HYPERTENSION DURING PREGNANCY AND FUTURE RISK OF CARDIOVASCULAR AND OTHER LONG-TERM HEALTH OUTCOMES

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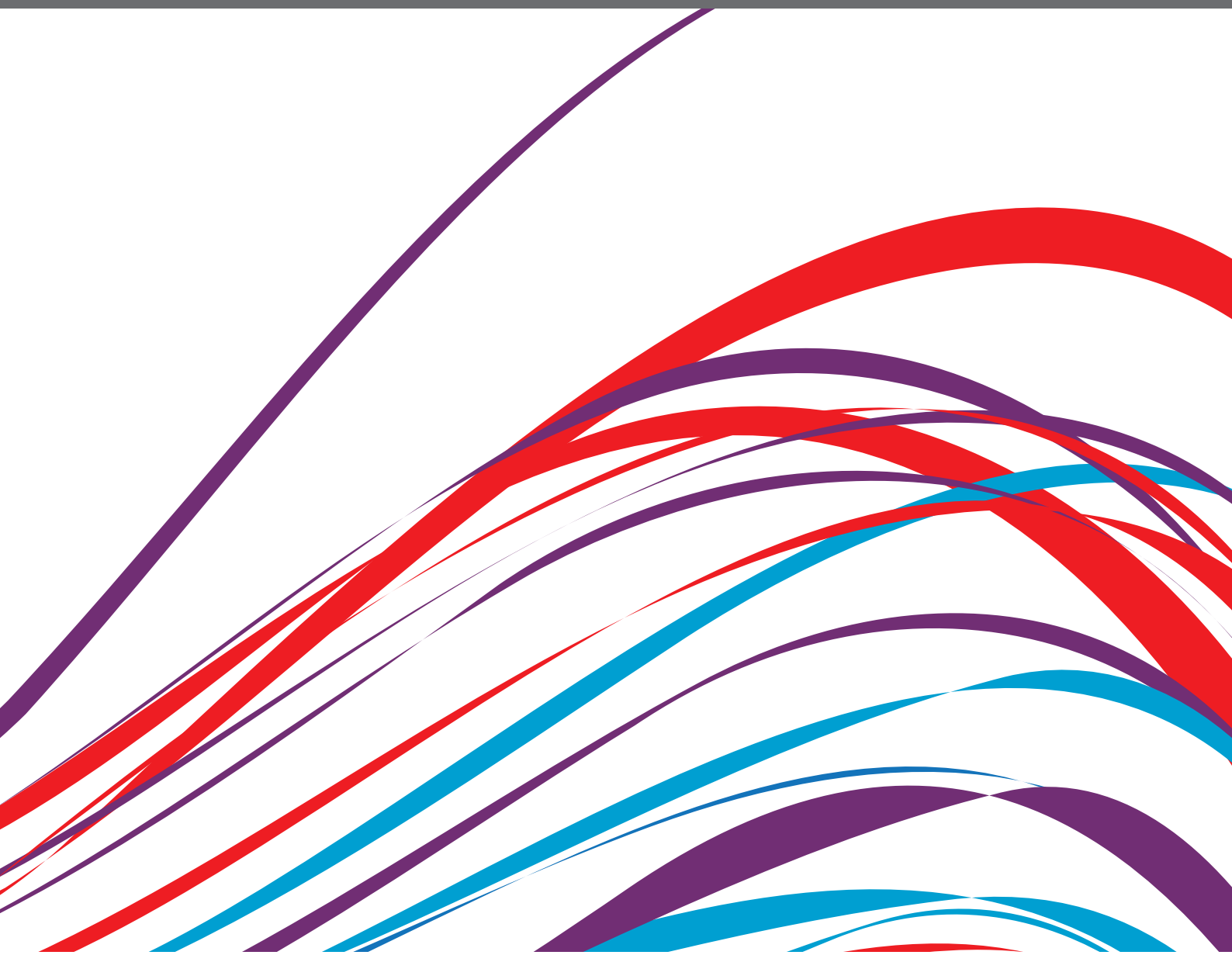

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HYPERTENSION DURING PREGNANCY AND FUTURE RISK OF CARDIOVASCULAR AND OTHER LONG-TERM HEALTH OUTCOMES

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EDITORIAL
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Editorial: Hypertension During Pregnancy and Future Risk of Cardiovascular and Other Long-Term Health Outcomes

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Keywords: preeclampsia, hypertensive disorders of pregnancy (HDP), cardiovascular disease, mental health, endothelial dysfunction, randomized controlled clinical trial (RCT), lifestyle behavior change, guidelines

Editorial on the Research Topic

Hypertension During Pregnancy and Future Risk of Cardiovascular and Other Long-Term Health Outcomes

"Hypertension during pregnancy and future risk of cardiovascular and other health outcomes" attracted a wide range of submissions across the spectrum of this topic, from consideration of underlying vascular mechanisms through to mental health, reviews of guidelines and existing intervention studies, protocols for trials in progress, and consideration of the importance of this area to low and middle income countries.

The catalyst for this special issue was the fact that mothers with hypertensive disorders of pregnancy (HDP), such as preeclampsia and gestational hypertension, have increased cardiometabolic health risks long after delivery. Melchiorre et al. remind us of the strength of the epidemiological evidence in this area, with both retrospective and prospective cohorts consistently finding 1.5–3 times increase in risk after HDP of cardiovascular conditions including essential hypertension, coronary artery disease, cerebrovascular disease, peripheral vascular disease, and heart failure. Adjustment for pre-existing risk factors attenuates but does not eliminate these relationships, which are strengthened in those who suffer early-onset or recurrent HDP.

Although the underlying mechanisms for CVD after HDP remain uncertain, Kirollos et al. provide some insights into pathophysiological links through their systematic review of vascular structure and function in preeclampsia and postpartum after preeclampsia. Collectively, the 59 included studies suggest impaired endothelial function during and after preeclamptic pregnancies compared to normotensive pregnancies, and structural abnormalities including increased carotid intima-media thickness and accelerated coronary calcification and plaque deposition. However, findings were not universal, and there was paucity of research beyond the first few years postpartum, underscoring the need for more studies in this area.

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In addition to physical sequelae of HDP, mental health is a key consideration. Roberts et al. reviewed the literature on depression, anxiety, and post-traumatic stress disorder after HDP. Their 17 included publications did not consistently find associations between HDP and mental health disorders. However, depression, anxiety, and post-traumatic symptoms trended toward increased prevalence and severity after HDP, especially in women who had given birth preterm or had preeclampsia with clinically severe features. The authors note that routine screening for mental health disorders on all women in the postpartum period may be beneficial, and with additional emphasis after HDP to alert clinicians to the need for additional follow-up and referral.

Although most literature on health after HDP is based on high-income country populations, both the acute burden of HDP and its associated maternal and neonatal mortality and morbidity, and the burden of cardiometabolic disorders, fall disproportionately on low and middle-income countries (LMICs). Nagraj et al. review the long-term health implications of cardiometabolic pregnancy complications, both HDP and gestational diabetes, in LMIC, and consider research priorities. A multi-dimensional strategy is proposed, including well-designed experimental studies of novel technologies including *mHealth* to first identify pregnancy complications and then aid follow-up postpartum to reduce long-term cardiometabolic disease burden. They also remind us of the importance of complex social factors that impact women's health across the life-course, and the importance of improving equity and access in LMIC to health interventions, including essential medications.

As it is impossible for healthcare practitioners to read all the original research on their areas of practice, guidelines and protocols are essential to summarize the evidence and provide authoritative guidance. Gamble et al. examine what current national and international guidelines have to say about HDP and subsequent cardiovascular disease. They found 16 guidelines from 2010 onwards, mostly from either obstetric or cardiology organizations/societies, that mentioned follow-up after HDP. Of these, only half provided any recommendation beyond the immediate postpartum period, recommendations varied with few details regarding appropriate frequency and timing of monitoring, and all were based on very low to moderate evidence grade. As noted by the authors, a number of research questions related to appropriate timing and nature of follow-up and interventions after HDP to prevent CVD need to be answered to improve the evidence base on which guidelines are built.

Lack of guidance on health after HDP is also noted by Roth et al., from the perspective of what the knowledge gaps of both women and healthcare providers are in this space. Their scoping review identified 12 studies, including 402 women and 1,215 healthcare providers. Most studies found that both women and healthcare providers had limited or no knowledge about links between HDP and CVD, and that when women had knowledge, this was primarily through their own sourcing of information and not from their healthcare provider. For healthcare providers, primary enablers of knowledge were the availability and awareness of guidelines, underscoring the importance of improving guidelines regarding health after HDP.

What, then, is being done to improve women's health after HDP? Lui et al., Aldridge et al., and Taylor et al. all examine various aspects of this question. Lui et al. performed a systematic review of randomized controlled trials (RCT) less than 10 years postpartum after HDP, looking for trialed interventions to reduce cardiovascular risk. Only two reported RCTs were identified, with a total of 352 women, highlighting the limited evidence for any effective intervention. There is an indication that lifestyle interventions may be effective, but further evidence is required. Four RCTs that are in progress were also identified, which will add to the evidence base once reported, including Be Healthe for Your Heart, whose protocol is published by Taylor et al. in this special issue. Their pilot RCT is evaluating, in Australian women less than 4 years post-preeclampsia, the acceptability of an online web-based lifestyle behavior change intervention aimed at supporting changes in modifiable CVD risk factors such as poor diet, physical inactivity, and excess body weight. Also in an Australian population, in a socioeconomically disadvantaged setting, Aldridge et al. are recruiting, albeit not in a randomized fashion, women after severe pregnancy complications including HDP. Women are followed up face-to-face 6 months postpartum (with planned 18-month and 5-year further follow-up), using an education and counseling model adapted from cardiac rehabilitation, and delivered by a nurse practitioner with cardiovascular expertise. They postulate this will provide both an appropriate and cost-effective follow-up model.

We hope you enjoy the breadth and depth of this issue's articles.

AUTHOR CONTRIBUTIONS

AH prepared the first draft of the editorial. DC reviewed and revised the editorial. Both authors have approved the final version.

Conflict of Interest: The work of AH is supported by a National Health and Medical Research Council (Australia) Early Career Fellowship (APP1141570) "Premature Cardiovascular Death in Women after hypertensive pregnancy: altering this trajectory." AH also receives funding in this topic area from the NSW Health Translational Research Grants Scheme. AH is a co-author on 2 of the manuscripts in this Research Topic. AH and DC have professional links to, and collaborations with, a number of authors on manuscripts included in this Research Topic. DC has received support from the British Heart Foundation, Oxford Martin School and the NIHR Oxford Biomedical Research Centre, and the views he expressed are not necessarily those of the funders. These potential conflicts of interest were declared when manuscripts were submitted and neither AH nor DC were involved in reviewing manuscripts where they had a potential conflict of interest.

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REVIEW
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Hypertensive Disorders of Pregnancy and Subsequent Cardiovascular Disease: Current National and International Guidelines and the Need for Future Research

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Background: It is well-established that hypertensive disorders of pregnancy (HDP) are associated with an increased risk of cardiovascular disease (CVD) in later life. National and International guidelines recognize this but due to a lack of research in this area few details are provided on how best to risk stratify or when and how to monitor these women.

Objectives: This article aims to summarize current guidelines in this area in order to raise awareness of need for further research in this important clinical area.

Search Strategy: A review of the published literature was carried out in August 2018 using the databases EMBASE and Medline and the websites of professional societies were searched manually using the search terms "pre-eclampsia," "hypertensive disorders of pregnancy," "management," "guidelines," "long term follow up" and "cardiovascular risk." Guidelines published in English were included and articles that provided guidance on follow up post-partum of women with HDP.

Main Results: The search identified 360 records. Of these, 16 guidelines mentioned the follow up of women with HDP; their reported years ranges from 2010 to 2018. Only 8 (50%) provided some level of recommendation for follow up beyond the immediate post-partum period. These recognized the future risk of CVD to women from HDP and provide detailed recommendations for the management of these conditions during pregnancy and in the immediate post-partum period. Guidelines recommended that women and primary care clinicians are made aware of this risk and some suggest yearly BP monitoring, and at least 5 yearly monitoring of renal functions, urinalysis and lipid profile testing alongside lifestyle modifications and control of CVD risk factors. Guidelines used a combination of meta-analysis, individual cohort studies and expert opinions to inform their recommendations.

Conclusions: There is a need for future studies of women with a history of HDP to define their trajectory for the development of CVD and candidate biomarkers in order to develop screening, risk stratification, and preventive measures to reduce the significant CV burden associated with HDP in women.

Keywords: pre-eclampsia, hypertensive disorder of pregnancy, guidelines, cardiovascular disease, cardiovascular disease in women

INTRODUCTION

Historically, hypertensive disorders of pregnancy (HDP) were believed to be self-limiting with little effect on health once blood pressure (BP) had returned to normal in the postnatal period. It is now well-established that this group of conditions, comprising gestational hypertension, pre-eclampsia and eclampsia, are associated with an increased risk of cardiovascular disease (CVD) in later life (1–3). CVD is one of the most important causes of death in women and has a huge impact on healthcare costs; in the UK the NHS spent more than £5.9 billion on heart disease between 2013 and 2014 (4).

Pre-eclampsia in particular has been shown in a number of systematic reviews and meta-analyses to impact on the health and well-being of women extending beyond pregnancy outcomes. A systematic review and meta-analysis in women with prior pre-eclampsia showed the relative risks [(95% CI) for heart failure (HF) and CVD death to be 4.19 (2.09–8.38) and 2.21 (1.83–2.66), respectively (1)]. In another systematic review and meta-analysis the relative risks (95% CI) in women with prior pre-eclampsia were 3.70 (2.70–5.05) for hypertension (HT), 2.16 (1.86–2.52) for ischaemic heart disease (IHD) and 1.81 (1.45–2.27) for stroke (2).

Some national and international guidelines recognize these future risks and recommend routine follow up of women who had suffered from HDP in order to prevent heart disease. However, due to a lack of research in this area, few details are provided on how best to do this. This article aims to summarize current guidelines in this area in order to raise awareness of this important clinical uncertainty.

Search Strategy/Methodology

A review of the published literature was carried out using the databases EMBASE (1980–2018) and Medline (1946–2018) and the websites of relevant professional societies such as The National Institute for health and Care Excellence (NICE), The European Society of Cardiology (ESC), The Institute of Obstetricians and Gynecologists of Ireland and The American college of Obstetricians and Gynecologists were hand-searched in August 2018. The search was undertaken using the search terms "pre-eclampsia," "hypertensive disorders of pregnancy," "management," "guidelines," "long term follow up" and "cardiovascular risk." All of the relevant articles returned were published between 2010 and 2018. Reference lists of identified articles were also scrutinized. Guidelines published in English (or with English translation) were included. Articles that provided guidance on follow up of women with HDP post-partum period were selected. The relevant data were collected from the published full text. Databases were last searched on 5th August 2018. The Prisma flow chart for guideline inclusion is shown in **Figure 1**.

Summary tables of identified guidelines were developed to outline details on referral to specialist teams, recommendations for investigations, monitoring frequency and follow up time and any other recommendations for risk factor modification or preventative actions. The guidance was also scrutinized for the level of evidence upon which these recommendations were based and assigned a final grade for the quality of evidence as "high," "moderate," "low," or "very low" based on the strength and quality of underlying evidence for the critically important outcomes based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) principles. This is also summarized.

RESULTS

Guidelines were summarized in **Table 1**, their recommendations were divided specialist referral, recommendations for investigations and monitoring frequency and follow up time and risk factor modification and other preventative actions. The graded level of underlying evidence was also specified. The search identified 360 records. Of these, 16 guidelines mentioned the follow up of women with HDP; their reported year ranges from 2010 to 2018. Only 8 (50%) provided some level of recommendation for follow up beyond the immediate post-partum period.

Summary of Guidelines

UK

The National Institute for health and Care Excellence (NICE) have issued clinical guideline 107 in 2011, titled Hypertension in pregnancy: diagnosis and management (5). This guideline provides detailed recommendations for the diagnosis and management of HDP during the pregnancy, intrapartum and immediate post-partum period. The guidance for follow up and ongoing intervention following discharge is focused specifically on those women who remain hypertensive or on hypertensive medication. For these women, it recommends that information should be provided to primary care including who will provide medical review, frequency of BP monitoring and thresholds for reducing or stopping treatment, although no specific details are given. It also provides guidance on frequency of post-natal and medical reviews for women who remain hypertensive and suggests hematological and biochemical monitoring for those with deranged blood tests on discharge or those who remain

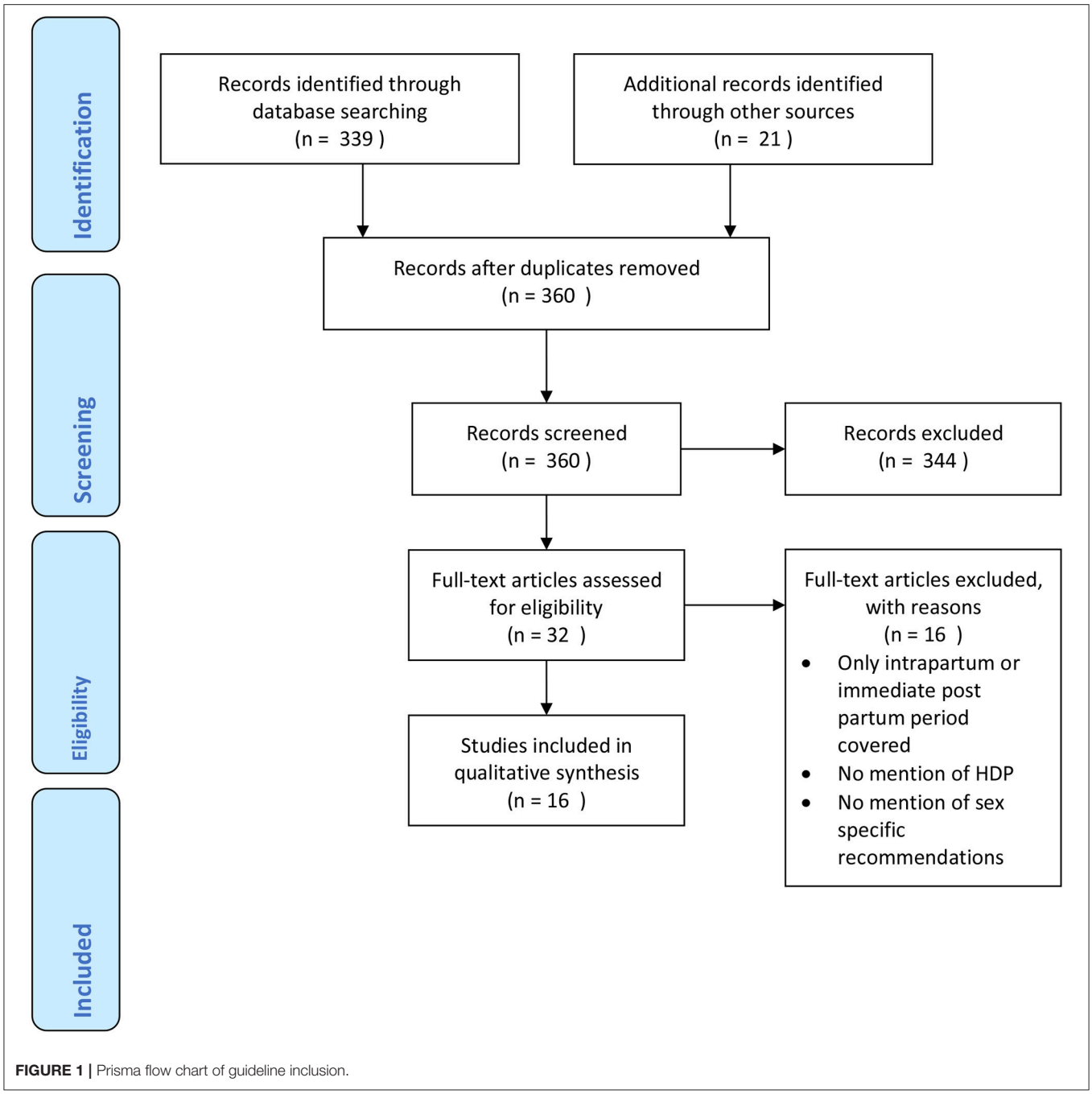

FIGURE 1 | Prisma flow chart of guideline inclusion.

proteinuric. It states that women who have had pre-eclampsia should be offered a medical review at the 6–8 week postnatal review, those who are still on antihypertensive treatment 2 weeks after discharge should be offered a medical review and those who still need antihypertensive treatment at the postnatal review should be offered a specialist assessment of their hypertension. However, whilst this guideline states that women who have had gestational hypertension or pre-eclampsia should be informed along with their primary care physicians that these conditions are associated with an increased risk of developing hypertension and its complications in later life, no details are provided on how to monitor these women once they are off their antihypertensive medication and their BP has normalized. It does nonetheless recommend that women with a history of pre-eclampsia who have no proteinuria and are normotensive at the postnatal review require no further renal follow-up or thrombophilia screening and that they should maintain a BMI between 18.5 and 24.9 kg/m^2, in line with NICE clinical guideline 43 titled Obesity prevention (22). NICE used a combination of individual observational cohort and case control studies to inform their recommendations. NICE are currently updating their recommendations in this guideline including their advice

TABLE 1 | Summary of international guidelines with the level of evidence for individual recommendations.

Guideline	Year	Specialist referral (graded level of evidence)	Recommendations for Investigations and monitoring frequency and follow up time (graded level of evidence)	Risk factor modification and other preventative actions (graded level of evidence)	Quality of evidence (based on GRADE principles)
National Institute for health and Care Excellence (NICE) clinical guideline 107 (5).	2011	Those who have no proteinuria and are normotensive at the postnatal review require no further renal follow-up (2^b).	Thrombophilia screening is not indicated (2^a).	Women should be told, along with their primary care physicians, that these conditions are associated with an increased risk of developing CVD (3a–)*1. Women should maintain a BMI between 18.5 to 24.9 kg/m2, in line with NICE clinical guideline 43 (2^b).	Moderate.
National Collaborating Center for Women's and Children's Health (UK). Hypertension in Pregnancy: The Management of Hypertensive Disorders During Pregnancy (6).	2010	Not specified.	Further follow-up is necessary but unsatisfactory evidence to support recommendations on frequency of follow up or BP monitoring (3^a).	Inform women and their primary care clinicians of the possibilities of developing high BP and its complication in the future (3a).	Low.
ESC/ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) (7).	2018	Not specified.	Recommends annual visits to a primary care physician for BP checks and to check other metabolic factors (2^a). Recommends long-term specialist follow-up.	Previous hypertension in pregnancy or pre-eclampsia should be part of a clinical history. Lifestyle modifications are indicated to reduce future cardiovascular risk (2^a).	low.
The European Society of Cardiology guideline on the management of cardiovascular diseases during pregnancy (8).	2011	Not specified.	Regular BP monitoring and control of metabolic risk factors (3a-)*4.	Lifestyle changes to minimize difficulties in future pregnancies and reduce the possibilities of developing cardiovascular disease in the future (2a–)*5.	Low.
Institute of Obstetricians and Gynecologists Ireland Clinical Practice guideline No. 3 (9).	2016	All patients with severe pre-eclampsia to be offered hospital follow-up within 12 weeks of delivery (5).	Blood pressure and proteinuria assessment should be carried out and specialist referral made if there is ongoing hypertension, need for antihypertensives or significant proteinuria (5).	Discuss potential risk factors such as obesity and aspirin therapy (5).	Very low.
Institute of Obstetricians and Gynecologists Ireland Clinical Practice guideline No. 37. (10).	2016	Further care after 6 weeks for any ongoing pregnancy related changes, in particular chronic high blood Pressure, ongoing need for antihypertensives, high BMI or incidence of pre-term pre-eclampsia (5). Provide expert review if still on antihypertensive medicines by 6–8 weeks (5).	Yearly BP and standard cardiovascular risk assessment including serum lipids and blood glucose (5). Women with persistent hypertension should undergo treatment and investigation in line with standard protocols (5).	Psychotherapy for women with history of had hypertensive disorders in pregnancy to promote their well-being and lifestyle advice including avoiding smoking, maintaining a healthy body mass, engaging in regular exercise and maintaining a balanced diet (5).	Very low.
Hypertension and Pregnancy: expert consensus statement from the French Society of Hypertension, an affiliate of the French Society of Cardiology (11).	2017	Women should be reviewed by a consultant to ensure that CVD and renal disease risk factors are identified and controlled (2^a). Assessment and management of all CVD and renal risk factors should be offered to all women via a multidisciplinary care-plan (2^a).	Women with a known past medical history of high BP during pregnancy should undergo BP (3^a), renal function and urinalysis monitoring (2^a).	Highlights the importance of a multi-disciplinary approach in monitoring and ensuring a healthy life style and modulation of CVD risk factors (5). Women should be provided with information concerning the possibilities of developing high BP and its complication in the future (3^a).	Low.

(Continued)

TABLE 1 | Continued

Guideline	Year	Specialist referral (graded level of evidence)	Recommendations for Investigations and monitoring frequency and follow up time (graded level of evidence)	Risk factor modification and other preventative actions (graded level of evidence)	Quality of evidence (based on GRADE principles)
Promoting Risk Identification and Reduction of Cardiovascular Disease in Women Through Collaboration With Obstetricians and Gynecologists: A Presidential Advisory From the American Heart Association and the American College of Obstetricians and Gynecologists (12).	2018	Recommendations are given for all women and not specific to those with HDP.	Blood pressure should be checked yearly for those ≥40 years or those with increased risk for high blood pressure (including HDP) (2^{a}).	Recommendations are given for all women and not specific to those with HDP.	Low.
ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines (13).	2017	Not specified.	No evidence that blood pressure thresholds, blood pressure targets, treatment choices or antihypertensive combinations should differ in women compared to men (1^{a}).	Not specified.	Moderate.
The American College of Obstetricians and Gynecologists Task Force on Hypertension in Pregnancy (14).	2013	Not specified.	Yearly BP and risk factor monitoring (such as lipids, fasting blood glucose and BMI) suggested for women with medical history of recurrent pre-eclampsia and pre-term pregnancy (<37 weeks) (5).	Women should maintain a healthy lifestyle in terms of maintaining an optimum body weight, consuming a diet high in fiber, fruit and vegetables and low in fat and avoid tobacco (5). Evaluate the future risk of cardiovascular disease (2^{a-})*6.	Very low.
Effectiveness Based Guidelines for The Prevention of CVD in Women: A Guideline From the American Heart Association (15).	2011	Women should be referred post-partum to a primary care physician or cardiologist to aid future care plan and manage risk factors (3^{a-})*1.	Not specified	Emphasizes the need for female-based guidelines (5). Hypertensive disorders of pregnancy should be part of a detailed cardiovascular history (3^{a-})*1.	Very low.
The Association of Ontario Midwives clinical practice guideline 15 (16).	2012	Thorough examination post-partum period within 4 weeks and further post-partum visits or clinician consultation if clinical manifestations of HDP beyond 4 weeks (3^{b}). Communication between clinicians and community healthcare providers on future blood pressure care (3^{a}).	Not specified	Inform women of their risk of developing pre-eclampsia in future pregnancies and Information about hypertensive disorders of pregnancy should be passed onto primary care physicians (3^{a-})*3. Dietary and lifestyle changes—exercise activity, reducing fat and salt intake to reduce high BP at the later life recommended for pregnant women (5).	Very low.
The Guidelines for the Prevention of Stroke in Women, a Statement for Healthcare Professionals from the American Heart Association and American Stroke Association (17).	2014	Review all women from 6 TO 12 months post-partum and menopausal women and record history of preeclampsia/eclampsia as a risk factor (3a–)*7.	Lipids levels should be tested (1c–*8).	Evaluate and treat for cardiovascular risk factors such as high BP (3a–*7), overweight women, smoking and elevated lipids levels (1c-)*8.	Moderate.

(Continued)

TABLE 1 | Continued

Guideline	Year	Specialist referral (graded level of evidence)	Recommendations for Investigations and monitoring frequency and follow up time (graded level of evidence)	Risk factor modification and other preventative actions (graded level of evidence)	Quality of evidence (based on GRADE principles)
Society of Obstetricians and Gynecologists of Canada Clinical Practice Guideline 307 (18)	2014	Referral to internal or renal medicine should be considered in women with refractory post-partum hypertension or indicators of renal disease beyond 3–6 months (3[a]).	Women with underlying hypertension or persistent postpartum hypertension should undergo urinalysis, renal function and electrolytes, fasting glucose, fasting lipids and 12-lead electrocardiography at least 6 weeks post-partum (3a). Women who are normotensive at discharge may benefit from assessment of cardiovascular risk factors and women with a history of severe pre-eclampsia should be screened for underlying hypertension or renal disease (2[a])	All women who have had a hypertensive disorder of pregnancy should maintain a healthy diet, lifestyle and BMI (2[a])	Low.
The SOMANZ Guideline for the Management of Hypertensive Disorders of Pregnancy (19)	2014	Not specified	Women should have an annual BP check and 5 yearly assessment of CVD risk factors including serum glucose and lipid profiles (5)	Women would benefit from a healthy lifestyle that included a healthy weight, not smoking, exercise and a healthy diet (3a−)*2.	Very low.
The Queensland Maternity and Neonatal Clinical Guidelines Program Guideline No. MN10.13.V4-R15 (20)	2010	Not specified	Women should be screened for pre-existing hypertension and underlying renal disease (2a) Cardiovascular risk factors (e.g., BP, lipid profile and serum glucose) should be assessed regularly with patient-centered follow up time (3[a]).	Post-natal counseling should include consultation on risk factors and preventative therapies such as calcium supplementation and low dose aspirin (3[a]). Women should maintain a healthy lifestyle in terms of diet, exercise and avoidance of tobacco (3[a] − *9).	Low.

Minus plus [*] indicated were there are issues with scoring the level of evidence as listed below such as heterogeneity/or has stated below.

*[*1] Heterogeneity $I^2 = 62.6\%$ for increased risk of future hypertension with evidence of small study projecting larger effects size. Low heterogeneity for Stroke = $I^2 = 0\%$ for Stroke (no evidence of small study bias $P = 0.82$) and IHD and $I^2 = 27.1\%$ (no evidence of small study bias $P = 0.59$). More recent paper in 2008 uses Systematic review on cohort with two additional cohorts and case control studies and scores heterogeneity I^2 scores ranging from 35.7 to 66.3%. Evidence also measures the severity of pre-eclampsia and CVD Risk using meta regression.*

*[*2] Similar papers on meta-analysis/systematic review used on lifestyle factors as annotated 1.*

*[*3] Same papers used as evidenced for annotated 1.*

*[*4] One of the evidence used focuses on maternal placental syndrome/poor fetal growth and no measurement on weight and HBP to reduce bias on obese women.*

*[*5] Systematic reviews examined for both randomized and large prospective cohort studies.*

*[*6] Clear evidence with pre-eclampsia and future CV, however the significance and applicable stages are not established.*

*[*7] Case control Dutch study and Cohort/systematic reviews similar papers as annotated 1.*

*[*8] Lipids in obese women doesn't have a clear focus on pregnant women.*

*[*9] Referenced Somanz guideline as per annotated 2, same evidence applies as annotated 1.*

Level of evidence 1:

1a,Systematic reviews (with homogeneity) of randomized controlled trials;1b,Individual randomized controlled trials (with narrow confidence interval); 1c, All or none randomized controlled trials;2a, Systematic reviews (with homogeneity) of cohort studies; 2b, Individual cohort study or low quality randomized controlled trials (e.g., <80% follow-up);2c, "Outcomes" Research; ecological studies; 3a, Systematic review (with homogeneity) of case-control studies; 3b, Individual case-control study; 4, Case series (and poor-quality cohort and case-control studies); 5, Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles;" (21).

on follow up care after transfer to community care. This updated guidance is expected to be published in June 2019. The specific recommendation in HDP have not been made available at the time of writing.

In 2010, The National Collaborating Centre for Women's and Children's Health (UK) issued a guidance titled "Hypertension in Pregnancy: The Management of Hypertensive Disorders During Pregnancy" (6). This echoes NICE CG 107 by recommending women and their primary care doctors to be informed of the future CVD risk. It highlights that there is insufficient evidence for practitioners to provide recommendations on the frequency of follow up. These Guidelines used meta-analysis from Bellamy et al. (2) and Macdonald et al. (3) for their recommendations as well as cohort studies by Wilson et al. (23).

Europe

In 2018 the ESC issued guidelines for the management of arterial hypertension (7). This recommends annual visits to a primary care physician for BP checks and to other metabolic risk factors. It also suggests previous hypertension in pregnancy or pre-eclampsia should be part of a clinical history and lifestyle modifications are indicated to reduce the risk of CVD in the future.

The ESC has issued guidance on the management of CVDs during pregnancy (8). Beyond the immediate post-partum period, it recommends lifestyle modifications, regular BP review and control of metabolic factors to mitigate maternal cardiovascular risk in the future. These Guidelines used meta-analysis from Macdonald et al. (3), cohort studies from Wilson et al. (23) and the Effectiveness-based guidelines for the prevention of CVD in women —2011 update: a Guideline from the American Heart Association as the basis for their recommendations.

The Institute of Obstetricians and Gynaecologists of Ireland have issued clinical practice guideline no. 3 in 2016, titled Diagnosis and management of severe pre-eclampsia and eclampsia (9). Again, their recommendations post-partum focuses on the immediate management of women with ongoing hypertensive needs, recommending BP monitoring every 1–2 days for up to 2 weeks after discharge until antihypertensive treatment has been discontinued and the patient is normotensive. It does suggest that, all patients with severe pre-eclampsia should be offered an appointment in secondary care within 3 months of delivery. Interestingly, the Institute of Obstetricians and Gynaecologists of Ireland provides little specific details. Other assessments, such as BP and proteinuria should also be performed. This includes referral to specialist services if antihypertensive treatment is ongoing and required or proteinuria is confirmed. It echos the NICE guidelines with regards to information that should be provided to primary care following discharge. The same institution issued The Clinical Practice Guideline no. 37 in 2016, titled the management of hypertension in pregnancy (10); this recommends that follow-up after 6 weeks post-partum is required to ensure resolution of pregnancy-related changes and to determine the need for ongoing care. It suggests those at high risk of ongoing hypertension include those with chronic hypertension, prolonged anti-hypertensive treatment, higher maximum BPs during pregnancy, higher BMI and those with pre-eclampsia that occurred preterm. Women with persistent hypertension not previously assessed should undergo routine work-up and be given advice regarding future lifestyle and optimization of risk factors in subsequent pregnancies. This includes those who are obese, have other cardiovascular risk factors, secondary hypertension or end-organ disease. They gathered evidence from Health professionals' opinions for their specialist referral, recommendations, risk factor modification, and other preventative actions.

The French Society of Hypertension, an affiliate of the French Society of Cardiology, issued an expert consensus statement on hypertension and pregnancy in 2017 (11). This recommends that, women with pre-eclampsia should be reviewed by a consultant to ensure CVD and renal disease risk factors are identified and controlled. It highlights that, regular monitoring, healthy life style, and modulation of CVD risk factors is essential to reducing CVD in the future. It also recommends communicating effectively to the patient. It suggests that, women who have had a hypertensive disorder of pregnancy should have the etiology of the disease assessed and undergo BP, renal function and urinalysis monitoring. They should also undergo long term BP monitoring, even after their BP has normalized post-delivery. They derived evidence from meta-analysis of observational studies by Bellamy et al. (2) as well as from Health professionals' opinions for their recommendations.

North America

In 2017 the American College of Cardiology/American Heart Association task force on clinical practice guidelines issued guidance on the prevention, detection, evaluation, and management of high blood pressure disorders in adults (13). This stated that there was no evidence that blood pressure thresholds, blood pressure targets, treatment choices, or antihypertensive combinations should differ in women compared to men but mentioned little else specific to women or HDP.

The American Heart Association and the American College of Obstetricians and Gynecologists have issued guidance titled "Promoting Risk Identification and Reduction of Cardiovascular Disease in Women Through Collaboration With Obstetricians and Gynecologists: A Presidential Advisory From" in 2018 (12). This recognizes the need for sex specific guidelines targeted to women. It provides recommendations for cardiovascular prevention including management for monitoring of hypertension, hyperlipidaemia, diabetes, and healthy lifestyle advice. However, despite listing HDP as an important risk factor for future CVD, specific recommendations for those who have suffered HDP are not provided other than yearly blood pressure checks with an increased risk for high blood pressure (including those who have suffered HDP). These recommendations are based on US Preventive Services Task Force final recommendation statement for high blood pressure in adults, which itself is based on evidence synthesis of systematic reviews of observational studies.

The American Heart Association issued a guideline in 2011 titled effectiveness-based guidelines for the prevention of CVD in women (15). This emphasizes the need for female based guidelines and an individualized approach to managing cardiovascular risk in women. In this guideline, a history of pre-eclampsia or pregnancy-induced hypertension puts women in a high risk category for CVD and it goes on to say that pregnancy provides an opportunity to estimate a woman's future cardiovascular risk, for which pre-eclampsia may be an early indicator. The guideline also states that women should be referred post-partum to a primary care physician or cardiologist to monitor and control cardiovascular risk factors and that HDP should be part of a detailed cardiovascular history in any setting. Whilst the guideline recognizes the building evidence base that pre-eclampsia is an important cardiovascular risk factor and acknowledges the need for future research in this field, it does not provide any details on how to monitor or determine the effectiveness of diagnostic and preventive interventions in this critical group. They used meta-analysis of observational studies such as Bellamy et al. (2) as the underlying evidence for their recommendations.

The American college of Obstetricians and Gynaecologists Task Force on Hypertension in Pregnancy issued a guidance titled hypertension in pregnancy in 2013. This states that pre-eclampsia, particularly if associated with pre-term delivery, is a strong risk factor for CVD. It recommends that, women should maintain a healthy lifestyle in terms of maintaining an optimum body weight, consuming a diet high in fiber, fruit and vegetables, and low in fat and to avoid tobacco. Furthermore, it states that future CVD risk factors should be considered and provides no further details regarding the timing and frequency of these evaluations. They gathered evidence from Health professionals' opinions for their recommendations on specialist referral, risk factor modification, and other preventative actions.

The Guidelines for the Prevention of Stroke in Women, a Statement for Healthcare Professionals from the American Heart Association and American Stroke Association in 2014 (17) recognizes the link between pre-eclampsia or eclampsia and CVD and stroke outcomes. It states that, "insufficient evidence exists to inform any recommendation for screening, prevention, or treatment in women with a history of pregnancy complications or adverse pregnancy outcomes." It does however suggest that those women with ongoing hypertension should be managed according to adult guidelines. It also recommends women with a history of pre-eclampsia or eclampsia should have this documented as a risk factor and that these women should have common CVD risk factors (including smoking and dyslipidaemia) identified and treated. These guidelines used evidence from meta-analysis of cohort studies including Macdonald et al. (3) for their recommendations as well as the Wilson et al. (23) cohort study.

The Association of Ontario Midwives issued clinical practice guideline 15 in 2012, titled HDP (16). This recommends that, midwives discuss the need for healthy lifestyle choices with women post-delivery and provide information on HDP to primary care physicians. They gathered evidence from systematic reviews of observational studies including Bellamy et al. (2) and Macdonald et al. (3) as well as Health professionals' opinions for the specialist referral, recommendations, risk factor modification, and other preventative actions.

The Society of Obstetricians and Gynaecologists of Canada issued clinical practice guideline 307 titled Diagnosis, Evaluation, and Management of HDP in 2014 (18). This echos NICE clinical guideline 107 by providing details on review frequency, treatment options and BP targets for the immediate 6 weeks period post-partum. It provides some guidance on ongoing care beyond 6 weeks, which again focuses predominantly on those still requiring hypertensive medication or those with persistently raised BP or deranged renal function. It states that women with a history of severe pre-eclampsia should be screened for underlying hypertension or renal disease and that referral to internal or renal medicine should be considered in those women with refractory post-partum hypertension or indicators of renal disease (e.g., proteinuria) beyond 3–6 months. It reveals that, those women with underlying hypertension or persistent postpartum hypertension should undergo urinalysis, renal function and electrolytes, fasting glucose, fasting lipids and 12-lead electrocardiography at least 6 weeks post-partum. It also reveals that, women who are normotensive at discharge may benefit from assessment of cardiovascular risk factors and all women who have had a hypertensive disorder of pregnancy should maintain a healthy diet, lifestyle, and BMI. These guidelines used a blend of individual observational cohort and case control studies to inform their recommendations.

Australia and New Zealand

The SOMANZ Guideline for the Management of HDP published by the Society of Obstetric Medicine of Australia and New Zealand in 2014 (19). This recommends that, women would benefit from a healthy lifestyle which includes: a healthy weight, smoking cessation program, exercise and a healthy diet. It also recommends that, these women should have an annual BP check and 5 yearly assessments of CVD risk factors including serum glucose and lipid profiles. The SOMANZ guidelines used a literature review as their evidence for lifestyle recommendations, the literature review referenced Bellamy et al. (2) meta-analysis as their evidence. They also used expert opinions to develop their recommendations.

The Queensland Maternity and Neonatal Clinical Guidelines Program issued Guideline No. MN10.13.V4-R15 in 2010, titled HDP (20). This recommends women to undergo screening for pre-existing hypertension and underlying renal disease, cardiovascular risk factors (e.g., BP, lipid profile, and serum glucose) and the necessity of women regularly assessed. According to them, women should also maintain a healthy lifestyle with their diet choice, exercise, and avoid tobacco. The Queensland Maternity and Neonatal Clinical Guidelines recommendations for investigations and monitoring BP used The National Collaborating Centre (NCC) 2011 revised version; The NCC referenced Bellamy et al. (2)'s work, to support their recommendations.

DISCUSSION

This is the first summary of current international guidelines evaluating long term follow up for women who have suffered HDP. Whilst all guidelines recognize the higher risk of CVD in those with these conditions, and in the most part recommend informing women and their general practitioner or family doctors (GPs) of this, there is no consensus regarding who to monitor intensively, for how long or how frequently and what parameters should be used for screening initially and perhaps at a future at risk period. Guidelines issued by obstetrics and gynecological societies focus on the management and identification of HDP during pregnancy and the immediate postpartum period. Few details are given regarding timing and frequency of monitoring, appropriate physical, and biomarkers for longer term monitoring or strategies for the prevention of CVD in later life. Guidelines issued by cardiological societies are more explicit with some recommending yearly BP monitoring, and at least 5 yearly renal functions, urinalysis and dyslipidaemia testing. Some also recommend lifestyle modifications to achieve a healthy weight, smoking cessation, and control of glucose and lipid profiles. The most detailed recommendations for future follow up comes from the ESC, Institute of Obstetricians and Gynecologists Ireland, The American College of Obstetricians and Gynaecologists, the American Heart Association and The SOMANZ Guidelines. They recommend up to yearly BP monitoring and yearly assessment of CVD risk factors. These guidelines used the highest available level of evidence from meta-analysis as well as specialist opinions from healthcare professionals to inform their recommendations. Interestingly, the ESC guidelines also make reference to the use of N-terminal pro-B natriuretic peptide (NT-proBNP) as part of an investigative work up for patients with hypertensive emergencies, including pre-eclampsia. NT-proBNP has been shown to be strongly related to cardiovascular events (24). Measurement of such biomarkers in women with prior HDP needs further evaluation as a potential predictor or tool to risk stratify for future cardiovascular events.

