as predictive variables for the ROC curve were derived exclusively from the HDP group. This model demonstrated a moderate discriminatory ability, with an area under the curve (AUC) of 0.7384 (Figures 2, 3).

Linear regression equation for defining the cSBP and cDBP threshold from PBP

Based on a normal pSBP of <140 mmHg and a diastolic pressure of <90 mmHg, the upper limit of cSBP in normotensive controls was calculated to be 130 mmHg, while the upper limit of cDBP was calculated to be 78 mmHg (see Tables 4, 5) (23).

Establishment of thresholds for severe central hypertension

Linear regression equation was used to calculate the thresholds for severe central hypertension from the thresholds of severe PBP, defined as a pSBP of ≥ 160 mmHg, and/or pDBP of ≥ 110 mmHg, among women

TABLE 4 Establishment of cSBP threshold in normotensives.

Normotensive controls (N = 270)		Unstandardized coefficients		Standardized coefficients	t	p value
1		B	Std. error	Beta		
	(Constant)	47.505	6.013		7.901	0.000
	pSBP (mmHg)	0.592	0.052	0.568	11.290	0.000

Using the simple regression formula, where predicted cSBP = $a + bx$ (with 'a' representing the constant, 'b' as the unstandardized coefficient for pSBP, and 'x' as any pSBP reading), if a pSBP of 139 mm Hg is chosen as a reference point for normal systolic pressure, then the upper limit of cSBP in normotensive controls = $47.505 + 0.592(139) = 130$ mmHg.

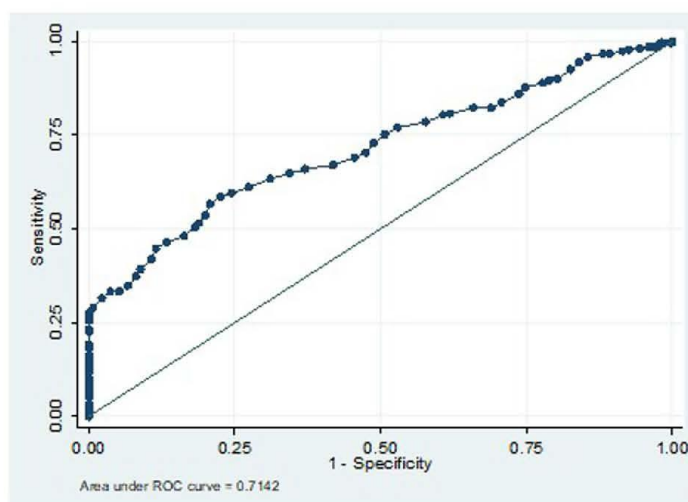


FIGURE 2
ROC for cSBP cut-off for prediction of central hypertension in women with HDP if 116 mmHg is chosen.


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Detailed report of sensitivity and specificity

Cutpoint	Sensitivity	Specificity	Correctly Classified	LR+	LR-
(>= 59)	100.00%	0.00%	50.00%	1.0000	0.0000
(>= 71)	100.00%	0.37%	50.19%	1.0037	0.0000
(>= 79)	100.00%	0.74%	50.37%	1.0075	0.0000
(>= 81)	100.00%	1.11%	50.56%	1.0112	0.0000
(>= 84)	100.00%	1.48%	50.74%	1.0150	0.0000
(>= 88)	100.00%	1.85%	50.93%	1.0189	0.0000
(>= 89)	100.00%	2.22%	51.11%	1.0227	0.0000
(>= 90)	100.00%	3.33%	51.67%	1.0345	0.0000
(>= 91)	100.00%	4.07%	52.04%	1.0425	0.0000
(>= 92)	100.00%	4.81%	52.41%	1.0506	0.0000
(>= 93)	99.26%	5.56%	52.41%	1.0510	0.1333
(>= 94)	98.52%	6.30%	52.41%	1.0514	0.2353
(>= 95)	98.52%	7.04%	52.78%	1.0598	0.2105
(>= 96)	98.52%	7.41%	52.96%	1.0640	0.2000
(>= 97)	97.41%	8.89%	53.15%	1.0691	0.2917
(>= 98)	97.41%	10.00%	53.70%	1.0823	0.2593
(>= 99)	97.04%	11.11%	54.07%	1.0917	0.2667
(>= 100)	95.93%	12.96%	54.44%	1.1021	0.3143
(>= 101)	95.56%	13.70%	54.63%	1.1073	0.3243
(>= 102)	94.81%	15.93%	55.37%	1.1278	0.3256
(>= 103)	93.70%	16.67%	55.19%	1.1244	0.3778
(>= 104)	93.70%	18.52%	56.11%	1.1500	0.3400
(>= 105)	92.96%	21.48%	57.22%	1.1840	0.3276
(>= 106)	90.74%	24.07%	57.41%	1.1951	0.3846
(>= 107)	90.00%	25.93%	57.96%	1.2150	0.3857
(>= 108)	89.63%	28.15%	58.89%	1.2474	0.3684
(>= 109)	88.89%	31.48%	60.19%	1.2973	0.3529
(>= 110)	87.04%	32.96%	60.00%	1.2983	0.3933
(>= 111)	85.93%	35.19%	60.56%	1.3257	0.4000
(>= 112)	83.70%	37.41%	60.56%	1.3373	0.4356
(>= 113)	82.22%	40.74%	61.48%	1.3875	0.4364
(>= 114)	81.48%	43.33%	62.41%	1.4379	0.4274
(>= 115)	79.63%	46.67%	63.15%	1.4931	0.4365
(>= 116)	78.52%	50.37%	64.44%	1.5821	0.4265
(>= 117)	75.93%	54.07%	65.00%	1.6532	0.4452
(>= 118)	74.44%	55.19%	64.81%	1.6612	0.4631
(>= 119)	74.07%	58.15%	66.11%	1.7699	0.4459
(>= 120)	71.48%	60.74%	66.11%	1.8208	0.4695
(>= 121)	69.26%	62.96%	66.11%	1.8700	0.4882
(>= 122)	66.67%	64.81%	65.74%	1.8947	0.5143
(>= 123)	64.07%	67.78%	65.93%	1.9885	0.5301
(>= 124)	62.33%	69.63%	66.48%	2.0854	0.5266
(>= 125)	60.74%	73.70%	67.22%	2.3099	0.5327
(>= 126)	59.63%	77.04%	68.33%	2.5968	0.5240
(>= 127)	57.41%	78.89%	68.15%	2.7193	0.5399
(>= 128)	54.81%	80.00%	67.41%	2.7407	0.5648
(>= 129)	51.11%	84.07%	67.59%	3.2093	0.5815
(>= 130)	48.89%	86.67%	67.78%	3.6667	0.5897
(>= 131)	47.04%	87.78%	67.41%	3.8485	0.6034
(>= 132)	44.44%	90.74%	67.59%	4.8000	0.6122
(>= 133)	42.22%	92.96%	67.59%	6.0000	0.6215
(>= 134)	38.89%	93.33%	66.11%	5.8333	0.6548
(>= 135)	35.19%	95.19%	65.19%	7.3077	0.6809
(>= 136)	32.59%	96.30%	64.44%	8.8000	0.7000
(>= 137)	31.11%	96.67%	63.89%	9.3333	0.7126
(>= 138)	30.37%	97.41%	63.89%	11.7143	0.7148
(>= 139)	28.15%	97.78%	62.96%	12.6667	0.7348
(>= 140)	25.93%	98.52%	62.22%	17.5001	0.7519
(>= 141)	23.33%	98.52%	60.93%	15.7501	0.7782
(>= 142)	21.85%	99.26%	60.56%	29.4998	0.7873
(>= 143)	21.11%	99.26%	60.19%	28.4998	0.7948
(>= 144)	19.63%	99.26%	59.44%	26.4998	0.8097
(>= 145)	18.89%	99.63%	59.26%	51.0002	0.8141
(>= 146)	17.41%	99.63%	58.52%	47.0002	0.8290
(>= 147)	15.56%	99.63%	57.59%	42.0002	0.8476
(>= 148)	13.70%	99.63%	56.67%	37.0001	0.8662
(>= 149)	11.48%	99.63%	55.56%	31.0001	0.8885
(>= 150)	11.11%	99.63%	55.37%	30.0001	0.8922
(>= 151)	9.63%	99.63%	54.63%	26.0001	0.9071
(>= 152)	8.15%	99.63%	53.89%	22.0001	0.9219
(>= 153)	8.15%	100.00%	54.07%		0.9185
(>= 154)	7.78%	100.00%	53.89%		0.9222
(>= 155)	6.30%	100.00%	53.15%		0.9370
(>= 156)	4.81%	100.00%	52.41%		0.9519
(>= 157)	4.44%	100.00%	52.22%		0.9556
(>= 159)	4.07%	100.00%	52.04%		0.9593
(>= 161)	3.70%	100.00%	51.85%		0.9630
(>= 164)	2.96%	100.00%	51.48%		0.9704
(>= 167)	2.22%	100.00%	51.11%		0.9778
(>= 170)	1.85%	100.00%	50.93%		0.9815
(>= 174)	1.48%	100.00%	50.74%		0.9852
(>= 180)	1.11%	100.00%	50.56%		0.9889
(>= 185)	0.74%	100.00%	50.37%		0.9926
(>= 193)	0.37%	100.00%	50.19%		0.9963
(> 193)	0.00%	100.00%	50.00%		1.0000

Obs	ROC Area	Std. Err.	—Asymptotic Normal— [95% Conf. Interval]
540	0.7384	0.0212	0.69692 0.77997

FIGURE 3

Sensitivity and specificity of cSBP cut-offs for prediction of central hypertension in women with HDP.

with HDP who were identified to have severe peripheral hypertension (23). The thresholds for severe central hypertension were found to be a cSBP of ≥ 148 mmHg and/or a cDBP of ≥ 95 mmHg (see Tables 6, 7).

Correlation of median pSBP, cSBP, pDBP, and cDBP as measured using microlife WatchBP office central among women with HDP and normotensive controls

Among the 270 normotensive controls, the median pSBP was 114.0 (IQR: 104.0–124.0) mmHg, and the median cSBP was 115.0 (IQR: 106.0–125.0) mmHg (see Figures 4, 5). There was a strong positive relationship between the two measurements (Spearman rank correlation coefficient = 0.583; $p < 0.0001$) as shown in Table 8. The linear regression analysis revealed a positive correlation between pSBP and cSBP, with changes in pSBP being associated with a shift in the cSBP ($B = 0.592$; $p < 0.0001$). The difference between median pSBP and cSBP was 1.0 mmHg, but this was not statistically significant (Wilcoxon Signed Rank $p = 0.122$).

Additionally, the median cSBP [110 (IQR: 101.0–120.0) mmHg] was less than the median pSBP [120.0 (IQR: 112.0–129.0) mmHg] in 119 participants (44%), the median cSBP [119.5 (111.0–128.0) mmHg] was greater than the median pSBP [109.0 (100.0–118.0) mmHg] in 146 participants (54%), and in 5 participants (1.9%), they were equal. The observed difference was not statistically significant (z based on positive ranks = -1.546 ; Wilcoxon Signed Rank $p = 0.122$).

Among the 270 normotensive controls, median cDBP was 64.0 (IQR: 55.0–73.0) mmHg, and the median pDBP was 61.5 (IQR: 52.0–69.0) mmHg. There was a strong positive correlation between the two measurements (Spearman rank correlation of 0.669, $p < 0.0001$) as shown in Table 8. Linear regression analysis also revealed that there was a positive correlation between cDBP and pDBP, with changes in pDBP being significantly associated with a shift in the cDBP ($B = 0.658$; $p < 0.0001$). The difference between median pDBP and cDBP was 2.5 mmHg, which was statistically significant (Wilcoxon Signed Rank $p < 0.0001$).

Additionally, cDBP [58.0 (50.0–66.0) mmHg] was less than pDBP [68.0 (60.0–70.0) mmHg] in 159/270 participants (59%), cDBP [64.0 (IQR: 57.0–73.0) mmHg] was greater than pDBP [57.0 (IQR: 49.0–65.0) mmHg] in 98 participants (36.3%) and was equal in only 13 participants (4.8%). The observed difference was statistically significant (z based on negative ranks = -4.342 ; Wilcoxon Signed Rank $p < 0.0001$).

Comparison of median pSBP and median pDBP with cSBP and cDBP among women with mild peripheral hypertension as measured using microlife WatchBP office central

Among 95 women with mild peripheral hypertension, the median pSBP was 144.0 (138.0–148.0) mmHg, while the median cSBP was

TABLE 5 Establishment of cDBP threshold in normotensives.

Normotensive (N = 270)		Unstandardized coefficients		Standardized coefficients	t	Sig.
1		B	Std. error	Beta		
	(Constant)	19.006	2.817		6.748	0.000
	pDBP (mmHg)	0.658	0.043	0.681	15.204	0.000

If the reference point of the pDBP in normotensive controls is taken as 89 mmHg (less than 90 mmHg), then the upper limit of cDBP in normotensive controls = $19.006 + 0.658 (89) = 77.6$ or 78 mmHg.

TABLE 6 Establishment of cSBP thresholds for diagnosis of severe central hypertension based on pSBP of ≥ 160 mmHg in women with severe peripheral hypertension.

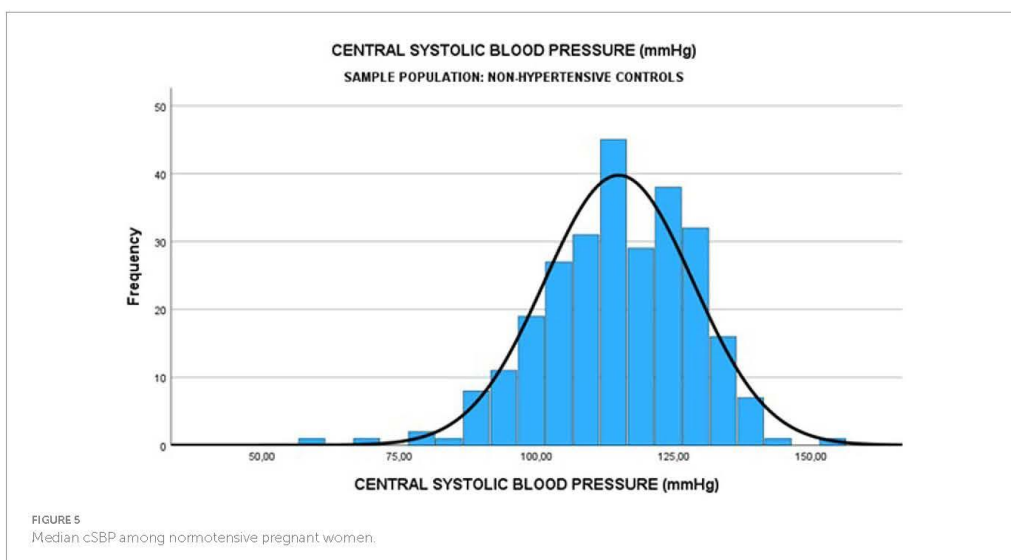
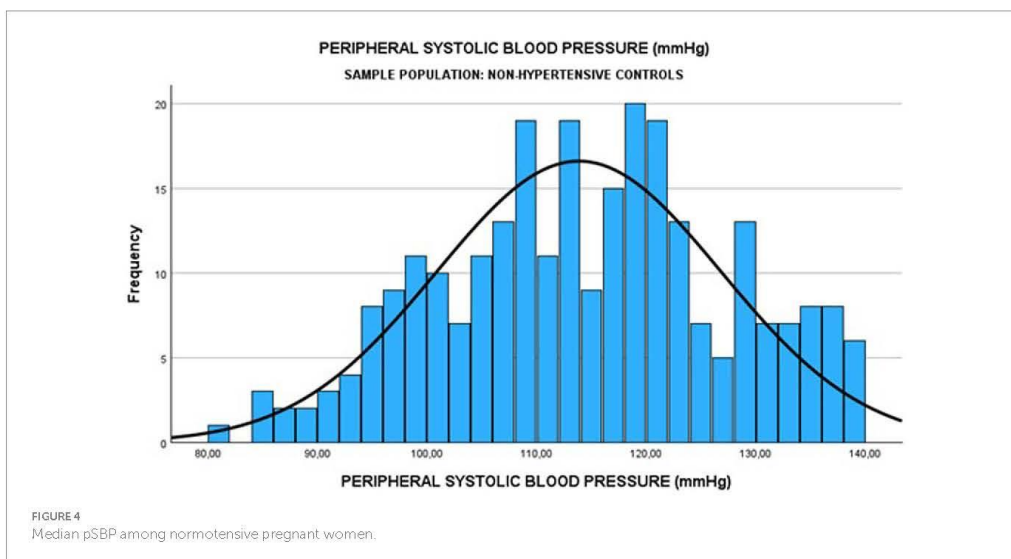
Severe peripheral hypertension		Unstandardized coefficients		Standardized coefficients	t	p value
1		B	Std. error	Beta		
	(Constant)	36.961	45.232		0.817	0.421
	pSBP (mmHg)	0.696	0.271	0.449	2.562	0.017

If the threshold for severe peripheral systolic blood pressure (pSBP) is taken as 160 mmHg, then the threshold for severe cSBP = $36.961 + 0.696 (160) = 148.321$ or 148 mmHg.

TABLE 7 Defining cDBP cut-off for severe central hypertension based on pDBP of ≥ 110 mmHg in women with severe peripheral hypertension.

Severe peripheral hypertension		Unstandardized coefficients		Standardized coefficients	t	p value
1		B	Std. error	Beta		
	(Constant)	6.512	13.149		0.495	0.625
	pDBP (mmHg)	0.806	0.126	0.783	6.420	0.000

If the threshold for severe peripheral diastolic blood pressure (pDBP) is taken as ≥ 110 mmHg, then the threshold for severe cDBP = $6.512 + 0.806 (110) = 95.172$ or 95 mmHg.



139.0 (132.0–147.0) mmHg as shown in Table 8. There was a strong positive relationship between the two measurements (Spearman rank $r = 0.445$; $p < 0.0001$). Linear regression analysis revealed a strong positive correlation between pSBP and cSBP, with changes in the pSBP being significantly associated with a shift in the cSBP ($B = 0.631$; $p < 0.0001$). The difference between the median pSBP and median cSBP was 1.0 mmHg, and this was statistically significant (Wilcoxon Signed Rank $p < 0.0001$).

Additionally, among the same 95 women with mild peripheral hypertension, the median cSBP was less than the median pSBP in 69

participants, and the median cSBP was greater than the median pSBP in 24 participants, while the two were equal in two participants. The analysis using the Wilcoxon Signed Rank test revealed a statistically significant difference ($p < 0.0001$).

Furthermore, among the same group of women with mild peripheral hypertension, the median pDBP was 91.0 (86.0–96.0) mmHg, while the median cDBP was 82.0 (77.0–89.0) mmHg. There was a strong positive correlation between the two measurements (Spearman's rank $r = 0.596$; $p < 0.0001$). Linear regression analysis revealed a strongly positive correlation between the pDBP and the

cDBP and cDBP, and changes in pDBP were associated with a shift in the cDBP ($B = 0.661$; $p < 0.0001$). The difference between the median pDBP and cDBP was 9.0 mmHg, which was statistically significant ($p < 0.0001$).

Additionally, among these women with mild peripheral hypertension, the median cDBP was less than the median pDBP in 81 participants, while in 14 participants, the median cDBP was greater than the median pDBP. The observed differences were statistically significant ($p < 0.0001$). Among the 14 participants with a higher median cDBP than the pDBP, four had eclampsia. The median cDBP for the four eclamptic patients was 108 mmHg, while their median pDBP was 93 mmHg. The difference between median cDBP and pDBP among the four participants was 15 mmHg, and it was statistically significant (z based on positive ranks = -6.5 ; Wilcoxon Signed Rank $p < 0.0001$).

Twenty-seven of the 102 eclamptic patients had mild peripheral hypertension, while the rest had severe peripheral hypertension. The median pSBP among eclamptic patients with mild peripheral hypertension was 138.0 mmHg (IQR: 133.0–148.0) while the cSBP level in the same group was 145.0 mmHg (IQR: 140.0–150.0).

The overall median cSBP among women with eclampsia ($n = 102$) was 133.0 mmHg (IQR 120.0–143.0) and the median cDBP was 73.0 mmHg (IQR: 60.0–83.0), and these were significantly higher ($p < 0.0001$) than the median cSBP of 128.0 mmHg (IQR: 114.0–139) and cDBP of 71.0 mmHg (IQR: 61.0–81.0) among preeclamptic women, with or without severe features, and much higher than the median cSBP of 115 mmHg (IQR: 106.0–125.0) and cDBP of 61.5 mmHg (IQR: 52.0–69.0) among normotensive controls (Table 9).

Discussion

Historically, measuring CBP required invasive methods, which limited its application. However, recent advancements in non-invasive technologies have improved the feasibility of obtaining reliable measurements in clinical environments. This transition toward non-invasive techniques facilitates better monitoring, particularly in vulnerable groups like pregnant women.

This study aimed to assess the relationship between peripheral and CBP and to determine the thresholds for mild and severe central hypertension among pregnant women in the third trimester.

The research established that the cut-off for diagnosing central hypertension is a cSBP of 116 mmHg and a cDBP of 78 mmHg. These findings are consistent with the work of Chulkova et al. (26), who noted that a cSBP of 115 mmHg in pregnant women might indicate a risk for PE. Additionally, these results align with a study by Booysen et al. (27), which reported a cSBP upper threshold of 112 mmHg among a cohort of 311 young Black South Africans with a median age of 31. The similarity in our findings can be attributed to the younger demographic and shared background, as both studies focused on younger Black South Africans.

Conversely, research involving older populations has indicated higher thresholds for CBP. For example, a study with over 6,000 participants conducted by Hao et al. (18) established a 90th percentile cutoff for cSBP at 125 mmHg for men and 126 mmHg for women. This is consistent with previous findings from Japan, where a threshold of 129 mmHg was reported (17). Additionally, Cheng et al. (19) demonstrated through a longitudinal study involving 1,272 older participants that a central BP greater than 130/90 mmHg significantly

TABLE 8 Comparison of median pSBP and pDBP with median cSBP and cDBP among women with normal and mild peripheral hypertension as measured using Microlife WatchBP Office Central.

