OBSTETRICS

# Placental function and fetal weight are associated with maternal hemodynamic indices in uncomplicated pregnancies at 35–37 weeks of gestation



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**BACKGROUND:** Over the years, there has been an increasing interest in the assessment of maternal hemodynamic responses during pregnancy. With the use of both noninvasive devices and/or maternal echocardiography, it has been shown that mothers who have pregnancy complications have altered hemodynamics compared with those who have uncomplicated pregnancies. It also has been suggested that preexisting maternal cardiac changes might drive the development of complications in pregnancy that are associated with impaired placentation. To understand, however, this potential link in complicated pregnancies, it is important to clarify whether placental function is associated with maternal cardiac functional indices in normal pregnancies.

**OBJECTIVE:** To determine whether placental function, perfusion, and fetal weight are associated with maternal cardiac hemodynamic responses at 35–36 weeks of gestation in normal pregnancies.

**STUDY DESIGN:** Prospective screening of women attending Kings' College Hospital for routine hospital visit at 35–37 weeks' gestation. We recorded maternal characteristics and measured mean arterial pressure, uterine artery pulsatility index, sonographic estimated fetal weight, and serum placental growth factor and soluble fms-like tyrosine kinase 1. We also performed maternal echocardiogram to assess cardiac output and peripheral vascular resistance as well as indices of diastolic and systolic function, including global longitudinal systolic function and left ventricular mass indexed to body surface area.

**RESULTS:** We studied 1386 women. Maternal characteristics were associated with both maternal hemodynamics and functional and structural indices. Uterine artery pulsatility index was associated with left ventricular mass ($P$=.03) and global longitudinal systolic function ($P$=.017). There were significant nonlinear associations between placental growth factor and cardiac output and peripheral vascular resistance ($P$<.001 for both) and between soluble fms-like tyrosine kinase 1 and peripheral vascular resistance ($P$=.018). Estimated fetal weight was associated with maternal cardiac output (mean increase=0.186, 95% confidence interval, 0.133–0.238, $P$<.001) and peripheral vascular resistance (mean decrease=−0.164, 95% confidence interval, −0.217 to −0.111, $P$<.001). No association was noted between placental and fetal parameters and maternal cardiac functional and structural indices. In multivariable analysis, placental growth factor remained strongly associated with maternal cardiac output and peripheral vascular resistance ($P$=.002 for both) over and above maternal characteristics and estimated fetal weight. Estimated fetal weight was associated with left ventricular mass (0.102, 95% confidence interval, 0.044–0.162, $P$=.001).

**CONCLUSION:** The results of this study suggest a strong link between maternal hemodynamic responses and fetoplacental needs across the whole spectrum in normal pregnancies. These findings would also indicate that to diagnose maternal cardiac dysfunction in pregnancies complicated by impaired placentation a more extensive echocardiographic assessment might be needed rather than relying on hemodynamics which are strongly associated with fetoplacental indices.

**Key words:** biomarkers, cardiac output, maternal hemodynamics, mean arterial pressure, peripheral resistance, placental growth factor, pregnancy, soluble fms-like tyrosine kinase-1, uterine artery Doppler

Normal pregnancy is characterized by major structural and functional changes in the cardiovascular system; these include increase in intravascular volume and cardiac output and reduction in blood pressure and peripheral vascular resistance, to ensure optimal blood supply to the placenta and fetus.[1] Along with these hemodynamic changes, systolic and diastolic cardiac functional alterations have been reported as pregnancy progresses from the first to the third trimester.[1,2] These cardiovascular adaptations, however, differ in pregnancies complicated by impaired placentation, which is also associated with increased pulsatility index in the uterine arteries (Ut-A PI), reduced serum levels of the proangiogenic placental growth factor (PLGF), and increase in the levels of antiangiogenic soluble fms-like tyrosine kinase-1 (sFLT-1).[3–6] Recent data suggest that raised impedance in the maternal uterine arteries is associated with low maternal cardiac output and high peripheral vascular resistance not only in complicated but also in uncomplicated pregnancies and provided the first evidence that placenta–cardiac interplay is part of the normal physiological adaptation.[7]

To explore whether fetoplacental parameters relate to maternal cardiac indices in the third trimester, we carried out a large screening study at 35–37 weeks' gestation to first, investigate the impact of maternal characteristics on maternal cardiac function, and second, to assess whether markers of placental perfusion and function as well as fetal weight are associated with maternal hemodynamic indices in uncomplicated pregnancies.