Guidelines used a variety of levels evidence to inform their recommendations. Many sited expert opinions as their underlying evidence; including The Institute of Obstetricians and Gynaecologists Ireland Clinical Guidelines 2010 and 2016 and The American College of Obstetricians and Gynaecologists Task Force on Hypertension in Pregnancy (14). The report from the American College of Cardiology (2017) used prospectively designed overviews of randomized trials. The ESC and the European Society of Hypertension (ESH) used retrospective cohort studies for their recommendations. The Society of Obstetricians and Gynaecologists Canada Clinical Practice Guideline 307 (2014) and NICE (2011) used a blend of individual observational cohort and case control studies as underlying evidence to their recommendations. A number of guidelines referenced the meta-analysis of Bellamy et al. (2), Macdonald et al. (3) and cohort studies by Wilson et al. (23). These included the French Society of Cardiology (2017), the American Heart Association (2011), The Association of Ontario Midwives Clinical Practice (2012), the SOMANZ guidelines and The Queensland Maternity and Neonatal Clinical. Whilst a number of guidelines used the highest available evidence, namely the meta-analysis of observational studies by Bellamy et al. (2) and Macdonald et al. (3) these studies focus primarily on describing the association between HDP and future CVD risk. There is still little high level evidence on how or when to initiate follow up on these women and no evidence on the effectiveness of recommended strategies in this unique patient population. This clinical area falls between obstetrics and gynecology and cardiology and general practitioners are perhaps best placed to follow up these high risk women once they are discharged into the community following the birth of their baby.

This article has a number of strengths. We have systematically reviewed all current English language guidelines on this subject, capturing the majority of major international guideline committees, and it is clear that there is an overwhelming paucity ofrecommendations for how to manage women with previous HDP going forward into later life.

This article has limitations that should be discussed. We have only included English language guidelines and it is possible that guidelines exist in other languages. Nonetheless, as we have captured the major international guideline committees on this subject it is unlikely that the guidelines that exist will change the overall conclusions of this article. As this is a review of clinical guidelines not clinical practice, it is possible that individual centers have their own protocols and clinical strategies not captured here. However, this is a novel and expanding area and it is likely most clinical centers will be influenced by these guidelines. It is possible that guidelines are influenced by the opinions and clinical experience of the guideline development group and not just the available objective evidence. However, we have captured large globally influential guideline groups and their opinions should be considered relevant and expert on this subject.

We have systematically searched for guidelines published in peer reviewed journals and by major professional societies using transparent inclusion and exclusion criteria agreed *a priori*. However, these were limited to English language publications or translations only. We have summarized the relevant guidance from the clinical guidelines and evaluated the evidence underpinning the recommendations. This process has highlighted gaps and uncertainties in clinical guidance on how to manage women who have had HDP in the longer term in order to monitor and mitigate their risk of CVD. Further research needs to address the following clinical questions:

- When should we start to monitor women with HDP after being discharged in the community following normalization of their BP?
- When and how frequently should women with HDP be monitored if their BP has returned to normal?
- What investigations should form part of their monitoring to maximize the chance of early detection of CVD risk?
- What interventions are effective in reducing the risk of subsequent CVD in women with HDP?

Once we have accumulated the evidence base from robust research, clinical guidelines should follow. Clinical guidelines are important in changing practice and behavior (25) provided they are consistent and based on clear evidence.

CONCLUSION

Whilst these guidelines recognize the future risk to women from HDP and deal appropriately with management of these conditions during pregnancy and in the immediate period post-partum there is a paucity of recommendations for how to manage these women going forward. There is a need for high quality studies of women with a history of HDP to define their trajectory for the development of CVD and then to develop screening, risk stratification, and preventive measures.

AUTHOR CONTRIBUTIONS

PM and SB conceived the study. Articles were searched by DG and BB. DG and BB drafted the paper and all of the authors contributed in writing and reviewing the paper.

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Be Healthe for Your Heart: Protocol for a Pilot Randomized Controlled Trial Evaluating a Web-Based Behavioral Intervention to Improve the Cardiovascular Health of Women With a History of Preeclampsia

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Background: Women with a history of preeclampsia are at greater risk of cardiovascular disease (CVD) related morbidity. Despite this knowledge, there is a lack of interventions available for women with a history of preeclampsia for the prevention of CVD. The aim of this pilot randomized controlled trial (RCT) is to determine the acceptability and preliminary efficacy of a web-based behavioral intervention targeted to women with a history of preeclampsia (Be Healthe for your Heart).

Method: Australian women aged 18–45 years, with a recent history (≤4 years post diagnosis) of preeclampsia will be recruited for a 3-months, 2-arm parallel group pilot RCT. Participants will be randomized into 2 study arms: (1) Be Healthe for your Heart or; (2) Control, with assessments conducted at baseline, and after 3-months. Be Healthe for your Heart is an intervention delivered online via the program website, with weekly emails to support changes in modifiable CVD risk factors (excess body weight, physical inactivity, poor diet, and stress), using behavior change techniques (e.g., self-monitoring, goal setting). Intervention acceptability (satisfaction, usability, appropriateness, and usage) and impact on absolute full CVD 30-years risk score, CVD risk markers, and modifiable risk factors will be assessed.

Discussion: No studies to date have evaluated acceptability and preliminary efficacy of a web-based intervention for the prevention of CVD in this high-risk population with preeclampsia. This pilot trial will inform development of a fully powered RCT if acceptability and preliminary efficacy are demonstrated.

Keywords: cardiovascular disease, preeclampsia, post-partum, health behavior, women, prevention

INTRODUCTION

Preeclampsia is a complex medical disorder in pregnancy, resulting in hypertension and multi-organ dysfunction (1). Globally, preeclampsia affects ∼2–8% of pregnancies per year (2), including 3% of pregnancies in Australia (3). There is increasing evidence that preeclampsia influences women's long-term cardiovascular health. A recent meta-analysis of 22 studies including more than 6.4 million women, found that preeclampsia was significantly associated with future risk of heart failure [Relative Risk (RR): 4.19, 95% Confidence Interval (CI): 2.09–8.38], coronary heart disease (RR: 2.50, 95% CI: 1.43–4.37), cardiovascular disease (CVD) mortality (RR: 2.21, 95% CI 1.83–8.26), and stroke (RR: 1.81, 95% CI: 1.29–2.55) (4). Other systematic reviews support this evidence of increased risk of CVD among women with a history of preeclampsia (5–7).

Current clinical guidelines acknowledge that preeclampsia is a primary CVD risk factor. For example, the 2018 Multi-society Guideline on the Management of Blood Cholesterol (8), list a history of preeclampsia as a key risk factor. The Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) Guideline for the Management of Hypertensive Disorders of Pregnancy (9), also acknowledges hypertension and CVD as potential long-term consequences of preeclampsia. The guidelines recommend counseling women post pregnancy regarding key modifiable risk factors for CVD (e.g., excess body weight, physical inactivity, poor diet), along with annual blood pressure monitoring, and a minimum of 5-yearly assessments of serum lipids and blood glucose.

Many women with a history of preeclampsia remain unaware that preeclampsia influences their lifetime cardiovascular health, and few are receiving the recommended monitoring and advice. An Australian survey of 127 women who had been diagnosed with preeclampsia within the last 2 years found 34.1% were unaware of their increased risk of CVD (10). While 94.5% of the entire sample reported recent monitoring of their blood pressure, < half (40.5%) reported monitoring of their serum lipids and/or blood glucose (40.9%), and <25% had received advice on modifiable CVD risk factors (10).

To date, limited research has evaluated the efficacy of different intervention approaches addressing cardiovascular health post pregnancy for women with a history of preeclampsia. To the authors' knowledge there has been one recent trial published from the United States (11) and another currently underway in Australia (12). Therefore, the aim of this pilot randomized controlled trial (RCT) is to determine the acceptability and preliminary efficacy of a web-based lifestyle behavioral intervention targeted to women with a recent history of preeclampsia (Be Healthe for your Heart). The study will:

1. Evaluate intervention acceptability (satisfaction, usability, appropriateness, and usage).
2. Estimate intervention impact on absolute full CVD 30-years risk score, CVD risk markers (body fat percentage, body mass index (BMI), waist circumference, blood pressure and blood lipids, and glucose), health behavior risk factors (dietary intake, physical activity, and stress) and general health and well-being, from pre to post-intervention compared with the control group.

MATERIALS AND METHODS

Study Design and Setting

Be Healthe for your Heart is a 3-months, 2-arm parallel group pilot RCT which is being undertaken at The University of Newcastle, New South Wales (NSW), Australia. Participants will be randomized into two study arms: (1) Be Healthe for your Heart or (2) Control, with assessments conducted at baseline and after 3-months. The study was prospectively registered with the Australian New Zealand Clinical Trials Registry (ANZCTR): 12618001528246. The template for intervention description and replication (TIDieR) checklist and guide (13) and the CONsolidated Standards of Reporting Trials (CONSORT) extension for randomized pilot and feasibility trials 2010 checklist (14) were applied for the reporting of this study. The funding bodies have no role in the design, conduct or reporting of the trial.

The pilot study received ethics approval from the Hunter New England Human Research Ethics Committee (18/09/19/4.09) and is registered with The University of Newcastle Human Research Ethics Committee. The trial will be undertaken in compliance with the Declaration of Helsinki (15). Prior to study enrolment, all participants will provide electronic or written informed consent for the 3-months study duration. Participants will be informed that they may withdraw from the study at any time without having to give a reason.

Participants: Eligibility, Recruitment, and Eligibility

Women aged 18–45 years with a recent history (within 4 years of diagnosis) of preeclampsia will be targeted for recruitment. Inclusion and exclusion criteria are summarized in **Table 1**. Notably, women were excluded if they required ongoing medical follow-up after their 6-weeks postpartum check-up or have been diagnosed with type 1 or type 2 diabetes, as health conditions and their associated treatment may impact on the preliminary efficacy outcomes.

Within the study setting (Hunter region, NSW, Australia) there is currently no routine system for follow-up of women with a history of preeclampsia to provide cardiovascular risk assessment or preventative health services. Therefore, the study will investigate a variety of strategies to reach and recruit the target population for the intervention. All potential participants screened for eligibility will be asked how they found out about the study to evaluate the effectiveness of different recruitment strategies. Participants will be recruited using the following strategies:

1. Emailing invitations to women who previously (April 2018) completed a "Preeclampsia Survey" (10) from The University of Newcastle and agreed to be contacted about the study.
2. Advertising on the Australian Action for Preeclampsia social media accounts and online newsletter.

TABLE 1 | Participant inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
History of preeclampsia (within 4 years of diagnosis)	Currently or recently pregnant (<3 months post-partum)
Aged 18–45 years	Planning to become pregnant within the next 3-months
Internet access and email address	Non-English speaking
Able to attend assessments at The University of Newcastle Callaghan campus	Type 1 or 2 diabetes mellitus
Interested in all or some of the topics below: a) Improving eating habits b) Improving physical activity levels c) Managing their weight d) Managing their stress	Currently participating in another lifestyle behavior intervention
Self-reported completion of post-partum check-up at 6 weeks with no further follow-up required	Unable to provide the contact details of a General Practitioner to share their physical measurements and blood test results with, for further follow-up if required.

3. Mailing invitations to all women who were treated at John Hunter Hospital, NSW, Australia for preeclampsia within the last 4-years.
4. Providing study details to General Practitioners within the Hunter New England and Central Coast regions via the Primary Health Network newsletter and a researcher visiting medical centers in close proximity to the University to encourage their participation. General Practitioners will be asked to provide information about the study to appropriate women who meet the inclusion criteria during standard consultations as well as advertise the study in waiting rooms using the provided flyers and posters.
5. Services that have contact with women within 4 years of birth such as childcare centers, playgroups, child recreation activities, and community centers will be asked via email or phone to advertise the study using their social media accounts or by displaying posters and/or flyers on their premises.

All recruitment materials including social media posts, posters and flyers direct women to the online participant information statement describing the study and an online survey to assess eligibility for participation in the study. Participants deemed eligible will be emailed or mailed a consent form. Ineligible participants will be contacted via email or phone to inform them of the outcome.

Randomization, Blinding, and Sample Size

The randomization sequence will be generated by an independent statistician, using a random number function in Microsoft Excel. Concealed envelopes will be distributed to the participants after baseline measurements for randomization to each study condition (1:1). A randomized block design, with a block size of 6, will be used to ensure the conditions are balanced. Randomization will be stratified by time since last pregnancy complicated by preeclampsia at time of enrolment (3 months to<1 year, ≥1 to<2 years, ≥2 to 4 years). Participant blinding will not be possible because they will be aware of the trial's conditions and the differences will be apparent. Researchers involved in the collection of physical measurements will be blinded to participant group allocation until completion of the 3-months follow-up appointment. The researchers will advise participants at the 3-months follow-up appointment that they cannot discuss their group allocation. A powered sample is not required for a pilot study, so a maximum of 90 participants (45/per group) will be recruited, as this is feasible within the funding timeline and budget.

Intervention

Intervention Development

The intervention delivery mode, duration and content were informed by formative research in Australian women with a history of preeclampsia, conducted via an online survey (10). Of the 100 survey respondents who provided feedback on intervention development, 96% indicated they were interested in participating in a lifestyle behavior intervention for women with a history of preeclampsia. Of the 96 who were interested in participating, the most preferred mode of delivery for the program was web-based (69.8%), with far fewer wanting in-person (18.8%), or telephone (1%) delivery. The most popular web-based delivery modes were via email (73.1%) and website (50.5%). Participant preferences for web-based delivery may be due to difficulties associated with attending in-person appointments during the postpartum period due to lack of time and childcare. This is consistent with previous research that found women with pregnancy complications, such as preeclampsia, who were referred to an in-person maternal health clinic in Canada for postpartum cardiovascular risk counseling had low attendance, with 54% failing to attend their appointment (16). Participants of the online survey (10) were also asked how much time they would be willing to commit to take part in the lifestyle behavior intervention, including both the number of weeks, and hours per week. The mean number of weeks they were willing to commit was 17.6 weeks, and mean hours per week were 5.3 hours. Participants also ranked their level of interest with proposed program topics (data not shown). Data from the research survey (10), along with existing evidence for CVD prevention (17, 18), and technology-delivered interventions (19–21) informed the intervention development. Also, members of the research team had previously developed (22) and demonstrated preliminary efficacy (23) of an eHealth weight loss intervention targeted to young women, so relevant components were adapted for use in this intervention.

Intervention Components and Delivery

Be Healthe for your Heart is a 3-months lifestyle behavior intervention delivered solely online via the program website (**Figure 1**) and weekly email newsletters. The program website and emails will provide participants with resources and tools related to nutrition, physical activity, stress management, and weight management consistent with the program recommendations. Program recommendations focus on improving modifiable risk factors to promote cardiovascular health and were informed by best practice guidelines (24–27). As per the Australian National Heart Foundation Heart Healthy Eating Principles, nutrition recommendations focus on eating plenty of fruit, vegetables, and wholegrain cereals, eating a variety of healthy protein sources, choosing reduced-fat dairy, selecting healthy unsaturated fat choices, and limiting salt intake through the use of herbs and spices (24). Physical activity recommendations focus on regular physical activity (most days), gradually building up to 2.5 hours of moderate intensity physical activity or 1.25 hours of vigorous intensity physical activity (or an equivalent combination of both) each week, doing muscle strengthening activities at least 2 days each week, and limiting the amount of time spent in prolonged sitting (26). Stress management recommendations focus on identifying and managing emotional stress, while weight management recommendations focus on returning to pre-pregnancy weight, and then reaching and maintaining a healthy weight (BMI 18.5–25 kg/m^2) (27). **Table 2** describes the key program components, which are aligned with 21 different behavior change techniques (28).

Participants randomized to the Be Healthe for your Heart program will be registered for the program following randomization at the baseline data collection session. They will receive an email with a link to the website (http://behealthe.newcastle.edu.au) and a username and password to log-in. Email newsletters will be automated, with the first received by participants ∼2 hours after registration, and weekly thereafter. Participants will receive no instructions from researchers about how to use the website.

Control Group

The control group will be sent an initial email with links to the National Heart Foundation of Australia website. They will receive access to the Be Healthe for your Heart program after completion of 3-months follow-up.

Study Procedure

All eligible participants will attend measurement sessions at the University of Newcastle, Callaghan campus at baseline and 3-months. Participants will receive reminders about their scheduled measurement sessions via email and text messages. The same procedure will be followed at both time-points, participants will have their height, weight, body fat percentage, waist circumference, and blood pressure measured by researchers trained in the study protocol by the Chief Investigator. Fasting blood samples will be collected by trained phlebotomists. Participants will complete online surveys about their dietary intake, physical activity levels, general health and well-being, stress levels, breastfeeding, pregnancies, and preeclampsia history. After all measurements have been collected at baseline, participants will be randomly allocated to the intervention or control group. Participants will receive a gift voucher (AU$20 baseline and AU$40 follow-up) to reimburse them for their time and costs associated with attending study measurement sessions.

Outcome Measures

Acceptability (Primary Outcome)

At 3-months, the participants in the intervention group will complete an online survey via the Qualtrics (Qualtrics, Seattle, Washington, US) platform with 40 questions related to program component usage, usability, appropriateness, satisfactions, and reasons for engagement or non-engagement. Participants will evaluate all components of the Be Healthe for your Heart website including the "How Healthy is your Heart?," "My Goals," "Track My Progress," website resources and weekly emails. Survey questions will require participants to indicate their level of agreement with specific statements and describe what they liked or disliked and what could be improved for each program component. Participants will also complete survey questions related to their overall satisfaction with the program. The study will also objectively measure the use of the intervention components by recording their website logins and website page visits and number of email newsletters opened.

Preliminary Efficacy (Secondary Outcome)

All secondary outcomes will be measured at baseline and after 3-months to allow evaluation of change in outcomes during the intervention period to provide an indication of the immediate impact of the intervention (i.e., preliminary efficacy). As this is a pilot RCT completion of each outcome measure will also be tracked, as a measure of the feasibility of the data collection procedures. The following objective measurements will be taken:

- *Weight, BMI, waist circumference, and body fat percentage:* Each participant's height, weight, waist circumference, and body fat percentage will be measured by researchers trained in the study protocol by the Chief Investigator. Height to the nearest 0.1 cm will be measured twice using the stretch stature method on a stadiometer (Inbody BSM370; Inbody Australia, Miami, QLD, Australia). A third measurement will be obtained when the difference between repeated height measures is >0.3 cm. Weight to the nearest 0.01 kg will be measured twice in light clothing, without shoes on a digital scale. A third measurement will be obtained when the difference in repeated weight measures is >0.4 kg. The mean of the 2 measurements with the least difference will be used for analysis. Body fat percentage will be determined using bioelectrical impedance (Inbody 720; Inbody Australia, Miami, QLD, Australia). BMI will be calculated as weight (kg) divided by height (m) squared, and categorized into underweight (BMI: <18.5), healthy (BMI: ≥18.5 to <24.9), overweight (BMI: ≥24.9 to <29.9), or obese (BMI: ≥30) categories according to the cut-off points defined by the World Health Organization (WHO) (29). Waist circumference to

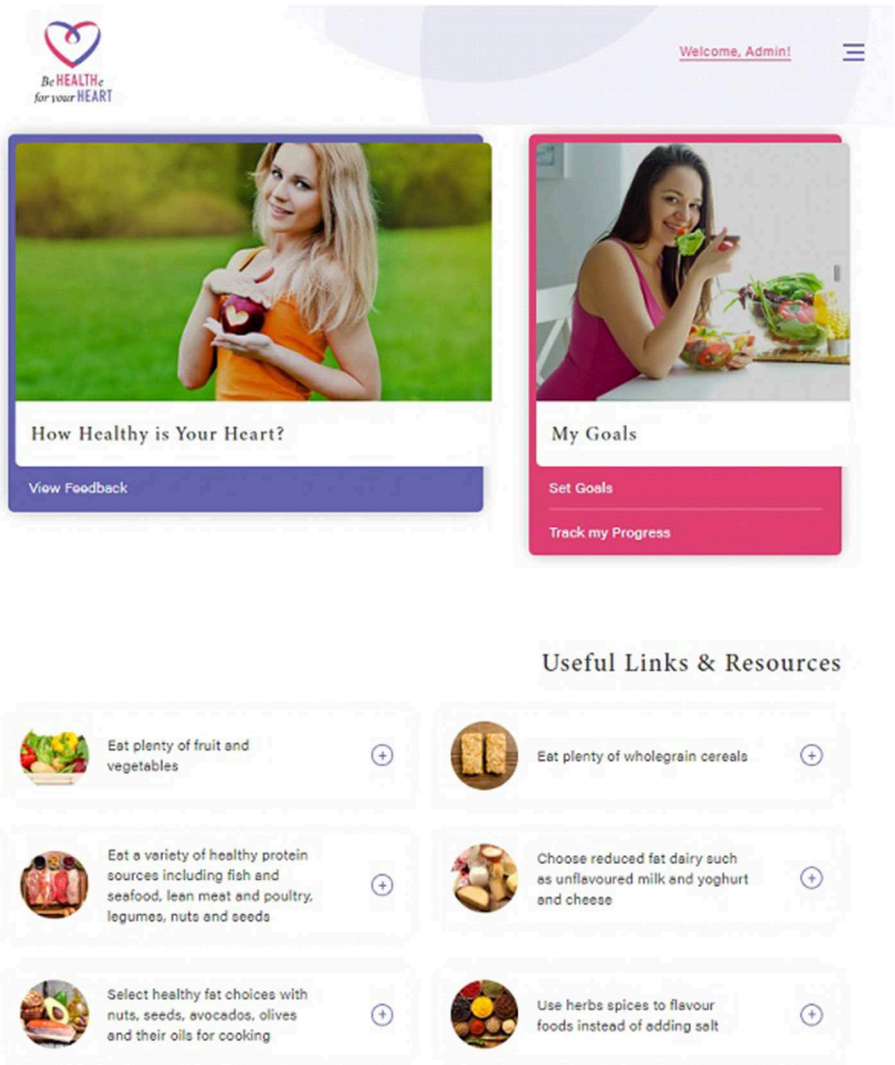

FIGURE 1 | Be Healthe for your Heart website. All images are reprinted from shutterstock.com under a Standard License, with permission from Shutterstock.

the nearest 0.1 cm will be measured twice at the midpoint between the lower costal (10th rib) border and the top of the iliac crest, with clothing raised so that the waist is exposed, using a non-extensible steel tape (30). Waist circumference will be measured by the same researcher at both time-points to ensure that consistent measurements are collected. A third waist measurements will be taken when the difference between repeated waist measurements is >0.5 cm. The mean of the 2 measurements with the least difference will be used for analysis.

- *Systolic and Diastolic Blood pressure:* Each participant will have 3 blood pressure measurements taken using the automatic sphygmomanometer (Inbody BPBIO320, Inbody Australia, Miami, QLD, Australia) which has been validated against the European Society of Hypertension International Protocol for clinical use in adults (31). Measurement procedures will be consistent with the National Heart Foundation's Guidelines for the diagnosis and management of hypertension in adults (32). Specifically, participants will be seated for 5 min before their first blood pressure measurement, then for 2 min between the remaining measurements. When there is a difference of more than 10 mmHg between any of the systolic or any of the diastolic values, a fourth measurement will be taken. The mean of the 2 measurements with the least difference will be used for analysis. Blood pressure readings displayed on the screen will not be visible to the participants during the measurement session.
- *Cardiovascular blood tests:* Each participant will have 4 mL blood samples collected by trained phlebotomists and assayed by a NSW Health Pathology, which is accredited by the National Association of Testing Authorities. Blood samples will be collected after an overnight (8–12 hours) fast and assayed for total cholesterol (mmol/L), high-density lipoprotein cholesterol (HDL-C) (mmol/L), low-density

TABLE 2 | Description of the Be Healthe for your Heart 3-months intervention.

Program component	Description	Behavior change techniques (28)
Website: How Healthy is your Heart?	A brief survey (37 questions) assesses the participant's eating habits, physical activity and stress levels, as well as body weight, during the first week of the program. Participants will receive automated individualized feedback on their current health behaviors compared to program recommendations. Feedback (**Figure 2**) will be reported for each program recommendation using a heart rating system ranging from "0 hearts = needs improvement" to "5 hearts = excellent." Participants will also receive an overall heart score ranging from 0 to 65, with 65 indicating compliance with all program recommendations.	• Feedback on behavior • Feedback on outcomes of behavior • Problem solving • Action planning
Website: My goals	Participants will use the feedback from "How Healthy is your Heart?" to set health behavior goals during the first week of the program using the website resource "My Goals." Participants will be able to select 1–4 goals related to eating habits, physical activity, stress and/or their weight, that are consistent with the program recommendations. Participants will be able to record their own strategies for achieving their selected goals.	• Goal setting • Action planning • Problem solving • Conserving mental resources
Website: Track my progress	Using the website resource "Track My Progress," participants will monitor their progress toward their goals and the program recommendations. "Track My Progress" will require participants to answer questions specific to their selected goals. Based on the participant's response, automated feedback using the heart rating system, as previously described, will indicate their progress toward their goals and the program recommendations. Participants will be able to self-monitor their progress throughout the 3-months and receive feedback. Participants will be encouraged via the email newsletters to use "Track My Progress" at least once during the 3-months intervention	• Self-monitoring of behavior • Self-monitoring of outcome(s) of behavior • Feedback on behavior • Feedback on outcomes of behavior • Discrepancy between current behavior and goal • Review behavior goals • Habit formation
Website: Resources	The resources include comprehensive written information related to the program recommendations for nutrition, physical activity, stress management and weight management, consistent with best practice guidelines (25–27). The resources are designed to educate participants about improving modifiable risk factors that will assist them to achieve their goals and the program recommendations. The resources will also provide external links to supporting information, videos, recipes and phone apps. Participants will be able to access any of the resources.	• Problem solving • Instruction on how to perform a behavior • Information about antecedents • Information about health consequences • Demonstration of the behavior • Information about emotional consequences • Behavior substitution • Habit reversal • Reduce negative emotions • Conserving mental resources
Emails	Participants will receive weekly emails, which will focus on a specific program recommendation and provide relevant links to the program website tools and resources, as well as remind the participants to take the quiz "How Healthy is your Heart?", set health goals and track their progress.	• Problem solving • Instruction on how to perform a behavior • Prompts/cues • Behavioral practice/ rehearsal • Conserving mental resources

lipoprotein cholesterol (LDL-C) (mmol/L), triglycerides (mmol/L), glucose (mmol/L), and insulin (mIU/L).

- *Overall cardiovascular health score:* Each participant's risk of CVD will be derived using the *Framingham CVD 30-years risk score* (33) which is derived using age (years), sex, total, and HDL-C (mg/dL), current smoking status (obtained from study surveys), systolic blood pressure (mmHg), use of antihypertensive treatment (obtained from study surveys), and whether they have been diagnosed with diabetes. Absolute full CVD risk (includes hard CVD or coronary insufficiency, angina pectoris, transient ischemic attack, intermittent claudication, or congestive heart failure) over 30 years will be classified as low risk (<10% or 1–2 points), intermediate risk (10–20% or 3–6 points), or high risk (>20% or 7 or more points). The *Framingham CVD 30-years risk score* has demonstrated an acceptable level of accuracy for predicting CVD risk in a cohort of adults ($n = 4506$) aged 20–59 years at baseline, based on cross-validated discrimination c = 0.803 and calibration chi-square = 4.25 ($p = 0.894$) (33).

At baseline and 3-months participants will be asked to complete online surveys administered via Qualtrics (Qualtrics, Seattle, Washington, US) to evaluate the following outcomes:

- *Physical activity duration and intensity* will be assessed using the International Physical Activity Questionnaire (IPAQ) (short-form) which has acceptable accuracy and reliability for the measurement of physical activity in adults aged 18–65 years across 12 countries (34). The IPAQ will require participants to recall the amount of time they spent in moderate activity, vigorous activity, walking and sitting in the past 7 days, and reported using metabolic equivalent of task (MET-minutes) per week. Based on the participant's responses to these questions, their level of physical activity over the previous 7 days will be categorized as either high, medium or low according to the IPAQ scoring protocol (35). Participants will also be asked additional questions about their amount (minutes per session) and frequency (times per week) of participation in resistance-based physical activity.

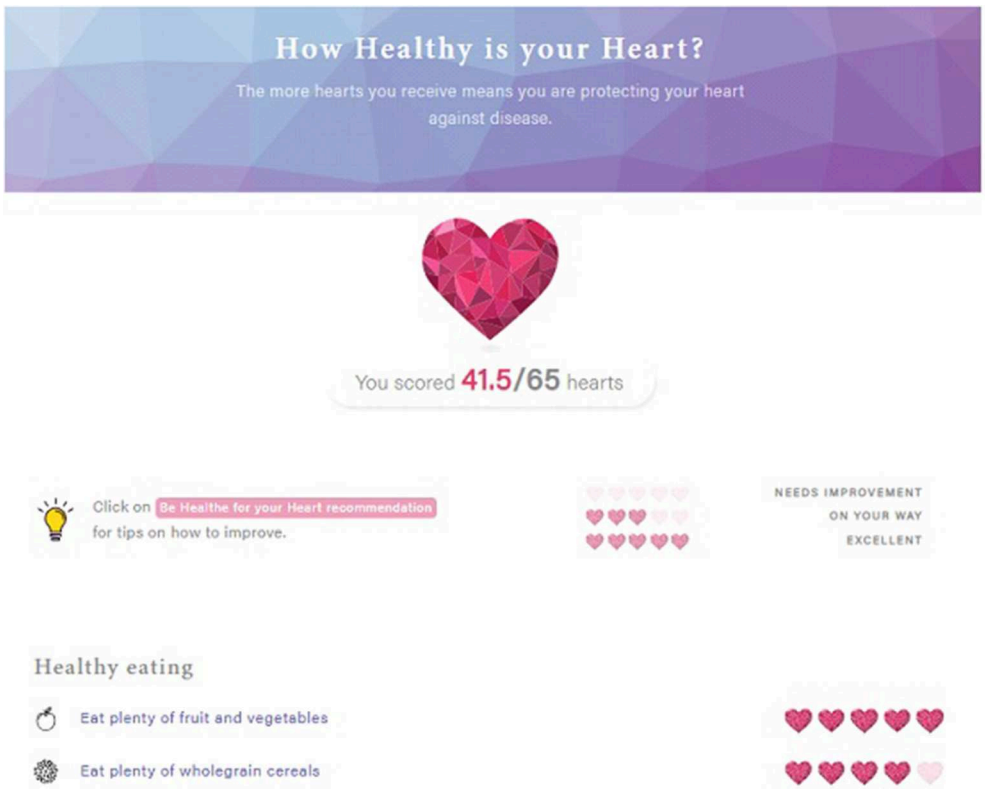

FIGURE 2 | Feedback provided from "How Healthe is your Heart?".

- *Sitting time* will be assessed using The Domain-Specific Sitting Questionnaire (adapted version) which has been validated in Australian adults (36, 37). This questionnaire includes 5-items that asks participants to report the number of hours and minutes spent sitting on each day (including weekdays and weekends) in the following 5 domains: traveling to/from work, at work, using a computer at home, watching television, and during leisure time (excluding watching television). Total daily sitting times on weekdays and non-weekdays will be calculated for each participant by summing reported sitting times across the domains.
- *Dietary intake* will be assessed using The Australian Eating Survey (AES). The AES is a validated measure of usual dietary intake in Australian adults, compared to 3-days weighed food records (38). The AES is a 120-item semi-quantitative Food Frequency Questionnaire (FFQ) with 15 supplementary questions related to age, vitamin and mineral supplement/s use and food behaviors. This study will use the CVD version of the AES which contains an additional 66 supplementary questions specific to foods and nutrients related to CVD health and has been shown to be more accurate for estimating long-chain polyunsaturated fatty acid intakes in hyperlipidaemic adults than the standard AES (39). Participants will be required to report their consumption of each food or food type, with frequency options which vary depending on the item and range from "Never" to "4 or more times per day" and for some beverages up to "7 or more glasses per day." Each participant's intake of 53 macro-and micro-nutrients will be calculated using the AUStralian Food and NUTrient database (AUSNUT) 2011-13 (Food nutrient database), using Stata/IC 15.1(Stata, College Station, Texas, USA) (40).
- *Depression, Anxiety and Stress* will be assessed using The Depression, Anxiety and Stress Scale (DASS) (short-version) which has 21 items in 3 scales: depression (DASS-D-7 items), anxiety (DASS-A-7 items), and stress (DASS-S-7 items) (41). The items are scored on a 4-point Likert-type scale of 0 to 3 (0 = not at all, 3 = most of the time), and the total scores for each scale are to be multiplied by 2. The total score for each scale may range from 0 to 42, with higher scores indicating more depression, anxiety and stress. The internal consistency coefficient values (Cronbach's alpha) of each subscale ranges between 0.81 and 0.97 (41).
- *Quality of life* will be assessed using the Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF), which requires participants to report their satisfaction with their physical health, feelings, work, household duties, school/course work, leisure time activities and social relations (42). Scores range from 0 to 100 and higher scores indicate greater life satisfaction and enjoyment. The Q-LES-Q-SF internal consistency and retest reliability correlation coefficients were 0.90 and 0.93, respectively (43). The Satisfaction with Life Scale (SWLS) has 5 questions had

requires participants to rate their response on a 7-point Likert scale from strongly disagree (1) to strongly agree (7), with higher scores reflecting greater satisfaction with life (44). The possible range of scores from this scale is 5–35. The SWLS has been shown to be a valid and reliable measure scale compared to other life satisfaction assessment measures (45).

- *Breastfeeding Practices:* Participants will be asked if they are currently breastfeeding, and if so they will be asked to indicate their child's date of birth they are breastfeeding, and whether the child consumes solid food, cow's milk or substitutes or infant formula. The responses will be used to determine whether the child is exclusively, complementarily, or not breastfed according to the WHO definitions (46).

Other Measures

At baseline participants will be asked about their age, country of origin, language spoken at home, highest level of education, individual and household income, marital status, postcode, working status, and living situation/family structure. They will also be asked about their pregnancy history (number of pregnancies, their outcome and whether they were complicated by preeclampsia or other pregnancy complications) and their awareness of their increased risk of CVD at baseline and 3-months. Participants will be asked whether a health professional had provided advice or screening regarding CVD risk factors as per the SOMANZ Guidelines (9) since their most recent pregnancy with preeclampsia, to identify if any treatment was received during the trial.

Statistical Methods

All analyses will be performed using Stata/IC (Stata, College Station, Texas, USA). Data will be presented as mean, standard deviation (SD) or median, interquartile range (IQR) for continuous variables and counts (percentages) for categorical variables. Changes in the impact on absolute CVD risk score, CVD risk markers and health behaviors will be determined, and differences between groups will be examined. Analysis for the preliminary efficacy outcomes will be conducted on an intention-to-treat basis (all participants who were randomized to groups and completed baseline assessments) and for completers only (those who provided data at 3-months). The effect of treatment on the efficacy outcomes will be assessed using linear mixed models. The efficacy outcome will be the outcome in the model, time (baseline, 3-months) and treatment group (intervention, control) as predictors, and group × time as an interaction term. The *p*-value of the interaction term will be used to determine the statistical significance of any difference between treatment groups in the change from baseline. Effect sizes will be calculated using the equation: Cohen's $d = (M_{1\ \text{change score}} - M_{2\ \text{change score}})/SD_{\text{pooled (change scores)}}$. Intervention acceptability will presented as the mean ± SD, with higher scores (maximum of 5) indicating greater acceptability. For qualitative data analysis, answers from open questions will be categorized into themes.

DISCUSSION

Women with a history of preeclampsia have an elevated lifetime risk of premature cardiovascular related morbidity and mortality. While risk modification is recommended, there is currently limited evidence to guide the adoption and implementation of behavioral strategies to improve modifiable risk factors to promote cardiovascular health among this high-risk target group.

Strengths of this pilot RCT include the collection of data on the acceptability of a web-based behavioral intervention for women with a history of preeclampsia, as an important first step in the translation of health programs into clinical practice. Participant satisfaction and usage data will be used to determine whether the target population find the intervention acceptable, and whether any refinements are required prior to further testing. Additionally, this trial will provide an indication of the potential intervention effect on important markers of cardiovascular health and modifiable risk factors, through the evaluation of secondary outcomes. Evaluation of primary and secondary outcomes will also provide evidence of the feasibility of the data collection procedures for future trials with this target population and/or intervention. Finally, the study will provide important data to evaluate the potential reach and effectiveness of a variety of recruitment strategies to potentially identify the best setting(s) to reach women with a history of preeclampsia.

There are also some limitations to the study protocol to be acknowledged. Firstly, although the recruitment strategies are varied, and will give an indication of potential settings to reach women with a history of preeclampsia, they will recruit a convenience sample of women, and therefore introduce potential selection bias. Secondly, as this is a pilot RCT, the study is not powered to detect changes in outcomes. Thirdly, the follow-up period for assessment of preliminary efficacy of the intervention is immediately post-intervention. Therefore, the study will not evaluate changes to modifiable risk factors or markers of cardiovascular health beyond the 3-months time point. Finally, some preliminary efficacy outcomes may introduce measurement error, due to lack of sensitivity in the target group (e.g., Framingham CVD 30 year risk score), lower accuracy compared to other measurement devices (e.g., use of automated blood pressure monitor), or the self-reported nature of the measures (i.e., measurement of modifiable risk factors).

Overall, the current pilot RCT protocol comprehensively describes the methods to be used to evaluate the acceptability and preliminary efficacy of a web-based intervention developed specifically for women with a history of preeclampsia. If the pilot RCT demonstrates the acceptability and preliminary efficacy of the intervention approach, the next step will be to evaluate the efficacy of the intervention in a fully powered RCT, evaluating both post-intervention and longer-term impact on modifiable risk factors and markers of cardiovascular health. Findings of the pilot RCT will also guide the design of the RCT including recruitment strategies, data collection procedures, and sample size calculations, as well as inform any changes to intervention design. Study findings will also have broader applications to researchers and

clinicians working with women with a history of preeclampsia, as they have potential to provide evidence of support for web-based interventions for risk factor modification, which may be used to inform the delivery of cardiovascular preventative health services.

AUTHOR CONTRIBUTIONS

MH conceptualized the research project. RT and MH drafted the manuscript. All authors were involved in the design of the study, edited and provided feedback, read, and approved the manuscript. The content in this manuscript is the original work of all authors involved.

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Depression, Anxiety, and Post-traumatic Stress Disorder Following a Hypertensive Disorder of Pregnancy: A Narrative Literature Review

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Introduction: Pregnancy and childbirth can be a source of anxiety and worry for women. This is probably more so for women with a complicated pregnancy. Anxiety and worry may contribute to, or exacerbate, mental health disorders including depression and post-traumatic stress disorder (PTSD). Mental health is an integral part of health and well-being and poor mental health can be detrimental to the woman's welfare and her infant's behavior and cognitive development. It may be undetected, potentially leading to a burden on the woman, her family, the health system, and society. Women with complicated pregnancies, such as those with hypertensive disorders of pregnancy (HDP), may be at greater risk of poor mental health. The aim of this review was to examine whether there is an association between depression, anxiety, and PTSD in postpartum women with a history of HDP.

Methods: A narrative literature review was undertaken. Using the key search terms: preeclampsia, gestational hypertension, hypertensive disorders, pregnancy complications, depression, anxiety, and post-traumatic stress disorder; electronic databases were searched to determine what is known about depression, anxiety, and PTSD after HDP.

Results: In total, 17 publications were included. The relationship between HDP and depression, anxiety, and PTSD was variable between studies and inconsistent. Although some studies reported no significant association, there is a trend for increased prevalence and symptom severity of depression, anxiety, and PTSD following HDP. This trend was particularly evident following the more severe presentations of HDP. It was uncertain whether this association was due to the hypertensive disorder itself, the sequelae of the HDP, such as giving birth to a preterm baby, or it predated the pregnancy.

Conclusions: Women who experience HDP may be at increased risk of developing postpartum depression, anxiety, and PTSD. Awareness of, and screening for, these mental health disorders in the postpartum period will alert clinicians to the need for additional follow-up and referral for women following HDP. More research on the benefits and risks of such an approach is needed.

Keywords: depression, anxiety, post-traumatic stress disorder, postpartum, hypertensive disorder of pregnancy, gestational hypertension, preeclampsia

INTRODUCTION

Pregnancy and childbirth can be a source of stress and worry for many women (1) and mental health disorders following childbirth are common. Worldwide 10% of pregnant women and 13% of women who have just given birth experience a mental health disorder, primarily depression (2). These rates are higher (15.6 and 19.8%, respectively) in low to middle income countries (2). One in 7 women experience depression in the year following birth and one in five experience anxiety, commonly in combination with depression, during the same period (3). Research on the global prevalence of postpartum post-traumatic stress disorder (PTSD) is sparse and has been reported as 1–2% (4) following childbirth, although a literature review by Simpson and Catling (5), including papers from several countries, found that 20–48% of women reported their birth as a traumatic event which could potentially lead to PTSD.

Pregnancy and childbirth are likely to be more stressful for a woman experiencing a pregnancy with complications (6) and as a psychological manifestation, stress may coexist with depression, anxiety, and trauma reactions (7). A pregnancy may be considered complicated when there is an increased risk compared to a healthy pregnancy (1) and implies a threat to the woman's health, well-being, her baby, or both (8). An example of such a pregnancy is one complicated by a hypertensive disorder.

