Longitudinal maternal cardiac function in hypertensive disorders of pregnancy

Hua Zen Ling, MD; Gavin Guy, MD; Kypros H. Nicolaides, MD; Nikos A. Kametas, MD

BACKGROUND: Compared with gestational hypertension, preeclampsia has traditionally been considered the worse end of the spectrum of hypertensive disorders of pregnancy. It is associated with worse pregnancy outcomes and future cardiovascular morbidities. Both hypertensive disorders may be associated with cardiac maladaptation in pregnancy. However, previous studies were limited by small numbers and a paucity of longitudinal data and unaccounted for the contribution of maternal characteristics that can affect hemodynamics.

OBJECTIVE: This study aimed to assess, in an unselected population, the maternal cardiac adaptation in normotensive and hypertensive pregnancies after controlling for important maternal characteristics that affect maternal cardiac function and the interaction among these covariates.

STUDY DESIGN: This was a prospective, multicenter longitudinal study of maternal hemodynamics, assessed by a noninvasive bioreactance technology, measured at 11 0/7 to 13 6/7, 19 0/7 to 24 0/7, 30 0/7 to 34 0/7, and 35 0/7 to 37 0/7 weeks of gestation in 3 groups of women. Group 1 was composed of women with preeclampsia (n=45), group 2 was composed of women with gestational hypertension (n=61), and group 3 was composed of normotensive women (n=1643). A multilevel linear mixed-effects model was performed to compare the repeated measures of hemodynamic variables controlling for maternal age, height, weight, weight gain, race, previous obstetrical history, and birthweight.

RESULTS: After adjusting for confounders that significantly affect maternal hemodynamics, both group 1 and group 2, compared with group 3, had pathologic cardiac adaptation. Group 1, compared with group 3, demonstrated hyperdynamic circulation with significantly higher cardiac output driven by greater stroke volume in the first trimester of pregnancy. As the pregnancies progressed to after 20 0/7 weeks of gestation, this hyperdynamic state transitioned to hypodynamic state with low cardiac output and high peripheral vascular resistance. Group 2, compared with group 3, had no significant differences in cardiac output, stroke volume, and heart rate before 20 0/7 weeks of gestation but thereafter demonstrated a continuous decline in cardiac output and stroke volume, similar to group 1. Both groups 1 and 2, compared with group 3, had persistently elevated mean arterial pressure and uterine artery pulsatility index throughout pregnancy.

CONCLUSION: After adjusting for confounders that affect maternal hemodynamics in an unselected pregnant population, women with preeclampsia and gestational hypertension, compared with normotensive women, demonstrated similar cardiac maladaptation. This pathologic profile was evident after 20 0/7 weeks of gestation and at least 10 weeks before the clinical manifestation of the disease.

Keywords: bioreactance, cardiac adaptation, cardiac output, gestational hypertension, hemodynamics, hypertensive disorders of pregnancy, peripheral vascular resistance, placental insufficiency, preeclampsia, pregnancy, pregnancy-induced hypertension

Introduction

Hypertensive disorders of pregnancy (HDP) encompass preeclampsia (PE) and gestational hypertension (GH). PE has conventionally been considered the worse end of the disease spectrum, whereas GH was thought to be possibly a milder disease.[1] The notion that both PE and GH are associated with underlying vascular dysfunction,[2] pathologic cardiac remodeling with systolic and diastolic dysfunction,[3–5] and increased long-term cardiovascular morbidity[6–8] has fueled research assessing maternal hemodynamics in HDP. However, most existing studies were cross-sectional studies[9–12] or conducted in high-risk pregnancies.[3] The few longitudinal studies were limited by small numbers of PE between 14 and 20 cases,[13–15] combining PE and fetal growth restriction as a single disease entity,[14] and the lack of a diverse ethnic cohort or adjustment for maternal characteristics that can affect maternal hemodynamics.[16–19]

In the investigation of any biological processes, one must consider demographic characteristics as potential confounders in markers for the disease. For example, outside pregnancy, the performance of serum creatinine in the classification of chronic kidney disease improved when patient demographic factors, such as age, sex, and height, were adjusted for in the equation for estimation of glomerular filtration rate.[20] Similarly, pregnancy adjustment for maternal characteristics, such as age, race, smoking, conception, and parity, improved the detection rate for screening for Down syndrome and PE.[21,22] Moreover, we have previously demonstrated that maternal height, weight, weight gain, age, race, previous obstetrical history, and birthweight were significant independent predictors of maternal cardiac function indices.[16–19,23] To date, there is no longitudinal study assessing the changes of maternal cardiovascular variables across gestation, independent of the aforementioned confounders.

This study aimed to assess, in an unselected population, the maternal cardiac adaptation in normotensive and hypertensive pregnancies after controlling for important maternal characteristics that affect maternal cardiac function.

Cite this article as: Ling HZ, Guy G, Nicolaides KH, et al. Longitudinal maternal cardiac function in hypertensive disorders of pregnancy. Am J Obstet Gynecol MFM 2023;5:100824.

2589-9333/$36.00

http://dx.doi.org/10.1016/j.ajogmf.2022.100824

AJOG MFM at a Glance

Why was this study conducted?

This study aimed to assess, in a large, unselected population, the maternal cardiac adaptation in normotensive and hypertensive pregnancies after controlling for maternal characteristics.

Key findings

Compared with normotensive women, those with preeclampsia (PE) demonstrated significantly higher cardiac output (CO) driven by greater stroke volume (SV) in the first trimester of pregnancy but transitioned to low CO and high peripheral vascular resistance (PVR) after 20 weeks of gestation. Compared with normotensive women, those with gestational hypertension had no difference in CO, SV, and heart rate but demonstrated a continuous decline in CO and SV after 20 weeks of gestation.

What does this add to what is known?

