OBSTETRICS

The effect of parity on longitudinal maternal hemodynamics

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BACKGROUND: Parous women have a lower risk for pregnancy complications, such as preeclampsia or delivery of small-for-gestational-age neonates. However, parous women are a heterogeneous group of patients because they contain a low-risk cohort with previously uncomplicated pregnancies and a high-risk cohort with previous pregnancies complicated by preeclampsia and/or small for gestational age. Previous studies examining the effect of parity on maternal hemodynamics, including cardiac output and peripheral vascular resistance, did not distinguish between parous women with and without a history of preeclampsia or small for gestational age and reported contradictory results.

OBJECTIVE: The objective of the study was to compare maternal hemodynamics in nulliparous women and in parous women with and without previous preeclampsia and/or small for gestational age.

STUDY DESIGN: This was a prospective, longitudinal study of maternal hemodynamics, assessed by a bioreactance method, measured at 11^{+0} to 13^{+6}, 19^{+0} to 24^{+0}, 30^{+0} to 34^{+0}, and 35^{+0} to 37^{+0} weeks' gestation in 3 groups of women. Group 1 was composed of parous women without a history of preeclampsia and/or small for gestational age ($n = 632$), group 2 was composed of nulliparous women ($n = 829$), and group 3 was composed of parous women with a history of preeclampsia and/or small for gestational age ($n = 113$). A multilevel linear mixed-effects model was performed to compare the repeated measures of hemodynamic variables controlling for maternal characteristics, medical history, and development of preeclampsia or small for gestational age in the current pregnancy.

RESULTS: In groups 1 and 2, cardiac output increased with gestational age to a peak at 32 weeks and peripheral vascular resistance showed a reversed pattern with its nadir at 32 weeks; in group 1, compared with group 2, there was better cardiac adaptation, reflected in higher cardiac output and lower peripheral vascular resistance. In group 3 there was a hyperdynamic profile of higher cardiac output and lower peripheral vascular resistance at the first trimester followed by an earlier sharp decline of cardiac output and increase of peripheral vascular resistance from midgestation. The incidence of preeclampsia and small for gestational age was highest in group 3 and lowest in group 1.

CONCLUSION: There are parity-specific differences in maternal cardiac adaptation in pregnancy.

Key words: bioreactance, cardiac output, fetal growth restriction, hemodynamics, nulliparous, parity, parous, peripheral vascular resistance, placental insufficiency, preeclampsia, pregnancy, small for gestational age

Incidence and severity of pregnancy complications, such as preeclampsia (PE) and birth of small-for-gestational-age (SGA) neonates, are significantly higher in nulliparous, compared with parous women.[1–4] However, parous women are a heterogeneous group of patients because they contain a low-risk cohort with previously uncomplicated pregnancies and a high-risk cohort with previous pregnancies complicated by PE and/or SGA. The latter represents a group of women at high risk not only of pregnancy complications but also of cardiovascular morbidity and mortality in the decades after pregnancy.[5–12]

Contrary to maternal cardiovascular adaptation in normal pregnancy, which is characterized by a drop in peripheral vascular resistance (PVR), and an increase in cardiac output (CO), which peaks at midgestation,[13–15] in pregnancies complicated by PE and/or SGA, distinct hemodynamic profiles have been described.[16–22]

Women destined to develop PE after 36 weeks' gestation show a hyperdynamic state from the first trimester of pregnancy, with high CO and low PVR.[23,24] This is maintained throughout the preclinical phase of the disease. Furthermore, a hemodynamic crossover with markedly reduced CO and significant vasoconstriction during the clinical disease was observed.[23]

On the other hand, pregnancies complicated by SGA, with or without hypertension, have consistently low CO and high PVR throughout gestation.[16–20,22,25,26] Previous studies comparing maternal cardiovascular adaptation between nulliparous and parous women have shown inconsistent results, with some studies showing better[27–29] and others reporting worse hemodynamic profiles in parous compared with nulliparous women.[30] None of the abovementioned studies stratified the parous women according to whether their previous pregnancies were complicated by PE and/or SGA.

We hypothesized that parous women without previous PE and/or SGA would have the best hemodynamic profile and pregnancy outcomes compared with nulliparous and parous women with previous PE or SGA. The objective of this study was to compare maternal hemodynamics between these 3 groups of pregnant women.

Materials and Methods

Study population

This was a prospective, longitudinal study assessing maternal hemodynamics

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AJOG at a Glance

Why was this study conducted?

The aim of this study was to compare maternal hemodynamics between nulliparous and parous women with and without previous preeclampsia or small for gestational age.

Key findings

Parous women without a history of preeclampsia or birth of small-for-gestational-age neonates have the most ideal hemodynamic profile during pregnancy with the greatest cardiac output and lowest peripheral vascular resistance; nulliparous women demonstrate a similar trend over gestation but with lower cardiac output and higher peripheral vascular resistance. Parous women with a history of preeclampsia or small for gestational age have decreasing cardiac output and increasing peripheral vascular resistance from midgestation.

What does this add to what is known?

There are parity-specific differences in maternal hemodynamic adaptation to pregnancy.

in women with singleton pregnancies attending routine pregnancy care at 11^{+0} to 13^{+6} weeks' gestation, conducted between November 2015 and May 2016 in 6 maternity hospitals in the United Kingdom. This is a substudy of the Aspirin for Evidence-Based Preeclampsia Prevention study; this multicenter study involved first-trimester screening for PE by maternal factors and biomarkers,[31] and those identified by screening to be at high risk of PE were invited to participate in a trial of aspirin vs placebo.[32]

In our study women undergoing screening were approached to participate in the hemodynamics study irrespective of their screening status, and therefore, they represent an unbiased sample of a general obstetric population, in which screen-positive and -negative women are randomly distributed within the subgroups of this study. Ethical approval was granted by the National Health Service Research Ethics Committee (REC reference 13/LO/1479).