Hypertensive disorders of pregnancy (HDP) are common and complicate 10% of pregnancies (9) which equates to ∼30,000 pregnancies a year in Australia and 13 million pregnancies a year globally and they are one of the leading causes of maternal and perinatal morbidity and mortality (10). The two pregnancy-specific disorders are gestational hypertension (GH) and preeclampsia (PE). GH is the new onset of hypertension after 20 weeks gestation (11) and when it presents at term, is usually a benign condition with little risk of adverse pregnancy outcomes (11, 12). However, the earlier GH presents in the pregnancy or the more severe the hypertension, the greater the risk of it progressing to PE or to an adverse pregnancy outcome (11, 13, 14). PE is a multi-system disorder which is described as the new onset of hypertension after 20 weeks gestation and the involvement of at least one other maternal organ system and/or the unborn baby (11, 12). Two particularly serious manifestations of PE are the syndrome HELLP (11, 12), comprising Hemolysis, Elevated Liver enzymes and a Low Platelet count, and eclampsia, which is seizures in a women with PE (11). There are long term physical health consequences for women after a HDP such as hypertension, stroke, heart attack, kidney disease, and diabetes (11, 15–19), however there is little known about women's mental health following this complication.

Poor mental health can impact both maternal and infant health negatively. In addition to affecting the woman's emotional welfare and everyday functioning, poor mental health may affect her parenting ability and can impair her relationship with her baby (20). Long term and/or untreated poor maternal mental health has been associated with poor infant well-being particularly in terms of behavioral and cognitive development (21). In severe cases, women with postpartum depression may commit suicide (2) and in those women with psychotic illnesses, the risk of infanticide, though rare, must be considered (2). Due to the serious consequences of poor mental health, early diagnosis, and treatment interventions are imperative for the health and well-being of the woman and her infant.

In the postpartum period, poor mental health is often undetected and untreated (22), potentially leading to a burden on the woman, her family, the health system and society. Guidelines highlight the importance of implementing interventions targeting women displaying the early signs and symptoms of poor mental health (23–25). However, it is not always known which women in the postpartum period would benefit from specific interventions. If women who experience HDP are identified as being at increased risk of poor mental health, targeted screening may be useful and lead to more timely referral and treatment initiation.

AIM

The aim of this review was to examine whether there is an increased risk of depression, anxiety, and PTSD in postpartum women with a history of HDP.

METHODS

A narrative literature review was undertaken. This approach was used as it enabled a broad search that was able to draw conclusions about the topic and assist in identifying gaps or inconsistencies in the body of knowledge (26). Ethics approval was not required for this review.

Search Strategy

A comprehensive search of the literature was undertaken using the electronic databases of EBM Reviews (Cochrane Database of Systematic Reviews), EMBASE, Ovid MEDLINE(R),

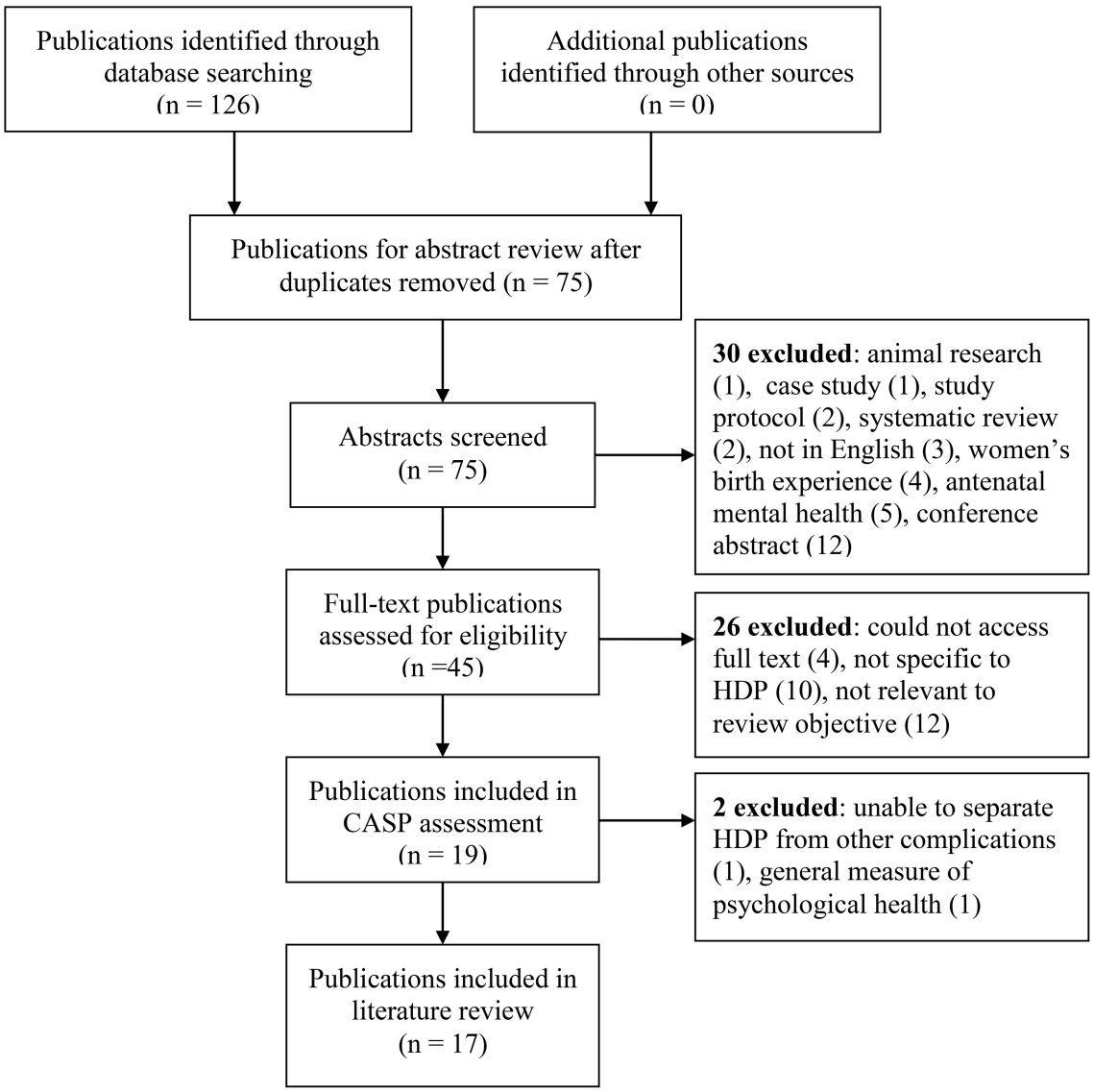

FIGURE 1 | Publication selection.

CINAHL (Cumulative Index to Nursing and Allied Health), Maternity and Infant Care, PsycINFO, and Google Scholar. The key search terms used were: preeclampsia, gestational hypertension, hypertensive disorders, pregnancy complications, depression, anxiety, and post-traumatic stress disorder. All possible combinations and spellings of these key search terms were used. Additionally, the reference lists of identified papers were manually examined for further studies that may have been missed in the initial search.

The search was undertaken in May 2019, limited to primary publications published in English from the year 2000 onwards, with full text available. Publications only available in abstract form, conference abstracts, and study protocols were excluded as were systematic reviews (**Figure 1**). Two systematic reviews were excluded as there was a concern that including these would mean double counting of some studies. All relevant individual studies within these systematic reviews were included in this review. One systematic review (27) focussed on the relationship between PTSD and severe maternal morbidity. Several pregnancy complications were included with PE in four publications (28–31). The other systematic review (32) reported on depression and/or anxiety following a pregnancy complicated with severe PE and included six publications (28, 29, 31, 33–35).

Following title and abstract screening, 45 publications were identified for possible inclusion and the full text was sourced. Subsequent to full text reading, 19 were considered relevant to the search objective and were further assessed using the Critical Appraisal Skills Programme (CASP) (36). The CASP is a tool developed in 1993 which is widely used to systematically examine research articles to help identify the strengths, weaknesses, and

usefulness of the study by appraising the validity, results and clinical relevance. Using the CASP checklist 17 publications were included in the review. Two publications were excluded at this stage as they: (1) reported on general quality of life following HDP and not specifically on depression, anxiety, or PTSD. Depression and anxiety are included in the screening instrument (SQL-90), but the overall results were reported as one score, so details specific to depression and anxiety could not be determined; and (2) reported the combined results of mental health for women after HDP and postpartum hemorrhage, making it impossible to separate the results for the HDP cohort.

RESULTS

In the included publications, the definition of HDP was sourced from different national and international guidelines (9, 37–39) (**Table 1**). Although these different sources were used, the definitions of the hypertensive disorders were consistent. However, the use of different study populations was not all directly comparable. For example, the severity of HDP varied, with some only including women with severe HDP and some only included women at a specific preterm gestation (**Table 1**).

The identified publications were grouped into three categories of mental health disorder, depression, anxiety, and PTSD. Some studies reported on more than one disorder and were included in more than one group. Furthermore, some studies reported on both prevalence and symptom severity. The results of depression, anxiety and PTSD were reported separately.

See **Box 1** for a summary of each publication included in this review and **Table 2** for a summary of the results.

Depression

Fifteen publications examined the association between HDP and depression (28, 29, 31, 33–35, 40–46, 48, 49). Eight reported on the prevalence of depression and 10 reported on symptom severity, using mean or median scores of the screening instrument used. Fourteen of these studies were observational cohort studies, and the other a descriptive design. The studies were conducted in The Netherlands ($n = 10$), United States (US) ($n = 2$), and one each in Iran, China, and Germany. There were seven different screening instruments used, and all bar one have been validated for accuracy and validity (see **Table 3** for the screening instruments used).

Prevalence of Depression

Reports of the prevalence of postpartum depression following HDP varied between 7 and 44% (29, 31, 33, 41, 43, 44, 46), which is up to four times higher than in the general postpartum population. This wide disparity in may be partly attributed to the inconsistencies in study design, particularly with regard to participant selection, severity of the hypertensive disorder, the screening instrument and the cut-off score used, and the timing of the evaluation.

When compared to women who did not have a history of HDP, a higher prevalence of depression was reported in women who experienced HDP (29, 31, 33, 45). It has been suggested that the psychological impact was influenced by the severity of the HDP, as characterized by gestational age at the onset, diagnosis of GH vs. PE, maternal complications, or adverse infant outcomes (29, 44). To investigate this more closely, Blom et al. (33) collected data from women following GH or PE separately and reported the prevalence of postpartum depression to be higher in the PE group compared with the GH group. Similarly, when data from women after mild or severe PE were analyzed separately, the prevalence of depression was higher in women with severe PE (33, 44). These results suggest that the prevalence of postpartum depression increases as the severity of the hypertensive disorder increases, however the results were not always statistically significant (44, 46).

A higher prevalence of depression was reported by women who gave birth preterm or term with PE when compared to women matched for gestation at birth with an otherwise uncomplicated pregnancy (29) suggesting that the PE contributed to the depression. In contrast, a Dutch study reported no difference in depression for women who gave birth preterm with or without PE (28), suggesting that maybe it was the consequences of a preterm birth rather than the HDP that was more strongly associated with depression.

When depression has been measured longitudinally at several postpartum time points following HDP, the prevalence was shown to decrease over time. A decrease from 27% at two-5 days postpartum to 17% at three-4 months postpartum was reported in one study (45) while a decrease from 10.5% at 6 weeks postpartum to 6.8% at 15 months postpartum was reported in another (31). However, there is no mention of any treatment that may have been undertaken during the period of the study, so it is unclear what contributed to the lessening depression.

Depression Symptom Severity

With regard to the severity of depressive symptoms, the evidence was mixed and inconclusive. Some studies report significantly higher mean scores on the screening instrument by women following HDP compared with women in the normal comparison group (41, 46, 48, 49). However, others report no significant difference in mean scores between women with or without prior HDP (28, 34, 35, 42), although there was a trend toward higher scores from women in the HDP group. Having a preterm birth, stillbirth, or neonatal death was significantly associated with higher depressive symptoms in one study (46) which reported on depression, on average, 14 years following the index pregnancy.

No significant differences in scores were reported comparing primiparous and multiparous women at 2 and 6 weeks postpartum following a pregnancy complicated with PE (40), although there were no details of the scores given. In another study, no significant difference in mean scores was found in four groups of women; preterm PE, term PE, preterm birth without HDP, and term birth without HDP ($p = 0.11$) (28). In a study examining depression following eclampsia and PE, statistically significant higher mean scores were reported by women who had experienced eclampsia compared to those women with a history of PE and those who were normotensive in pregnancy ($p = 0.02$) (48).

TABLE 1 | The definition of hypertension in pregnancy and inclusion criteria for the included studies.

References	Source	Gestational hypertension	Preeclampsia	
			Mild	Severe
Abedian et al. (40)	ACOG	Not eligible	At least BP ≥ 140/90 and proteinuria ≥ 30 mg/dl	
Baecke et al. (28)	National high blood pressure education program working group	Not eligible	BP ≥ 140/90 after 20 weeks gestation and proteinuria ≥ 300 mg/24 h Two groups: <37 weeks gestation ≥37 weeks gestation	
Blom et al. (33)	ISSHP	BP ≥ 140/90 after 20 weeks gestation	BP ≥ 140/90 after 20 weeks gestation and proteinuria ≥300 mg/24 h	
Brusse et al. (34)	ACOG	Not eligible	Not eligible	BP ≥ 140/90 and *de novo* proteinuria ≥300 mg/day and one or more of: • BP ≥160/110 mmHg on two occasions at least 6 h apart • Oliguria of <500 ml/24 h • Persistent headache or cerebral or visual disturbances • Epigastric pain • Increased serum creatinine level • Impaired liver function • Thrombocytopenia • Fetal growth restriction
Chen (41)	ACOG	Not eligible	Not stated	
Engelhard et al. (29)	National high blood pressure education program working group	Not eligible	Not stated Two groups: <37 weeks gestation ≥37 weeks gestation	
Fields et al. (42)	Not stated	Not eligible	Hospital adaptation of the International Classification of Disease codes used in record linkage	
Gaugler-Sedden et al. (35)	Not stated	Not eligible	Not eligible	DBP ≥ 110 mmHg and proteinuria 1 g/L, with or without • Eclampsia or HELLP (platelet count <100,000/μL, AST or ALT >70 U/L, lactate dehydrogenase >600 U/L) Two groups: <24 weeks gestation 24–32 weeks gestation
Habli et al. (43)	Not stated	Not eligible	Not eligible	HELLP—serum haptoglobin level <0.24 g/L and/or lactic dehydrogenase levels >600 U/L, AST>70 U/L, ALT >70 U/L, and platelet count ≤100,000/μL Two groups: <28 weeks gestation ≥28 weeks gestation
Hoedjes et al. (44) PND	ACOG	Not eligible	BP ≥ 140/90 and ≥300 mg/day proteinuria after 20 weeks gestation	At least one of: • BP ≥160/110 mmHg, • Proteinuria ≥5 g/day, • HELLP (platelet count <100,000/μL, AST >30 U/L, ALT >30 U/L), • Convulsion, • Fetal growth restriction
Hoedjes et al. (44) PTSD	ISSHP (mild PE) ACOG (severe PE)	Not eligible	BP ≥140/90 and ≥300 mg/day proteinuria after 20 weeks gestation	At least one of: • BP ≥160/110 mmHg, • Proteinuria ≥5 g/day, • HELLP (platelet count <100,000/μL, AST >30 U/L, ALT >30 U/L), • Convulsion, • Fetal growth restriction
Mautner et al. (45)	German guidelines	Not stated	Not stated	Not stated
Mommersteeg et al. (46)	ISSHP	Not eligible	DBP ≥90 with proteinuria (≥0.3 g/24 h) 20–32 weeks gestation	
Porcel et al. (47)	None	Self-reported	Self-reported	Self-reported
Postma et al. (48)	ISSHP	Not eligible	*De novo* hypertension after 20 weeks gestation plus proteinuria Eclampsia: new onset of seizures in women with preeclampsia Two groups: < 34 weeks gestation ≥ 34 weeks gestation	
Postma et al. (48)	ISSHP	Not eligible	*De novo* hypertension after 20 weeks gestation plus proteinuria Eclampsia: new onset of seizures in women with preeclampsia	
Stramrood et al. (31)	ISSHP	Not eligible	Not stated	Not stated

ALT, alanine aminotransferase; AST, aspartate aminotransaminase; BP, blood pressure; DBP, diastolic blood pressure; HELLP, Hemolysis, Elevated Liver enzymes, Low Platelets; PE, preeclampsia.

TABLE 2 | Results of included studies reporting on HDP and postpartum depression, anxiety, or PTSD.

References	Study design recruitment	Location	Instrument	When measured	Cohort (*N*)	Results		
						Depression	**Anxiety**	**PTSD**
Abedian et al. (40)	Descriptive study	Iran	BDI STAI PPQ	2 weeks pp 6 weeks pp	PE ($n = 100$) 56 primiparous 44 multiparous	No significant difference at both time points (no figures given)	No significant difference at both time points (no figures given)	**Mean scores:** Primip 4.4 Multip 5.4 ($p = 0.05$) **Prevalence:** Primip 21% Multip 32% ($p = 0.24$) (unclear which time these results are from)
Baecke et al. (28)	Cohort study Recruited after birth	Netherlands 1 Hospital	BDI IES >25 STAI	6–18 months pp	Preterm PE ($n = 48$) Term PE ($n = 18$) PTB ($n = 32$) Term birth ($n = 72$)	**Mean scores:** Preterm PE 2.7 Term PE 1.3 PTB 1.2 Term birth 1.8 ($P = 0.11$)	**Mean scores:** Preterm PE 39.9 Term PE 39.6 PTB 35.4 Term birth 37.2 ($P = 0.27$)	**Prevalence:** Preterm PE 44% Term PE 11% PTB 41% Term birth 11% ($P < 0.001$) **Mean scores:** Preterm PE 25.3 Term PE 10.5 PTB 20.0 Term birth 12.7 ($P < 0.001$)
Blom, et al. (33)	Prospective cohort study Recruited antenatally	Netherlands Women in Rotterdam with EDC 04/2002-01/2006	EPDS > 12	2 months pp	PE ($n = 183$) Other ($n = 3917$) Normal ($n = 770$)	**Prevalence:** PE 16.9% GH 7.6% PE associated with increased risk of PND (OR 2.58, 95% CI 1.30–5.14)		
Brusse et al. (34)	Cohort study Recruited after birth	Netherlands 1 hospital	CES-D STAI	3–7 months pp	PE ($n = 10$) Normal ($n = 10$)	**Median scores:** PE 7.5 Normal 8 ($P = 0.67$)	**Median scores:** PE 39 Normal 31 ($P = 0.21$)	
Chen et al. (41)	Retrospective	China 1 hospital	EPDS ≥ 10	6 weeks pp	PE ($n = 90$) N ($n = 90$)	**Mean scores:** PE 7.27 N 4.42 ($p = 0.05$) **Prevalence:** PE 27% N 12% ($p = 0.014$)		

(Continued)

TABLE 2 | Continued

References	Study design recruitment	Location	Instrument	When measured	Cohort (*N*)	Results		
						Depression	**Anxiety**	**PTSD**
Engelhard et al. (29)	Cohort study Recruited after birth	Netherlands 1 Hospital	BDI>15 PSS	Within 2 years of hospital admission	Preterm PE ($n = 18$) PTB ($n = 29$) Term PE ($n = 23$) Term birth ($n = 43$)	**Prevalence:** Preterm PE 33% PTB 24% Term PE 26% Term birth 7%		**Prevalence:** Preterm PE 28% PTB 28% Term PE 17% Term birth 0%
Fields et al. (42)	Cohort study Women identified via medical record linkage	US	BDI BAI	Once, average 34.7 years since index pregnancy	PE ($n = 40$) N ($n = 40$)	**Mean scores:** PE 4 N 2 ($p = 0.64$)	**Mean scores:** PE 3 N 105 ($p = 0.58$)	
Gaugler-Senden et al. (35)	Cohort study Recruited after birth	Netherlands 1 hospital birthed 1993–2004	ZDS IES >19	In 2008 asked to recall symptoms in pp period and at current time	PE ($n = 104$) Normal ($n = 78$)	**Mean scores:** *Postpartum recall:* PE 11.78 N 11.37 ($P = 0.59$) *In 2008:* PE 5.4 Normal 5.51 ($P = 0.87$)		**Mean scores:** *Postpartum recall:* PE 29.72 Normal 27.53 ($P = 0.41$) *Currently:* PE 28.66 Normal 25.69 ($P = 0.02$)
Habli et al. (43)	Cohort study	US Advertised on HELLP Syndrome Society website	Study designed survey	1–31 years after birth	HELLP ($n = 128$)	**Prevalence:** 32%	**Prevalence:** 26%	
Hoedjes et al. (44)	Prospective cohort study Recruited within 6 weeks pp	Netherlands 4 hospitals	EPDS $\geq$ 10 EPDS $\geq$ 13	6 weeks pp 12 weeks pp 26 weeks pp	Mild PE ($n = 39$) Severe PE ($n = 122$)	**Prevalence:** ($\geq$10) at any time: Mild PE 23.1% Severe PE 44.3% ($P = 0.018$) ($\geq$13) at any time: Mild PE 15.4% Severe PE 26.2% ($P = 0.165$)		
Hoedjes et al. (30)	Prospective cohort study Recruited within 6 weeks pp	Netherlands 4 hospitals	Self-rating Inventory for PTSD	6 weeks pp 12 weeks pp	Mild PE ($n = 35$) Severe PE ($n = 114$)			**Prevalence total study population:** 6 weeks pp 8.6% 12 weeks pp 5.1% ($P = 0.083$)
Mautner et al. (45)	Prospective cohort study Recruited antenatally between 24 and 37 weeks gestation	Germany 1 tertiary referral hospital	EPDS $\geq$10	24–37 weeks gestation 2–5 days pp 3–4 months pp	HDP ($n = 18$) PTB ($n = 32$) Normal ($n = 29$)	**Mean scores:** 2–5 days pp HT 7.83 PTB 9.91 Normal 4.69 3–4 months HT 3.67		

(Continued)

TABLE 2 | Continued

References	Study design recruitment	Location	Instrument	When measured	Cohort (*N*)	Results		
						Depression	**Anxiety**	**PTSD**
			PTB 6.53 Normal 5.48			**Prevalence in HT:** 39% antenatally 27% 2–5 days pp 17% 3–4 months pp		
Mommersteeg et al. (46)	Cohort study	Netherlands 1 hospital	PHQ-9 ≥5 GAD-7 ≥5	Once, average 14 years after index pregnancy	PE ($n = 265$) N ($n = 268$)	**Prevalence:** PE 27% N 23% ($p = 0.27$) **Mean scores:** PE 3.6 N 2.9 ($p = 0.03$)	**Prevalence:** PE 31% N 27% ($p = 0.33$) **Mean scores:** PE 3.6 N 3.5 ($p = 0.72$)	
Porcel et al. (47)	Cross sectional online survey First pregnancy 1990–2010	Worldwide PE Foundation US based	BSSS for DSM IV ≥4	Once	HDP ($n = 1,076$) Normal ($n = 372$)			**Prevalence:** HDP 43% Normal 14% ($P \leq 0.01$)
Postma et al. (48)	Observational cohort study Recruited 1–27 years after index pregnancy	Netherlands	HADS	Once, at least 12 months after the index pregnancy	Eclampsia ($n = 46$) PE ($n = 51$) Normal ($n = 48$)	**Mean scores:** Eclampsia 5 PE 4 Normal 3 ($P = 0.02$)	**Mean scores:** Eclampsia 7 PE 6 Normal 5 ($P < 0.005$)	
Postma et al. (49)	Retrospective cohort study	Netherlands	HADS	1–27 years since index pregnancy (mean = 6 years)	PE ($n = 90$) Normal ($n = 47$)	**Mean total scores:** PE 11 N 8 ($p < 0.001$)	**Mean total scores:** PE 11 N 8 ($p < 0.001$)	
Stramrood et al. (31)	Prospective cohort study Recruited antenatally when hospitalized (PE) or at 38 weeks gestation (controls)	Netherlands 1 hospital 1 midwifery practice	BDI > 20 PSSR-SR	Pregnancy 6 weeks pp 15 months pp	PE ($n = 63$) Normal ($n = 65$)	**Prevalence:** *Pregnancy* PE 19% Normal 7.7% *6 weeks pp* PE 10.5% Normal 6.2% *15 months pp* PE 6.8% Normal 0%		**Prevalence:** *6 weeks pp* PE 10.5% Normal 3% *15 months pp* PE 11.4% Normal 0%

BDI, Beck Depression Inventory; BSSS, Breslau Short Screening Scale; CES-D, Center for Epidemiological Studies Depression Scale; CI, Confidence Interval; DSM IV, Diagnostic Statistical Manual of Mental Disorders 4th Edition; EDC, expected date of confinement; EPDS, Edinburgh Postnatal Depression Scale; GH' gestational hypertension; HADS, Hospital Anxiety and Depression Scale; HELLP, Hemolysis Elevated Liver enzymes Low Platelets; HDP, hypertensive disorder of pregnancy; IES, Impact of Event Scale; OR, Odds Ratio; PE, preeclampsia; PND, postnatal depression; pp, postpartum; PSS, Post-traumatic stress Symptom Scale; PSSR-SR, PTSD Symptom Scale self-report questionnaire; PTB, preterm birth; PTSD, post-traumatic stress disorder; SCL-90, 90 item Symptom Check List; STAI, State Trait Anxiety Inventory; ZDS, Zung Depression Scale.

BOX 1 | Summary of papers selected for review

Abedian et al. (40) was a descriptive study undertaken in Iran. Women diagnosed with PE ($n = 100$) were studied at 2 weeks and again at 6 weeks postpartum for depression, anxiety, and PTSD. The main focus of the paper was PTSD and the aim was to compare PTSD in primiparous ($n = 56$) and multiparous ($n = 44$) women.

Baecke et al. (28) was a cohort study undertaken in The Netherlands that included 170 women six-18 months postpartum, and measured depression, anxiety, and PTSD. Women with PE were included at term and preterm in addition to a normal comparison group who gave birth at term and preterm. The main focus of this study was cognitive function after PE.

Blom et al. (33) was a cohort study undertaken in The Netherlands that recruited 4,941 women over a 4 year period with various pregnancy complications; HDP contributing 254 to the cohort and 770 in the normal comparison group. Women were recruited in the antenatal period and depression was measured at 2 months postpartum.

Brusse et al. (34) was a small pilot study undertaken in The Netherlands that assessed 20 women three-7 months postpartum. Depression and anxiety were measured in 10 women with a history of severe PE and 10 women who had a history of an uncomplicated pregnancy formed the normal comparison group. The main focus of this study was cognitive function after PE.

Chen et al. (41) was a cohort study undertaken in China that examined depression at 6 week postpartum. The study cohort consisted of 90 women with a history of PE and 90 women, matched for the same time period of giving birth, who had normal blood pressure in pregnancy. The cohort was divided into two groups according to whether they screened positive for depression, and the analysis was performed comparing these two groups.

Englehard et al. (29) was a cohort study undertaken in The Netherlands that recruited 113 women within 2 years of hospital admission. Women with preterm and term PE were included and matched for gestational age with a normal comparison group. Depression and PTSD were measured. The women and their partners completed the screening instruments by post.

Fields et al. (42) used a medical data linkage to identify women for a long-term follow-up of cognitive impairment. Forty women who had a history of PE and 40 women with no such history were assessed 35–40 years following their pregnancy. Depression and anxiety formed part of the overall assessment but is reported separately.

Gaugler-Senden et al. (35) was a cohort study undertaken in The Netherlands that recruited 182 women who gave birth over an 11 year period. The cohort consisted of 104 women who had a history of preterm PE (<32 weeks gestation) and 78 women who had normal blood pressure in pregnancy, matched for gestational age at birth. Depression and PTSD was measured at two time points; women were asked to recall how they felt shortly after giving birth and the current time which was 7 years postpartum on average.

Habli et al. (43) was a retrospective cohort study undertaken in the US, using the US based HELLP Syndrome Support website to recruit 128 women. These women had experienced severe PE one to 31 years ago, with the mean follow-up being 5 years. Study designed surveys were completed via post, telephone or interview. Depression and anxiety prevalence was determined according to whether women reported being diagnosed by a physician with either of these mental health disorders.

Hoedjes et al. (44) was a cohort study undertaken in The Netherlands that recruited 174 women within 6 weeks after the birth. Depression was measured in women who experienced mild or severe PE at three time points: 6, 12, and 26 weeks postpartum. Comparisons were made between the two groups at each of the time points.

Hoedjes et al. (30) was a cohort study undertaken in The Netherlands, recruiting 149 women within 6 weeks after the birth. PTSD symptoms were measured in women who experienced mild or severe PE, at 6 and again at 12 weeks postpartum. Comparisons were made between the two groups at each of the time points.

Mautner et al. (45) was a cohort study undertaken in Germany that recruited 90 women with a complicated pregnancy, between 24 and 37 weeks gestation. Depression was measured during the pregnancy, 2-5 days and 3-4 months postpartum. The cohort consisted of women with HDP ($n = 18$), gestational diabetes ($n = 11$), preterm birth (32), and an uncomplicated pregnancy ($n = 29$). Comparisons were made between pregnancy groups at each of the time points.

Mommersteeg et al. (46) was a long term follow-up study conducted in The Netherlands examining depression and anxiety in women with a history of early onset PE (20–32 weeks gestation at onset), compared with a maternal aged matched non-PE comparison group. Questionnaires regarding depression and anxiety were completed, on average 14 years after the index pregnancy.

Porcel et al. (47) was a cross sectional online survey conducted via the worldwide Preeclampsia Foundation website. Women self-reported a diagnosis of HDP and were asked to invite friends and family who did not have a history of HDP to complete the survey, forming a normal comparison group. It was a large study with 1,076 women in the HDP group and 372 in the normal comparison group. The time between the index pregnancy and completion of the questionnaire is not stated.

Postma et al. (48) was an observational cohort study conducted in The Netherlands. It was a long-term follow-up of women already participating in a research project. There were 46 women with a history of eclampsia, 51 with a history of PE, and 48 women who had a normotensive pregnancy, matched for age. The average elapsed time since the index pregnancy was 7 years. The main focus of this study was neurocognitive function after PE and eclampsia, however depression and anxiety were assessed.

Postma et al. (49) was a retrospective cohort study undertaken in The Netherlands. Women with a history of eclampsia or PE were combined to form one group and the results were compared to women who were normotensive in their pregnancy. Although difficult to confirm, this study seems to have been an extension of the follow-up period in the above study. The cohort consisted of 41 women with prior eclampsia, 49 with a history of PE, and 47 women with no such history. The main focus of the study was cerebral white matter lesions and cognitive functioning following HDP, with depression and anxiety included in the assessment.

Stramrood et al. (31) was a prospective longitudinal cohort study undertaken in The Netherlands. The objective was to compare the prevalence and risk factors for PTSD in women with PE or preterm premature rupture of membranes (PPROM) compared to women with uncomplicated pregnancies. Women with PE were recruited in the antenatal period and depression and PTSD were measured at three time points: in pregnancy, 6 weeks and 15 months after the birth. The cohort consisted of women with PE or PPROM, and controls.

Mean scores between women with a history of preterm severe PE and preterm birth without PE at two time points postpartum reported no statistical difference in scores between the two groups (36), but notes that the mean scores improved with time (36). Women in this study were asked to recall and score symptoms from the immediate postpartum period for the first time point, with an average elapsed time of 7 years since the index pregnancy for the second time point.

Anxiety

There were eight studies that investigated the association between HDP and anxiety (28, 34, 40, 42, 43, 46, 48, 49). Prevalence of

TABLE 3 | Summary of screening instruments for depression.

	Design	Score	Validated	Cost	Comments
BDI	21 questions Answer on feelings in past 2 weeks Scored on scale 0–3	>13 indicates depression Higher scores indicate greater depressive symptoms	Yes	Yes	Includes questions on tiredness and sleeping difficulties
CES-D	20 questions Answer on feelings in past week Scored on scale 0–3	>15 indicates depression Higher scores indicate greater depressive symptoms	Yes	No	Includes questions on tiredness and sleeping difficulties
EPDS	10 questions Answer on feelings in past week Scored on scale 0–3	Higher scores indicate greater depressive symptoms	Yes	No	Used widely through pregnancy and the postpartum period
HADS	14 questions Answer on feelings in past week Scored on scale 0–3	>10 indicates depression Higher scores indicate greater depressive symptoms	Yes	No	Mixture of questions regarding depression and anxiety. Depression and anxiety can be scored separately
PQH-9	9 questions Answer on feelings in past 2 weeks Scored on scale 0–3	>4 indicates depression Higher scores indicate greater depressive symptoms	Yes	No	Includes questions on difficultly sleeping and energy levels
ZDS	20 questions Scored on a scale of 1–4 Answer on feelings in 'past several days'	Higher scores indicate greater depressive symptoms	Yes	No	Includes questions on difficultly sleeping and feeling tired

BDI, Beck Depression Inventory (50); CES-D, Center for Epidemiological Studies Depression Scale (51); EPDS, Edinburgh Postnatal Depression Scale (52); HADS, Hospital Anxiety and Depression Scale (53), PQH-9, Patient Health Questionnaire (54); ZDS, Zung Depression Scale (55).

anxiety was reported in six of these studies and symptom severity in seven using mean or median scores. Seven of the studies were observational cohort studies and one was a descriptive study. The studies originated from three different countries; The Netherlands ($n = 5$), US ($n = 2$), and Iran ($n = 1$). There were five different screening instruments used, and all except one have been validated for accuracy and validity (**Table 4**).

Prevalence of Anxiety

The prevalence of anxiety following HDP was reported between 26 and 32% in two publications (43, 46), which is slightly higher than the general postpartum population. Both of these studies were long term follow-up studies with assessment of anxiety undertaken up to 31 years postpartum.

There was no difference in the prevalence of mild anxiety in women who had experienced early onset PE compared to women without a history of PE (46), with a reported prevalence of 31 vs. 27%, respectively ($p = 0.325$). The average time elapsed since the index pregnancy in this study was 14 years. On further analysis, adjusting for age, education level, body mass index (BMI), having a partner, being unemployed, and physical activity, the results showed no difference in the prevalence of anxiety between the two groups.

The prevalence of anxiety in women who experienced HELLP syndrome was reported as 26% (43). In this study anxiety was measured by women within 1 month of the birth, self-reporting a diagnosis made by a physician and treated accordingly. The gestation at the time of birth was not important, with 27% of those who gave birth at 28 weeks gestation or less and 26% of those women giving birth after 28 weeks gestation, reporting a diagnosis of postpartum anxiety ($p > 0.99$).

Anxiety Symptom Severity

Seven studies reported on anxiety symptom severity using mean or median scores derived from a validated instrument (28, 34, 40, 42, 46, 48, 49). Higher scores were reported from women in the HDP group when compared with women in the normal comparison group, however the majority of studies did not reach statistical significance. The two studies that reported statistically significant higher anxiety scores in the PE group compared to the comparison group (48, 49) were small studies where women completed the questionnaire, on average, 6 years after their pregnancy. The main focus of both these studies was cognitive functioning after a pregnancy complicated with PE, and there was no reporting of any other factors or life events that may have affected the woman's anxiety.

No significant difference in anxiety scores was reported by primiparous compared with multiparous women at both the 2 and 6 week postpartum following a pregnancy complicated with PE (40), although there were no details of the scores given in the publication. No significant difference in mean scores was found in the four groups studied by Baecke et al. (28). These groups were women who experienced preterm PE, term PE, preterm birth without HDP, and term birth without HDP ($p = 0.27$). In a study examining anxiety following eclampsia and PE, statistically significant higher mean scores were reported by women who had experienced eclampsia compared to those women with a history of PE and those who were normotensive in pregnancy ($p < 0.005$) (48), suggesting that the more severe the HDP, the more severe the anxiety is.

Post-traumatic Stress Disorder

There were seven studies that investigated the association of PTSD with HDP (28–31, 35, 40, 59), with six reporting

TABLE 4 | Summary of screening instruments for anxiety.

	Design	Score	Validated	Cost	Comments
BAI	21 questions Answered on feelings in past week Scored on scale 0–3	0–21 low anxiety 22–35 moderate anxiety >35 potentially concerning levels of anxiety	Yes	Yes	Designed to minimize the overlap between depression and anxiety
GAD-7	7 questions Answer on feelings in past 2 weeks Scored on scale 0–3	0–5 mild anxiety 6–10 moderate anxiety 11–21 severe anxiety	Yes	No	Concludes with extra question about the impact on everyday activities
HADS	14 questions Answer on feelings in past week Scored on scale 0–3	>10 indicates anxiety Higher scores indicate greater anxiety	Yes	No	Mixture of questions regarding depression and anxiety. Depression and anxiety can be scored separately
STAI	40 questions (20 on state anxiety, 20 on trait anxiety) 4 point Likert Scale	State and trait anxiety scored separately. Scores range from 20 to 80 in each sub-scale >40 clinically significant. Higher scores indicate greater anxiety	Yes	Yes	Used widely in research Lengthy questionnaire requiring 15–20 min to complete

BAI, Beck Anxiety Inventory (56); GAD-7, General Anxiety Disorder scale (57); HADS, Hospital Anxiety and Depression Scale (53); STAI, State Trait Anxiety Inventory (58).

TABLE 5 | Summary of screening instruments for PTSD.

	Design	Score	Validated	Cost	Comments
BSSS	7 yes/no questions Scored 1 for 'yes', 0 for 'no' Answered on feelings in past month	>4 PTSD	Yes	No	Measures avoidance and numbing, hyperarousal
IES	22 items Scored on scale 0–4 Answered on feelings in past week	24–32 some symptoms 33–37 probable diagnosis of PTSD >37 PTSD	Yes	No	Measures intrusions, avoidance, and numbing, hyperarousal
PPQ	14 items Scored on scale 0–4	>18 PTSD	Yes	No	Designed to measure PTSD symptoms related to childbirth and symptoms during postnatal period Measures intrusions, re-experiencing, avoidance, and numbing, hyperarousal
PSS	17 items Scored on a scale 0–3	13 and over likely PTSD	Yes	Yes	Measures re-experiencing, avoidance, and arousal Based on DSM-IV
SRI for PTSD	22 items Scored on a scale 1–4	>51 PTSD	Yes		Based on DSM-IV

BSSS, Breslau Short Screening Scale (60); IES, Impact of Event Scale (61); PPQ, Perinatal Post-traumatic Stress Questionnaire (62); PSS, Post-traumatic stress Symptom Scale (63); SRI for PTSD, Self-rating inventory for PTSD (64).

on prevalence and three reporting on symptom severity by using mean scores for the instruments used. There were five observational cohort studies, one descriptive study and one cross-sectional on-line survey. The studies were conducted in The Netherlands ($n = 5$), Iran ($n = 1$), and the remaining one was a world-wide survey led by researchers in the US. All studies used validated instruments to screen for PTSD and there were five different instruments used (**Table 5**).

Prevalence of PTSD

The prevalence of PTSD following HDP varied between 5.1 and 43% across the seven studies. When compared to women who did not have a history of HDP, a higher prevalence of PTSD was reported in women who experienced HDP in some of the studies (29, 31, 47). In the world wide survey via the PE Foundation website (47), 43% of women with a history of HDP screened positive for PTSD compared to 14% of women in the normal comparison group ($p < 0.01$). In this study, after adjusting for psychiatric treatment, parity, and age at the time of the pregnancy, women with a history of PE were more than four times as likely to screen positive for PTSD when compared to women with a normotensive pregnancy (OR = 4.46, 95% CI: 3.20–6.20).

The study by Stramrood et al. (31) measured PTSD at two postpartum time points (6 weeks and 15 months) and compared results between women in the PE and normotensive groups at

each of these time points. There was a slight change in prevalence over time in both groups (10.5–11.4% in the PE group and 3–0% in the normotensive group), with the PE group consistently reporting a higher prevalence of PTSD. The other study to report PTSD prevalence at two time points (30), found no statistically significant difference in PTSD in women with a history of PE, at 6 and 12 weeks postpartum, with rates of 8.6 and 5.1%, respectively ($p = 0.083$).

Irrespective of the cause of the preterm birth, Baecke et al. (28) found that more women with a history of a preterm birth met the threshold score for PTSD than women who gave birth at term (preterm PE 44%, preterm birth 41%, term PE 11%, term uneventful 11%). This study suggests that the sequelae of a preterm birth led to PTSD, not the PE itself. In the Dutch study by Engelhard et al. (29), 28% of women who gave birth preterm, with or without PE, met the diagnostic criteria for PTSD, suggesting that the preterm birth rather than PE is the trigger. However, in this same study, the term PE group reported a PTSD prevalence of 17%, similar to that in preterm PTSD, while the normotensive term group women had no PTSD, suggesting that PE may have an impact at term.

A further study compared PTSD prevalence in multiparous and primiparous women with a history of PE (40). Although the reported PTSD prevalence was higher in the multiparous PE group, the result was not significant (32 vs. 21%, respectively $p = 0.24$) suggesting that parity is not a contributing factor.

PTSD Symptom Severity

There were three studies that reported on PTSD symptom severity following PE (28, 35, 40), all with different study designs and all using a validated instrument to score PTSD symptoms.

When mean scores were compared between primiparous and multiparous women following PE, the results were not statistically significant although the multiparous women scored slightly higher (mean score 4.4 for primiparous women and 5.4 for multiparous women $p = 0.05$) (40).

The mean PTSD scores for women with a history of preterm birth, irrespective of the cause, were higher than the term birth group, suggesting a preterm birth contributes to more symptom severity (28).

Another study (35) compared mean PTSD scores between women with a history of preterm severe PE and preterm birth without PE at two time points. There was no difference in mean scores between the groups at the postpartum recall time-point. However, there was a significant difference ($p = 0.02$) between the groups at the time of the study being undertaken which was, on average, 7 years after the index pregnancy, despite the mean score being slightly lower. There is no information about other life events that may have contributed to this difference.

DISCUSSION

There is limited literature available to address the important issue of depression, anxiety, and PTSD following pregnancies complicated by hypertension with only 17 studies identified that looked specifically at this association. The current evidence suggests that women with a history of HDP have a greater likelihood of depression and PTSD, but the heterogeneity, different study populations and different methods of assessment preclude any definitive interpretation. There was no association found between HDP and the prevalence or severity of postpartum anxiety in the majority of studies included in this review. The current literature also suggests that the severity of the HDP may be positively correlated with the severity of depressive, anxiety and PTSD symptoms. However, it is not clear what the main driver for the psychological morbidity might be—the demands of PE, the associated events such as a preterm birth or if it predated the pregnancy. The focus of this review was on postpartum mental health conditions, hence pre-existing and/or antenatal mental conditions were not investigated.