PE and gestational hypertension have equal pathologic hemodynamic profiles. From 20 weeks of gestation, the former crossed over from the hyperdynamic profile to the hypodynamic profile, whereas the latter demonstrated a continuous decline in CO and an increase in PVR.

Material and Methods

Study population

Between November 2015 and May 2016, women with singleton pregnancies attending routine pregnancy care at 11 0/7 to 13 6/7 weeks of gestation in 6 maternity hospitals in London, United Kingdom, were invited to participate in the longitudinal assessment of maternal hemodynamics. Of 1929 women approached, 1918 (99%) agreed to participate in the study. Gestational age was confirmed from the measurement of fetal crown-rump length.[24] We excluded patients with fetal anomalies (n=13), miscarriage or termination (n=16), poor cardiac signals (n=22), missing pregnancy outcomes (n=16), and those who withdrew consent (n=62); a total of 1789 women were followed up. None of the patients had preexisting maternal cardiac diseases. The timings of the 4 visits coincided with the routine antenatal visits for dating and screening for chromosomal abnormalities at 11 0/7 to 13 6/7 weeks of gestation, second-trimester routine anomaly scan at 19 0/7 to 24 0/7 weeks of gestation, and fetal well-being scans at 30 0/7 to 34 0/7 and 35 0/7 to 37 0/7 weeks of gestation. During each of these 4 visits, we performed a noninvasive maternal cardiovascular assessment. The study was approved by the National Health Service Research Ethics Committee (reference: 13/LO/1479).

Maternal factors and pregnancy outcomes

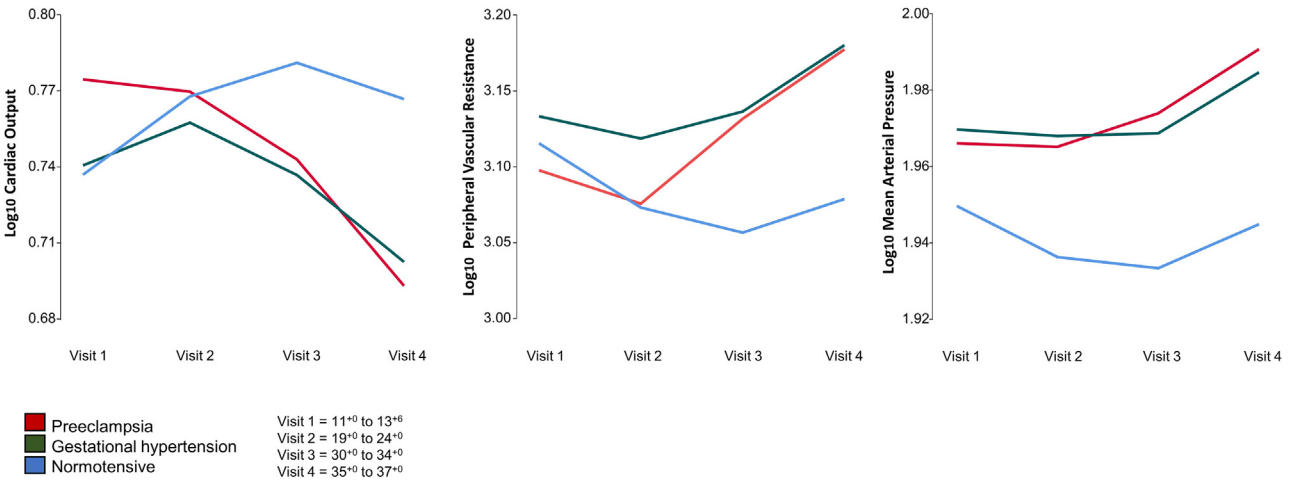
Maternal factors recorded included age, height, weight, cigarette smoking, asthma, self-reported race (White, Black, South Asian, East Asian, and mixed), parity (nulliparous and parous with and without previous PE), artificial reproductive techniques (ARTs), and medical history, such as asthma and preexisting diabetes mellitus. Pregnancy outcomes included PE, GH, gestational age at delivery, birthweight, induction of labor, emergency cesarean delivery, operative delivery for fetal distress, and neonatal unit admission rates.

Maternal cardiovascular function assessment. Maternal cardiac function was assessed using a noninvasive, cardiac monitor (NICOM; Cheetah Medical Ltd, Maidenhead, Berkshire, United Kingdom). The bioreactance technology calculates stroke volume (SV) by recording the relative phase shifts when an alternating electrical current passes the thoracic cavity. We have previously validated the NICOM for use in all 3 trimesters in pregnancy.[25] After 15 minutes of rest, 4 electrodes were applied across the maternal back. After successful calibration, maternal cardiac variables (cardiac output [CO], SV, heart rate [HR], peripheral vascular resistance [PVR], and mean arterial pressure [MAP]) were recorded in a sitting position for 10 minutes at 30-second intervals (20 cycles). The averages of the final 10 cycles of the hemodynamic variables were included in the analysis. This was to control for the differences in SV that can occur with the negative intrathoracic pressure at inspiration. In addition, the uterine artery pulsatility index (UA-PI) was measured as previously described.[26]

Definitions

The definitions of PE and GH were those of the International Society for the Study of Hypertension in Pregnancy.[27] GH was defined as the systolic blood pressure (BP) being ≥140 mm Hg and/or the diastolic BP being ≥90 mmHg on at least 2 occasions 4 hours apart developing after 20 weeks of gestation in previously normotensive women. PE was defined as GH accompanied by at least one of the following: renal involvement (proteinuria of ≥300 mg per 24 hours and/or creatinine level of ≥90 μmol/L or 1 mg/dL), liver impairment (transaminases of >70 IU/L), neurologic complications (eg, eclampsia), thrombocytopenia (platelet count of <150,000/μL).[27] Here, the initiation of antihypertensives was based on clinician preference, guided by the National Institute for Health and Care Excellence guidelines. Maternal hemodynamic parameters were not used to affect medication administration. We classified the study population into 3 groups based on the development of any HDP: group 1, women with PE; group 2, women with GH; and group 3, normotensive women. In the current analysis, we excluded 40 patients with chronic hypertension (3 had superimposed PE) to ensure that the hemodynamic findings were not due to hemodynamic abnormalities predating the pregnancy or the use of antihypertensive medications. Birthweight z score and percentiles were derived from the Fetal Medicine Foundation reference range.[28]

FIGURE 1
Linear mixed effect models with estimated marginal means: cardiac output, peripheral vascular resistance and mean arterial pressure



The *red line* indicates women with preeclampsia, the *green line* indicates women with gestational hypertension, and the *blue line* indicates normotensive women.

