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The effect of parity on longitudinal maternal hemodynamics

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Condensation: Parous women with previous normal pregnancies have the most favorable cardiac adaptation compared to nulliparous and to those with previous complicated pregnancies.

Short title: Effect of parity on maternal cardiac adaptation.

AJOG at a glance:

A. 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.

B. Parous women without history of preeclampsia or birth of small for gestational age neonates have the most ideal hemodynamic profile during pregnancy with 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 history of preeclampsia or small for gestational age have decreasing cardiac output and increasing peripheral vascular resistance from mid-gestation.

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

Abstract

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

Objectives: To compare maternal hemodynamics, in nulliparous women and in parous women with and without previous PE and / or SGA.

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

Results: In groups 1 and 2, CO increased with gestational age to a peak at 32 weeks and PVR showed a reversed pattern with its nadir at 32 weeks; in group 1, compared to group 2, there was better cardiac adaptation, reflected in higher CO and lower PVR. In group 3 there was a hyperdynamic profile of higher CO and lower PVR at

first trimester followed by an earlier sharp decline of CO and increase of PVR from mid-gestation. The incidence of PE and SGA was highest in group 3 and lowest in group1.

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

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

Introduction

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 to parous women.[1-4] However, parous women are a heterogeneous group of patients as 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 increase in cardiac output (CO) which peaks at mid-gestation,[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 to nulliparous women.[30] None of the above-mentioned studies stratified the parous women according to whether their previous pregnancies were complicated by PE and / or SGA.

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

Methods

Study population

This was a prospective, longitudinal study assessing maternal hemodynamics in women with singleton pregnancies attending routine pregnancy care at 11^{+0} to 13^{+6} week's gestation, conducted between November 2015 and May 2016 in six maternity hospitals in the UK. This is a sub-study of the Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) study; this multicentre 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 versus 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, where screen positive and negative women are randomly distributed within the subgroups of this study. Ethical approval was granted by the NHS Research Ethics Committee (REC reference: 13/LO/1479). The funding source had no role in the conduct of the research and preparation of the article.

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 non-invasive, bioreactance method (NICOM, Cheetah Medical Ltd, Maidenhead, Berkshire, UK) validated both in pregnant and non-pregnant populations[33-35] was used to assess maternal hemodynamics. Bioreactance uses the relative phase shifts occurring when an alternating electrical current traverse the thoracic cavity to calculate stroke volume (SV). Four dual-surface electrodes were applied across the maternal back and after 15 minutes of rest, cardiac variables [CO, SV, heart rate (HR), 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 hemodynamic recordings were included in the analysis.

Definitions

We classified the study population into three groups: group 1, parous without history of PE or SGA; group 2, nulliparous and group 3, parous with history of PE or SGA. The definitions of non-proteinuric gestational hypertension (GH) 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 birthweight < 5th 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 livebirths or stillbirths at or after 24 weeks' gestation and attendance for hemodynamic studies for at least three of the four visits. Exclusion criteria were maternal age <18 years, pre-existing 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 three groups were compared using the chi-square test or Fisher's 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 one-way ANOVA tests with post hoc analysis were used for not-normally and normally distributed data, respectively. Data are presented as median (interquartile range) and mean (standard deviation) or for not-normally and normally distributed continuous variables and as n (%) 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 four visits), a multilevel linear mixed-effects model was performed. The fixed-effect component

included time (the four 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 co-morbidities including chronic hypertension, autoimmune disease, asthma, diabetes mellitus type I and type II, medication use (labetalol, nifedipine or methyldopa, prednisolone), development of PE and SGA and first-order interaction between time and parity group. The likelihood radio (LR) test was used to define the best multilevel model (including only the random slope for time or random intercept versus 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, USA) was used for the statistical analysis (IBM Corp, Released 2015, IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY: IBM Corp).