The literature on the psychological impact of HDP was methodologically varied, including selection and recall bias and most study sample sizes were small. There was a variation in the study populations including gestation, severity of HDP and time since the index pregnancy. Furthermore, multiple instruments were used, along with different threshold cut-off scores to define abnormal results. These methodological limitations made it difficult to determine if there is a true association between HDP and depression, anxiety and PTSD.

A key feature with the studies included is that they originate from just five countries; 11 from The Netherlands, three from the US, and one each from China, Germany, and Iran. It may not be possible to accurately translate the results of these studies to other countries, due to the differences in culture, health care systems, and management of HDP and/or mental health disorders. The performance of the measuring instruments may also be affected by cultural practices, differences in access and availability of, obstetric and psychiatric care and differences in emotional support provided. Some researchers (65, 66) suggest that culture affects the response people make to psychiatric assessments due to the differences in their underlying attitudes, beliefs, and behavior. Beliefs of mental health distress, cultural understanding of mental health, and culturally or context specific terms can also lead to different scores on measuring instruments (67).

Previous reviews of women's mental health following HDP have made similar conclusions to those drawn here. A systematic review (32) reported on postpartum depression, anxiety, and PTSD following a pregnancy complicated with HDP. The authors conclude that the evidence regarding depression is mixed but overall suggests an association between PE/HELLP and depression, with higher depression prevalence and severity in the women with previous PE/HELLP compared to women without such history. In regards to anxiety, there were no significant associations between PE and anxiety scores although higher scores were reported among women with PE. PTSD was reported in this same review and although higher PTSD prevalence and severity was reported by women following PE/HELLP, results were not statistically significant. In another systematic review (27) investigating the possible association between PTSD and several pregnancy complications, including PE, the authors conclude that there may be some evidence to suggest a link between PE and PTSD but the evidence was not robust (27). However, they suggest that PTSD and its symptoms may present following particularly severe cases of maternal morbidity (not specifically HDP), that involve poor neonatal outcomes.

CONCLUSION

While there is no definitive evidence that having HDP leads to increased postpartum depression, anxiety, or PTSD, women who experience HDP may be at increased risk of developing these mental health disorders. This is particularly true for those women who experience the more severe forms of HDP and/or give birth preterm. Routine screening for all these mental health disorders on all women in the postpartum period may be beneficial, however there is an increased need for screening to be undertaken in women who experience HDP. Screening this group of high risk women will alert clinicians to the need for additional follow-up and referral. More research on the benefits and risks of such an approach is needed.

AUTHOR CONTRIBUTIONS

LR, GD, and CH contributed to the conception and design of the review. LR led the review of the literature, the analysis, and wrote the first draft including drafting the tables and figure. All authors contributed to manuscripts drafts and revisions, and all approved the final submitted version.

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REVIEW
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A Systematic Review of Vascular Structure and Function in Pre-eclampsia: Non-invasive Assessment and Mechanistic Links

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Hypertensive disorders of pregnancy, such as pre-eclampsia, are known to be independently associated with the development of premature cardiovascular disease (CVD) in women. In pre-eclampsia, the placenta secretes excess anti-angiogenic factors into the maternal circulation, leading to widespread endothelial damage, and inflammation. This endothelial damage is evidenced to persist beyond the acute illness. However, whether it is permanent and responsible for the elevated rates of premature CVD seen in this at-risk group remains unclear. A systematic review of the available literature with respect to vascular structure and function prior to, during and after a pregnancy complicated by pre-eclampsia was performed. Studies non-invasively assessing vascular structure using carotid intima-media thickness (CIMT), retinal microvasculature caliber, CT coronary angiogram, or coronary calcium scores were included. Vascular function was assessed using brachial flow-mediated dilation (FMD), pulse wave analysis (PWA), and peripheral arterial tonometry (PAT). In total 59 articles were included (13 CIMT, 5 CTCA/Ca score, five retinal microvasculature, 27 FMD, 7 PAT, and 14 PWV/PWA), consisting of prospective and retrospective cohort, and case-control studies. Change in vascular structure was evidenced with significant increases in CIMT by 73–180 μm greater than that of non-affected women. This is tempered by other studies reporting resolution of structural changes postpartum, highlighting the need for further research. Accelerated coronary calcification and plaque deposition was identified, with greater rates of increased calcium scores and subclinical coronary artery disease shown by CTCA in women with a history of pre-eclampsia at 30 years postpartum. Impaired endothelial function was consistently reported prior to, during and immediately after pregnancy as evidenced by differences in FMD of 1.7–12.2% less than non-affected women, an increase in PWV by 13.2–26%, and reduced retinal microvascular caliber and arterial elasticity indices. The evidence was less conclusive for the persistence of long-term endothelial dysfunction. Understanding the underlying mechanistic links between pre-eclampsia and CVD is a key step to identifying targeted therapies

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aimed at "repairing the endothelium" and attenuating risk. This review has highlighted the need for a greater understanding of vascular structure and function following pre-eclampsia through high quality studies with large sample sizes, particularly in the longer postpartum period when clinical CVD disease starts to manifest.

Keywords: pre-eclampsia, vascular changes, endothelial dysfunction, cardiovascular disease, pregnancy

INTRODUCTION

Pre-eclampsia (PE) is a malignant syndrome of pregnancy mediated by abnormal placentation and subsequent dysfunction. It affects 2–8% of all pregnancies (1) and occurs most commonly in the third trimester but may also develop intrapartum or early postpartum (2). Pre-eclampsia is characterized by hypertension (>140/90 mmHg) after 20 weeks gestation, with either proteinuria, maternal organ dysfunction (hematological, renal, neurological or hepatic), or uteroplacental dysfunction such as fetal growth restriction (2). Globally, it is a leading cause of both maternal and fetal death (3).

The relevance of PE to maternal health, however, extends beyond the acute pregnancy and early postpartum period. PE has been identified in numerous studies to be an independent risk factor for the development of premature maternal cardiovascular disease (CVD). These studies include cohort and case-control studies of both retrospective and prospective design; and several systematic reviews and meta-analysis of large populations (up to 2 million women). Each study population varies in terms of patient composition, severity of the illness, maternal age and follow-up period. Although this heterogeneity naturally leads to variations in specific disease hazard ratios, they all demonstrate a strong association between CVD and PE. The CHAMPS study, for example, demonstrated a more than doubling of the risk of CVD in women who had experienced a pre-eclamptic pregnancy as compared to women with an unaffected pregnancy (HR 2.1; 95% CI, 1.8–2.4) (4).

Whilst the epidemiological link has been clearly demonstrated, the mechanisms through which PE potentially confers this elevated risk of CVD are incompletely understood, nor is it proven to be a causal relationship. Pathological failure in the vascular remodeling of maternal spiral arteries and resultant hypoperfusion of the placenta is integral to the development of PE (1). This sets off an acute cascade of oxidative stress, inflammation and endothelial dysfunction. Systemic endothelial dysfunction has also been demonstrated to be involved in the development and progression of atherosclerosis and kidney disease, and thus it has been postulated that this may explain the link between PE and CVD (5). Whether pre-eclampsia-induced inflammation and endothelial function persist beyond pregnancy, however, has not been conclusively elucidated.

A further challenge in the understanding of PE and its vascular ramifications is that rather than being one single disease process, it is likely comprised of distinct phenotypes with differing long-term risk profiles. Early-onset PE (onset before 34 weeks gestation) has been linked to impaired trophoblastic differentiation within maternal spiral arteries causing placental hypoxia, release of placental debris such as sFlt1 (soluble fms-like tyrosine kinase) and soluble endoglin (sEng) into maternal circulation and thereby systemic inflammation and oxidative stress (6). Whereas, late-onset PE (>34 weeks at disease onset) is more often associated with pre-existing maternal conditions/cardiometabolic risk factors that may compromise the integrity of the endothelium (6). Current evidence suggests that early-onset PE is a stronger risk factor for the development of CVD than the later onset form (7).

To date, there has been no comprehensive review of the available evidence with respect to maternal vascular structure and function in association with a pre-eclamptic pregnancy. The aim of this systematic review, therefore, is to evaluate the current evidence base with respect to vascular structure and function prior to disease onset, during PE, immediately postpartum and long term. This will involve analysis via non-invasive modalities including flow mediated dilation (FMD), peripheral arterial tonometry (PAT), carotid intima-media thickness (CIMT), retinal microvasculature, pulse wave analysis and velocity (PWA/PWV), CT coronary angiogram, and calcium scores. The evidence presented intends to shed light on the pathophysiological links between PE and CVD.

Method

We performed a systematic review of studies reporting on non-invasive assessment of endothelial structure and function in association with PE (prior, during, after). This review was conducted in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) statement (8).

Search Strategy, Study Selection, and Data Extraction

Medline via Ovid (from 1946 to September 2019) and EMBASE via Ovid (from 1980 to September 2019) were searched systematically for relevant trials (**Table 1**). The search had no language restriction and used subject headings relevant to PE and hypertensive disorders of pregnancy.

Our primary aim was to assess the vascular structure and function associated with PE using these key non-invasive modalities: Carotid intima media thickness, coronary artery calcification, retinal microvasculature, flow-mediated dilatation, peripheral arterial tonometry, and pulse wave analysis/velocity. The titles and abstracts of all identified articles were extracted and screened for an initial assessment of eligibility. Full text versions of potentially eligible studies were reviewed to reach a final decision on inclusion or exclusion. We excluded studies not conducted in humans, reviews, editorials, letters, non-English, abstract-only, and duplicate reports. Data were

TABLE 1 | Electronic database search terms.

MEDLINE via OVID	*EMBASE via OVID*
1 Pre-eclampsia.mp. or Pre-Eclampsia/	1 Pre-eclampsia.mp. or Pre-Eclampsia/
2 Hypertension, Pregnancy-Induced/, or Pre-Eclampsia/ or Pregnancy complications, Cardiovascular/ or Hypertensive disorder of pregnancy.mp.	2 Hypertension, Pregnancy-Induced/ or Pre-Eclampsia/ or Pregnancy complications, Cardiovascular/ or Hypertensive disorder of pregnancy.mp.
3 Gestational Hypertension.mp. or Hypertension, Pregnancy-Induced/	3 Gestational Hypertension.mp. or Hypertension, Pregnancy-Induced/
4 Intima media thickness.mp. Carotid Intima-Media Thickness/	4 Intima media thickness.mp. Carotid Intima-Media Thickness/
5 Retinal Microvasculature.mp.	5 Retinal Microvasculature.mp.
6 Flow mediated dilatation.mp.	6 Flow mediated dilatation.mp.
7 Pulse wave velocity.mp. or Pulse Wave Analysis/	7 Pulse wave velocity.mp. or Pulse Wave Analysis/
8 Computed Tomography Angiography/ or Tomography, X-Ray Computed/ or Coronary Angiography/ or CT coronary angiography.mp.	8 Computed Tomography Angiography/ or Tomography, X-Ray Computed/ or Coronary Angiography/ or CT coronary angiography.mp.
9 Peripheral arterial tonometry.mp.	9 Peripheral arterial tonometry.mp.
10 Vascular structure.mp.	10 Vascular structure.mp.
11 Endothelial dysfunction.mp.	11 Endothelial dysfunction.mp.
12 Endothelium, Vascular/ or endothelial function.mp.	12 Endothelium, Vascular/ or endothelial function.mp.
13 vascular function.mp.	13 vascular function.mp.
14 1 or 2 or 3	14 1 or 2 or 3
15 4 or 5 or 6 or 7 or 8 or 9	15 4 or 5 or 6 or 7 or 8 or 9
16 10 or 11 or 12 or 13	16 10 or 11 or 12 or 13
17 humans.mp. or Humans/	17 humans.mp. or Humans/
18 14 and 15 and 16 and 17	18 14 and 15 and 16 and 17

extracted into an electronic spreadsheet and review of trials for eligibility, data extraction, and quality assessment were conducted independently by two authors (SK, SP) using a standardized approach. Any disagreement was settled by consultation with a third author (CA).

The key outcomes studied were vascular structure and function, arterial stiffness and endothelial dysfunction. Reference lists of journal articles were also screened for additional citations that could be included in the search criteria. Given the heterogeneity of study design, cohorts and timing of investigations, a meta-analysis was not performed. The key results of the included studies were discussed methodically by investigative tool and timeline in the results.

RESULTS

Systematic Review

In total 59 studies were identified for inclusion; 23 related to vascular structure (13 CIMT, five CTCA or Ca score, five retinal microvasculature) and 48 relative to vascular function (27 FMD, 7 PAT, 14 PWV/PWA) were included, with several studies implementing more than one modality (**Figure 1**). A meta-analysis was not performed due to the heterogeneity of studies with respect to participant population, disease severity, multiple modality use, methodology and timing of follow-up. However, the key findings for each modality are described in detail below.

Vascular Structure

Carotid Intima-Media Thickness

Carotid intima-media thickness (CIMT) is a well validated, non-invasive marker of pre-clinical atherosclerotic disease. It involves ultrasound evaluation of the thickness of the intimal and medial carotid arterial wall. Data have shown that an increased CIMT confers an elevated risk of coronary atherosclerotic lesions and future cardiovascular disease in both histological and epidemiological studies (9, 10).

CIMT is an attractive tool for the assessment of vascular structure in pregnancy as it is non-invasive and does not rely on the use of ionizing radiation. The key consistent findings from the systematic review of 13 available CIMT studies in PE is that CIMT increases during a pre-eclamptic pregnancy as compared to a non-effected pregnancy and persists up to 10 years postpartum.

Evidence supporting an increase in CIMT prior to PE onset, however, is limited. One study measuring CIMT in 601 pregnant women found that CIMT was significantly increased within the first trimester in the 143 who subsequently developed PE compared to the 420 women who remained normotensive (580 ± 100 vs. $340 \pm 160\,\mu m$; $P < 0.03$) (11). Further to this, the women who subsequently develop gestational hypertension did not have a significantly increased CIMT.

There are several studies evaluating CIMT during pregnancy with varied cohorts and heterogenous results (12–14). For example, a prospective study of 22 women with late onset PE reported a significant increase of $108\,\mu m$ in CIMT during pregnancy as compared to pregnant controls (459 ± 95 vs. $351 \pm 85\,\mu m$, $P = 0.0001$) (15). Another study, comparing 50 early-onset and 50 late-onset PE cases determined that CIMT was significantly increased in late-onset PE compared to the normotensive controls, yet this increase was not significant in the early-onset group, even though similar blood pressures were observed between the two PE groups; this suggests distinct aetiological vascular changes contributing to the two forms of PE (13). Conversely, other studies have only identified elevated CIMT in women with chronic hypertension in pregnancy rather than PE (16). Whilst inconclusive, these studies raise the possibility that vascular structural changes may manifest as a

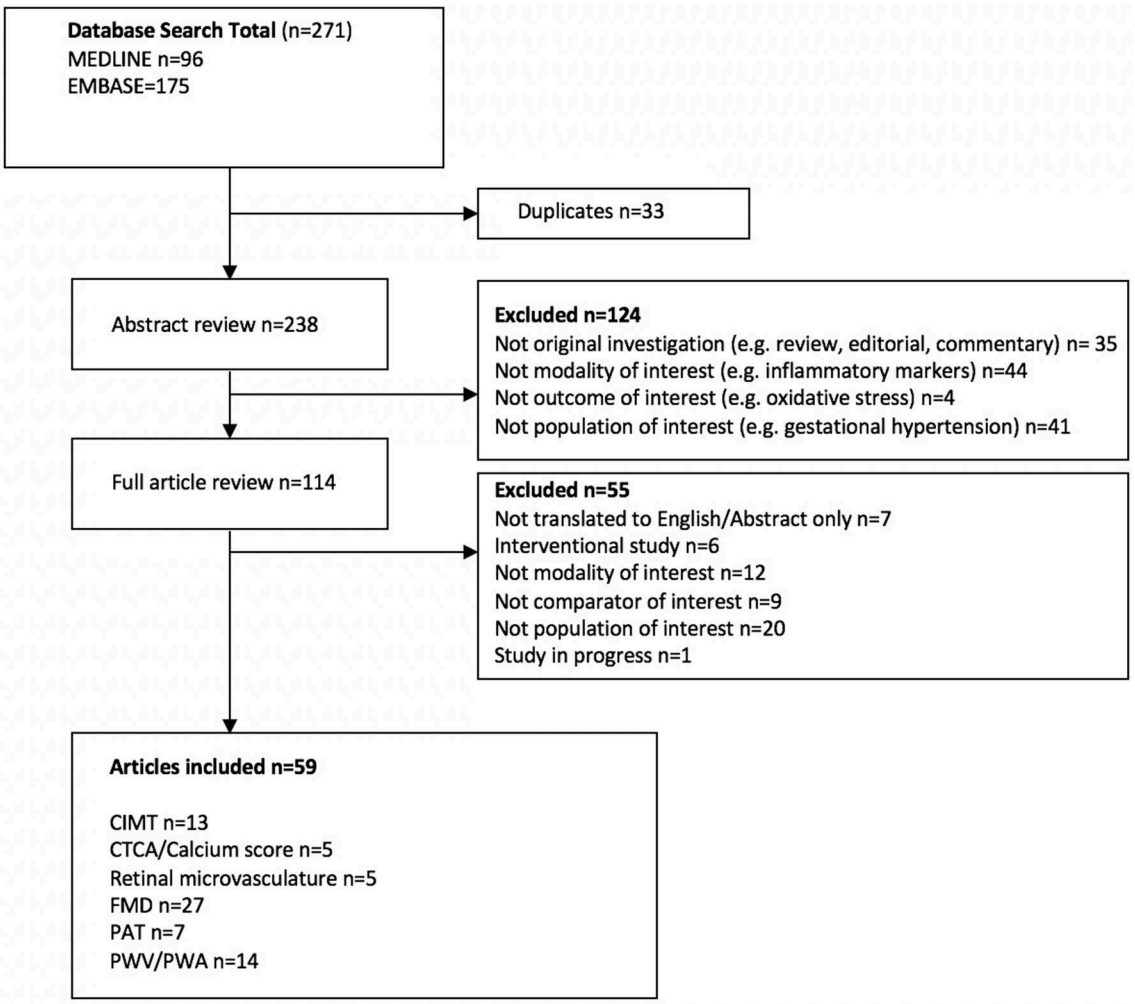

FIGURE 1 | Flow diagram illustrating the process of study identification.

result of hypertension during pregnancy and may be an adaptive response to increased arterial stress.

In the post-partum period, several studies report discrepant findings with respect to the persistence of increased CIMT following a pregnancy complicated by gestational hypertension or PE. A study of 22 early-onset PE cases found that CIMT was significantly increased in women at least 3 months postpartum by 73 μm ($p < 0.001$) as compared to 22 nulliparous women, but it was not found to be significantly increased compared to 22 women with a normotensive pregnancy (14). These findings suggest that an increased CIMT may reflect a normal physiological response to pregnancy rather than a pathological response to a hypertensive disorder of pregnancy. This is supported by an epidemiological study linking the number of births to a concurrent increase in CIMT in females over a 6 years follow-up period, suggesting that childbearing may independently impact the risk of cardiovascular disease (17). A more recent study of 34 women with previous PE, however, reported increased CIMT at least 12–24 months after pre-eclamptic pregnancy, suggesting that there is persistent structural arterial damage (18). Conversely, Yuan et al. refuted this finding, suggesting that the increase in CIMT seen during PE resolved by 18 months postpartum in their cohort. They suggested that carotid arterial remodeling may occur during pregnancy, but reverses or attenuates in the postpartum period (15). Interestingly, a prospective case-control study implementing a 12-weeks aerobic exercise training program in 24 women 6–12 months postpartum PE showed a significant decrease in CIMT after completing the training program (530 ± 138 vs. 580 ± 92 μm; $P < 0.01$). This decrease was also evident in healthy controls, suggesting that both groups can significantly decrease their cardiovascular risk profile postpartum (19).

The evidence with respect to the longer postpartum period is minimal. One study of women with a history of PE reported a significantly increased intima-media thickness ratio at both 1 and 7 years postpartum suggesting that there are still signs of sub-clinical atherosclerosis (20). Providing some clarity was a recent meta-analysis including a total of 813 women with a history of PE ≥ 10 years postpartum. This reported greater CIMT in the PE group compared to controls [0.18 mm (95% CI, 0.05–0.30 mm; *P*

$= 0.004$)] (21). Women with a history of PE who were on antihypertensives, but had no prior diagnosed cardiovascular event, still had a greater CIMT than women who had no history of PE, suggesting minimal CIMT recovery and chronic vascular changes after PE.

Taken together, these studies highlight the need for more robust prospective studies assessing CIMT throughout the course of a PE pregnancy and long-term postpartum to clearly elucidate the time course and persistence of subclinical vascular changes. From a clinical and practical perspective, the user-dependence and varied acquisition protocols in CIMT measurement and the lack of evidence that using CIMT to guide clinical decisions results in better outcomes, makes this a challenging clinical tool to implement broadly to evaluate the extent of vascular changes in women who have been affected by PE.

Cardiac Computed Tomography and Calcium Score

Coronary artery calcification (CAC) is an important marker of CVD. Coronary calcium scores are measured by Agatston units (AU) using computed tomography (CT). The St. Francis Heart study determined that for a coronary calcium score >100 AU, the relative risk for atherosclerotic CVD was 9.6 (6.1–13.9; 95% CI) (22). Additionally, calcification is believed to contribute to arterial stiffness, which further confers an increased risk of CVD (23). There is currently no evidence with respect to coronary calcium scores in women preceding or during a pre-eclamptic pregnancy. This is understandable, given the risks of exposing young women or a developing fetus to radiation.

Five studies were identified evaluating CT coronary angiogram (CTCA) or calcium score postpartum in PE. The data in the postpartum period suggests a strong association between PE and vascular structural changes. Coronary calcification has been evaluated in 4 studies using formal CTCA and in 1 study using CAC score alone. In a recent multicentre prospective cohort study, 164 women aged 45–55 years old with a history of PE 10–20 years prior demonstrated a higher risk of CAC >0 AU as compared to the cohort studies in the Multi-Ethnic Study of Atherosclerosis (RR 1.7; 95% CI, 0.4–19.3) (24, 25). A further study of a population of 151 women with a history of hypertension during pregnancy found that the odds of having a higher CAC was 1.52 (95% CI, 0.96–2.39) greater after adjustment for BMI, waist-hip ratio, and systolic/diastolic blood pressure; suggesting that hypertension during pregnancy independently increases the risk of CVD (26). Similar findings were demonstrated in another sample of 51 Caucasian women with a history of hypertension during pregnancy, of which 24 had an identified history of PE. Hypertension during pregnancy remained significantly associated with CAC even with additional adjustment for serum creatinine levels, urinary albumin creatinine ratio, menopause status, diabetes status and antihypertensive medication use (27). Furthermore, in a sample of 40 women >30 years after affected pregnancy, the frequency of a CAC >50 AU was greater in women with a history of PE (23 vs. 0%; $P = 0.001$). This prospective cohort study found that the odds of having a higher CAC in women with a history of PE was 3.2 (95% CI, 1.21–8.49) and 2.61 (95% CI, 0.95–7.14) times greater when adjusted for BMI and current hypertension, respectively (28). Lending further weight to this argument is a study of postmenopausal women 35 years following PE. In this cohort of 37 women, there was a significant increase in CAC scores ranging from 0 to 25 ($P = 0.026$) compared to those without a history of PE (29).

Whether PE inherently alters the vascular system of women or rather pregnancy unmasks subclinical CVD and potentiates a pathological increase in blood pressure cannot be elucidated from these above CAC and CTCA studies. These, however, are potential tools to assess the long-term extent of vascular damage associated with this disease, and to assist in risk stratifying women.

Retinal Microvasculature

Assessment of retinal vessel architecture using fundus photography is a novel potential cardiovascular risk marker. Increasing evidence suggests that retinal microvascular abnormalities are a reflection of hypertension and other vascular risk factors such as hyperglycaemia, central obesity and dyslipidaemia (30). Specifically, narrowing of retinal arteriolar vessels and widening of venular vessels has been shown to be associated with increased risk of hypertension (31).

In total, there were five studies identified that evaluated retinal microvasculature as a marker of deteriorating vascular structure in PE. These studies suggested persistent structural changes evident prior to disease onset, during PE and postpartum. Normally, a decrease in blood pressure during a normotensive pregnancy correlates with a significant increase in retinal arteriolar and venular caliber, before returning to normal after pregnancy (32). In PE, the assessment of retinal arterial vessels has been utilized to potentially assess a vascular response to systemic changes induced by the release of inflammatory markers into the maternal circulation. In a particular cohort of 92 women, a significant reduction in the caliber of arteriolar and venular vessels at 13 and 19 weeks gestation was found in the 9 women that subsequently developed PE, as measured by central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE), respectively (33). These findings were coupled with an absence in the normal physiological drop in blood pressure, suggesting an increase in peripheral vascular resistance occurring prior to clinical diagnosis of PE. Abnormalities of the retinal vasculature have been shown to reflect the existence of prior or current hypertension and have been associated with endothelial dysfunction and inflammation potentiated by cardiovascular risk factors (34). Therefore, given this is the first study to record a structural abnormality so early on in pregnancy, this correlation is suggestive of either pre-existing maternal factors that contribute to increased risk of developing PE, or the onset of dynamic vascular changes before the clinical presentation of PE. This is of potential great importance and relevance to first trimester PE screening algorithms and warrants further investigation.

Similar findings have been found both during PE and at 1 year postpartum (35). A study of the same population both during and 1 year postpartum found a significant decrease in central retinal artery equivalent diameter (CRAE) and central retinal vein equivalent diameter (CRVE) during PE followed by

a small recovery postpartum, however the decrease persisted. Furthermore, 63 women with a history of PE who were followed up at 6 years postpartum recorded a decrease in retinal arterial caliber (137.8 ± 14.4 *vs.* 145.8 ± 16.9 μm; $P < 0.001$). These findings remained when adjusted for various cardiovascular risk factors, including mean arterial pressure.

As a non-invasive, simple and inexpensive modality for assessing vascular resistance, this is a tool that requires further investigation. It has great potential to assist in the identification of women at risk of developing PE as well as a potentially simple clinical tool in monitoring consequential vascular damage in women previously affected by PE.

Vascular Function

Flow Mediated Dilatation and Peripheral Arterial Tonometry

Brachial flow-mediated dilatation (FMD) is an established non-invasive, ultrasound technique that allows for the investigation of endothelial function and cardiovascular risk. It measures endothelial dependent dilatation by recording the change in brachial arterial diameter mediated by nitric oxide release in response to an increase in shear stress (36). Normally, pregnancy is associated with an increase in FMD, which reflects improved endothelial function. A meta-analysis of 23 studies including 14,753 subjects found that brachial FMD is inversely associated with future CVD events (37). As such, it has become a potential modality for examining endothelial function in disease states throughout pregnancy and postpartum. Peripheral arterial tonometry (PAT) is based on similar physiological mechanisms, where the brachial artery is occluded to elicit transient ischemia peripherally and stimulate reactive vasodilatation, before hyperemia is induced once the cuff is deflated. The difference in PAT is that the endpoint that is measured is arterial pulse volume amplitude in the finger to thereby calculate a reactive hyperemia index (RHI) (38). A meta-analysis of 6 PAT studies and 1,602 subjects predicted a decrease in the relative risk of cardiovascular events for every 0.1 increase in the logarithmic value of RHI (RR 0.79; 95% CI, 0.71–0.87) (39).

Twenty-seven studies of FMD and seven of PAT were identified in this systematic review, with some predominant findings related to endothelial dysfunction in PE. Studies in high risk women who consequently develop PE have demonstrated that endothelial dysfunction precedes onset of the clinical disease. A prospective study of 15 high risk women who subsequently develop PE found significantly decreased FMD compared to those who remained normotensive prior to clinical disease onset, particularly between 24 and 28 weeks gestation (3.6 ± 2.38% vs. 8.42 ± 3.15%; $P = 0.001$) (40). Moreover, sensitivity of FMD as a predictor for high risk pregnant women in developing PE was 87.5% for early-onset and 95.5% for late-onset when a decrease of <2.5% on FMD was detected between 16 and 19 weeks and 24–27 weeks, suggesting that FMD can become a potential tool in predicting PE (6). In a recent cohort of 62 women who screened high risk for the development of PE, the 10 women who subsequently developed early-onset PE illustrated a significant difference in FMD measurements at 24–27 weeks gestation and at delivery as compared to uncomplicated pregnancies. There was no meaningful difference, however, at 16–19 weeks gestation, suggesting the absence of prior endothelial dysfunction (41). With respect to PAT as a measure of endothelial function, however, a study of 180 women in whom PAT was measured at 16 and 28 weeks gestation, of the 24 women who subsequently developed PE there was no significant difference in RHI between the cases and controls at either 16 or 28 weeks gestation (42).

Whilst there is strong evidence to suggest that endothelial function as measured by FMD is decreased during a pre-eclamptic pregnancy (16, 43–45), the timing and magnitude of this change is unclear. Supporting this, PAT measured in 105 PE cases with an average gestational age of 30 weeks illustrated a significantly reduced RHI compared to 110 normotensive controls at 1.70 (1.04–3.61) vs. 1.81 (1.18–4.62) ($P = 0.0269$), respectively (46). Interestingly, FMD has been demonstrated to be significantly reduced in pre-eclamptic women who present with bilateral uterine artery notches compared to those without (47). Bilateral uterine artery notching, in turn, is associated with placental ischemia, suggesting that there is increased high resistance in the uteroplacental circulation. This is shown to be linked with a more severe degree of endothelial dysfunction, but whether it is associated with early or late-onset PE has not been elucidated.

Evaluation of endothelial function via FMD in the postpartum setting reveals that the dysfunction seen in PE likely persists beyond the time of pregnancy. In the short term, studies have demonstrated that FMD is significantly lower in pre-eclamptic women between 3 and 6 months postpartum (48). At 3 months postpartum, FMD measurements were significantly reduced in 20 women ($p < 0.001$), who also exhibited impaired diastolic and systolic left ventricular function during pregnancy, which interestingly did not persist concurrently with endothelial dysfunction (45). This finding, however, was not universally reported, with one study of 30 women reporting no significant difference in FMD at 1 month after delivery in both mild and severe PE (16). The majority of studies, however, report reduced FMD postpartum. For example, a study of 20 women 2–3 years postpartum, reported a reduced FMD (10.7 ± 8.6% vs. 17.9 ± 7.9%; $P = 0.04$) and arterial distensibility in women following PE, which was found to be proportionate to decreased infant birthweight (49–51).

In consolidation, a recent meta-analysis examining FMD throughout different time courses of PE concluded that FMD was reduced both before the clinical onset and during PE. This lower FMD persisted 3 years postpartum after excluding studies that included women with chronic hypertension and a history of smoking (52).

Evidence regarding the long-term persistence of endothelial dysfunction following a pre-eclamptic pregnancy remains unclear. Studies have shown endothelial dysfunction to persist up to 5 years postpartum (53–55). However, PAT measured in 26 women with previously affected pregnancies 5–8 years prior showed no significant difference in endothelial function ($P = 0.7$). Interestingly, the 11 women in the PE group who delivered a small for gestational age infant had a significantly lower RHI compared to the controls ($P = 0.005$), suggesting other factors such as low birth weight and preterm birth playing

a role in persistent endothelial dysfunction (56). Studies that assessed FMD <10 years following the index PE pregnancy, do not support the hypothesis of persistent endothelial dysfunction mediating CVD risk. In 39 women 9–11 years postpartum PE, no significant difference in mean FMD was observed compared to women with uncomplicated pregnancies (8.28 ± 3.68% vs. 8.21 ± 4.02%; $P = 0.90$) (57). Further supporting this finding, another population of women followed up at both 1 year and 11 years postpartum PE reported that FMD was significantly decreased at 1 year, but had normalized at 11 years, therefore further suggesting endothelial function recovery over time (58).

Pulse Wave Analysis and Pulse Wave Velocity

Arterial stiffness is a pathological process that develops secondary to changes within the arterial system such as degeneration of elastin and increases in collagen, leading to a thickening of the arterial wall. Pulse wave velocity (PWV) is considered to be the most accurate non-invasive modality in evaluating arterial stiffness. Pulse wave analysis (PWA) is another modality which measures arterial function by deriving variables from arterial waveforms using applanation tonometry. These waveforms are characterized by variables including Augmentation Index (AIx), which is a measure of the proportion of the central pulse pressure attributed to the reflected pulse wave (59). A recent meta-analysis of 14,673 Japanese participants showed that an increase in brachial-ankle (ba)PWV independently predicted an increased risk of developing CVD (60). Similarly, a recent study of the Framingham Heart Study cohort found that high carotid-femoral (cf)PWV, adjusted for age and sex, was associated with significantly increased risk of a cardiovascular event and this was further increased when coupled with central pulse pressure (HR 1.79; 95% CI, 1.30–2.46) (61). As such, PWV is considered the gold standard in measuring arterial stiffness and a potential tool in monitoring vascular function within women affected by PE (59).

The key consistent findings of the 14 studies identified was an increase in cfPWV and AIx prior to disease onset, during and up to 2–3 years postpartum. Although there is little evidence, cfPWV has been previously demonstrated to be increased in women at 23 weeks gestation who subsequently developed PE (62). Further to this, there was no significant difference between women with early-onset and those with late-onset as well as those with abnormal and normal doppler uterine artery examination. CfPWV has been reported to be a strong predictor for the development of PE in high risk women when measured between 22 and 26 weeks gestation, especially in early-onset PE (63). These findings suggest that arterial stiffness pre-dates the development of the clinical presentation. To consolidate this finding, in a cross sectional study of a rural South African population, 85 women with PE displayed significantly increased cfPWV and AIx (64).

With respect to the postpartum period, Robb et al. reported that arterial stiffness increases in both normal pregnancy and PE compared to nulliparous women, however augmentation index and cfPWV had a significantly greater and more prolonged increase within the PE group, persisting up to 7 weeks postpartum (65). Similarly, a significantly increased AIx was reported in 20 women with previous PE 2–3 years postpartum (37.7 ± 5.1% vs. 23.8 ± 4.4%; $P < 0.001$) (49). Conversely, 30 women 5–6 years after the index pre-eclamptic pregnancy exhibited no significant increase in pulse-wave reflections, thereby suggesting there is no permanent difference in arterial distensibility postpartum (66). This was supported by 2 other observational cohort studies where PWV was measured at <10 years postpartum. There was no significant difference in cfPWV in the pre-eclamptic women analyzed in either of these studies (58, 67). Although a non-significant increase in PWV was reported, this may be correlated to an increase in blood pressure prevalent within the PE group (67).

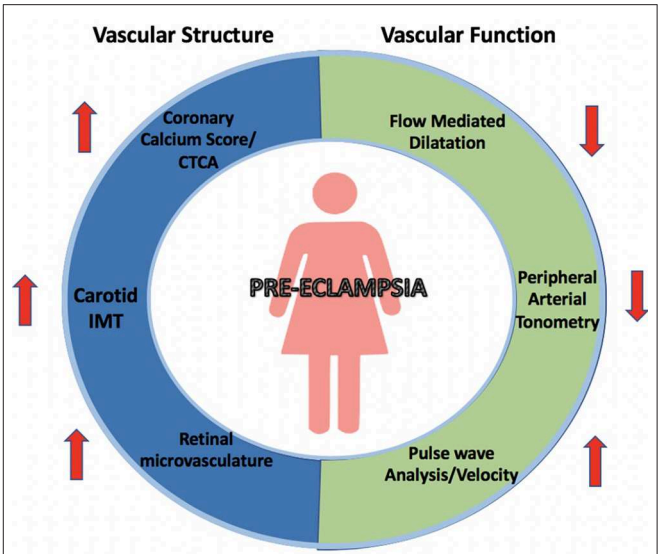

FIGURE 2 | Changes in vascular structure and function associated with pre-eclampsia. Summary of measurements of vascular structural and functional changes illustrated by non-invasive modalities including coronary calcium scores and CT coronary angiograms, carotid IMT, retinal microvasculature, flow-mediated dilation, peripheral arterial tonometry and pulse wave velocity and analysis.

The key modalities used for non-invasively assessing vascular structure and function associated with PE are outlined in **Figure 2**. An overview of the available studies identified in the systematic review and samples sizes of each study are outlined in **Table 2**.

Postulated Mechanisms Linking PE to Abnormal Vascular Structure and Function

During normal pregnancy, adaptations such as increased intravascular volume and a reduction in vascular resistance within the maternal circulation result in an overall decreased blood pressure. In PE, impaired placentation occurs as a result of a complex interplay between vascular, immunological, and genetic factors. This leads to the placenta releasing soluble, toxic, antiangiogenic factors in response to hypoperfusion leading to inflammation and maternal systemic disease (3, 84).

Soluble Flt1 is believed to be the predominant factor released in the pathogenesis of PE. It primarily counteracts the function of pro-angiogenic proteins that usually reduce microvascular resistance, including vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), by binding to them and preventing their ability to act on the endothelium (3). The

TABLE 2 | Overview of studies evaluating vascular structure and function prior to, during and after pre-eclampsia.

MODALITY	TIMEFRAME		
	Prior to PE	**During PE**	**Postpartum**
Carotid Intima-Media Thickness	Brueckmann et al. (11) (143 PE cases)	Yuan et al. (15) (22 late-onset PE cases) Stergiotou et al. (13) (100 PE cases; 50 early onset and 50 late-onset) Blaauw et al. (14) (22 early-onset PE cases) Memari et al. (12) (21 PE cases) Mori et al. (16) (30 PE cases; 14 mild and 16 severe PE)	Akhter et al. (20) (23 PE cases) Aykas et al. (53) (25 PE cases) Christensen (67) (21 PE cases; 4 early-onset and 17 late-onset) Ciftci et al. (68) (33 mild PE) Garovic et al. (21) (40 PE cases; 813 PE cases in meta-analysis) Goynumer et al. (18) (34 PE cases) Sandvik et al. (57) (39 PE cases)
Coronary CT and coronary calcium score	No current data	No current data	Beckman et al. (29) (37 PE cases Cassidy-Bushrow et al. (27) (24 PE cases) Sabour et al. (26) (151 had a history of hypertension during pregnancy) White et al. (28) (40 PE cases) Zoet et al. (24) (164 PE cases)
Retinal microvasculature	Lupton et al. (33) (9 PE cases) Porto et al. (41) (10 early-onset PE)	Soma-Pillay et al. (35) (40 PE cases; 24 early-onset and 16 late-onset)	Benschop et al. (5) (63 PE cases) Soma-Pillay et al. (35) (40 PE cases; 24 early-onset and 16 late-onset)
Brachial flow mediated dilatation	Alves et al. (69) (9 early-onset and 22 late-onset PE) Brandao et al. (40) (15 cases; 6 early-onset and 9 late-onset) Brandao et al. (6) (19 PE cases; 8 early-onset and 11 late-onset) Mori et al. (16) (30 PE cases; 14 mild and 16 severe PE) Porto et al. (41) (10 early-onset PE) Savvidou et al. (70) (10 PE cases) Weissgerber et al. (52) (156 PE cases) Magee et al. (71) (6 PE cases)	Adali et al. (72) (35 PE cases) Brodszki et al. (47) (28 PE cases; 15 with bilateral uterine artery notches and 13 without) Guimaraes et al. (44) (42 PE cases) Hamad et al. (48) (35 PE cases; 8 early-onset and 27 late-onset) Mannaerts et al. (73) (33 PE cases) Mori et al. (16) (30 PE cases; 14 mild and 16 severe PE) Oliveira et al. (43) (40 PE cases) Tyldum et al. (45) (20 PE cases; 7 early-onset and 13 late-onset Weissgerber et al. (52) (333 PE cases)	Agatisa et al. (50) (16 PE cases) Aykas et al. (53) (25 PE cases) Barry et al. (74) (49 PE cases) Breetveld et al. (55) (67 PE cases) Goynumer et al. (18) (34 severe PE cases) Hamad et al. (48) (35 PE cases; 8 early-onset and 27 late-onset) Hamad et al. (51) (18 PE cases) Lopes van Balen et al. (54) (79 PE cases) Mori et al. (16) (30 PE cases; 14 mild and 16 severe PE) Ostlund et al. (58) (15 PE cases) Paez et al. (49) (20 PE cases) Sandvik et al. (57) (39 PE cases) Tripathy et al. (75) (45 PE cases) Tyldum et al. (45) (20 PE cases; 7 early-onset and 13 late-onset Weissgerber et al. (52) (429 PE cases <3 years postpartum; 325 PE cases >3 years postpartum) Yinon et al. (76) (24 PE cases; 15 early-onset and 9 late-onset)
Pulse wave analysis and pulse wave velocity	Katsipi et. al (63) (11 early-onset; 10 late-onset—cfPWV measured) Savvidou et al. (62) (29 PE cases—cfPWV measured) Magee et al. (71) (6 PE cases; cfPWV)	Franz et al. (77) (21 PE cases; 11 early-onset and 10 late-onset—AIx measured) Oylumlu et al. (78) (45 PE cases; cfPWV measured) Namugowa et al. (64) (85 PE cases; 64 early-onset and 21 late-onset—cfPWV measured) Robb et al. (65) (15 PE cases; 7 preterm and 8 term—cfPWV measured) Rönnback et al. (79) (26 PE cases—cfPWV measured)	Christensen (67) (21 PE cases; 4 early-onset and 17 late-onset—aortic PWV measured) Lampinen et al. (66) (30 PE cases—PWA assessed) Orabona et al. (80) (30 early-onset and 30 late-onset PE cases—cfPWV measured) Ostlund et al. (58) (15 PE cases—cfPWV measured) Paez et al. (59) (20 PE cases—cfPWV measured) Souwer et al. (81) (14 early-onset PE—PWA assessed)
Peripheral arterial tonometry	Carty et al. (42) (143 PE cases)	Kumer et al. (82) (26 PE cases) Mannaerts et al. (83) (14 PE cases) Mannaerts et al. (73) (33 PE cases) Meeme et al. (46) (105 PE cases)	Kvehaugen et al. (56) (26 PE cases) Orabona et al. (80) (60 PE cases; 30 early-onset and 30 late-onset)

vascular effects of sFlt1 have been clearly elucidated in a mouse model where virally induced overexpression of sFlt-1 led to the development of hypertension and proteinuria (85). Soluble endoglin (sEng), a placenta-derived soluble TGF-β1(transforming growth factor-β1) inhibitor, is another anti-angiogenic factor involved in PE (3). It inhibits the TGF-β1 signaling pathway thereby preventing capillary tube formation and increasing vascular permeability. Its effect in pregnant rats has been shown to enhance the vascular impact of sFlt1, leading to severe PE (86).