Ling. Maternal cardiac adaptation in hypertensive disorders of pregnancy. Am J Obstet Gynecol MFM 2023.

Statistical analysis

We examined the longitudinal changes of maternal cardiovascular variables stratified according to the development of HDP. The normality of the distribution of numerical data was assessed by the Kolmogorov-Smirnov test. The distribution of maternal weight, CO, SV, MAP, and PVR were made Gaussian after $\log_{10}$ transformation. For comparison of numerical data, the Kruskal-Wallis or the 1-way analysis of variance tests were used for not-normally and normally distributed data, respectively. For categorical data, the chi-square test or Fisher exact test was used, where appropriate. Data are presented as median (interquartile range) and mean (standard deviation) for not-normally and normally distributed continuous variables, respectively, and as number (percentage) for categorical variables.

We performed a multilevel linear mixed-effects model for the repeated measures analysis of the maternal hemodynamic variables controlling for maternal age, $\log_{10}$ weight, height, racial origin, smoking, asthma, parity (nulliparous and parous with and without previous PE), diabetes mellitus, birthweight *z* score, time (the 4 visits), and the interaction between group and time. The likelihood ratio test was used to define the best multilevel model comparing the base model to either the random intercept or the random intercept and slope. The estimated marginal means of each hemodynamic variable at each hypertension group or time combination are presented in Figure 1, Figure 2, and Table 2.

The software program IBM SPSS (SPSS Statistics for Windows 2015; version 25.0, IBM Corporation, Armonk, NY) was used for statistical analysis.

Results

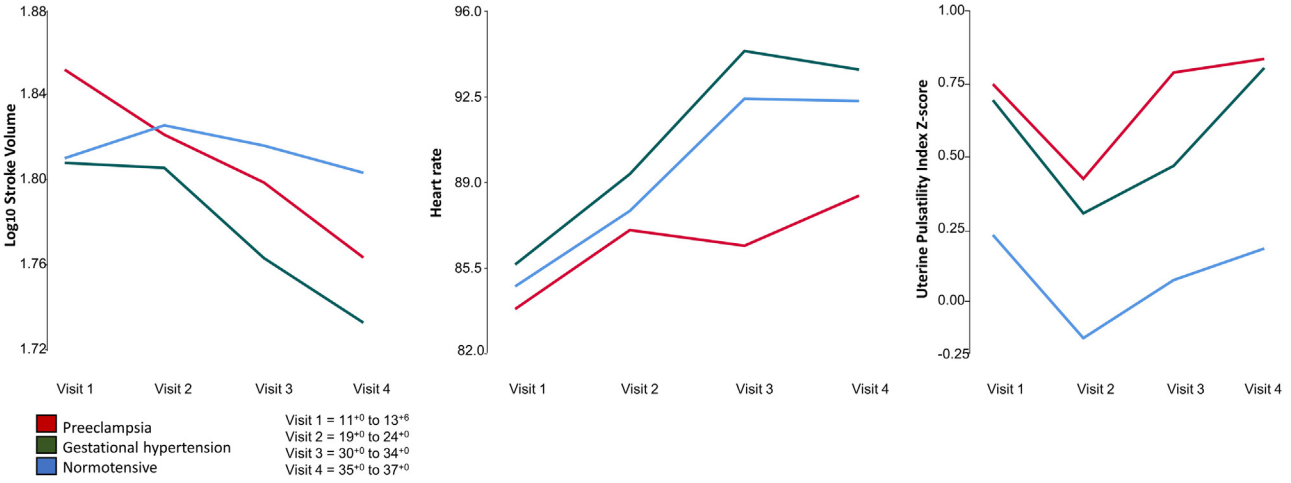
Overall, 1749 women were included in the final analysis, and the 3 groups included 45 women in group 1, 61 women in group 2, and 1643 women in group 3.

Maternal demographics and pregnancy outcomes

This is presented in Table 1. There was no significant difference in maternal age, height, smoking, racial origins, ART, diabetes mellitus, and birthweight percentile among the 3 groups. Women in groups 1 and 2 were significantly heavier with higher BP at booking and more likely to have had a family history of PE, to be nulliparous, to undergo induction of labor, and to have a higher rate of emergency cesarean delivery and operative birth for fetal distress than women in group 3. Group 1 had a higher prevalence of parous women with previous PE or FGR and delivered earlier with more small-for-gestational-age babies in the current pregnancy than group 3. Women in group 2 were 4 times more likely to have asthma and delivered significantly earlier than women in group 3.

At the third visit, there were 6 women (0.3%) who developed GH and PE, and 5 of them were treated with antihypertensives. At the fourth visit, 19 women (1.1%) developed GH and PE, and 13 of them were treated with antihypertensives. Overall, most cases of PE (29 [64%]) and GH (51 [84%]) occurred after the fourth visit; therefore, their hemodynamic variables were not significantly affected by antihypertensive treatment. Furthermore, there were 11 patients (24%) with PE and 2 patients (3%) with GH who delivered before

FIGURE 2
Linear mixed-effects model with estimated marginal means: Stroke volume, heart rate, uterine pulsatility index z-score



The *red line* indicates women with preeclampsia, the *green line* indicates women with gestational hypertension, and the *blue line* indicates normotensive women.