In our study, we recorded maternal demographic characteristics and medical history and performed hemodynamic studies at 11^{+0} to 13^{+6}, 19^{+0} to 24^{+0}, 30^{+0} to 34^{+0}, and 35^{+0} to 37^{+0} weeks' gestation.

Maternal factors

Maternal factors recorded included age, height, weight at each visit, racial origin (white, black, south Asian, east Asian, and mixed), method of conception (spontaneous or use of assisted reproductive technologies), cigarette smoking during pregnancy, medical history, medications, parity, and obstetric history (nulliparous, parous with and without previous PE and/or SGA).

Maternal hemodynamics

A noninvasive, bioreactance method (NICOM; Cheetah Medical Ltd, Maidenhead, Berkshire, United Kingdom) validated in both pregnant and nonpregnant populations[33–35] was used to assess maternal hemodynamics. Bioreactance uses the relative phase shifts occurring when an alternating electrical current traverses the thoracic cavity to calculate the stroke volume (SV). Four dual-surface electrodes were applied across the maternal back, and after 15 minutes of rest, the cardiac variables (CO, SV, heart rate [HR], PVR, and mean arterial pressure [MAP]) were recorded with the women in a sitting position for 10 minutes at 30 second intervals (20 cycles). The averages of the final 10 cycles of hemodynamic recordings were included in the analysis.

Definitions

We classified the study population into 3 groups: group 1, parous without a history of PE or SGA; group 2, nulliparous; and group 3, parous with a history of PE or SGA. The definitions of nonproteinuric gestational hypertension and PE were those of the International Society for the Study of Hypertension in Pregnancy.[36]

Birthweight percentile for gestational age was derived from the Fetal Medicine Foundation reference range.[37] SGA was defined as a birthweight less than the fifth percentile for gestational age. Neonatal morbidity was defined by the presence of any one of respiratory distress syndrome (requiring administration of surfactant and ventilation), need for ventilation (need of continuous positive airway pressure or intubation), neonatal sepsis (confirmed bacteremia in cultures), necrotizing enterocolitis requiring surgical intervention, or neonatal hypoglycemia (blood glucose <46.8 mg/dL).

Inclusion and exclusion criteria

The inclusion criteria were singleton pregnancies resulting in the birth of morphologically normal live births or stillbirths at or after 24 weeks' gestation and attendance for hemodynamic studies for at least 3 of the 4 visits. Exclusion criteria were maternal age <18 years, preexisting maternal cardiac conditions, fetal abnormalities, incomplete follow-up, and termination of pregnancy or miscarriage.

Statistical analysis

Maternal demographics, medical history, medication use, and pregnancy outcomes between the 3 groups were compared using the χ^2 test or Fisher exact test for categorical variables. The Kolmogorov-Smirnov test was used to assess the normality of the distribution of the numerical data.

For the comparison of continuous data, the Kruskal-Wallis or the 1-way analysis of variance tests with post hoc analysis was used for not normally and normally distributed data, respectively. Data are presented as median (interquartile range) and mean (SD) or for not normally and normally distributed continuous variables and as n (percentage) for categorical variables.

The distribution of maternal weight, CO, SV, MAP, and PVR were made Gaussian after $\log_{10}$ transformation. For

the repeated-measures analysis of the maternal hemodynamic variables, controlling for demographic characteristics, past medical history, medication use, pregnancy outcomes, and time (the 4 visits), a multilevel linear mixed-effects model was performed.

The fixed-effect component included time (the 4 visits), study group, maternal age, $\log_{10}$ weight, height, race (white, black, south and east Asian, and mixed), conception, smoking, family history of PE, medical comorbidities including chronic hypertension, autoimmune disease, asthma, diabetes mellitus type 1 and type 2, medication use (labetalol, nifedipine or methyldopa, prednisolone), development of PE and SGA, and first-order interaction between time and parity group.

The likelihood ratio test was used to define the best multilevel model (including only the random slope for time or random intercept vs including both the random intercept and slope) and to compare it with the base-model (with no random effects). The estimated marginal means of each hemodynamic variable at each race/time combination are presented.

The software program IBM SPSS Statistics 23 (SPSS Inc, Chicago, IL) was used for the statistical analysis (IBM Corp, released 2015; IBM SPSS Statistics for Windows, version 23.0, Armonk, NY).

Results

Study population

The study population of 1574 women included 632 in group 1, 829 in group 2, and 113 in group 3. The maternal characteristics and pregnancy outcomes for the 3 groups at the screening visit are shown and compared in Table 1.

In group 1, compared with group 2, maternal age and weight were higher, there was a higher incidence of women of black racial origin, smoking, spontaneous conception, and a lower incidence of PE and need for labetalol. Groups 1 and 2, compared with group 3, were taller and less likely to be smokers, to have a family history of PE, and more likely to be of white race. Furthermore, groups 1 and 2 compared with group 3, had less prevalence of medical comorbidities, such as chronic hypertension and preexisting diabetes, less prevalence of PE and preterm PE, and of delivery of neonate with birthweight below the fifth percentile and less need for treatment with nifedipine or methyldopa.

Group 3 delivered the smallest infants compared with groups 1 and 2. Women in group 2, compared with group 1, had a higher rate of neonatal morbidity.

Multilevel linear mixed-effects models

The fixed effects of the multilevel models are shown in Tables 2 and Supplemental Tables 1 and 2 and in Figures 1 and 2.

Maternal demographic characteristics medical history

Increasing maternal age was associated with a decrease in Log_{10} CO, Log_{10} SV, HR, and higher Log_{10} MAP. Increasing maternal height was associated with higher Log_{10} CO, Log_{10} SV, and lower HR and Log_{10} PVR. Maternal Log_{10} weight was associated with higher Log_{10} CO, Log_{10} SV, HR, and Log_{10} MAP. Compared with white race, black, south Asian, and east Asian race were associated with lower Log_{10} CO, Log_{10} SV, and Log_{10} MAP and greater Log_{10} PVR in Asians and HR in blacks.

