Echocardiographic structure and function in hypertensive disorders of pregnancy

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Title: Echocardiographic structure and function in hypertensive disorders of pregnancy: A systematic review

Short title: Echocardiography and hypertension in pregnancy

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Abstract

Background: Echocardiography is commonly used to direct the management of hypertensive disorders in medical patients, but its application in pregnancy is unclear. Our objective was to define the use of echocardiography in pregnancies complicated by gestational hypertension (GH) and preeclampsia (PET).

Methods and Results: We performed a systematic review of articles using an electronic search of databases from inception to March 2015, prospectively registered with PROSPERO (CRD42015015700). Eligible studies included pregnant women with GH or PET, evaluating left-ventricular (LV) structure and function using echocardiography. The search strategy identified 36 studies, including 745 women with GH and 815 women with PET. The populations were heterogeneous with respect to clinical characteristics, parity and risk of bias. Increased vascular resistance and LV mass were the most consistent findings in GH and PET. Differentiating features from normal pregnancy were LV wall thickness ≥1.0cm, exaggerated reduction in E/A and lateral e' <14cm/s. There was disagreement between studies with regard to cardiac output due to the timing of echocardiography, although reduced stroke volume was an indicator of adverse prognosis. Diastolic dysfunction and left ventricular remodeling are most marked in severe and early-onset PET, but are also markers of PET before clinical manifestation, and are associated with adverse outcomes.

Conclusion: Echocardiography is a valuable tool to stratify risk and can guide management and counseling in the preclinical and clinical phases of GH and PET. Changes in cardiac function and morphology are recognizable at an asymptomatic early stage and correlate with disease severity and adverse outcomes.

Introduction

Cardiac disease is the leading non-obstetric cause of death in pregnancy and the puerperium.[1] In uncomplicated pregnancy there is no significant change in systolic blood pressure.[2, 3] Diastolic blood pressure and mean arterial pressure decrease during the first trimester, then plateau in the second trimester before rising in the final weeks of pregnancy.[2, 3] Hypertension is seen in 6-8% of pregnancies[4] and the incidence is increasing as the obstetric population becomes older and more obese.[5] Hypertension causes one third of severe maternal morbidity[4] and is the second most common direct cause of maternal mortality worldwide, accounting for approximately 14% of maternal deaths.[6] Adverse fetal outcomes include preterm birth, growth restriction and stillbirth.[4]

The hypertensive disorders specific to pregnancy are gestational hypertension (GH) and preeclampsia (PET). Guidelines and terminology vary across the world.[4, 7-10] The diagnosis and classification of these conditions depend on the gestation at which elevated blood pressure is identified (GH and PET are acquired conditions in the second half of pregnancy), the presence or absence of multisystem involvement or significant proteinuria (traditionally the hallmark of PET[4]), and whether the blood pressure normalizes in the postnatal period. The onset of hypertension in GH and PET must be after 20 weeks' gestation to distinguish them from chronic hypertension. PET can develop in patients with GH and also be superimposed on chronic hypertension.

Understanding the structure and function of the heart in pregnancy is vital if we are to recognize abnormalities at an early stage and plan appropriate interventions to avoid adverse outcomes. Echocardiography is a safe, non-invasive technique to assess cardiac structure and function in pregnancy.[11-14] Although operator-dependent and requiring training to provide reproducible measurements[11], the temporal variability of echocardiography is small.[15] Modern ultrasound technologies can demonstrate subtle changes in cardiac geometry and performance[16-19], and echocardiography has important potential for longitudinal assessment in view of its non-invasive nature. However, evidence for the role of echocardiography for serial measurements in pregnancy is lacking, and despite common use in clinical practice, the application of echocardiography to study hypertensive disorders of pregnancy is inconsistent.

Our aim was to systematically review the current literature to assess changes in echocardiographic structure and function in women developing GH and PET. We hypothesized that echocardiography would be a useful screening tool to identify: (1) high-risk women in whom recognizable cardiovascular changes occur before manifesting clinically as a hypertensive disorder; and (2) women at increased risk following a diagnosis of GH or PET.

Methods

Information sources and search strategy

Studies using echocardiography in pregnancies complicated by GH or PET were eligible for inclusion in our systematic review. The definitions of GH and PET used by each individual study were accepted. **Figure 1** shows a typical algorithm for the classification of hypertensive disorders of pregnancy. Our search included MEDLINE, EMBASE, CINAHL and the Cochrane Library from inception to March 2015, as well as relevant reference lists. The MEDLINE search strategy is shown in **Supplementary Table 1**, and was adapted for the requirements of the other databases. There was no restriction on the type of study design or publication language. Full text articles were obtained after screening the title and/or abstract of eligible studies by two authors (JSC and FT). The review process was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [20], and prospectively registered with the PROSPERO database (CRD42015015700); (http://www.crd.york.ac.uk/PROSPERO/DisplayPDF.php?ID=CRD42015015700).

Figure 1 LEGEND: Diagnosis of hypertensive disorders in pregnancy

A flow chart for contemporary diagnosis of the hypertensive disorders of pregnancy based on international guidelines.

Eligibility criteria and study selection

The population of interest was pregnant women with GH or PET. Our inclusion criteria required an echocardiogram during pregnancy (before and/or after the diagnosis of GH/PET). Pregnant women with normal blood pressure were included as a comparison group. The exclusion criteria were: (1) studies published only in abstract form; (2) duplicate publications or publications using the same dataset (in the latter case only the largest study including the same patients would be included, unless different data were presented in each paper); (3) case reports, editorials, opinion articles, commentaries and letters; (4) animal studies; (5) studies including only multiple pregnancies; (6) studies assessing therapeutic effects; and (7) studies of pregnant women with chronic hypertension, unless a group with GH or PET were also included.

Data collection, outcomes and quality assessment

A standardized data extraction form was used. Outcome measures included any echocardiographic assessment of left-ventricular (LV) structure or function (see **Supplementary Table 2** and **Supplementary Figure 1**). The Risk of Bias Assessment Tool for Non-Randomized Studies (RoBANS)[21] was used to critique methodological and reporting quality of the included manuscripts, addressing key criteria such as selection bias, exposure measurement, blinding, the completeness of outcome data and selectivity of reporting. Two authors (JSC and FT) completed the data quality assessment independently, and any disagreements were resolved by consensus.