Ling. Maternal cardiac adaptation in hypertensive disorders of pregnancy. Am J Obstet Gynecol MFM 2023.

term (<37 weeks of gestation) iatrogenically. The statistical analysis was repeated after removing the patients who developed PE or GH at visits 3 and 4. Because of the small number of these patients, the hemodynamic results were not affected (data not shown).

Maternal hemodynamic changes in different hypertensive groups

The fixed effects of the best multilevel models and the pairwise comparison of the estimated marginal means with 95% confidence intervals (CIs) are shown in Table 2 and Figures 1 and 2. The data are presented in the antilog form to facilitate an appreciation of the hemodynamic differences among groups. For all maternal hemodynamic variables (apart from HR), a random intercept-random slope model provided a significantly better fit to the data than did the base model or a random intercept model (data presented in the Supplemental Materials and Methods section).

Log_{10} Cardiac output, Log_{10} Peripheral vascular resistance, Log_{10} Mean arterial pressure, Log_{10} Stroke volume, Heart rate, and Uterine artery pulsitility index z score: relationship with maternal demographic characteristics (Supplementary Table 1). Increasing maternal age was significantly associated with lower Log_{10}CO and HR but higher Log_{10}PVR and UA-PI *z* scores. Maternal height was significantly associated with greater Log_{10}CO and Log_{10}SV but lower Log_{10}PVR and HR. Maternal booking weight had no significant contribution to Log_{10}PVR but was associated with higher Log_{10}CO, Log_{10}MAP, Log_{10}SV, HR, and UA-PI *z* scores. Women of Black and South and East Asian race had significantly lower Log_{10}CO and Log_{10}SV than White women. South and East Asian women had higher Log_{10}PVR and Black women had lower BP than White women. Women who smoke had significantly lower Log_{10}MAP, whereas those with asthma had higher Log_{10}MAP and UA-PI *z* scores. Parous women had higher Log_{10}CO and HR and lower Log_{10}PVR than nulliparous women. Birthweight *z* score is associated with higher Log_{10}CO and HR but lower Log_{10}PVR and UA-PI *z* scores. There was a significant interaction between hypertensive groups and time for all cardiac variables.

Log_{10}CO, Log_{10}PVR, Log_{10}MAP, Log_{10}SV, HR, and UA-PI z score: changes with time after controlling for maternal characteristics and outcomes (Table 2, Figure 1, and Supplementary Figure 1). Log_{10} CO in group 3 demonstrated a physiological increase from visit 1 to visit 3 followed by a decrease thereafter. Similar to group 3, group 2 also demonstrated an increase in Log_{10} CO from visit 1 to visit 2 but had an earlier decline in a linear pattern from visit 2 to visit 4. In contrast, group 1 started with a significantly higher Log_{10} CO than group 3 at visit 1 and remained stagnant from visit 1 to visit 2, followed by an abrupt drop from visit 2 to visit 4. Both groups 1 and 2 had significantly lower Log_{10} CO than group 3 in visits 3 and 4.

Log_{10} PVR was similar among the 3 groups at visit 1, and all groups demonstrated a physiological fall from visit 1 to visit 2. Although group 3 continued to demonstrate a decline in Log_{10} PVR toward visit 3, groups 1 and 2 showed an increase in Log_{10} PVR from visit 2 onward. Log_{10} MAP and UA-PI in groups 1 and 2 were significantly higher throughout pregnancy than in group 3.

TABLE 1
Demographic characteristics and pregnancy outcomes of the study groups

Variables	Group 1: PE (n=45)	Group 2: gestational hypertension (n=61)	Group 3: normotensive (n=1643)	*P* value
Age (y), mean (SD)	31.2 (5.2)	30.6 (5.6)	31.2 (5.3)	.727
Height (cm), mean (SD)	163.6 (6.3)	164.4 (6.2)	164.7 (6.6)	.723
Weight (kg), median (IQR)	79.1 (18.6)‡‡‡	82.1 (21.4)‡‡‡	70.5 (15.1)	.000
Systolic blood pressure (mm Hg), mean (SD)	122.1 (14.5)‡‡‡	123.8 (12.6)‡‡‡	114.7 (10.5)	.000
Diastolic blood pressure (mm Hg), mean (SD)	78.4 (9.3)‡‡	79.6 (9.2)‡‡‡	74.5 (7.7)	.000
Smoking, n (%)	1 (2.2)	1 (1.6)	93 (5.7)	.231
Asthma, n (%)	1 (2.2)	5 (8.2)‡‡	33 (2.0)	.006
Family history of PE, n (%)	6 (13.3)‡	8 (13.1)‡	91 (5.5)	.006
Racial origin, n (%)				
White	35 (77.8)	43 (70.5)	1230 (74.9)	.714
Black	7 (15.6)	14 (23.0)	236 (14.4)	.089
South Asian	3 (6.7)	3 (4.9)	91 (5.5)	.955
East Asian	0 (0.0)	0 (0.0)	39 (2.4)	.266
Mixed	0 (0.0)	1 (1.6)	47 (2.9)	.423
Nulliparous, n (%)	33 (73.3)‡‡	40 (65.6)‡	844 (51.4)	.001
Parous, with previous PE or FGR	6 (13.3)‡	5 (8.2)	96 (5.8)	.000
Parous, without previous PE or FGR	6 (13.3)‡‡‡	16 (26.2)‡	703 (42.8)	.000
Assisted reproductive techniques, n (%)	3 (6.3)	0 (0.0)	50 (3.0)	.165
Preexisting diabetes mellitus, n (%)	0 (0.0)	0 (0.0)	11 (0.7)	.693
Pregnancy outcomes				
Gestational age at birth (wk), median (IQR)	38.4 (2.6)‡‡‡,+++	40.0 (1.6)	39.9 (1.9)	.000
Birthweight percentile, median (IQR)	35.8 (57.7)	40.8 (60.5)	48.3 (52.7)	.097
Birthweight<10th percentile, n (%)	10 (22.2)‡	12 (19.7)	228 (13.9)	.047
Gestational diabetes mellitus, n (%)	4 (8.9)	6 (9.8)‡‡‡	62 (3.8)	.017
Induction of labor	31 (68.9)‡‡‡	33 (54.1)‡‡‡	440 (26.8)	.000
Emergency cesarean delivery	19 (42.2)‡‡‡	18 (29.5)‡‡	258 (15.7)	.000
Operative birth for fetal distress	12 (26.7)‡‡	12 (19.7)‡‡	180 (11.0)	.000