Maternal chronic hypertension, use of labetalol, nifedipine, or methyldopa were associated with higher Log_{10} MAP and Log_{10} PVR. Use of prednisolone was associated with higher Log_{10}SV. Autoimmune disease was associated with lower Log_{10} CO and higher Log_{10} PVR and Log_{10} MAP. The development of PE was associated with lower HR and higher Log_{10} MAP. The delivery of SGA neonates was associated with lower HR and higher Log_{10} MAP.

There was no significant contribution in any of the models from spontaneous conception, family history of PE, and diabetes mellitus type 1 or 2. There was significant interaction between parity groups and time for all the cardiac variables.

Changes with time after controlling for maternal characteristics and outcome

Log_{10} CO in both groups 1 and 2 increased during the first 3 visits and declined thereafter, with group 1 demonstrating greater Log_{10} CO throughout gestation (Figure 1, Table 2, and Supplemental Table 3). Log_{10} PVR (Figure 1, Table 2, and Supplemental Table 3) and Log_{10} MAP (Figure 2, Table 2, and Supplemental Table 3) demonstrated in both groups 1 and 2 a similar decline with gestation, with group 1 having lower values at all time points. Log_{10} SV in both groups 1 and 2 increased from the first to second visit, after which in the former it plateaued from the second to third visit and declined after that, whereas in the latter group, it demonstrated a linear decrease from the second visit onward (Figure 2, Table 2, and Supplemental Table 3).

HR in both groups 1 and 2 demonstrated a similar increase with gestation during the first 3 visits, but contrary to group 1, which demonstrated a further small increase, HR of group 2 declined in the fourth visit (Figure 2, Table 2, and Supplemental Table 3).

In group 3, Log_{10} CO demonstrated a sharp decline and Log_{10} PVR showed a linear increase after the second visit (Figure 1, Table 2, and Supplemental Table 3) At the first and second visit, compared with group 1, Log_{10} CO was at a higher level, whereas Log_{10} PVR was lower. However, in the subsequent visits, group 3 demonstrated lower Log_{10} CO (Figure 1, Table 2, and Supplemental Table 3) and higher Log_{10} PVR (Figure 1, Table 2, and Supplemental Table 3) when compared with group 1.

Log_{10} SV in groups 1 and 3 showed an opposing trend, with the latter group starting at a higher point in the first visit, followed by a small and then a sharp decline from the second visit onward (Figure 2, Table 2, and Supplemental Table 3). On the contrary, Log_{10} SV in group 1 showed an increase from the first visit to the third visit and a decline at the fourth visit only.

HR in groups 1 and 3 shared similar incremental trends until the third visit, with group 3 being significantly higher than group 1 in the second visit (Figure 2, Table 2, and Supplemental Table 3). Log_{10} MAP in both groups 1 and 3 showed similar linear decrease from the first to the third visit, followed

TABLE 1
Demographic characteristics and pregnancy outcome in the study population

Variables	Parous, no previous PE/SGA n=632	Nulliparous (n = 829)	Parous, previous PE/SGA n=113	*P* value
Age, y, mean (SD)	32.0 (4.9)[a]	30.3 (5.5)	31.6 (5.8)[b]	< .0001
Weight at booking, kg, median (IQR)	70.0 (61.5 to 82.0)[c]	67.3 (59.3 to 79.0)	69.0 (59.3 to 86.4)[e]	.006
BMI at booking >35, n, %	61 (9.7)[c]	56 (6.8)[d]	22 (19.5)[e]	< .0001
Height, cm, mean (SD)	165.0 (6.4)	164.8 (6.6)[f]	162.4 (6.8)[e]	.001
Smoking, n, %	45 (7.1)[c]	32 (3.9)[g]	15 (13.3)[b]	< .0001
Family history of PE, n, %	29 (4.6)	56 (6.8)[f]	14 (12.4)[h]	.005
Spontaneous conception, n, %	625 (98.9)[a]	791 (95.4)	112 (99.1)	< .0001
Ethnicity				
White, n, %	456 (72.2)[i]	642 (77.4)[f]	67 (59.3)[b]	.000
Black, n, %	110 (17.4)[i]	109 (13.1)	28 (24.8)[e]	.002
South Asian, n, %	31 (4.9)	41 (4.9)	9 (8.0)	.371
East Asian, n, %	16 (2.5)	18 (2.2)	1 (0.9)	.544
Mixed, n, %	19 (3.0)	19 (2.3)[g]	8 (7.0)[e]	.018
Chronic hypertension, n, %	13 (2.1)	10 (1.2)[f]	9 (8.0)[b]	< .0001
Asthma, n, %	6 (0.9)	15 (1.8)[g]	4 (3.5)	.097
Preexisting diabetes, n, %	4 (0.6)	2 (0.2)[g]	3 (2.7)[e]	.006
Autoimmune, n, %	1 (0.2)	6 (0.7)	0 (0.0)	.209
Labetalol, n, %	22 (3.5)[i]	51 (6.2)[f]	12 (10.6)	.003
Nifedipine or methyldopa, n, %	4 (0.6)	13 (1.6)[d]	7 (6.2)[e]	< .0001
Prednisolone, n, %	4 (0.6)	2 (0.2)	7 (6.2)	.407
Pregnancy outcomes				
PE, n, %	8 (1.3)[c]	34 (4.1)[d]	9 (8.0)[b]	< .0001
Preterm PE <37 weeks, n, %	1 (0.2)[c]	8 (1.0)[d]	2 (1.8)[h]	.001
Gestational hypertension, n, %	15 (2.4)	40 (4.8)	5 (4.4)	.050
Gestational diabetes, n, %	27 (4.3)	40 (4.8)	7 (6.2)	.654
Birth <37 weeks, n, %	10 (1.6)[c]	38 (4.6)	8 (7.1)[b]	.001
Gestational age at birth, median (IQR)	39.7 (39.0 to 40.7)[i]	40.0 (39.0 to 40.9)[d]	39.0 (38.2 to 40.1)[b]	< .0001
Neonatal outcomes				
Birthweight, g	3483.3 (504.9)[a]	3323.4 (551.5)[f]	3122.2 (591.5)[b]	< .0001
Birthweight z-score	0.14 (1.02)[a]	−0.27 (1.09)[g]	−0.55 (1.29)[b]	< .0001
Birthweight percentile	57.6 (29.2 to 80.5)[a]	40.4 (17.7 to 69.3)[d]	28.5 (8.5 to 61.2)[b]	< .0001
Birthweight <5th centile	31 (4.9)[c]	74 (8.9)[f]	20 (17.7)[b]	< .0001
Perinatal mortality	1 (0.2)	3 (0.3)	1 (0.9)	.573
Neonatal morbidity, n, %[j]	18 (2.8)[c]	49 (5.9)	4 (3.5)	.017