Data synthesis

Statistical pooling of data from separate studies was not possible because of marked variation in study design and reported outcome measures, thus precluding meta-analysis. Data were therefore synthesized qualitatively.

Results

Study selection and study characteristics

The search strategy identified 36 studies, including 745 women with GH, 815 women with PET and 7189 normotensive pregnant controls (see **Figure 2**). The characteristics of included studies are shown in **Table 1**. All studies had an observational design, with 25 case-control studies,[22-46] 8 cross-sectional studies [47-54] and 3 longitudinal cohort studies.[55-57] The majority of studies (n=20) were of women with PET.[22, 27, 29, 30, 32, 33, 39-42, 44-47, 49-51, 54, 56] There were nine studies assessing GH only [24, 26, 28, 31, 37, 38, 43, 53, 57] and seven studies evaluating both GH and PET.[23, 25, 31, 34, 48, 52, 55] All investigators recruited women during antenatal visits to hospital. In three of the studies where women were scanned prior to the onset of hypertension, the women had already been identified as a high risk group due to fetal growth restriction,[47] raised uterine artery Doppler [35] or PET in a previous pregnancy.[56]

Figure 2 LEGEND: Flow chart of systematic review

Summary of steps in the identification and selection of studies.

The majority of studies investigated patients with a single echocardiogram during the third trimester (n=29). Of the three longitudinal studies, one included echocardiography in each trimester[55] and the other two covered two trimesters.[56, 57] Considerable heterogeneity was seen between and within the study populations (see **Table 2**), such that meta-analysis was not deemed appropriate. In six studies, a proportion of the patients were on antihypertensive therapy.[33, 39, 43, 48, 56, 57] In two studies, the PET group included a small number of women with chronic hypertension and superimposed PET.[48, 56]

Other obstetric outcomes, for example birthweight and gestation at delivery, were recorded in 15 of the studies.[29, 32, 34, 39, 40, 45-47, 49, 51-56] Only three authors analyzed the relationship between these pregnancy outcomes and echocardiographic measurements[32, 34, 53] (see **Supplementary Table 3**).

The risk of bias assessment identified variable study quality (see **Supplementary Table 4**). Due to the nature of the studies, the risk of specific biases (particularly blinding) was uncertain due to limited reporting in the individual studies.

<u>Synthesis of results</u>

Results are summarized below according to hemodynamic parameters and systolic function, diastolic function, and cardiac structure. **Table 3** presents an overview of findings for the main echocardiographic variables investigated in the third trimester studies. The details of extracted parameters from all studies (including the earlier screening studies) are presented in **Supplementary Table 5**. **Figure 3** highlights the major echocardiographic changes that may be seen in hypertensive disorders as compared to normal pregnancy. **Supplementary Figure 2** provides representative images from echocardiograms of women with and without gestational hypertensive disease.

<u>Figure 3 LEGEND: Summary of results</u>

Summary of major findings comparing normotensive pregnancy with gestational hypertension/preeclampsia and association with adverse outcomes. * A progressive and slight increase in left ventricular wall thickness and mass is seen during normal pregnancy that regresses post-partum.[58, 59]

Hemodynamics and systolic function

Total vascular resistance was significantly higher in GH compared with normotensive pregnant controls [25, 36, 37, 43, 55] but lower than in PET.[31, 55] In GH, there were conflicting reports for cardiac output, including an increase[23, 48, 55, 57] or no change compared to normal pregnancy.[25, 36, 37] Myocardial performance index and left ventricle (LV) function were unchanged in a longitudinal study of GH with second and third trimester measurements.[57] In GH studies with a third trimester echocardiogram, only one showed a significant reduction in LV ejection fraction [37], whilst three others showed no difference.[24, 37, 57]

In PET, studies covering early trimesters demonstrated that the preclinical phase is characterized by a hyperdynamic circulation with high cardiac output and low peripheral resistance.[48, 49, 51, 55] In the second trimester, women who go on to develop PET have increased total vascular resistance at mid-gestation, with lower cardiac output.[51, 54] Once PET manifests clinically, there is reduced cardiac output and increased resistance,[50, 55] described as a "hemodynamic crossover" in the clinical phase of PET.[55] The increased total vascular resistance seen in PET[23, 27, 31, 40, 47, 50] is an independent predictor of adverse maternal and fetal outcomes.[53] In the clinical phase, early onset PET (<34 weeks gestation) is characterized by significantly lower cardiac output and higher total vascular resistance compared with late onset PET.[51, 54] Pregnant women who develop recurrent PET have also been shown to have lower cardiac output and higher peripheral resistance than women without recurrent disease.[56]

Stroke volume is lower in PET than in normal pregnancy [31, 32] and in the first trimester this is an independent predictor of subsequent development of PET.[49] Due to the factors discussed, cardiac output in PET has been shown to be both lower [23, 27, 32, 39, 47, 50] and higher [27, 31, 40, 48, 49] compared to normotensive pregnancies. The variation in cardiac output is shown in **Supplementary Table 5**, which also indicates its derivation, since the use of different calculations (based either on Doppler or volume calculation) is likely to contribute to the disparity for this parameter. There was similar variability with regard to LV ejection fraction, with the majority of studies showing no significant difference compared with normotensive pregnant women[27, 41, 45, 46, 50] and only one showing a decrease.[22] Myocardial performance index was reduced in a study of women with PET and fetal growth restriction in the third trimester.[47] Systolic dysfunction, with marked LV hypertrophy, is significantly more common in preterm PET compared to term PET [35], even before the condition manifests clinically.[51]

Diastolic function

Several studies have shown that in normal pregnancy the E/A ratio decreases towards term.[3, 17, 58, 60, 61] A greater reduction in E/A has been shown in GH compared to pregnancy unaffected by hypertension.[24, 36, 37, 44, 57]

Diastolic function is also impaired in PET,[29, 35, 42] where the usual reduction in E/A is exaggerated.[22, 29, 35, 44] The ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity (E/e'), was significantly higher in women with PET in five studies, suggesting higher LV filling pressures.[27, 29, 42, 46, 51] Interestingly E/e' was shown to be significantly higher in an early-onset PET subgroup compared with a late-onset subgroup.[29] One study used a composite of diastolic indices to diagnose diastolic dysfunction and demonstrated diastolic dysfunction in 40% of pregnancies complicated by PET at term, compared with 14% of controls.[34] In another study, diastolic dysfunction was already present at 20-23 weeks in women who developed preterm PET, but not PET at term.[51]