FGR, fetal growth restriction; *IQR*, interquartile range; *PE*, preeclampsia; *SD*, standard deviation.

Compared to group 1: **P*<.05; ***P*<.01; ****P*<.001.

Compared to group 2: ^{+}P<.05; ^{++}P<.01; ^{+++}P<.0001.

Compared to group 3:

‡ *P*<.05; ‡‡ *P*<.01; ‡‡‡ *P*<.0001.

Ling. Maternal cardiac adaptation in hypertensive disorders of pregnancy. Am J Obstet Gynecol MFM 2023.

Log_{10} SV in group 3 demonstrated the physiological increase from visit 1 to visit 2, after which it declined gradually with advancing pregnancy. Log_{10} SV in group 1 was significantly higher than in groups 2 and 3 in visit 1 but demonstrated a dramatic linear decline immediately after which persisted toward visit 4. Log_{10} SV in group 2 plateaued from visit 1 to visit 2, followed by a steeper decline, compared with group 3 after visit 2. By visit 4, both groups 1 and 2 had significantly lower Log_{10} SV than group 3. All 3 groups increased their HR from visit 1 to visit 2 without any significant difference among groups. From visit 2 to visit 3, group 1 plateaued and stayed at a significantly lower level than groups 2 and 3 in the last 2 visits.

All 3 groups demonstrated a drop in UA-PI *z* score from visit 1 to visit 2 followed by an increase that continued

TABLE 2
Multilevel linear mixed-effects models: estimated marginal means with 95% confidence interval

Variable	Visit 1	Visit 2	Visit 3	Visit 4
Cardiac output (L/min)				
Group 1	5.98‡ (5.57–6.43)	5.92 (5.50–5.57)	5.56‡ (5.15–5.99)	4.97‡‡‡ (4.58–5.37)
Group 2	5.52 (5.19–5.87)	5.74 (5.39–6.12)	5.48‡‡ (5.14–5.83)	5.07‡‡‡ (4.75–5.40)
Group 3	5.46 (5.36–5.57)	5.86 (5.75–5.98)	6.05 (5.93–6.18)	5.86 (5.74–5.98)
Peripheral vascular resistance (dyn·s·cm^{-5})				
Group 1	1247.38 (1150.80–1348.96)	1185.77 (1093.96–1285.29)	1348.96‡‡‡ (1241.65–1465.55)	1499.69‡‡‡ (1377.21–1636.82)
Group 2	1355.19 (1264.74–1448.78)	1312.20‡‡ (1221.80–1406.05)	1364.58‡‡‡ (1273.50–1462.18)	1510.10‡‡‡ (1409.29–1618.10)
Group 3	1303.17 (1273.50–1330.45)	1180.32 (1153.45–1207.81)	1137.63 (1111.73–1164.13)	1196.74 (1169.50–1224.62)
Mean arterial pressure (mm Hg)				
Group 1	91.62‡‡ (89.13–94.62)	91.62‡‡‡ (88.92–94.41)	93.54‡‡‡ (90.57–96.38)	97.10‡‡‡ (93.97–100.23)
Group 2	92.68‡‡‡ (90.16–95.06)	92.26‡‡‡ (89.74–94.84)	92.47‡‡‡ (89.95–94.84)	95.94‡‡‡ (93.33–98.40)
Group 3	92.68 (87.10–89.74)	85.70 (84.33–87.10)	85.11 (83.75–86.49)	87.49 (86.10–88.92)
Stroke volume (mL)				
Group 1	70.96+,‡ (65.77–76.74)	66.22 (61.24–71.61)	62.95 (57.94–68.08)	57.94‡ (54.08–63.53)
Group 2	64.27 (60.11–68.55)	63.83 (59.70–68.23)	57.94‡‡‡ (54.20–61.94)	54.08‡‡‡ (50.58–57.81)
Group 3	64.42 (63.20–68.19)	66.83 (65.61–68.23)	65.46 (64.12–66.83)	63.53 (62.23–64.86)
Heart rate (bpm)				
Group 1	84.164 (81.208–87.120)	87.393 (84.390–90.396)	86.780‡‡‡ (83.705–89.857)	88.829‡,+ (85.658–92.002)
Group 2	85.813 (83.240–88.386)	89.534 (86.931–92.137)	94.591 (91.976–97.207)	93.867 (91.241–96.491)
Group 3	84.781 (83.828–85.734)	87.901 (86.953–88.850)	92.526 (91.576–93.477)	92.455 (91.498–93.413)
Uterine artery pulsatility index *z* score				
Group 1	0.733‡‡‡ (0.408–1.058)	0.406‡‡‡ (0.075–0.737)	0.772‡‡‡ (0.432–1.112)	0.819‡‡‡ (0.465–1.172)
Group 2	0.677‡‡‡ (0.398–0.957)	0.288‡‡ (0.004–0.571)	0.451‡‡ (0.166–0.736)	0.788‡‡‡ (0.502–1.074)
Group 3	0.212 (0.076–0.348)	−0.142 (−0.279 to −0.004)	0.057 (−0.080 to 0.196)	0.166 (0.026–0.305)

Compared to group 1: *P<.05; **P<.01; ***P<.001.