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## AJOG at a Glance

### Why was this study conducted?

To explore the association between fetal and placental parameters with maternal cardiac hemodynamics and structural and functional indices in the third trimester of pregnancy.

### Key findings

Placental function is associated with maternal cardiac hemodynamics (cardiac output and peripheral vascular resistance) but not with functional and structural indices.

### What does this add to what is known?

This study demonstrates that fetal weight and placental function are not associated with maternal structural and functional indices but only with cardiac output and peripheral vascular resistance in uncomplicated pregnancies. By extrapolating these findings, one could argue that in pregnancies complicated by impaired placentation, a more extensive echocardiographic assessment is needed to diagnose maternal cardiac dysfunction rather than relying on hemodynamic measurements, which are strongly related to changes in placental function.

## Methods

### Study design and participants

The data for this study were derived from prospective screening in women attending for their routine hospital visit in the third trimester ($35^{+0}$-$36^{+6}$) of pregnancy at King's College Hospital, London, United Kingdom, between April and November 2018. The inclusion criteria were singleton pregnancy unaffected by diabetes mellitus or hypertension (chronic hypertension, pregnancy-induced hypertension, and preeclampsia) resulting in the birth of a nonmalformed neonate. We excluded women with breast implants, as these commonly compromise the echocardiographic acoustic windows.[8]

This visit included: first, recording of maternal demographic characteristics and medical history; second, ultrasound examination for fetal anatomy and measurement of fetal head circumference, abdominal circumference, and femur length for calculation of estimated fetal weight (using the formula by Hadlock et al,[9] because a systematic review identified this as being the most accurate model[10]); third, transabdominal color Doppler ultrasound for measurement of the left and right Ut-A PI and calculation of the mean value of the 2 arteries[11]; fourth, measurement of mean arterial pressure by validated automated devices and a standardized protocol[12]; fifth, maternal echocardiogram; and sixth, measurement of maternal serum concentration of PLGF and sFLT-1 using an automated biochemical analyzer (Brahms Kryptor Compact Plus, Thermo Fisher Scientific Hennigsdorf, Germany) and conversion of the measured concentrations to multiples of the median after adjustment for maternal and pregnancy characteristics.[13,14] Gestational age was determined by the measurement of fetal crown-rump length at 11−13 weeks or the fetal head circumference at 19−24 weeks.[15,16] All participants provided written informed consent to take part in the study of Advanced Cardiovascular Imaging, which was approved by the National Research Ethics Committee (REC No 18/NI/0013, IRAS ID:237936).

### Maternal characteristics

We recorded information on maternal age, racial origin (white, black, Asian, and mixed), method of conception (natural or assisted by in vitro fertilization or use of ovulation drugs), cigarette smoking during pregnancy, medical history, medications, and parity (nulliparous if there was no previous pregnancy with delivery at ≥24 weeks' gestation). In parous women, we recorded if a previous pregnancy was affected by preeclampsia or birth of small for gestational age neonate. We also measured height and weight.

### Maternal echocardiogram

All participants were studied by 2-dimensional and Doppler transthoracic echocardiography at rest in the left lateral decubitus position and data were acquired during unforced expiration. The protocol included standard parasternal and apical views acquired with a Canon Aplio i900 scanner (Canon Medical Systems Europe BV, Zoetermeer, The Netherlands) as per the European Association for Echocardiography and American Society of Echocardiography guidelines.[17] Echocardiography was performed by 7 Fetal Medicine Fellows who were trained in acquisition and analysis of echocardiograms. Reproducibility of the fellows was assessed by comparing echocardiographic values obtained by the fellows in 10 participants to each other (interobserver) and to a cardiologist accredited in echocardiography (experienced sonographer) who repeated the assessment and was regarded as the "gold standard."

Cardiac output was calculated from stroke volume (derived from the left ventricular outflow tract velocity-time integral) multiplied by heart rate. Left atrial area was calculated in end-systole from the 4-chamber view. Left ventricular mass was calculated with the Devereux formula using measurements of the anatomical M-mode applied in the parasternal long axis. The mitral peak early (E) and late (A) diastolic flow velocities were measured, and the E/A ratio was calculated. Pulsed tissue Doppler recordings were obtained at the septal and lateral aspects of basal LV at the junction with the mitral valve annulus in the apical 4-chamber view. The E/e′ ratio was calculated using the mean value between septal and lateral peak e′ waves. Speckle tracking was employed to assess global longitudinal function (GLS) of the left ventricle.