An imbalance in these anti-angiogenic factors is seen in women who develop PE; prior to the clinical condition, during PE and postpartum. For example, in a cohort of 159 women, sFlt1 and sEng measured at 10–17 weeks gestation were significantly increased in the 21 women who subsequently developed PE as compared to those with a normal pregnancy outcome. In conjunction, the increase in sFlt1 and sEng was consistent with a significant decrease in FMD indicative of endothelial dysfunction (87). Interestingly, it was found that the rise in sFlt1 did not correlate with an increase in mean arterial pressure until the 26–33-weeks time point, suggesting that the increased blood pressure is a consequence of endothelial dysfunction. A meta-analysis investigating the predictive value of sFlt1/PlGF ratio in PE found a pooled sensitivity of 80% (95% CI, 68–88%) and a pooled specificity of 92% (95% CI, 87–96%), suggesting this ratio may be a useful tool during the clinical assessment of women during early pregnancy (88). Moreover, increases in sFlt1 are found to be greater in early-onset vs. late-onset PE (89). This is further highlighted in a study suggesting sFlt1 levels directly correlate with the severity of disease (90). More recently, a prospective cohort study of 46 women with suspected or confirmed PE found that sFlt-1/PlGF ratio >38 at 30 weeks gestation continues to double in subsequent weeks, possibly reflecting an amplification of the disease process, before rapidly decreasing postpartum (91).

There has been one report demonstrating that women 5–8 years postpartum PE have a significantly increased level of circulating sFlt1 (79.7 ± 15 vs. 70.9 ± 11.2 pg/mL; $P = 0.02$) (56), illustrating that women with a history of PE have a persistent antiangiogenic profile. The role of persistent circulation of antiangiogenic factors in PE and increased risk of CVD, however, remains unclear. Increase in circulating sFlt1 has been shown to be associated in the development of heart failure (92) and in patients immediately after myocardial infarction (93), suggesting sFlt1 may be released in response to hypoperfusion or pain. However, the mechanism for sFlt1 release and endothelial interactions remain incompletely understood. In light of the findings noted above, sFlt1 may be associated with an overall acceleration in endothelial dysfunction and enhanced adverse vascular outcomes.

Likewise, expression of endoglin within the circulation is thought to be in response to endothelial damage and inflammation (94). Increased levels of soluble endoglin have been correlated with hypertension and diabetes, and to have a positive association with increased PWV and retinopathy, suggesting that endoglin plays a vital role in vascular function and development of disease (95). Similarly, elevation of sEng levels has been shown to be an indicator for major adverse cardiovascular events in patients with chronic coronary artery disease, suggesting increased levels may correlate to greater vascular damage, thereby resulting in an increased risk of vascular failure (96).

Clinical Considerations

The ability to identify women at risk of PE prior to disease onset would be extremely valuable but remains elusive, particularly for late onset PE. First trimester screening using multi-variable risk prediction models based primarily on placental factors has proven partially successful in identifying women at risk of early onset PE but has a low predictive value in late onset disease (97). A proposed reason for this is that these algorithms fail to appropriately account for maternal endothelial function, with the only included maternal vascular marker a peripheral blood pressure measurement. Non-invasive vascular assessment using one of the above methodologies may have a role to play in this risk prediction model. Given the technical expertise, time and user dependence of FMD and PWV these may not be the most user friendly and practical options. Retinal photography, however, is relatively inexpensive, fast and reproducible and thus has the potential to be of benefit, in conjunction with current risk prediction models, to help predict risk of PE in women. This hypothesis, however, requires testing and confirmation.

In the long-term following PE there is no clear clinical pathway for maternal cardiovascular follow-up. Beyond intensive primary prevention and close control of modifiable risk factors such as fasting cholesterol, glucose and bodyweight; CTCA and CAC may play an important role. A careful balance, however, must be struck between the predictive benefit and the risks of overdiagnosis and exposing relatively young women to ionizing radiation.

CONCLUSIONS

PE is associated with an increased risk of premature CVD in woman, independent of concomitant risk factors. Studies suggest that this condition is associated with subclinical changes in vascular structure, such as an increase in CIMT and retinal microvascular caliber during pregnancy, and long-term elevations in coronary calcification. Abnormal endothelial function has also been demonstrated through reductions in flow mediated dilatation and increased PWV and AIx, however the timing and persistence of these changes is unclear. The pathophysiology linking PE with CVD is yet to be fully elucidated but has been postulated to involve inflammation and endothelial dysfunction. Whether PE initiates these pathologic changes or acts as a stress test unmaking latent disease in at-risk women is yet to be determined.

AUTHOR CONTRIBUTIONS

SK was responsible for the systematic review, synthesis of information, and drafting of the manuscript. MS and SP were responsible for review analysis, synthesis, and manuscript preparation. CA was responsible for the concept design, synthesis, analysis, and drafting of the manuscript. All authors approve the paper for submission.

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SYSTEMATIC REVIEW
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Postpartum Interventions to Reduce Long-Term Cardiovascular Disease Risk in Women After Hypertensive Disorders of Pregnancy: A Systematic Review

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Introduction: Hypertensive disorders (HDP) affect ∼7% of pregnancies. Epidemiological evidence strongly suggests HDP independently increases that individual's risk of later cardiovascular disease (CVD). Focus on reduction or mitigation of this risk has been limited. This review seeks to identify trialed interventions to reduce cardiovascular risk after HDP.

Methods: Online medical databases were searched to identify full-text published results of randomized controlled trials (RCT) in women <10 years postpartum after HDP that trialed interventions to reduce cardiovascular risk. Outcomes sought included cardiovascular disease events, chronic hypertension, and other measures of cardiovascular risk such as obesity, smoking status, diet, and physical activity. Publications from January 2008 to July 2019 were included.

Results: Two RCTs were identified. One, a trial of calcium vs. placebo in 201 women with calcium commenced from the first follow-up visit outside of pregnancy and continued until 20 weeks' gestation if another pregnancy occurred. A non-significant trend toward decreased blood pressure was noted. The second RCT of 151 women tested an online education programme (vs. general information to control group) to increase awareness of risk factors and personalized phone-based lifestyle coaching in women who had a preeclampsia affected pregnancy in the 5 years preceding enrolment. Significant findings included increase in knowledge of CVD risk factors, reported healthy eating and decreased physical inactivity, however adoption of a promoted heart healthy diet and physical activity levels did not differ significantly between groups. Several observational studies after HDP, and one meta-analysis of studies of lifestyle interventions not performed specifically after HDP but used to extrapolate likely benefits of lifestyle interventions, were identified which supported the use of lifestyle interventions. Several ongoing RCTs were also noted.

Discussion: There is a paucity of intervention trials in the early years after HDP to guide evidence-based cardiovascular risk reduction in affected women. Limited evidence suggests lifestyle intervention may be effective, however degree of any risk reduction remains uncertain.

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Conclusion: Sufficiently powered randomized controlled trials of appropriate interventions (e.g., lifestyle behavior change, pharmacological) are required to assess the best method of reducing the risk of cardiovascular disease in this at-risk population of women.

Keywords: cardiovascular risk reduction, pre-eclampsia, gestational hypertension, hypertensive disorders of pregnancy, systematic review, cardiovascular disease, lifestyle behavior change

INTRODUCTION

Preeclampsia [PE] and hypertensive disorders of pregnancy [HDP] can now be acknowledged as independent risk factors for later cardiovascular disease (CVD) (1, 2). PE is a multisystem disorder diagnosed at >20 weeks' gestation with evidence of hypertension and involvement of one or more other organ systems (3). PE remains a leading cause of maternal death globally as well as serious morbidity for mother and baby (4).

Several systematic reviews of cohort and case control studies, including over 100,000 women post-PE and 2 million after normotensive pregnancy, have found that after PE, women have at least triple the risk of chronic hypertension, and double the risk of ischemic heart disease, stroke, and death related to cardiovascular disease, than their normotensive pregnancy counterparts (1, 5–7). Where confounding of other risk factors was able to be accounted for, this effect persists, strongly suggesting that history of PE is an independent risk factor for CVD. Although the absolute risk of cardiovascular disease in young women is small, the existing data would also suggest that the increased CVD relative risk is already present in the first 10 years postpartum (7) and continues lifelong (8). Although data is less extensive for gestational hypertension (GH), new-onset hypertension in the second half of pregnancy without the multisystem features of PE, it also appears to be associated with an approximately doubling of CVD risk (8, 9). Chronic hypertension in pregnancy (CH), hypertension already existing <20 weeks gestation, flags women already at increased risk of CVD. Given the prevalence of HDP in the population, affecting 7–10% of pregnancies (PE 2–5%, GH 4–6%, CH 1–2%) (4, 10), in combination with CVD being the largest cause globally of female mortality, the potential burden of disease is significant.

This phenomenon can be paralleled to the increased risk of Type 2 diabetes (T2DM) seen in women whose pregnancies have been affected by gestational diabetes (11). An increasing awareness of this risk has seen the encouragement to maintain lifestyle modifications that have been shown, albeit mostly in trials performed some years postpartum, to lower the risk of progression to T2DM, and the implementation of stricter follow-up policies to identify early development of changes to glucose metabolism (12, 13). A similar approach needs now to be considered to implement risk-reduction strategies and closer follow-up for women who have experienced a pregnancy affected by hypertensive diseases, in order to decrease CVD risk. Indeed, the latest International Society for the Study of Hypertension in Pregnancy (ISSHP) guidelines recommend follow-up of all women after HDP, assessment of CVD risk factors, education regarding long-term CVD risks associated with HDP, and counseling regarding lifestyle modification (3). However, the guidelines also acknowledge the paucity of the evidence base for what recommendations to give women and interventions to institute to lower CVD risk after HDP and note ongoing studies may give more guidance in this area.

The purpose of this systematic review is therefore to identify and assess trialed interventions to reduce long-term cardiovascular risk in women whose baseline risk has been increased given a pregnancy affected by hypertensive disease.

METHODS

A systematic review was conducted, reviewing any trialed interventions to reduce long-term CVD risk in women whose baseline risk has been increased due to a pregnancy affected by HDP, according to the PRISMA guidelines for systematic reviews (14). The protocol was prospectively registered in the PROSPERO database (CRD 4201920072).

The included population was women enrolled <10 years postpartum after a pregnancy affected by PE or GH, enrolled into any intervention trial to reduce cardiovascular risk. Women who were known to have another primary cause for hypertension or essential hypertension were excluded as these represent a group already known to be at increased CVD risk pre-pregnancy.

The search was limited to randomized controlled trials (including other trials where any randomization has occurred, including crossover and cluster), where an intervention aimed at reducing long term cardiovascular risk after GH or PE was interrogated. Postpartum intervention trials primarily based on another group, such as gestational diabetes or high BMI, which incidentally reported on women with previous HDP, were not included. There were no limitations on the nature of the intervention (e.g., life-style based, pharmacological or other). A control group not receiving the intervention was expected.

Primary outcomes were identified as a cardiovascular disease events or the development of chronic hypertension after the index pregnancy. Secondary outcomes, of (a) risk markers for CVD, and (b) markers of compliance (in order to assess feasibility of the trialed interventions) are listed in **Table 1**.

The systematic review was carried out by two independent reviewers who employed a pre-defined search strategy to interrogate online medical databases (MEDLINE, EMBASE, PubMed, Cochrane Database, Cochrane Register of Controlled Trials) to identify relevant trials (**Appendix 1**). There were no conflicts requiring the mediation of a third party. There were no

TABLE 1 | Secondary outcomes considered.

Secondary outcomes	
Modifiable	Obesity (BMI ≥ 30 and/or waist circumference)
	Smoking status, however measured (e.g., self-reported, salivary cotinine)
	Diabetes/Impaired glucose tolerance
	Exercise participation, as measured by improvement in fitness scores using controlled fitness tests
	Diet quality, as recorded in food diaries
Compliance	Barriers to engaging in lifestyle modification programmes, as defined by patient questionnaire
	Compliance with long term medical therapy if prescribed, as measured by pill count and/or patient questionnaire.
	Compliance of patients with long term follow-up, as defined by attendance records

language restrictions on initial results. Publications from January 2008 were included to ensure relevance (as the first meta-analysis of CVD risk after preeclampsia was published in 2007, it was not expected intervention trials meeting inclusion criteria would appear until after this time). On completion of the formal search strategy, titles and abstracts were reviewed to ensure inclusion criteria are met. Full text documents were obtained and assessed. Reference lists of included studies were searched to identify further studies, and a *post-hoc* decision was made to also search clinical trial registries (clinicaltrials.gov and all primary registries listed in the WHO International Clinical Trials Registry platform https://www.who.int/ictrp/network/primary/en/) for any further relevant studies.

A standardized form was created to compile a pre-specified set of extracted data of those eligible studies. Extracted data included: study setting, participant demographic details, details pertaining to the intervention and control, study methodology, recruitment and loss to follow-up rates, identification of barriers to completion of study, outcomes, and an assessment of risk of bias. Two reviewers independently assessed each study, with a plan to resolve discrepancies by way of discussion or deferring to a third reviewer, however this was not necessary. Any missing data would have been sought from study authors as required.

Each of the two individual reviewers completed an assessment of bias for each study included, using the Cochrane Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. Those studies deemed to be of poor quality were not included in the final assessment.

Meta-analysis, including subgroup analysis, was pre-specified, if sufficient studies with similar endpoints had been identified.

RESULTS

Of 522 titles found in the initial literature search (**Figure 1**), only two studies were identified that met inclusion criteria (**Table 2**). Four other studies, whilst not meeting criteria based on study design, were also reviewed in the interests of scoping the evidence base on this topic (**Table 3**). A further 104 studies were reviewed however were excluded as they did not meet the inclusion criteria generally, mostly as they were not assessing a specific intervention or were not studying cardiovascular risk reduction postpartum (**Table 4**). These findings are summarized in the PRISMA flow diagram below (**Figure 1**). As described, trial registry data was also searched; this search yielded four randomized controlled trial registrations. Three are currently recruiting and one has closed recruiting and expects to report results in early 2020. These have been summarized below for the reader's information.

As only two randomized controlled trials were identified, with largely heterogeneous outcomes, a qualitative (narrative) synthesis only was performed.

RCT-1 was a sub-group analysis of the larger WHO Calcium and preeclampsia study (CAP) (15) which in itself is a subset of the PRE-EMPT (Pre-eclampsia, Eclampsia, Monitoring, prevention, and Treatment) study. This trial was a placebo-controlled trial investigating the pharmacological intervention of the addition of 500 mg/day of calcium to non-pregnant women who have a low dietary calcium intake. Eight hundred and thirty-six women were randomized however a complete dataset was only available for 201 women.

This was a multicenter trial based in South Africa, Zimbabwe, and Argentina. Inclusion criteria were limited to non-pregnant women whose most recent pregnancy had been affected by preeclampsia. Calcium was commenced outside of pregnancy at the time of randomization and continued until 20 weeks' gestation if another pregnancy occurred. The placebo group received an identical tablet. At 20 weeks' gestation, all women were switched to unblinded calcium in accordance with WHO guidelines. Follow-up was at recruitment and then every 12 weeks until the next pregnancy. Recruitment fell short of the power calculation however baseline characteristics were the same across both groups.

A non-statistically significant trend toward a decrease in blood pressure at follow-up was found (reduction of 1–2.5 mgHg). There was a statistically significant reduction in diastolic blood pressure of the sub-group of women who had a pregnancy previously affected by severe preeclampsia (defined here as eclampsia, HELLP syndrome, systolic blood pressure >160 mmHg, diastolic blood pressure >110 mmHg, onset earlier than 28 weeks gestation or ICU admission). In this group, there was a mean difference in diastolic blood pressure between the treatment group and placebo of −3.4 mmHg (95% CI −0.4–6.4, $p = 0.025$). Compliance was noted to be an average of 80% across all groups.

RCT-2 was identified at final search immediately prior to finalization of this analysis. Heart Health 4 Moms (HH4M) (16) tested an online intervention to modify lifestyle risk factors in women who had recently been diagnosed with preeclampsia with a view to reducing cardiovascular risk.

Participants were recruited from the United States of America via online advertising on social media in both English and Spanish. Participants were included if the index PE affected pregnancy was within the preceding 5 years, if they had a normal current blood pressure and BMI between 18.5 and 40 kg/m^2, if they had internet access and could communicate in English or

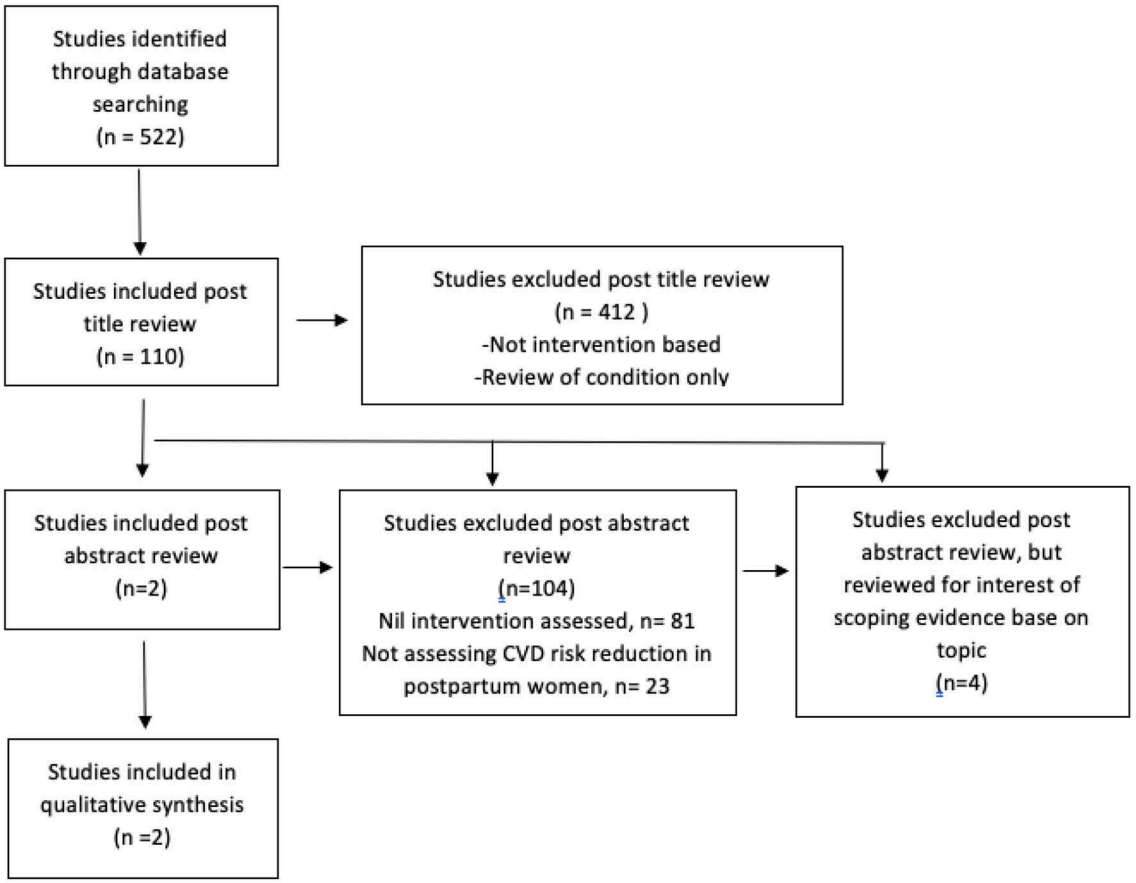

FIGURE 1 | PRISMA flow chart (14).

Spanish at an eighth-grade level. Any women with active or past medical problems (including but not limited to diabetes, kidney disease or cardiovascular disease), who was currently pregnant, who had a history of bariatric surgery or who was taking any anti-hypertensive medications or medications affecting weight were excluded. The control group was given access to the Control-HH4M website which contained standard, publicly available information on reduction of CVD risk. The intervention group had access to the intervention website which included modules regarding risk reduction specific to their condition, details on a specifically recommended diet, and physical activity; on completion of these modules the participant was acknowledged with an online "badge." Direct access to a life-style coach was also arranged that was provided by way of scheduled phone-calls and personalized emails. Three assessments were carried out through the 9 months programme. Validated questionnaires were used. Data was missing for 0–9% of each primary outcome and 19% for the Dietary Approaches to Stop Hypertension (DASH)-frequency questionnaire.

After screening of 1,493 women, 151 were eventually included and randomized (76 to intervention and 75 control). At baseline, approximately half of women in each group were <12 months since the affected pregnancy, and for the majority it had been their first baby. Baseline demographics suggest that a higher socio-demographic group than the USA average was recruited, as over 90% of both groups had at least some post-high school education, and only 3% were African American. During the intervention, 69% of controls accessed the control website and 99% accessed the intervention website with good retention rates at the completion of the study (93 and 91%, respectively). Results showed the participants' self-efficacy in eating a healthy diet improved significantly ($p = 0.03$) in the intervention group; as did a decrease in physical inactivity (e.g., watching television) ($p = 0.0006$). Intervention participants also felt better informed regarding their risk profile ($p = 0.01$). However, there were no significant differences in participation in physical activity, adherence to the recommended diet and secondary outcomes of self-reported weight and blood pressure remained unchanged.

Characteristics of Excluded but Relevant Studies (Table 3)

Four studies identified comprised largely observational studies. Janmohamed et al. (18) was a retrospective cohort study, assessing outcomes from a dedicated multidisciplinary preeclampsia follow-up clinic at the study hospital designed to focus on lifestyle modifications known to reduce the risk of

TABLE 2 | Summary of included studies.

Study	Setting	Study design	Sample size	Subjects	Trial period	End-points	Method or intervention	Outcomes
The effect of calcium supplementation on blood pressure in non-pregnant women with previous pre-eclampsia: an exploratory, randomized placebo-controlled study (15)	Sub-study of WHO Calcium and Pre-eclampsia (CAP) Trial	RCT	$N = 836$ randomized $N = 367$ first visit $N = 217$ History severe PE	Non-pregnant women who had PE or eclampsia in their immediately previous pregnancy.	12 or 24 weeks after randomization	Blood pressure (systolic and diastolic)	500 mg/day Calcium or placebo	Overall trend toward decreased BP in supplemented group but NS (reduction of 1–2.5 mmHg) Statistically significant reduction in diastolic BP of severe PE group
Randomized Trial to Reduce Cardiovascular Risk in Women with Recent Preeclampsia (16)	Standalone controlled intervention trial.	RCT	$N = 151$ (assessed for eligibility $n = 1,493$)	Women with PE affected pregnancy, within 5-years of index pregnancy	9 months	Healthy diet and increase activity, change in physical in/activity, DASH diet, knowledge of risk. Weight/BP	Online intervention (educational modules, community forum, life-style coach communication) Control: Links to standard CVD risk information	High rate of access of intervention information [84% of participants accessed a minimum of 1 online module) and access to coach [89% had 3 calls with a coach) Self-reported increased knowledge of CVD risk factors ($p = 0.01$ corrected), self-efficacy for healthy eating ($p = 0.03$), less physical inactivity ($p = 0.0006$). No difference in adherence to DASH diet, sense of control of risk factors, self-efficacy for physical activity or reported physical activity. No difference in secondary outcomes (weight, blood pressure)

RCT, Randomized Controlled Trial; WHO, World Health Organization; NS, Not significant; PE, Preeclampsia; DASH, Dietary Approaches to Stop Hypertension; CVD, Cardiovascular disease.

TABLE 3 | Summary of relevant articles not included based on study type.

	Setting	Study design	Sample size	Subjects	Trial period	End-points	Method or intervention	Outcomes
Reduction of cardiovascular risk after preeclampsia: the role of framing and perceived probability in modifying behavior (17)	Questionnaire	Survey	$N = 175$ answers $N = 165$ complete (people who declined not recorded)	Female obstetric nurses	N/A	Willingness to modify behavior (Likert scale) - Activity - Diet - Annual BP check	Survey presenting two cases (high and low risk of CVD post PE pregnancy)	Statistically significant willingness to modify behavior; affected by the perceived probability of poor outcome ($p = 0.001$).
Cardiovascular risk reduction and weight management at a hospital-based postpartum preeclampsia clinic (18)	Retrospective cohort study	Review of medical records Single center (Edmonton, Alberta, CA)	$N = 104$ (initial visit) $N = 21$ completing 6 months		Minimum 6 months; Average 4.4 ± 1.4 months post-partum	BMI Physical activity	Attending dedicated, MDT, post-partum clinic (PPPEC) - Education on risks; - Assessment of risk - Weight mgmt. focus	Non-significant changes in BMI (mean weight loss 0.4 ± 4.5 kg; mean BMI decrease 0.1 ± 1.7 kg/m^2) Significant changes in physical activity [14% prior to pregnancy, to 76% at mean 4.4 months postpartum) NB: Mean GA = 31, Mean BMI 31
Prevention of cardiovascular risk in women who had hypertension during pregnancy after 36 weeks gestation (19)	Subgroup cohort from prior RCT	Survey and risk assessment	$N = 306$ random sample from HYPITAT for risk assessment, $N = 257$ answered questionnaires	Women with hypertension affected pregnancy who participated in prior HYPITAT trial	3.5 years post-partum, 1 year after CVD risk assessment	Hypertension, BMI reduction, smoking status, lipid and BSL levels	Survey 1 year after CVD risk assessment	Reduction in self-reported smoking (42%), reduction in BMI ≥ 5% (31%)
Risk of cardiovascular disease after pre-eclampsia and the effect of lifestyle interventions: a literature -based study (20)	Literature-based study	Estimate diff in CVD risk in PE v uncomplicated pregnancy. Effects of lifestyle intervention estimated Risk prediction models used.	$N = 16$ studies included	Women with hypertension affected pregnancy and women with uncomplicated pregnancies	N/A	Primary: Cardiovascular risk after pre-eclampsia compared with an uncomplicated pregnancy Secondary: effects of lifestyle interventions on cardiovascular risk	Review of cardiovascular risk in 16 studies Calculation of difference in risk and odds ratio using risk prediction models, and calculation of risk reduction with lifestyle interventions of (exercise, dietary habits, and smoking cessation decrease)	After PE, lifestyle interventions (diet/exercise), smoking cessation, decreased CVD risk by 4–13% (OR 0.91)

PE, Preeclampsia; CVD, Cardiovascular disease; BP, blood pressure; BMI, Body Mass Index; MDT, multidisciplinary team; BSL, blood sugar level; GA, gestational age; OR, odds ratio.

TABLE 4 | Summary of other excluded studies ($n = 104$).

Reason for exclusion	Number of studies excluded	References
No specific intervention assessed	81	- Preventing cardiovascular disease after hypertensive disorders of pregnancy: searching for the how and when (21). - Preeclampsia and the risk of future vascular disease and mortality: a review (22). - Counseling and management of cardiovascular risk factors after preeclampsia (23). - Long-term renal and cardiovascular risk after preeclampsia: toward screening and prevention (24) - Health workers' knowledge on future vascular disease risk in women with pre-eclampsia in south western Nigeria (25). - Determinants of future cardiovascular health in women with a history of preeclampsia (26). - Pregnancy characteristics and women's future cardiovascular health: an underused opportunity to improve women's health? (27) - Risk of future cardiovascular disease in women with prior preeclampsia: a focus group study (28). - Cardiovascular disease in menopause: does the obstetric history have any bearing? (29) - Postpartum evaluation and long-term implications (30). - 10-Year cardiovascular event risks for women who experienced hypertensive disorders in late pregnancy: the HyRAS study (31). - Preeclampsia and future cardiovascular disease in women: how good are the data and how can we manage our patients? (32) - Hypertension in pregnancy and later cardiovascular risk: common antecedents? (33) - Hypertensive disorders in pregnancy and subsequently measured cardiovascular risk factors (34). - Preeclampsia and cardiovascular risk: general characteristics, counseling and follow-up (35). - How should women with pre-eclampsia be followed up? New insights from mechanistic studies (36). - Pregnancy: a screening test for later life cardiovascular disease (37). - The unchartered frontier: preventive cardiology between the ages of 15 and 35 years (38). - Women-specific factors to consider in risk, diagnosis and treatment of cardiovascular disease (39). - The Maternal Health Clinic: a new window of opportunity for early heart disease risk screening and intervention for women with pregnancy complications (40). - Pre-eclamptic pregnancies: an opportunity to identify women at risk for future cardiovascular disease (41). - Similarities between pre-eclampsia and atherosclerosis: a protective effect of physical exercise? (42) - Preeclampsia: a challenge also for Cardiologists (43). - Blood pressure profile 1 year after severe preeclampsia (44). - Preventing stroke and assessing risk in women (45). - Preeclampsia: pathogenesis, prevention, and long-term complications (46). - Hypertension in pregnancy and future maternal health (47). - Association of pre-eclampsia with metabolic syndrome and increased risk of cardiovascular disease in women: a systemic review (48). - Risk factors of hypertensive disorders among Chinese pregnant women (49). - Alterations to the maternal circulating proteome after preeclampsia (50). - Cardiovascular implications of preeclampsia (51). - Pregnancy: window into women's future cardiovascular health (52). - Adverse pregnancy outcomes and cardiovascular risk factor management (53). - Pregnancy as a window to future health (54). - Preeclampsia: short-term and Long-term Implications (55). - Present status of clinical care for postpartum patients with hypertensive disorders of pregnancy in Japan: findings from a nationwide questionnaire survey (56). - Cardiovascular risk factors 1 year after a hypertensive disorder of pregnancy (57). - Risk factors of hypertensive pregnancies in women with diabetes and the influence on their future life (58). - Hypertension in pregnancy greater risk than previously thought (59). - Is there a relationship between pregnancy induced hypertension and obstructive sleep apnea? Case report (60). - Cardiovascular risk, lipids and pregnancy: preeclampsia and the risk of later life cardiovascular disease (61). - Renovascular prognosis of preeclampsia on the mother and the child (62). - Preeclampsia as cardiovascular risk factor (63). - Importance of engaging obstetrician/gynecologists in cardiovascular disease prevention (64). - Hypertensive pregnancy disorders as a risk factor for future cardiovascular and metabolic disorders (65). - Biochemical cardiovascular risk factors after hypertensive pregnancy disorders: a systematic review and meta-analysis (66). - Cardiovascular risk management after a hypertensive disorder of pregnancy (67). - Ten-year, thirty-year, and lifetime cardiovascular disease risk estimates following a pregnancy complicated by preeclampsia (68). - Preeclampsia (marker of chronic kidney disease): from genesis to future risks (69). - Prevention of vascular dysfunction after preeclampsia: a potential long-term outcome measure and an emerging goal for treatment (70). - Gestational hypertension: a neglected cardiovascular disease risk marker (71). - Preeclampsia as a female-specific risk factor for chronic hypertension (72).

(Continued)

TABLE 4 | Continued

Reason for exclusion	Number of studies excluded	References
		- Role of pre-eclamptic toxemia or eclampsia in hypertensive women attending cardiac clinic of Ahmadu Bello University Teaching Hospital Zaria, Nigeria (73). - Pregnancy-related hypertension: a cardiovascular risk situation (74). - Investigating the risk of hypertension shortly after pregnancies complicated by preeclampsia (75). - Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses (5). - Recognizing pregnancy-associated cardiovascular risk factors (76). - Ethnic and racial disparities in hypertension management among women (77). - Cardiovascular disease screening (78). - Heart, arteries and women, a care pathway for women at high cardiovascular risk (79). - Cardiovascular risk in women: focus on hypertension (80). - Pregnancy as a window to future health (81). - Aspirin use in women: current perspectives and future directions (82). - Maternal deaths due to hypertensive disorders in pregnancy (83). - Pregnancy risks associated with obesity (84). - Clinical applications of biomarkers in preeclampsia (85). - Nitrergic system and plasmatic methylarginines: evidence of their role in the perinatal programming of cardiovascular diseases (86). - Cardiovascular disease in women: primary and secondary cardiovascular disease prevention (87). - Effects of preeclampsia on maternal and pediatric health at 11 years postpartum (88). - Early gestational age at preeclampsia onset is associated with subclinical atherosclerosis 12 years after delivery (89). - Effect of early-onset preeclampsia on cardiovascular risk in the fifth decade of life (90). - Hypertension in pregnancy is associated with elevated homocysteine levels later in life (91). - Preeclampsia and cardiovascular disease death: prospective evidence from the child health and development studies cohort (92). - Cardiology for gynecologists–a mini review (93). - Stroke in women–oral contraception, pregnancy, and hormone replacement therapy (94). - Hypertension in pregnancy and women of childbearing age (95). - Chronic hypertension in pregnancy: diagnosis, management, and outcomes (96). - To prevent cardiovascular disease, pay attention to pregnancy complications (97).
Not studying cardiovascular risk reduction in women post-partum	23	- The potential role of statins in preeclampsia and dyslipidemia during gestation: a narrative review (98). - Preventing deaths due to the hypertensive disorders of pregnancy (99). - Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: a meta-analysis (100). - Guided imagery for treating hypertension in pregnancy (101). - Interventions for treating pre-eclampsia and its consequences: generic protocol (102). - Safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia in high-risk pregnant women: a pilot randomized controlled trial (103). - Blood pressure patterns and body mass index status in pregnancy: an assessment among women reporting for antenatal care at the Korle-Bu Teaching hospital, Ghana (104). - Systematic Review of Vitamin D and Hypertensive Disorders of Pregnancy (105). - Potent Vasoconstrictor Kisspeptin-10 Induces Atherosclerotic plaque progression and instability: reversal by its receptor GPR54 antagonist (106). - Exercise during pregnancy and risk of gestational hypertensive disorders: a systematic review and meta-analysis (107). - The performance of risk prediction models for pre-eclampsia using routinely collected maternal characteristics and comparison with models that include specialized tests and with clinical guideline decision rules: a systematic review (108). - Selenium status in U.K. pregnant women and its relationship with hypertensive conditions of pregnancy (109). - Pre-eclampsia, eclampsia, and hypertension (110). - Hypertension in pregnancy (111). - Pregnancy Outcomes Associated with Stage 1 Hypertension in a High-Risk Cohort (112). - Antiplatelet agents and anticoagulants for hypertension (113). - First-line drugs for hypertension (114). - Calcium supplementation for prevention of primary hypertension (115). - Pharmacotherapy for hypertension in adults aged 18 to 59 years (116). - Reducing women's cardiovascular disease risk profile (117). - How to stay heart healthy in 2011: considerations for the primary prevention of cardiovascular disease in women (118). - Comprehensive primary prevention of cardiovascular disease in women (119). - Identifying and managing younger women at high risk of cardiovascular disease (120).
Non-randomized study (i.e., not appropriate study type]	6	- To prevent cardiovascular disease, pay attention to pregnancy complications (97). - Identifying and managing younger women at high risk of cardiovascular disease (120). - Comprehensive primary prevention of cardiovascular disease in women (119). - Cardiology for gynecologists–a mini review (93).

(Continued)

TABLE 4 | Continued

Reason for exclusion	Number of studies excluded	References
		- Stroke in women–oral contraception, pregnancy, and hormone replacement therapy (94). - Pregnancy outcomes associated with stage 1 hypertension in a high-risk cohort (112, 121).
Included women with other primary cause for hypertension or essential hypertension	9	- Cardiovascular disease in women: primary and secondary cardiovascular disease prevention (87). - Reducing women's cardiovascular disease risk profile (117). - How to stay heart healthy in 2011: considerations for the primary prevention of cardiovascular disease in women (118). - Hypertension in pregnancy and women of childbearing age (95). - Chronic hypertension in pregnancy: diagnosis, management, and outcomes (96). - First-line drugs for hypertension (114). - Pharmacotherapy for hypertension in adults aged 18 to 59 years (116). - Antiplatelet agents and anticoagulants for hypertension (113). - Calcium supplementation for prevention of primary hypertension (115).
Pregnancy not affected by PE or GH only	1	- Hypertensive pregnancy in diabetes–risk factors and influence on future life (58).
>10 years postpartum	5	- Effects of preeclampsia on maternal and pediatric health at 11 years postpartum (88). - Early gestational age at preeclampsia onset is associated with subclinical atherosclerosis 12 years after delivery (89). - Effect of early-onset preeclampsia on cardiovascular risk in the fifth decade of life (90). - Hypertension in pregnancy is associated with elevated homocysteine levels later in life (91). - Preeclampsia and cardiovascular disease death: prospective evidence from the child health and development studies cohort (92).

Studies may have more than one reason for exclusion. The table above shows the primary reason for exclusion, assessed in a sequential fashion, as follow: (1) No intervention assessed; (2) Not assessing CVD risk reduction in postpartum women; (3) Non-randomized study (i.e., not appropriate study type); (4) Included women with other primary cause for hypertension and essential hypertension; (5) Pregnancy not affected by PE or GH only; (6) >10 years postpartum.

hypertension. Twenty-one of 104 women completed 6 months of follow-up. The women in this study mostly represented a high-risk cohort with early-onset preeclampsia, in that average gestation at birth of the index pregnancy was 31 weeks and women had a mean starting BMI of 31. There was a non-statistically significant trend toward a decrease in BMI and increase in physical activity.

van Kesteren et al. (19) examined the effect of cardiovascular risk assessment 2.5 years postpartum on health behaviors 12 months later (i.e., at 3.5 years postpartum) in a subgroup of women who participated in the HYPITAT I trial of timing of delivery in women with gestational hypertension or preeclampsia at 36 weeks gestation or more (122). A random sample of 306 women from HYPITAT were invited to attend a cardiovascular risk assessment 2.5 years postpartum [HyRAS study (31)], with results fed-back to the women by way of a letter detailing their risk. One year later, women were invited to complete a follow-up questionnaire regarding their behaviors, which 257 of the 306 completed. This study showed some lifestyle behavior improvements over time, particularly a decrease in BMI >5 in 31% of previously obese women and 42% of women who reported smoking had quit. Of women who had established hypertension at 2.5 years (91 women), 36% were taking antihypertensive agents at the time of questionnaire follow-up. This study suggests that increasing awareness of risk can promote modest change without any specific lifestyle behavior change or pharmacological intervention.

Bokslag et al. (17) was a prospective questionnaire-based study which focused on women's intentions regarding modification of behavior when presented with two clinical cases suggestive of low or high-risk chance of developing a long-term increase in cardiovascular risk. Study participants were limited to female obstetric nurses of childbearing age. The Likert scale was used to assess willingness to modify behavior (activity, diet, annual BP checks). The study showed a statistically significant willingness toward modifying behavior when considering the high-risk case suggestive of a higher chance of a poor outcome.

We also identified one relevant meta-analysis, published in 2013 (20). This analysis aimed to estimate the difference in the risk of long-term CVD in preeclampsia against an uncomplicated pregnancy and the effect of lifestyle interventions, through extrapolation from lifestyle studies performed in other settings and populations (including five studies that had between 35 and 69% female participation). Sixteen studies were included for the post PE analysis. The range in time after follow-up was 1.0–19.0 years (majority of studies <10 years). Appropriate risk prediction models were employed to determine life-time risk of CVD events. After adjustments, it was concluded that lifestyle interventions (diet/exercise) and smoking cessation would be likely to decrease the overall cardiovascular risk by 4–13% in women who had a pregnancy complicated by PE.

Relevant but Not Yet Reported Studies

The following four trials would meet the criteria for this analysis however are not yet completed. A summary of the methodology of each is provided herein. Together, these studies are expected to yield a further 660 individual patient datasets for analysis.

"RedCarRisk" (123) is a study aimed at detecting an objective improvement in arterial stiffness after engagement with a 6 months conditional workout programme with midwifery support after a PE affected pregnancy. This study has closed recruiting and is due to report outcomes in 2020.

"Heart Health 4 New Moms (HH4NM)" (112) is similar in design to the original HH4M trial described above. This

pilot trial will focus on recruitment of overweight and obese women in the first year after their PE-affected pregnancy. It will randomize to an online lifestyle-based intervention to improve weight-loss at 1 year postpartum and will include home blood pressure monitoring. The trial will investigate the feasibility of the intervention as well as the effect of home blood pressure monitoring on progression to chronic hypertension. This study is currently recruiting.

"BP2" (124) is a 3-arm post-partum intervention trial targeting the first 12 months after a pregnancy affected by a hypertensive disorder. The arms comprise: (1) optimized usual care, (2) brief education (30 min consultation with physician and then dietician), and (3) extended lifestyle intervention (as for group 2 with enrolment in the NSW Get Healthy Service for intensive lifestyle behavior change coaching over 6 months). Primary outcomes include change in blood pressure, weight and waist circumference (clinically recorded) and secondary outcomes include self-reported changes (validated questionnaire), serological measures, vascular function, maternal satisfaction with the programme and cost-effectiveness. This trial is currently recruiting.

"Be Healthy for your Heart (BH4YH)" (125) is a postpartum intervention trial where participants will be randomized to either access to the National Heart Foundation website (control group) or specific online resources developed by the trial team that will require participant interaction in goal setting and monitoring progress with lifestyle modifications over a 3 months course. Primary end-points include acceptability and resource efficiency. Secondary endpoints include objective measures of blood pressure, diet, and routine serology as well as life-quality questionnaires. This trial is currently recruiting.

DISCUSSION

Current guidelines acknowledge the long-term CVD risk associated with hypertensive disorders of pregnancy and currently recommend long-term follow-up for cardiovascular risk factor assessment and management, as well as adoption of a healthy lifestyle (3, 126). However, guidance on specific postpartum interventions to decrease cardiovascular risk is lacking. This systematic review identified a paucity of RCTs on postpartum interventions to reduce CVD risk after PE or GH. What evidence was available from the two included studies, and the relevant but excluded studies, suggests that implementing CVD risk factor and lifestyle education and intervention strategies, either online or face to face, has a modest but appreciable effect in changing CVD risk factor incidence in affected women. However, this requires confirmation from the several registered but not yet reported RCTs in this space.

Pregnancy has long considered to be a stress-test unique to the female population. The development of particular diseases during this confined period where the body is expending energy at more than twice its non-pregnant metabolic rate (127) and sees marked changes in maternal physiology offers a window into the future health risks particular to that woman. As a result, interventions to reduce the cardiovascular risk posed by PE and GH are required.

The Hofmeyr et al. study is suggestive that the pharmacological intervention of calcium supplementation in those deficient in dietary calcium may be beneficial in lowering blood pressure long term. However, this study was underpowered for the primary outcome and unfortunately suffered a high attrition rate. Moreover, the reductions were modest and their ability to be borne out over a period longer than 12 weeks has not been proven. The HH4M trial suggests that online education and lifestyle interventions show promise in promoting healthy behaviors after preeclampsia. However, although not suffering the high attrition rate of the Hofmeyr et al. study, HH4M had a high number of women screened for each inclusion (∼10–1). It is also of some concern that included women overall represented a highly-educated group with under-representation of African Americans, the group with the worst maternal health outcomes in the USA (128). It would be important to ensure that in a wider implementation of online interventions, efforts are made to be as inclusive as possible of all at-risk women.