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 three groups at the screening visit are shown and compared in Table 1. In group 1, compared to 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 to 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 to 3, had less prevalence of medical co-morbidities, such as chronic hypertension and pre-existing

diabetes, less prevalence of PE and preterm PE and of delivery of neonate with birthweight below the 5th percentile and less need for treatment with nifedipine or methyldopa.

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

Multilevel linear mixed-effects models

The fixed effects of the multilevel models are shown in Tables 2 and S1 and S2 and in Figures1 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 to White race, Black, South, East Asian race were associated with lower Log_{10} CO, Log_{10} SV, Log_{10} MAP and greater Log_{10} PVR in Asians and HR in Black.

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 I or II. 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 three visits and declined thereafter, with group 1 demonstrating greater Log_{10} CO throughout gestation (Figure 1, Table 2, Supplementary Table 3). Log_{10} PVR (Figure 1, Table 2, Supplementary Table 3) and Log_{10} MAP (Figure 2, Table 2, Supplementary 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, whilst in the latter group it demonstrated a linear decrease from the second visit onwards (Figure 2, Table 2, Supplementary Table 3). HR in both groups 1 and 2, demonstrated a similar increase with gestation during the first three 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, Supplementary 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, Supplementary Table 3) At the first and second visit, compared to group 1, Log_{10} CO was at higher level whilst Log_{10} PVR was lower. However, in the subsequent visits, group 3 demonstrated lower Log_{10} CO (Figure 1, Table 2, Supplementary Table 3) and higher Log_{10} PVR (Figure 1, Table 2, Supplementary Table 3) when compared to 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 onwards. (Figure 2, Table 2, Supplementary Table 3). On the contrary, Log_{10} SV in group 1 showed an increase from the first to 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, Supplementary Table 3). Log_{10} MAP in both groups 1 and 3 showed similar linear decrease from first to third visit, followed by an increase towards the fourth visit, with group 3 having a persistently higher Log_{10} MAP than group 1 throughout gestation (Figure 2, Table 2, Supplementary 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 previous history of PE and / or SGA compared to nulliparous women and parous women with previous history of PE and / or SGA. The most favorable profile with 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 where in the first half of pregnancy there was a high CO and low PVR but subsequently there was an abrupt decline in CO and increase in PVR.

The incidence of PE and SGA in the current pregnancy was highest in parous women with previous PE and / or SGA and lowest in 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 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 two 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 remodelling from their previous healthy pregnancy.[43-45] There is evidence that healthy pregnancy related cardiac remodelling persists for several years.[46,47,48] Such persistent remodelling has also been reported in individuals undertaking temporary endurance training.[49,50,51]

Group 3 represents the cohort with the least favourable adaptive response to pregnancy. These women have failed the 'cardiovascular screening test' in their previous pregnancies and may have an underlying cardiovascular deficit, causing a failure in adaptation in situations of circulatory stress. Furthermore, previous

pregnancies complicated by PE and / or SGA may have inflicted additional insults to their pre-existing vulnerable cardiac function[41,52] persisting after pregnancy and increasing their susceptibility to cardiovascular decompensation.[9,53,54] Post-delivery, more than half of 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 heart 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 to groups 1 and 2. A similar pattern has been described in non-pregnant 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 two and three times more when compared to group 1 and 2. It has been reported that overactivity of the renin-angiotensin-aldosterone system (RAAS) 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 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 loss of plasma volume to the interstitial space and a gradual cross-over to a low-cardiac output and vasoconstricted state.[23]

Group 2 is a mixed cohort containing 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 finding in previous studies