Compared to group 2: +P<.05; ++P<.01; +++P<.0001.

Compared to group 3:

‡ P<.05; ‡‡ P<.01; ‡‡‡ P<.0001.

Ling. Maternal cardiac adaptation in hypertensive disorders of pregnancy. Am J Obstet Gynecol MFM 2023.

toward visit 4. Groups 1 and 2 demonstrated significantly higher UA-PI *z* scores than group 3 throughout pregnancy.

Comment

Principal findings

The results of this study demonstrated that, after adjusting for confounders that affect maternal hemodynamics, groups 1 and 2, compared with group 3, had pathologic cardiac adaptation. Group 1 demonstrated significantly higher CO driven by greater SV in the first trimester of pregnancy but transitioned to low CO and high PVR than group 3. compared with group 3, group 2 had no significant difference in CO, SV, and HR in the first 2 visits but thereafter demonstrated a continuous decline in CO and SV. Compared with group 3, both groups 1 and 2 had persistently elevated MAP and UA-PI throughout pregnancy.

Results in the context of what is known

The cardiac adaptation in the normotensive group is in keeping with previous reports that described an increase in CO and a decline in PVR and MAP from conception to the early third trimester of pregnancy with a subsequent decrease in CO and an increase in MAP and PVR in the late third trimester of pregnancy.[29,30] In PE and GH in nulliparous and predominantly White women, Easterling et al[31] described persistently hyperdynamic profiles, whereas Bosio et al[15] described a late crossover in PE and persistent hyperdynamic profile in GH. Our results disagreed with this, as we demonstrated that the timing of hemodynamic crossover in PE manifested earlier, just after visit 2 (19–24 weeks) and

at least 10 weeks before the clinical diagnosis of PE. Similarly, contrary to these studies, group 2 had a pathologic profile after visit 2 rather than a persistently hyperdynamic profile. These studies were limited by small numbers, the exclusion of parous women, no adjustment for maternal characteristics, and mild severity of PE as most cases were delivered at term with no difference in birthweight, compared with normotensive pregnancies. In addition, contrary to our findings, Easterling et al[31] reported no difference in the hemodynamics of GH and normotensive women, likely because of inappropriate classification. GH had an unusually high incidence of 45%, as it was defined as a 15 mm Hg rise in diastolic BP from booking.[31] Another more recent longitudinal study reported no hemodynamic difference between PE and non-PE.[14] However, this study was limited by only 3 cases of PE and no GH case, indicative of a small sample size.

Strength and limitations

The strengths of this study included the large sample size, the unselected population, and the longitudinal assessment of maternal cardiac variables. We adjusted for maternal demographic characteristics, such as weight, height, age, race, previous obstetrical history, and fetal growth that affect maternal hemodynamics[16–19,23] and excluded chronic hypertension to avoid any confounding effects of antihypertensives and hemodynamic abnormalities predating pregnancy. A limitation of this study was that prepregnancy and postpartum BPs were unknown. Therefore, we could not exclude cases of undiagnosed chronic hypertension masked by the physiological drop of BP in early pregnancy or those where hypertension persisted after delivery.

Clinical implications and interpretation of findings

In our study, both hypertensive groups demonstrated a pathologic hemodynamic profile throughout pregnancy. The more severe form of cardiac maladaptation in our study, compared with those of previous studies,[15,31] is likely explained by the diverse population, containing women with previous PE, Black or Asian race, and other medical comorbidities. Although this cohort had been shown to have a reduced cardiovascular reserve,[18,19] their diversities are true representations of an unselected antenatal population.

Group 1, contrary to group 2, showed a hyperdynamic profile in visit 1. This could be because the former may be at the early stage of borderline chronic hypertension with established endothelial function impairment.[32,33] Outside pregnancy, borderline hypertension is characterized by elevated CO, because of the translocation of blood volume from the periphery to the cardiopulmonary circulation, which leads to increased shear stress with progressive exacerbation of the endothelial impairment and hypertrophy of the vascular smooth muscles.[34] A similar picture, where outside pregnancy takes many years to evolve, is possibly seen in a shorter timeframe because of the exaggerated hemodynamics of pregnancy, in women with PE who transition from a high CO state to the sudden increase in PVR after visit 2. These changes will cause concentric left ventricular (LV) hypertrophy,[35] reduced cardiac compliance, and impaired diastolic function[36] and explain the decline in SV and CO as early as 20 to 23 weeks of gestation.

More importantly, our results in group 2 defeated the notion that GH is a milder disease compared with PE, at least in terms of maternal cardiac adaptation. Group 2 demonstrated impaired hemodynamics with elevated MAP, PVR, and UA-PI z score throughout pregnancy, with a decline in SV after visit 2, leading to significantly higher compensatory HR to maintain CO. An explanation for their pathologic cardiac adaptation could be the high prevalence of women of Black race, higher booking weight, and medical conditions, such as asthma. We have previously shown that women of Black race have a pathologic pattern of maternal hemodynamic adaptation,[19] and asthma is a unique risk factor for hypertension because of augmented systemic inflammatory response and the use of steroids and betamimetics.[37] Furthermore, the higher HR in group 2 has been shown to be a risk factor for future hypertension.[38] It is believed to be associated with an excessive sympathetic drive[39] and is typically found among overweight individuals with greater insulin resistance.[40]

This befits the characteristics of women in group 2 who were heavier at booking and subsequently had a higher prevalence of gestational diabetes mellitus. These findings were in keeping with epidemiological studies showing that, similar to PE, GH signals an equal predisposition toward increased risk of future cardiovascular morbidity[41] and echocardiographic evidence that women with GH have cardiac maladaptation and impaired placentation from the first trimester[42–44] and that, in the third trimester of pregnancy, the elevated PVR causes reduced LV end-diastolic dimensions and pathologic concentric hypertrophy.[45,46]