The failure to identify further completed trials may be as a result of the emerging nature of this research. A trial to identify a change in actual cardiovascular disease outcomes would be required to have a large enough power to show a significant reduction in risk in an outcome that is not expected for many years following the index pregnancy. In addition, the follow-up period would need to be up to several decades long in order to capture the population at the time of the index cardiac event, rendering such a trial a challenge to conduct.

Shorter follow-up studies focusing on hypertension, and other risk factors and surrogate markers as end-points for CVD, are therefore more realistic. Both some of the non-randomized research found and the registered but not yet completed RCTs are focusing on these populations. Interventions including the development of a close monitoring system and linkage with a regular healthcare provider, lifestyle modifications (diet and exercise to aid in weight loss and general health) whether internet-based or phone based in conjunction with follow-up of neonatal and infant development are all currently under study. These can all potentially act as the starting point for a longer follow-up study. These ongoing studies are expected to yield a further 660 cases from which to draw experience.

As noted in the RCTs reviewed, enrolling an appropriately powered cohort can be challenging. Reasons for this are likely associated with the nature of the disease: as time away from the index pregnancy increases, the perceived risk and need to continue intervention can decrease as women do not necessarily "feel" particularly unwell and the experience of complicated, high risk pregnancy becomes far removed. Challenges noted in the Janmohamed 2015 study, particularly maintaining participation in follow-up are of particular interest in this case: if women are not educated regarding the ongoing risk to themselves in the long-term, the impetus to maintain follow-up with risk reduction practices is not felt. Discussed studies show that when provided with structured education on risk, the information is retained. This may be a simple first step at the time of delivery that could help to involve women in long-term follow-up studies aimed at risk reduction interventions.

Education of health care providers has been demonstrated to be effective in the Bokslag 2016 study. Whilst the findings of "willingness to change" in the cohort surveyed was clear, the cohort was somewhat biased given a presumed baseline level of knowledge regarding physiology and natural history of disease as a result of occupation (obstetric nurses). This does show, however, if an appropriate level of education can be attained in the target population, perhaps a similar "willingness" may be elicited and in turn, a change in behavior affected. Indeed, a working party in conjunction with the Heart Foundation (Australia) have developed a patient information sheet outlining the long term risks of having had an HDP affected pregnancy and basic steps to start to mitigate that risk (129). While awaiting high-level evidence to support appropriate postpartum interventions to decrease women's risk of CVD after GH/PE, this approach to information provision, risk factor assessment, and encouragement of healthy lifestyle, appears unlikely to do harm and a reasonable strategy to pursue.

CONCLUSION

There is a paucity of intervention trials conducted attempting to decrease the increased cardiovascular risk of women who have been affected by a hypertensive disorder of pregnancy. Current studied interventions focusing on lifestyle modification by way of prescribed (online) programmes have had some effect in reduction of secondary end-points for cardiovascular disease risk. This corroborates current guidelines in the management of these long-term risks. Given the significant burden to women's health presented by long term CVD, appropriately powered randomized trials of further interventions to reduce this risk in this particular group are an important area for future research.

AUTHOR CONTRIBUTIONS

AH and NL contributed to the conception and design of the study. NL and GJ carried out the search strategy independently. NL and AH contributed to the analysis of the included studies. NL wrote the draft manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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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.

APPENDIX 1: SEARCH TERMS

Search strategy:
1 hypertension, pregnancy-induced OR pre-eclampsia OR gestational hypertension OR "pregnancy AND hypertension"
2 risk factors OR causality
3 cardiovascular diseases OR pregnancy complications, cardiovascular OR cardiovascular diseases [prevention and control]
4 risk reduction intervention.mp. or ∗Risk Reduction Behavior
5 limit to year "2008–Current."

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Assessing Knowledge Gaps of Women and Healthcare Providers Concerning Cardiovascular Risk After Hypertensive Disorders of Pregnancy—A Scoping Review

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Background: A history of a Hypertensive Disorder of Pregnancy (HDP) at least doubles a woman's risk of cardiovascular disease (CVD). The risk increases within 10 years after HDP and continues for life, making long-term health after HDP of major public health importance. Understanding knowledge gaps in health care professionals and women regarding cardiovascular health after HDP is an important component in addressing these risks.

Objectives: The primary aim was to examine what women and healthcare providers (HCP) know about cardiovascular risks after HDP. The secondary aims were to identify enablers and barriers to knowledge and action on knowledge.

Methods: A scoping review was conducted. This was a narrative synthesis, using PRISMA-ScR guidelines, of English-language full text articles that included assessment of knowledge of women, and/or HCP, on long term cardiovascular risk after HDP. The databases Embase, Medline, Scopus, ProQuest, Cochrane, and PsycInfo were searched from 01 January 2005 to 31 May 2019.

Results: Twelve studies were included, six addressing women's knowledge, five addressing HCP knowledge, and one addressing both. The studies included 402 women and 1,215 HCP from seven countries. Regarding women's knowledge, six of seven studies found women had limited or no knowledge about the link between HDP and CVD. Where women were aware of the link, the majority had sourced their own information, rather than obtaining it through their HCP. In five of six studies, HCP also mostly had limited knowledge about HDP-CVD links. Primary enablers for HCP acquisition of knowledge and counseling were the availability and knowledge of guidelines. Where comparisons between HCP groups were made, obstetricians had greater knowledge than family physicians, internal medical specialists, or midwives.

Conclusion: There was a low level of knowledge amongst HCP and women about increased CVD risk after HDP. Where women had higher levels of knowledge, the

information was often obtained informally rather than from HCP. There were variations in knowledge of HCP, with obstetricians generally more aware than other professions. Further country and context-specific research on current status of women's and HCP's knowledge is therefore necessary when creating educational strategies to address knowledge gaps after HDP.

Keywords: knowledge, women, healthcare providers, preeclampsia, hypertension, cardiovascular risk

INTRODUCTION

Preeclampsia (PE) is a multi-system disorder unique to human pregnancy characterized by hypertension and involvement of one or more other organ systems and/or the fetus (1). Preeclampsia is well-recognized as a major cause of poor pregnancy outcome. It is one of the top three causes of maternal mortality and severe morbidity in both high and low resource countries, leading directly to over 50,000 maternal deaths globally per year (2). For babies, up to one in five premature births occur following their mothers having preeclamptic pregnancies (3).

In addition to the short-term impacts, long-term adverse maternal health outcomes after preeclampsia and other Hypertensive Disorders of Pregnancy (HDP) may be an even greater burden of disease. Cardiovascular disease (CVD), the leading cause of death in women globally (4), is 2–2.5 times higher for women who have experienced preeclampsia at some stage in their life compared with those who had normotensive (normal blood pressure) pregnancies (5–7). This risk of premature death is present 8–20 years after the affected pregnancy (6, 8, 9). Gestational Hypertension (GH), new-onset hypertension without any other complications during pregnancy, has little association with adverse pregnancy outcomes (1), however is associated with long-term cardiovascular sequela (7, 10). Together with essential hypertension (EH), which indicates pre-existing increased cardiovascular risk, these HDP conditions complicate ∼10% of pregnancies (3).

Peak cardiovascular health organizations, such as the American Heart Foundation, now recommend health care providers ask women about their HDP history when assessing their cardiovascular health and risk factors. The International Society for the Study of Hypertension in Pregnancy (ISSHP) recommendations (5) address the postpartum management of HDP and recommend a review at 3 months to ensure screening tests are within normal range or alternatively ensure appropriate referral occurs. ISSHP also recommends informing women of their long-term CVD risk, adoption of a healthy lifestyle with maintenance of an ideal weight and regular aerobic exercise, and regular follow-up with a general practitioner to monitor blood pressure and periodic measurement of fasting lipids and blood sugar.

Despite these recommendations, clinicians may not be aware of the association between HDP and CVD, suggesting that women are not given appropriate information about health after HDP (11–16). Several studies conclude that both health care providers and women should be provided with information regarding the link between HDP and later CVD (17–19). Therefore, the primary aim of this paper was to undertake a scoping review to examine what women and healthcare providers (HCP) know about cardiovascular risks after HDP. Secondary aims were to identify the aspects of care that can be seen as enablers and barriers to knowledge and action on knowledge.

METHODS

A scoping review of published literature on knowledge of women and/or health care providers about CVD risk after preeclampsia or gestational hypertension was undertaken. Scoping reviews follow a systematic approach to identify main concepts, evidence, and knowledge gaps on a specific topic (20). This methodology was appropriate given our interest in the broad topic of knowledge on health after HDP and the likely heterogeneous nature of the body of literature. This scoping review adheres to PRISMA-ScR guidelines (20) (**Appendix 1**) and the CASP (21) qualitative checklist was also used to assess quality in the of included qualitative literature (**Appendix 2**). Narrative synthesis was applied to analyze the included literature.

We searched multiple Databases including Embase, Medline, Scopus, ProQuest, Cochrane, and PsycInfo. The year of publication was limited to 1st January 2005 to 31st May 2019. Key words descriptors, Medical Subject Headings as well as MeSH terms were (but not limited to): "Health Knowledge, Attitudes, Practice," "Education*," "Communication Barriers," "Risk perception," "Enablers," "Knowledge," "Knowledge gap," "Knowledge sharing," "Pre-eclampsia," "gestational hypertension," "Hypertension, Pregnancy-Induced," "future cardiovascular disease," "long-term cardiovascular risk" (**Appendix 3**).

Key words were developed and separated into search categories. One was knowledge/education/risk perception, another was PE/GH/HDP and a third was long-term CVD risk. Database searches were accompanied by hand searching reference lists and citations of all included studies to identify any additional, relevant studies.

Papers were included (**Supplementary Table 1**) if they were original research addressing knowledge assessments, communication and awareness of long-term increased CVD risk after PE (including HELLP and eclampsia) or GH, full-text, available in English and if published during the selected timeframe. The date limit was applied as most initial cohort studies showing increased risk of CVD after preeclampsia were not published until the early 2000s, and the first risk meta-analysis was not published until 2007 (22). Studies of any

methodology (qualitative/quantitative/mixed methods), sample size and type were eligible for inclusion.

Papers were excluded (**Supplementary Table 1**) if they were a conference or research abstract only, a review article without novel research, or items (e.g., study protocol or trial registration) that pertained to planned or in-progress research without published results. Where abstracts matched our search criteria and topic but with no details on study method and results and no full-text associated publications were found, authors were contacted for further details. However, this did not yield further inclusions by the cut-off of 31st May 2019.

Research that concerned chronic hypertension only (without superimposed PE) was excluded, as chronic hypertension is recognized by healthcare professionals as conveying increased CVD risk. Additionally, papers with focus only on the application of lifestyle recommendations to reduce the CVD risk after experiencing a pregnancy with hypertensive disease were excluded.

All articles were independently reviewed for inclusion by two reviewers who read the title, abstract, and full text. Discussion between the two reviewers resolved discrepancies. After summarizing the included papers, the papers were split into two categories: women's knowledge, and HCP's knowledge.

The Critical Appraisal Skills Programme (CASP) (21) tool was used to assess quality of the included literature. Although this is a tool designed to assist in systematic review inclusions, this quality appraisal tool was helpful in the systematic approach to enquire and reason about the studies eligible within the boundaries of the inclusion/exclusion criteria. The CASP checklist addresses three areas when appraising literature to be included in a review, these are validity, results and clinical relevance.

RESULTS

Of 1,467 identified articles, 12 studies met inclusion criteria (**Supplementary Figure 1**). **Supplementary Table 2** summarizes the characteristics of the studies included.

Out of the 12 studies, six addressed women's knowledge (11, 13–16, 23), five addressed HCP's knowledge (24–28) and one addressed both women and HCP (12). The studies include eight quantitative (surveys, chart reviews) (15, 16, 23–28) and four qualitative studies (11–14) (focus group, group interview, semi-structured interviews). Of the qualitative studies, most were assessed as moderate to high quality on CASP criteria and details are itemized in **Appendix 2**. In total, the studies collected information from 402 women to 1,215 HCP.

Five studies were conducted in the United States of America (USA) (13–15, 27, 28) two from Canada (12, 26) one each from Australia (23), Germany (25), Nigeria (24), Portugal (16), and the United Kingdom (UK) (29).

The included studies displayed various levels of focus on knowledge assessment of CVD after HDP. Eleven conducted surveys or interviews exploring the women's or HCP's knowledge specifically and more extensively. One study's focus was on exploring general follow up of women with a history of PE and women's knowledge of CVD risk factors in general but did include a single question regarding women's knowledge on the link between PE and future CVD (16).

Women's Knowledge

Seven (including the study addressing both women and HCP) studies addressed women's knowledge (11–16, 23). Three were quantitative (15, 16, 23) and four were qualitative studies (11–14). Six studies focused on the exploration of women's knowledge (11–15, 26) while one (within a study with a different main focus) included a question about whether counseling of HDP link to CVD had occurred (16).

Six out of the seven studies found that women had limited or no knowledge about the link between HDP and CVD. In the USA, Seely et al. (13) found that in 20 women after PE, the "majority" were not aware of their HDP CVD risks. In another study in the USA, 10 of the 14 participating women (71%) were unaware of the link between PE and CVD (14). A survey of 78 women in Portugal found that nearly 70% were not counseled on the link between PE and CVD (16). There was some evidence that women's knowledge of future CVD risk perception differed according to the type of severity of their HDP. A study of 146 women in the USA (of which 52% were without severe features, 28% PE had severe features such as HELLP and Eclampsia and 20% had Chronic Hypertension alone) found that CVD risk awareness was higher in those with severe PE (65%) and chronic hypertension (75%) than those with PE without severe features (43%) (13, 15). In Canada, Hird et al. (12) reported that the five women in their study were either not at all informed or partially informed. When informed this was limited to two out of five women finding out about potential recurrence of PE in a subsequent pregnancy. Four of the five women were not advised to have any follow-up blood tests. Only one out of the five women was advised about her CVD risk. In the UK, Brown et al (11) found that five of their 12 participants could not recall the HDP-CVD risk being raised with their HCP. Of those who were counseled of their risk, it was found that especially those women without a family history of CVD did not perceive the risk to apply to them.

The one exception was the Australian study by Hutchesson et al. (23), where close to two thirds of 127 women with a recent history of PE ($\leq$ 2 years post PE) had higher knowledge about certain aspects of future CVD risk (96% answered "true" for future risk of hypertension and 66% answered "true" for future risk of stroke).

Women's Knowledge in the Early Postpartum Period vs. Later

There were conflicting findings regarding whether women in the first few years after HDP had higher knowledge about future CVD risk than those 5 years or more post-pregnancy. In Australia, Hutchesson et al. found 67% of women with recent PE ($\leq$2 years) were aware of future CVD risk. However, in the USA a focus group study of women who had preeclampsia <5 years ago, the majority of the 20 women did not know of their future CVD risk until they attended the focus groups (13). There were similar findings in another focus group study of 14 women (14) where

most (10/14) of the women were unaware of the link between PE and future CVD.

Sources of Knowledge, Enablers, and Barriers to Knowledge Acquisition in Women

Three of the seven studies explored sources of knowledge acquisition by the women (12, 14, 23). These showed that women in general wanted information on their HDP and to understand more about its link to future CVD. For example, in Brown et al. (29), all 12 women interviewed with a history of PE wanted to receive more information on PE and future implications on health. Enablers and barriers to women's knowledge acquisition were also addressed by most of the studies.

Of the seven studies that enquired about women's perceptions of being given information, major themes were that women did not receive information, or felt they received insufficient information, from their healthcare practitioners about risks after HDP. For those who were aware of long-term risks prior to being surveyed or interviewed, this knowledge had often been self-acquired. Hutchesson et al. (23) undertook a cross-sectional survey with women who had a recent preeclampsia diagnosis to examine their knowledge about whether they were at greater risk of developing a list of health complications. The participants ($n = 127$) displayed high awareness about being at greater risk of developing hypertension later in life (98%) and being more susceptible to stroke and CVD (67%). However, 60% of the "aware" participants reported that they gained knowledge by doing their own research, while only 25% heard about their long-term risk from their obstetrician, about 13% from their general practitioner and 6% from their midwife. Despite most participants (about 95%) having had their blood pressure measured, a lower proportion reported serum cholesterol and/or glucose screening (about 41%), and fewer had received advice on various lifestyle risk factors (ranging from 2% for smoking and about 30% for weight management, exercise and healthy eating).

The one study addressing both women's and HCP's knowledge assessed how relationships between risk, pregnancy, and women's health are understood and acted upon. Five women were interviewed, and they reported being either minimally or not informed around diagnosis about long-term CVD risk after PE. Recurrence of PE in a subsequent pregnancy was addressed with two of the five interviewees. Only one was tested and counseled at 6 weeks postpartum. Women were unsure whether their pregnancy history was transmitted to their family physician. Women did not always trust the skills and knowledge base as well as the decisions made by their care givers. Finally, participants had made extensive efforts to source information relating to their condition from places like the internet, online discussion boards, magazines, and even television series (12).

One of the qualitative studies in the UK showed that women with a family history of CVD disease had greater awareness of future CVD risk (29). Of the 12 women interviewed, seven had family history of CVD (29). Women without traditional risk factors found it hard to envisage themselves as being at risk and did not see the relevance of such information. The authors noted timing of discussions as an important element to consider when communicating about postpartum risk, taking into account situational factors of new motherhood, and when women are ready to consider their own health as well as their baby's, to engage successfully with this group of women (29). A study conducted in Portugal of 78 women with either history of PE or CH and superimposed PE showed that addressing of risk after PE by HCP predominantly did not happen (54 no vs. 24 yes) (16).

Healthcare Provider's Knowledge

The studies about health providers' knowledge varied in the screening questions and detail of knowledge inquiry. Six studies addressed HCP's knowledge (including the study which addressed both groups) (12, 24–28). The studies assessed knowledge with varying depth, therefore the results display different aspects of knowledge.

A Canadian study with 554 participants (obstetrician/gynecologist, midwives, and family physicians) (26) showed that almost two-thirds (64%) knew that women with a history of gestational hypertension had a higher risk of developing hypertension in the future. About one-half of the clinicians were aware that women with a history of PE were at higher risk than nulliparous women to develop hypertension in the future. The study did not compare knowledge between the different HCP groups.

In one of the USA studies (28), participants were asked about their typical counseling for CVD risk reduction. This showed that of 161 participants (118 internists/internal medicine physicians, 53 obstetricians) 95% of internists and 70% of obstetricians reported providing general CVD risk reduction counseling. When asked about knowledge of future cardiovascular risks in women with preeclampsia, the majority in both groups were incorrect or unsure about the risk of several future comorbidities associated with a history of PE. With the exception of risk of future hypertension, where only 6% internists and 17% of obstetricians answered incorrectly, the comorbidities that were surveyed yielded a significant knowledge gap. The other risks surveyed were future risk of ischemic heart disease (56% internists and 23% obstetricians answered incorrect/unsure), stroke (48% internists and 38% obstetricians answered incorrect/unsure), and a shorter life expectancy which displayed the highest percentage of incorrect/unsure answers (79% internists and 77% obstetricians). Only 5% of internists and 42% of obstetricians asked about PE as part of taking a woman's medical history. Of the doctors asking about a PE history, only a small group (9% of internists and 38% of obstetricians) provided counseling to women at risk. The findings suggested that clinicians are not aware of the association between adverse pregnancy outcomes such HDP and CVD (28).

Wilkins-Haug et al. (27) undertook an anonymous survey in the USA. The survey was case-based, had 124 participants and explored obstetrician/gynecologist vs. internists' recognition of long-term CVD risk after preeclampsia. One aspect of the survey was to assess the participants' understanding of how pregnancy history may influence long-term cardiovascular risk, where information was collected through a combination of direct query, multiple choice responses, case-based questions, and branch logic. The second aspect assessed their general knowledge of CVD risk. Overall, about 28 and 15% of internists

and obstetricians, respectively, indicated they would not obtain a pregnancy history when specifically assessing a patient's history for cardiovascular risk. When history of PE was obtained, internists were more likely to order fasting glucose test than gynecologists (48% vs. 21%).

In Germany, a survey about knowledge of the association between preeclampsia and long-term risks of CVD was distributed to a random sample of 500 obstetrician-gynecologists with 121 participating. Overall, the doctors with better knowledge of existing guidelines had better understanding of risks and were more likely to offer counseling to women with a history of PE. More specifically, 87% of doctors knew of the association between PE and future hypertension, whilst 79% knew about the association with stroke risk. Although the majority of the respondents were aware of the increased CVD risk post preeclampsia, the awareness of existing guidelines on long term follow up care and counseling of affected women remained deficient. Only 45% of participants were aware of these guidelines, however knowledge was higher amongst these participants (25).

The only study in a low to middle income country (LMIC) was undertaken by Adekanle et al. (24) in south western Nigeria. A survey was distributed to 146 healthcare professionals as part of a workshop at a teaching hospital. The majority (87%) were knowledgeable about future hypertension risk after PE and about ischemic heart disease (63%), stroke (69%), and kidney disease risk (73%). Forty-six percent counseled on CVD risk after hypertensive disease. The doctors had better knowledge (78% overall) than both nurses (58%) and community healthcare workers (54%). However, the majority (64%) were not aware that a shorter life expectancy is linked with preeclampsia, while only 38 (26%) asked about preeclampsia on routine visits and 46% counseled on cardiovascular risk.

Enablers and Barriers to Knowledge Acquisition for Healthcare Providers

A Canadian study (26) identified weaknesses in knowledge base and communication amongst the maternity care providers and community health care (family physicians). There was a significant discrepancy when addressing the communication between the hospital to community handover after HDP. Of the participating maternity care providers, 83% stated that they informed the family physician with regards to the woman's history after HDP. However, only 58% of the participating family physicians stated that they received HDP information about the women transitioning back into the community. Furthermore, only 12% of family physicians stated that they were made aware that women post HDP are at increased risk of CVD, despite 41% of maternity HCP claiming that this happened. This study suggests that effective identification and follow-up of women with HDP is not occurring.

A follow up Canadian study assessed whether HCP shared information with women about their increased CVD risk (12). In this study of 8 healthcare practitioners, three of the eight did not inform women of increased risk more than 50% of the time. Interviews were undertaken to explore participants' perceptions of and attitudes toward the relationship between PE and CVD risk. Structural, practical, and ideological barriers were shown to impede knowledge sharing between health care providers and women about the relationship between preeclampsia and CVD risk (12). Patient electronic records were not consistently available to all HCP, hence the community health care providers are reliant on written records transferred to them. One obstetrician in Hird et al.'s study (12) relied on assumed knowledge of midwives and family physicians to link PE to long-term CVD risk. HCP reported filtering what they said and when about a certain situation. Some were cautious about the timing (e.g., in high stress situation) and others felt that if the women did not ask they would probably not want to know and hence the HCP would not address the topic.

Three of the six studies mentioned guidelines (12, 24, 25). In Adekanle et al. (24) it is unclear which guideline participants are asked about. Their discussion refers to a national guideline, however declares that PE guidelines are institution based. Only 16% of participants were aware of a guideline, the authors suggest this number may reflect the medical practitioners as there was a smaller number of them. Heidrich et al. (25) asked about awareness of current national guidelines which comment on follow up of PE and future CVD risk management. Overall only 45% knew about these guidelines with significantly more knowledge in the group with guideline awareness. The group with guideline knowledge counseled women more frequently about long term risks, more frequently assessed blood pressure, had better knowledge of the link between HDP and CVD and screened for family history of PE more frequently. The third study (12) found that the absence of clinical practice guidelines had a possible effect on the postpartum management of PE and CVD risks. The current guidelines' focus was more on the diagnosis and the intrapartum management of HDP.

DISCUSSION

This scoping review found that, in most studies, women's and HCP's knowledge about the increased risk of CVD after HPD was low. The various studies explored differing aspects of knowledge. Some studies included one question about knowledge of the association of HDP and CVD, whereas other studies used further questions to differentiate amongst the various aspects of knowledge on this topic. Three studies used the term "risk perception" which showed a distinction between basic factual knowledge vs. how a woman at risk may perceive her own risk as true or not true. Issues with communication between different HCP (between hospital and community) as well as between HCP and women was identified, particularly when asking about pregnancy history when CVD risk assessing, transferring pregnancy history and risk factors to community health care providers, and counseling women on the long-term CVD risk. Due to the diversity in explored aspects of knowledge within the included studies it is difficult to compare and contrast the studies themselves. A common ground however is found in their discussion of enablers and barriers to the acquisition of knowledge.

Women

Enablers to Acquisition of and Action on Knowledge

There were a number of enabling features for knowledge acquisition. The internet and access to a variety of information via online communities and networks appeared to be an enabler for women. Where women displayed reasonably high aspects of knowledge, it was found that had sourced this information by conducting their own research (12, 23). Women felt it was beneficial to receive information on how this risk could be reduced (29).

Clarification on the extent to which a history of preeclampsia and gestational hypertension are an independent factor for future CVD are considered helpful in the provision of effective communication (29). Interestingly, risk perception of HDP recurrence and future CVD due to HDP was higher in women who had a family history of CVD and/or PE with severe features (15, 29), further indicating that many other HDP affected women do not identify with the increased risk. They may not be aware that they could be affected in the future and are less likely to seek information as a result. Poor self-reporting of a PE and GH history may also accentuate the issue (30–33).

Some women felt that having access to other women who have had a similar pregnancy experience with HDP may have been a supportive move toward risk reducing lifestyle changes. Access to community of women who have experienced HDP or similar support groups may be helpful in feeling less isolated, more informed and supported (13, 14, 29). The thought of being able to support other women in similar situations was a motivator. The suggestion to have privacy maintained in this online community and a moderator who could validate medical information exchanged as well as keep the community's communication positive. In other areas of women's healthcare, including breastfeeding and polycystic ovarian syndrome, online community groups have been effective (34, 35) for women's emotional support and empowerment, so could be explored further for post-HDP women.

Online tracking of weight and blood pressure was deemed to be helpful in the application of knowledge with regards to lifestyle changes. Having support from family members when implementing lifestyle changes was deemed important and their family also benefiting from the healthy changes was a further motivator (14). Women felt that a reminder by their health care providers to follow up after HDP was needed to bring the mother's health back into mind after having given birth and transitioning to parenthood (29).

Barriers to Acquisition of and Action on Knowledge

A lack of knowledge from their health care provider on the link between HDP and CVD was a barrier to women, as well as their poor insight into or lack of action toward risk reducing lifestyle changes. The lack of knowledge about the link is also a barrier for women to then act on possible modifiable CVD risks or to simply gain insight into and understanding of the HDP they experienced. Barriers to action for women were predominantly related to family and caregiving responsibilities, lack of knowledge, lack of appropriate, and timely follow up as well as remembering what type of follow up and monitoring they needed, as well as poor recovery postpartum (13, 29). The amount and type of information given at any particular healthcare encounter was considered to be a barrier (12).

From the HCP perspective, HCP felt some information needed to be repeated over multiple visits to be truly understood, and that limited consultation time required them to prioritize the type of information shared with women. Some only responded to questions raised by the women and withheld other information. In turn, women were not confident they are being given all the information they need postpartum to manage their risk (12). Transition from hospital-based obstetric care to primary community-based care was also a barrier for women (and a system level barrier) as was lack of health insurance (in the USA) (13).

Healthcare Providers

Where comparisons between HCP groups were made, obstetricians had a higher level of knowledge than family physicians, internal medical specialists, midwives or community health workers (24, 26, 28). Knowledge and application into practice was demonstrated when guidelines were available, and their existence was known (25).

There was only one study conducted in a LMIC (24). In this setting (Nigeria), knowledge was higher amongst doctors compared with "lower cadre" health workers (examples cited in the included paper include associate nurses, community health workers). Although different contextually, this statement could be applicable to high income countries where community-based health care providers (such as general practitioners/family physicians/community nurses) are close to the community.

Enablers to Acquisition of and Action on Knowledge

Implementation and knowledge of guidelines may provide an enabling environment for better knowledge and application of this knowledge (25, 28). An example of positive influence of the implementation of guidelines can be found in the Netherlands (36), where an increase in counseling following preeclampsia occurred. This is likely to reflect an increase in education of gynecologists over time regarding cardiovascular risk, resulting in confidence addressing these concerns with the women in their care.

The type of specialty training in the HCP domain was a further enabler. When knowledge amongst professions was compared, obstetricians were more knowledgeable than family physicians and midwives for example (24, 27, 28). This may be linked to the training, scope of practice as well as exposure to women with HDP that this medical specialty has. More generally, although potentially linked to specialty training, Wilkins-Haug et al. (27) found that when there was better overall knowledge of CVD risk factors and screening knowledge, this was associated with greater knowledge of association of PE with later life CVD.

Barriers to Acquisition of and Action on Knowledge

Poor communication between hospital and community HCP was mentioned in almost all HCP papers (13, 24, 26, 28). In areas where knowledge was high this did not translate into action-taking on the reduction of long-term risk factors (24).

There were also a number of examples of withholding or not sharing information from women during CVD counseling or post HDP counseling (26, 28). Even when providers know about the association of PE with later CVD they did not apply this knowledge when counseling women. Further information on what a history of HDP means in terms of increased future risk and follow-up needed was perceived as not frequently shared by maternity specialists (26). Here too the gap between the information sharing by maternity HCP and information reception by community HCP was significant (26), with participants' answers possibly reflecting the intention of communication rather than what actually occurs in daily practice.

Studies comparing latest clinical guidelines in different countries highlight the variations in clinical recommendations (most likely due to lack of high-level evidence base for what is effective post-HDP follow-up) and lack of cost effective follow up. Some authors suggested further studies take place in order to inform practice guidelines and optimize prevention strategies (37). These include adjustment of general CVD guidelines to include taking a pregnancy history (38–40) and associating HDP with the increased risk of developing CVD.

A large amount of research exploring various aspects of women's increased CVD risk with a history of HDP have suggested that education as well as addressing modifiable risk factors could be targeted for improving the short- and long-term sequela for women (8, 17). The literature shows that poor pregnancy history taking is common. Recent population research has found women are less likely than men to have their cardiovascular (CVD) risks (not including preeclampsia history) fully assessed, and less often have risks appropriately managed when they are assessed (41). The gap may occur due to a number of potential barriers. Firstly, at individual and social levels, physicians may not be aware or familiar with existing guidelines on best practice in this matter. Secondly, physicians and women may have the old misconception of CVD being a man's disease. Furthermore, the misconception of senior physicians may have been passed on to the younger generation of physicians. In addition to financial and time and resource constraints, it is likely that women have been disadvantaged in receiving appropriate CVD risk factor assessment. When assessments do happen, women also are less likely than men to have their risks managed appropriately. Therefore, an increased rate of assessment and management of CVD risks are needed are needed in women generally, over and above specific management after HDP (41).

Considering pregnancy history when assessing a woman's CVD risk may assist in targeted efforts to initiate risk-reduction strategies in women with a history of pregnancy complications and improve communication between women and health care providers as well as communication between maternity and community providers. This may help decrease the burden of CVD in women (40, 42) and minimize the need for women having to rely mainly on exploring resources online to educate themselves (23).

Implications for Practice

Overall, there appears to be a knowledge gap in women and HCP on the association of HDP and risk of CVD. This gap could be narrowed and the information about this topic needs to be distributed in a suitable, accessible and targeted way.

The study that reflected reasonably high knowledge levels and counseling of women reasoned that the participants were aware of the existence of guidelines on the topic and showed application of these in practice (25). Guidelines are available (5) however their existence alone may prove to be insufficient. A potential education campaign of guideline awareness is one of the solutions, to encourage implementation of guidelines into practice.

Knowledge of HDP link to future CVD in both the HCP and women would be optimal in order to make progressive adjustments to potentially reduce the risk of future disease. Studies conducting research on lifestyle adjustments for women with a history of HDP have already been published in some countries. This shows attempts to reduce risk by applying the knowledge HCP and women have.

A specific follow up clinic may be an effective method of prevention of future risk for women (43, 44) as knowledge alone about risk may not translate into motivation or changes to lifestyle in order to reduce risk (45). There are early benefits of counseling about lifestyle modifications in order to prevent CVD in women with recent preeclampsia. Channeling women into appropriate health centers once pregnancy care is completed may be an enabling approach (43, 44). Careful pregnancy screening and appropriate escalation to the right health care provider, women's risk profile can be identified and addressed. Appropriate referral offers opportunity to determine effective treatments that can prevent the progression of hypertensive disorders in pregnancy and in turn reduce future CVD (43).

The Gap Identified in the Literature

This review has identified some gaps in the literature. The lack of evidence and hence of clear guidance on how to provide information to women who have experienced HDP identifies one of these gaps. More specific aspects of knowledge on the topic need to be assessed in women and HCP such as more specific knowledge of individual risk factors. Furthermore, higher numbers of women and HCP in a variety of countries and healthcare settings could be assessed and contribute to a more in-depth insight into knowledge levels and also on possible targeted knowledge enhancing strategies. Despite having gained insight into some of the enablers to knowledge acquisition and application, little evidence has been collected addressing what form education should take.

Strengths and Limitations

Strengths of the review include the comprehensive search strategy and scoping review by two independent reviewers according to PRISMA-ScR criteria. It provides an up-to-date evidence-base of the literature on the topic of women's and HCP's knowledge of cardiovascular health after hypertensive pregnancy. Our scoping review looked at both perspectives (women and HCP) and contextualized these findings amongst a larger context of CVD screening and prevention, enablers and barriers as well as from a primary health perspective.

The included literature is limited to English language. The methods of the research we included are diverse and different aspects of knowledge were examined amongst different HCP. Women's medical conditions examined also slightly varied from one paper to another. Having included international literature, cultural health context with access to healthcare are different, this makes the findings more difficult to compare and contextualize. Knowledge is contextual, and knowledge of risk factors and risk reducing behavior does not imply action on this knowledge. This aspect is hard to measure and by participation alone, this may already show a sign of bias to being receptive to knowledge and possibly motivated to make lifestyle changes. When planning knowledge transmission and action on health after HDP, it is important to consider the local context. This applies to the country's available health services, workforce, and scope of follow-up care postpartum. Despite the different settings of the included studies, there were several common themes around knowledge gaps, barriers, and enablers of acquisition of knowledge that were found in this review, including low knowledge among women and HCP of CVD after HDP, lack of communication of knowledge by HCP with higher knowledge (usually obstetricians) to HCP colleagues and women, and women's use of informal sources to gain knowledge. This suggests some generalizability regardless of context.

CONCLUSION

In general, there is a lack of knowledge amongst HCP and women regarding CVD risks after HDP Where women had higher levels of knowledge, the information was often obtained informally rather than from HCP. Obstetricians were generally more aware than other professions of the HDP-CVD link, however did not necessarily communicate this knowledge to either women or other HCP. Awareness of risk factors may provide, in conjunction with further research on effective risk reduction methods, a unique opportunity to plan future screening and preventative health recommendations by primary health care providers, which currently appears to be insufficient in women with a history of HDP. Further country and context-specific research on current status of women's and HCP's knowledge is therefore necessary when creating educational strategies to address knowledge gaps after HDP.

AUTHOR CONTRIBUTIONS

HR, AH, and CH contributed to the conception and design of the review. HR led the review of the literature, the analysis, and wrote the first draft. GL was the second reviewer of the literature, contributed to the analysis and drafting, and designed the tables, figures, and appendixes. All authors contributed to drafts and revising of the paper and approved the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2019.00178/full#supplementary-material

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A Protocol for Nurse-Practitioner Led Cardiovascular Follow-Up After Pregnancy Complications in a Socioeconomically Disadvantaged Population

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Background: Women who experience pregnancy complications have an increased risk of future cardiovascular disease when compared to their healthy counterparts. Despite recommendations, there is no standardized cardiovascular follow-up in the postpartum period for these women, and the Australian follow-up protocols that have been previously described are research-based. This study proposes a new model of care for a nurse practitioner-led postpartum intervention clinic for women who experience severe hypertensive disorders of pregnancy, gestational diabetes mellitus requiring medication, severe intrauterine growth restriction, idiopathic preterm delivery, or placental abruption, in a socioeconomically disadvantaged population.

Methods: All women receiving antenatal care or who deliver at the Lyell McEwin Hospital, a tertiary acute care facility located in the northern Adelaide metropolitan area, following a severe complication of pregnancy are referred to the intervention clinic for review at 6 months postpartum. A comprehensive assessment is conducted from demographics, medical history, diet and exercise habits, psychosocial information, health literacy, pathology results, and physical measurements. Subsequently, patient-specific education and clinical counseling are provided by a specialized nurse practitioner. Clinic appointments are repeated at 18 months and 5 years postpartum. All data is also collated into a registry, which aims to assess the efficacy of the intervention at improving modifiable cardiovascular risk factors and reducing cardiovascular risk.

Discussion: There is limited information on the efficacy of postpartum intervention clinics in reducing cardiovascular risk in women who have experienced pregnancy complications. Analyses of the data collected in the registry will provide essential information about how best to reduce cardiovascular risk in women in socioeconomically disadvantaged and disease-burdened populations.

Keywords: cardiovascular disease, pregnancy complications, postpartum follow-up, lifestyle intervention, prevention, women

INTRODUCTION

As well as a major cause of death, cardiovascular disease (CVD) is a significant cause of years of life lost for Australian women, resulting in 87,323 years life lost in 2015 (1). CVD remains a national public health crisis, costing over $5 billion in 2012–13 in healthcare for admitted patients (both male and female) and accounting for over 11% of total health expenditure (2). Awareness of CVD risk among women remains poor, despite them being almost three times more likely to die from CVD than from breast cancer (3). Emerging evidence demonstrates that although both men and women presenting with acute myocardial infarction experience the same symptoms (4), sex disparities in revascularization procedures still exist; a recent Australian cohort study reported that even after adjusting for age, sociodemographic and health-related variables, men were 50% more likely than women to receive percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) after admission to hospital with acute myocardial infarction (adjusted HR = 1.51, 1.38–1.67) (5). Men presenting with angina were also 150% more likely to receive PCI or CABG than women presenting with angina (adjusted HR = 2.44, 2.16–2.75) (5). Furthermore, both local and international literature has demonstrated that women who present with premature heart disease (age $\leq$ 55 years) take longer to receive emergency intervention and are more likely to experience worse outcomes following a cardiovascular event than men (6–8). Women who are socioeconomically disadvantaged are at even higher risk (9), and women in the lowest socioeconomic group in Australia have up to a 39% increase in number of years of life lost from CVD when compared to the national average (1, 10).

There now exists a plethora of literature detailing the relationship between pregnancy complications (including hypertensive disorders of pregnancy, gestational diabetes mellitus, intrauterine growth restriction, idiopathic preterm birth, and placental abruption) and an increased risk of future CVD (11–19). During pregnancy, maternal physiology undergoes complex and substantial changes, resulting in heightened organ function to cope with fetal demand and to maintain pregnancy (20). Failure to adapt to this physiological "stress test" and subsequent development of a complication of pregnancy is associated with an increased risk for future CVD. Pregnancy can therefore be viewed as a "window" into a woman's future health (16); however, it remains unclear if pregnancy reveals a pre-existing, underlying susceptibility to future CVD, or if the pregnancy itself leads to pathological changes, including inflammation and endothelial dysfunction, which in turn leads to a higher risk of future CVD.

In Australia, ∼25% of all pregnancies are complicated by at least one of the previously described pregnancy complications. The subsequent risk of heart disease following a complicated pregnancy is significant; for example, in a recent meta-analysis, preeclampsia was found to be independently associated with an increased risk of future heart failure (risk ratio [RR] = 4.19; 95% confidence interval [CI], 2.09–8.38), coronary heart disease (RR = 2.50; 95% CI, 1.43–4.37), CVD death (RR = 2.21; 95% CI, 1.83–2.66), and stroke (RR = 1.81; 95% CI, 1.29–2.55) (11). Women with a history of preeclampsia are also twice as likely to develop Type 2 diabetes mellitus (RR = 2.37; 95% CI, 1.89–2.97) (21), and three times more likely to develop hypertension than their healthy counterparts (RR = 3.13, 95% CI, 2.51–3.89) (22).

The onset of hypertension and metabolic disease following preeclampsia has been shown to occur as early as 2 years postpartum (23, 24). Similarly, metabolic disease can declare itself during pregnancy, manifesting as gestational diabetes mellitus, resolving clinically postpartum only to recur in subsequent years (19). However, there remains a lack of knowledge and awareness among the broader medical community of the need for ongoing care after preeclampsia and other pregnancy complications that are manifestations of maternal placental syndromes or metabolic disease, despite wide acceptance of the traditional risk factors for CVD.

Although there exists broad international and national guidelines for postpartum follow-up following hypertensive disorders of pregnancy and gestational diabetes (25–27), these are somewhat inconsistent and there remains little consensus on the ideal time to commence follow-up. Other pregnancy complications within the maternal placental syndrome spectrum that are associated with an increased risk of CVD, such as intrauterine growth restriction and preterm delivery, do not have any specific postpartum follow-up guidelines. Emergent literature has explored the feasibility and effectiveness of an early postpartum intervention for women who have experienced a pregnancy complication in an effort to reduce cardiovascular risk (16, 28–31). These interventions promote education regarding cardiovascular risk and offer advice, treatment and prevention strategies to improve both short- and long-term cardiovascular and metabolic health. Despite some positive initiatives with research-based approaches (32), there remains no standardized model of care for Australian women who experience pregnancy complications. Furthermore, there is a paucity of literature focusing on low socioeconomic, disease-burdened populations, where pregnancy complication rates are likely higher than the national average of 25%. Most follow-up protocols for women who experience pregnancy complications are currently conducted within the context of research and are not considered routine care clinics; thereby the possibility of bias exists.

This article describes a new postpartum intervention clinic and registry introduced as part of standard care, that commenced in late 2018 for women who experienced severe complications during pregnancy in a low socioeconomic population located in the northern suburban areas of Adelaide in South Australia. The primary aim of the associated registry is to facilitate the assessment of the effectiveness of the clinic as a primary prevention program for women with a history of complicated pregnancies.

MATERIALS AND METHODS

Study Design and Setting

This postpartum intervention clinic is routine care for women who receive antenatal care at the Lyell McEwin Hospital (based in the northern metropolitan area of Adelaide, South Australia) and experience at least one serious complication of pregnancy.

TABLE 1 | Referral eligibility criteria for the postpartum pregnancy complication clinic.