Diastolic dysfunction in PET is more marked in cases associated with fetal growth restriction[47], despite evidence that left atrial mechanical function is similar in PET and normotensive pregnant controls.[30]

Cardiac structure and remodeling

In most studies, LV mass was significantly increased in GH compared to normotensive pregnant controls in the second [37] and third trimester [24, 26, 28, 36, 37, 43], and increased in the second half of pregnancy when measured serially.[57] One study identified ventricular remodeling or hypertrophy in 91% of patients with GH .[36] The concentric hypertrophy seen in GH[24, 26] is an independent predictor of adverse pregnancy outcomes.[53] Other investigators found no change in LV mass in GH, showing this instead to be a feature of chronic hypertension.[38, 41] LV/left atrial diameters were increased in GH compared to normotensive controls.[27, 44]

LV remodeling is more common in PET compared to normotensive pregnant women in the third trimester,[45] with numerous studies confirming increased LV mass in PET.[22, 24, 27, 29, 30, 34, 39] Hypertrophy in PET tends to be of the concentric type[39], and has been shown in preterm[22, 29, 35] and term PET.[30, 34, 35, 44] In one study, concentric LV remodeling was demonstrated at 20-23 weeks gestation in 33% of women who subsequently developed PET.[51] In women who progressed to PET from GH, 27% had abnormal LV structure and function at the time of echocardiography.[24]

Comment

We performed a systematic review of all literature pertaining to the use of echocardiography in pregnant women with a hypertensive disorder. Our major findings were increased peripheral resistance in GH and PET, diastolic dysfunction in PET and conflicting evidence regarding changes in cardiac output. The echocardiographic changes in cardiac structure and function can be detected before the condition is clinically apparent. Current evidence suggests that alterations in PET are not due to hypertension alone, but rather reflect PET as a multisystem disorder. PET has a greater impact on the heart than GH, and changes are most pronounced in early onset, severe disease.

Currently, echocardiography is not widely used in the clinical management of hypertensive disorders in pregnancy, or as a screening tool for PET. The application of echocardiography in pregnancy has traditionally been in patients with adult congenital cardiac disease, in acute illness or for research purposes. The management of hypertensive disorders in pregnancy is based on maternal clinical assessment (symptoms, blood pressure and laboratory parameters) and fetal wellbeing. A decision to deliver the baby can be for maternal or fetal reasons. Whereas other reviews have focused on congenital heart disease[62] or described echocardiographic changes in the context of a broad overview of the management of PET[63], ours is the first systematic review of cardiac structure and function in gestational hypertensive disease.

Clinicians now recognize that PET should no longer be considered as a single disease process. There is evidence to suggest that preterm hypertension and proteinuria associated with fetal growth restriction is different to hypertension and proteinuria at term when birthweights tend to be normal or increased.[64] The possible difference in the mechanism of disease and how it manifests clinically[65] may be responsible for the conflicting results between studies when early- and late-onset PET are considered as one entity. The contradictory hemodynamic models described can be explained by noting the distinction between early PET [51, 54] and late-onset disease.[53, 55]

Although based on observational data, our review suggests that echocardiography has the potential to improve the management of patients with hypertension during pregnancy and categorize patients with GH or PET into high and low risk groups. Patients with increased vascular resistance and LV mass are more likely to have complications.[53] As a predictor of long term cardiovascular morbidity, diastolic dysfunction in pregnancy is important to identify,[34] and reduced e' (and therefore elevated E/e') may be a useful and early predictor of PET.[47] Echocardiography can also help to identify the small numbers of women with LV systolic impairment who are more likely to deteriorate during pregnancy or post-partum. With the currently available data, we suggest the most efficient use of echocardiography is after the diagnosis of hypertension, to direct resources to the most vulnerable patients in order to improve maternal (and fetal) outcomes (see **Figure 4**). The optimal timing of echocardiography needs further study. Whereas an early echocardiogram in the first and second trimesters may be helpful for risk stratification, the available data on clinical impact is currently limited.

Figure 4 LEGEND: Potential value of echocardiography in hypertensive disorders of pregnancy

BP, blood pressure; GH, gestational hypertension; PET, preeclampsia. * Diastolic dysfunction can be further graded into impaired myocardial relaxation (E/A <0.73, deceleration time [DT] >194ms, isovolumetric relaxation time [IVRT] >83ms), pseudonormal filling (E/A 0.73-2.33, DT 138-194ms, IVRT 51-83ms) and restrictive filling

(E/A >2.33, DT <138ms, IVRT <51ms). Left atrial dilatation is also a useful echocardiographic marker. For further details, see Melchiorre *et al.*, 2011 [34], adapted from recommendations by Nagueh *et al.*[66] GH/PET risk assessment based on UK National Institute for Health and Clinical Excellence guidelines.[4]

It has also been suggested that echocardiography can stratify hypertensive pregnant women into hemodynamic subgroups, thereby enabling clinicians to tailor their choice of antihypertensive therapy.[49] Hypertension characterized by vasoconstriction responds better to beta-blockade whereas in hypertension with reduced plasma volume, calcium channel blockers are preferable, as they reduce afterload and improve cardiac function.[67] Echocardiography can also have an important role in guiding fluid balance, one of the most challenging aspects in the management of PET. Overzealous fluid administration can lead to pulmonary edema, and conversely if a patient is under-filled, end-organ dysfunction may worsen. In selected centers and patients, myocardial strain imaging has been shown to be more sensitive than LV ejection fraction in detecting differences in LV systolic function in women with and without PET.[36] Strain measurements can potentially provide more information about cardiac function but due to limited data[33, 34, 39, 52], further investigation is required.

In summary, echocardiography can reveal cardiac impairment in GH and PET, which changes antenatal management (medication, frequency of monitoring, timing of delivery) and can indicate when postnatal follow-up is warranted. More longitudinal studies are required to evaluate the cardiovascular changes in hypertensive disorders throughout pregnancy and to further define the role of echocardiography in the antenatal assessment of women with GH and PET, and in subsequent pregnancies. It would be useful in clinical and research practice to define an ideal dataset for echocardiographic assessment in pregnancy, and agreed outcome measures for studies of cardiac structure and function, so that results are comparable and pooled data can be analyzed quantitatively. Clinicians should follow the American and European consensus guidelines[68] with specific focus on the variables listed in Figure 4. Developing collaboration between Cardiologists and Obstetricians has the potential to open up new areas of research and further improve patient care.