### Pregnancy outcomes

Data on pregnancy outcome were collected from hospital delivery records

or the general medical practitioners. Birthweight for gestational age was converted to a z score based on the Fetal Medicine Foundation fetal and neonatal weight chart.[18]

## Statistical analysis

Normally distributed continuous variables are presented as mean (± standard deviation) and variables not following normal distribution as median (25th−75th percentile). Nominal variables are summarized as counts and absolute percentages. Distribution of continuous variables was graphically assessed by histograms and quantile-quantile plots. The Pearson and/or Spearman correlation coefficient was used to evaluate the correlation between maternal, fetal, and placental parameters and cardiac measurements. We employed the nonparametric Mann−Whitney *U* test to compare maternal cardiac measurements between independent subgroups (such as different racial groups). Regression analysis was used to assess the influence of maternal characteristics that were previously shown to modify maternal hemodynamics (racial origin, weight, height, parity status, smoking, gestational age, mean arterial pressure, and heart rate),[2] placental parameters (Ut-A PI, PLGF, and sFLT-1), and estimated fetal weight on maternal cardiac measurements. In the first step of the analysis, we employed univariable regression models; subsequently, we implemented multivariable regression models adjusted for all maternal characteristics plus selected parameters that were shown to be significantly ($P<.05$) related with the outcome of interest in the first step. To ensure normality assumptions in regression analyses, we used the inverse ranking normalization for all continuous variables used in respective models.[19] This method involves a 2-step transformation: (1) the sample measurements are first mapped to the probability scale by replacing the observed values with fractional ranks and (2) ranks are then transformed into z scores using the probit function.

Aiming to capture nonlinear associations, we first used restricted cubic splines with 3 knots (at 10th, 50th, and 90th percentile of respective distribution) and assessed the significance (Wald test) of the nonlinear term for the placental and fetal parameters, and second, repeated the regression analysis by using a quartile format (highest vs lower quartiles) of placental and fetal variables. Restricted cubic splines do not require transformations of the continuous independent variable and can provide unbiased evaluation of the functional association with an outcome of interest beyond a presumed linear relationship. Maternal cardiac variables that were used as outcome variables included hemodynamic parameters (cardiac output and systemic vascular resistance), structural markers (left ventricular mass indexed for body surface area [LVMI]), and functional parameters (E/A, E/E', GLS), which have been previously shown to be altered during pregnancy as part of the maternal cardiovascular

**TABLE 1**
**Descriptive characteristics of the study population of 1386 singleton pregnancies**

| Variable | Estimate |
|---|---|
| Gestational age at assessment, wk | 36.0 (35.9−36.4) |
| Gestational age at birth, wk | 40.0 (39.3−40.9) |
| Estimated fetal weight, g | 2900 (2700−3000) |
| Birthweight, g | 3500 (3100−3700) |
| Birthweight z score | −0.08 (0.90) |
| Uterine artery pulsatility index | 0.66 (0.56−0.79) |
| Placental growth factor, pg/mL | 251 (136−461) |
| Soluble fms-like tyrosine kinase 1, pg/mL | 2200 (1600−3200) |
| Placental growth factor in multiples of the median | 0.99 (0.55−1.79) |
| Soluble fms-like tyrosine kinase 1 in multiples of the median | 1.00 (0.75−1.45) |
| Cardiac output, L/min | 5.0 (4.3−5.8) |
| Peripheral vascular resistance, dynes/s | 1395 (1204−1638) |
| Mitral peak early diastolic flow velocity (E), cm/s | 74 (64−86) |
| Mitral peak late diastolic flow velocity (A), cm/s | 54.0 (46.6−62.9) |
| Isovolumic contraction time, ms | 58 (50−69) |
| Ejection time, ms | 257 (236−275) |
| Isovolumic relaxation time, ms | 72 (58−86) |
| E/A | 1.3 (1.2−1.6) |
| E/e′ | 5.9 (5.0−6.9) |
| Mean septal and lateral left ventricular, e prime | 12.75 (11.1−14.6) |
| Mean septal and lateral left ventricular, a prime | 8.0 (7.0−9.1) |
| Mean septal and lateral left ventricular, s prime | 9.8 (8.8−10.9) |
| Left atrium volume indexed | 18 (14−22) |
| Left ventricular mass indexed for body surface area | 61.0 (54.1−68.5) |
| Global left ventricular longitudinal function, % | −21 (−23 to −20) |
| Ejection fraction, % | 58 (55−63) |

Values given as median (interquartile range) or mean (standard deviation).