Previous studies comparing 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 to nulliparous women are consistent with the results of previous studies which reported that in parous, compared to nulliparous women, maternal plasma volume increase is steeper and more prolonged during pregnancy,[59,60] blood pressure is lower[61],[61-64] and the incidence of SGA and PE is lower.[3,4] In a previous study of women with 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 of 19-50 patients, reported that the hemodynamic profile of parous compared to 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, FGR) influence or are associated with maternal cardiac function variables. One option is to remove some of the above 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 one parameter may influence interactions with other variables in the statistical model and third, removal of one 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 to 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 as 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, as it has been associated with worse cardiovascular[65] and pregnancy outcomes.[2,66] This is because we only had 27 grand multipara, and hence not adequate power for such comparisons. However, it is likely that any possible effect in our models is controlled by correction for maternal age as women with high parity and long pregnancy interval also tend to be older. Another limitation is that when reporting previous pregnancy outcome, we did not examine different subgroups according to the severity of PE and FGR and the gestational age at 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 hemodynamic profile and pregnancy outcome should stratify women according to the outcome of previous pregnancies.

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Table 1. Demographic characteristics and pregnancy outcome in the study population.

	Parous no previous PE/SGA n=632	Nulliparous n=829	Parous previous PE/SGA n=113	p-value
Age in years, mean (SD)	32.0 (4.9) ***	30.3 (5.5)	31.6 (5.8) ‡‡‡	<0.0001
Weight at booking in kg, median (IQR)	70.0 (61.5 to 82.0) **	67.3 (59.3 to 79.0)	69.0 (59.3 to 86.4) ‡‡	0.006
BMI at booking>35, n (%)	61 (9.7) **	56 (6.8) +++	22 (19.5) ‡‡	<0.0001
Height in cm, mean (SD)	165.0 (6.4)	164.8 (6.6) ++	162.4 (6.8) ‡‡	0.001
Smoking, n (%)	45 (7.1) **	32 (3.9) +	15 (13.3) ‡‡‡	<0.0001
Family history of PE, n (%)	29 (4.6)	56 (6.8) ++	14 (12.4) ‡	0.005
Spontaneous conception, n (%)	625 (98.9) ***	791 (95.4)	112 (99.1)	<0.0001
Ethnicity				
- White, n (%)	456 (72.2) *	642 (77.4) ++	67 (59.3) ‡‡‡	0.000
- Black, n (%)	110 (17.4) *	109 (13.1)	28 (24.8) ‡‡	0.002
- South Asian, n (%)	31 (4.9)	41 (4.9)	9 (8.0)	0.371
- East Asian, n (%)	16 (2.5)	18 (2.2)	1 (0.9)	0.544
- Mixed, n (%)	19 (3.0)	19 (2.3) +	8 (7.0) ‡‡	0.018
Chronic hypertension, n (%)	13 (2.1)	10 (1.2) ++	9 (8.0) ‡‡‡	<0.0001
Asthma, n (%)	6 (0.9)	15 (1.8) +	4 (3.5)	0.097
Pre-existing diabetes, n (%)	4 (0.6)	2 (0.2) +	3 (2.7) ‡‡	0.006
Autoimmune, n (%)	1 (0.2)	6 (0.7)	0 (0.0)	0.209
Labetalol, n (%)	22 (3.5) *	51 (6.2) ++	12 (10.6)	0.003
Nifedipine or methyldopa, n (%)	4 (0.6)	13 (1.6) +++	7 (6.2) ‡‡	<0.0001
Prednisolone, n (%)	4 (0.6)	2 (0.2)	7 (6.2)	0.407
Pregnancy outcomes				
- PE, n (%)	8 (1.3) **	34 (4.1) +++	9 (8.0) ‡‡‡	<0.0001