Limitations

The main limitation of our assessment was the wide variation in patient groups (age, ethnicity, body habitus, parity, timing of assessment, disease severity) and reported outcome measures. In several studies the participants were grouped based on outcomes other than hypertensive disorder diagnosis. This heterogeneity restricts quantitative synthesis of results and meta-analysis. Many of the included studies involve small numbers of patients, with varying levels of risk for important bias and likely different levels of echocardiographer experience. A substantial amount of data is derived from load-dependent indices, which may be inferior to measurements that take into account the different loading conditions seen in pregnancy. The cross sectional studies capture women at different stages of the disease and offer only a snapshot at a single point in time. At present, there is a paucity of longitudinal data in pregnancy. Only one of the longitudinal studies considered the reproducibility of the echocardiographic measurements, and whilst these results were encouraging (intraobserver variability 2.4% for cardiac output and 2.0 % for total vascular resistance[55]), further data in pregnant patients are clearly needed.

Conclusion

This systematic review demonstrates that cardiac structure and function using echocardiography are altered in the preclinical and clinical phases of gestational hypertension and preeclampsia. For women with preeclampsia, diastolic dysfunction and increased peripheral vascular resistance correlate with disease severity. Recognition of impairment in cardiac function is important in the contemporary management of gestational hypertension and preeclampsia, in order to improve pregnancy outcomes and long-term cardiovascular health.

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Author contributions

JSC performed the literature search and selection of studies for inclusion in the review, methodological assessment and data extraction, analysis and interpretation and drafted the manuscript. FT performed the literature search and methodological assessment. DK provided supervision and drafted the manuscript. GYHL provided supervision and critical review. RG and RPS provided specialist input and critical review.

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Table 1: Characteristics of included studies

Trimester	Author, year	Population (Country)	Inclusion criteria	Exclusion criteria	Controls/comparison	Timing of echocardiography (gestational age in weeks)
Longitudinal cohort studies						
1-3	Bosio, 1999 [55]	Antenatal patients attending hospital (Ireland)	GH or PET	Parity >0; cardiac disease; essential hypertension; chronic illness; long term medication; multiple pregnancy; significant obstetric or medical complication	Nil	5 appointments: 10-14; 20-24; 28-32; 34-36; 37-40
1-2	Sep, 2011[56]	Women with PET in previous pregnancy (Netherlands)	Previous early onset PET	Multiple pregnancy; renal disease; missed > 2 appointments	Nil	Prior to pregnancy and 12, 16, 20 weeks
2-3	Vlahovic-Stipac, 2010 [57]	Antenatal patients attending hospital (Serbia)	GH	Essential hypertension; diabetes; structural heart disease	Normotensive pregnant	24±3 and 36±1
Cross sectional studies						
1	De Paco, 2008 [48]	Antenatal patients attending hospital (UK)	Live singleton pregnancy	Multiple pregnancy; missing outcome data; miscarriage; termination of pregnancy; major anomalies at birth	Normotensive pregnant women split into two groups: SGA (n=532) and uncomplicated (n=3591)	11+0 to 13+6
	Khaw, 2008 [49]	Antenatal patients attending hospital (UK)	PET	Parity >0; medications; unavailable outcomes; fetal loss; maternal disease	Nil	11-14
2	Melchiorre, 2013[51]	Uterine artery Doppler pulsatility index > 95th centile (UK)	Uterine artery pulsatility index >95th centile	Parity >0; essential hypertension; proteinuria prior to 20 weeks gestation; comorbidities; smoking; medication; fetal anomalies; persistent hypertension after 12 weeks post-partum	Women with normal uterine artery pulsatility index and women with raised pulsatility index (term delivery)	20-23
2	Valensise, 2008 [54]	Normotensive pregnant women with bilateral notching of umbilical artery at 20-22 weeks (Italy)	Bilateral umbilical artery notching	Multiple pregnancy; undetermined gestational age; smoking; multiple pregnancy; cardiac disease; pre-existing medical problem; fetal anomalies; persistent hypertension at 1 year follow up	Normotensive pregnant	24

Trimester	Author, year	Population (Country)	Inclusion criteria	Exclusion criteria	Controls/comparison	Timing of echocardiography (gestational age in weeks)
3	Bamfo, 2008 [47]	Pregnant women with fetal growth restriction (UK)	Diagnosis of fetal growth restriction	GH; multiple pregnancy; co-morbidities; medication; fetal anomalies; chromosomal abnormalities; genetic syndromes; infections	Normotensive with fetal growth restriction	28 (24-35)
	Estensen, 2013 [50]	Antenatal patients attending hospital (Norway)	PET	Essential hypertension; diabetes; renal impairment; hyperlipidemia; uncontrolled endocrine or rheumatological disease; cardiovascular disease	Non-pregnant with previous PET	36
	Shahul, 2012 [52]	Antenatal patients attending hospital (USA)	GH or PET	Multiple pregnancy; age < 18 years; gestation < 24 weeks pre-existing cardiovascular disease; pulmonary disease; diabetes; poor image quality; preterm prelabor rupture of membranes	Nil	NTP 38 (35.6-39.6); GH 36.4 (33.4-38.1); PET 36.6 (32.7-37.4)
	Valensise, 2006 [53]	Antenatal patients attending hospital (Italy)	Mild GH	Systolic blood pressure >150; diastolic blood pressure >100; proteinuria; essential hypertension; hemolysis, elevated liver enzymes and low platelets ('HELLP'); antihypertensive therapy; small for gestational age fetus; abnormal fetal Doppler; abnormal liquor volume; undetermined gestational age; smoking; multiple pregnancy; maternal heart disease; maternal chronic medical problems; fetal anomaly	Normotensive pregnant	28-31
Case control studies						
3	Borghi, 2000 [22]	Antenatal patients attending hospital (Italy)	PET	Essential hypertension; secondary hypertension; obesity; diabetes; cardiomyopathy; valvular heart disease; major electrocardiogram abnormality	Normotensive pregnant and non-pregnant	NTP 30.9±4.0; PET 28.4±6.0
	Borghi, 2011 [23]	Antenatal patients attending hospital (Italy)	GH or PET	Possible double or overlapping diagnosis	Chronic hypertension, normotensive pregnant	NTP 30.5±5; GH 31.2±4; PET 30.0±5
	Cho, 2011[24]	Antenatal patients attending hospital (South Korea)	GH	Diabetes; essential hypertension; cardiac disease	Normotensive pregnant	NTP 35.1±3.4; GH 33.3±3.6
	Degani, 1989 [25]	Antenatal patients attending hospital (Israel)	GH or PET	Multiple pregnancy; previous hypertension; previous heart disease; antihypertensive therapy	Normotensive pregnant	third trimester