Hypertensive groups	cSBP median (IQR)	pSBP median (IQR)	Spearman rank	<i>p</i> value	cDBP median (IQR)	pDBP median (IQR)	Spearman rank	<i>p</i> value
Normotensive ($n = 270$)	115.0 (106.0;125.0)	114.0 (104.0;124.0)	0.583	<0.0001*	64.0 (55.0;73.0)	61.5 (52.0;69.0)	0.669	<0.0001*
Mild hypertensive ($n = 67$)	139.0 (132.0;147.0)	144.0 (138.0;148.0)	0.445	<0.0001*	82.0 (77.0;89.0)	91.0 (86.0;96.0)	0.596	<0.0001*

Normal central blood pressure = cSBP of <116 and/or cDBP <78; mild central hypertension = cSBP of 116–147 and/or cDBP of 78–94; severe central hypertension = cSBP of ≥148 and/or cDBP of ≥95 mmHg; Mild peripheral hypertension = pSBP of 140–159 and/or cDBP of 90–109. cDBP, central diastolic blood pressure; pDBP, peripheral diastolic blood pressure; cSBP, central systolic blood pressure; pSBP, peripheral systolic blood pressure. *Statistically significant.

TABLE 9 Comparison of central blood pressure readings among the different phenotypes of HDP and normotensive controls.

Blood pressure	Study groups						Kruskal-Wallis Sig.
	Control	A	B	C	D	E	
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	
cSBP (mmHg)	115.0 (106.0–125.0)	132.0 (122.0–143.0)	119.5 (116.0–128.0)	128.5 (114.5–142.0)	128.0 (114.0–139.0)	133.0 (120.0–143.0)	<0.0001
cDBP (mmHg)	61.5 (52.0–69.0)	71 (63.0–80.0)	65 (61.0–71.0)	69.0 (61.0–83.0)	71.0 (61.0–81.0)	73.0 (60.0–83.0)	<0.0001

A, Gestational hypertension; B, Chronic hypertension; C, Preeclampsia without severe features; D, Preeclampsia with severe features; E, Eclampsia; cSBP, central systolic blood pressure; cDBP, central diastolic blood pressure.

predicts cardiovascular events over a median follow-up of 15 years. While the cut-off values determined by Cheng et al. (19) serve as important benchmarks, they may not fully apply to pregnant populations, where physiological changes result in unique cardiovascular dynamics (20). Moreover, aging is often associated with aortic stiffness, which leads to an earlier return of reflected waves in late systole, contributing to higher central BP levels (10).

For severe central hypertension, our study found that among pregnant women in their third trimester with severe brachial hypertension, cSBP was ≥ 148 mmHg and cDBP was ≥ 95 mmHg. To our knowledge, this work is the first to document the threshold for severe central hypertension. However, further studies are needed to validate these findings. These thresholds are considerably lower than those of PBP (160/110 mmHg), which is expected, as CBP is generally lower than PBP due to the inherent physiological differences between the two vascular systems.

One limitation in our calculations is that some normotensive controls displayed higher cSBP and/or cDBP values than their peripheral counterparts. Under typical conditions, cSBP should be lower than pSBP, with minimal variation between pDBP and cDBP. The possible explanation for this finding in our study is that while the participants had normal PBP, their CBP may have already been abnormal.

In comparison of peripheral and CBP, a positive correlation was found between pSBP and cSBP, as well as between pDBP and cDBP among normotensive pregnant women, aligning with previous findings by Fujime et al. (28). Importantly, Fujime et al. analyzed a larger sample of 830 participants, which adds strength to their findings. Similarly, a cross-sectional study by Priyadarsini et al. (29) involving 107 pregnant women and 53 age-matched non-pregnant women also confirmed a strong relationship between brachial systolic blood pressure and cSBP in healthy normotensive pregnant women (29).

These positive correlations could be explained physiologically by the impact of arterial elasticity on circulatory pressure distribution (30). With healthy, elastic arteries, a strong correlation between peripheral and central measurements is expected. Healthy, elastic arteries allow for a more efficient transmission of pressure waves generated by the heartbeat. When arteries are elastic, they can accommodate the surge of blood during systole, dampening the pressure peaks and maintaining a more stable blood flow throughout the body (31).

Additionally, several studies have demonstrated that CBP has a better relationship to future cardiovascular events and mortality and is also more relevant than peripheral brachial BP in predicting target organ damage, as it represents the true load imposed on the heart, brain, kidneys, and the large arteries (32–34). Nevertheless, additional research is necessary to validate these findings, given that some authors dispute the stronger correlation between CBP and cardiovascular events (35, 36).

In this study, the median cSBP among normotensive pregnant women was found to be 115 mmHg. This finding is consistent with the results of Turi et al. (37), who reported a similar mean cSBP of 115 mmHg in healthy pregnant women. However, in our study, the cSBP value was slightly higher, though not significantly, than the pSBP value of 114 mmHg that was observed. Typically, in normotensive individuals, cSBP is expected to be lower than pSBP. This atypical finding raises the possibility that individuals with higher cSBP in this

study may have an underlying increase in arterial stiffness or could be at risk of developing it. As arterial stiffness increases, systolic pressure tends to rise. This is due to the early merging of the fast-reflected wave with the forward wave (38). Furthermore, increased arterial stiffness damages more elastic fibers in the blood vessel walls, leading to inadequate buffering and transmission of pulsatile pressure from the heart to target organs (39). Such changes can ultimately result in organ damage, so it is a good idea to closely monitor these patients to assess their risk of high blood pressure in the future.

In this study, cDBP in normotensive controls was less than pDBP in 159 participants, and it was greater than pDBP in 98 participants. This is again an unexpected finding in normotensive controls, as under physiological conditions, the cDBP should either be the same as the pDBP or less than the pDBP (40). This suggests that the 98 individuals with higher cDBP may be having central diastolic hypertension or are at risk of developing central hypertension, while their peripheral diastolic blood pressure puts them in the normal blood pressure category. Only a prospective follow-up study can test this explanation.

There is little correlation between the pBP and the occurrence of eclampsia. Several studies indicate that the blood pressure may be normal or only mildly elevated in women with eclampsia and even with stroke (41–43). The present study found that the median central systolic and diastolic blood pressures, as well as pDBP, were significantly higher in cases of eclampsia compared with those with other HDP and with non-hypertensive controls. This implies that CBP measurement may be better able to distinguish between the subtypes of HDP and phenotypes of PE than PBP.

In addition, the median cSBP for women with eclampsia and mild peripheral hypertension was relatively severe. This suggests that some eclamptic patients with mild pSBP actually have a cSBP that falls into the severe range. This finding may help explain why some patients with mild peripheral hypertension experience eclampsia. This implies that the cSBP might be a better predictor of eclampsia than the pSBP. Central aortic blood pressure plays a crucial role in regulating blood flow to the brain (15). Consequently, it could be inferred that in cases of eclampsia, vasogenic oedema might occur due to elevated CBP, even when brachial blood pressure remains only slightly elevated in the affected women.

The limitation of this study is that all hypertensive patients received antihypertensive treatment, which may have affected their blood pressure readings. However, patients were recruited within 24 h of admission, a time frame during which the pharmacological treatment might not have fully taken effect.

Conclusion

This study established the threshold values for central hypertension as 116/78 mmHg, with severe central hypertension defined as 148/95 mmHg. This study also reinforces the positive correlation between peripheral and CBP in both normotensive and hypertensive populations. Notably, women with eclampsia showed higher CBP levels compared with those having mild hypertension in the severe range. This may clarify why some patients with mild peripheral hypertension experience eclampsia and may thus indicate

that CBP is a better predictor of eclampsia than PBP. Further research is needed to confirm these findings.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Walter Sisulu University Human Research Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

XM: Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Formal analysis, Investigation, Methodology. SG: Supervision, Writing – review & editing. AH: Supervision, Writing – review & editing. CB: Writing – review & editing, Conceptualization, Methodology, Supervision, Validation. MN: Writing – review & editing, Formal analysis. GB: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Arterial stiffness after 6 weeks postdelivery in women with a history of hypertensive disorders of pregnancy: a systematic review and meta-analysis

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Introduction: The main objective of this systematic review was to determine if the arterial stiffness remains elevated after 6 weeks post-delivery in women with a history of hypertensive disorders of pregnancy (HDP).

Methods and analysis: A comprehensive systematic literature search was conducted across multiple electronic databases, including Medline, PubMed, Embase, Cochrane Library, Google Scholar, Web of Science, and CINAHL. We included studies assessing arterial stiffness in women with a history of HDP between 43 days and 10 years postdelivery, with participants under 60 years of age. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines. We extracted data on arterial stiffness indices, including carotid-femoral pulse wave velocity (cfPWV), augmentation index (AIx), and heart rate adjusted augmentation index (AIx@75), along with the mean $\pm$ standard deviation for each study. A random-effects model was used to pool data, and heterogeneity was explored through sensitivity and subgroup analyses. The Newcastle Ottawa Scale (NOS) and Grading of Recommendations Assessment, Development, and Evaluation (GRADE) were used to assess risk of bias and quality of evidence.

Results: Out of 121 identified articles, 12 studies involving a total of 856 women were included in the final review after eliminating duplicates and irrelevant studies. The overall pooled data revealed a significantly elevated AIx and cfPWV among women with a history of HDP. Specifically, the mean difference (MD) in AIx was 11.63 (95% Confidence Interval (CI): [1.72–21.54]), and for cfPWV, the MD was 0.53 (95% CI: [0.27–0.78]). Notably, while AIx showed no significant change in women within 1 year postpartum (MD 14.85, 95% CI [–6.03–35.72]), an elevation was observed in those beyond 1 year post-delivery (MD 9.11, 95% CI [4.20–14.02]). cfPWV was also found to be elevated in HDP patients both within 1 year (MD 0.59, 95% CI [0.32–0.86]) and beyond 1 year (MD 0.45, 95% CI [0.03–0.88]). In cases of early-onset preeclampsia, AIx did not show a significant increase; however, a significant increase in cfPWV was observed, with AIx having an MD of 1.55 (95% CI: [–0.74–3.84]) and cfPWV an MD of 1.86 (95% CI: [0.25–3.47]). For late-onset preeclampsia, there was no significant difference in AIx (MD 2.44, 95% CI: [–8.82–13.70]) or cfPWV (MD 0.10, 95% CI: [–0.42–0.62]).

Conclusion: This systematic review and meta-analysis suggest that arterial stiffness may remain elevated beyond 6 weeks postpartum in women with a

history of HDP. However, the findings should be interpreted with caution due to heterogeneity across studies and limited number of available studies. Larger and standardized longitudinal studies are needed to confirm these results. In the meantime, regular cardiovascular monitoring for these women is recommended while awaiting more conclusive evidence.

Systematic review registration: <https://www.crd.york.ac.uk/PROSPERO/search>, CRD42023461867.

KEYWORDS

hypertensive disorders of pregnancy, arterial stiffness, cardiovascular disease, pulse wave velocity, augmentation index, preeclampsia, maternal morbidity, postdelivery risk

Introduction

Hypertensive disorders of pregnancy (HDP), including gestational hypertension and preeclampsia, contribute significantly to maternal morbidity and mortality worldwide (1). Research has consistently indicated that women with a history of HDP face an increased risk of long-term cardiovascular issues, such as hypertension, stroke, and heart disease (2, 3). One important marker of cardiovascular health is arterial stiffness, which has been observed to be elevated in women with HDP both during and after pregnancy (4, 5). Evidence suggests that arterial stiffness and central aortic blood pressure are more closely linked to future cardiovascular events and renal complications than peripheral blood pressure in non-pregnant populations, a trend that may extend to HDP women in terms of their long-term cardiovascular outcomes.

From a physiological standpoint, the six-week mark post-delivery is noteworthy as it typically signals the stabilization of hemodynamics (6, 7). Throughout pregnancy, women experience considerable metabolic demands and cardiovascular adaptations that differ by trimester and gradually normalize after delivery (8). Key cardiovascular changes during pregnancy include an increase in cardiac output and blood volume, accompanied by a decrease in systemic vascular resistance (SVR). In particular, during pregnancy, elevated serum levels of progesterone and relaxin, a peptide hormone produced by the corpus luteum and placenta, facilitate systemic vasodilation (7, 8). This process results in a 25 to 30% reduction in SVR during pregnancy, with levels normalizing within 2 weeks postpartum and other vascular changes returning to normal during the six-week puerperal phase (7). Examining how arterial stiffness evolves after this timeframe is essential for understanding a woman's cardiovascular health trajectory and potential long-term risks.

Although studies indicate that central blood pressure and arterial stiffness measured before 14 weeks of gestation can predict preeclampsia (37–39), further evaluation is needed on their impact on future cardiovascular health. Importantly, increased maternal arterial stiffness in hypertensive pregnancies has also been associated with intrauterine growth restriction and small-for-gestational-age infants (9). Research has also found associations between elevated maternal arterial stiffness and central blood pressure, foetal growth restriction, and small for gestational age infants, as well as increased blood pressure in offspring by the age of 3 (9, 10). However, there is limited global data on whether arterial stiffness remains elevated beyond 6 weeks postpartum in women who have a history of HDP.

Global research examining this issue has included: (i) The United Kingdom indicates that women with a history of HDP face significant long-term cardiovascular risks, including accelerated cardiovascular aging and a greater variety of conditions such as valvular heart disease (11); (ii) Canada has shown a significant association between HDP and long-term cardiovascular risk, particularly highlighting that women who have experienced preeclampsia may exhibit increased arterial stiffness for up to 6 years after giving birth (12). This growing body of evidence suggests that arterial stiffness may remain elevated beyond puerperium, reinforcing the need for regular cardiovascular monitoring in women with a history of HDP; (iii) In Asia, particularly Korea, research suggest that elevated arterial stiffness seen in women with HDP during pregnancy may return to baseline levels after delivery (13). This variation in findings emphasizes the importance of conducting a global review to understand the long-term effects of HDP on arterial health and; (iv) In Africa, where HDP is a major cause of maternal mortality, research on the lasting cardiovascular effects of HDP is still emerging but gradually increasing. Some studies suggest that women with a history of HDP may contend with a greater risk of cardiovascular disease; however, further research is essential to evaluate the specific role of arterial stiffness after delivery (5, 14). Given the significant long-term cardiovascular risks associated with HDP, it is crucial to understand the duration of elevated arterial stiffness. This systematic review synthesized the existing literature to provide a better picture of the long-term effects of HDP on arterial health.

Objective

The objective of this systematic review was to determine if the arterial stiffness remains elevated after 6 weeks post-delivery in women with a history of hypertensive disorders of pregnancy.

Methods

This protocol was developed following the Preferred Reporting Items for Systematic reviews and Meta-Analysis protocols (PRISMA-P) 2015 Guidelines (15). A comprehensive search was conducted in Medline, PubMed, Embase, Cochrane Library, Google Scholar, Web of Science, and CINAHL. The following MeSH terms for database searches were used: ("Arterial stiffness" OR "central blood pressure" OR "Pulse wave velocity" OR "Augmentation index" OR

TABLE 1. PUBMED 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]	21,613
2	Preeclampsia [tw] OR Eclampsia[tw] OR Hypertensive disorders of pregnancy [tw] OR pregnancy-induced hypertension [tw] OR Gestational hypertension [tw] OR Chronic hypertension [tw]	69,722
3	After postpartum [tw] OR after delivery [tw] OR after puerperium [tw]	25,178
4	#2 AND #3	2,098
5	#1 AND #4	23

“PWV” OR “AIx” OR “AIx@75”) AND (“Preeclampsia” OR “Eclampsia” OR “Gestational hypertension” OR “Chronic hypertension” OR “Hypertensive disorders of pregnancy” OR “pregnancy induced hypertension”) AND (“After postpartum” OR “after delivery” OR “after puerperium”). One example of the search strategies used is shown in Table 1.

The exposure

The exposure was hypertensive disease during pregnancy or within 42 days post-delivery. The hypertensive diseases included preeclampsia, gestational hypertension, chronic hypertension, and chronic hypertension with superimposed preeclampsia. Preeclampsia was 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 $\mu\text{mol/L}$ 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 $<150,000/\mu\text{L}$, disseminated intravascular coagulation, haemolysis). Uteroplacental dysfunction includes fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or stillbirth (16, 17). Gestational hypertension was defined as persistent *de novo* hypertension that develops at or after 20 weeks of gestation in the absence of features of preeclampsia. Chronic hypertension referred to high blood pressure predating the pregnancy or recognized at < 20 weeks of gestation. Chronic hypertension with superimposed preeclampsia was diagnosed when preeclampsia occurred in a pregnant woman who had pre-existing chronic hypertension.

Inclusion criteria

We included randomized and non-randomized control trials, prospective and retrospective cohort studies, case-control studies, and

cross-sectional studies performed in humans. The studies were included based on the following criteria:

1. Women with a history of HDP, aged under 60 years.
2. Studies reporting arterial stiffness indices (cPWV, AIx, and AIx@75) at least 43 days postpartum.

There were no restrictions by the date of publication.

Exclusion criteria

We excluded 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 were also excluded. Studies that only assess arterial stiffness measurements during pregnancy, labour, and delivery or within 6 weeks post-partum were excluded.

Comparator

The control group consisted of women under 60 years old with no history of HDP, cardiovascular diseases, renal failure, or diabetes.

Data collection

Mendeley Reference Manager was used to store and manage searched items under the following headings in a separate table: Authors, publication year, title of the study, location of the study, participants ages, country, and main study findings. Two independent reviewers screened all the titles and abstracts using the predetermined inclusion and exclusion criteria. We followed PRISMA-P guidelines. Records identified as potentially eligible based on title, abstract, and full texts were obtained to screen. Where consensus on eligibility could not be achieved, a third review author was involved in the discussion. When the same cohort was reported in multiple articles, the study which contains the largest sample was selected. Data from selected studies were extracted and entered into a Microsoft Excel spreadsheet.

Risk of bias

Two independent authors evaluated the methodological quality of all included studies. Where consensus on eligibility could not be achieved, a third reviewer was involved in the discussion. The Newcastle Ottawa Scale (NOS) and Grading of Recommendations Assessment, Development, and Evaluation (GRADE) were used to assess risk of bias and quality of evidence (18). Disagreements among the two authors was resolved by consultation with the other authors to reach a consensus. No studies were excluded based on the risk of bias assessment.

Potential sources of heterogeneity were first assessed using the I^2 statistic (19). Values of 25% or less were classified as low, around 50% as moderate, and 75% or more as high (20). The subgroup and sensitivity analyses using RevMan 5.4 and NOS assessment scale

were performed. Since all subgroups contained fewer than ten studies, a funnel plot was only created for those with six or more studies.

Statistical analysis

Estimates of mean and $\pm$ SD for arterial stiffness indices (cfPWV, AIx, AIx@75) for women who had HDPs (for each subtype of HDP, as available) and normotensive women was obtained from the relevant studies. For studies where the estimates were reported as the median and interquartile range, approximate estimates of mean and $\pm$ SD were calculated using the available estimates of the median and, first quartile and third quartile. These data were summarized using a DerSimonian and Laird random-effects model (21). A separate meta-analysis was conducted for each hemodynamic indices of interest (cfPWV, AIx, AIx@75) for the combined outcome in those who had HDPs. For studies that provided data on the association between these hemodynamic variables and the outcome of interest, we meta-analyzed these effect measures using a random effects model. We performed a subgroup analysis for each subtype of HDP, as available.

Results

Study selection

Through our literature search, we identified 121 articles. After removing 22 duplicates and excluding 70 based on title and abstract screening (see Figure 1), Twenty-nine articles remained that were eligible for full-text review. Out of these, 12 studies were included in the final review. Specifically, there were 4 cross-sectional studies, 5 cohort studies, and 3 case-control studies (Table 2). The total number of participants across the studies was 856 women with HDP and healthy women.

Study characteristics

The included studies, conducted between 2009 and 2023, came from various countries: South Africa (1), Argentina (1), Denmark (1), Portugal (1), United States (3), Austria (1), Canada (1), the United Kingdom (1), Norway (1) and Italy (1) (see Table 2). These studies evaluated arterial stiffness, with some utilizing carotid-femoral pulse wave velocity (cfPWV) and/or augmentation index (AIx) and/or Augmentation index adjusted for heart rate (AIx@75).

HDP encompasses various types (16). While only two studies, Ehrenthal et al. (22) and Moe et al. (23), examined composite HDP, other studies focused on specific types, including preeclampsia, early preeclampsia, and late-onset preeclampsia. As a result, the findings were categorized into four groups: composite HDP, preeclampsia, early preeclampsia, and late-onset preeclampsia.

Risk of bias assessment

The risk of bias was assessed using the NOS for cohort and case-control studies, and a modified NOS for cross-sectional studies. The

assessment indicated that all studies had a low risk of bias (Tables 3, 4). Recognizing that NOS evaluates risk of bias but does not fully capture the overall certainty of evidence, the GRADE framework was further applied. This comprehensive assessment, which considers factors such as consistency, directness, and precision, rated the overall certainty of the evidence as moderate to high (Table 5).

Comparison of augmentation index and pulse wave velocity between women with all hypertensive disorders of pregnancy and normotensive women

A total of 7 studies assessed the AIx in patients with all various HDP compared to normotensive women (Figure 2A). The pooled data demonstrated a significantly elevated AIx among women with HDP, indicating a Mean difference (MD) of 11.63 and a 95% confidence interval (CI) of [1.72–21.54]. This analysis included 345 participants, comprising 167 women with HDP and 178 normotensive controls. The heterogeneity among the studies was high, with an I^2 value of 98%. Additionally, the analysis of funnel plots indicated the presence of publication bias, with a p value of 0.045 in the Egger's test (Figure 3).

Furthermore, a total of 11 studies examined cfPWV in women with all various HDP compared to normotensive women (Figure 2B). The pooled data showed a significantly elevated cfPWV in women with HDP, with a MD of 0.53 and a 95% CI of [0.27–0.78]. This analysis included 738 participants, comprising 363 women with HDP and 375 normotensive controls. The studies showed moderate heterogeneity, with an I^2 value of 64%. Additionally, the analysis of funnel plots indicated the presence of publication bias, with a p value of 0.002 in the Egger's test (Figure 4).