The 3 groups were compared using the χ^2 test or Fisher exact test for categorical variables. The Kruskal-Wallis test or the 1-way analysis of variance tests with post hoc analysis was used for not normally and normally distributed data, respectively.

BMI, body mass index; *IQR*, interquartile range; *PE*, preeclampsia; *SGA*, small for gestational age.

[a] $P < .001$, group 1 vs group 2; [b] $P < .001$, group 1 vs group 3; [c] $P < .01$, group 1 vs group 2; [d] $P < .001$, group 2 vs group 3; [e] $P < .01$, group 1 vs group 3; [f] $P < .01$, group 2 vs group 3; [g] $P < .05$, group 2 vs group 3; [h] $P < .05$, group 1 vs group 3; [i] $P < .05$, group 1 vs group 2; [j] Includes respiratory distress syndrome, need for ventilation, sepsis, necrotizing enterocolitis, and neonatal hypoglycemia.

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

Variables	Visit 1	Visit 2	Visit 3	Visit 4
Log_{10} cardiac output				
Group 1	0.706 (0.678–0.734)	0.733 (0.706–0.761)	0.758[a] (0.730–0.786)	0.743[a] (0.715–0.771)
Group 2	0.700[b] (0.672–0.727)	0.725[c] (0.698–0.752)	0.730 (0.703–0.757)	0.720[c] (0.693–0.747)
Group 3	0.737[d] (0.704–0.770)	0.758[e] (0.725–0.790)	0.736[e] (0.703–0.768)	0.687[f] (0.654–0.720)
Log_{10} peripheral vascular resistance				
Group 1	3.225 (3.188–3.262)	3.181[g] (3.144–3.217)	3.154[a] (3.117–3.191)	3.181[a] (3.145–3.218)
Group 2	3.228[c] (3.192–3.264)	3.196[b] (3.160–3.232)	3.188 (3.152–3.224)	3.210[h] (3.173–3.246)
Group 3	3.194[d] (3.154–3.235)	3.156[e] (3.116–3.196)	3.189[d] (3.148–3.229)	3.235[f] (3.194–3.275)
Log_{10} stroke volume				
Group 1	1.854 (1.811–1.898)	1.868 (1.824–1.911)	1.870[a] (1.826–1.913)	1.853[i] (1.810–1.897)
Group 2	1.854[c] (1.810–1.897)	1.864 (1.820–1.907)	1.847 (1.803–1.890)	1.840[c] (1.797–1.8830
Group 3	1.889[d] (1.841–1.936)	1.882 (1.835–1.929)	1.848 (1.801–1.896)	1.807[f] (1.759–1.854)
Heart rate				
Group 1	82.679 (81.034–84.324)	85.493 (83.878–87.109)	90.014 (88.401–91.627)	90.430[a] (88.815–92.044)
Group 2	81.712 (80.163–83.262)	84.883 (83.361–86.406)	89.232 (87.710–90.753)	88.669 (87.139–90.198)
Group 3	82.476 (80.174–84.779)	87.959 (85.770–90.147)	90.425 (88.252–92.598)	89.072 (86.890–91.255)
Log_{10} mean arterial pressure				
Group 1	2.008 (1.991–2.024)	1.991[a] (1.975–2.007)	1.988[a] (1.972–2.004)	2.000[a] (1.984–2.016)
Group 2	2.009 (1.993–2.024)	2.001[c] (1.985–2.017)	1.998 (1.982–2.014)	2.010[h] (1.994–2.026)
Group 3	2.009 (1.992–2.025)	1.995[e] (1.978–2.012)	1.999[d] (1.983–2.016)	2.000 (1.983–2.017)

[a] $P < .001$, group 1 vs group 2; [b] $P < .001$, group 2 vs group 3; [c] $P < .01$, group 2 vs group 3; [d] $P < .01$, group 1 vs group 3; [e] $P < .05$, group 1 vs group 3; [f] $P < .001$, group 1 vs group 3; [g] $P < .01$, group 1 vs group 2; [h] $P < .05$, group 2 vs group 3; [i] $P < .05$, group 1 vs group 2.