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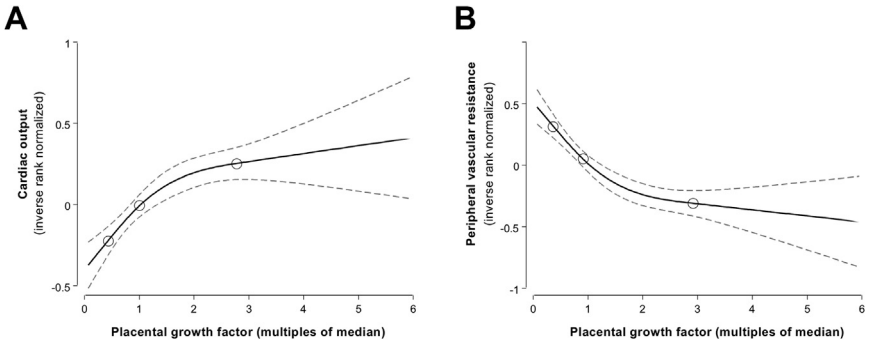
FIGURE 1
**Placental perfusion and function**




Smoothed restricted cubic spline plot of (**A**) cardiac output and (**B**) peripheral vascular resistance vs levels of placental growth factor. Three knots were fixed at the 10th, 50th, and 90th percentile of placental growth factor (indicated by respective *hollow circles*). The upper- and lower-most *dotted curves* represent the 95% confidence interval around the nonlinear prediction (*middle solid line*) of cardiac output or peripheral vascular resistance according to placental growth factor levels. For visual clarity, placental growth factor levels exceeding the 99th percentile were truncated in (**A**) and (**B**).

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adaptation.[1,2] Collinearity among independent variables was assessed by calculating the variance inflation factor. Finally, to assess model improvement for each independent variable as well as for groups of relevant variables (ie, maternal characteristics) in multivariable linear regression analysis, we calculated the adjusted R squared; subsequently, we employed bootstrapping with 1000 replicates and compared R squared values for different parameters (maternal, fetal, and placental) by independent samples Student *t* test.

Statistical analysis was conducted with STATA package, version 13.1 (StataCorp, College Station, TX). We deemed statistical significance at $P=.05$.

## Results

### Study population

Maternal, placental, and fetal characteristics of our population of 1386 pregnant women are shown in Table 1.

### Determinants of maternal cardiac function at 35−37 weeks

Interobserver reproducibility of various cardiac markers between 7 different operators was excellent (intraclass correlation coefficient was 0.98 for mitral annular early diastolic velocity and 0.78 for LVMI). Reproducibility between the same fellow and an experienced sonographer was satisfactory to excellent (intraclass correlation coefficient was 0.85 for mitral annular early diastolic velocity, 0.83 for LVMI)

#### Maternal characteristics

Women of Asian origin, compared with white women, had lower median cardiac output (4.59, interquartile range [IQR], 3.98−5.4 vs 5.1, IQR, 4.31−5.8 L/min), LVMI (57.3, IQR, 52−63.8 vs 61.3, IQR, 54.3−68.9), and reduced GLS (−20.9%, IQR, −22.9 to −19.4% vs −21.6%, IQR, −23.2 to −20%). Age, weight, height, smoking, parity status, heart rate, and mean arterial pressure correlated with multiple indices of maternal cardiac function (Supplemental Table 1).

#### Placental perfusion and function

In univariate analysis, a linear association was found between Ut-A PI and LVMI and GLS. PLGF was nonlinearly associated with cardiac output ($P<.001$) and peripheral vascular resistance ($P=.001$) (Figure 1). Accordingly, a nonlinear association of sFLT1 with peripheral vascular resistance ($P=.018$) was found. No association was found between markers of placental function and functional maternal cardiac parameters (Supplemental Table 2).