Clinical and research implications

Both PE and GH have similar pathologic hemodynamic profiles in pregnancy. Therefore, contrary to current guidelines, which consider GH a more benign disease, both PE and GH should be targeted equally in antenatal and postpartum surveillance to mitigate short-term pregnancy complications and long-term cardiovascular risk. It is possible that the cardiac maladaptation shown in our study resulted from either a suboptimal stimulus because of poor placentation or a preexisting impaired cardiovascular system. More importantly, cardiac maladaptation in both HDP occurred as early as the first and second trimesters of pregnancy. Therefore, interventions to reduce the risk of HDP should focus on either modifying preconception factors, such as reversing maternal obesity, or early pregnancy. Finally, the adjusted cardiovascular parameters indicated that absolute cutoff values for cardiac parameters are unlikely to distinguish between disease and normality in the first half of pregnancy. Alternatively, more research should focus on the trends of adjusted cardiac variables in monitoring the progression of HDP.

Conclusion

After adjusting for confounders that affect maternal hemodynamics in an unselected pregnant population, women with PE and GH, compared with normotensive women, demonstrated similar cardiac maladaptation after 20 weeks of gestation. ■

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ajogmf.2022.100824.

References

1. Melamed N, Ray JG, Hladunewich M, Cox B, Kingdom JC. Gestational hypertension and preeclampsia: are they the same disease? J Obstet Gynaecol Can 2014;36:642–7.

2. Corrêa RR, Gilio DB, Cavellani CL, et al. Placental morphometrical and histopathology changes in the different clinical presentations of hypertensive syndromes in pregnancy. Arch Gynecol Obstet 2008;277:201–6.

3. Stott D, Nzelu O, Nicolaides KH, Kametas NA. Maternal hemodynamics in normal pregnancy and in pregnancy affected by preeclampsia. Ultrasound Obstet Gynecol 2018;52:359–64.

4. Melchiorre K, Sharma R, Khalil A, Thilaganathan B. Maternal cardiovascular function in normal pregnancy: evidence of maladaptation to chronic volume overload. Hypertension 2016;67:754–62.

5. deMartelly VA, Dreixler J, Tung A, et al. Long-term postpartum cardiac function and its association with preeclampsia. J Am Heart Assoc 2021;10:e018526.

6. Lo CCW, Lo ACQ, Leow SH, et al. Future cardiovascular disease risk for women with gestational hypertension: a systematic review and meta-analysis. J Am Heart Assoc 2020;9:e013991.

7. Khosla K, Heimberger S, Nieman KM, et al. Long-term cardiovascular disease risk in women after hypertensive disorders of pregnancy: recent advances in hypertension. Hypertension 2021;78:927–35.

8. Erez O, Romero R, Jung E, et al. Preeclampsia and eclampsia: the conceptual evolution of a syndrome. Am J Obstet Gynecol 2022;226:S786–803.

9. Melchiorre K, Sutherland G, Sharma R, Nanni M, Thilaganathan B. Mid-gestational maternal cardiovascular profile in preterm and term pre-eclampsia: a prospective study. BJOG 2013;120:496–504.

10. Di Pasquo E, Ghi T, Dall'Asta A, et al. Maternal cardiac parameters can help in differentiating the clinical profile of preeclampsia and in predicting progression from mild to severe forms. Am J Obstet Gynecol 2019;221. 633.e1–9.

11. Guy GP, Ling HZ, Garcia P, Poon LC, Nicolaides KH. Maternal cardiac function at 35-37 weeks' gestation: prediction of pre-eclampsia and gestational hypertension. Ultrasound Obstet Gynecol 2017;49:61–6.

12. Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. Hypertension 2008;52:873–80.

13. Tay J, Foo L, Masini G, et al. Early and late preeclampsia are characterized by high cardiac output, but in the presence of fetal growth restriction, cardiac output is low: insights from a prospective study. Am J Obstet Gynecol 2018;218. 517.e1–12.

14. Foo FL, Mahendru AA, Masini G, et al. Association between prepregnancy cardiovascular function and subsequent preeclampsia or fetal growth restriction. Hypertension 2018;72:442–50.

15. Bosio PM, McKenna PJ, Conroy R, O'Herlihy C. Maternal central hemodynamics in hypertensive disorders of pregnancy. Obstet Gynecol 1999;94:978–84.

16. Ling HZ, Garcia Jara P, Nicolaides KH, Kametas NA. Effect of maternal age on cardiac adaptation in pregnancy. Ultrasound Obstet Gynecol 2021;58:285–92.

17. Ling HZ, Jara PG, Nicolaides KH, Kametas NA. Impact of maternal height, weight at presentation and gestational weight gain on cardiac adaptation in pregnancy. Ultrasound Obstet Gynecol 2022;60:523–31.

18. Ling HZ, Guy GP, Bisquera A, Poon LC, Nicolaides KH, Kametas NA. The effect of parity on longitudinal maternal hemodynamics. Am J Obstet Gynecol 2019;221. 249.e1–14.

19. Ling HZ, Jara PG, Bisquera A, Poon LC, Nicolaides KH, Kametas NA. Effect of race on longitudinal central hemodynamics in pregnancy. Ultrasound Obstet Gynecol 2020;56:37–43.

20. Pottel H, Björk J, Courbebaisse M, et al. Development and validation of a modified full age spectrum creatinine-based equation to estimate glomerular filtration rate: a cross-sectional analysis of pooled data. Ann Intern Med 2021;174:183–91.

21. Kagan KO, Wright D, Spencer K, Molina FS, Nicolaides KH. First-trimester screening for trisomy 21 by free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-a: impact of maternal and pregnancy characteristics. Ultrasound Obstet Gynecol 2008;31:493–502.