Trimester	Author, year	Population (Country)	Inclusion criteria	Exclusion criteria	Controls/comparison	Timing of echocardiography (gestational age in weeks)
	Demir, 2003 [26]	Antenatal patients attending hospital (Turkey)	GH	Essential hypertension	Normotensive pregnant	38
	Dennis, 2012 [27]	Antenatal patients attending hospital (Australia)	PET	In labor; smoking; vasoactive medication; critically ill requiring urgent antihypertensive or magnesium sulfate	Normotensive pregnant and non-pregnant	36±4
	Escudero, 1988 [28]	Antenatal patients attending hospital (Argentina)	GH	Parity >0; age under 16; history of heart disease; multiple pregnancy	Non-pregnant	26-42
	Hamad, 2009 [29]	Antenatal patients attending hospital (Sweden)	PET	Parity >0; smoking; assisted conception; multiple pregnancy; clinically unstable; antihypertensive therapy; chronic disease; extreme obesity	Normotensive pregnant	NTP 33±4; PET 35±4
	Ingec, 2005 [30]	Antenatal patients attending hospital (Turkey)	PET	Not stated	Normotensive pregnant	NTP 38±1; PET 37±3
	Kuzniar, 1982 [32]	Antenatal patients attending hospital (Poland)	PET	Multiple pregnancy; uncomplicated pregnancy; cardiorespiratory disease	Normotensive pregnant and pregnant with essential hypertension	30-40
	Kuzniar, 1992 [31]	Antenatal patients attending hospital (Poland)	Mild GH	Previous hypertension; renal disease; persistent hypertension 3 months post-partum; hypertension prior to 3rd trimester; SBP > 160; DBP >110	Normotensive pregnant	32-41
	Lang, 1991 [33]	Antenatal patients attending hospital (USA)	PET	Parity >0; regional wall motion abnormalities	Normotensive pregnant	"early labor" "late third trimester"
	Melchiorre, 2011[34]	Antenatal patients attending hospital (UK)	GH or PET	Multiple pregnancy; co-morbidities; smoking; antihypertensive therapy	Normotensive pregnant	37 (37.5 - 39)
	Melchiorre, 2012[35]	Antenatal patients attending hospital (UK)	PET	Multiple pregnancy; comorbidity; smoking; medication;	Normotensive pregnant (50 term; 54 preterm)	preterm NTP 32 (28.6 - 35.7); preterm PET 35.5 (28.1-35.8)
	Novelli, 2003 [36]	Antenatal patients attending hospital (Italy)	GH	Multiple pregnancy; medications other than vitamins/iron; indeterminate gestational age; smoking; cardiac disease; antihypertensive therapy; pre-existing medical problem	Normotensive pregnant and non-pregnant with essential hypertension	31(3) weeks

Trimester	Author, year	Population (Country)	Inclusion criteria	Exclusion criteria	Controls/comparison	Timing of echocardiography (gestational age in weeks)
	Oren, 1996 [37]	Antenatal patients attending hospital (Israel)	GH	Essential hypertension; diabetes; renal disease; molar pregnancy; hydrops	Normotensive pregnant and patients with gestational diabetes mellitus	NTP 32±3.3; GH 32±2.4
	Sanchez, 1986 [38]	Antenatal patients attending hospital (Argentina)	GH	Complicated pregnancy; cardiorespiratory disease	Normotensive pregnant; non-pregnant; pregnant with essential hypertension	32
	Simmons, 2002 [39]	Antenatal patients attending hospital (Australia)	PET	Medical co-morbidities; essential hypertension; diabetes; multiple pregnancy; vasoactive medication	Normotensive pregnant and non-pregnant	NTP 12±2, 22±1, 35±5; PET 35±4
	Solanki, 2011 [40]	Antenatal patients attending hospital (India)	PET	Multiple pregnancy; unsure of dates; essential hypertension; cardiac disease; moderate or severe anemia; multiple pregnancy; alcohol use; smoking	Normotensive pregnant	> 34 weeks
	Thompson, 1986 [41]	Antenatal patients attending hospital (USA)	PET	Essential hypertension; medication	Normotensive pregnant	32-38
	Tyldum, 2012 [42]	Antenatal patients attending hospital (Norway)	PET	Diabetes; essential hypertension; cardiac disease; multiple pregnancy	Normotensive pregnant	27-40 (mean 35)
	Veille, 1984 [43]	Antenatal patients attending hospital (USA)	GH	Essential hypertension; antihypertensive therapy other than magnesium sulfate or diuretics; multiple pregnancy	Normotensive pregnant	38±2
	Yuan, 2006 [44]	Antenatal patients attending hospital (China)	PET	Essential hypertension; renal disease; cardiac disease; diabetes	Normotensive pregnant	mean 39
	Yuan, 2014 [45]	Antenatal patients attending hospital (China)	PET	Parity >0; multiple pregnancy; GH; essential hypertension; risk factors for arterial stiffening (smoking; obstructive sleep apnea; in vitro fertilization; diabetes; hypercholesterolemia)	Normotensive pregnant	35.6±3.4
	Zieleskiewicz, 2014 [46]	Antenatal patients attending hospital (France)	PET	Age under 18; post-partum PET	Normotensive pregnant	NTP 37 (36-39); PET 34 (31-35)

Data are presented as means ± standard deviation or medians (interquartile range).
GH, gestational hypertension; NTP, normotensive pregnant control; PET, preeclampsia.