Hypertensive disorders requiring any medication and/or delivery at <37 weeks' gestation
Gestational diabetes mellitus requiring any medication
Intrauterine growth restriction and/or delivering a small-for-gestational age neonate (<5th percentile)
Preterm delivery occurring at <34 weeks' gestation
Placental abruption

The registry associated with this clinic includes all clinical, demographic and lifestyle data collected during the clinic appointments. All patients attending this clinic are included in the registry, and data is stored confidentially in an electronic database. The Central Adelaide Local Health Network Human Research Ethics Committee waived the requirement for written informed consent for participants in this study due to its primary aim as a quality control study for a standard care hospital outpatient clinic. This approval is in accordance with national legislation and institutional requirements.

The postpartum intervention clinic is led by a nurse practitioner who has both vast experience in cardiac rehabilitation practices and has completed further education in postpartum cardiovascular follow-up. A nurse practitioner was the preferred clinician of choice as they can provide holistic and well-rounded care. A nurse practitioner is a more cost-effective choice than a medical practitioner, as well as a more practical option than allied health professionals, who tend to specialize in only one specific area. The clinic is also supported by a research team that assists with the data collection process.

Participants: Eligibility and Referral

Women of any parity are referred to the postpartum intervention clinic as routine practice by the antenatal care team either during pregnancy or during admission for delivery after being diagnosed with at least one pregnancy complication meeting the referral eligibility criteria (**Table 1**). There are currently no maternal age or parity restrictions for referral to the clinic. Non-English-speaking patients are also accepted, and interpreters are booked accordingly.

Due to the overwhelming number of patients experiencing a complication of pregnancy, the clinic is currently only able to accept patients at the most severe end of the disease spectrum, on the assumption that this group is at greatest risk of future CVD. There are some limited data supporting this assumption (33–35). **Table 1** describes the classification and severity of each condition required for acceptance into the clinic.

Referral typically takes place during pregnancy or at time of admission for delivery. The obstetrics team considers referral to the clinic for all patients as a standard component of discharge from hospital to ensure all eligible women are offered an appointment.

Study Procedure

Patients are scheduled an appointment in the clinic at 6 months postpartum. Clinic visits are conducted as outpatient appointments within the Department of Cardiology at the Lyell McEwin Hospital. Patients receive a letter advising of the appointment date and time. The letter also contains some basic information about the link between pregnancy complications and CVD to provide rationale for attending the appointment. Enclosed with the letter is a pathology request form for fasting blood and urine tests to be completed prior to clinic attendance. A further SMS reminder the day prior to their scheduled appointment is also sent.

Fasting blood and urine samples are collected by trained phlebotomists at SA Pathology ideally at least 1 day prior to the scheduled appointment. Any patients who fail to provide blood and urine specimens in advance are still able to attend their appointments, but they are asked to have their pathology tests completed within the week following the appointment to allow for a complete assessment and accurate advice. These patients are either rebooked for a second appointment to discuss their pathology results, or they receive their results and any additional counseling from the nurse practitioner via telephone.

Information obtained from patients during the appointment includes demographics, medical history, family history, substance use, breastfeeding history and status, diet and exercise habits, psychosocial information, health literacy, pathology test results, and physical measurements. Patients are firstly asked to complete several short questionnaires themselves, and the remainder of the data is obtained by a clinic researcher or the nurse practitioner. Information is originally recorded on paper copies and is later entered into the medical case notes. The information is also recorded electronically in the registry. Once collected, this data is considered by the nurse practitioner and the patient receives specific advice and clinical counseling to improve modifiable cardiovascular risk factors. A detailed account of the outcome measures is described below.

Patients are automatically scheduled follow-up appointments at 18 months and 5 years postpartum. Most measures and questionnaires are repeated at the follow-up appointments. Pathology tests are repeated at all 5 year appointments but are only repeated at 18 months where clinically indicated. Initial appointments typically last for 45–60 min. Review appointments last for ∼30 min.

Intervention

The intervention within the postpartum clinic specifically refers to the education and clinical counseling provided by the nurse practitioner. Development of the style and content of the intervention was informed by the Maternal Health Clinic in Kingston, Canada (29). A face-to-face style intervention was chosen due to the need for obtaining measurements and performing physical assessments. There is also a significant lack of literature exploring the effectiveness of remote, online or telephone lifestyle interventions for women experiencing pregnancy complications. The decision regarding time of intervention at 6 months was somewhat influenced by the Canadian clinic (29), although there are suggested benefits of intervening prior to any subsequent pregnancies (36).

A major point of difference in the clinic described in this protocol is that it is led by a nurse practitioner. Nurse-led interventions are becoming increasingly popular in hospitals

and other health services in Australia and worldwide (37). Nurse practitioners have expert knowledge of specific health conditions, which is ideal for leading clinics that rely on counseling and education. Although there remains a paucity of research demonstrating the specific effectiveness of nurse practitioner-led clinics, nurse-led clinics for instilling secondary prevention strategies in patients with CVD have demonstrated a positive impact on all-cause mortality rates, rates of significant cardiac events and medication adherence among patients (38). In Australia, nurse practitioners represent a more cost-effective solution for multidisciplinary education clinics than medical specialists, and provide a more holistic approach than allied health specialists who normally have expertise in one specific domain. Furthermore, nurses and nurse practitioners are generally able to undertake longer appointments, thereby establishing better rapport with the patient and obtaining assessments that are more comprehensive. Emergent literature explores these benefits and details the scope of specific health areas that may reap advantages from utilizing nurse-led interventions (37, 39, 40) but further research in this field is necessary.

Following collection of all relevant information, the nurse practitioner considers the patients' results and provides specific health and lifestyle education and clinical counseling based on improving modifiable cardiovascular risk factors. Breastfeeding practices are considered by the nurse practitioner during education and clinical counseling to ensure any recommended health practices are safe for mothers that are still breastfeeding.

The nurse practitioner provides general dietary advice based on the Australian Heart Foundation Heart Healthy Eating Patterns position statement which broadly recommends eating plenty of fruit, vegetables and whole grains, eating a variety of heart-healthy protein sources and limiting the intake of red meat, consuming healthy dairy choices (and choosing reduced-fat dairy if blood cholesterol is high), choosing healthy fat sources, and using herbs and spices in the place of salt (14). Advice regarding numbers of daily serves of each food group is based upon those recommended by the Australian Dietary Guidelines (41).

Physical activity advice is based on *Australia's Physical Activity and Sedentary Behavior Guidelines (18–65 years)* which recommend being active on most or all days, engaging in muscle strengthening exercises at least twice weekly, and accumulating 150–300 min of moderate-intensity exercise, or 75–150 min of vigorous-intensity, or a combination of these, each week (42). These guidelines are also recommended by the Australian Heart Foundation (43), although there are some minor differences.

Any abnormalities in the pathology results will prompt further investigation, and medications may be prescribed where necessary. Additional diagnostic tests, including echocardiograms, ambulatory blood pressure monitoring, and ultrasounds may also be ordered where required. The nurse practitioner will also further refer patients where appropriate to additional health providers, including general practitioners, mental health services, allied health or medical specialists. Formal reports summarizing each patient's results are forwarded to their nominated general practitioner.

Outcome Measures

The following outcome measures will be recorded and compared at baseline (6 months postpartum), 18 months postpartum and 5 years postpartum. Cardiovascular risk scores will not be routinely calculated, as there are none suitably validated for Australian women under the age of 35 years.

Demographics

Basic details including social demographics (e.g., marital status, education, occupation, household income, etc.), medical history, family health history, substance use (e.g., smoking, alcohol, and other drugs), obstetric history and breastfeeding history are collected from a combination of patient self-reporting and medical case note review where necessary. This information will be updated at each appointment to ensure the most recent and accurate data is captured.

Physical Activity

The International Physical Activity Questionnaire (IPAQ) Long Form for English, which has been extensively tested for reliability and validity, is used to assess all occupational, incidental and planned physical activity (44). Data collected with this questionnaire will be reported as both continuous and categorical measure. The continuous measure is reported as median metabolic equivalent of task (MET-minutes) and calculates the median and interquartile range values using specific formulae for walking, moderate-intensity activities and vigorous-intensity activities across four domains (work, active transport, domestic and garden, and leisure time). The total volume of physical activity and the number of days and sessions are graded into one of three categories according to the scoring protocol; "low," "moderate," and "high." This questionnaire is completed at all visits to assess any changes in physical activity habits.

Dietary Intake

An informal food frequency style questionnaire developed by our research group assesses adherence to major food groups and identifies general dietary intake compared against the Australian Dietary Guidelines 2013 (45). This tool is not validated, but provides detailed information of intake of whole grains, dairy, proteins, fruit and vegetables, discretionary foods, and drinks. This questionnaire identifies dietary deficiencies and highlights areas that may require improvement and is repeated at all appointments.

Psychosocial Measures

The General Anxiety Disorders (GAD 7-item scale) is a validated self-report questionnaire that assesses symptoms of anxiety over the past fortnight (46). Symptoms of depression over the past fortnight are assessed with the validated Patient Health Questionnaire (PHQ 9-item scale) (47). The GAD 7 and PHQ 9 are completed at all appointments to assess current symptoms of anxiety and depression.

The Medical Outcomes Study Social Support Scale (MOS-SSS) is a validated, frequency scale questionnaire that assesses the level of physical and emotional support available to the patient (48). This questionnaire is only completed by patients at the

baseline visit to provide insight into the level of support available to new mothers.

Health Awareness

Health awareness is assessed via a mixed-methods survey to determine knowledge and awareness of pregnancy complications and the associated risk of future CVD. The survey questions and answer options are available in **Table 2**. This survey is also only completed at the first clinic appointment.

Physical and Hemodynamic Measurements

The measurements obtained at the appointment clinic include waist circumference, weight and height, and are taken by trained clinic staff. Waist circumference is measured at the midpoint between the lowest rib and the topmost point of the iliac crest. Body mass index (BMI) is also calculated. Hemodynamic measurements include peripheral blood pressure, central blood pressure, pulse rate, and augmentation index, all performed on the USCOM BP+ [USCOM, Sydney, Australia]. Referral pregnancy booking weight (typically taken from 6 to 12 weeks' gestation in the antenatal clinic) is recorded from the medical case notes for comparison with weight at the time of the clinic appointment. Reliable pre-pregnancy weights and measures of weight gain in pregnancy are not available. All physical and hemodynamic measurements are conducted at each clinic appointment.

Cardiovascular Biomarkers

Fasting blood and urine samples are collected and assayed at SA Pathology prior to clinic attendance. The full panel of requested pathology tests are summarized in **Table 3**. These tests are repeated at 18 months postpartum only when deemed clinically necessary by the nurse practitioner but are all repeated at 5 years postpartum.

Physical Examination

The nurse practitioner undertakes a physical examination of the patients' lungs and heart sounds, checks for peripheral oedema, and performs any other examinations deemed clinically relevant for the individual.

TABLE 2 | Health awareness survey.

	Question	Answer option
1	Before receiving your clinic referral letter, were you aware that you had experienced a complication of pregnancy?	Yes/No
2	Which complication/s did you have during pregnancy?	*Select all that apply* Gestational hypertension Preeclampsia Eclampsia HELLP syndrome Gestational diabetes Growth-restricted baby Placental abruption Delivery of a small for gestational age baby Other (text line)
3	How satisfied are you with the care you received after being diagnosed with a pregnancy complication?	*Score out of 10, where 0 is very unsatisfied and 10 is very satisfied* 0–10
4	After diagnosis of your complication, were you made aware of the link between pregnancy complications and the higher risk of heart disease down the track?	*If no, skip to question 6* Yes/No
5	Who told you about this link?	*Select all that apply* Obstetrician Midwife/nurse General practitioner Cardiologist Other
6	Please tick all of the pregnancy complications that you have heard of:	*Select all that apply* Gestational hypertension Preeclampsia Eclampsia HELLP syndrome Gestational diabetes Growth-restricted baby Placental abruption Delivery of a small for gestational age baby
7	Where did you first hear about any one of these complications?	*Select all that apply* Obstetrician Midwife/nurse General practitioner Other healthcare provider Pregnancy book/magazine Family member/friend Website Social media Mobile app Television Other (text line)

DISCUSSION

This clinic is the first example of a standard care Australian, nurse practitioner-led, postpartum intervention clinic and registry for women who experience serious pregnancy complications associated with an increased risk of future cardiovascular risk. This new model of care is an evolution of cardiac rehabilitation and prevention strategies and resources, usually reserved for secondary prevention of ischemic heart disease, into the primordial and primary prevention arena.

Awareness of the relationship between pregnancy complications and CVD remains poor in both the medical community and general population, despite wide acceptance of the more traditional risk factors for heart disease. Improving this awareness through widespread community education will likely have a profound impact on the uptake of postpartum health assessments, both by patients and primary care providers. Future research stemming from our model of care will aim to engage with and educate patients, general community members, primary care physicians, and antenatal care teams, and to drive guideline writing in Australia to ensure follow-up protocols are consistent and clear. Pinpointing the ideal time to intervene and educate women following pregnancy complications will also be a main future priority.

TABLE 3 | Requested pathology tests for postpartum review at the postpartum pregnancy complication clinic.

Pathology test	Unit of measurement
Urine chemistry	
Creatinine	mmol/L
Albumin urine	mg/L
Albumin/creatinine ratio	mg/mmol
Lipid studies	
Total cholesterol	mmol/L
Triglyceride	mmol/L
HDL cholesterol	mmol/L
LDL cholesterol	mmol/L
Total cholesterol/HDL ratio	
Non-HDL cholesterol	mmol/L
Glucose studies	
HbA1c	mmol/L & %
Glucose	mmol/L
Insulin	mU/L
Complete blood examination	
Hemoglobin	g/L
White cell count	×10^9/L
Platelet count	×10^9/L
Red cell count	×10^12/L
Packed cell volume	L/L
Mean corpuscular volume	fL
Mean corpuscular hemoglobin	pg
Mean corpuscular hemoglobin concentration	g/L
Red cell distribution width	%
Mean platelet volume	fL
Neutrophils	×10^9/L & %
Lymphocytes	×10^9/L & %
Monocytes	×10^9/L & %
Eosinophils	×10^9/L & %
Basophils	×10^9/L & %
Biochemical Analyses	
Sodium	mmol/L
Chloride	mmol/L
Bicarbonate	mmol/L
Creatinine	umol/L
Urea	mmol/L
Anion gap	mmol/L
Calcium	mmol/L
Phosphate	mmol/L
Albumin	g/L
Total protein	g/L
Bilirubin	umol/L
Globulin	g/L
Alkaline phosphatase	U/L
Alanine aminotransferase	U/L
Aspartase aminotransferase	U/L
Gamma Glutamyl Transpeptidase	U/L
Lactate dehydrogenase	U/L
Urate	mmol/L
Estimated glomerular filtration rate	mL/min/1.73 m^2
Ionized calcium calculated	mmol/L

The nurse practitioner leading this postpartum intervention clinic provides a holistic approach to cardiovascular and overall health. Family participation is also encouraged, where possible, through the promotion of healthy eating habits and physical activity practices that can include partners and children. This clinic therefore holds potential to improve health for the whole family, although this will not be quantitatively assessed.

The described postpartum clinic services the northern Adelaide area, which is complicated by some of the highest rates of chronic disease, smoking, obesity and physical inactivity, diabetes, heart disease, mental illness, and socioeconomic disadvantage in urban Australia (49). The aim of our preventive clinic in an area burdened by this level of disease and social disadvantage is to prevent these women from progressing to serious cardiovascular and metabolic disease. Such early intervention may help alleviate some of the significant burden of disease in the northern Adelaide area.

The quantitative success of this postpartum intervention clinic approach will be evaluated on an ongoing basis through comparison of baseline results with data from future appointments. Future directions will explore development and validation of cardiovascular risk algorithms specific to younger women, as current risk scores are not suitable for this population. Future research will also focus on developing strategies for earlier identification of women who are less likely to engage with the health system following birth of their baby. This will inform particular social factors that identify these high-risk individuals and provide potential opportunities to develop interventions that are more effective.

DATA AVAILABILITY STATEMENT

The datasets generated for this study will not be made publicly available as the authors are not permitted to share datasets for this research.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Central Adelaide Local Health Network Human Research Ethics Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

EA prepared the manuscript. All authors were involved in the design of the clinic and associated research study. All authors edited the draft manuscript, provided critical feedback, and approved the final manuscript.

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MINI REVIEW
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Cardiometabolic Risk Factors in Pregnancy and Implications for Long-Term Health: Identifying the Research Priorities for Low-Resource Settings

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Cardiometabolic disorders (CMDs), including ischemic heart disease, stroke and type 2 diabetes are the leading causes of mortality and morbidity in women worldwide. The burden of CMDs falls disproportionately on low and middle-income countries (LMICs), placing substantial demands on already pressured health systems. Cardiometabolic disorders may present up to a decade earlier in some LMIC settings, and are associated with high-case fatality rates. Early identification and ongoing postpartum follow-up of women with pregnancy complications such as hypertensive disorders of pregnancy (HDPs), and gestational diabetes mellitus (GDM) may offer opportunities for prevention, or help delay onset of CMDs. This mini-review paper presents an overview of the key challenges faced in the early identification, referral and management of pregnant women at increased risk of CMDs, in low-resource settings worldwide. Evidence-based strategies, including novel diagnostics, technology and innovations for early detection, screening and management for pregnant women at high-risk of CMDs are presented. The review highlights the key research priorities for addressing cardiometabolic risk in pregnancy in low-resource settings.

Keywords: high-risk pregnancy, preeclampsia, gestational diabetes, cardiometabolic disorders, cardiovascular disease

INTRODUCTION

Significant physiological changes occur during pregnancy. These may affect a woman's cardiovascular, immune and metabolic functions and unmask susceptibility for developing cardiometabolic disorders (CMDs) (1, 2). Women with a history of Hypertensive Disorders of Pregnancy (HDPs, including preeclampsia), Gestational Diabetes Mellitus (GDM), spontaneous preterm birth, and delivery of a small for gestational age (SGA) baby, display increased risk of future CMDs: including cardiovascular disease (CVD), stroke, Type 2 Diabetes (T2DM) and chronic

kidney disease (CKD) (3–7). Pregnancy complications are no longer seen as isolated conditions affecting pregnancy, but independent risk factors for future CVD (5, 8).

Women are more likely to die from CVD because of late presentation and differences in symptomatology (9). The burden of premature deaths from complications of pregnancy such as preeclampsia, preterm birth and SGA babies and CVD later in life, fall disproportionately upon Low-and Middle-Income Countries (LMICs) (10, 11). Women in rural areas of LMICs are further disadvantaged due to limitations in healthcare access and infrastructure, issues of poverty, and educational and socio-cultural barriers in accessing timely care as well as engaging with ongoing treatment (12, 13).

This review discusses the research priorities for improving women's cardiometabolic health in low-resource settings in LMICs following a high-risk pregnancy. We focus on three main areas related to the provision of universal health coverage: (1) Community-level interventions for high-risk pregnancies; (2) The need for life-course based approaches to women's health, and (3) Improving equity and access to affordable treatments for CMDs.

Community-Level Interventions for High-Risk Pregnancies

Preventative efforts to avert CMDs often start too late to be effective (3). Early detection and management of women with pregnancy complications associated with a high-risk of future CMDs requires active community engagement to encourage early, regular antenatal care (ANC) attendance (14).

In low-resource settings, where multiple clinic visits may not be feasible, point-of-care tests (POCT) have been used by Community Health Workers (CHWs), nurses and doctors to screen for HIV/AIDS, malaria and anemia during pregnancy (14). Potential biomarkers for first trimester preeclampsia screening include serum placental growth factor (PlGF), serum pregnancy-associated plasma protein A (PAPP-A), mean arterial pressure (MAP) and uterine artery pulsatility index (UTPI) (15). Point of care tests for these emerging biomarkers merit further country-specific, clinical, and economic evaluation (16). The implementation of novel diagnostics in LMICs, must be coupled with upgrading of laboratory facilities in primary care settings, which are insufficiently prioritized by governments worldwide (17).

The detection of HDPs mainly involves blood pressure (BP) measurement and urinalysis. Whilst non-invasive, these skills can be intimidating to rural healthcare workers. To improve community-level detection of HDPs in LMICs, low-cost instruments have been developed and validated for use by frontline healthcare workers in low-resource settings. The CRADLE Vital Signs Alert device is a novel, semi-automated BP device, validated for use in pregnancy and to stratify risk in pregnant women with both high and very low BP, costing ∼$20 USD (18). Feasibility studies have shown high levels of acceptability by Community Health Workers (CHWs) in Nigeria, Mozambique, Zimbabwe, Ethiopia and India (18, 19). A large stepped-wedge cluster-randomized controlled trial across 10 LMICs was; however, unable to demonstrate impact on the primary composite outcomes of maternal mortality and morbidity (20). This may be due, in part, to insufficient power and sample size, and significant variations between clusters (20). Low cost urinalysis devices for proteinuria detection have also been developed and piloted (21–23), although evidence of impact on clinical endpoints is lacking.

Community-based screening for GDM is complicated by a lack of attendance, and lack of consolidated criteria for testing and diagnosis of GDM (24). Routine application of the gold standard fasting oral glucose tolerance test (OGTT), followed by venous blood being drawn at 0, 1, and 2 hours post-glucose load is not feasible in rural settings where mothers have to travel long distances and wait substantial amounts of time to receive antenatal services, and healthcare staff skilled in drawing blood are not available at specified times (24). Some rural centers perform OGTTs irrespective of fasting status. A study from India, testing women irrespective of their fasting state, did not reveal statistically different results compared to the WHO-recommended fasting 75-g OGTT (25). Subsequent studies have, however, found the sensitivity of non-fasting tests to be low (26). In response to the growing burden of GDM in India, pragmatic guidelines for low-resource settings have been developed (24, 27); however, the operability of such guidelines relies heavily on the presence of good laboratory and primary care infrastructure.

The Role of Mobile Technologies

Mobile health (mHealth) technologies have the potential to increase equity, quality and efficiency of service delivery in LMICs (28). mHealth technologies have contributed to reductions in delays in accessing maternal health in LMICs (29), and can be useful in the diagnosis, monitoring, providing clinical decision support, education and health promotion (30, 31).

A large-scale cluster randomized trial of a multi-faceted smartphone-based mHealth intervention (ImTECHO) used by CHWs to deliver care to pregnant women in their homes, involving a population of almost half a million in rural Gujarat in India, demonstrated improved engagement and delivery of antenatal and postnatal care by CHWs (32). The platform facilitated longitudinal tracking, scheduling of health services, screening for complications, counseling and behavior change communication, and real-time mentoring and supportive supervision of CHWs. This study highlighted the feasibility and effectiveness of mobile phone technologies as job aids to frontline healthcare workers to strengthen the local health system, but did not demonstrate a positive impact on maternal or neonatal mortality (32).

Similar interventions have potential to extend beyond the immediate postpartum period for long-term follow up of women at high risk of future CMDs. Future research should focus on rigorous evaluation of mHealth interventions beyond pilot studies (33), and include process evaluation and cost-effectiveness analyses, with a focus on local ownership and integration within existing health systems.

Risk stratification tools for pregnant women with preeclampsia have been developed for predicting risk of adverse maternal outcomes (34, 35). The full-Pre-eclampsia

Integrated Estimate of RiSk model (fullPIERS) is a prediction model based on clinical history, signs and symptoms and laboratory tests. Developed in a High-Income Country (HIC) context, it has also been validated for use in low-resource settings (36, 37); however, is reliant on full laboratory-based support (35). A succinct version, based on symptoms and signs alone (miniPIERS), has also been developed for community-based risk assessment (34). These tools provide clinical decision support to frontline healthcare workers and may be integrated into mHealth platforms, such as the PIERS-on-the-move (POM) mHealth platform (38). A study of the POM mHealth platform, demonstrated good levels of acceptability, feasibility, and moderate utility for the prediction of adverse maternal outcomes in women with HDPs (39).

While these tools may be used for identification and risk-stratification of high-risk women during pregnancy, little evidence is currently available to calculate or predict long-term cardiovascular risk in this population (40). Robust data collection systems are needed for the long-term follow-up of women in LMICs to study the true prevalence and impact of high-risk conditions in pregnancy on future CMDs, and enable accurate risk stratification of high-risk women. It is unclear if existing cardiovascular risk prediction models could be improved through the addition of history of pregnancy complications (41, 42). There is a need for prognostic models using sample populations reflecting the diversity of target populations, and involving both nulliparous and multiparous women to better identify women at high-risk of CMD during and after pregnancy (40). Women who develop T2DM following GDM in some LMIC settings are more likely to exhibit certain characteristics such as increased body mass index postpartum, family history of T2DM, and certain ethnicities (43, 44). It is unclear, however, if these clinical features may be used to guide risk stratification of women with GDM and their progression to T2DM across other LMIC settings, as they are based on small-scale studies. A systematic review on the progression of GDM to T2DM concluded that a markedly raised fasting glucose level during pregnancy was most highly predictive of progression to T2DM, and did not support the use of features such as ethnicity, BMI, and family history of T2DM for risk stratification of progression to T2DM in pregnant women (45).

Task-Sharing in the Community

Task-sharing has potential to empower and engage community members, improve efficiency, and "*expand the reach of delegated medical acts*" (46). In areas with a shortage of doctors and nurses in LMICs, CHWs have been deployed to deliver interventions for the early detection of high-risk pregnant women (18, 47–49) and enable community-based data collection (50). CHWs have high levels of trust and respect within their communities, and motivate women to engage with antenatal care (51). Task-sharing relies upon continuous training and supervision, as CHWs may have limited literacy in low-resource settings (14).

The community-based management of hypertension in Nepal (COBIN) cluster randomized controlled trial in the general adult population of Nepal, established the effectiveness of a CHW-led home-based health education and screening for the reduction of Systolic BP (of almost 5 mmHg), in adults with hypertension; and amelioration of age-related increases in BP in adults without hypertension (52). Further examples of community-based programmes with potential to reduce cardiovascular risk in LMIC settings exist (53–56), however as the COBIN trial team concluded; long-term trials with hard clinical outcomes, such as myocardial infarction and stroke as primary endpoints are needed to confirm the effect of CHW-led interventions on cardiovascular mortality and morbidity (52). Important areas for future research would be to conduct adequately sized, robustly designed trials, demonstrating tangible impact upon mortality across the life-course, including cost effectiveness analyses, and exploration of the impact of climate change and seasonal variations on BP-related endpoints (57, 58).

LMIC-Based Data Repositories and Biobanks

Research associating pregnancy complications with CVD risk have, to date, been derived from linkage of large national data sets from high income countries (HIC) (41, 59, 60). Unlike HICs, the majority of CVD deaths in sub-Saharan Africa are due to stroke rather than ischemic heart disease (61), which may reflect differences in etiology. Currently, there are insufficient data on the life-long health of women living in LMIC settings. Encouraging collaboration across LMICs to form consortia for uniform women's health related data collection such as the COLLECT database for collaborative pregnancy and placental research (62), started by the Global Pregnancy Collaboration (CoLab) (63), might facilitate the use of big data analytics to enable risk stratification of women with pregnancy-related risk factors for CMDs in LMICs, and identify key timings for interventions.

With the fast-developing world of genomics, proteomics and metabolomics, LMICs might benefit from establishing biobanks. This would encourage locally-driven -omics research, based on the needs and priorities of LMICs, with local data ownership. South-south as well as north-south collaborations have potential to improve research into biomarkers for risk factors for CMD in women, including pregnancy-related risk factors such as preterm birth, pre-eclampsia, and GDM. The significant genetic variations in South Asian and African populations are important to furthering our knowledge of disease etiology and drug development. Currently, the majority of DNA used for research studies come from participants of European descent, with only 2% of data contributed from African data sets (64). In response, a new pan-Africa biobank start-up, 54-gene (64) and additionally, the first pan-Asia biobank have launched (65), both with the aim of solving the problem of lack of global representation. Similar initiatives are found in Brazil (66). Due to the heterogeneity of the samples and different collection strategies of existing biobanks, adequate skills training, capacity-building of LMIC-based researchers, and regulatory environments would need to be in place to support standardization of biobanks globally (63), as well as the infrastructure (such as 24-h electricity) for sample storage.

THE NEED FOR LIFE-COURSE BASED APPROACHES TO WOMEN'S HEALTH

Health systems in low-resource settings are often designed to provide emergency services only. Preventative services, however, are fundamental to ensuring a healthy population. A recent study showed that each dollar spent on a package of essential preventive services leads to a net health gain of 1.8 dollars in India (67). Provision of integrated care for women throughout their life-course is one way in which women may be engaged within the health system at key intervals in their life. By using entry points (e.g., antenatal care) into the health system as opportunities to engage women, opportunistic screening for cardiometabolic risk factors might be feasible at critical points during the life-course.

There are few integrated care models that link antenatal care and non-communicable disease (NCD) prevention (68–71), although those demonstrating effectiveness for *communicable* diseases such as HIV and life-long health, exist (72, 73). Future research into how existing successful models of integrated care (such as the HIV programmes in sub-Saharan Africa) could be adapted for NCD prevention will be valuable in designing health systems responsive to the needs of women throughout their life-course.

There is a 2-fold increased risk of developing CVD, and a 3-5-fold risk of chronic hypertension in the decades following a pregnancy complicated by HDP (59, 74–77). The cumulative incidence of T2DM following GDM increases markedly within the first 5 years postpartum and plateaus after 10 years (45, 78). The American Heart Association (79) and the American Diabetes Association (80) have recommended incorporating pregnancy-related risk factors as part of screening for adult cardiovascular disease (81). Postpartum screening for ongoing problems with BP (79, 82) and glucose control through the use of an OGTT at 6–12 weeks postpartum and 1–3 yearly thereafter are advised (80). Despite these recommendations, most women with a complicated pregnancy do not routinely receive postpartum follow-up (83, 84) and certainly not for 5 years following the index pregnancy, when the long-term sequelae are likely to manifest.

Although challenges to postpartum screening of women are faced worldwide, there are specific contextual challenges in LMICs. Postnatal follow-up is lower in LMICs than in high income settings (85, 86). In low-resource settings, the burden of CMDs on daily life, household expenditure and economic stability have considerable implications for women and their entire household. Cultural practices after birth, workforce shortages, particularly in rural areas, and a lack of health system infrastructure are additional barriers to providing life-long care. Many women with hypertension and T2DM remain undiagnosed, although population-based screening for GDM shows high rates of conversion from GDM to T2DM in both urban and rural areas of LMICs (87). Further education and training of women and healthcare staff are needed to encourage postpartum follow-up and repeat testing of women at high risk of CMDs (84). Postpartum interventions targeting high-risk women might learn from adult NCD prevention programmes that have shown evidence of clinical benefit (88, 89). Successful lifestyle interventions are characterized by addressing more than one area of prevention and taking a holistic approach to change (90).

IMPROVING EQUITY AND ACCESS TO AFFORDABLE TREATMENTS FOR CMDS

A study of 596 urban and rural communities in 18 countries concluded that improving the availability and affordability of medicines for CMDs is essential for increasing their uptake and use (91). This is of great importance for women identified at high-risk of CMDs early in their life-course. Although common medications for cardiovascular disease and diabetes are widely

TABLE 1 | Summary of research recommendations.

Recommended area of research	Sub-topics	Skills required
Community-level interventions for High-Risk Pregnancies (HRPs)	Development and evaluation of affordable point of care tests for HRPs.	Community engagement for developing contextually-relevant and usable tools in low resource settings.
	Designing and evaluating community-based interventions through robust clinical trials and significant clinical endpoints.	Novel methodologies for real-world, pragmatic clinical trials.
	Pragmatic evidence-based guidelines for screening and diagnosis of HRPs in the community.	Contextual-based multidisciplinary research to guide development.
	Building the evidence-base for accurate cardiovascular risk prediction in high-risk pregnant women.	Building capacity for local LMIC biobanks and data repositories, alongside improving local research capabilities and governance systems.
	Task-sharing and workforce planning	Understanding the needs of healthcare workers in low- resource settings.
Life-course approaches to women's health	Integrated care linking antenatal care to long-term women's health.	Learning from other successful models for integrated care throughout the life-course e.g., HIV.
Improving equity and access	Advocacy aimed at Governments to provide essential medications for secondary prevention of CMDs.	
	Understanding the socio-cultural barriers to prescribing and medicine use in low resource settings.	Contextually-based research involving social scientists and anthropologists.

available in some LMICs, the out-of-pocket expenditure for households already struggling to meet their daily needs, is a significant barrier to their continued life-long use for women diagnosed with CMDs earlier in their life-course. The situation is even more pronounced in rural areas (92). Even with improved access to affordable medicines, there are significant socio-cultural barriers affecting compliance to lifelong treatment (93).

The WHO has committed to achieving the goal of 80% availability of affordable, essential medicines for NCDs by 2025 in their Global Action Plan (94). Current rates of medicine use for the secondary prevention of CVD are, however, substantially lower (91, 92, 95). The proportion of patients with coronary heart disease receiving medications for secondary prevention of CVD in 10 countries (including several LMICs) in the Prevention of REcurrences of Myocardial Infarction and StrokE (WHO-PREMISE) PREMISE study, was lower than 50% for all major classes of CVD prevention medicines, including beta blockers (48%), ACE inhibitors (40%), and statins (30%) (96).

Governments need to set policy objectives to ensure that essential medicines to stem the tide of the rising CMD epidemic are affordable and available to their populations, including those in rural areas, by ensuring continuity of supply chains, i.e., the manufacturing, transport and distribution of medicines. Multidisciplinary research is needed to explore socio-cultural barriers to prescribing and taking medications, if we are to ensure that women with, or at risk of CMDs in LMICs, receive essential care.

DISCUSSION: THE RESEARCH AGENDA FOR LMICS

Only a multi-dimensional research strategy can help improve women's health in LMICs. Our review highlights the need for further well-designed experimental studies of novel technologies and biomarkers, embedded within the real-world context. Such studies would need to be adequately powered to demonstrate tangible benefit to clinical outcomes, such as maternal and neonatal mortality in the short-term, and cardiovascular endpoints in the longer term, and include cost-effectiveness analyses for future scalability. Data collection and monitoring are important strategies for improving healthcare provider practices (90). Future research should prioritize high-quality community-based data collection and linkage to existing hospital level health information systems, through prospective cohort studies with appropriate representation of women living in low-resource settings. Exploration of the complex social factors that impact the health of women both during pregnancy and beyond, with reference to CMDs has also been highlighted as a key area for future research (see **Table 1**).

The Academy of Medical Sciences have emphasized the need to develop locally driven solutions and diagnostics for NCDs, including disruptive technologies (17). Significant challenges include the commercially unattractive nature of research into novel low-cost diagnostics for low-resource settings, affecting the development and scalability of new diagnostic tests (17). Nevertheless, given that pregnancy complications associated with future CMDs still result in significant maternal mortality worldwide (97), there is a moral imperative to give women in LMICs the same access as those living in HICs to screening tests that predict life-threatening conditions in pregnancy, and beyond.

AUTHOR CONTRIBUTIONS

SN was responsible for the conceptualisation of the mini-review and for writing the first draft. All authors contributed to the subsequent editing and review of the draft paper for publication.

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REVIEW
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Hypertensive Disorders of Pregnancy and Future Cardiovascular Health

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Hypertensive disorders of pregnancy (HDP) occur in almost 10% of gestations. These women are known to have higher cardiovascular morbidity and mortality later in life in comparison with parous controls who had normotensive pregnancies. Several studies have demonstrated that women with preeclampsia present in a state of segmental impaired myocardial function, biventricular chamber dysfunction, adverse biventricular remodeling, and hypertrophy, a compromised hemodynamic state and indirect echocardiographic signs of localized myocardial ischemia and fibrosis. These cardiac functional and geometric changes are known to have strong predictive value for cardiovascular disease in non-pregnant subjects. A "dose effect" response seems to regulate this relationship with severe HDP, early-onset HDP, coexistence of fetal growth disorders, and recurrence of HDP resulting in poorer cardiovascular measures. The mechanism underlying the relationship between HDP in younger women and cardiovascular disease later in life is unclear but could be explained by sharing of pre-pregnancy cardiovascular risk factors or due to a direct impact of HDP on the maternal cardiovascular system conferring a state of increased susceptibility to future metabolic or hemodynamic insults. If so, the prevention of HDP itself would become all the more urgent. Shortly after delivery, women who experienced HDP express an increased risk of classic cardiovascular risk factors such as essential hypertension, renal disease, abnormal lipid profile, and diabetes with higher frequency than controls. Within one or two decades after delivery, this group of women are more likely to experience premature cardiovascular events, such as symptomatic heart failure, myocardial ischemia, and cerebral vascular disease. Although there is general agreement that women who suffered from HDP should undertake early screening for cardiovascular risk factors in order to allow for appropriate prevention, the exact timing and modality of screening has not been standardized yet. Our findings suggest that prevention should start as early as possible after delivery by making the women aware of their increased cardiovascular risk and encouraging weight control, stop smoking, healthy diet, and daily exercise which are well-established and cost-effective prevention strategies.

Keywords: preeclampsia, gestational hypertension, hypertensive disorders of pregnancy, essential hypertension, cardiovascular disease, heart failure, coronary artery disease

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INTRODUCTION

Numerous epidemiological studies have proven the relationship between hypertensive disorders in pregnancy (HDP) and increased cardiovascular risk factors and diseases (CVD) later in life (1, 2). This is not surprising as several studies already demonstrated that women with preeclampsia (PE) present in pregnancy a state of impaired myocardial contractility and relaxation, biventricular systo-diastolic chamber dysfunction, adverse biventricular remodeling and hypertrophy, an impaired hemodynamic state, and indirect echocardiographic signs of localized myocardial ischemia and fibrosis (3–5). The above described structural and functional cardiovascular changes do not completely reverse at 1 year postpartum notwithstanding the unloading conditions and are known to be highly predictive for future cardiovascular adverse outcome (3, 6). Furthermore, clinical data has shown that the cardiopulmonary complications already occur in 6% of severe PE and are associated with increased maternal mortality (7). The American Heart Association has already recognized PE as independent risk factor for CVD and introduced this complication of pregnancy in the algorithms for the evaluation of future cardiovascular risk score (8). The physiopathology for this additional CVD risk is still unknown with the existing literature hypothesizing the possibility of pregnancy-induced CVD risk vs. pre-conceptional susceptibility toward an increased risk of CVD or both. The aim of this review is to elucidate the association between HDP and future cardiovascular risk factors and CVD. HDP include gestational hypertension (GH), PE or eclampsia, chronic hypertension, and PE superimposed on top of chronic hypertension. This review will focus on HDP involving new-onset hypertension after 20 weeks' gestation, but other complications of pregnancy such as normotensive small for gestational age or fetal growth restriction as well as normotensive preterm birth, placental abruption, and stillbirth will not be included. This review will focus on the future cardiovascular health of these women, but other outcomes, such as renal failure, diabetes, or other dysmetabolic conditions will not be examined.

SEARCH STRATEGY AND SELECTION OF ARTICLES

A literature examination was accomplished to identify all reports in the English language literature (Medline, National Library of Medicine) published after 2000 until now as previous meta-analysis showed that there were not suitable papers on this topic from 1946 to 1999 (9). The search terms used were "pre-eclampsia," "gestational hypertension," "hypertension during pregnancy," "hypertensive disorders of pregnancy," "long term outcomes," "cardiovascular risk," "cardiovascular health," "cardiovascular disease," "essential hypertension," "peripheral artery disease," "asymptomatic atherosclerosis," "diastolic dysfunction," "heart failure," "coronary artery disease," "cerebrovascular disease." We excluded abstracts of oral communications and posters of congresses even if available on Medline. Furthermore, the bibliography of the selected papers were dissected to further identify pertinent studies. The combined set encompassed 230 articles which were reviewed, and a total of 87 articles were considered appropriate for this review. The relevant data were extracted from the full text of the published papers.

RESULTS

The research yielded 59 prospective (3, 6, 10–66) and 28 retrospective studies (67–93) which were synthetically described in **Table 1**. The number of women analyzed in each study ranged from 58 to 1,072,330 in prospective studies and from 71 to 1,452,926 in retrospective ones. The year of pregnancy included into the studies ranged from 1952 to 2017 in prospective studies and from 1939 to 2016 in retrospective articles. The following complications of pregnancy were included into the studies: HDP, placental infarction and abruption, preterm delivery, low birth weight offspring, small-for-gestational-age fetuses, fetal growth restriction, stillbirth, gestational diabetes mellitus, and pre-gestational diabetes mellitus. The interval between delivery and cardiovascular risk assessment or between delivery and cardiovascular event occurrence were assessed in the majority of the studies, the median of follow up ranging from at least 7 weeks post-partum to more than 30 years after delivery. The median age of the women at the assessment of CV risk or at the occurrence of CV event ranged from 25 to 71 years in the different studies. The following cardiovascular risks or events were differently assessed in the numerous included studies: essential hypertension, heart failure, coronary, cerebro-vascular and peripheral artery disease, asymptomatic atherosclerosis, dyslipidemia, metabolic syndrome, type II diabetes, and renal dysfunction.

The following outcomes will be analyzed in this review:

- Essential hypertension
- Peripheral artery disease
- Asymptomatic atherosclerosis
- Asymptomatic heart failure
- Heart failure
- Coronary artery disease
- Cerebrovascular disease.

DISCUSSION

Essential Hypertension

All authors who addressed the issue of the relationship between HDP and future development of essential hypertension unanimously found that women who developed HDP have an increased risk of having high blood pressure later in life **(Table 1).** There seems to be a "dose-dependent" effect of HDP and future risk of developing chronic hypertension depending on the severity of the hypertension in pregnancy, the onset of the complication in pregnancy, the need of iatrogenic preterm delivery, the association to fetal growth disorders and the numbers of pregnancies complicated by HDP. In particular Hauspurg et al. found that "*HDP were associated with an aOR of 1.86 (95%CI 1.37–2.52) of development hypertension at one year with PE having an aOR of 2.35 (95%CI 1.63–3.41) whereas*

TABLE 1 | Studies included in this review.