In multivariable analysis, the association between PLGF and maternal hemodynamic profile remained (Tables 2 and 3). When PLGF was used by quartiles to account for nonlinearity, the association between PLGF and cardiac output (mean increase, 0.152; 95% confidence interval [CI], 0.019−0.284, $P=.025$), and peripheral vascular resistance (mean decrease, −0.174, 95% CI, −0.301 to −0.05, $P=.007$) remained.

### Estimated fetal weight

Estimated fetal weight was associated with maternal cardiac output (mean increase, 0.186, 95% CI, 0.133−0.238, $P<.001$) and peripheral vascular resistance (mean decrease, −0.164, 95% CI −0.217 to −0.111, $P<.001$) (Supplemental Table 2 and Figure 2). Increased fetal weight was associated with increased atrial filling pressure, resulting in reduced E/A (mean decrease, $-0.10^9$, 95% CI, −0.162 to −0.056, $P<.001$) and increased LVMI (Table 3). In multivariable analysis, estimated fetal weight was not associated with cardiac output or peripheral vascular resistance ($P>.1$ for both, Table 2) but only with LVMI (mean increase, 0.103, 95% CI, 0.044−0.162, $P=.001$).

## Comment

### Main findings of the study

This study demonstrates that in normal pregnancies, placental function is associated with maternal cardiac output and peripheral vascular resistance over and above maternal characteristics, whereas no association with maternal functional and structural cardiac indices was noted. Although causal mechanisms cannot be established, our findings would suggest, first, the presence of a strong link between maternal hemodynamic responses and fetoplacental needs across the whole spectrum in normal pregnancies, and, second, that in pregnancies complicated with impaired placentation a more extensive echocardiographic assessment is indicated to characterize normal from abnormal cardiovascular responses.

**TABLE 2**
**Multivariable regression analysis of placental and fetal variables on maternal cardiac parameters**

| Variable | Placental growth factor | | Soluble fms-like tyrosine kinase 1 | | Uterine artery pulsatility index | | Estimated fetal weight | |
|---|---|---|---|---|---|---|---|---|
| | Coefficient (95% CI) | *P* value | Coefficient (95% CI) | *P* value | Coefficient (95% CI) | *P* value | Coefficient (95% CI) | *P* value |
| Cardiac output | 0.11 (0.04/0.17) | .002 | −0.04 (−0.10/0.02) | .232 | — | — | 0.02 (−0.04/0.09) | .416 |
| Peripheral vascular resistance | −0.10 (−0.167/-0.04) | .002 | 0.04 (−0.02/0.09) | .226 | — | — | −0.02 (−0.07/0.04) | .567 |
| Mitral peak early to late diastolic flow velocity (E/A) | — | — | — | — | −0.03 (−0.09/0.02) | .193 | −0.02 (−0.07/0.03) | .434 |
| Left ventricular mass indexed to surface area | — | — | — | — | 0.04 (−0.02/0.09) | .173 | 0.10 (0.04/0.16) | .001 |
| Global left ventricular longitudinal function | −0.02 (−0.08/0.04) | .480 | — | — | −0.02 (−0.07/0.04) | .604 | — | — |

All models are adjusted for maternal age, weight, height, parity status, gestational age, smoking, race, mean arterial pressure, and heart rate and all fetoplacental parameters of the same row.
Variables were normalized using inverse rank normalization method before entering the linear regression models.
*CI*, confidence interval.
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## Interpretation of results and comparison with existing literature

A number of different studies have consistently demonstrated maternal cardiac dysfunction in pregnancies complicated by impaired placentation resulting in preeclampsia and fetal growth restriction, but the mechanisms responsible for these associations remain unclear.[20] For instance, it has been speculated that a "silent" underlying cardiovascular pathology may exist in women with cardiovascular risk factors and the stress of pregnancy may unravel the fragility of their cardiovascular system.[21] However, such an approach is not applicable to women without cardiovascular risk factors and in these pregnancies a change in placental function might be the primary cause for the altered maternal hemodynamic responses. To understand, however, abnormal maternal cardiac functional responses in complicated pregnancies, we need to explore whether there is an association between placental function and perfusion and maternal cardiovascular function in normal pregnancies.