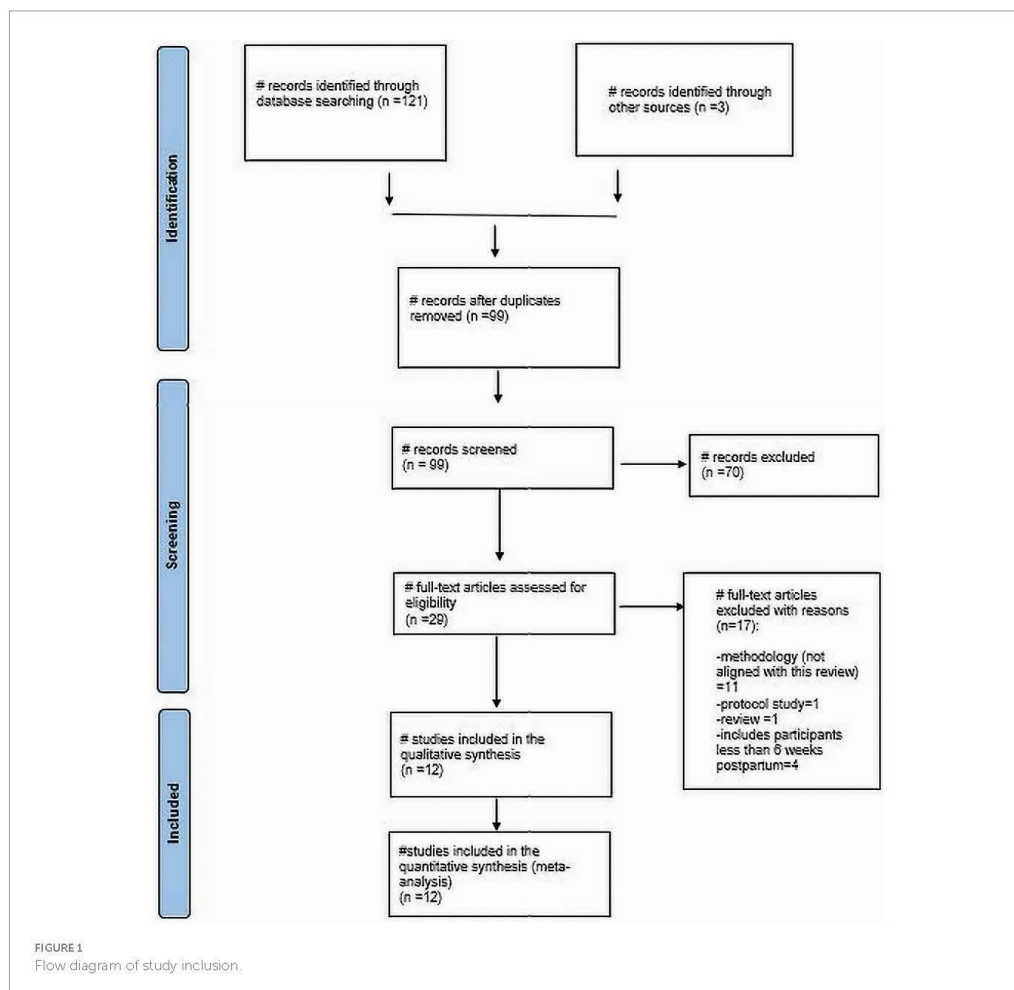
Comparison of augmentation index and pulse wave velocity between women with hypertensive disorders of pregnancy and normotensive women, within a year after delivery and after more than a year after delivery

Four studies investigated AIx in patients with HDP compared to normotensive controls within 1 year after delivery (see Figure 5A). The results showed no significant increase in AIx for women with HDP, reporting a MD of 14.85 and a 95% CI of [−6.03–35.72]. Additionally, there was high heterogeneity among these studies, with an I^2 value of 97%.

In contrast, other studies focused on AIx in patients with HDP compared to normotensive controls more than 1 year after delivery (see Figure 5B). The findings indicated a significant increase in AIx for women with HDP, with a MD of 9.11 and a 95% CI of [4.20–14.02]. The heterogeneity in these studies was also high, with an I^2 value of 94%.

Six studies evaluated cfPWV in women with HDP compared to normotensive controls within 1 year after delivery (Figure 6A). The results demonstrated a significantly higher cfPWV for women with HDP, reporting an MD of 0.59 and a 95% CI of [0.32–0.86]. The heterogeneity among these studies was moderate, with an I^2 value of 41%.

Additionally, five studies focused on cfPWV in women with HDP compared to normotensive controls more than 1 year after delivery



(Figure 6B). The findings also revealed a significant increase in cPWV for women with HDP, with an MD of 0.45 and a 95% CI of [0.03–0.88]. Heterogeneity in these studies was also moderate, with an I^2 value of 67%.

Comparison of augmentation index and pulse wave velocity in preeclamptic versus normotensive women

A total of 4 studies assessed the AIx in patients with preeclampsia compared to normotensive women (Figure 7A). This pooled data demonstrated a significantly elevated AIx among women with preeclampsia, with a mean difference (MD) of 8.57 and a 95% confidence interval (CI) of [4.22–12.92]. The analysis included 207 participants, comprising 102 women with preeclampsia and 105 normotensive controls. The heterogeneity among the studies was high

at 91%, indicating varying results across the studies. In two studies (12, 14) that adjusted the AIx for heart rate (AIx@75), the augmentation index remained significantly elevated after the adjustment, with a MD of 7.50 and a 95% CI of [6.09–8.90] (Figures 7A,B). These two studies showed no heterogeneity.

Additionally, an examination of cPWV across eight studies indicated a significant increase in cPWV among women with preeclampsia, demonstrating an MD of 0.47 with a 95% CI of [0.20–0.74] (Figure 7C). This analysis involved 600 patients (298 preeclamptic and 302 normotensive). The studies displayed moderate heterogeneity, with an I^2 value of 62%.

The funnel plot was generally symmetrical; however, a few studies deviated from the main axis, indicating the possibility of a small sample effect or publication bias. To further investigate potential bias, Egger's test was conducted, which showed no significant publication bias ($p = 0.144$) (Figure 8).

TABLE 2 Data extraction table.

Study	Authors (year)	Country	Study design	Sample size	Population characteristics (age, comorbidities)	Time postpartum	Arterial stiffness measure (cPWV, AIx)	Mean $\pm$ SD of arterial stiffness	Comparison group	Elevated arterial STIFFNESS (Yes/No)	Risk of bias assessment (Cochrane/NOS)	Other key findings
1	Namugowa et al. (2017) (14)	South Africa	case-control	30 (15 preclampsia 15 control)	African Black; 16–40 years; no CVD	15 weeks	cPWV, AIx	Mean: 5.9 m/s $\pm$ 0.09; 23 $\pm$ 16%	Normal pregnancy group	Yes	Low risk	Significant difference in cPWV between HDP and normal group
2	Paez et al. (2009) (11)	Argentina	Case-control	40 (20:20)	18–33 years old; no CVD	2 years	cPWV, AIx	Mean: 10.5 m/s $\pm$ 2.3; 37.5 $\pm$ 5.1%	Normal pregnancy group	Yes	Low risk	Significant difference in cPWV between HDP and normal group
3	Christensen et al. (2017) (16)	Denmark	cohort	48 (24:24)	Average 40 years old; no CVD	1 year	cPWV, AIx	Mean: 8.03 m/s $\pm$ 0.93; 22.1 $\pm$ 9.22%	Normal pregnancy group	No	Low risk	The hypertension exposed women tended to have a higher aPWV compared to unexposed women, but the difference was not significant
4	Polónia et al. (2014) (77)	Portugal	Cross-sectional	100 (45:55)	no CVD	10 years	cPWV, AIx	6.7 m/s $\pm$ 1.1; 25.7 $\pm$ 5.1%	Normal pregnancy group	Yes	Low risk	Significant difference in cPWV between HDP and normal group
5	Ehrenthal et al. (2014) (22)	United States of America	cohort	74 (33:41)	18 years and above; White and African Americans; no CVD or Diabetes	1 year	cPWV, AIx	6.2 m/s $\pm$ 1.5; 22.0 $\pm$ 13.4	Normal pregnancy group	Yes	Low risk	Significant difference in cPWV between HDP and normal group

(Continued)

TABLE 2 (Continued)

Study	Authors (year)	Country	Study design	Sample size	Population characteristics (age, comorbidities)	Time postpartum	Arterial stiffness measure (cPWV, AIx)	Mean $\pm$ SD of arterial stiffness	Comparison group	Elevated arterial STIFFNESS (Yes/No)	Risk of bias assessment (Cochrane/NOS)	Other key findings
6	Franz et al. (2013) (34)	Austria	cohort	74 (53:21)	Unknown	3–6 months	cPWV, AIx	9.9 ± 1.6 -10.7 ± 21.1	Normal pregnancy group	yes	Low risk	Presence of a higher cardiovascular risk in patients after early-onset pre-eclampsia.
7	Wierlang et al. (2023) (12)	Canada	Cross-sectional	80 (40:40)	Average 36 years; no CVD	6 months–6 years	cPWV, AIx	$6.3 \text{ m/s} \pm 1.0$; $16.2 \pm 2.5\%$	Normal pregnancy group	yes	Low risk	Significant difference in cPWV between HDP and normal group
8	Robb et al. (2009) (33)	United Kingdom	cohort	37 (22:15)	Average 30 years; no CVD	7 weeks	cPWV	$7.3 \text{ m/s} \pm 0.3$	Normal pregnancy group	Yes	Low risk	Significant difference in cPWV between HDP and normal group
9	Evans et al. (2011) (30)	United States of America	cohort	68 (18:50)	18–40 years Black and White participants; no preexisting cardiac disease or diabetes mellitus	16 months after delivery	cPWV	cPWV Mean: $2.39 \text{ m/s} \pm 0.8$	Normal pregnancy group	No	Low risk	No significant difference in AIx between HDP and normal group
10	Moe et al. (2020) (33)	Norway	Cross-sectional	221 (126:95)	18 years and above; no CVD or renal disease	1 year after delivery	cPWV	$6.3 \text{ m/s} \pm 2.9$	Normal pregnancy group	Yes	Low risk	Significant difference in AIx between HDP and normal group
11	Uselman et al. (2020) (10)	United States of America	Cross-sectional	24(12:12)	White, Hispanic, Black women; no CVD	6–24 months after delivery	cPWV	$7.1 \text{ m/s} \pm 1.1$	Normal pregnancy group	yes	Low risk	Significant difference in AIx between HDP and normal group

(Continued)

TABLE 2 (Continued)

Study	Authors (year)	Country	Study design	Sample size	Population characteristics (age, comorbidities)	Time postpartum	Arterial stiffness measure (cPWV, Aix)	Mean $\pm$ SD of arterial stiffness	Comparison group	Elevated arterial STIFFNESS (Yes/No)	Risk of bias assessment (Cochrane/NOS)	Other key findings
12	Orabona et al. (2017) (15)	Italy	Case-control	60 (30/30)	No CV risk factors, smoking, dyslipidemia, overweight, diabetes mellitus or chronic hypertension.	6 months-4 years after delivery	cPWV	cPWV Mean: 8.47 m/s $\pm$ 1.92	Normal pregnancy group	yes	Low risk	Significant difference in cPWV between HDP and normal group

TABLE 3 NOS for the risk of bias and quality assessment of NRSs.

Author Year	Selection				Comparability	Exposure	Selection	Nonresponse rate	Total Score
	Adequate definition of patient cases	Representativeness of patient cases	Selection of controls	Definition of controls	Control for important or additional factors	Ascertainment of exposure	Same method of ascertainment for participants		
Namigowa et al. 2019 (22)	*	*		*	**	*	*		7
Christensen et al. 2017 (26)	*	*		*	**	*	*	*	8
Robb et al. (2009) (33)	*	*		*	**	*	*		7
Orabona et al. (2017) (15)	*	*		*	**	*	*		8
Paez et al. (2008) (31)	*	*		*	**	*	*		7
Ehrenthal et al. (2014) (23)	*	*		*	**	*	*		7
Franz et al. (2013) (34)	*	*		*	**	*	*		7
Evans et al. (2011) (30)	*			*	**	**	*		8

NOS, Newcastle-Ottawa scale, NRS, non-randomized study.

Each study is evaluated across three domains:

- Selection of the study population (maximum: 4 stars).

- Comparability of groups (maximum: 2 stars).

- Exposure (Ascertainment of exposure, Same method of ascertainment for participants and Nonresponse rate)(maximum: 3 stars).

A star (*) indicates the score, or criteria met.

TABLE 4 NOS (adapted for cross-sectional studies) for the risk of bias and quality assessment of NRSs.

Author Year	Representativeness of the sample	Selection				Comparability	Exposure	Total score
		Sample size	Non-respondents	Ascertainment of the exposure (risk factor)	Control for important or additional factors	Assessment of the outcome	Statistical test	
Polonia et al. (2014) (7)	*		*	**	**	**	*	9
Wierfang et al. (2023) (17)	*		*	*	**	**	*	8
Moe et al. (2020) (13)								7
Uselman et al. (2020) (18)	*		*	*	**	**	*	8

NOS, Newcastle-Ottawa scale; NRS, non-randomized study.

Each study is evaluated across three domains:

- Selection of the study population (maximum: 4 stars).
- Comparability of groups (maximum: 2 stars).
- Outcome (for cohort studies) or Exposure (for case-control studies) (maximum: 3 stars).

A maximum score of 9 stars represents the highest quality, indicating the lowest risk of bias. A star (*) indicates the score, or criteria met.

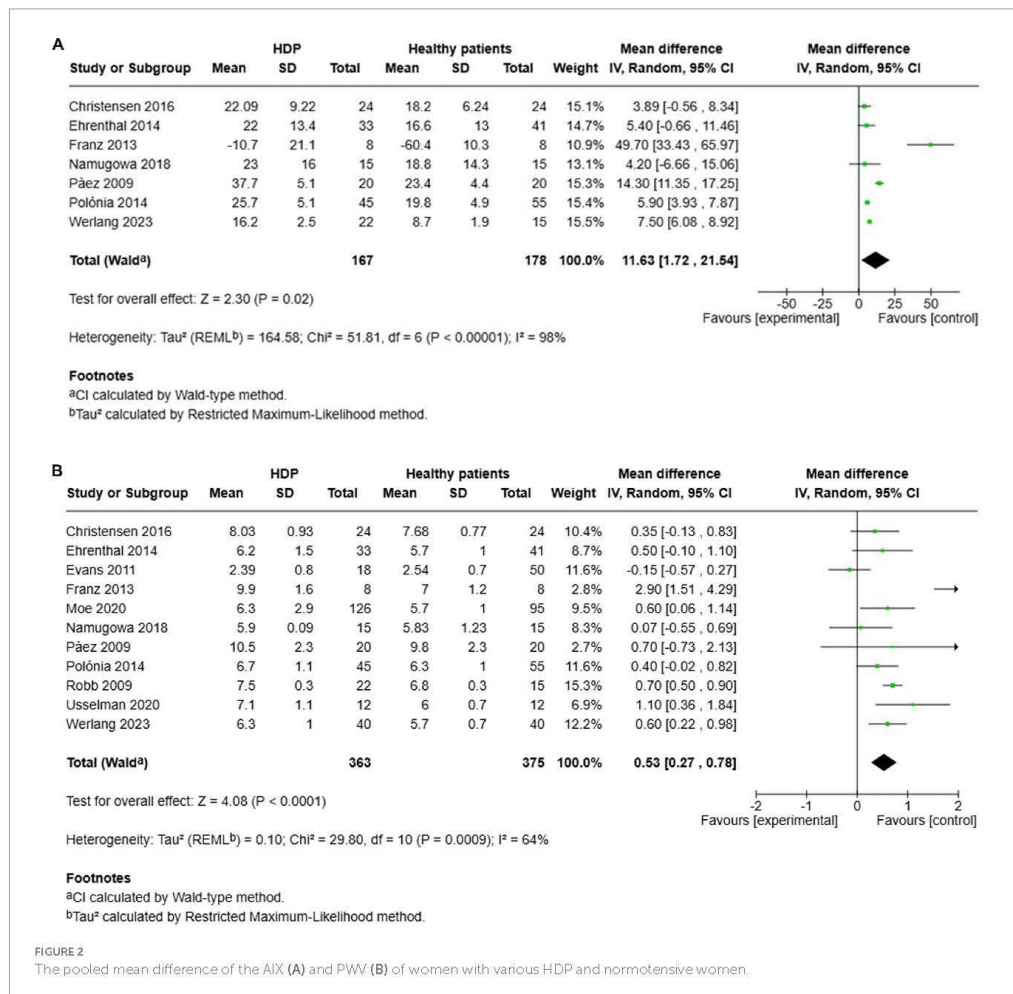
TABLE 5 Risk of bias assessment using NOS and GRADE for included studies (case-control and cross-sectional designs).

Author	Year	Study design	Selection	Comparability	Exposure/Outcome	Total NOS score	GRADE quality
Namagowa et al.	2019	Case-Control	3 *	2 **	2 *	7	Moderate
Christensen et al.	2017	Case-Control	3 *	2 **	3 *	8	Moderate to High
Robb et al.	2009	Case-Control	3 *	2 **	2 *	7	Moderate
Orabona et al.	2017	Case-Control	3 *	2 **	3 *	8	Moderate to High
Paez et al.	2008	Case-Control	3 *	2 **	2 *	7	Moderate
Ehrenthal et al.	2014	Case-Control	3 *	2 **	2 *	7	Moderate
Franz et al.	2013	Case-Control	3 *	2 **	2 *	7	Moderate
Evans et al.	2011	Case-Control	2 *	2 **	3 **	8	Moderate to High
Polonia et al.	2013	Cross-Sectional	2 *	2 **	3 ** + *	9	High
Wierfang et al.	2023	Cross-Sectional	2 *	2 **	3 ** + *	8	Moderate to High
Moe et al.	2020	Cross-Sectional	1	2	2	7	Moderate
Uselman	2020	Cross-Sectional	2 *	2 **	3 ** + *	8	Moderate to High

Each study is evaluated across three domains:

- Selection of the study population (maximum: 4 stars).
- Comparability of groups (maximum: 2 stars).
- Outcome (for cohort studies) or Exposure (for case-control studies) (maximum: 3 stars).

A maximum score of 9 stars represents the highest quality, indicating the lowest risk of bias. A star (*) indicates the score, or criteria met.



Comparison of augmentation index and pulse wave velocity in women with HDP versus normotensive women

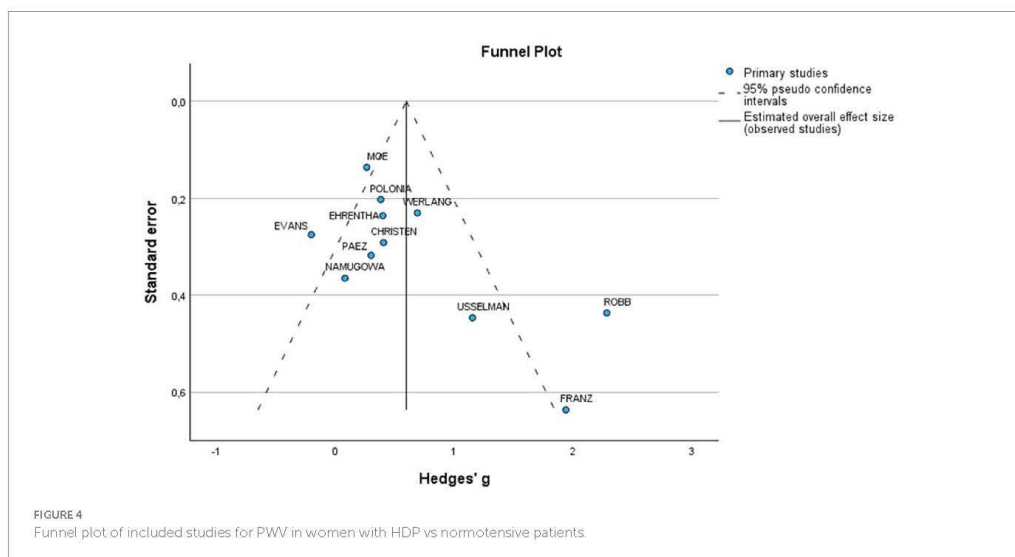
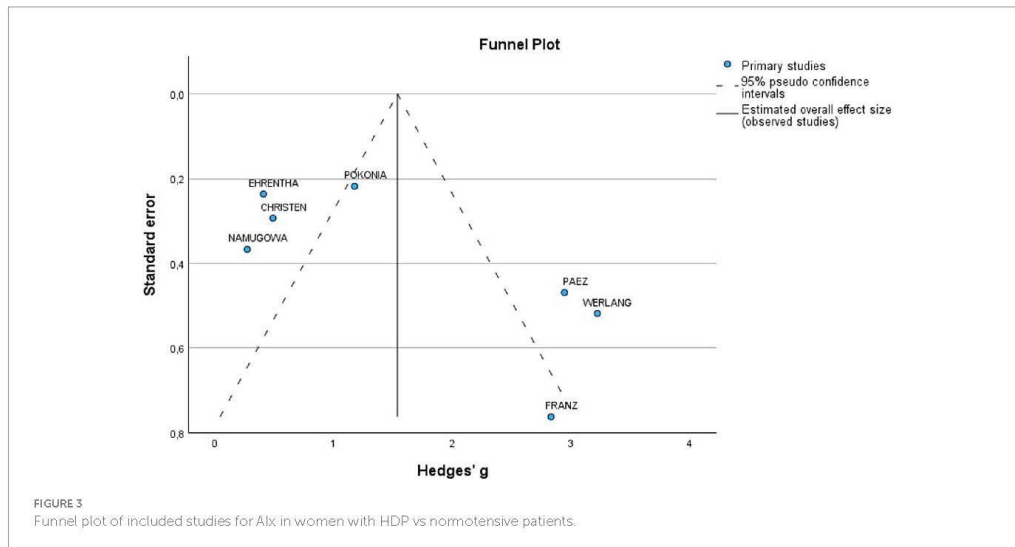
One study focused on AIx in patients with composite HDP against normotensive controls (22). The results indicated no significant increase in AIx for women with HDP (MD 5.40, 95% CI [-0.66–11.46]). The heterogeneity assessment was not applicable due to the design being based on a single study. This analysis included a total of 74 participants, with 33 diagnosed with HDP and 41 who were normotensive. However, AIx was found to be significantly elevated after adjusting for heart rate (AIx@75) (MD 6.40, 95% CI [0.52–12.28]) (15).