- Preterm PE<37 weeks, n (%)	1 (0.2) **	8 (1.0) $^{+++}$	2 (1.8) ‡	0.001
- Gestational hypertension, n (%)	15 (2.4)	40 (4.8)	5 (4.4)	0.050
- Gestational diabetes, n (%)	27 (4.3)	40 (4.8)	7 (6.2)	0.654
- Birth < 37 weeks gestation, n (%)	10 (1.6) **	38 (4.6)	8 (7.1) ‡‡‡	0.001
- Gestational age at birth, median (IQR)	39.7 (39.0 to 40.7) *	40.0 (39.0 to 40.9)	39.0 (38.2 to 40.1) ‡‡‡	<0.0001
Neonatal outcomes				
- Birth-weight (g)	3483.3 (504.9) ***	3323.4 (551.5) $^{++}$	3122.2 (591.5) ‡‡‡	<0.0001
- Birth-weight z-score	0.14 (1.02) ***	-0.27 (1.09) $^{+}$	-0.55 (1.29) ‡‡‡	<0.0001
- Birth-weight percentile	57.6 (29.2 to 80.5) ***	40.4 (17.7 to 69.3)	28.5 (8.5 to 61.2) ‡‡‡	<0.0001
- Birth-weight <5th centile	31 (4.9) **	74 (8.9) $^{++}$	20 (17.7) ‡‡‡	<0.0001
Perinatal Mortality	1 (0.2)	3 (0.3)	1 (0.9)	0.573
Neonatal morbidity,^{a} n (%)	18 (2.8) **	49 (5.9)	4 (3.5)	0.017

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

a = includes respiratory distress syndrome, need for ventilation, sepsis, necrotizing enterocolitis, neonatal hypoglycemia

PE= preeclampsia; SGA = small for gestational age; CS = cesarean section

The three groups were compared using the chi-square test or Fisher's exact test for categorical variables. The Kruskal-Wallis test or the one-way ANOVA tests with post hoc analysis was used for not-normally and normally distributed data, respectively.

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

	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 *** (0.730- 0.786)	0.743 *** (0.715- 0.771)
Group 2	0.700^{+++} (0.672- 0.727)	0.725^{++} (0.698- 0.752)	0.730 (0.703- 0.757)	0.720 $^{++}$ (0.693- 0.747)
Group 3	0.737‡‡ (0.704- 0.770)	0.758‡ (0.725- 0.790)	0.736‡ (0.703- 0.768)	0.687‡‡‡ (0.654- 0.720)
Log_{10} Peripheral vascular resistance				
Group 1	3.225 (3.188- 3.262)	3.181** (3.144- 3.217)	3.154*** (3.117- 3.191)	3.181*** (3.145- 3.218)
Group 2	3.228^{++} (3.192- 3.264)	3.196^{+++} (3.160- 3.232)	3.188 (3.152- 3.224)	3.210^{+} (3.173- 3.246)
Group 3	3.194‡‡ (3.154- 3.235)	3.156‡ (3.116- 3.196)	3.189‡‡ (3.148- 3.229)	3.235‡‡‡ (3.194- 3.275)
Log_{10} Stroke Volume				
Group 1	1.854 (1.811-1.898)	1.868 (1.824-1.911)	1.870*** (1.826-1.913)	1.853* (1.810-1.897)
Group 2	1.854^{++} (1.810-1.897)	1.864 (1.820-1.907)	1.847 (1.803-1.890)	1.840^{++} (1.797-1.8830
Group 3	1.889‡‡ (1.841-1.936)	1.882 (1.835-1.929)	1.848 (1.801-1.896)	1.807‡‡‡ (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*** (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*** (1.975-2.007)	1.988*** (1.972-2.004)	2.000*** (1.984-2.016)
Group 2	2.009 (1.993-2.024)	2.001^{++} (1.985-2.017)	1.998 (1.982-2.014)	2.010^{+} (1.994-2.026)
Group 3	2.009 (1.992-2.025)	1.995‡ (1.978-2.012)	1.999‡‡ (1.983-2.016)	2.000 (1.983-2.017)

Figure legends

Figure 1. 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 to nulliparous women (red line) to parous women with previous preeclampsia or small for gestational age (blue line).

Figure 2. 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 to nulliparous women (red line) and to parous women with previous preeclampsia or small for gestational age (blue line).