Table 2: Characteristics of patients in included studies

Author, year	Number of women	Number of cases			Age			Parity		
		NTP	GH	PET	NTP	GH	PET	NTP	GH	PET
Bamfo, 2008 [47]	36	19	0	17	26±6	n/a	29±7	38% P0; 21% P1; 5% P2	n/a	94% PO; 6% P2
Borghi, 2000 [22]	85	35	0	40	31±3	n/a	31±5	2±7	n/a	2±1
Borghi, 2011 [23]	112	39	24	33	31±4	29±5	32±5	2±1	2±1	2±1
Bosio, 1999 [55]	378	334	24	20	24 (95% CI 24, 25)	28 (95% CI 26, 30)	24 (95% CI 23, 26)	100% P0	100% P0	100% P0
Cho, 2011 [24]	199	93	106	0	30±4	32±4	n/a	not reported		
De Paco, 2008 [48]	4617	4123	87	83	32 (range 15-47)	32 (range 17-46)	32 (range 18-49)	48% P0	56% P0	64% P0
Degani, 1989 [25]	32	14	18	0*	27±6	25±5	n/a	100% P0	100% P0	n/a
Demir, 2003 [26]	92	56	36	0	26±6	29±9	n/a	not reported		
Dennis, 2012 [27]	100	40	0	40 (6 early; 34 late)	32±4	n/a	31±5	25% P0	n/a	65% P0
Escudero, 1988 [28]	29	10	9	0	27 (SD not given)	24 (SD not given)	n/a	100% P0	100% P0	n/a
Estensen, 2013 [50]	145	65	0	40	32±5	n/a	32±6	58% P0	n/a	67% P0
Hamad, 2009 [29]	65	30	0	35 (8 early; 27 late)	31±4	n/a	31±5	100% P0	n/a	100% P0
Ingec, 2005 [30]	37	17	0	20	29±6	n/a	32±7	not reported		
Khaw, 2008 [49]	534	457	0	27	30 (25 - 33)	n/a	without SGA 31 (22 -33); with SGA 31 (24 - 35)	100% P0	n/a	100% P0
Kuzniar, 1982 [32]	47	19	0	19	26 (range 17 - 31)	n/a	27 (range 15 - 32)	100% P0	n/a	100% P0
Kuzniar, 1992 [31]	72	27	22	23	24±4	24±4	22.5±4.1	100% P0	100% P0	100% P0
Lang, 1991 [33]	20	10	0	10	22±5	n/a	20±4			
Melchiorre, 2011 [34]	120	50	20	50	32 (26-36)	n/a	32.0 (29-37)	100% P0	n/a	100% P0
Melchiorre, 2012 [35]	181	104 (50 term; 54 preterm)	0	77 (27 preterm; 50 term)	32 (28-36)	n/a	30 (27-35)	59% P0	n/a	67% P0

Author, year	Number of women	Number of cases			Age			Parity		
		NTP	GH	PET	NTP	GH	PET	NTP	GH	PET
Melchiorre, 2013 [51]	214	168	0	46 (18 preterm; 28 term)	low risk 32 (26-34); high risk 32 (26-35)	n/a	term 32 (30-37); preterm 30 (24-34)	100% P0	n/a	100% P0
Novelli, 2003 [36]	114	38	36	0	32±6	31±6	n/a	not reported		
Oren, 1996 [37]	30	10	10	0	23±2	23±3	n/a	not reported		
Sanchez, 1986 [38]	69	22	16	0	23 (range 21-24)	26 (range 16-36)	n/a	100% P0	100% P0	n/a
Sep, 2011 [56]	34	24	0	10	33±5	n/a	30±5	100% parous	n/a	100% parous
Shahul, 2012 [52]	39	17	11[†]	11 (3 severe; 8 mild)	29 (25-33)	35.5 (28-39)	32 (26-34)	0 (0-0)	0 (0-1)	0 (0-2)
Simmons, 2002 [39]	71	44	0	15	29±5	n/a	32±6	not reported		
Solanki, 2011 [40]	40	20	0	20 (12 mild; 8 severe)	25±2	n/a	26±4	not reported		
Thompson, 1986 [41]	35	11	0	10	24 (range 19-29)	n/a	24 (range 16-34)	mean 1 (range 0-5)	mean 0 (range 0-1)	n/a
Tyldum, 2012 [42]	40	20	0	20	27±4	n/a	29±5	65% P0	n/a	65% P0
Valensise, 2006 [53]	309	41	268	17 (in comp. group)	32±3	uncomp. 32±4; comp. 33±4	n/a	27% P0	Uncom p. 29% P0; comp. 44% P0	n/a
Valensise, 2008 [54]	1226	1119	0	107 (75 early; 32 late)	32±5	n/a	early 34±4; late 32±4	100% P0	n/a	100% P0
Veille, 1984 [43]	40	17	23	0*	29±4	25±5	n/a	21% P0	96% P0	n/a
Vlahovic-Stipac, 2010 [57]	47	12	35	0	30±4	30±6	n/a	not reported		
Yuan, 2006 [44]	56	24	0	32	27±3.1	n/a	27±3	not reported		
Yuan, 2014 [45]	63	40	0	23	27±3	n/a	29±6	100% P0	n/a	100% P0
Zieleskiewicz, 2014 [46]	40	20	0	20	30 (26-34)	n/a	31 (26-38)	35% P0	n/a	45% P0

Data are presented as means ± standard deviation or medians (interquartile range).
* Definition of GH could include patients with PET; † GH group includes patients with essential hypertension.

Comp., complicated; uncomp., uncomplicated; GH, gestational hypertension; n/a, not applicable; NTP, normotensive pregnant control; P1, parity 1 etc.; PET, preeclampsia; SGA, small for gestational age fetus.