Two studies, Ehrenthal et al. (22) and Moe et al. (23) analysed cPWV in the context of HDP, reporting no significant increase in cPWV among affected women (MD 0.35, 95% CI [-0.13–0.83]), with

zero statistical heterogeneity noted (Figure 9). This part of the analysis comprised 305 individuals (169 with HDP and an equivalent number of normotensive controls).

Comparison of augmentation index and pulse wave velocity among women with early onset preeclampsia and normotensive women

In the context of early onset preeclampsia (EOP), two studies, conducted by Christensen et al. (26) and Franz et al. (24), evaluated the AIx and found no significant increase associated with EOP (MD 1.55, 95% CI [-0.74–3.84]), with a heterogeneity of 88% (Figure 10A). The studies included a total of 64 participants, comprising 32 EOP and 32 normotensive women. Orabona et al. (25) was the only study

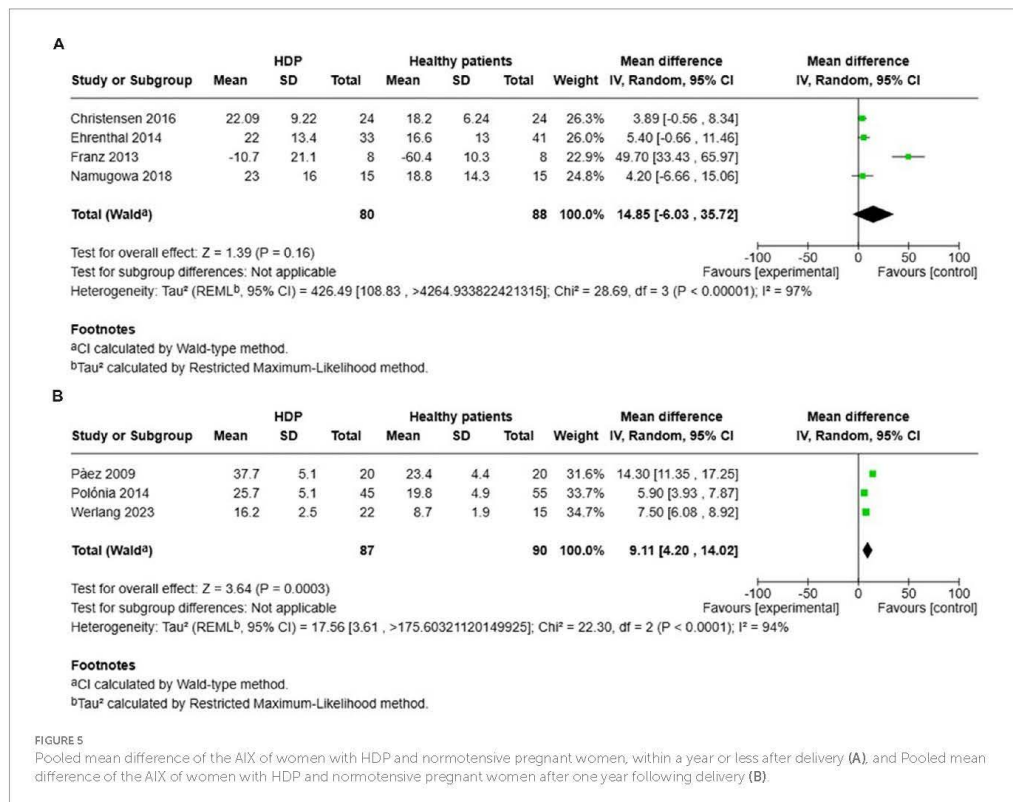


to evaluate AIx after adjusting for heart rate, and it indicated a significant elevation in AIx following this adjustment (MD 0.94, 95% CI [2.17–3.70]).

Additionally, Christensen et al. (26), Franz et al. (24), and Orabona et al. (25) also assessed cPWV in patients with EOP. The results indicated a significant increase in cPWV (MD 1.86, 95% CI [0.25–3.47]) and a heterogeneity of 92%. A total of 124 participants were included in these studies, consisting of 62 EOP and 62 normotensive women (Figure 10B).

Comparison of augmentation index and pulse wave velocity among women with late onset preeclampsia and normotensive pregnancy

Christensen et al. (26) and Franz et al. (24) also studied the AIx in cases of late-onset preeclampsia. Their analysis showed no significant difference (MD of 2.44, 95% confidence interval [–8.82–13.70]) and indicated a heterogeneity of 65%



(Figure 11A). This study included a total of 64 participants, comprising 32 individuals with LOP and 32 normotensive controls. However, after adjusting for heart rate, Orabona et al. (25) found that the augmentation index was significantly higher in the LOP group (MD of 4.80, 95% confidence interval [0.60–9.00]).

Furthermore, Christensen et al. (26), Franz et al. (24), and Orabona et al. (25) also assessed cPWV in patients with LOP. Their findings indicated no significant increase in cPWV (MD 0.10, 95% CI [-0.42–0.62]), with a heterogeneity of 56% (Figure 11B). The total sample size in this analysis was 124 participants, including 62 with LOP and 62 normotensive individuals.

Comparison of augmentation index and pulse wave velocity among women with HDP and normotensive pregnancy in cohort studies

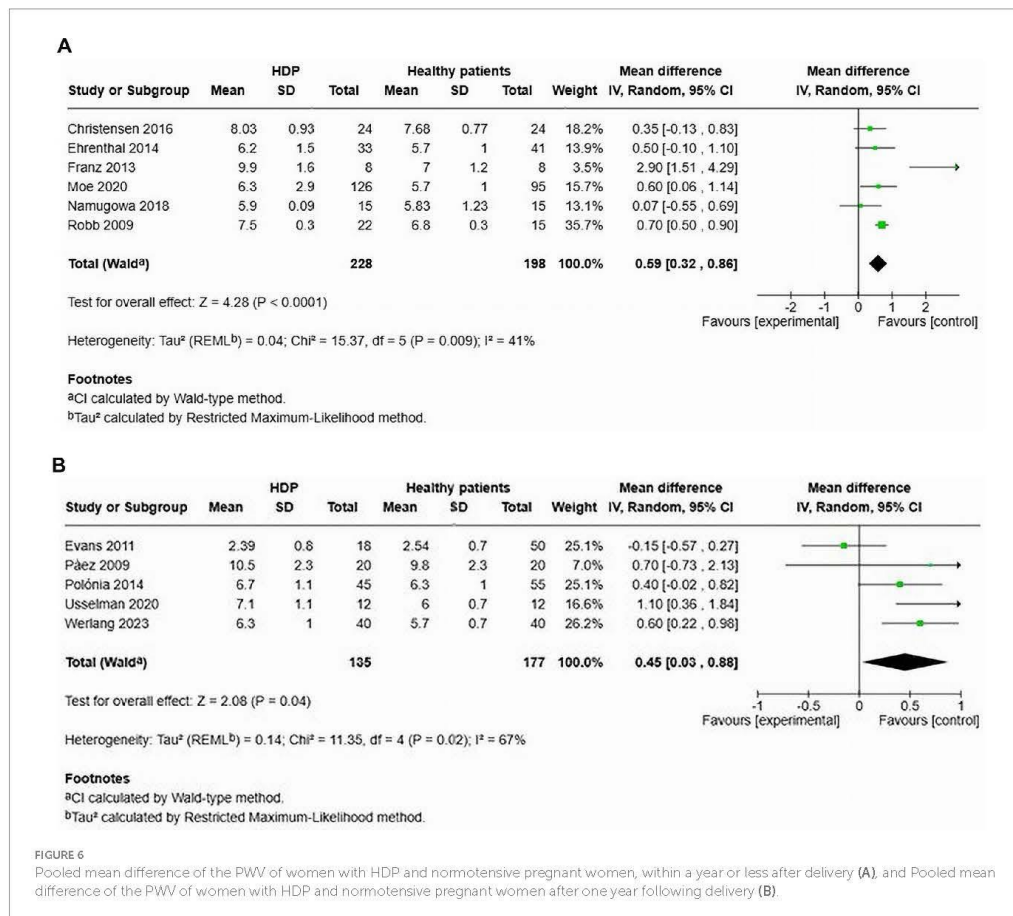
A total of three studies assessed the AIX in patients with HDP compared to normotensive women (22, 24, 26) (see Figure 12A). The pooled data demonstrated a significantly elevated AIX among women with HDP, indicating a MD of 16.82 and a 95% CI of

[1.11–12.92]. This analysis included 138 participants, comprising 65 women with HDP and 73 normotensive controls. The heterogeneity among the studies was high at 93%, suggesting varying results across the studies. In the only study that adjusted the AIX for heart rate (AIX@75), the augmentation index remained significantly elevated after adjustment, with a MD of 6.40 and a 95% CI of [0.52–12.28] (22).

Furthermore, an examination of cPWV across five studies showed no significant increase in cPWV among women with HDP, demonstrating a MD of 0.70 with a 95% CI of [-0.10–1.49] (see Figure 12B). The heterogeneity was again high at 93%, and this analysis involved 243 patients (105 with HDP and 138 normotensive).

Comparison of augmentation index and pulse wave velocity in women with HDP versus normotensive women in cross-sectional studies

Two studies focused on AIX in patients with HDP compared to normotensive controls (12, 27) (see Figure 13A). The results indicated a significant increase in AIX for women with HDP, with a MD of 6.85 and a 95% CI of [5.31–8.39]. The heterogeneity among



these studies was low at 40%. This analysis included a total of 137 participants, with 67 diagnosed with HDP and 70 who were normotensive. In one study, the AIx remained significantly elevated after adjusting for heart rate, with a MD of 7.50 and a 95% CI of [0.68–8.92] (12).

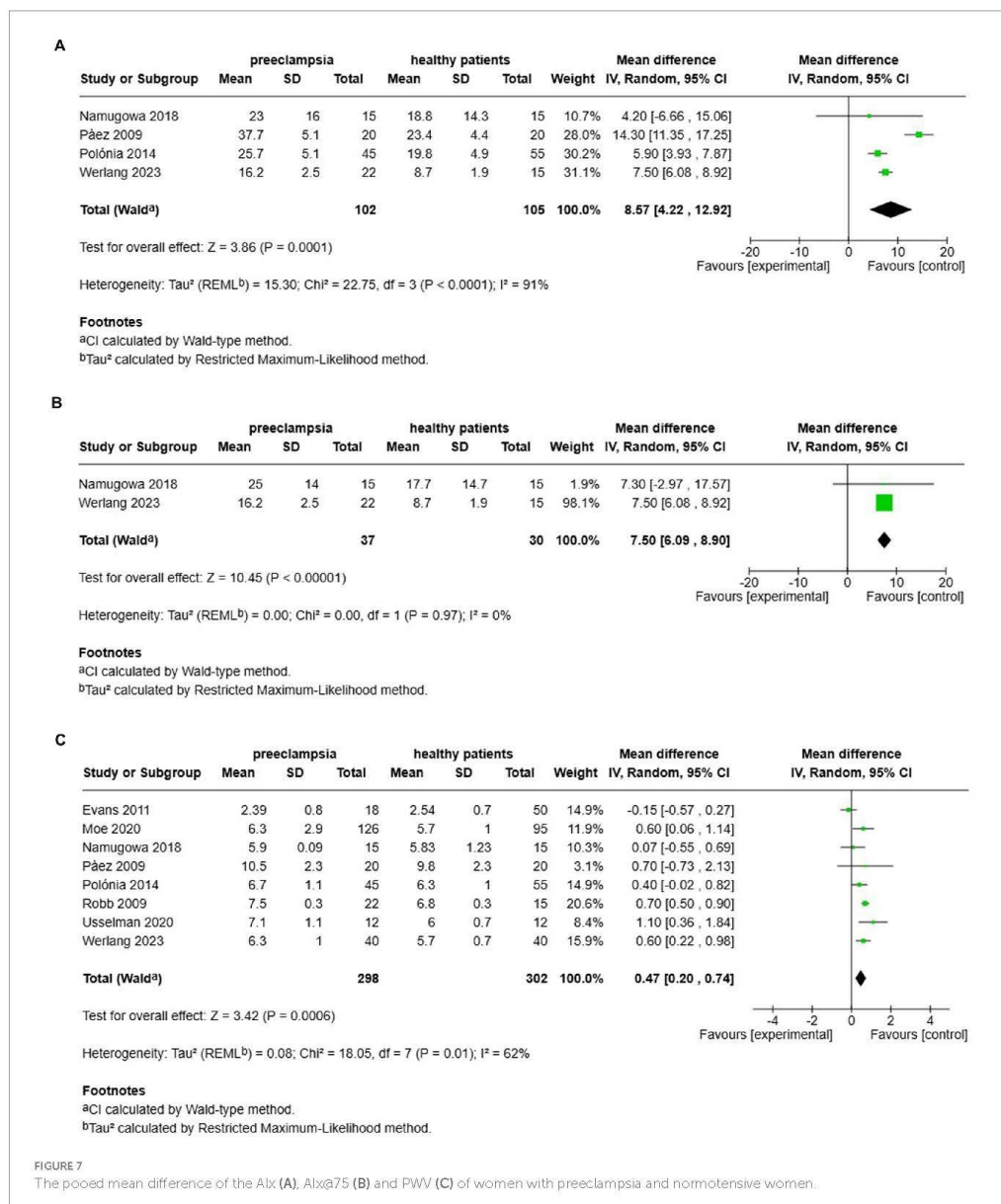
Four studies analysed cPWV in the context of HDP, reporting a significant increase in cPWV among affected women, with a MD of 0.59 and a 95% CI of [0.35–0.82] (12, 23, 27, 28). No statistical heterogeneity was observed in this analysis (see Figure 13B). This part of the analysis comprised 305 individuals (223 with HDP and 203 normotensive controls).

Discussion

The systematic review presents a comprehensive analysis of the literature regarding arterial stiffness in women with previous history of HDP, particularly pre-eclampsia. Most studies revealed elevated

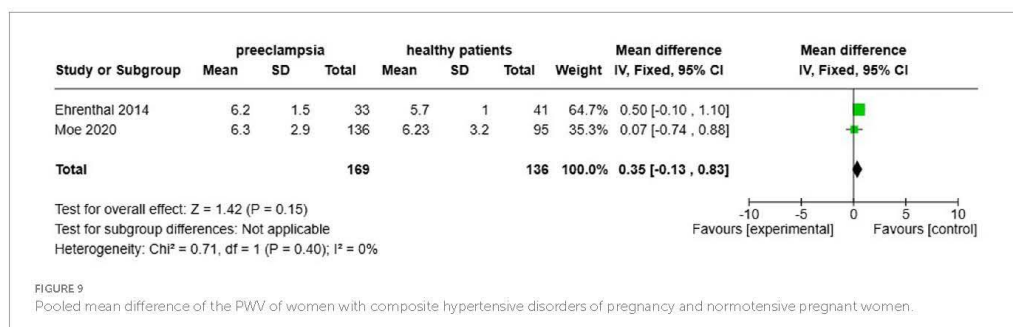
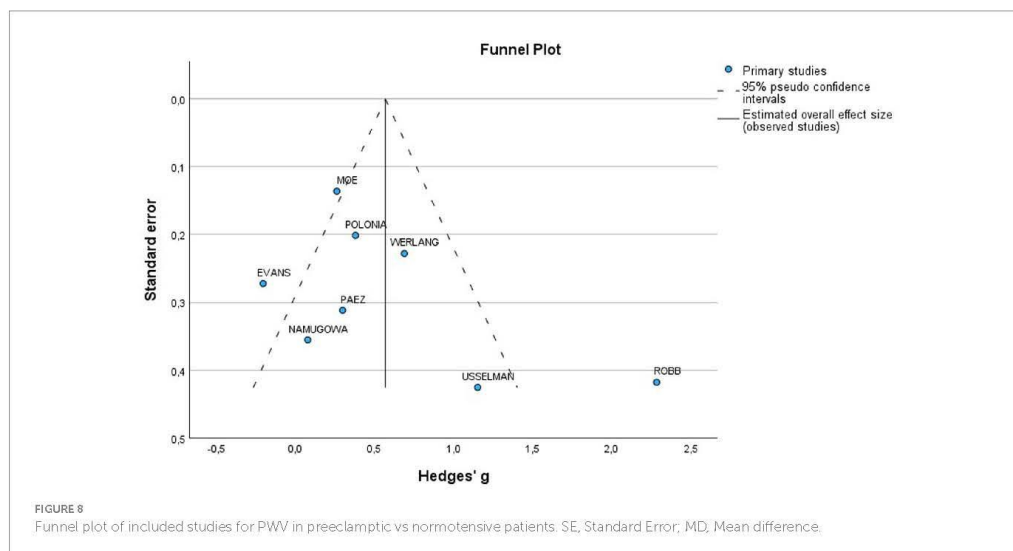
arterial stiffness after 6 weeks post-delivery in women with a history of preeclampsia, suggesting ongoing vascular dysfunction that could lead to an increased cardiovascular risk lingering even years after pregnancy (29). The duration of the studies ranged from 7 weeks postpartum to 10 years post-pregnancy, showcasing the long-term implications of preeclampsia on cardiovascular health. However, not all studies demonstrated a consistent association between HDP and increased arterial stiffness. For example, a Danish study by Christensen et al. and research by Evans et al. in the United States reported no increase in arterial stiffness as measured by cPWV and AIx (26, 30). This indicates that, while a relationship may exist, its impact can vary based on the demographic and clinical characteristics of the populations studied.

The AIx, particularly after adjusting for heart rate, was found to be elevated in women with HDP (12, 25, 27, 31, 32). This includes specific types such as composite preeclampsia and both early and late onset preeclampsia, when compared to normotensive women (25). This suggests a considerable increase in arterial



stiffness, which may indicate a heightened cardiovascular risk in this preeclampsia population. The high heterogeneity (87%) observed among the studies points to variability in results, potentially due to differences in study populations, methodologies, or measurement techniques. Additionally, a single study examining AIx@75 in women with composite HDP also reported

a significant increase, although heterogeneity assessment was not applicable in this case (22). These findings reinforce the idea that women with various types of hypertensive disorders experience increased arterial stiffness, emphasizing the associated cardiovascular risk. The consistently elevated AIx in both cohort and cross-sectional studies further supports the notion that there

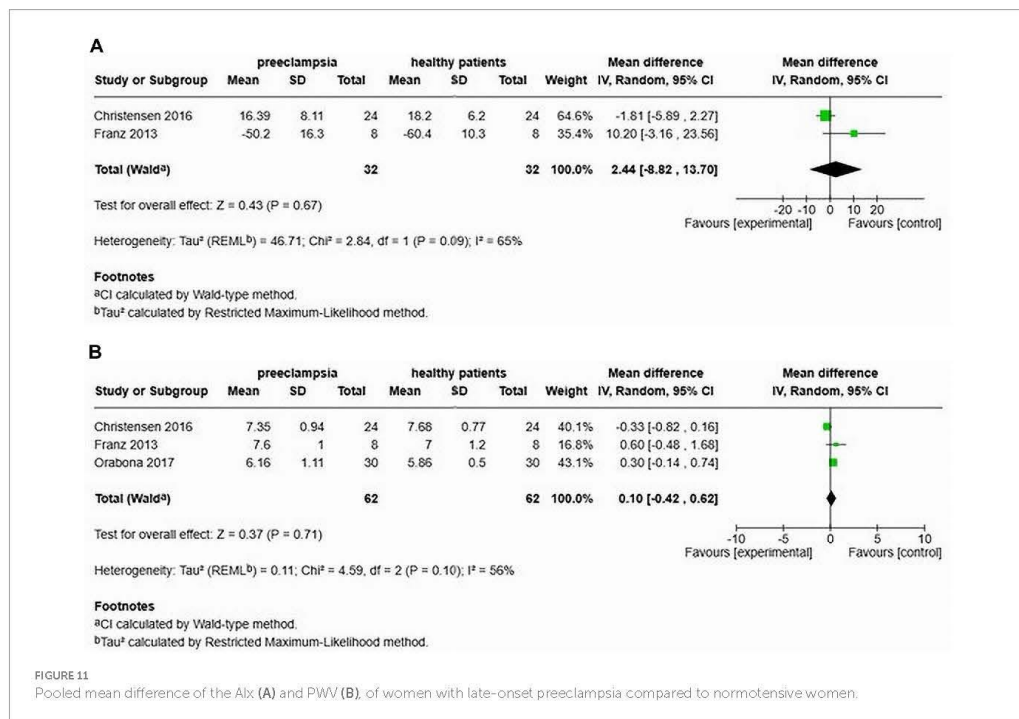
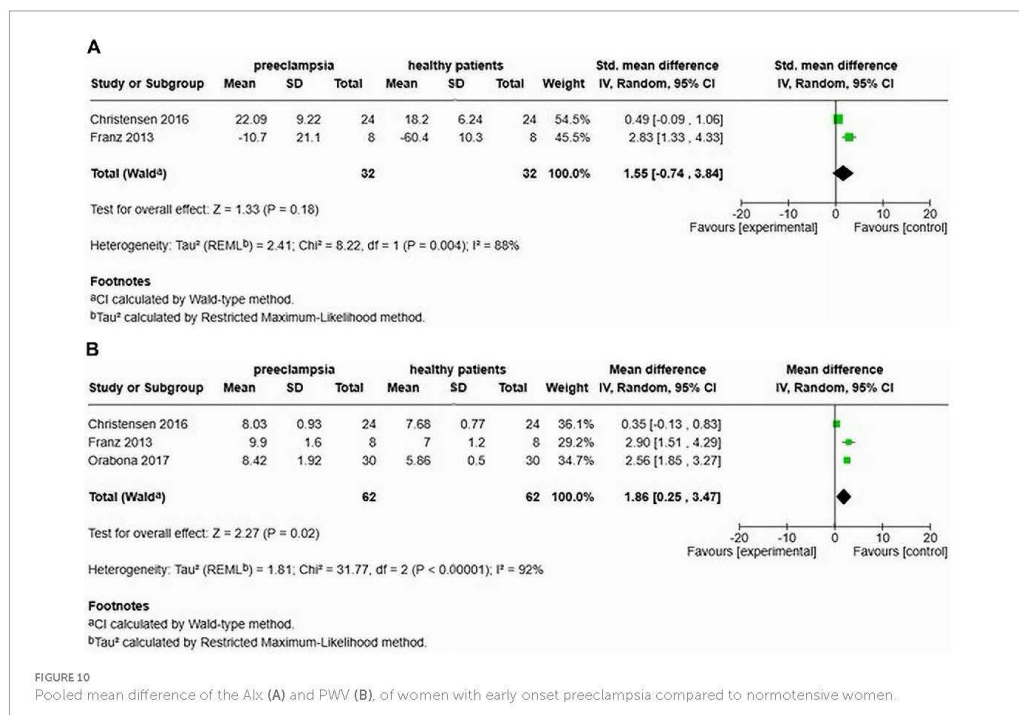


is a significant alteration in arterial function among women with a history of HDP. Additionally, a review of AIx findings 1 year after delivery indicates changes in vascular function in women with a history of HDP, suggesting a lasting cardiovascular risk. Although arterial stiffness, as indicated by AIx, may not differ significantly within the first year postpartum, long-term effects of HDP could increase arterial stiffness and potentially, cardiovascular risk. Importantly, both women in their first year after delivery and those beyond that period demonstrated a significant increase in cfPWV.