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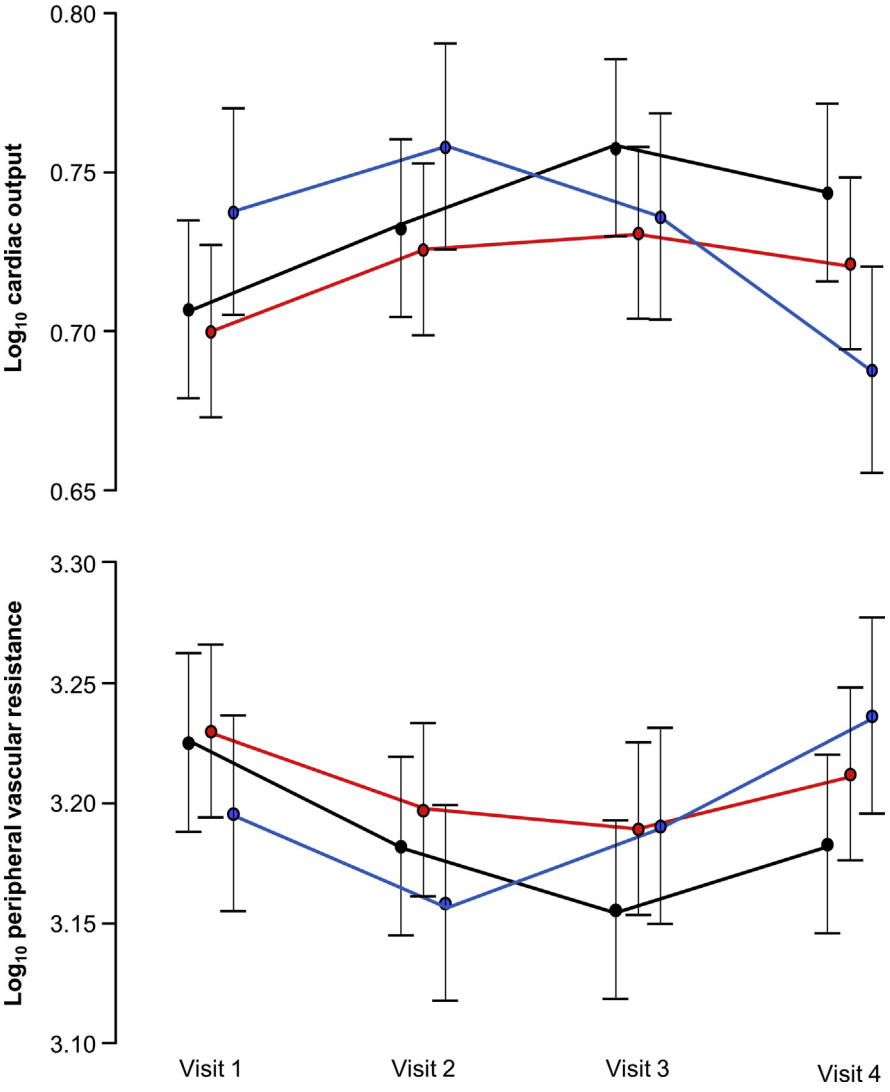
FIGURE 1
Model for Log_{10} cardiac output and Log_{10} peripheral vascular resistance



Linear mixed-effects model with estimated marginal means and 95% confidence intervals for Log_{10} cardiac output and Log_{10} peripheral vascular resistance in parous women without previous preeclampsia or small for gestational age (*black line*) compared with nulliparous women (*red line*) and with parous women with previous preeclampsia or small for gestational age (*blue line*).

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by an increase toward the fourth visit, with group 3 having a persistently higher Log_{10} MAP than group 1 throughout gestation (Figure 2, Table 2, and Supplemental Table 3).

Comment

Main findings of the study

The results of this study have demonstrated that the hemodynamic profile in the current pregnancy is different in parous women without a previous history of PE and/or SGA compared with nulliparous women and parous women with a previous history of PE and/or SGA.

The most favorable profile with an increase in CO and decrease in PVR with advancing gestation was observed in parous women without previous PE and/or SGA; the increase in CO was associated with an increase in both SV and HR. In nullipara there was also an increase in CO and decrease in PVR, but the magnitude of the changes was less; in these women HR was consistently lower and SV declined after the second visit.

The most unfavorable hemodynamic profile was observed in parous women with previous PE and/or SGA in which in the first half of pregnancy, there was a high CO and low PVR, but subsequently there was an abrupt decline in CO and an increase in PVR.

The incidence of PE and SGA in the current pregnancy was highest in the parous women with previous PE and/or SGA and lowest in the parous women without previous PE and/or SGA.

Interpretation of findings

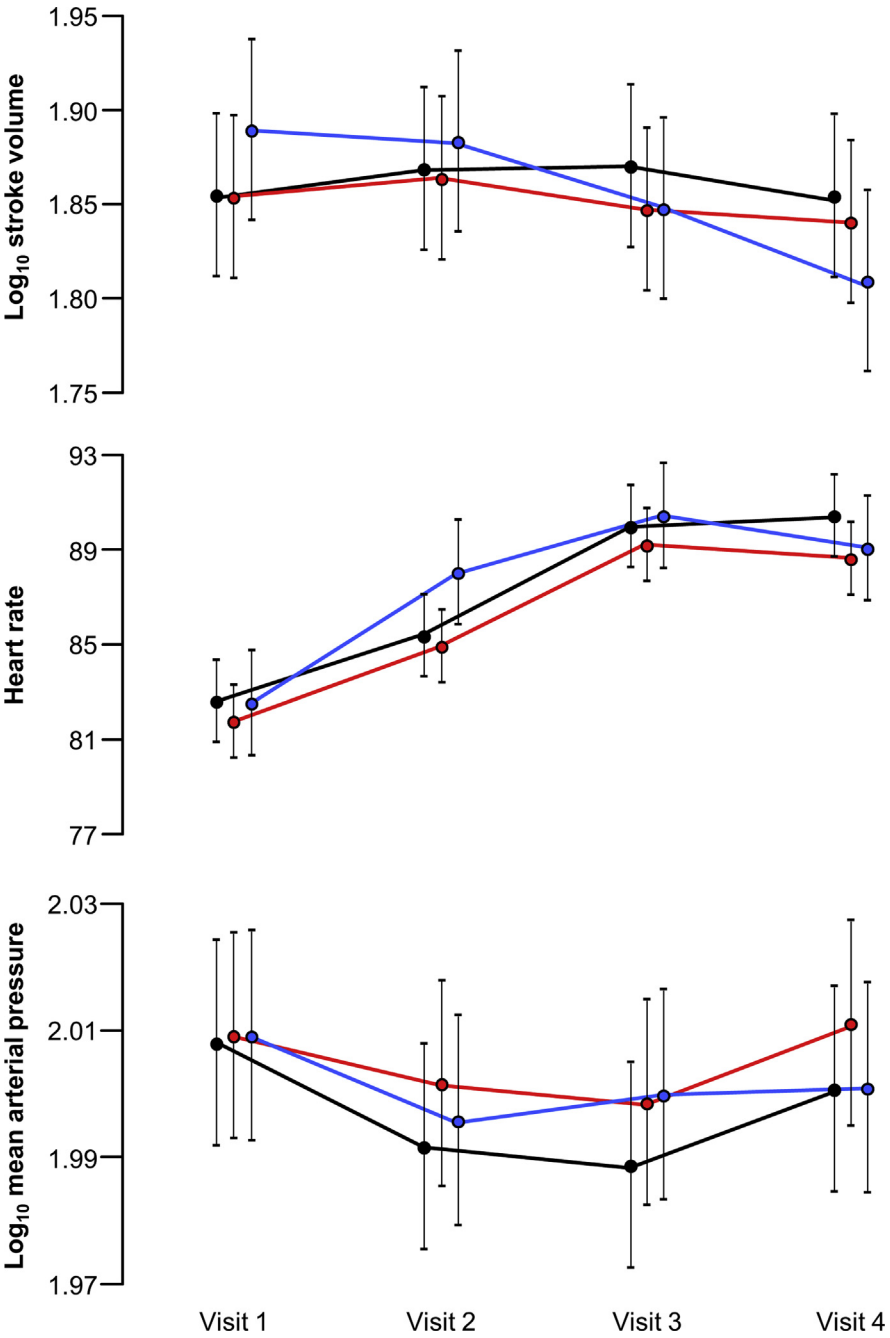
Maternal cardiovascular adaptation in normal pregnancy involves a decline in PVR that triggers a series of compensatory mechanisms, including an increase in maternal HR[13,15,38] and in SV[39] leading to a 40% increase in CO that peaks around 32 weeks' gestation.[14] Women who fail to achieve these adaptational changes have been shown to have higher rates of PE and/or SGA[40–42] and a higher risk for cardiovascular disease.[5–12]