Table 3: Summary of findings in third trimester studies

Study	Vlahovic-Stipac, 2010 [57] ‡	Bamfo, 2008 [47]	Borghi, 2000 [22]	Borghi, 2011 [23]	Cho, 2011 [24]	Degani, 1989 [25]	Demir, 2003 [26] ‡	Dennis, 2012 [27]	Escudero, 1988 [28]	Estensen, 2013 [50] ‡	Hamad, 2009 [29]	Ingec, 2005 [30]	Kuzniar, 1982 [32]	Kuzniar, 1992 [31] ‡	Lang, 1991 [33] ‡	Melchiorre, 2012 [35]	Novelli, 2003 [36]	Oren, 1996 [37]	Sanchez, 1986 [38] ‡	Shahul, 2012 [52] ‡	Simmons, 2002 [39]	Solanki, 2011 [40] ‡	Thompson, 1986 [41] ‡	Tyldum, 2010 [42]	Valensise, 2006 [53] ‡	Veille, 1984 [43]	Yuan, 2006 [44]	Yuan, 2014 [45]	Zieleskiewicz, 2014 [46]
TVR		**P** =	**P**† =	**P** ↑		**G** ↑							**P** ↑	**P** ↑	**P** =		**G** ↑	**G** ↑			**P** ↑	**P** ↑			**P** ↑				
CO	**G** ↑	**P** ↓	**P**† ↓	**G** ↑ **P** ↑		**G** =		**P** ↑		**P** ↑			**P** ↓		**P** =	**P** ↓	**G** =	**G** =			**P** ↓	**P** ↑		**P** =	**P** ↓		**P** =		
LVEF			**P**† ↓		**G** =	**G** =	**G** =	**P** =		**P** =								**G** ↓		**G** =			**P** =				**P** ↑	**P** =	**P** =
E/A	**G** ↓	**P** =	**P**† ↓		**G** ↓						**P** ↓					**P** ↓	**G** ↓	**G** ↓						**P** =			**P** ↓	**P** =	**P** =
E/e’	**G** ↑	**P** ↑									**P** ↑					**P** ↑								**P** ↑					**P** ↑
LVM	**G** ↑			**P** ↑	**G** ↑		**G** ↑	**P** ↑	**G** ↑	**P** ↑	**P** ↑	**P** ↑			**P** =		**G** ↑	**G** ↑	**G** =		**P** ↑				**P** ↓	**G** ↑		**P** ↑	

* third trimester results from longitudinal study; † all cases early preeclampsia (before 34 weeks gestation); ‡ studies with post natal follow up.
↑, significant increase; ↓, significant decrease; =, no significant difference compared to controls; CO, cardiac output; G, gestational hypertension; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; P, preeclampsia; TVR, total vascular resistance.