Furthermore, pooled data from eleven studies comparing various hypertensive disorders in normotensive women, as well as data from eight studies comparing preeclampsia and normotensive women, revealed a significant increase in cfPWV (12, 23, 27, 28, 30–33). However, studies on cfPWV for women with composite HDP and late onset preeclampsia showed no significant increases (15, 29). This suggests that while AIx is elevated, reflecting

increased arterial stiffness, cfPWV might not indicate a similar degree of change, potentially highlighting that the two measurements assess different aspects of arterial function. cfPWV directly measures the speed at which pressure waves travel through the arterial tree. A faster cfPWV indicates stiffer arteries and is more representative of large artery function. It is less influenced by peripheral changes and wave reflections from smaller arteries (34). On the other hand, AIx measures the augmentation of pressure waves in the arteries caused by reflected waves from peripheral sites (35, 36). This metric reflects not only the stiffness of the arteries but also the timing and intensity of these reflections.

Notably, the assessment of early-onset preeclampsia also revealed a significant rise in cfPWV, contrasting with late-onset preeclampsia, which showed no significant changes. This discrepancy may indicate that the early onset of preeclampsia is associated with distinct hemodynamic changes that are absent in the later onset. Furthermore,



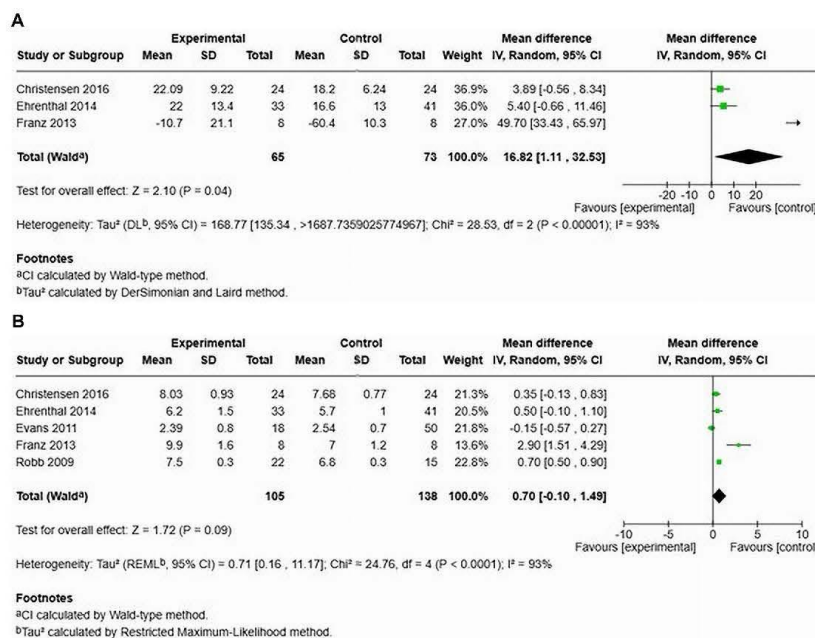


FIGURE 12

The pooled mean difference of the Alx (A) and PWV (B) of women with HDP and normotensive women in cohort studies.

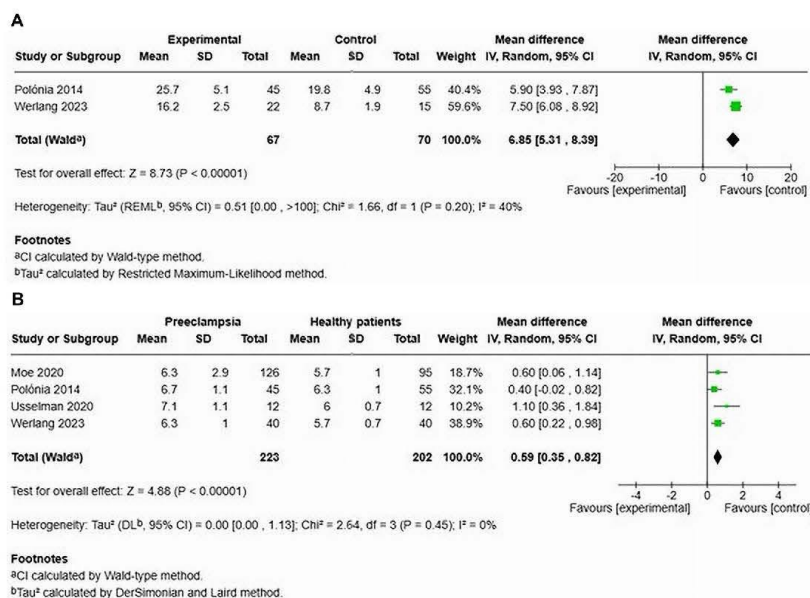


FIGURE 13

Pooled mean difference of the Alx (A) and PWV (B) of women with HDP and normotensive pregnant women in cross-sectional studies.

the absence of significant mean differences in cohort studies, alongside notable findings in cross-sectional studies, suggests that cPWV may be a more variable measure influenced by various factors present in different study designs. The contrasting results warrant further investigation to understand better the relationship between cPWV and HDP.

Limitations

This review had a limited number of studies, which could introduce bias. Additionally, a high level of heterogeneity was observed in most group analyses. However, assessments using the NOS revealed a low risk of bias in all studies, with the GRADE framework rating the evidence as moderate to high certainty. Furthermore, the review adhered to the PRISMA-P guidelines, and a comprehensive search was performed across several databases.

Conclusion

This systematic review and meta-analysis suggest that arterial stiffness may remain elevated for more than 6 weeks postpartum in women with a history of HDP. However, the findings should be interpreted with caution due to heterogeneity across studies and limited number of available studies. Larger and standardized longitudinal studies are needed to confirm these results. In the meantime, regular cardiovascular monitoring for these women is recommended while awaiting more conclusive evidence.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

XM: Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. SG: Writing – review &

editing. AH: Supervision, Writing – review & editing. JM: Writing – review & editing. CB: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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

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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 HDP 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 $\pm$ SD for arterial stiffness indices (cPWV, Alx and Alx@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 $\pm$ 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.

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

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.

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

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Elevated central blood pressure, NT-proBNP and hs-cTnI in women with maternal complications of hypertensive disorders of pregnancy

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ABSTRACT

Objective: The main objective of the study was to compare the levels of CBP and these cardiac biomarkers in women with maternal complications of hypertensive disorders of pregnancy (HDP).

Methods: This was a cross-sectional study that enrolled 270 women with HDP and 270 normotensive pregnant controls. Data on basic characteristics and incidence of maternal complications were collected among the two groups. Additionally, information on cardiac biomarkers and CBP was gathered from the women with HDP, to compare the levels of these biomarkers with maternal complications experience by this group.

Results: Non-hypertensive controls were significantly older than hypertensive cases and had a higher median gestational age at recruitment compared to hypertensive cases. The median levels of CBP and cardiac biomarkers were significantly higher among hypertensive participants with maternal complications ($n = 107/270$) than those without complications ($n = 163/270$). Specifically, central systolic blood pressure (CSBP) was 133 (120–142) mmHg vs 128 (109–129) mmHg ($p = 0.033$) and central diastolic blood pressure (CDBP) was 75 (62–86) mmHg vs 69 (56–73) mmHg ($p < 0.01$), while NT-proBNP was 446 (145–1126) vs 57 (21–167) pg.mL⁻¹; $p < 0.0001$, and hs-cTnI was 12 (7–35) ng.L⁻¹ compared to 8 (3–8) ng.L⁻¹; $p < 0.0001$, in cases v. controls, respectively.

Conclusion: In conclusion, the study found that pregnant hypertensive women with maternal complications had significantly higher median values of CSBP and CDBP, NT-proBNP, and hs-cTnI in compared to those without complications. These findings suggest that measuring these vital signs and cardiac biomarkers in hypertensive pregnancies might be helpful for screening and monitoring maternal complications.

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Preeclampsia; systolic blood pressure; eclampsia; cardiac biomarkers

Introduction

Central blood pressure (CBP) and cardiac biomarkers such as NT-proBNP and hs-cTnI, are among several variables that have been studied in women with hypertensive disorders of pregnancy (HDP) (1–5). The inactive N-terminal pro B-type natriuretic peptide is co-secreted with a 32-amino acid polypeptide, B-type natriuretic peptide (BNP), from the left and right cardiac ventricle in response to ventricular volume expansion and pressure overload, while hs-cTnI is a cardiac enzyme whose levels in the circulation respond to cardiomyocyte damage (6–8). In general, both biomarkers are associated with cardiac injuries and can indicate future cardiac disease risk, and, to some degree, the severity of cardiovascular events generally used for diagnosing cardiomyocyte

injury (6,9–11). Lam et al. (2018) demonstrated that patients with heart failure and elevated BNP are more likely to experience death and rehospitalisation compared to those with low levels (12).

HDP are a leading cause of maternal morbidity and mortality globally (13). They account for approximately 14–18% of all maternal deaths globally, with an estimated 62,000–77,000 maternal deaths, and 500,000 perinatal deaths annually (13–15). Maternal complications of HDP include stroke, pulmonary edema, Haemolysis Elevated Liver enzymes and Low Platelets (HELLP) syndrome, abruptio placentae, acute kidney injury, intensive care unit (ICU) admission, low Glasgow coma scale (GCS), and others (16,17). Studies have shown an association between preeclampsia (PE) and cardiovascular complications during pregnancy or many years after pregnancy

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burden and improving Quality of life. With the widespread use of HEMT, there are more pregnancies in women with CF. However, HEMT are known to cross the placenta and be present in breast milk. Studies of HEMT in rates demonstrated development of infant cataracts and case reports in the US reported presence of non-congenital cataracts in early exposure. This abstract assesses the development of cataracts in foetuses who were exposed in-utero and through lactation and emphasises the need to counsel patients who continue HEMT during pregnancy and breast feeding.

Methods: This is a cross sectional study looking at 6 cystic fibrosis patients receiving CFTR modulator therapy and assessing for the development of cataracts in infants during eye screening 6 months post birth.

Results: A total of 6 patients were included in the eye screening programme all born to mothers between the age of 21–34. None of the patients had other risk factors for developing cataracts. 83.3% of the mothers with CF also had diabetes and 50% had hypertension. 16.7% of patients attended the screening which showed no subclinical cataracts. Out of the 5 patients that did not attend, 60% of patients were contacted and reported no symptoms of cataracts although we are unable to rule out subclinical cataracts. 20% of patients moved out of the area and were no longer under follow up in our hospital and 20% of patients were not reached.

Conclusion: Although based on the above, the probability of developing cataracts post Intra-uterine exposure is low, we are unable to rule out subclinical cataracts and thus a screening programme is needed particularly as case reports in other countries have emerged showing link between that. Counselling is also required to ensure expecting mothers are aware of the risks.

eP-355 | Central blood pressure, cardiac biomarkers and maternal complications in hypertensive pregnancies

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Objective: The objective of the study was to explore the relationships between high-sensitivity cardiac Troponin I (hs-cTnI), NT-proBNP, central blood pressure (CBP) and maternal complications in hypertensive cases.

Design: This was a prospective case-control study evaluating CBP and biomarkers in pregnant women with hypertensive disorders of pregnancy (HDP) at Nelson Mandela Academic Hospital, Eastern Cape, South Africa.

Method: The study used a consecutive sampling method to recruit patients who were admitted with HDP and normotensive controls. The estimated required sample size was 400 participants. Blood samples were taken for hs-cTnI and NT-proBNP, and CBP was measured antenatally. Follow-up evaluations were conducted one day after delivery and at discharge. The data was analysed using SPSS statistical software, and a *p*-value of less than 0.05 was considered statistically significant.

Results: 466 participants were enrolled in the study: 258 (55.4%) hypertensive cases and 208 (44.6%) normotensive controls. More

than half of the hypertensive cases (136/258, 52.1%) had pre-eclampsia, 80 (31%) eclampsia, 25 (9.7%) gestational hypertension, and 17 (6.6%) chronic hypertension.

The median levels (p25, p75) of the cardiac biomarkers were significantly higher among hypertensive participants with maternal complications (80/258) than those without complications (178/258). These were hs-cTnI 11.5 (7.0–32.5) ng/L vs 8.5 (5.0–16.0) ng/L, *p*=0.006 and NT-proBNP 349.0 (133.5–1009.5) ng/L vs 160.0 (50.0–513.0) ng/L, *p*=0.001.

Patients with HELLP (Haemolysis, Elevated Liver enzymes, Low Platelets) syndrome, disseminated intravascular coagulopathy (DIC), or those who were admitted to the intensive care unit (ICU) had significantly higher median central diastolic blood pressure (CDBP) compared to those who did not have these complications [79 (64.5–94) vs 70 (54–83); 121(121–121) vs 73 (60–89); 97(95–121) vs 73(60–88)]. Additionally, hypertensive cases with high CBP had a 3.1 times higher risk of being admitted to the ICU. However, the central systolic blood pressure did not show any significant difference between cases with and without maternal complications [129(119.5–140.5) vs. 129(117–140)].

Conclusion: Pregnant women with hypertension and maternal complications had higher levels of cardiac biomarkers (hs-cTnI and NT-proBNP) compared to women without these complications. This indicates that measuring these biomarkers in hypertensive pregnancies might be helpful in screening and monitoring maternal complications. Furthermore, it suggests that women with HDP and maternal complications may be more susceptible to developing cardiovascular problems than those without maternal complications. Finally, the CDBP was higher in patients with HELLP syndrome, DIC, or those admitted to the ICU, suggesting the importance of monitoring this vital sign in these patients.

eP-356 | Estimation of serum fibrinogen level as a predictive marker for PPH

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Objective:

1. To estimate the level of fibrinogen level in antenatal women > 28 weeks of gestation who will be delivering at kgmu obstetrics and gynaecology department.
2. To evaluate the amount of blood loss during labour.
3. To correlate the level of serum fibrinogen with occurrence of PPH.

Study design: Prospective analytical study.

Method: This is a prospective analytical study done in department of obstetrics and gynaecology, Kgm from duration August 2022 to December 2024. Total 200 patients enrolled in the study meeting inclusion and exclusion criteria. Patients' demography, detailed history and thorough physical examination done. Along with routine relevant investigations additional 2 mL of blood sample taken for assessment of serum fibrinogen level by Clauss method, which has a low coefficient variation. All the women followed up till 24 hrs of delivery and amount of bleeding is assessed by graduated V- bag and the pad soaked during delivery.

Result: The majority of cases of PPH occurred in the lower fibrinogen level ranges, particularly between 200 and 400 mg/



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Correlation of peripheral blood pressure with central blood pressure and estimation of central blood pressure thresholds for diagnosis of hypertension during pregnancy

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Objective: The main objective of the study was to evaluate the correlation and comparative use of peripheral blood pressure and central blood pressure (CBP) in identifying hypertension among pregnant women.

Methods: A cross-sectional study was conducted at Nelson Mandela Academic Hospital from December 2022 to April 2024, involving 270 inpatients diagnosed with hypertensive disorders of pregnancy (HDP) and 270 normotensive controls in their second and third trimesters. Blood pressure measurements were obtained using the Microlife WatchBP Office Central, both at enrolment and within 7 days postpartum. A linear regression equation and a receiver operating characteristic curve (ROC) analysis were used to determine the thresholds for normal, mild, and severe CBP.

Results: The ROC revealed that a central systolic blood pressure (cSBP) of 116 mm Hg or higher has a sensitivity of 78.5% and a specificity of 50.3% for diagnosing hypertension during pregnancy. Considering a normal peripheral diastolic pressure of less than 90 mm Hg, the upper limit of central diastolic blood pressure (cDBP) in normotensive controls was calculated to be 78 mm Hg. A significant positive correlation was found between peripheral systolic blood pressure (pSBP) and cSBP among normotensive and hypertensive women ($p < 0.05$). The median pSBP among patients with eclampsia with mild peripheral hypertension was 138.0 mmHg (IQR: 133.0–148.0) while the cSBP level in the same group was 145.0 mmHg (IQR: 140.0–150.0) mmHg. The overall median cSBP among women with eclampsia ($n = 102$) was 133.0 mmHg (IQR 120.0–143.0), and the median cDBP was 73.0 mmHg (IQR: 60.0–83.0), and these were significantly higher ($p < 0.0001$) than the median cSBP of 128.0 mmHg (IQR: 114.0–139) and cDBP of 71.0 mmHg (IQR: 61.0–81.0) among preeclamptic women.

Conclusion: This study established the threshold values for central hypertension as 116/78 mmHg, with severe central hypertension defined as 148/95 mmHg or more. It reinforces the positive correlation between peripheral and CBP in both normotensive and hypertensive populations. CBP may serve as a better



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Arterial stiffness after 6 weeks postdelivery in women with a history of hypertensive disorders of pregnancy: a systematic review and meta-analysis

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Introduction: The main objective of this systematic review was to determine if the arterial stiffness remains elevated after 6 weeks post-delivery in women with a history of hypertensive disorders of pregnancy (HDP).

Methods and analysis: A comprehensive systematic literature search was conducted across multiple electronic databases, including Medline, PubMed, Embase, Cochrane Library, Google Scholar, Web of Science, and CINAHL. We included studies assessing arterial stiffness in women with a history of HDP between 43 days and 10 years postdelivery, with participants under 60 years of age. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines. We extracted data on arterial stiffness indices, including carotid-femoral pulse wave velocity (cfPWV), augmentation index (AIx), and heart rate adjusted augmentation index (AIx@75), along with the mean $\pm$ standard deviation for each study. A random-effects model was used to pool data, and heterogeneity was explored through sensitivity and subgroup analyses. The Newcastle Ottawa Scale (NOS) and Grading of Recommendations Assessment, Development, and Evaluation (GRADE) were used to assess risk of bias and quality of evidence.

Results: Out of 121 identified articles, 12 studies involving a total of 856 women were included in the final review after eliminating duplicates and irrelevant studies. The overall pooled data revealed a significantly elevated AIx and cfPWV among women with a history of HDP. Specifically, the mean difference (MD) in AIx was 11.63 (95% Confidence Interval (CI): [1.72–21.54]), and for cfPWV, the MD was 0.53 (95% CI: [0.27–0.78]). Notably, while AIx showed no significant change in women within 1 year postpartum (MD 14.85, 95% CI [–6.03–35.72]), an elevation was observed in those beyond 1 year post-delivery (MD 9.11, 95% CI [4.20–14.02]). cfPWV was also found to be elevated in HDP patients both within 1 year (MD 0.59, 95% CI [0.32–0.86]) and beyond 1 year (MD 0.45, 95% CI [0.03–0.88]). In cases of early-onset preeclampsia, AIx did not show a significant increase; however, a significant increase in cfPWV was observed, with AIx having an MD of 1.55 (95% CI: [–0.74–3.84]) and cfPWV an MD of 1.86 (95% CI: [0.25–3.47]). For late-onset preeclampsia, there was no significant difference in AIx (MD 2.44, 95% CI: [–8.82–13.70]) or cfPWV (MD 0.10, 95% CI: [–0.42–0.62]).

Conclusion: This systematic review and meta-analysis suggest that arterial stiffness may remain elevated beyond 6 weeks postpartum in women with a

history of HDP. However, the findings should be interpreted with caution due to heterogeneity across studies and limited number of available studies. Larger and standardized longitudinal studies are needed to confirm these results. In the meantime, regular cardiovascular monitoring for these women is recommended while awaiting more conclusive evidence.

Systematic review registration: <https://www.crd.york.ac.uk/PROSPERO/search,CRD42023461867>.

KEYWORDS

hypertensive disorders of pregnancy, arterial stiffness, cardiovascular disease, pulse wave velocity, augmentation index, preeclampsia, maternal morbidity, postdelivery risk

Introduction

Hypertensive disorders of pregnancy (HDP), including gestational hypertension and preeclampsia, contribute significantly to maternal morbidity and mortality worldwide (1). Research has consistently indicated that women with a history of HDP face an increased risk of long-term cardiovascular issues, such as hypertension, stroke, and heart disease (2, 3). One important marker of cardiovascular health is arterial stiffness, which has been observed to be elevated in women with HDP both during and after pregnancy (4, 5). Evidence suggests that arterial stiffness and central aortic blood pressure are more closely linked to future cardiovascular events and renal complications than peripheral blood pressure in non-pregnant populations, a trend that may extend to HDP women in terms of their long-term cardiovascular outcomes.

From a physiological standpoint, the six-week mark post-delivery is noteworthy as it typically signals the stabilization of hemodynamics (6, 7). Throughout pregnancy, women experience considerable metabolic demands and cardiovascular adaptations that differ by trimester and gradually normalize after delivery (8). Key cardiovascular changes during pregnancy include an increase in cardiac output and blood volume, accompanied by a decrease in systemic vascular resistance (SVR). In particular, during pregnancy, elevated serum levels of progesterone and relaxin, a peptide hormone produced by the corpus luteum and placenta, facilitate systemic vasodilation (7, 8). This process results in a 25 to 30% reduction in SVR during pregnancy, with levels normalizing within 2 weeks postpartum and other vascular changes returning to normal during the six-week puerperal phase (7). Examining how arterial stiffness evolves after this timeframe is essential for understanding a woman's cardiovascular health trajectory and potential long-term risks.