To address this issue, we performed a phenotype study in healthy women in which we used the gold standard technique, echocardiography, to assess not only maternal hemodynamics but also functional and structural alterations in maternal heart. Consistent with previous observations, we showed in the largest reported cohort of pregnant women that maternal weight and height affects a wide range of cardiac parameters.[1,22] Maternal age in our study was only associated with functional cardiac indices, as previously reported in non-obstetric population, whereas no association was noted with cardiac output and peripheral vascular resistance. In contrast to previous reports, we found no relationship between Ut-A PI and maternal cardiac functional parameters. Although we cannot exclude that an association might be present earlier in pregnancy and this may account for the discrepancy between studies, our data would suggest that the expected drop in maternal cardiac output towards term is unlikely to be responsible for fetal

**TABLE 3**
**Incremental value of placental and fetal parameters over maternal characteristics in multivariable linear regression models for cardiac output and peripheral vascular resistance**

| | Cardiac output | | Peripheral vascular resistance | |
|---|---|---|---|---|
| Variable | Adjusted R-squared for individual variables | Adjusted R-squared for fetoplacental parameters on top of maternal characteristics | Adjusted R-squared for individual variables | Adjusted R-squared for fetoplacental parameters on top of maternal characteristics |
| Age | 0.0 | 16.50 | 0 | 20.20 |
| Height | 0.86 | | 0.20 | |
| Weight | 8.89 | | 3.0 | |
| Race | 0.80 | | 0 | |
| Smoking | 0.40 | | 0.03 | |
| Mean arterial pressure | 0.84 | | 5.99 | |
| Heart rate | 7.70 | | 5.18 | |
| Parity | 1.20 | | 2.61 | |
| Gestational age | 0.24 | | 0.20 | |
| placental growth factor | 3.32 | 17.50[a] | 5.42 | 21.30[a] |
| Soluble fms-like tyrosine kinase 1 | 1.30 | 16.70 | 2.59 | 20.60 |
| Estimated fetal weight | 3.36 | 16.60 | 2.60 | 20.30 |

Comparisons are based on bootstrapping with 1000 replicates.

[a] Indicates significant difference ($P<.05$) from adjusted R-squared corresponding to the multivariable linear regression model composed of maternal characteristics only (age, height, weight, race, smoking, mean arterial pressure, heart rate, parity, and gestational age).

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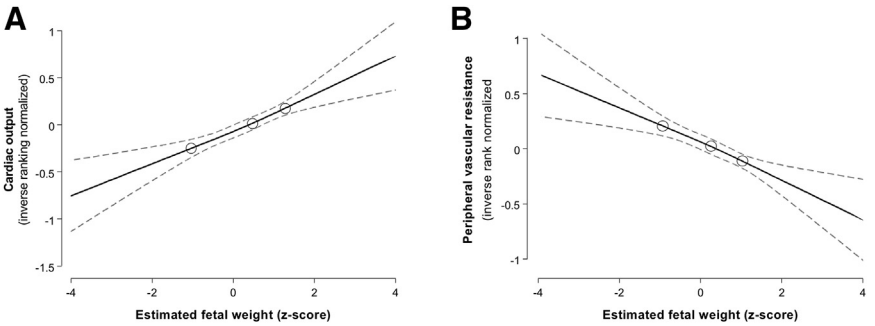
circulatory changes and stillbirth in otherwise-normal grown fetuses.

A tight balance between proangiogenic (PLGF) and antiangiogenic (sFLT-1) factors is also necessary for optimal placental function.[23] In this study, placental angiogenesis was associated with maternal hemodynamics, and this relationship was independent of maternal characteristics. Lower PLGF was associated with reduced cardiac output and greater peripheral vascular resistance but at greater PLGF levels the rate of change was modified so that further increases in PLGF had minimal impact on maternal hemodynamics. Interestingly, the association between PLGF and maternal cardiac output and peripheral vascular resistance, although relatively small, remained significant even after accounting for a wide range of maternal characteristics and fetal weight. Women with reduced PLGF and increased sFlt-1 are more at risk of a complicated pregnancy,[3–6,24,25] and our data would suggest that a reduction in maternal cardiac output and increase in peripheral vascular resistance would also be an expected associated response without being able to decipher which is the primary culprit.

In a recent study, PLGF concentrations in mid pregnancy have been inversely associated with left atrial dimensions and left ventricular mass after pregnancy,[26] suggesting that low PLGF levels might not only reflect a suboptimal cardiovascular status during pregnancy but greater cardiovascular impairment during postpartum and thereafter. This pattern of abnormal maternal cardiac remodeling in relation to PLGF levels, however, could not be confirmed in our study, as no association between PLGF and maternal functional or structural parameters could be established. Considering that in our analysis we excluded women at increased long-term cardiovascular risk, ie, women with hypertension, diabetes or preeclampsia, it is possible that such an association might be evident in the presence of pregnancy complications.