Figure 1

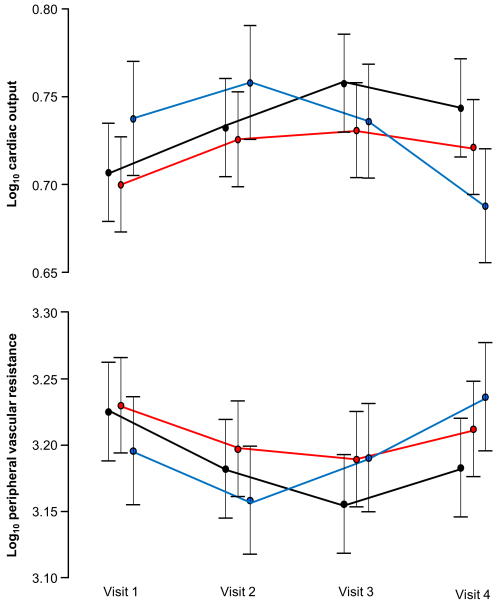
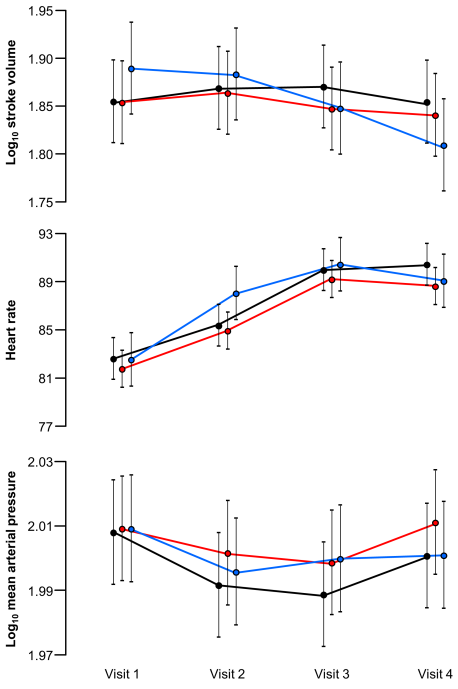


Figure 2



Supplementary results: Multilevel linear mixed-effects models

The fixed and random effects of the best multilevel models are shown in Supplementary 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, $P < 0.01$) 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, $P < 0.01$) or a random intercept model (LR=12, degrees of freedom = 1, $P < 0.01$).

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, $P < 0.01$) or a random intercept model (LR=6, degrees of freedom = 1, $P < 0.025$).

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 < 0.01) or a random intercept model (LR=10, degrees of freedom = 1, P =0.01).

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 < 0.01) or a random intercept – random slope model (LR=9, degrees of freedom = 1, P < 0.01).

Parameter	**Log_{10} Cardiac output**			**Log_{10} Peripheral vascular resistance**			**Log_{10} Stroke volume**		
Fixed part	Estimate	Standard error	p-value	Estimate	Standard error	p-value	Estimate	Standard error	p-value
Intercept	0.227	0.045	< 0.0001	3.637	0.051	< 0.0001	1.052	0.050	< 0.0001
Age (years)	-0.002	0.0003	< 0.0001				-0.0008	0.0003	0.023
Height (cm)	0.003	0.0002	< 0.0001	-0.003	0.0003	< 0.0001	0.004	0.0003	< 0.0001
Weight (Kg)	0.0007	0.0001	< 0.0001				0.0003	0.0001	0.015
Race (reference White)			< 0.0001			< 0.0001			< 0.0001
Black	-0.014	0.004	0.003	0.007	0.005	0.156	-0.027	0.005	< 0.0001
South Asian	0.030	0.008	< 0.0001	0.025	0.009	0.005	-0.038	0.008	< 0.0001
East Asian	-0.047	0.011	< 0.0001	0.047	0.013	< 0.0001	-0.049	0.012	0.0001
Mixed	-0.013	0.010	0.189	0.0004	0.011	0.966	-0.010	0.011	0.370
Smoking (reference non-smokers)									
Medical co-morbidities (reference no)									
Chronic Hypertension				0.035	0.015	0.02			
Asthma									
Autoimmune	-0.061	0.026	0.020	0.086	0.030	0.004			
Anti-hypertensives (reference no)									
Labetalol				0.048	0.009	< 0.0001			
Nifedipine/Methyldopa)				0.051	0.016	0.002			
Prednisolone (reference no)							0.088	0.0431	0.041
Preeclampsia (reference yes)									
Small for gestational age (reference no)									
Groups (reference nulliparous)			< 0.0001			< 0.0001			0.036
Multiparous, previous PE/SGA	-0.032	0.010	0.002	0.024	0.011	0.0301	-0.033	0.011	0.002
Multiparous, no previous PE/SGA	0.023	0.005	< 0.0001	-0.0281	0.005	< 0.0001	0.013	0.005	0.020
Time (four visits)			< 0.0001			< 0.0001			< 0.0001
Interaction Groups with time			< 0.0001			< 0.0001			< 0.0001