Although studies indicate that central blood pressure and arterial stiffness measured before 14 weeks of gestation can predict preeclampsia (37–39), further evaluation is needed on their impact on future cardiovascular health. Importantly, increased maternal arterial stiffness in hypertensive pregnancies has also been associated with intrauterine growth restriction and small-for-gestational-age infants (9). Research has also found associations between elevated maternal arterial stiffness and central blood pressure, foetal growth restriction, and small for gestational age infants, as well as increased blood pressure in offspring by the age of 3 (9, 10). However, there is limited global data on whether arterial stiffness remains elevated beyond 6 weeks postpartum in women who have a history of HDP.

Global research examining this issue has included: (i) The United Kingdom indicates that women with a history of HDP face significant long-term cardiovascular risks, including accelerated cardiovascular aging and a greater variety of conditions such as valvular heart disease (11); (ii) Canada has shown a significant association between HDP and long-term cardiovascular risk, particularly highlighting that women who have experienced preeclampsia may exhibit increased arterial stiffness for up to 6 years after giving birth (12). This growing body of evidence suggests that arterial stiffness may remain elevated beyond puerperium, reinforcing the need for regular cardiovascular monitoring in women with a history of HDP; (iii) In Asia, particularly Korea, research suggest that elevated arterial stiffness seen in women with HDP during pregnancy may return to baseline levels after delivery (13). This variation in findings emphasizes the importance of conducting a global review to understand the long-term effects of HDP on arterial health and; (iv) In Africa, where HDP is a major cause of maternal mortality, research on the lasting cardiovascular effects of HDP is still emerging but gradually increasing. Some studies suggest that women with a history of HDP may contend with a greater risk of cardiovascular disease; however, further research is essential to evaluate the specific role of arterial stiffness after delivery (5, 14). Given the significant long-term cardiovascular risks associated with HDP, it is crucial to understand the duration of elevated arterial stiffness. This systematic review synthesized the existing literature to provide a better picture of the long-term effects of HDP on arterial health.

Objective

The objective of this systematic review was to determine if the arterial stiffness remains elevated after 6 weeks post-delivery in women with a history of hypertensive disorders of pregnancy.

Methods

This protocol was developed following the Preferred Reporting Items for Systematic reviews and Meta-Analysis protocols (PRISMA-P) 2015 Guidelines (15). A comprehensive search was conducted in Medline, PubMed, Embase, Cochrane Library, Google Scholar, Web of Science, and CINAHL. The following MeSH terms for database searches were used: ("Arterial stiffness" OR "central blood pressure" OR "Pulse wave velocity" OR "Augmentation index" OR

TABLE 1 PUBMED 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]	21,613
2	Preeclampsia [tw] OR Eclampsia[tw] OR Hypertensive disorders of pregnancy [tw] OR pregnancy-induced hypertension [tw] OR Gestational hypertension [tw] OR Chronic hypertension [tw]	69,722
3	After postpartum [tw] OR after delivery [tw] OR after puerperium [tw]	25,178
4	#2 AND #3	2,098
5	#1 AND #4	23

"PWV" OR "Aix" OR "Aix@75") AND ("Preeclampsia" OR "Eclampsia" OR "Gestational hypertension" OR "Chronic hypertension" OR "Hypertensive disorders of pregnancy" OR "pregnancy induced hypertension") AND ("After postpartum" OR "after delivery" OR "after puerperium"). One example of the search strategies used is shown in Table 1.

The exposure

The exposure was hypertensive disease during pregnancy or within 42 days post-delivery. The hypertensive diseases included preeclampsia, gestational hypertension, chronic hypertension, and chronic hypertension with superimposed preeclampsia. Preeclampsia was 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 $\mu\text{mol/L}$ 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 $<150,000/\mu\text{L}$, disseminated intravascular coagulation, haemolysis). Uteroplacental dysfunction includes fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or stillbirth (16, 17). Gestational hypertension was defined as persistent *de novo* hypertension that develops at or after 20 weeks of gestation in the absence of features of preeclampsia. Chronic hypertension referred to high blood pressure predating the pregnancy or recognized at <20 weeks of gestation. Chronic hypertension with superimposed preeclampsia was diagnosed when preeclampsia occurred in a pregnant woman who had pre-existing chronic hypertension.

Inclusion criteria

We included randomized and non-randomized control trials, prospective and retrospective cohort studies, case-control studies, and

cross-sectional studies performed in humans. The studies were included based on the following criteria:

1. Women with a history of HDP, aged under 60 years.
2. Studies reporting arterial stiffness indices (cfPWV, AIX, and AIX@75) at least 43 days postpartum.

There were no restrictions by the date of publication.

Exclusion criteria

We excluded 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 were also excluded. Studies that only assess arterial stiffness measurements during pregnancy, labour, and delivery or within 6 weeks post-partum were excluded.

Comparator

The control group consisted of women under 60 years old with no history of HDP, cardiovascular diseases, renal failure, or diabetes.

Data collection

Mendeley Reference Manager was used to store and manage searched items under the following headings in a separate table: Authors, publication year, title of the study, location of the study, participants ages, country, and main study findings. Two independent reviewers screened all the titles and abstracts using the predetermined inclusion and exclusion criteria. We followed PRISMA-P guidelines. Records identified as potentially eligible based on title, abstract, and full texts were obtained to screen. Where consensus on eligibility could not be achieved, a third review author was involved in the discussion. When the same cohort was reported in multiple articles, the study which contains the largest sample was selected. Data from selected studies were extracted and entered into a Microsoft Excel spreadsheet.

Risk of bias

Two independent authors evaluated the methodological quality of all included studies. Where consensus on eligibility could not be achieved, a third reviewer was involved in the discussion. The Newcastle Ottawa Scale (NOS) and Grading of Recommendations Assessment, Development, and Evaluation (GRADE) were used to assess risk of bias and quality of evidence (18). Disagreements among the two authors was resolved by consultation with the other authors to reach a consensus. No studies were excluded based on the risk of bias assessment.

Potential sources of heterogeneity were first assessed using the I^2 statistic (19). Values of 25% or less were classified as low, around 50% as moderate, and 75% or more as high (20). The subgroup and sensitivity analyses using RevMan 5.4 and NOS assessment scale

were performed. Since all subgroups contained fewer than ten studies, a funnel plot was only created for those with six or more studies.

Statistical analysis

Estimates of mean and $\pm$ SD for arterial stiffness indices (cfPWV, AIx, AIx@75) for women who had HDPs (for each subtype of HDP, as available) and normotensive women was obtained from the relevant studies. For studies where the estimates were reported as the median and interquartile range, approximate estimates of mean and $\pm$ SD were calculated using the available estimates of the median and, first quartile and third quartile. These data were summarized using a DerSimonian and Laird random-effects model (21). A separate meta-analysis was conducted for each hemodynamic indices of interest (cfPWV, AIx, AIx@75) for the combined outcome in those who had HDPs. For studies that provided data on the association between these hemodynamic variables and the outcome of interest, we meta-analyzed these effect measures using a random effects model. We performed a subgroup analysis for each subtype of HDP, as available.

Results

Study selection

Through our literature search, we identified 121 articles. After removing 22 duplicates and excluding 70 based on title and abstract screening (see Figure 1), Twenty-nine articles remained that were eligible for full-text review. Out of these, 12 studies were included in the final review. Specifically, there were 4 cross-sectional studies, 5 cohort studies, and 3 case-control studies (Table 2). The total number of participants across the studies was 856 women with HDP and healthy women.

Study characteristics

The included studies, conducted between 2009 and 2023, came from various countries: South Africa (1), Argentina (1), Denmark (1), Portugal (1), United States (3), Austria (1), Canada (1), the United Kingdom (1), Norway (1) and Italy (1) (see Table 2). These studies evaluated arterial stiffness, with some utilizing carotid-femoral pulse wave velocity (cfPWV) and/or augmentation index (AIx) and/or Augmentation index adjusted for heart rate (AIx@75).

HDP encompasses various types (16). While only two studies, Ehrenthal et al. (22) and Moe et al. (23), examined composite HDP, other studies focused on specific types, including preeclampsia, early preeclampsia, and late-onset preeclampsia. As a result, the findings were categorized into four groups: composite HDP, preeclampsia, early preeclampsia, and late-onset preeclampsia.

Risk of bias assessment

The risk of bias was assessed using the NOS for cohort and case-control studies, and a modified NOS for cross-sectional studies. The

assessment indicated that all studies had a low risk of bias (Tables 3, 4). Recognizing that NOS evaluates risk of bias but does not fully capture the overall certainty of evidence, the GRADE framework was further applied. This comprehensive assessment, which considers factors such as consistency, directness, and precision, rated the overall certainty of the evidence as moderate to high (Table 5).

Comparison of augmentation index and pulse wave velocity between women with all hypertensive disorders of pregnancy and normotensive women

A total of 7 studies assessed the AIx in patients with all various HDP compared to normotensive women (Figure 2A). The pooled data demonstrated a significantly elevated AIx among women with HDP, indicating a Mean difference (MD) of 11.63 and a 95% confidence interval (CI) of [1.72–21.54]. This analysis included 345 participants, comprising 167 women with HDP and 178 normotensive controls. The heterogeneity among the studies was high, with an I^2 value of 98%. Additionally, the analysis of funnel plots indicated the presence of publication bias, with a p value of 0.045 in the Egger's test (Figure 3).

Furthermore, a total of 11 studies examined cfPWV in women with all various HDP compared to normotensive women (Figure 2B). The pooled data showed a significantly elevated cfPWV in women with HDP, with a MD of 0.53 and a 95% CI of [0.27–0.78]. This analysis included 738 participants, comprising 363 women with HDP and 375 normotensive controls. The studies showed moderate heterogeneity, with an I^2 value of 64%. Additionally, the analysis of funnel plots indicated the presence of publication bias, with a p value of 0.002 in the Egger's test (Figure 4).

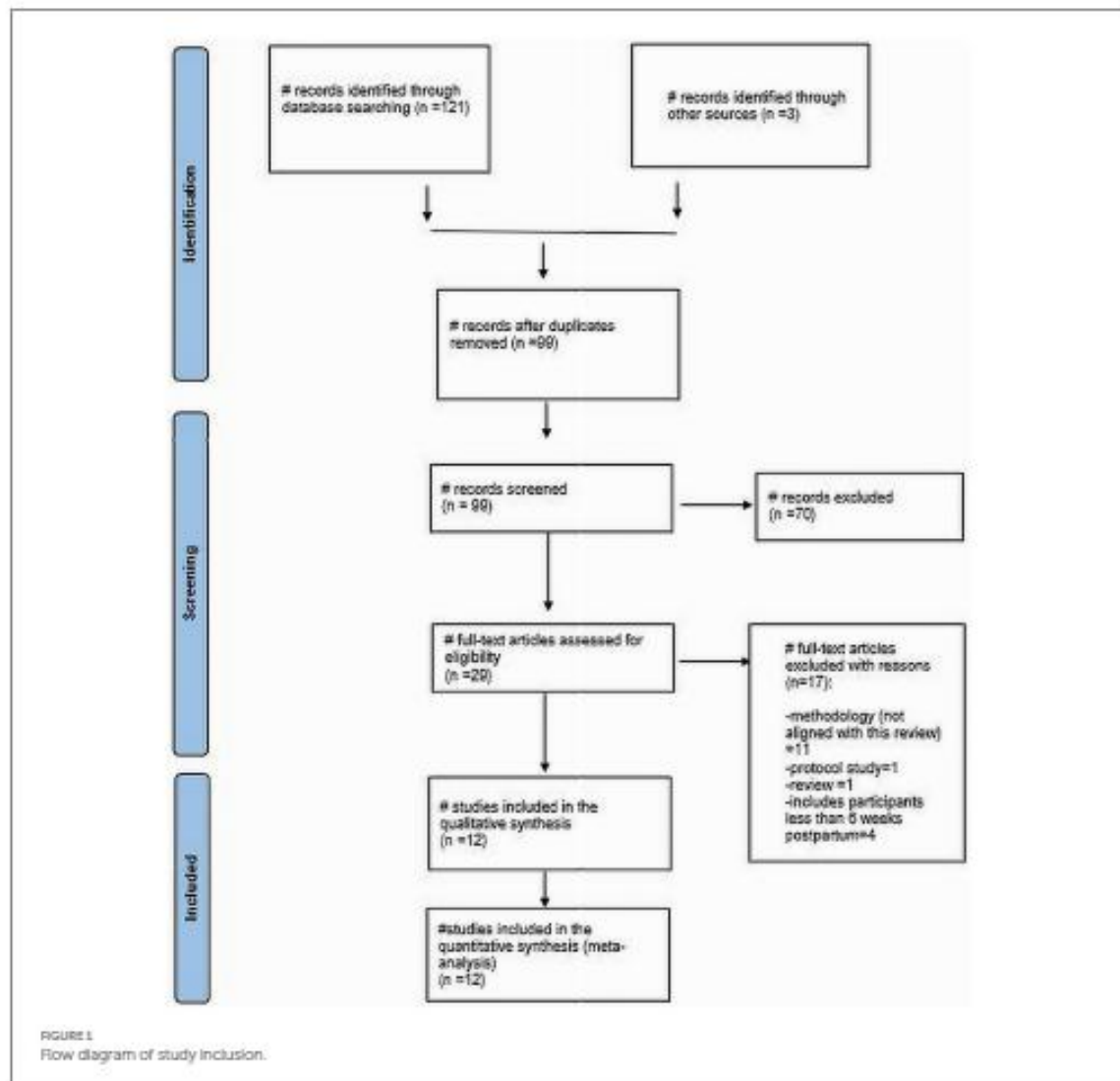
Comparison of augmentation index and pulse wave velocity between women with hypertensive disorders of pregnancy and normotensive women, within a year after delivery and after more than a year after delivery

Four studies investigated AIx in patients with HDP compared to normotensive controls within 1 year after delivery (see Figure 5A). The results showed no significant increase in AIx for women with HDP, reporting a MD of 14.85 and a 95% CI of [–6.03–35.72]. Additionally, there was high heterogeneity among these studies, with an I^2 value of 97%.

In contrast, other studies focused on AIx in patients with HDP compared to normotensive controls more than 1 year after delivery (see Figure 5B). The findings indicated a significant increase in AIx for women with HDP, with a MD of 9.11 and a 95% CI of [4.20–14.02]. The heterogeneity in these studies was also high, with an I^2 value of 94%.

Six studies evaluated cfPWV in women with HDP compared to normotensive controls within 1 year after delivery (Figure 6A). The results demonstrated a significantly higher cfPWV for women with HDP, reporting an MD of 0.59 and a 95% CI of [0.32–0.86]. The heterogeneity among these studies was moderate, with an I^2 value of 41%.

Additionally, five studies focused on cfPWV in women with HDP compared to normotensive controls more than 1 year after delivery



(Figure 6B). The findings also revealed a significant increase in cPWV for women with HDP, with an MD of 0.45 and a 95% CI of [0.03–0.88]. Heterogeneity in these studies was also moderate, with an I^2 value of 67%.

Comparison of augmentation index and pulse wave velocity in preeclamptic versus normotensive women

A total of 4 studies assessed the AIx in patients with preeclampsia compared to normotensive women (Figure 7A). This pooled data demonstrated a significantly elevated AIx among women with preeclampsia, with a mean difference (MD) of 8.57 and a 95% confidence interval (CI) of [4.22–12.92]. The analysis included 207 participants, comprising 102 women with preeclampsia and 105 normotensive controls. The heterogeneity among the studies was high

at 91%, indicating varying results across the studies. In two studies (12, 14) that adjusted the AIx for heart rate (AIx@75), the augmentation index remained significantly elevated after the adjustment, with a MD of 7.50 and a 95% CI of [6.09–8.90] (Figures 7A,B). These two studies showed no heterogeneity.

Additionally, an examination of cPWV across eight studies indicated a significant increase in cPWV among women with preeclampsia, demonstrating an MD of 0.47 with a 95% CI of [0.20–0.74] (Figure 7C). This analysis involved 600 patients (298 preeclamptic and 302 normotensive). The studies displayed moderate heterogeneity, with an I^2 value of 62%.

The funnel plot was generally symmetrical; however, a few studies deviated from the main axis, indicating the possibility of a small sample effect or publication bias. To further investigate potential bias, Egger's test was conducted, which showed no significant publication bias ($p = 0.144$) (Figure 8).

TABLE 2 Data extraction table.

Study	Authors (year)	Country	Study design	Sample size	Population characteristics (age, comorbidities)	Time postpartum	Arterial stiffness measure (cfPWV, AIx)	Mean $\pm$ SD of arterial stiffness	Comparison group	Elevated arterial STIFFNESS (Yes/No)	Risk of bias assessment (Cochrane/NOS)	Other key findings
1	Namugowa et al. (2017) (14)	South Africa	case-control	30 (15 pre-eclampsia 15 control)	African Black; 16–40 years; no CVD	15 weeks	cfPWV, AIx	Mean: 5.9 m/s $\pm$ 0.09; 23 $\pm$ 16%	Normal pregnancy group	Yes	Low risk	Significant difference in cfPWV between HDP and normal group
2	Páez et al. (2009) (31)	Argentina	Case-control	40 (20;20)	18–33 years old; no CVD	2 years	cfPWV, AIx	Mean: 10.5 m/s $\pm$ 2.3; 37.5 $\pm$ 5.1%	Normal pregnancy group	Yes	Low risk	Significant difference in cfPWV between HDP and normal group
3	Christensen et al. (2017) (26)	Denmark	cohort	48 (24;24)	Average 40 years old; no CVD	1 year	cfPWV, AIx	Mean: 8.03 m/s $\pm$ 0.93; 22.1 $\pm$ 9.22%	Normal pregnancy group	No	Low risk	The hypertension exposed women tended to have a higher aPWV compared to unexposed women; but the difference was not significant
4	Polónia et al. (2014) (27)	Portugal	Cross-sectional	100 (45;55)	no CVD	10 years	cfPWV, AIx	6.7 m/s $\pm$ 1.1; 25.7 $\pm$ 5.1%	Normal pregnancy group	Yes	Low risk	Significant difference in cfPWV between HDP and normal group
5	Ehrenthal et al. (2014) (22)	United States of America	cohort	74 (33;41)	18 years and above; White and African Americans; no CVD or Diabetes	1 year	cfPWV, AIx	6.2 m/s $\pm$ 1.5; 22.0 $\pm$ 13.4;	Normal pregnancy group	Yes	Low risk	Significant difference in cfPWV between HDP and normal group

(Continued)

TABLE 2 (Continued)

Study	Authors (year)	Country	Study design	Sample size	Population characteristics (age, comorbidities)	Time postpartum	Arterial stiffness measure (cfPWV, AIx)	Mean $\pm$ SD of arterial stiffness	Comparison group	Elevated arterial STIFFNESS (Yes/No)	Risk of bias assessment (Cochrane/NOS)	Other key findings
6	Prinz et al. (2013) (24)	Austria	cohort	74 (53;21)	Unknown	3–6 months	cfPWV, AIx	9.9 ± 1.6 ; -10.7 ± 21.1	Normal pregnancy group	yes	Low risk	Presence of a higher cardiovascular risk in patients after early-onset pre-eclampsia.
7	Werlang et al. (2023) (12)	Canada	Cross-sectional	80 (40;40)	Average 36 years; no CVD	6 months–6 years	cfPWV, AIx	$6.3 \text{ m/s} \pm 1.0$; $16.2 \pm 2.5\%$	Normal pregnancy group	yes	Low risk	Significant difference in cfPWV between HDP and normal group
8	Robb et al. (2009) (33)	United Kingdom	cohort	37 (22;15)	Average 30 years; no CVD	7 weeks	cfPWV	$7.3 \text{ m/s} \pm 0.3$	Normal pregnancy group	Yes	Low risk	Significant difference in cfPWV between HDP and normal group
9	Evans et al. (2011) (30)	United States of America	cohort	68 (18;50)	18–40 years Black and White participants; no preexisting cardiac disease or diabetes mellitus	16 months after delivery	cfPWV	cfPWV Mean: $2.39 \text{ m/s} \pm 0.8$	Normal pregnancy group	No	Low risk	No significant difference in AIx between HDP and normal group
10	Moe et al. (2020) (23)	Norway	Cross-sectional	221 (126;95)	18 years and above; no CVD or renal disease	1 year after delivery	cfPWV	$6.3 \text{ m/s} \pm 2.9$	Normal pregnancy group	Yes	Low risk	Significant difference in AIx between HDP and normal group
11	Usselman et al. (2020) (18)	United States of America	Cross-sectional	24 (12;12)	White, Hispanic, black women; no CVD	6–24 months after delivery	cfPWV	$7.1 \text{ m/s} \pm 1.1$	Normal pregnancy group	yes	Low risk	Significant difference in AIx between HDP and normal group

(Continued)

TABLE 2 (Continued)

Study	Authors (year)	Country	Study design	Sample size	Population characteristics (age, comorbidities)	Time postpartum	Arterial stiffness measure (cfPWV, AIx)	Mean $\pm$ SD of arterial stiffness	Comparison group	Elevated arterial STIFFNESS (Yes/No)	Risk of bias assessment (Cochrane/NOS)	Other key findings
12	Orabona et al. (2017) (25)	Italy	Case-control	60 (30;30)	No CV risk factors, smoking, dyslipidemia, overweight, diabetes mellitus or chronic hypertension.	6 months–4 years after delivery	cfPWV	cfPWV Mean: 8.42 m/s $\pm$ 1.92	Normal pregnancy group	yes	Low risk	Significant difference in cfPWV between IHD and normal group

TABLE 3 NOS for the risk of bias and quality assessment of NRSs.

Author Year	Selection				Comparability	Exposure	Selection	Nonresponse rate	Total Score
	Adequate definition of patient cases	Representativeness of patient cases	Selection of controls	Definition of controls	Control for important or additional factors	Ascertainment of exposure	Same method of ascertainment for participants		
Namugowa et al. 2019 (32)	★	★		★	★★	★	★		7
Christensen et al. 2017 (26)	★	★		★	★★	★	★	★	8
Robb et al. (2009) (33)	★	★		★	★★	★	★		7
Orabona et al. (2017) (25)	★	★		★	★★	★	★		8
Páez et al. (2008) (31)	★	★		★	★★	★	★		7
Ehrenthal et al. (2014) (22)	★	★		★	★★	★	★		7
Franz et al. (2013) (24)	★	★		★	★★	★	★		7
Evans et al. (2011) (30)	★			★	★★	★★	★		8

NOS, Newcastle-Ottawa scale; NRS, non-randomized study.