22. Wright D, Wright A, Nicolaides KH. The competing risk approach for prediction of preeclampsia. Am J Obstet Gynecol 2020;223:12–23. e7.

23. Ling HZ, Guy GP, Bisquera A, Nicolaides KH, Kametas NA. Maternal cardiac adaptation and fetal growth. Am J Obstet Gynecol 2021;224. 601.e1–18.

24. Robinson HP, Fleming JE. A critical evaluation of sonar "crown-rump length" measurements. Br J Obstet Gynaecol 1975;82:702–10.

25. Ling HZ, Gallardo-Arozena M, Company-Calabuig AM, Nicolaides KH, Kametas NA. Clinical validation of bioreactance for the measurement of cardiac output in pregnancy. Anaesthesia 2020;75:1307–13.

26. Bower S, Vyas S, Campbell S, Nicolaides KH. Color doppler imaging of the uterine artery in pregnancy: normal ranges of impedance to blood flow, mean velocity and volume of flow. Ultrasound Obstet Gynecol 1992;2:261–5.

27. Brown MA, Magee LA, Kenny LC, et al. Hypertensive disorders of pregnancy: Isshp classification, diagnosis, and management recommendations for international practice. Hypertension 2018;72:24–43.

28. Nicolaides KH, Wright D, Syngelaki A, Wright A, Akolekar R. Fetal medicine foundation fetal and neonatal population weight charts. Ultrasound Obstet Gynecol 2018;52:44–51.

29. Meah VL, Cockcroft JR, Backx K, Shave R, Stöhr EJ. Cardiac output and related haemodynamics during pregnancy: a series of meta-analyses. Heart 2016;102:518–26.

30. de Haas S, Ghossein-Doha C, van Kuijk SM, van Drongelen J, Spaanderman ME. Physiological adaptation of maternal plasma volume during pregnancy: a systematic review and meta-analysis. Ultrasound Obstet Gynecol 2017;49:177–87.

31. Easterling TR, Benedetti TJ, Schmucker BC, Millard SP. Maternal hemodynamics in normal and preeclamptic pregnancies: a longitudinal study. Obstet Gynecol 1990;76:1061–9.

32. Lee RM, Dickhout JG, Sandow SL. Vascular structural and functional changes: their association with causality in hypertension: models, remodeling and relevance. Hypertens Res 2017;40:311–23.

33. Nzelu D, Dumitrascu-Biris D, Nicolaides KH, Kametas NA. Chronic hypertension: first-trimester blood pressure control and likelihood of severe hypertension, preeclampsia, and small for gestational age. Am J Obstet Gynecol 2018;218. 337.e1–7.

34. Julius S. Transition from high cardiac output to elevated vascular resistance in hypertension. Am Heart J 1988;116:600–6.

35. Simmons LA, Gillin AG, Jeremy RW. Structural and functional changes in left ventricle during normotensive and preeclamptic pregnancy. Am J Physiol Heart Circ Physiol 2002;283:H1627–33.

36. Melchiorre K, Sutherland GR, Watt-Coote I, Liberati M, Thilaganathan B. Severe myocardial impairment and chamber dysfunction in preterm preeclampsia. Hypertens Pregnancy 2012;31:454–71.

37. Ferguson S, Teodorescu MC, Gangnon RE, et al. Factors associated with systemic hypertension in asthma. Lung 2014;192:675–83.

38. Nardin C, Maki-Petaja KM, Miles KL, et al. Cardiovascular phenotype of elevated blood pressure differs markedly between young males and females: the enigma study. Hypertension 2018;72:1277–84.

39. Inoue T, Iseki K, Iseki C, Kinjo K, Ohya Y, Takishita S. Higher heart rate predicts the risk of developing hypertension in a normotensive screened cohort. Circ J 2007;71:1755–60.
40. Shigetoh Y, Adachi H, Yamagishi S, et al. Higher heart rate may predispose to obesity and diabetes mellitus: 20-year prospective study in a general population. Am J Hypertens 2009;22:151–5.
41. Behrens I, Basit S, Melbye M, et al. Risk of post-pregnancy hypertension in women with a history of hypertensive disorders of pregnancy: nationwide cohort study. BMJ 2017;358:j3078.
42. Khaw A, Kametas NA, Turan OM, Bamfo JE, Nicolaides KH. Maternal cardiac function and uterine artery doppler at 11-14 weeks in the prediction of pre-eclampsia in nulliparous women. BJOG 2008;115:369–76.
43. De Paco C, Kametas N, Rencoret G, Strobl I, Nicolaides KH. Maternal cardiac output between 11 and 13 weeks of gestation in the prediction of preeclampsia and small for gestational age. Obstet Gynecol 2008;111:292–300.
44. Sağol S, Özkinay E, Öztekin K, Özdemir N. The comparison of uterine artery doppler velocimetry with the histopathology of the placental bed. Aust N Z J Obstet Gynaecol 1999;39:324–9.
45. Vázquez Blanco M, Roisinblit J, Grosso O, et al. Left ventricular function impairment in pregnancy-induced hypertension. Am J Hypertens 2001;14:271–5.
46. Valensise H, Novelli GP, Vasapollo B, et al. Maternal diastolic dysfunction and left ventricular geometry in gestational hypertension. Hypertension 2001;37:1209–15.

Author and article information

From the Fetal Medicine Research Institute, King's College London, Denmark Hill, London.

Received Oct. 3, 2022; revised Nov. 21, 2022; accepted Nov. 28, 2022.

Research data are not shared.

The authors report no conflict of interest.

This study was supported by a grant from the Fetal Medicine Foundation (charity number 1037116).

Corresponding author: Nikos A. Kametas, MD. nick.kametas@kcl.ac.uk