Figure 1: Diagnosis of hypertensive disorders in pregnancy

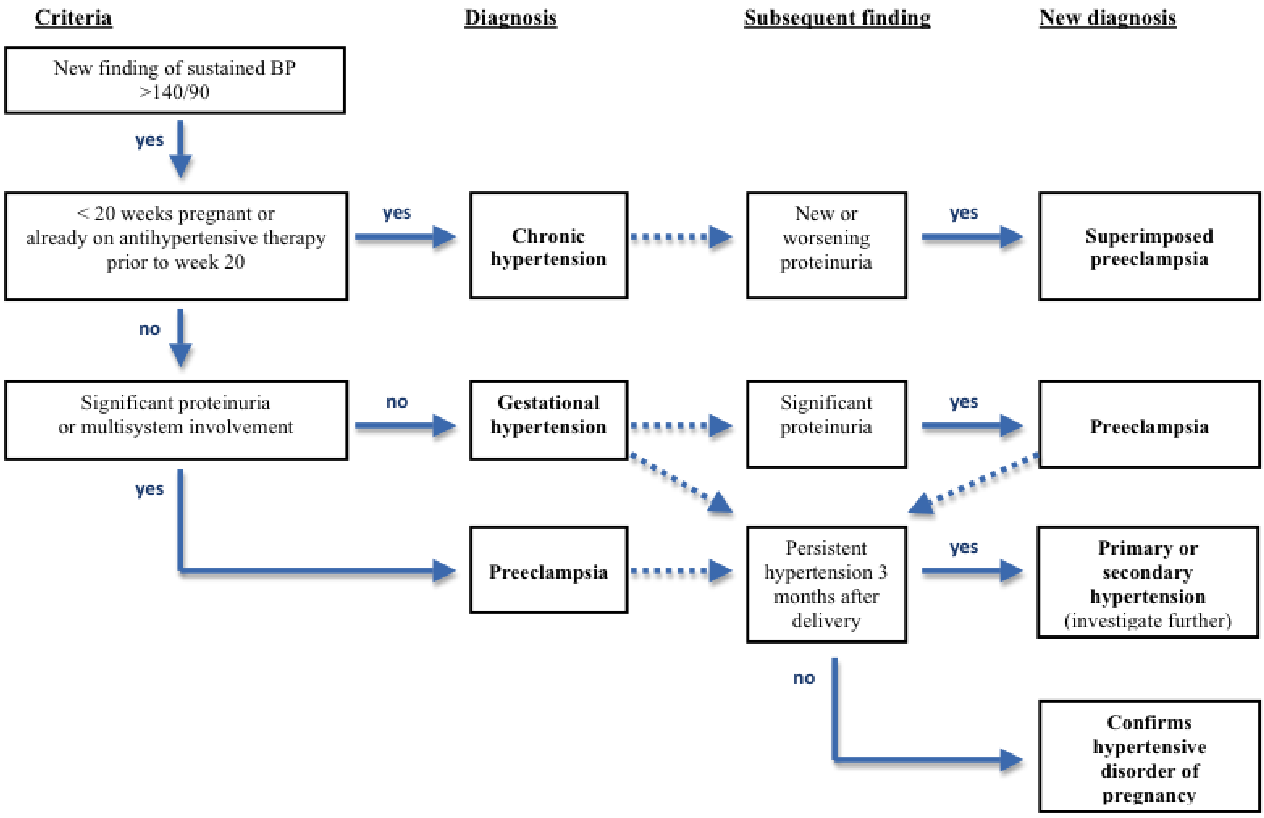

Figure 2: Flow chart of systematic review

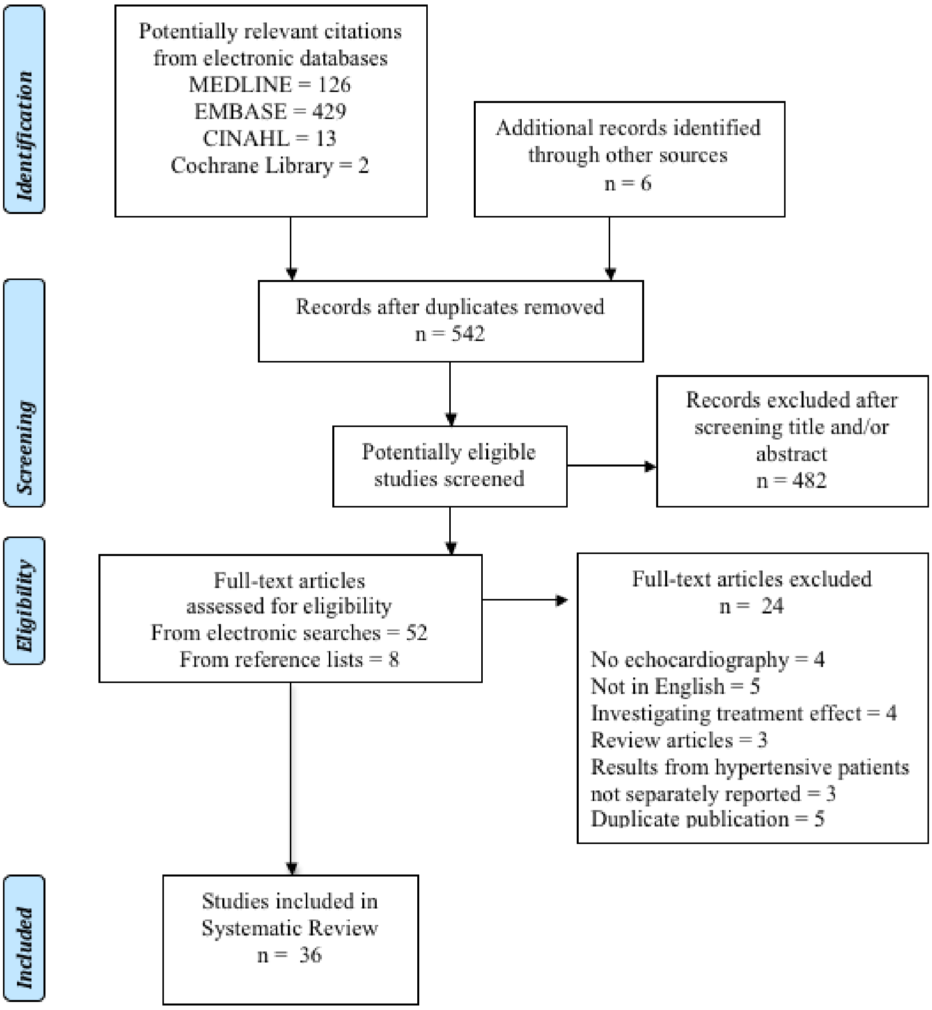

Figure 3: Summary of results

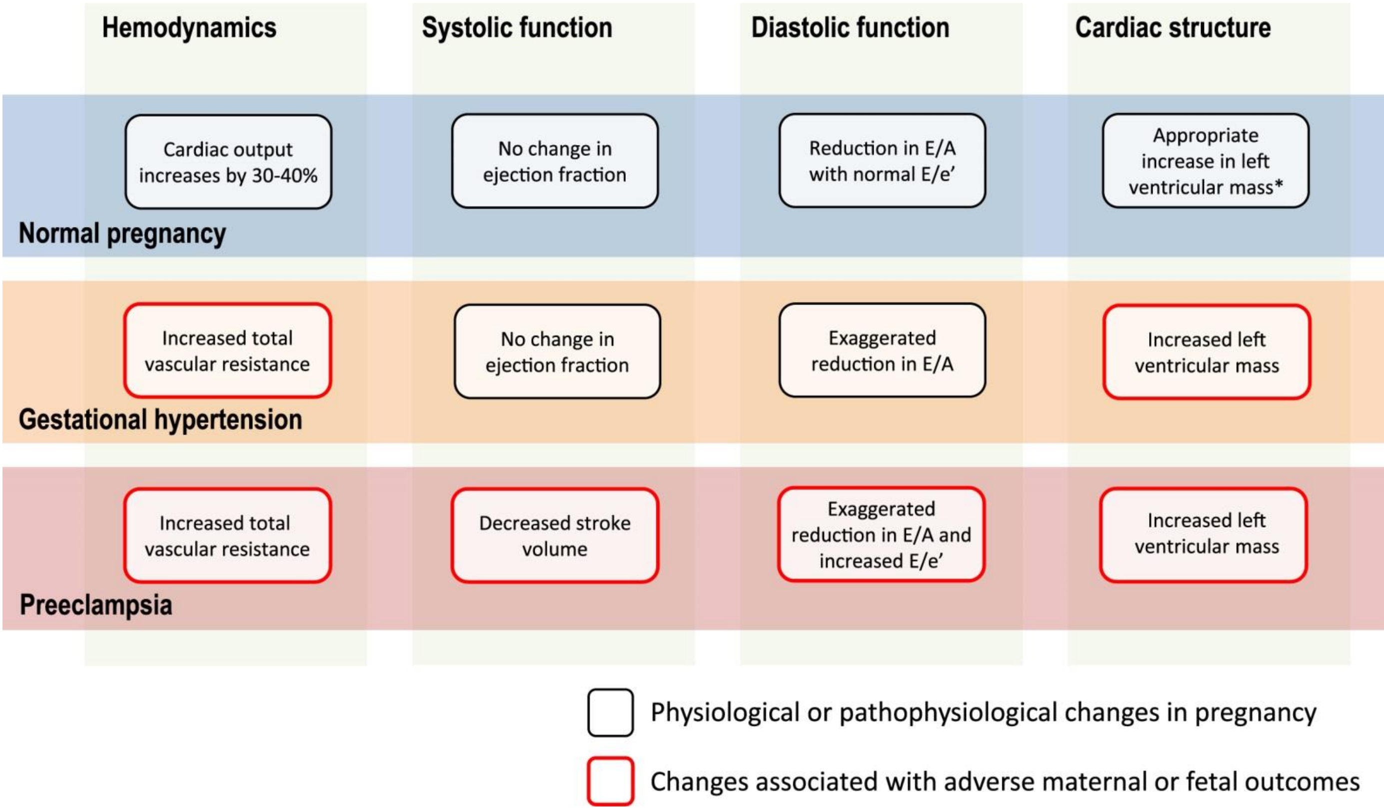

Figure 4: Potential value of echocardiography in hypertensive disorders of pregnancy