Group 1 represents a subset of women who have successfully completed previous pregnancies with good outcomes and exhibit an optimal cardiovascular adaptation in the current pregnancy. There are 2 possible explanations for the optimal performance of this group. First, they have an inherent low risk for cardiovascular disease and adapt well to the cardiovascular stress of consecutive pregnancies. Second, their good response in their index pregnancy is the consequence of cardiac remodeling from their previous healthy pregnancy.[43–45]

There is evidence that healthy pregnancy-related cardiac remodeling persists for several years.[46–48] Such persistent remodeling has also been reported in individuals undertaking temporary endurance training.[49–51]

Group 3 represents the cohort with the least favorable adaptive response to pregnancy. The cardiovascular screening test of these women in their previous pregnancies has failed, and they may have an underlying cardiovascular deficit, causing a failure in adaptation in

FIGURE 2
Model for Log_{10} stroke volume, heart rate, and Log_{10} mean arterial pressure



Linear mixed-effects model with estimated marginal means and 95% confidence intervals for Log_{10} stroke volume, heart rate, and Log_{10} mean arterial pressure in parous women without previous preeclampsia or small for gestational age (*black line*) compared with nulliparous women (*red line*) and with parous women with previous preeclampsia or small for gestational age (*blue line*).

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situations of circulatory stress. Furthermore, previous pregnancies complicated by PE and/or SGA may have inflicted additional insults to their preexisting vulnerable cardiac function[41,52] persisting after pregnancy and increasing their susceptibility to cardiovascular decompensation.[9,53,54]

After delivery, more than half of the women with previous preterm PE have asymptomatic stage B heart failure and 40% develop essential hypertension within 2 years of delivery.[46] Therefore, when the hearts of these women is at the edge of its reserve, any additional stress by yet another pregnancy would deplete its coping capabilities and result in maladaptation.

It is noteworthy that women in group 3 began with a hyperdynamic output state with significantly higher CO and lower PVR compared with groups 1 and 2. A similar pattern has been described in nonpregnant populations in the pre-hypertension state,[55] particularly in obesity-induced hypertension, which is more commonly observed in individuals younger than 60 years of age.[56]

In our cohort, the proportion of women who booked with severe obesity (BMI above 35 kg/m^2) in group 3 was 2 and 3 times more when compared with groups 1 and 2. It has been reported that overactivity of the renin-angiotensin-aldosterone system is the main pathophysiology of obesity-induced hypertension,[57] which explains the highest starting SV and CO observed in group 3.

Initially, the overtly high CO causes a compensatory vasodilatation to maintain a near-normal MAP, but the excessively dilated terminal arterioles would expose the endothelium to high shear stress, exhausting the vasodilatory rescue functions and resulting in damaged endothelium.[58] The endothelial damage results in the loss of plasma volume to the interstitial space and a gradual crossover to a low-cardiac output and vasoconstricted state.[23]

Group 2 is a mixed cohort comprising women that at the end of their pregnancies will be classified either in group 1 or 3. Therefore, their hemodynamic profile reflects the combination of good and bad cardiovascular reserve in this unscreened cohort for cardiovascular risk.

Comparison with findings in previous studies

Previous studies comparing the hemodynamic profile and pregnancy between parous and nulliparous women did not

stratify parous women according to the outcomes of their previous pregnancies. Our findings in parous women without previous PE and/or SGA by comparison with nulliparous women are consistent with the results of previous studies that reported that in parous, compared with nulliparous women, maternal plasma volume increase is steeper and more prolonged during pregnancy,[59,60] blood pressure is lower,[61–64] and the incidence of SGA and PE is lower.[3,4]

In a previous study of women with a normal pregnancy outcome, we found that during the first-trimester CO, HR and SV were higher in parous than nulliparous women.[27] Several small studies, comprising 19–50 patients, reported that the hemodynamic profile of parous compared with nulliparous women was better or worse.[28–30]

Strengths and limitations of the study

Strengths of this study include first, the large sample size, second, the longitudinal assessment throughout pregnancy, and third, controlling in the mixed models for all those variables that may influence the hemodynamic variables, such as maternal demographic characteristics, medical history, and PE or SGA in the current pregnancy.