Impaired placentation also is associated with small-for-gestational age fetuses.[24,27,28] We used estimated fetal weight as a proxy for birth weight to understand the association between maternal hemodynamics and fetal size. Consistent with previous reports in early and late pregnancy, a linear association between fetal weight and maternal cardiac output and peripheral vascular resistance was established.[27,29,30] Although our study was not designed to assess the difference between pathologically growth restricted fetuses and small-for-gestational age ones, our findings would suggest a more complex interaction between PLGF and hemodynamic indices toward fetal outcomes. In this direction, researchers should use

FIGURE 2
**Estimated fetal weight**




Smoothed restricted cubic spline plot of (**A**) cardiac output and (**B**) peripheral vascular resistance vs estimated fetal birth weight. Three knots were fixed at the 10th, 50th, and 90th percentile of fetal weight distribution (indicated by respective *hollow circles*). The upper- and lower-most *dotted curves* represent the 95% confidence interval around the nonlinear prediction (*middle solid line*) of cardiac output or peripheral vascular resistance according to fetal birth weight.

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risk factors or confounders such as PLGF, peripheral vascular resistance, and cardiac output as continuous parameters for predicting small babies and not to dichotomize them to avoid spurious findings of false-positive associations in the context of misleading regression coefficients, inflation of type I error, and increased residual confounding.[31] Apart from maternal hemodynamic changes, we noted an association between fetal weight and maternal left ventricular mass that was independent of maternal characteristics and placental parameters. This finding would imply that mothers of macrosomic babies have greater left ventricular mass that, if sustained after pregnancy, might increase the woman's long-term cardiovascular risk.

## Strengths and limitations

Our study is the largest reported cohort to assess women without cardiovascular risk factors in the third trimester and report on associations between placental and fetal parameters and maternal cardiac function using the gold standard technique of echocardiography. Fellows who were trained in echocardiography performed all measurements, and their reproducibility values were comparable with the cardiologist, validating the accuracy of our observations. Paired associations were performed for placental and fetal parameters at the time of maternal cardiac assessment to minimize variability. The noted associations, however, although highly significant, are of moderate strength and explain only a part of the variability in the measures of maternal cardiac output and peripheral vascular resistance. These findings suggest that other factors may be important in determining maternal cardiovascular function, and it is possible that the current associations may be stronger in cases of pregnancy complications, such as fetal growth restriction.

## Clinical perspective

The current data are of value in understanding maternal cardiac function in normal pregnancies and its association with placental and fetal indices. Although the design of our study does not allow us to ascribe causality, it provides evidence for the presence of a close relationship between placental function, fetal weight, and maternal cardiovascular adaptation across the whole spectrum. This would suggest that in pregnancies characterized by impaired placentation, a more extensive maternal cardiovascular assessment, rather than simple evaluation of maternal hemodynamics, might be needed to identify cardiac dysfunction as cardiac output and peripheral vascular resistance are strongly associated with fetal and placental indices and as such it is difficult to distinguish normal from abnormal responses.

Although maternal echocardiography is expensive and requires extensive training, the reported associations also would be translatable to other noninvasive devices, which are widely used in obstetrics, as these have shown to have good agreement with echocardiography in the third trimester.[22]

## Conclusion

In conclusion, in the largest reported study, we showed an association between fetal and placental indices and maternal hemodynamic responses in pregnancy. These results are important in understanding normal physiological responses but are also of value when assessing and managing compromised pregnancies. The relevance and difference in the reported associations in complicated pregnancies requires further investigation. ■