References	Demographic	Design of the study	Study population	Year of pregnancy	Complications of pregnancy	Post-partum follow-up time in years	Age of the women at the assessment in years	Cardiovascular outcomes assessed
Kestenbaum et al. (10)	North America (USA)	Population-based cohort study	*N* = 31,239 cases *N* = 92902 controls	1987–1998	HPD	7.8 (mean)	36 (mean)	Cardiovascular event
Sattar et al. (11)	Europe (UK)	Prospective case control	*N* = 40 cases *N* = 40 controls	1975–1985	PE	15–25 (range)	43 (median)	Essential chronic hypertension
Ray et al. (67)	North America (Canada)	Population-based retrospective cohort study	*N* = 75380 cases *N* = 950885 controls	1990–2004	PE, HDP, PA	8.7 (median)	Age at delivery28 (mean) Age at first CV event 38.3 (mean)	Coronary heart disease Cerebro-vascular disease Peripheral artery disease
Manten et al. (12)	Europe (Netherlands)	Prospective case control	*N* = 256 cases *N* = 53 controls	NA	PE	0.82 (mean) cases 0.48 (mean) controls	31 (mean) cases 33 (mean) controls	Essential chronic hypertension Cardiovascular risk
Berends et al. (13)	Europe (Netherlands)	Prospective case control	*N* = 106 cases *N* = 106 controls	1983–2004	PE and FGR	7.1 (median)	NA	Essential chronic hypertension Asymptomatic atherosclerosis
Valensise et al. (3)	Europe (Italy)	Prospective longitudinal case-control study	*N* = 107 *N* = 1119 controls	1999–2007	PE	1	34 (median) early onset PE 32 (median) late onset PE 32 (median) controls	Essential chronic hypertension Cardiac dysfunction and remodeling
Edlow et al. (14)	North America (USA)	Prospective case-control study	*N* = 79 cases *N* = 140 controls	2006	PE	0.5–1 (range)	NA	Essential chronic hypertension
Haukkamaa et al. (15)	Europe (Finland)	Cross-sectional study	*N* = 96 cases *N* = 489 controls	NA	HDP	NA	55.1 (mean)	Essential chronic hypertension Coronary heart disease Asymptomatic atherosclerosis
Lykke et al. (16)	Europe (Denmark)	Registry-based cohort study	*N* = 782287 cases	1978–2007	HDP	14.6 (median)	NA	Essential chronic hypertension Coronary heart disease Cerebrovascular disease Heart failure Peripheral artery disease Cardiovascular risk
Magnussen et al. (17)	Europe (Norway)	Registry-based cohort study	*N* = 15065 cases	NA	HDP	16.5 (median)	NA	Essential chronic hypertension Cardiovascular risk

(Continued)

TABLE 1 | Continued

References	Demographic	Design of the study	Study population	Year of pregnancy	Complications of pregnancy	Post-partum follow-up time in years	Age of the women at the assessment in years	Cardiovascular outcomes assessed
Nijdam et al. (68)	Europe (Netherlands)	Retrospective case control	*N* = 35 cases *N* = 150 control	2000–2007	PE	2.9 (mean)	NA	Essential chronic hypertension Coronary heart disease Cerebrovascular disease
Smith et al. (18)	North America (Canada)	Prospective cohort	*N* = 70 cases *N* = 70 control	NA	PE	1	30.5 (mean)	Cardiovascular risk
Canti et al. (19)	South America (Brazil)	Cross sectional	*N* = 40 cases *N* = 14 controls	NA	PE	15.9 (mean)	39.2 (mean)	Cardiovascular risk
Ben-Ami et al. (69)	Asia (Israel)	Retrospective case-control study	*N* = 101 cases *N* = 101 controls	NA	HDP, PA, PD, SGA, abortions	NA	43.3 (mean) cases 41.9 (mean) controls	Essential chronic hypertension Coronary heart disease Cerebrovascular disease Peripheral artery disease Cardiovascular event
Lykke et al. (70)	Denmark	Retrospective cohort study	*N* = 782287	1978–2007	PD, SGA, HDP, PA and stillbirth	14.8 (median)	41.6 (mean)	Death from cardiovascular causes
Mongraw-Chaffin et al. (20)	California (USA)	Prospective cohort study	*N* = 24 cases *N* = 242 controls	1959–1967	PE	30	56 (median)	Cardiovascular risk
Callaway et al. (21)	Australia	Prospective cohort study	*N* = 191 cases *N* = 1921 controls	1981–1983	HDP	21	46.4 (mean)	Essential chronic hypertension Cardiovascular risk
Melchiorre et al. (6)	Europe (London, UK)	Prospective longitudinal case-control study	*N* = 64 cases *N* = 78 controls	2008–2009	PE	Two time points: 1 and 2 years	31 preterm PE (median) 33 term PE (median) 33.5 (median) controls	Essential chronic hypertension Asymptomatic heart failure (stage B)
Andersgaard et al. (22)	Europe (Norway)	Registry-based cohort study	*N* = 901 cases *N* = 9073 controls	NA	PE	25.4 (median)	48.8 (median)	Asymptomatic atherosclerosis Cardiovascular risk
Bhattacharya et al. (23)	Europe (UK)	Registry-based cohort study	*N* = 10917 cases *N* = 23937 controls	1950–2012	HDP	NA	NA	Essential chronic hypertension Coronary heart disease Cerebrovascular disease Peripheral artery disease Cardiovascular risk
Borna et al. (71)	Asia (Iran)	Retrospective case-control study	*N* = 345 cases *N* = 345 controls	NA	HDP	32.2 (mean) cases 31.5 (mean) control	58.1 (mean) cases 55.9 (mean) controls	Coronary heart disease

(Continued)

TABLE 1 | Continued

References	Demographic	Design of the study	Study population	Year of pregnancy	Complications of pregnancy	Post-partum follow-up time in years	Age of the women at the assessment in years	Cardiovascular outcomes assessed
Gastrich et al. (72)	North America (USA)	Retrospective case-control study	*N* = 302 cases *N* = 864 controls	1994–2009	PE	Within 16	NA	Coronary heart disease Cerebrovascular disease Cardiovascular event
Drost et al. (24)	Europe (Netherlands)	Prospective case-control study	*N* = 339 cases *N* = 332 controls	1991–2007	PE	10	38.9 (mean)	Essential chronic hypertension Cardiovascular risk
Fraser et al. (25)	Europe (UK)	Prospective cohort study	*N* = 2172 cases	1991.1992	HDP	18	48 (mean)	Cardiovascular risk
Ray et al. (73)	North America (Canada)	Retrospective cohort study	*N* = 75242 cases *N* = 1 055 522 controls	1992–2009	PE, HDP, PA	7.8 (median)	37.8 (mean)	Heart failure C and dysrhythmias
Skjaerven et al. (26)	Europe (Norway)	Prospective cohort study	*N* = 34824 cases	1967–2009	PE	25	NA	Coronary heart disease Cerebrovascular disease Cardiovascular risk Cardiovascular event
Smith et al. (27)	North America (Canada)	Prospective longitudinal cohort	*N* = 99 cases *N* = 118 control	2003–2009	PE	1 time 1 3 time 2	30.3 (mean) time 1 30.5 (mean) time 2	Cardiovascular risk
Spaan et al. (28)	Europe (Netherlands)	Prospective longitudinal Cohort	*N* = 683 cases	1996–2010	PE	0.66	31.4 (mean)	Cardiovascular risk
Mangos et al. (29)	Australia	Prospective case control	*N* = 66 cases *N* = 35 controls	NA	HDP	PE: 3.8 (mean) GH: 2.9 (mean) Controls: 4.3 (mean)	PE: 37 (mean) GH: 36 (mean) Controls: 38 (mean)	Essential chronic hypertension Cardiovascular risk
Drost et al. (30)	Europe (Netherlands)	Longitudinal Cohort study	*N* = 689 cases *N* = 2703 controls	1987–2007	HDP	Every 5 years	38.4 (mean) time 1 46.7 (mean) time 2 50.8 (mean) time 3 54.1 (mean) time 4	Essential chronic hypertension Cardiovascular risk
Hermes et al. (31)	Europe (Netherlands)	Prospective, case-control	*N* = 94 cases *N* = 300 controls	2005–2008	HDP	2.5	As the woman was 60 years old for the extrapolation at 10-year risk Current age (34 years old) for extrapolation at 30-year risk	Essential chronic hypertension Cardiovascular risk
Scholten et al. (32)	Europe (Netherlands)	Prospective Cohort study	*N* = 1297 cases	2004–2010	PE	0.58 (median)	32 (median)	Essential chronic hypertension Cardiovascular risk

(Continued)

TABLE 1 | Continued

References	Demographic	Design of the study	Study population	Year of pregnancy	Complications of pregnancy	Post-partum follow-up time in years	Age of the women at the assessment in years	Cardiovascular outcomes assessed
Van Rijn et al. (33)	Europe (Netherlands)	Prospective cohort study	*N* = 243 cases *N* = 374 control	1994–2007	PE	0.75 (mean)	30.5 (mean)	Cardiovascular risk
Kurabayashi et al. (34)	Japan	Cross–sectional	*N* = 1219 cases *N* = 9237 controls	2001–2007	HDP	NA	≥ 45 at time of survey	Essential chronic hypertension
Nakimuli et al. (35)	Uganda	Prospective Cohort study	*N* = 64 cases *N* = 124 controls	2009–2011	PE, Eclampsia	0.25	27.3 (mean) cases 24 (mean) controls	Persistent hypertension 3 months after delivery
Tooher et al. (36)	Australia	Observational cohort study	*N* = 7706 cases *N* = 64113 controls	2006–2009	HDP	NA	≥ 45 years age at study	Essential chronic hypertension Cerebro-vascular disease
McDonald et al. (74)	North American (Canada)	Retrospective cohort study	*N* = 109 cases *N* = 218 controls	1986–1995	PE	20 (median)	49 (median)	Asymptomatic atherosclerosis
Watanabe et al. (75)	Asia (Japan)	Retrospective cohort study	*N* = 101 cases *N* = 1,084 controls	NA	HDP	NA	46.5 (mean)	Essential chronic hypertension
Barry et al. (76)	North American (USA)	Retrospective case-control study	*N* = 49 cases *N* = 22 controls	2014	PE	>8 months	34 (mean)	Essential chronic hypertension Peripheral artery disease
Hosaka et al. (37)	Asia (Japan)	Prospective cohort study	*N* = 28 cases *N* = 785 controls	1994–1998	HDP	7 (median)	37 (mean)	Essential chronic hypertension
Black et al. (38)	North American (California)	Prospective cohort study	*N* = 5960 cases *N* = 358 controls	2005–2010	HDP	1 (median)	28 (mean)	Essential chronic hypertension
Cain et al. (77)	North American (State of Florida)	Population-based retrospective cohort study	*N* = 847 cases *N* = 1854 controls	2004–2007	HDP, PA, PD, SGA	4.9 (median)	25 (median)	Cardiovascular event
Ray et al. (78)	North America (Canada)	Population-based retrospective cohort study	*N* = 362 cases *N* = 1623 controls	Delivery was at least 90 days preceding the index coronary artery revascularization date (1993–2012)	PE, HDP, PA	11.3 (mean) cases 14.2 (controls)	44.7 (mean) controls 46.5 (mean) controls	Death after coronary artey revascularization
White et al. (36)	North America (USA)	Prospective, cohort study	*N* = 40 cases *N* = 40 controls	1976–1982	PE	30 (median)	59.5 (mean)	Essential chronic hypertension Coronary heart disease
Behrens et al. (37)	Europe (Denmark)	Prospective cohort study	*N* = 23 235 cases *N* = 459.737 controls	1995–2012 (first cohort) 1978–2012 (second cohort)	HDP	10 (mean), first cohort 20 (mean), second cohort	30 (median)	Essential chronic hypertension
Breetveld et al. (41)	Netherlands	Prospective longitudinal cohort study,	*N* = 69 cases	2005–2007	PE	1 and 4 y post-partum	32 (mean) at 1sr assessment 35 (mean) at 2nd assessment	Asymptomatic heart failure (stage B)

(Continued)

TABLE 1 | Continued

References	Demographic	Design of the study	Study population	Year of pregnancy	Complications of pregnancy	Post-partum follow-up time in years	Age of the women at the assessment in years	Cardiovascular outcomes assessed
Facca et al. (79)	South American (Brazil)	Retrospective cohort study	*N* = 25 cases *N* = 60 controls	1976–2016	HDP	16 (mean)	46 (mean)	Essential chronic hypertension Peripheral artery disease
Fatma et al. (72)	Asia (India)	Retrospective case control study	*N* = 50 cases *N* = 50 controls	NA	PE	NA	20–45 (range)	Essential chronic hypertension Peripheral artery disease
Ghossein-Doha et al. (42)	Netherlands	Cross-sectional cohort study	*N* = 107 cases *N* = 41 controls	NA	PE	4–10	36 (mean) cases 40 (mean) controls	Asymptomatic heart failure (stage B)
Grandi et al. (43)	Europe (UK)	Population-based cohort study	*N* = 5399 cases *N* = 141349 controls	1990–2013	HDP	4.7 (median)	29.5 (mean)	Essential chronic hypertension Cardiovascular event
Mito et al. (44)	Asia (Japan)	Prospective cohort study	*N* = 25 cases *N* = 746 controls	2003–2005	HDP	5 (median)	40.3 (mean)	Essential chronic hypertension
Orabona et al. (81)	Europe (Italy)	Retrospective case–control study	*N* = 109 cases *N* = 60 controls	2007–2013	PE	4 (median)	38 (median)	Cardiac dysfunction and remodeling
Tooher et al. (82)	Australia	Retrospective cohort study	*N* = 4387 cases *N* = 27262 controls	1980–1989	HDP	20 (median)	48 (median)	Essential chronic hypertension Coronary heart disease Cerebrovascular disease
Wang et al. (83)	Asia (China)	Retrospective cohort study	*N* = 94 cases *N* = 1167 controls All GDM patients	2005–2009	HDP with GDM	2.29 (mean)	33 (mean)	Essential chronic hypertension
Benschop et al. (45)	Europe (Netherlands)	Prospective cohort	*N* = 200	2011–2017	Severe PE	1 (median)	31.6 (mean)	Essential chronic hypertension
Bergen et al. (46)	Europea (Netherlands)	Prospective cohort study	*N* = 300 cases *N* = 4612 controls	NA	HDP	6 (median)	30 (mean)	Essential chronic hypertension Cardiac dysfunction and remodeling
Bokslag et al. (84)	Europe (Netherlands)	Retrospective case control study	*N* = 131 cases *N* = 56 controls	1998–2005	Early onset PE	9–16 (range)	45 (mean)	Essential chronic hypertension Asymptomatic heart failure (stage B) Peripheral artery disease
Breetveld et al. (47)	Europe (Netherlands)	Prospective case control study	*N* = 67 cases *N* = 37 controls	2009–2011	PE	5.3 (median)	36 (median)	Asymptomatic heart failure (stage B) Peripheral artery disease
Chen et al. (85)	Asia (Taiwan)	Population–based retrospective cohort study	*N* = 29.186 cases *N* = 116.744 controls	2000–2013	HDP	5.72 (mean)	NA	Heart failure
Cho et al. (86)	Asia (Korea)	Retrospective observational cohort study	*N* = 148 cases *N* = 1762 controls	2004	PE	8 (mean)	NA	Essential chronic hypertension

(Continued)

TABLE 1 | Continued

References	Demographic	Design of the study	Study population	Year of pregnancy	Complications of pregnancy	Post-partum follow-up time in years	Age of the women at the assessment in years	Cardiovascular outcomes assessed
Clemmensen et al. (48)	Europe (Denmark)	Observational cohort study	*N* = 53 cases *N* = 40 controls	1998–2008	PE	12 (median)	41 (mean)	Coronary flow velocity reserve
Ditisheim et al. (49)	European (Switzerland)	Prospective cohort study	*N* = 115 cases *N* = 41 controls	2010–2013	PE	0.11–0.23 (range)	33.7 (mean)	Essential chronic hypertension
Dunietz et al. (87)	North American (USA)	Retrospective cohort study	*N* = 301 cases *N* = 366 controls	1998–2004	HDP	11 (mean)	38 (mean)	Essential chronic hypertension
Egeland et al. (50)	Europe (Norway)	Prospective cohort study	*N* = 1480 cases *N* = 58.547 controls	2004–2009	HDP, pre-gestational DM, GDM, PD, FGR	7.1 (mean)	NA	Essential chronic hypertension
Escouto et al. (51)	Europe (UK)	Prospective longitudinal cohort study	*N* = 412 cases *N* = 65 controls	2009–2013	HDP	0.13 (median)	29.6 (mean)	Cardiovascular risk
Fossum et al. (88)	Europe (Norway Netherlands)	Population based retrospective cohort study	*N* = 13.348 cases *N* = 164.883 controls	1967–1998	HDP	18 (mean)	41 (mean)	Essential chronic hypertension
Grandi et al. (52)	North American (Canada)	Population-based prospective cohort study	*N* = 5399 cases *N* = 141,349 controls	1999–2015	HDP	5 (median)	29.5 (mean)	Essential chronic hypertension Cardiovascular event
Hauspurg et al. (53)	North American (USA)	Prospective cohort study	*N* = 61 cases *N* = 254 controls	NA	HDP	0.58 (mean)	23,9 (mean)	Essential chronic hypertension
Jarvie et al. (89)	North American (USA)	Retrospective cohort study	*N* = 108.875 cases *N* = 1.344.051controls	2004–2010	HDP	3 (median)	27.2 (mean)	Acute myocardial infarction Stroke Heart failure
Kuo et al. (90)	Asia (Taiwan)	Retrospective longitudinal study	*N* = 1295 cases *N* = 5180 controls	1996–2010	PE or Eclampsia	9.8 (median)	30 (median)	Essential chronic hypertension Heart failure Cerebro-vascular disease
Markovitz et al. (54)	Europe (Norway)	Prospective cohort study	*N* = 7936 cases *N* = 18608 controls	1967–2008	HDP, SGA, PD	8.2 (median)	52 (median)	Cardiovascular event
Riise et al. (55)	Europe (Norway)	Prospective cohort study	*N* = 41 434 cases *N* = 576155 controls	1980–2009	HDP, SGA, PD	14.3 (median)	NA	Coronary heart disease Cerebro-vascular disease Cardiovascular event
Soma-Pillay et al. (56)	Africa (South African)	Prospective, case control study	*N* = 96 cases *N* = 45 controls	2013–2015	PE	1 (median)	28 (mean)	Cardiac dysfunction and remodeling
Stuart et al. (57)	North American (USA)	Observational cohort study	*N* = 5386 cases *N* = 53274 controls	1989–2009	HDP	28 (median)	55 (mean)	Essential chronic hypertension
Theilen et al. (91)	North American (USA)	Retrospective cohort study	*N* = 57,384 cases *N* = 114,768 controls *N* = 4722 cases deceased *N* = 7172 controls deceased	1939–2012	HDP	cause of death for deaths occurring at age ≤50 years vs. age >50 years	NA (mean age at childbirth 26)	Coronary heart disease Cerebro-vascular disease

(Continued)

TABLE 1 | Continued

References	Demographic	Design of the study	Study population	Year of pregnancy	Complications of pregnancy	Post-partum follow-up time in years	Age of the women at the assessment in years	Cardiovascular outcomes assessed
Timpka et al. (58)	Europe (Sweden)	Prospective cohort study	Cohort 1 *N* = 952 cases *N* = 6600 controls Cohort 2 *N* = 658 cases *N* = 4702 controls	1955–1997	HDP, LBW offspring (<2500 g)	20 (median)	50 (mean) Cohort 1 60 (mean) Cohort 2	Cardiovascular risk
Zoet et al. (59)	Europe (Netherlands)	Multicenter, prospective cohort study	*N* = 164 Cases *N* = 387 Controls	NA	HDP	10–20 (range)	48.4 (mean)	Asymptomatic atherosclerosis
Akhter et al. (60)	Europe (Sweden)	Case control study	*N* = 23 cases *N* = 35 controls	2008–2011	PE	7	39 (median)	Asymptomatic atherosclerosis
Clemmensen et al. (61)	Europe (Denmark)	Case control study	*N* = 49 cases *N* = 39 controls	1998–2008	PE	12 (median)	41.5 (mean)	Coronary heart disease
Haug et al. (62)	Europe (Norway)	Prospective cohort study	*N* = 2119 cases *N* = 21766 controls	1984–2008	HDP	18 (median)	49 (mean)	Cerebro-vascular disease Coronary heart disease
Hromadnikova et al. (63)	Europe (Czech Republic)	Prospective cohort study	*N* = 186 cases *N* = 90 controls	2007–2013	HDP, FGR	5.4 (mean)	38 (median)	Essential chronic hypertension Cardiovascular event
Groenhof et al. (64)	Europe (Netherlands)	Population-based cohort study	*N* = 1005 cases *N* = 1811 controls	1997–2012	HDP	15 (median)	48.6 (median)	Essential chronic hypertension
Orabona et al. (92)	Europe (Italy)	Retrospective Case control study	*N* = 60 cases *N* = 30 controls	2009–2013	PE	2.35 (mean)	37 (mean)	Cardiac dysfunction and remodeling
Riise et al. (65)	Europe (Norway)	Population-based prospective cohort study	*N* = 1246 cases *N* = 18829 controls	1980–2003	HDP	10.7 (mean)	37.2 (mean)	Cerebro-vascular disease Coronary heart disease Cardiovascular risk Cardiovascular event
Sia et al. (93)	North American (Canada)	Retrospective case control study	*N* = 244 cases (Coronary artery disease) *N* = 246 controls	NA	HDP	NA	NA	Coronary heart disease
Timokhina et al. (66)	Russia	Prospective observational case-control	*N* = 90 cases *N* = 55 controls	2012–2015	PE	0,17 (mean) time 1 0,5 (mean) time 2	31,7 (median)	Cardiac dysfunction and remodeling

NA, not available; PE, pre-eclampsia; FGR, fetal growth restriction; HDP, hypertensive disorders of pregnancy; SGA, small for gestational age; LBW, low birth weigth; PD, preterm delivery; PA, placental abruption; GDM, gestational diabetes mellitus.

GH having an aOR of 1.61 (95%CI 1.09–2.39)" (53). Moreover, "*women who had PE showed an aOR of 3.23 (95%CI 1.56–6.68) of hypertension with abnormal biomarkers later in life*" (53). Other authors found that early vs. late onset PE had a higher risk of developing chronic hypertension late in life (3, 6). Furthermore, Tooher et al. found that "*the severity of hypertension in pregnancy tracked with increased risk of future hypertension*" (82), while subsequent pregnancies did not seem to confound a first episode of HDP and later CVD (82). Moreover, in a recent meta-analysis. Brouwers et al. have demonstrated that subjects with recurrent PE had a higher risk of future essential hypertension than formerly PE women with a successive unaffected gestation (RR 2.3, 95% CI 1.9 to 2.9) (94). The relation between HDP, future occurrence of essential hypertension and other pre-pregnancy CV risk has also been assessed to try and isolate the effect of pregnancy on this outcome. On this subject, Cho et al. found that the development of high blood pressure in pre-eclamptic women was related to pre-pregnancy factors such as family history, obesity and high blood pressure (86). This latter result is only partially confirmed by Mito et al. who found that women who had HDP presented an higher risk of developing high blood pressure 5 years after the index pregnancy "*even after adjusting for confounding factors such as age, body mass index, family history of hypertension and salt intake (odds ratio 7.1, 95% CI, 2.0–25.6, $P < 0.003$)*" (44). Bergen et al. also found that although adjustment for BMI attenuate the relationship between HDP in childbirth age and future chronic hypertension by 65%, however it remained significant (46). In contrast, Wang et al. (83) found that "*history of HDP had a four-fold multivariable-adjusted risk (95% CI 2.29–6.24) of hypertension,*" while no influence was established by pre-conceptional anthropometric indices on the incidence of high blood pressure after delivery (83). A stratification of the risk of hypertension depending on the year post-partum after a gestation affected by HDP has also been addressed in several studies. Interestingly, Behrens et al. found that the risk of hypertension associated with HDP was high closely after a complicated gestation and continued for more than two decades (40). About 30% of subjects who suffered from a HDP may develop high blood pressure within 10 years after a complicated gestation; "*this risk was 12- to 25-fold higher in the first year, up to 10-fold in 10 year, 2-fold after 20 year*" (40). In term of number of women to be screened to detect one case of essential hypertension, Groenhof et al. found that at the age of 35, 9 women with HDP needed to be screened to detect 1 clinically relevant hypertension (64). The risk of developing essential high blood pressure after a gestation affected by HDP has also been correlated to the presence of specific echocardiographic findings (6). Specifically, Melchiorre et al. found that formerly pre-eclamptic normotensive women with moderate-severe echocardiographic left ventricle (LV) anomalies identified at 1 year after delivery were more likely to develop high blood pressure at 2 years after delivery (50%) in comparison to those with normal LV function/geometry or mild LV dysfunction/remodeling (3.5%) with a relative risk of chronic high blood pressure in women with LV moderate-severe abnormalities of 14.5 (95% CI 5.14 to 40.89, $P < 0.001$) (6). In the above mentioned study the severity of LV dysfunction and hypertrophy was graded according to the European Association and American Society of Echocardiography guidelines (EAE/ASE) (95, 96). Specifically: LV remodeling-hypertrophy was defined mild, moderate or severe if LV mass/body surface area (g/m^2) was between 96 and 108, 109 and 121 or ≥122, respectively; LV diastolic dysfunction was defined as mild in the case of impaired myocardial relaxation pattern (grade I), moderate in the case of pseudo-normal filling pattern (grade II) or severe if restrictive filling was seen (grade III) accordingly to the EAA/ASE diagnostic algorithms for the diagnosis and grading of diastolic dysfunction (96). LV systolic function was graded based on the ejection fraction value (EF) as mildly, moderately or severely abnormal if EF (%) was between 45 and 54, 30 and 44 or <30. This finding has been confirmed by the subsequent echocardiographic studies (97).

Peripheral Artery Disease

HDP have also been associated with increased risk of developing peripheral artery disease (98).

"Peripheral artery disease" (PAD) refers to an abnormal narrowing of arteries other than those that supply the heart or brain, commonly caused by atherosclerosis. PAD most commonly affects the lower extremities vessels (99). "*Depending on the degree of narrowing at each vascular site, a range of severity of symptoms may occur, while many patients will remain asymptomatic throughout their life. Occasionally acute events occur, often associated with thrombosis and/or embolism and/or occlusion of a major artery*" (ESC task force PAD) (99).

Ray et al. in their population-based retrospective cohort study on more than one million women, assessed the association between HDP, placental abruption and infarction (defined as maternal placental syndromes) and the occurrence of hospital admission or revascularization for PAD at least 90 days after the delivery discharge date (67). They found that the risk of PAD in women who suffered from maternal placental syndromes was 3.8 (2.4–5.9) higher than that of women who had an uneventful pregnancy (67). The future risk of PAD remained significant after adjusting for traditional risk factors for CVD, including maternal smoking and metabolic syndrome (adjusted risk 3: 1.9–4.8) and was highest in women who had HDP in combination with fetal compromise, compared to women who had not (67). Lykke et al. also found that severe PE increased the risk of subsequent thromboembolism of 1.9-fold (range 1.35–2.70) and that the relationship was "dose-dependent" (16). Subsequent studies confirmed the increased risk of PAD in women who had HDP.

Asymptomatic Atherosclerosis

Several studies have addressed the issue of the relationship between HDP and asymptomatic/pre-clinical atherosclerosis (**Table 1**). "Asymptomatic atherosclerosis" refers to the coronary/carotid artery inflammatory disease while the condition is still in a subclinical stage but the presence of atherosclerosis can be well-identified and quantified by several invasive and non-invasive techniques, including coronary angiography, ultrasonography, computed tomography, and magnetic resonance imaging (100). In a prospective cohort study, "*a history of PE was associated with an increased risk of*

coronary artery calcifications (CAC) >30 years after the index pregnancy", even after controlling individually for traditional risk factors although this association was not more significant when corrected for current hypertension (39). Specifically, the authors found that the odds of presenting a higher CAC score was 3.54 (CI: 1.39–9.02) times greater in formerly pre-eclamptic women compared to women who did not develop PE without adjustments and it was 2.61 (CI: 0.9–7.14) times greater after correction for current high blood pressure (39). On the contrary, the association between CAC score and history of PE remained significant after adjusting for body mass index alone (odds: 3.20; CI: 1.21–8.49) (39). It has been also shown that one third of subjects who had PE express features of coronary atherosclerosis on vascular computed tomography imaging as compared to one fifth of women from the reference group imaging and this result is manifest as early as at age 45–55 years when women are on average 16 ± 6 years postpartum (59). In contrast, a prospective case-control study showed that the "*average maximum carotid intima media thickness (CIMT) was similar among women with vs. without PE (0.831 mm vs. 0.817, p = 0.38), and PE was not a significant predictor of CIMT in a multiple linear regression model (p = 0.63), despite more electrocardiograms compatible with coronary disease*" (74). Specifically, the authors of the above mentioned prospective study defined "abnormal electrocardiograms" the ones with at least one of the following: the presence of Q waves/isolated infarct, new left bundle branch block, ST elevation, ST depression, T wave inversion (74). The conventional measurement of common carotid artery intima-media thickness (CCA-IMT) does not represent this (60) as opposed to measurement of the individual CCA intima and media thicknesses which visibly reflect augmented vascular risk (60).

Asymptomatic Heart Failure

Several studies assessed the relationship between HDP and the subsequent development of asymptomatic (stage B) or symptomatic (stage C) heart failure (97, 101). The American Heart Association and American College of Cardiologists define asymptomatic stage B heart failure as any subject being affected by LV hypertrophy or dysfunction (102). At this regard, it should be taken into account that several echocardiographic studies in pregnancy already showed a state biventricular dysfunction and hypertrophy, low cardiac output and high total vascular resistancein pre-eclamptic women in pregnancy vs. normotensive matched pregnant controls (3–5) A subsequent prospective longitudinal follow-up study of PE vs. controls assessed at 1 and 2 years post-partum showed, integrating conventional echocardiography, color and pulsed wave tissue Doppler, strain and strain rate techniques, that the prevalence of asymptomatic stage B heart failure (HF-B) at one year postpartum follow-up was significantly higher in preterm vs. term preeclampsia and controls (70 vs. 25 vs. 10%, respectively; $p < 0.001$), but not in term preeclampsia vs. controls (6). Similarly, moderate-severe left ventricular (LV) dysfunction and remodeling (according to the EAE/ASE diagnosis and grading of abnormal LV structure and function) were significantly more prevalent in formerly preterm PE women compared with those who had term preeclampsia and controls (3, 6). Similarly, Soma-Pillay et al. showed that women with early onset PE had an increased risk of diastolic dysfunction at 1 year post-partum (RR 3.41, 95% CI: 1.11–10.5, $p = 0.04$) and regardless of the presence of chronic hypertension (56). Breetveld et al. in their prospective longitudinal cohort study confirmed that the prevalence of HF-B was consistently high (1 in 4) amongst formerly PE women at 1 and 4 years postpartum (41). Moreover, in a subsequent observational case-control study, he confirmed that the prevalence of HF-B in formerly PE women was three-fold higher than that detected for healthy parous controls (25 vs. 8%, $P < 0.05$) at more than 4 years post-partum (47). The increased risk of asymptomatic HF in formerly PE women was further confirmed by Ghossein-Doha et al. who also found that prehypertension increased this risk significantly, while metabolic syndrome elements did not (42). Orabona et al. conducted a prospective study on hemolysis, elevated liver enzymes, and a low platelet count syndrome (HELLP) and PE women and also documented in both HELLP and PE groups a higher prevalence of LV concentric remodeling, diastolic dysfunction and reduced LV ejection fraction at 6 months to 4 years post-partum vs. matched healthy controls (81). Bokslag et.al. also found that history of PE predisposes in middle age, 9–16 years after pregnancy, to worse LV diastolic function, which could increase the likelihood of later heart failure with preserved ejection fraction (84).

Heart Failure

Several large registry-based studies addressed the issue of the relationship between HDP and symptomatic heart failure. Specifically, in a retrospective registry-cohort study on short term cardiovascular outcome in women who had HDP, Jarvie et al. scrutinized all hospital-based deliveries in Florida from 2004 to 2010 and following cardiovascular (CV), non-CV and any second hospitalization to any Florida hospital within 36 months of index delivery excluding subsequent deliveries (89). They found that "*women with HDP had twice the risk of CV readmission within 3 years of delivery (6.4 vs. 2.5/1,000 deliveries; P < 0.001), with higher rates among African American women. Heart failure was the most common reason for CV readmission accounting for 78.6% of all CV readmissions and 84.4% of CV readmissions in women with HDP*" (89). Furthermore, in a retrospective longitudinal registry study on long term outcome in women who had HDP, Kuo et. al. using National Health Insurance Research Database, found that formerly PE and eclamptic women were at increased risks of congestive heart failure (hazard ratio 9.1, and 7.4, respectively) with a drastic increase of congestive heart failure occurrence at 3 and 10 years since the index pregnancy (90). Similarly, Chen et al. in a retrospective cohort study found that heart failure incidence was greater in the HDP group than controls (9.83 vs. 1.67 per 10,000 person-years), was more likely to develop within 5 years and that severe or recurrent HDP had a greater risk (85).

Coronary Heart Disease

Numerous studies have assessed the relationship between HDP and subsequent coronary heart disease (**Table 1**).

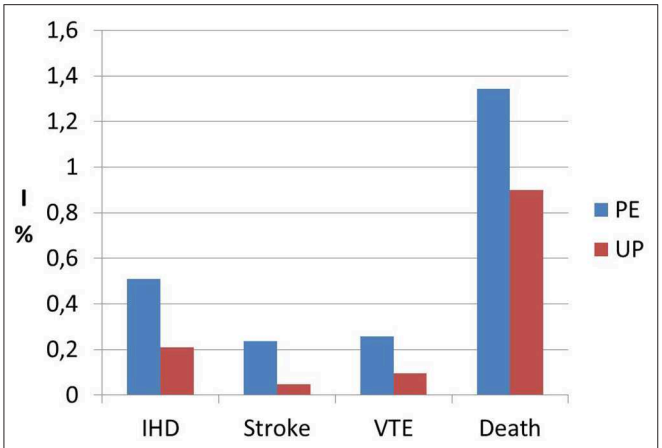

FIGURE 1 | Incidence data (I) of ischemic heart disease (IHD), stroke, venous thromboembolism (VTE) and death from any cause in formerly PE women (PE) vs. women who had an uneventful pregnancy (UP). Modified from Bellamy et al. (1).

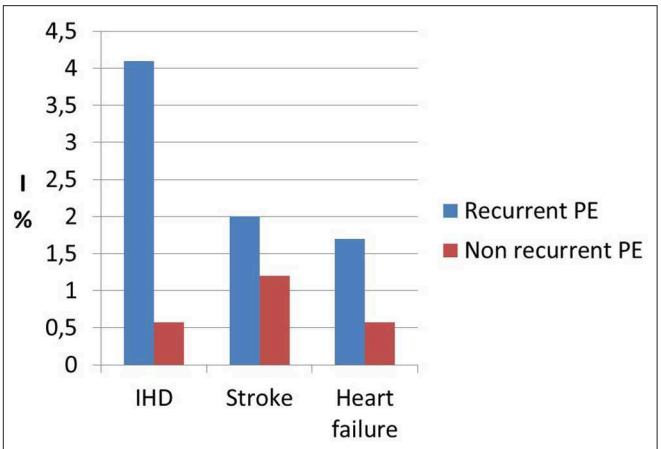

FIGURE 3 | Incidence data (I) of ischemic heart disease (IHD), stroke and heart failure in recurrent preeclamspia women (recurrent PE) vs. women affected by a single pregnancy with PE and subsequent normal pregnancy (not recurrent PE) showing the "dose effect" response of recurrent preeclampsia. Modified from Brouwers et al. (94).

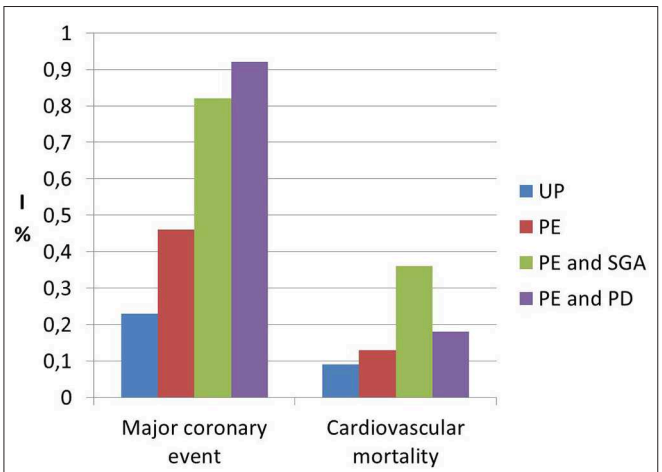

FIGURE 2 | Incidence data (I) of future risk of major coronary events and cardiovascular mortality in formerly PE women (PE) vs. women who had an uneventful pregnancy (UP), showing the dose effect response of specific characteristics of pregnancy with preeclamspia such as small for gestational age (SGA) and preterm delivery (PD). Modified from Riise et al. (55).

"Coronary artery disease" refers to the clinical manifestations of atherosclerosis and comprehends a range of diseases that result from atheromatous change in coronary vessels. Specifically, it includes the following: (stable and unstable) angina pectoris, myocardial infarction, sudden cardiac death (100).

Interestingly, a previous study on cardiac function and structure in pre-eclamptic women showed the presence of echocardiographic findings suggestive of segmental myocardial ischemia and fibrosis (4–6). Specifically, significantly higher prevalence of basal septal post-systolic shortening, identified by Color Tissue Doppler-derived strain analysis, associated to septal bugling and segmental abnormal myocardial strain and strain rate indices were found in a minority of pre-eclamptic women with severe disease vs. normotensive pregnant controls and these echocardiographic findings have been associated in human autopsy studies and in animal *in vitro* studies to regional myocardial ischemia (4–6). Not surprising the prevalence of ischemic heart disease in formerly PE women is significantly higher than in parous controls with an uneventful pregnancy (1, 101) **(Figure 1).** As well as it has been demonstrated in chronic hypertension, this higher risk of developing coronary artery disease in women who had HDP show a "dose dependent effect,", being higher in the presence of a more severe disease in pregnancy, in the case of associated fetal growth abnormalities and iatrogenic preterm birth and if PE recurred in subsequent pregnancies (55, 94) (**Figures 2**, **3**). Moreover, the association was not explained by adjustment for confounding variables, although it was attenuated by the presence of other CV risk factors (55, 94). In particular, Tooher et. al. directed a retrospective cohort study on all subjects who delivered at a tertiary hospital in Sydney between the years 1980 and 1989 (n = 31,656) of whom 4,387 had HDP (82). The whole cohort were studied for linkage analysis to future CVDs and he found that the formerly HDP women were at increased risk of admission for future CVD vs. normotensive parous controls (OR 2.1; 95% CI, 1.7–2.6) (82). The median time from the index gestation to the occurrence of CVD was 20 years with a range of 3–29 years (82). Another study demonstrated that among a cohort of subjects with acute coronary syndrome, positive history of pregnancy adverse outcome was related with more severe disease and worse outcome (103). In particular, at presentation with acute coronary syndrome, women who had PE were younger and had more conventional CV risk factors such as essential high blood pressure and an increased soluble fms-like tyrosine kinase:placental growth factor ratio compared to women who had uncomplicated gestation (103). There was also an increased risk of recurrence of acute coronary syndrome at 1 year in women with previous PE (hazard ratio, 6.8) (103). Moreover, women with ≥2 complicated gestation had an increased cardiac mortality

risk as shown by Theilen et al. (aHR = 3.3, 95% CI 2–5.4) (91). A large registry-study in Norway also revealed that GH was associated with increased risk of subsequent cardiovascular disease and the highest risk was noticed when GH was combined with fetal growth abnormalities infants and/or preterm delivery (65). Subsequent studies confirmed this association between HDP and increased risk of myocardial infarction at 40–70y with an HR of 2.08 for formerly PE women and 1.56 or formerly GH women (62). Furthermore, an interesting study on the relationship between coronary flow velocity reserve (CFVR) by Doppler echocardiography and previous HDP found that the mean coronary flow velocity reserve was significantly impaired in the early-onset than in the late-onset PE and in the control group with a positive relation between gestational age at PE diagnosis and coronary flow velocity reserve which notable persisted significant after adjustment for conventional cardiac risk factors such as body mass index, blood pressure, and glycated hemoglobin (61).

Cerebro-Vascular Disease

There is general agreement on the link between HDP and subsequent risk of stroke (**Table 1**). It has been demonstrated that not only PE/Eclampsia increase the risk of cerebrovascular events with an HR of 10.7 ($p < 0.0001$) (90), but Haug et al. (62) and Tooher et al. (82) is also associated with increased risk of stroke. A large population-based study found that formerly GH women had a 1.3-fold (95% CI 0.9–1.7) higher risk of suffering from cerebrovascular disease compared with parous controls with uncomplicated gestation (55). In general, HDP women seem to have an increased risk of cerebrovascular events (HR 1.47, 1.15–1.87) at 40–70 years (62). Moreover, no significant difference was found in relation to the use of antihypertensive drugs or the duration of HDP and subsequent hospitalization for stroke (82). Again, there seems to be a "dose dependent" effect of HPD on cerebrovascular mortality, with women who had more than two complicated gestation showing an increased mortality from stroke (aHR = 5.10), as well as the other causes of cardiovascular mortality, compared to parous women who had only 1 or 0 pregnancies complicated by HDP (1, 91, 94) (**Figures 1**, **3**).

CONCLUSIONS

HDP is associated with increased risk of cardiovascular diseases later in life. This is not surprising as several studies have demonstrated that women with PE present in a state of cardiac dysfunction, ventricular hypertrophy and indirect echocardiographic signs of localized myocardial ischemia and fibrosis (103, 104). Moreover, the structural and functional cardiovascular changes do not completely reverse at 1 year post-partum and are known to have strong prognostic value for future cardiovascular morbidity and mortality in non-pregnant subjects (104). The relationship is stronger in the case of severe or early-onset HDP, concomitant fetal growth disorders, need for iatrogenic preterm delivery and recurrent HDP. Adjustments for confounders (such as family history of cardiovascular diseases, high BMI, hypertension, diabetes, and dyslipidemia) do not eliminate, but attenuate this relationship. The underlying mechanisms have not been fully elucidated, but a concomitance of pre-pregnancy predisposition to increased risk of cardiovascular disease and a direct effect of pregnancy on the cardiovascular system may play a role in determining this excess of cardiovascular morbidity and mortality in women who experienced PE and GH in pregnancy. Guidelines regarding timing and extent of cardiovascular follow-up as well as strategies of prevention after HDP are lacking, but it is reasonable to recommend that screening should be started as early as 1 year after delivery and should primarily include awareness of the women of their future increased CV risk and lifestyle modifications with weight control, smoking cessation, healthy diet, and daily exercise. Future studies should address the issue of a structured screening for cardiovascular disease and the impact of timely preventive intervention in improving cardiovascular health in this group of young women.

AUTHOR CONTRIBUTIONS

AK, BT, and KM conceived the study. Articles were examined by AM, VG, AR, and KM. KM drafted the paper. All authors contributed in writing and revising the paper.

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