When planning studies assessing maternal hemodynamics, one needs to consider a plethora of variables that affect cardiac function. For example, gestational age, maternal height and weight, medical comorbidities (such as chronic hypertension, diabetes, asthma, autoimmune diseases, renal disease), medication (such as steroids, antihypertensives, metformin, beta-mimetics), and pregnancy outcomes (PE, fetal growth restriction) influence or are associated with maternal cardiac function variables.

One option is to remove some of the previously discussed confounders; however, this would result in first, removal of a large number of patients to the degree that the final sample is not representative of the initial population, second, removal of 1 parameter may influence interactions with other variables in the statistical model, and third, removal of 1 specific parameter is arbitrary and not based on any logical process of preference against other parameters. For example, would chronic hypertension have more of an impact compared with an asthmatic patient who is receiving steroids and beta-mimetics?

The second option is to allow all the population to be examined, controlling for the parameters that may influence the dependent variable. We have chosen the second approach because it is a more realistic representation of the overall population and it allows interactions to be highlighted.

A limitation of this study is that we did not examine the effect of grand multiparity because it has been associated with worse cardiovascular[65] and pregnancy outcomes.[2,66] This is because we had only 27 grand multipara and hence not adequately power for such comparisons. However, it is likely that any possible effect in our models is controlled by correction for maternal age because women with high parity and a long pregnancy interval also tend to be older.

Another limitation is that when reporting a previous pregnancy outcome, we did not examine different subgroups according to the severity of PE and fetal growth restriction and the gestational age at the onset of these conditions. However, such an attempt would necessitate the study of a much higher number of patients.

Conclusion

Our study has shown that the hemodynamic profile during pregnancy in parous women is different, depending on the outcome of previous pregnancies. Consequently, studies investigating the relationship between the hemodynamic profile and pregnancy outcome should stratify women according to the outcome of previous pregnancies. ■

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Supplementary results: multilevel linear mixed-effects models

The fixed- and random-effects of the best multilevel models are shown in Supplemental Table 1, and the estimated marginal means are shown in Table 2 and Figures 1 and 2.

For $Log_{10}CO$, a random intercept−random slope model provided a significantly better fit to the data than did the base model (LR, 670, degrees of freedom, 20, $P < .01$) or a random intercept model (LR, 12, degrees of freedom, 1, $P < 0.01$).

For $Log_{10}SV$, a random intercept−random slope model provided a significantly better fit to the data than did the base model (LR, 472, degrees of freedom, 20, $P < .01$) or a random intercept model (LR, 12, degrees of freedom, 1, $P < .01$).

For HR, a random intercept−random slope model provided a significantly better fit to the data than did the base model (LR, 1716, degrees of freedom, 21, $P < .01$) or a random intercept model (LR, 6, degrees of freedom, 1, $P < .025$).

For $Log_{10}PVR$, a random intercept−random slope model provided a significantly better fit to the data than did the base model (LR, 558, degrees of freedom, 21, $P < .01$) or a random intercept model (LR, 10, degrees of freedom, 1, $P = .01$).

For $Log_{10}MAP$, a random intercept model provided a significantly better fit to the data than did the base model (LR, 799, degrees of freedom, 25, $P < .01$) or a random intercept−random slope model (LR, 9, degrees of freedom, 1, $P < .01$).

CO, cardiac output; *HR*, heart rate; *LR*, likelihood ratio; *MAP*, mean arterial pressure; *PVR*, peripheral vascular resistance; *SV*, stroke volume.

SUPPLEMENTAL TABLE 1

Multilevel linear mixed-effects models for maternal hemodynamic variables: fixed effects

Parameter	Log_{10} cardiac output			Log_{10} peripheral vascular resistance			Log_{10} stroke volume		
Fixed part	Estimate	SE	*P* value	Estimate	SE	*P* value	Estimate	SE	*P* value
Intercept	0.227	0.045	<.0001	3.637	0.051	< 0.0001	1.052	0.050	< .0001
Age, y	−0.002	0.0003	< .0001				−0.0008	0.0003	.023
Height, cm	0.003	0.0002	< .0001	−0.003	0.0003	< 0.0001	0.004	0.0003	< .0001
Weight, kg	0.0007	0.0001	< .0001				0.0003	0.0001	.015
Race (reference, white)			< .0001			< 0.0001			< .0001
Black	−0.014	0.004	.003	0.007	0.005	0.156	−0.027	0.005	< .0001
South Asian	0.030	0.008	< .0001	0.025	0.009	0.005	−0.038	0.008	< .0001
East Asian	−0.047	0.011	< .0001	0.047	0.013	< 0.0001	−0.049	0.012	.0001
Mixed	−0.013	0.010	.189	0.0004	0.011	0.966	−0.010	0.011	.370
Smoking (reference, nonsmokers)									
Medical comorbidities (reference, no)									
Chronic hypertension				0.035	0.015	0.02			
Asthma									
Autoimmune	−0.061	0.026	.020	0.086	0.030	0.004			
Antihypertensives (reference, no)									
Labetalol				0.048	0.009	< 0.0001			
Nifedipine/methyldopa)				0.051	0.016	0.002			
Prednisolone (reference, no)							0.088	0.0431	.041
Preeclampsia (reference yes)									
Small for gestational age (reference, no)									
Groups (reference, nulliparous)			< .0001			< 0.0001			.036
Multiparous, previous PE/SGA	−0.032	0.010	.002	0.024	0.011	0.0301	−0.033	0.011	.002
Multiparous, no previous PE/SGA	0.023	0.005	< .0001	−0.0281	0.005	< 0.0001	0.013	0.005	.020
Time (4 visits)			< .0001			< 0.0001			< .0001
Interaction groups with time			< .0001			< 0.0001			< .0001

A multilevel linear mixed-effects model was performed for the repeated-measures analysis of the maternal hemodynamic variables. There was no significant contribution from smoking, chronic hypertension, asthma, preeclampsia, and small for gestational age on Log_{10} cardiac output and Log_{10} stroke volume. There was no significant contribution from age, Log_{10}weight, smoking, asthma, prednisolone, preeclampsia, and small for gestational age Log_{10} peripheral vascular resistance.