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## SUPPLEMENTAL TABLE 1
## Correlation matrix among cardiac parameters and maternal characteristics

| Cardiac indices | Mean arterial pressure | Heart rate | Age | Weight | Height | Smoking | Race | Parity | Gestational age |
|---|---|---|---|---|---|---|---|---|---|
| Cardiac output | 0.0955[a] | 0.2782 | −0.0139 | 0.2993 | 0.0968 | 0.0667 | −0.0493 | 0.1064 | 0.1853 |
| | 0.0004[b] | <0.001 | 0.61 | <0.001 | 0.0004 | 0.0141 | 0.0759 | <0.001 | <0.001 |
| Peripheral vascular resistance | 0.2461 | −0.2291 | −0.0065 | −0.1752 | −0.0560 | −0.07 | 0.0068 | −0.1592 | −0.1636 |
| | <0.001 | <0.001 | 0.8119 | <0.001 | 0.0392 | 0.0099 | 0.8074 | <0.001 | <0.001 |
| Mitral peak early to late diastolic flow velocity (E/A) | −0.0538 | −0.4028 | −0.0697 | −0.0908 | 0.0448 | 0.0005 | −0.0287 | −0.0041 | −0.1091 |
| | 0.0467 | <0.001 | 0.0099 | 0.0008 | 0.0973 | 0.9865 | 0.2996 | 0.8799 | 0.0001 |
| E/e′ | 0.0591 | −0.0194 | 0.0724 | 0.0956 | −0.0428 | 0.0001 | 0.0997 | 0.0496 | −0.0174 |
| | 0.0293 | 0.4737 | 0.0076 | 0.0004 | 0.1149 | 0.9982 | 0.0003 | 0.0674 | 0.5226 |
| Stroke volume | −0.1186 | −0.4171 | 0.1436 | −0.1990 | −0.0049 | 0.0414 | −0.1581 | 0.0586 | −0.0437 |
| | <0.001 | <0.001 | <0.001 | <0.001 | 0.8578 | 0.127 | <0.001 | 0.0309 | 0.1079 |
| Left ventricular mass indexed for body surface area | 0.0309 | −0.0539 | 0.0626 | 0.0199 | −0.0476 | 0.0463 | −0.0715 | 0.0335 | 0.0883 |
| | 0.2533 | 0.0461 | 0.0205 | 0.4612 | 0.0784 | 0.0869 | 0.0095 | 0.2147 | 0.0011 |
| Global longitudinal systolic function | 0.0682 | 0.3243 | −0.1583 | 0.2004 | 0.0067 | −0.003 | 0.1579 | −0.037 | 0.0466 |
| | 0.0183 | <0.001 | <0.001 | <0.001 | 0.8161 | 0.9179 | <0.001 | 0.205 | 0.1067 |

[a] Values indicate Pearson correlation coefficient, except from the parity variable where Spearman correlation coefficient has been used; [b] Observed *P* values.

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SUPPLEMENTAL TABLE 2

**Univariable regression analysis of placental and fetal variables on maternal cardiac parameters**

| | Placental growth factor | | Soluble fms-like tyrosine kinase 1 | | Uterine artery pulsatility index | | Estimated fetal weight | |
|---|---|---|---|---|---|---|---|---|
| Variable | Coefficient (95% CI) | *P* value | Coefficient (95% CI) | *P* value | Coefficient (95% CI) | *P* value | Coefficient (95% CI) | *P* value |
| Cardiac output | 0.19 (0.13/0.24) | <.001 | −0.12 (−0.17/−0.06) | <.001 | −0.03 (−0.09/0.02) | .206 | 0.19 (0.13/0.24) | <.001 |
| Peripheral vascular resistance | −0.24 (−0.29/−0.18) | <.001 | 0.16 (0.11/0.22) | <.001 | 0.04 (−0.02/0.09) | .187 | −0.16 (−0.22/−0.11) | <.001 |
| Mitral peak early to late diastolic flow velocity (E/A) | −0.01 (−0.07/0.05) | .751 | −0.04 (−0.09/0.02) | .151 | 0.05 (−0.01/0.11) | .056 | −0.11 (−0.16/−0.06) | <.001 |
| E/E′ | −0.01 (−0.06/0.05) | .840 | 0.01 (−0.05/0.07) | .729 | 0.042 (−0.01/0.09) | .122 | −0.02 (−0.07/0.04) | .523 |
| Left ventricular mass indexed to surface area | 0.04 (−0.02/0.09) | .191 | −0.01 (−0.07/0.05) | .827 | 0.06 (0.01/0.11) | .030 | 0.09 (0.04/0.14) | .0011 |
| Global left ventricular longitudinal function | 0.06 (−0.01/0.12) | .057 | 0.01 (−0.0/0.06) | .885 | −0.070 (−0.13/−0.01) | .017 | 0.05 (−0.01/0.10) | .107 |

Variables were normalized using inverse rank normalization transformation prior to entering the linear regression models.

*CI*, confidence interval.

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