Each study is evaluated across three domains:

- Selection of the study population (maximum: 4 stars).

- Comparability of groups (maximum: 2 stars).

- Exposure (Ascertainment of exposure, Same method of ascertainment for participants and Nonresponse rate)(maximum: 3 stars).

A star (★) indicates the score, or criteria met.

TABLE 4 NOS (adapted for cross-sectional studies) for the risk of bias and quality assessment of NRSs.

Author Year	Selection					Comparability	Exposure	Total score
	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of the exposure (risk factor)	Control for important or additional factors	Assessment of the outcome	Statistical test	
Polonia et al. (2014) (27)	★		★	★★	★★	★★	★	9
Werlang et al. (2023) (12)	★		★	★	★★	★★	★	8
Moe et al. (2020) (23)								7
Usselman et al. (2020) (18)	★		★	★	★★	★★	★	8

NOS, Newcastle-Ottawa scale; NRS, non-randomized study.

Each study is evaluated across three domains:

- Selection of the study population (maximum: 4 stars).

- Comparability of groups (maximum: 2 stars).

- Outcome (for cohort studies) or Exposure (for case-control studies) (maximum: 3 stars).

A maximum score of 9 stars represents the highest quality, indicating the lowest risk of bias. A star (★) indicates the score, or criteria met.

TABLE 5 Risk of bias assessment using NOS and GRADE for included studies (case-control and cross-sectional designs).

Author	Year	Study design	Selection	Comparability	Exposure/Outcome	Total NOS score	GRADE quality
Namagawa et al.	2019	Case-Control	3★	2★★	2★	7	Moderate
Christensen et al.	2017	Case-Control	3★	2★★	3★	8	Moderate to High
Robb et al.	2009	Case-Control	3★	2★★	2★	7	Moderate
Orabona et al.	2017	Case-Control	3★	2★★	3★	8	Moderate to High
Páez et al.	2008	Case-Control	3★	2★★	2★	7	Moderate
Ehrenthal et al.	2014	Case-Control	3★	2★★	2★	7	Moderate
Franz et al.	2013	Case-Control	3★	2★★	2★	7	Moderate
Evans et al.	2011	Case-Control	2★	2★★	3★★	8	Moderate to High
Polonia et al.	2013	Cross-Sectional	2★	2★★	3★★+★	9	High
Werlang et al.	2023	Cross-Sectional	2★	2★★	3★★+★	8	Moderate to High
Moe et al.	2020	Cross-Sectional	1	2	2	7	Moderate
Usselman	2020	Cross-Sectional	2★	2★★	3★★+★	8	Moderate to High

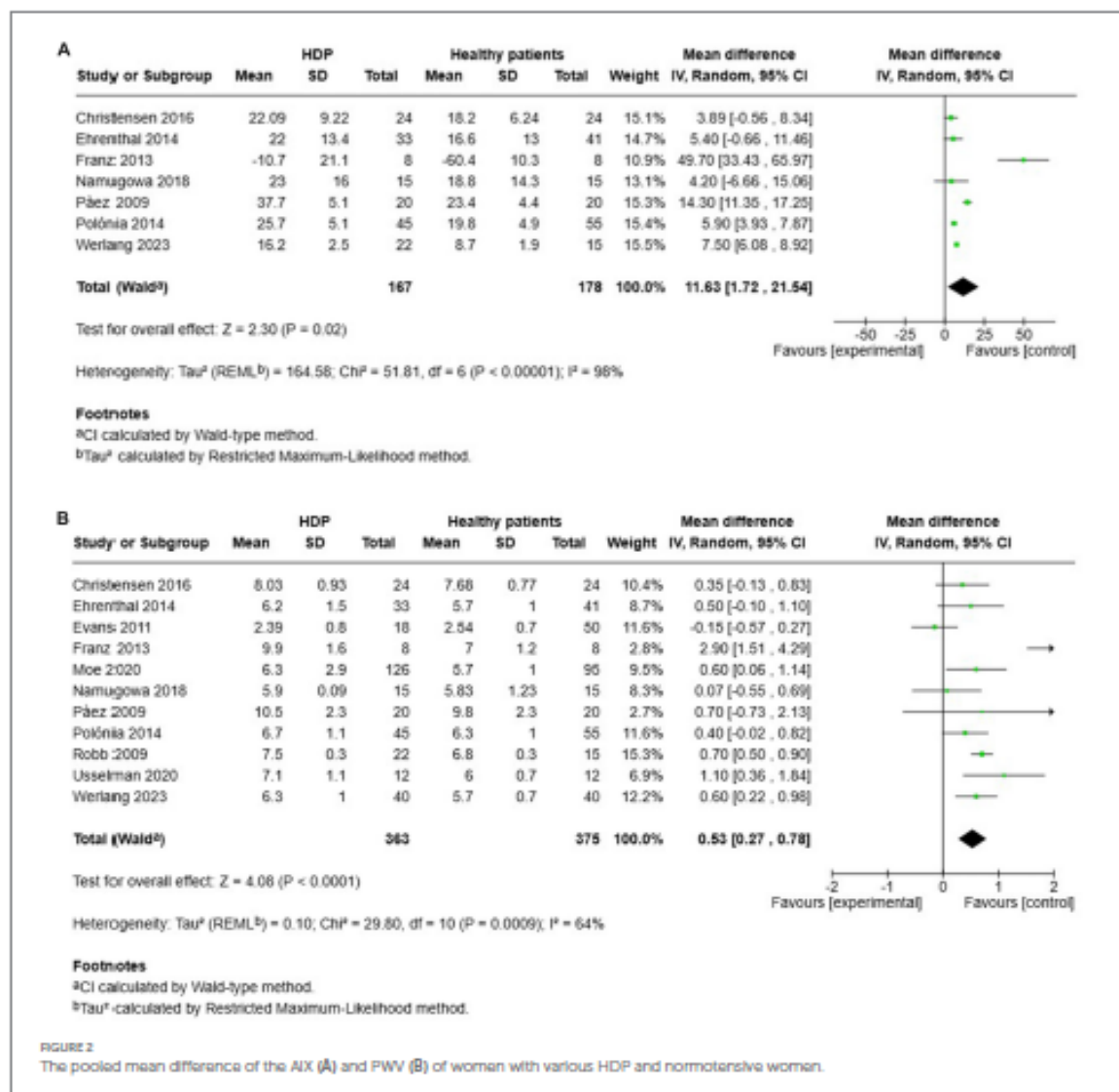
Each study is evaluated across three domains:

- Selection of the study population (maximum: 4 stars).

- Comparability of groups (maximum: 2 stars).

Outcome (for cohort studies) or Exposure (for case-control studies) (maximum: 3 stars).

A maximum score of 9 stars represents the highest quality, indicating the lowest risk of bias. A star (★) indicates the score, or criteria met.



Comparison of augmentation index and pulse wave velocity in women with HDP versus normotensive women

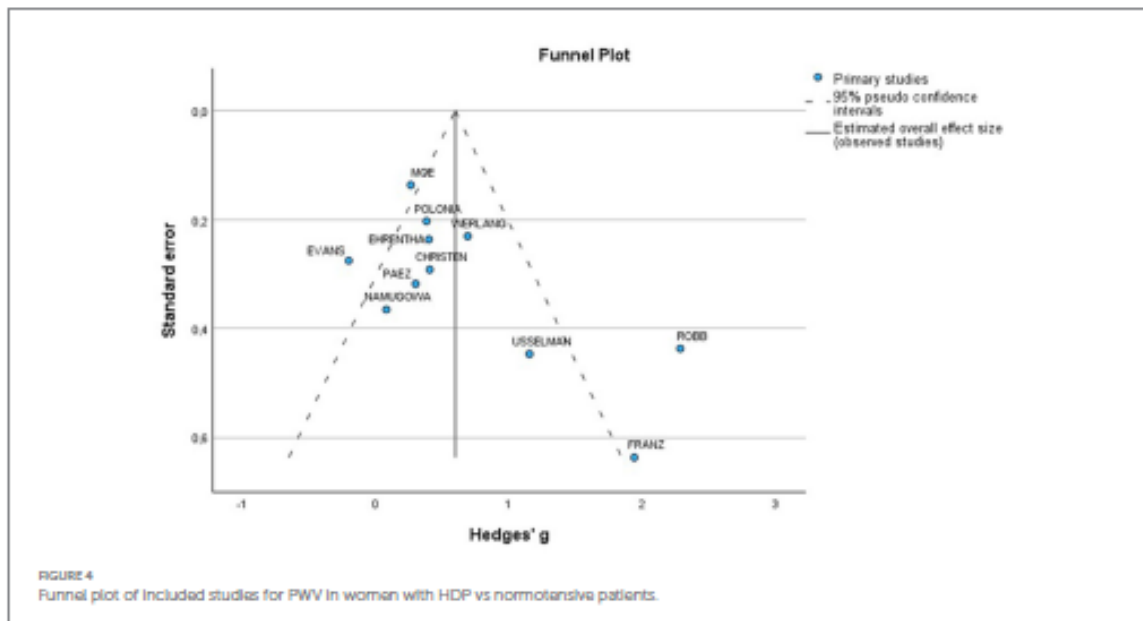
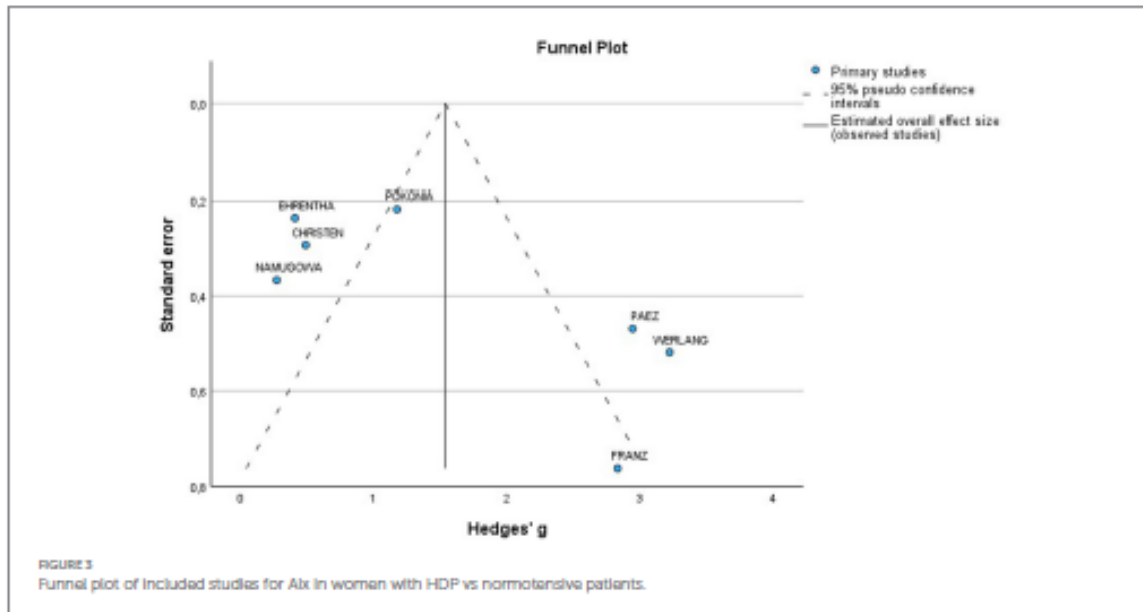
One study focused on AIX in patients with composite HDP against normotensive controls (22). The results indicated no significant increase in AIX for women with HDP (MD 5.40, 95% CI [-0.66–11.46]). The heterogeneity assessment was not applicable due to the design being based on a single study. This analysis included a total of 74 participants, with 33 diagnosed with HDP and 41 who were normotensive. However, AIX was found to be significantly elevated after adjusting for heart rate (AIX@75) (MD 6.40, 95% CI [0.52–12.28]) (15).

Two studies, Ehrenthal et al. (22) and Moe et al. (23) analysed cPWV in the context of HDP, reporting no significant increase in cPWV among affected women (MD 0.35, 95% CI [-0.13–0.83]), with

zero statistical heterogeneity noted (Figure 9). This part of the analysis comprised 305 individuals (169 with HDP and an equivalent number of normotensive controls).

Comparison of augmentation index and pulse wave velocity among women with early onset preeclampsia and normotensive women

In the context of early onset preeclampsia (EOP), two studies, conducted by Christensen et al. (26) and Franz et al. (24), evaluated the AIX and found no significant increase associated with EOP (MD 1.55, 95% CI [-0.74–3.84]), with a heterogeneity of 88% (Figure 10A). The studies included a total of 64 participants, comprising 32 EOP and 32 normotensive women. Orabona et al. (25) was the only study

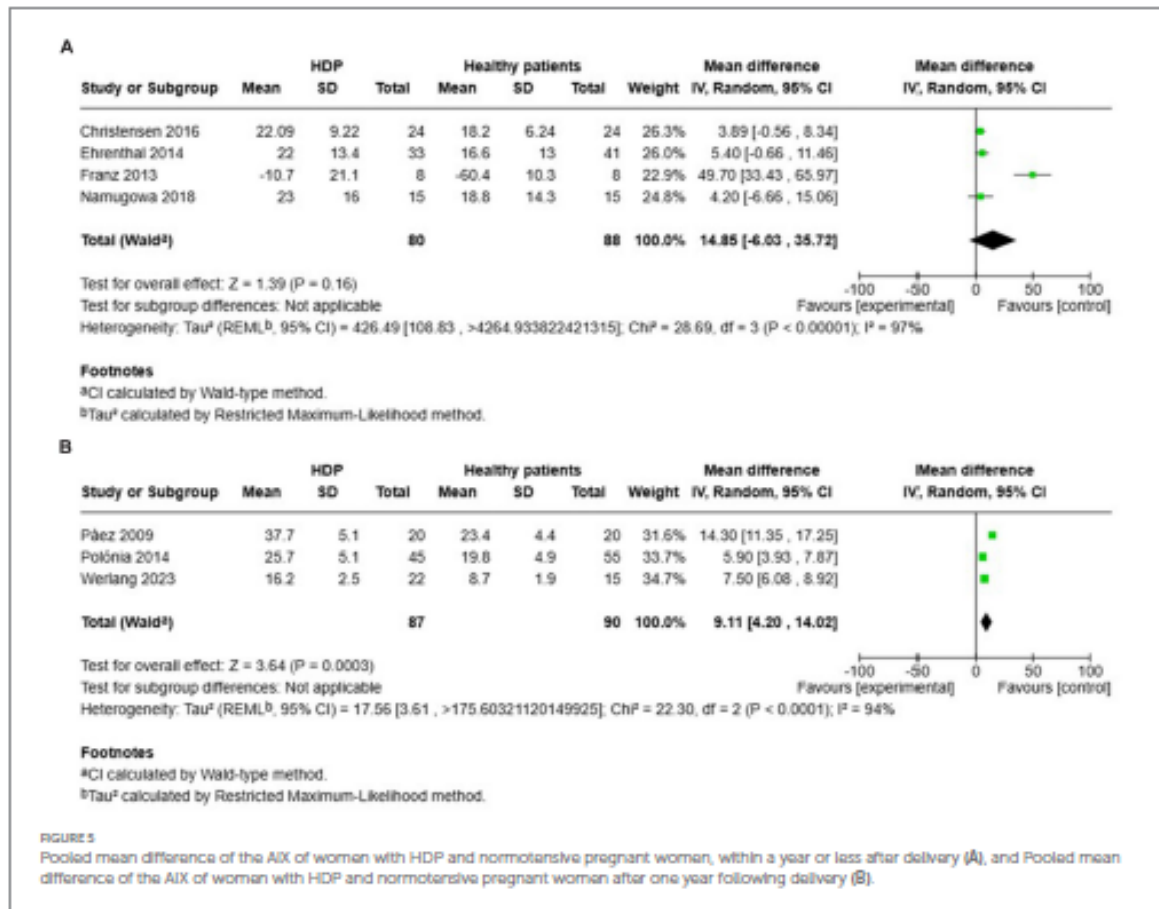


to evaluate AIx after adjusting for heart rate, and it indicated a significant elevation in AIx following this adjustment (MD 0.94, 95% CI [2.17–3.70]).

Additionally, Christensen et al. (26), Franz et al. (24), and Orabona et al. (25) also assessed cfpWV in patients with EOP. The results indicated a significant increase in cfpWV (MD 1.86, 95% CI [0.25–3.47]) and a heterogeneity of 92%. A total of 124 participants were included in these studies, consisting of 62 EOP and 62 normotensive women (Figure 10B).

Comparison of augmentation index and pulse wave velocity among women with late onset preeclampsia and normotensive pregnancy

Christensen et al. (26) and Franz et al. (24) also studied the AIx in cases of late-onset preeclampsia. Their analysis showed no significant difference (MD of 2.44, 95% confidence interval [−8.82–13.70]) and indicated a heterogeneity of 65%



(Figure 11A). This study included a total of 64 participants, comprising 32 individuals with LOP and 32 normotensive controls. However, after adjusting for heart rate, Orabona et al. (25) found that the augmentation index was significantly higher in the LOP group (MD of 4.80, 95% confidence interval [0.60–9.00]).

Furthermore, Christensen et al. (26), Franz et al. (24), and Orabona et al. (25) also assessed cPWV in patients with LOP. Their findings indicated no significant increase in cPWV (MD 0.10, 95% CI [-0.42–0.62]), with a heterogeneity of 56% (Figure 11B). The total sample size in this analysis was 124 participants, including 62 with LOP and 62 normotensive individuals.

Comparison of augmentation index and pulse wave velocity among women with HDP and normotensive pregnancy in cohort studies

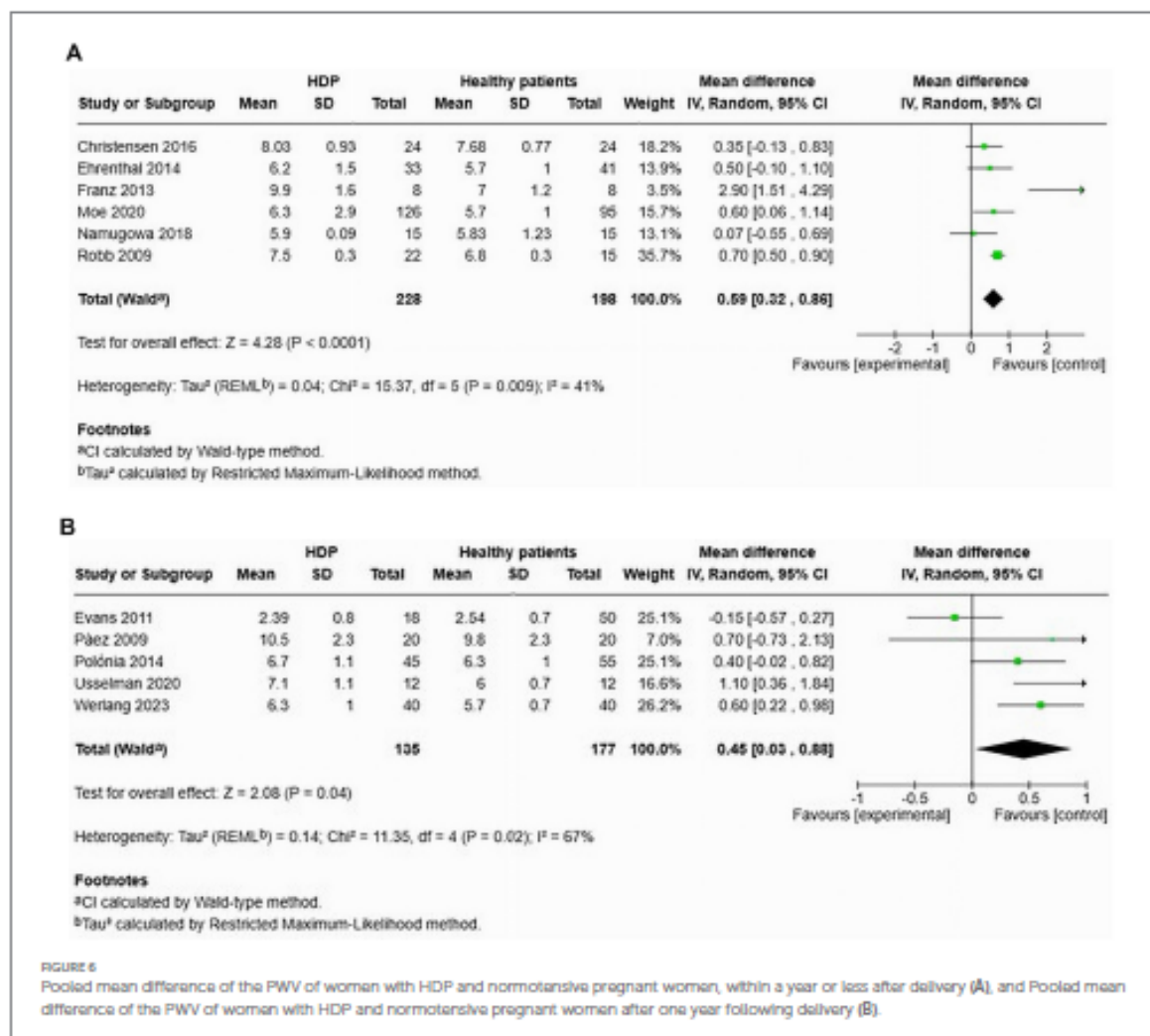
A total of three studies assessed the AIX in patients with HDP compared to normotensive women (22, 24, 26) (see Figure 12A). The pooled data demonstrated a significantly elevated AIX among women with HDP, indicating a MD of 16.82 and a 95% CI of

[1.11–12.92]. This analysis included 138 participants, comprising 65 women with HDP and 73 normotensive controls. The heterogeneity among the studies was high at 93%, suggesting varying results across the studies. In the only study that adjusted the AIX for heart rate (AIX@75), the augmentation index remained significantly elevated after adjustment, with a MD of 6.40 and a 95% CI of [0.52–12.28] (22).