Table S1. Multilevel linear mixed-effects models for maternal hemodynamic variables: fixed effects.

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.

	Heart rate				Log_{10} Mean Arterial Pressure		
Fixed part	Estimate	Standard error	p-value	Fixed part	Estimate	Standard error	p-value
Intercept	139.338	5.164	< 0.0001	Intercept	1.878	0.003	< 0.0001
Age (years)	-0.368	0.036	< 0.0001	Age (years)	0.0003	0.0001	0.031
Height (cm)	-0.274	0.032	< 0.0001	Height (cm)			
Log10 Weight (Log10 Kg)	0.097	0.012	< 0.0001	Log10 Weight (Log10 Kg)	0.0007	0.000047	< 0.0001

Table S2. Multilevel linear mixed-effects models for maternal hemodynamic variables: fixed effects.

Race (reference White)			< 0.0001	Race (reference White)			0.013
Black	2.762	0.557	< 0.0001	Black	-0.006	0.002	0.003
South Asian	1.442	0.922	0.118	South Asian	-0.006	0.003	0.051
East Asian	0.599	1.350	0.657	East Asian	-0.004	0.005	0.413
Mixed	-0.962	1.177	0.413	Mixed	-0.006	0.004	0.156
Smoking (reference non-smokers)				Smoking (reference non-smokers)	-0.008	0.003	0.009
Medical co-morbidities (reference no)				Medical co-morbidities (reference no)			
Chronic Hypertension				Chronic Hypertension	0.031	0.006	< 0.0001
Asthma				Asthma	0.018	0.006	0.002
Autoimmune				Autoimmune	0.0243	0.011	0.037
Anti-hypertensives (reference no)				Anti-hypertensives (reference no)			
Labetalol				Labetalol	0.024	0.004	< 0.0001
Nifedipine/Methyldopa)				Nifedipine/Methyldopa)	0.020	0.006	0.003
Prednisolone (reference no)				Prednisolone (reference no)			
Preeclampsia (reference no)	-2.888	1.138	0.011	Preeclampsia (reference no)	0.012	0.0052	0.017
Small for gestational age (reference no)	-1.830	0.744	0.014	Small for gestational age (reference no)	0.007	0.002	0.013
Group (reference nulliparous)			0.025	Group (reference nulliparous)			< 0.0001
Multiparous, previous PE/SGA	0.403	0.970	0.677	Multiparous, previous PE/SGA	-0.009	0.004	0.016
Multiparous, no previous PE/SGA	1.761	0.503	< 0.0001	Multiparous, no previous PE/SGA	-0.010	0.002	< 0.0001
Time (four visits)			< 0.0001	Time (four visits)			< 0.0001
Interaction Group with time			0.004	Interaction Group with time			< 0.0001

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.

Table S3. 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)