PE, preeclampsia; *SGA*, small for gestational age.

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SUPPLEMENTAL TABLE 2

Multilevel linear mixed-effects models for maternal hemodynamic variables: fixed effects

Parameter	Heart rate			Log_{10} mean arterial pressure		
Fixed part	Estimate	SE	*P* value	Estimate	SE	*P* value
Intercept	139.338	5.164	< .0001	1.878	0.003	< .0001
Age, y	−0.368	0.036	< .0001	0.0003	0.0001	.031
Height, cm	−0.274	0.032	< .0001			
Log_{10} weight (Log_{10}, kg)	0.097	0.012	< .0001	0.0007	0.000047	< .0001
Race (reference, white)			< .0001			.013
Black	2.762	0.557	< .0001	−0.006	0.002	.003
South Asian	1.442	0.922	.118	−0.006	0.003	.051
East Asian	0.599	1.350	.657	−0.004	0.005	.413
Mixed	−0.962	1.177	.413	−0.006	0.004	.156
Smoking (reference, nonsmokers)				−0.008	0.003	.009
Medical comorbidities (reference, no)						
Chronic hypertension				0.031	0.006	< .0001
Asthma				0.018	0.006	.002
Autoimmune				0.0243	0.011	.037
Antihypertensives (reference, no)						
Labetalol				0.024	0.004	< .0001
Nifedipine/methyldopa)				0.020	0.006	.003
Prednisolone (reference, no)						
Preeclampsia (reference, no)	−2.888	1.138	.011	0.012	0.0052	.017
Small for gestational age (reference, no)	−1.830	0.744	.014	0.007	0.002	.013
Group (reference, nulliparous)			.025			< .0001
Multiparous, previous PE/SGA	0.403	0.970	.677	−0.009	0.004	.016
Multiparous, no previous PE/SGA	1.761	0.503	< .0001	−0.010	0.002	< .0001
Time (4 visits)			< .0001			< .0001
Interaction group with time			.004			< .0001

There was no significant contribution from smoking, chronic hypertension, asthma, autoimmune, anti-hypertensives and prednisolone on heart rate. There was no significant contribution from height on Log_{10} mean arterial pressure.

PE, preeclampsia; *SGA*, small for gestational age.

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SUPPLEMENTARY TABLE 3

Multilevel linear mixed-effects models for maternal hemodynamic variables: estimated marginal means with 95% confidence interval: antilog values

	Visit 1	Visit 2	Visit 3	Visit 4
Cardiac output (L/min)				
Group 1	5.081 (4.764 - 5.420)	5.407 (5.081- 5.767)	5.727*** (5.370-6.109)	5.533*** (5.188- 5.902)
Group 2	5.011^{+++} (4.698-5.333)	5.308^{++} (4.988-5.649)	5.370 (5.046-5.714)	5.248^{++} (4.931-5.584)
Group 3	5.457‡‡ (5.058-5.888)	5.727‡ (5.308-6.165)	5.445‡ (5.046-5.861)	4.864‡‡‡ (4.508-5.248)
Peripheral vascular resistance (dyn·s·cm−5)				
Group 1	1678.804 (1541.7-1828.1)	1517.05** (1393.157-1648.162)	1425.608*** (1309.182-1552.387)	1517.05*** (1396.368-1651.962)
Group 2	1690.441^{++} (1555.966-1836.538)	1570.363^{+++} (1445.44-1706.082)	1541.7 (1419.058-1674.943)	1621.81^{+} (1489.361-1761.976)
Group 3	1563.148‡‡ (1425.608-1717.908)	1432.188‡ (1306.171-1570.363)	1545.254‡‡ (1406.048-1694.338)	1717.908‡‡‡ (1563.148-1883.649)
Stroke Volume (ml)				
Group 1	71.449 (64.714-79.067)	73.790 (66.680-81.470)	74.131*** (66.988-81.846)	71.285* (64.565-78.886)
Group 2	71.449^{++} (64.565-78.886)	73.113 (66.069-80.723)	70.307 (63.533-77.624)	69.183^{++} (62.661-76.383)
Group 3	77.446‡‡ (69.342-86.297)	76.207 (68.391-84.918)	70.469 (63.241-78.704)	64.120‡‡‡ (57.411-71.449)
Heart Rate (bpm)				
Group 1	82.679 (81.034-84.324)	85.493 (83.878-87.109)	90.014 (88.401-91.627)	90.430*** (88.815-92.044)
Group 2	81.712 (80.163-83.262)	84.883 (83.361-86.406)	89.232 (87.710-90.753)	88.669 (87.139-90.198)
Group 3	82.476 (80.174-84.779)	87.959 (85.770-90.147)	90.425 (88.252-92.598)	89.072 (86.890-91.255)
Mean arterial pressure (mmHg)				
Group 1	101.859 (97.949-105.681)	97.949*** (94.406-101.624)	97.274*** (93.756-100.925)	100*** (96.382-103.752)
Group 2	102.093 (98.401-105.681)	100.230^{++} (96.605-103.992)	99.540 (95.940-103.276)	102.329^{+} (98.627-106.169)
Group 3	102.093 (98.174-105.925)	98.855‡ (95.060-102.801)	99.770‡‡ (96.161-103.752)	100 (96.161-103.992)

Group 1 vs Group 2: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$; Group 2 vs Group 3: $^{+}$ $P < 0.05$, $^{++}$ $P < 0.01$, $^{+++}$ $P < 0.001$; Group 1 vs Group 3: ‡ $P < 0.05$, ‡‡ $P < 0.01$, ‡‡‡ $P < 0.001$.

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