Furthermore, an examination of cPWV across five studies showed no significant increase in cPWV among women with HDP, demonstrating a MD of 0.70 with a 95% CI of [-0.10–1.49] (see Figure 12B). The heterogeneity was again high at 93%, and this analysis involved 243 patients (105 with HDP and 138 normotensive).

Comparison of augmentation index and pulse wave velocity in women with HDP versus normotensive women in cross-sectional studies

Two studies focused on AIX in patients with HDP compared to normotensive controls (12, 27) (see Figure 13A). The results indicated a significant increase in AIX for women with HDP, with a MD of 6.85 and a 95% CI of [5.31–8.39]. The heterogeneity among



these studies was low at 40%. This analysis included a total of 137 participants, with 67 diagnosed with HDP and 70 who were normotensive. In one study, the AIx remained significantly elevated after adjusting for heart rate, with a MD of 7.50 and a 95% CI of [0.68–8.92] (12).

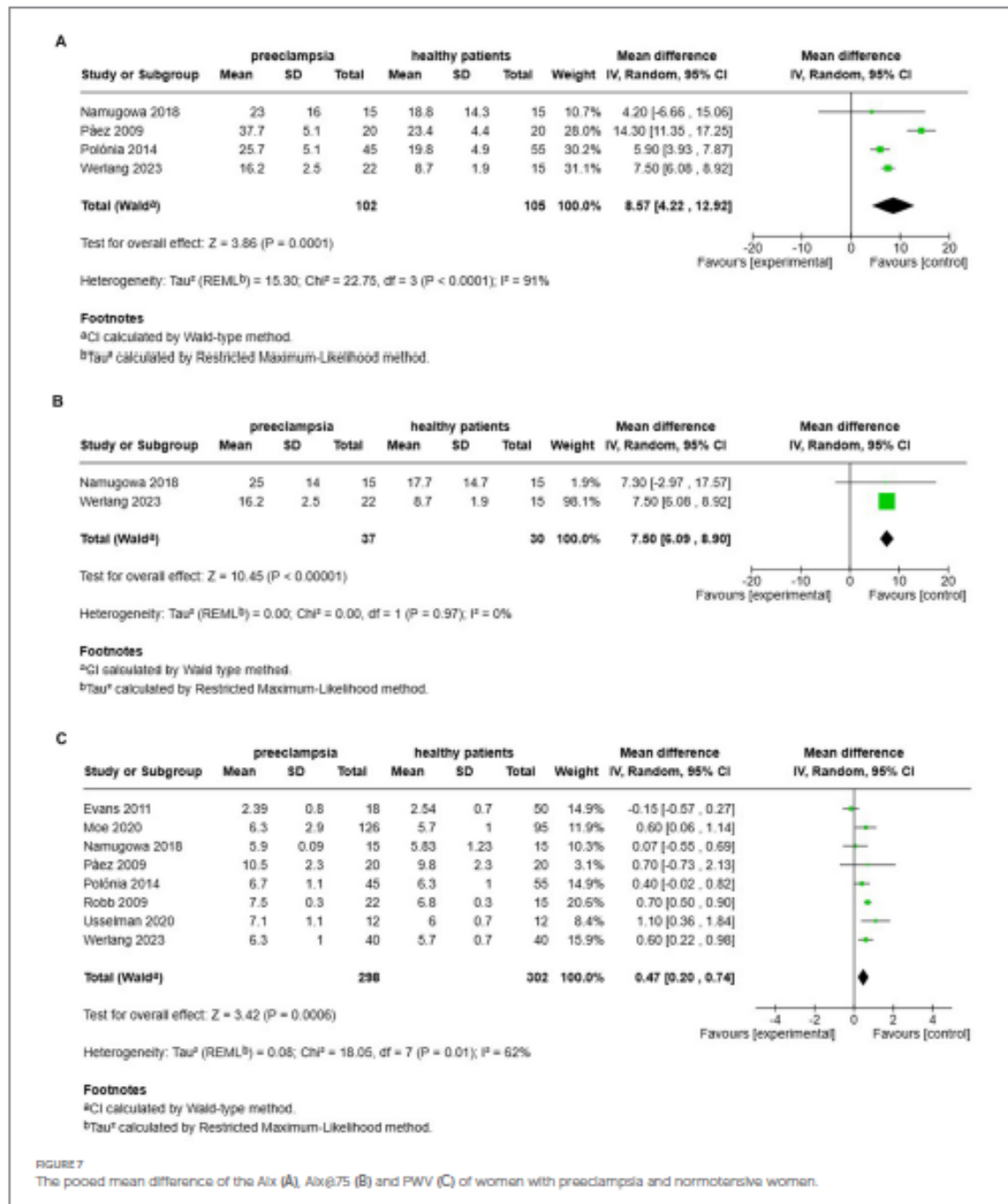
Four studies analysed cPWV in the context of HDP, reporting a significant increase in cPWV among affected women, with a MD of 0.59 and a 95% CI of [0.35–0.82] (12, 23, 27, 28). No statistical heterogeneity was observed in this analysis (see Figure 13B). This part of the analysis comprised 305 individuals (223 with HDP and 203 normotensive controls).

Discussion

The systematic review presents a comprehensive analysis of the literature regarding arterial stiffness in women with previous history of HDP, particularly pre-eclampsia. Most studies revealed elevated

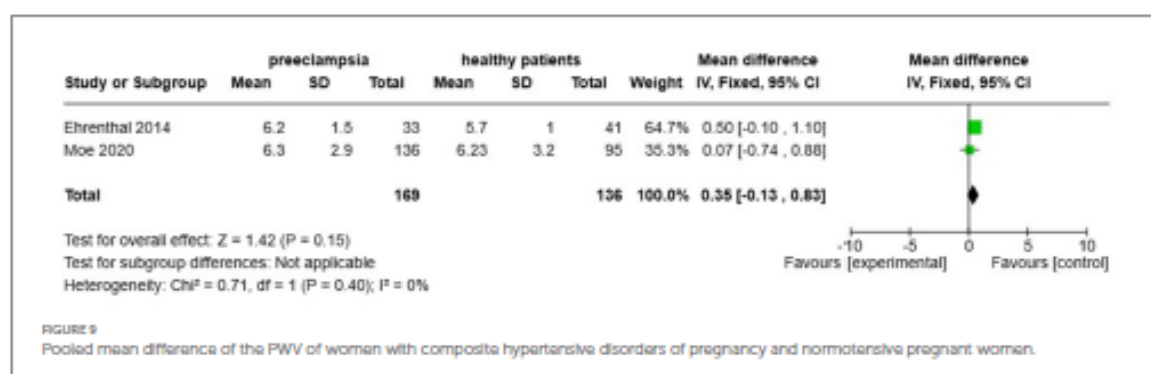
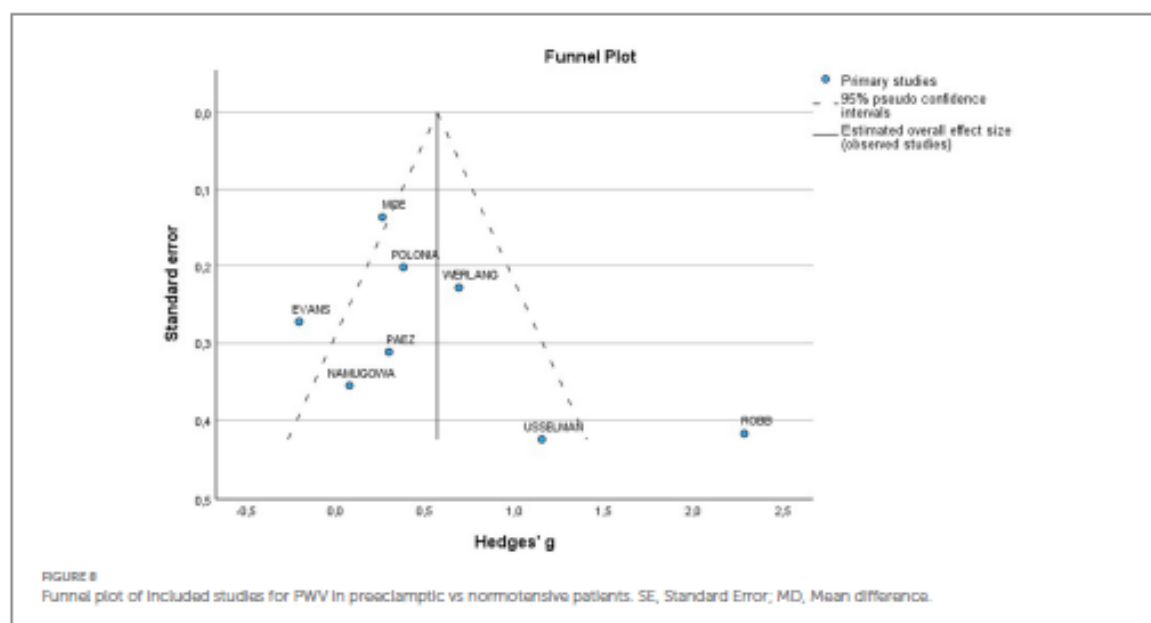
arterial stiffness after 6 weeks post-delivery in women with a history of preeclampsia, suggesting ongoing vascular dysfunction that could lead to an increased cardiovascular risk lingering even years after pregnancy (29). The duration of the studies ranged from 7 weeks postpartum to 10 years post-pregnancy, showcasing the long-term implications of preeclampsia on cardiovascular health. However, not all studies demonstrated a consistent association between HDP and increased arterial stiffness. For example, a Danish study by Christensen et al. and research by Evans et al. in the United States reported no increase in arterial stiffness as measured by cPWV and AIx (26, 30). This indicates that, while a relationship may exist, its impact can vary based on the demographic and clinical characteristics of the populations studied.

The AIx, particularly after adjusting for heart rate, was found to be elevated in women with HDP (12, 25, 27, 31, 32). This includes specific types such as composite preeclampsia and both early and late onset preeclampsia, when compared to normotensive women (25). This suggests a considerable increase in arterial



stiffness, which may indicate a heightened cardiovascular risk in this preeclampsia population. The high heterogeneity (87%) observed among the studies points to variability in results, potentially due to differences in study populations, methodologies, or measurement techniques. Additionally, a single study examining AIX@75 in women with composite HDP³ also reported

a significant increase, although heterogeneity assessment was not applicable in this case (22). These findings reinforce the idea that women with various types of hypertensive disorders experience increased arterial stiffness, emphasizing the associated cardiovascular risk. The consistently elevated AIX in both cohort and cross-sectional studies further supports the notion that there



is a significant alteration in arterial function among women with a history of HDP. Additionally, a review of AIx findings 1 year after delivery indicates changes in vascular function in women with a history of HDP, suggesting a lasting cardiovascular risk. Although arterial stiffness, as indicated by AIx, may not differ significantly within the first year postpartum, long-term effects of HDP could increase arterial stiffness and potentially, cardiovascular risk. Importantly, both women in their first year after delivery and those beyond that period demonstrated a significant increase in cPWV.

Furthermore, pooled data from eleven studies comparing various hypertensive disorders in normotensive women, as well as data from eight studies comparing preeclampsia and normotensive women, revealed a significant increase in cPWV (12, 23, 27, 28, 30–33). However, studies on cPWV for women with composite HDP and late onset preeclampsia showed no significant increases (15, 29). This suggests that while AIx is elevated, reflecting

increased arterial stiffness, cPWV might not indicate a similar degree of change, potentially highlighting that the two measurements assess different aspects of arterial function. cPWV directly measures the speed at which pressure waves travel through the arterial tree. A faster cPWV indicates stiffer arteries and is more representative of large artery function. It is less influenced by peripheral changes and wave reflections from smaller arteries (34). On the other hand, AIx measures the augmentation of pressure waves in the arteries caused by reflected waves from peripheral sites (35, 36). This metric reflects not only the stiffness of the arteries but also the timing and intensity of these reflections.

Notably, the assessment of early-onset preeclampsia also revealed a significant rise in cPWV, contrasting with late-onset preeclampsia, which showed no significant changes. This discrepancy may indicate that the early onset of preeclampsia is associated with distinct hemodynamic changes that are absent in the later onset. Furthermore,

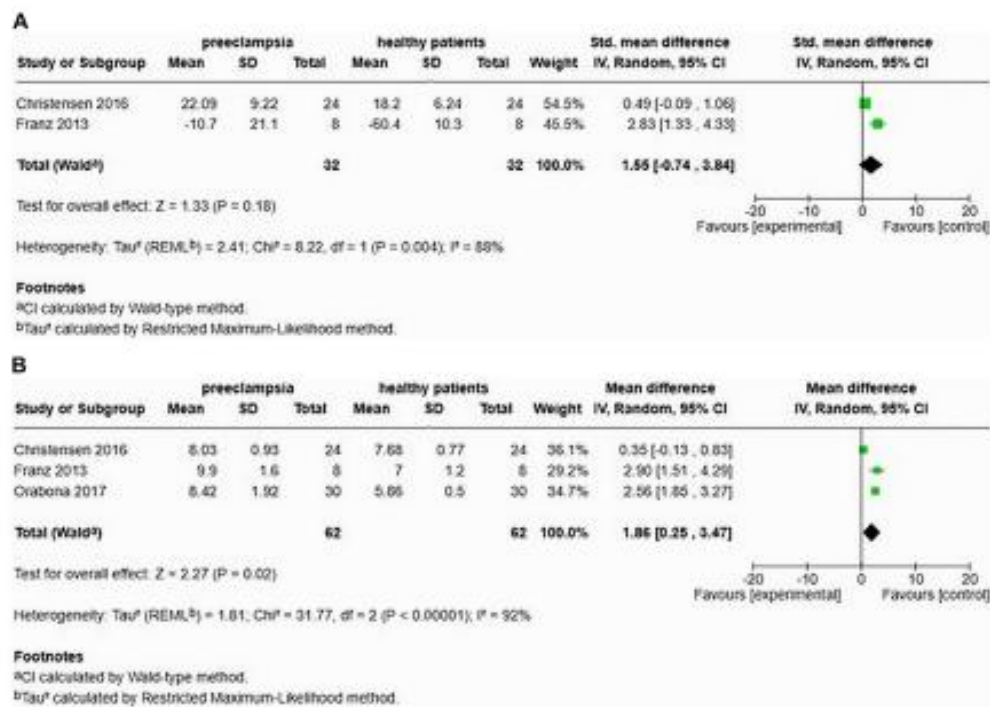


FIGURE 10

Pooled mean difference of the AIX (A) and PWV (B), of woman with early onset preeclampsia compared to normotensive women.

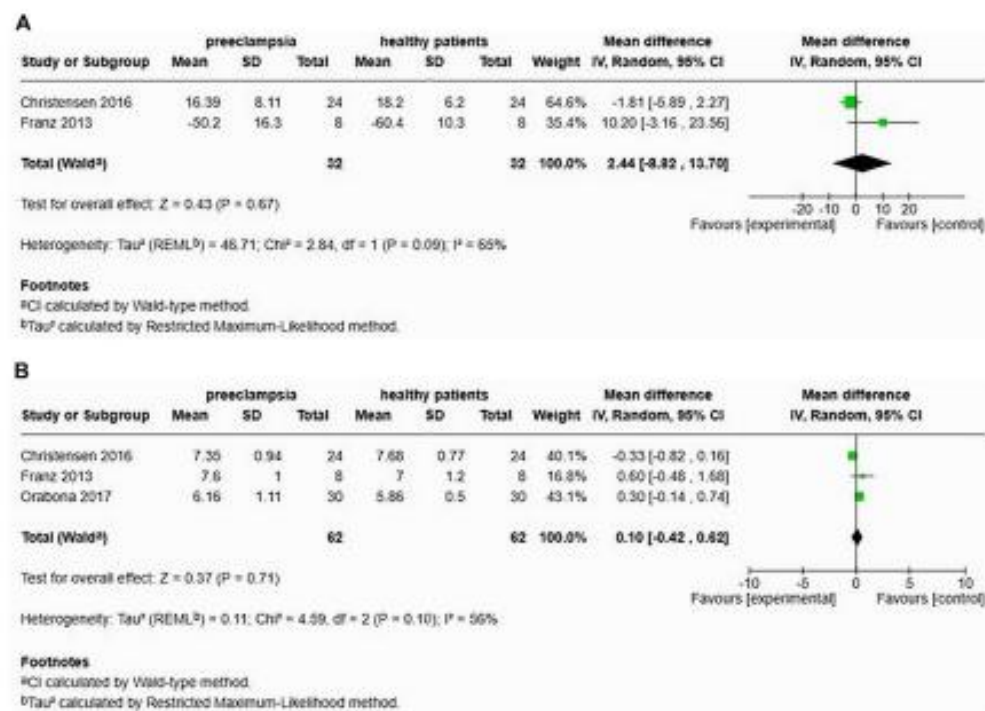


FIGURE 11

Pooled mean difference of the AIX (A) and PWV (B), of woman with late-onset preeclampsia compared to normotensive women.

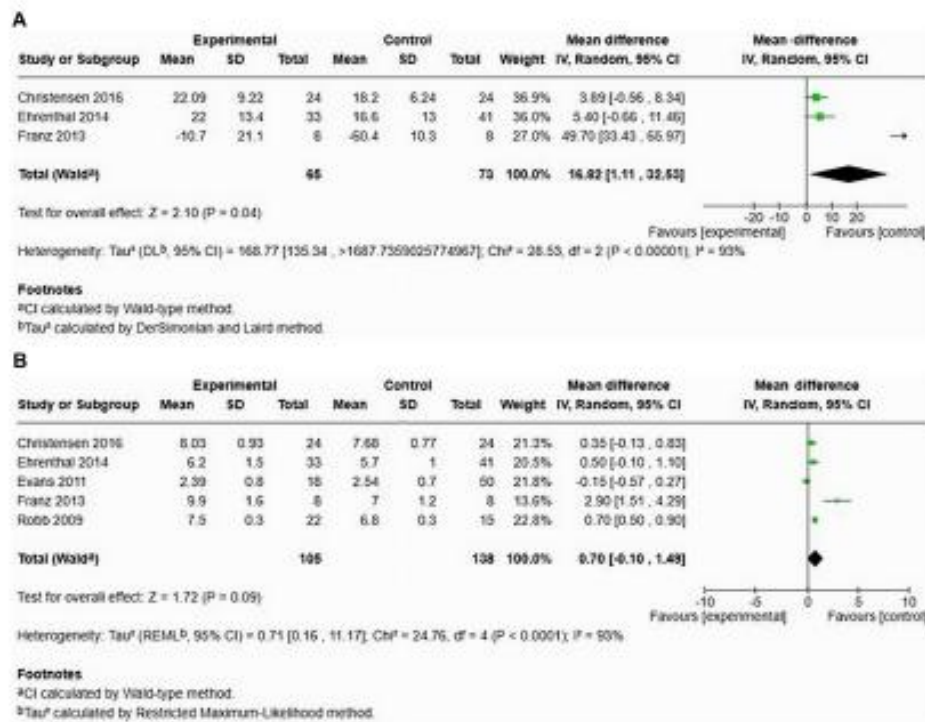


FIGURE 12
The pooled mean difference of the Aik (A) and PWV (B), of women with HDP and normotensive women in cohort studies.

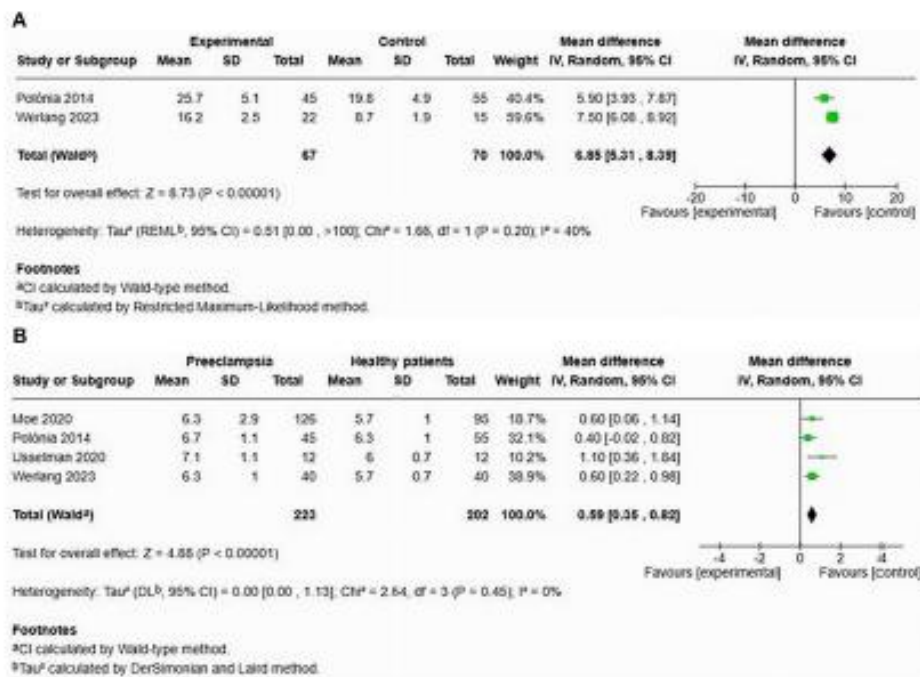


FIGURE 13
Pooled mean difference of the Aik (A) and PWV (B) of women with HDP and normotensive pregnant women in cross-sectional studies.

the absence of significant mean differences in cohort studies, alongside notable findings in cross-sectional studies, suggests that cfpWV may be a more variable measure influenced by various factors present in different study designs. The contrasting results warrant further investigation to understand better the relationship between cfpWV and HDP.

Limitations

This review had a limited number of studies, which could introduce bias. Additionally, a high level of heterogeneity was observed in most group analyses. However, assessments using the NOS revealed a low risk of bias in all studies, with the GRADE framework rating the evidence as moderate to high certainty. Furthermore, the review adhered to the PRISMA-P guidelines, and a comprehensive search was performed across several databases.

Conclusion

This systematic review and meta-analysis suggest that arterial stiffness may remain elevated for more than 6 weeks postpartum in women with a history of HDP. However, the findings should be interpreted with caution due to heterogeneity across studies and limited number of available studies. Larger and standardized longitudinal studies are needed to confirm these results. In the meantime, regular cardiovascular monitoring for these women is recommended while awaiting more conclusive evidence.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

XM: Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. SG: Writing – review &

editing. AH: Supervision, Writing – review & editing. JM: Writing – review & editing. CB: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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