OBSTETRICS

At mid-gestation, markers of placental function rather than maternal cardiac function are stronger determinants of birthweight

Ioannis Papastefanou, MD; Vita Mesaric, MD; Renata Gomes Castello, MD; Kypros H. Nicolaides, MD; Marietta Charakida, MD

BACKGROUND: The role of maternal cardiac and hemodynamic assessment during normal and complicated pregnancies has gained attention during the last few years. Some researchers suggested that the manifestation of complications in pregnancy suffering from impaired placentation is mainly driven by preexisting cardiac changes, identifiable at an early stage by echocardiographic and hemodynamic assessment. It is therefore of great importance to determine the link between placental perfusion and maternal cardiac function and hemodynamics. Also, the impact of maternal cardiac function on birth weight has not been thoroughly studied.

OBJECTIVE: To elucidate the possible association of maternal cardiovascular indices with placental perfusion at mid-gestation and birthweight.

STUDY DESIGN: Prospective study on women with singleton pregnancies attending Kings' College Hospital, London, UK for a routine hospital visit at 19 to 24 weeks of gestation. We recorded maternal characteristics and medical history, measured mean arterial pressure, heart rate, uterine artery pulsatility index, umbilical artery pulsatility index, middle cerebral artery pulsatility index, and serum placental growth factor. We also performed maternal echocardiogram to assess cardiac output and peripheral vascular resistance as well as indices of diastolic and systolic cardiac function. Multivariable regression modeling was used.

RESULTS: Our cohort included 4006 women. Higher uterine artery pulsatility index values were associated with lower mean arterial pressure, heart rate, and left ventricular systolic function, after adjustment for maternal characteristics and subsequent development of hypertensive disorders of pregnancy and gestational diabetes mellitus. In a multivariable approach that explained 17.9% of the variance of the birthweight, we found that some cardiovascular indices provided small but significant contribution to the model after accounting for maternal factors and development of hypertensive disorders of pregnancy and gestational diabetes mellitus, uterine artery pulsatility index, and placental growth factor.

CONCLUSION: The findings of our study indicate a weak but significant association between maternal cardiovascular indices with placental perfusion at mid-gestation and birthweight. Our data would not support routine maternal cardiovascular assessment for predicting birthweight.

Key words: angiogenic factors, biomarkers, birthweight, cardiac output, echocardiography, hemodynamics, maternal cardiovascular function, mean arterial pressure, peripheral vasculat resistance, placenta, placental growth factor, preeclampsia, pregnancy, uterine artery pulsatility index

Introduction

During normal pregnancy, a number of hemodynamic changes occur in the mother to accommodate the increase in volume loading with advancing gestational age. The maternal cardiac output is increased, whilst peripheral vascular resistance is reduced to allow perfusion of the placenta.[1,2] Additionally, maternal left ventricular systolic and diastolic function is reduced with increasing gestation.[1] In women who develop pregnancy complications, including preeclampsia (PE), gestational hypertension, or fetal growth restriction, maternal hemodynamics are deranged even from the first-trimester and cardiac functional alterations are accentuated.[3–23] These findings raise the concern whether the maladaptive maternal cardiovascular responses are the cause of the development of pregnancy complications.

Previous studies demonstrated an interplay between biomarkers of impaired placentation and maternal cardiovascular function and hemodynamics throughout gestation.[10,11] It has been also suggested that this interplay between maternal cardiac function and placental profile could be reflected on birthweight.[12] In a previous study, in low risk uncomplicated pregnancies at 35 to 37 weeks of gestation we reported a linear association between uterine artery pulsatility index (UtA-PI), sonographic estimated fetal weight, serum placental growth factor (PlGF) and soluble fms-like tyrosine kinase 1 with cardiovascular function and hemodynamic indices.[24] In another recent study, we reported a linear association between maternal cardiovascular status and placental angiogenesis.[10]

The linear association between markers of placental perfusion and function and maternal cardiac function in uncomplicated pregnancies would argue that the maternal cardiovascular system adapts to accommodate fetal demands; however, it remains unclear whether this link is driven by development of maternal pregnancy complications, such as hypertension or diabetes mellitus.

The aim of the current study is to explore the association between maternal cardiac function, placental perfusion, and function at mid-gestation

Cite this article as: Papastefanou I, Mesaric V, Gomes Castello R, et al. At mid-gestation, markers of placental function rather than maternal cardiac function are stronger determinants of birthweight. Am J Obstet Gynecol 2025;233:127.e1-8.

0002-9378

https://doi.org/10.1016/j.ajog.2025.01.018

Click Supplemental Materials and Video under article title in Contents at ajog.org

AJOG at a Glance

Why was this study conducted?

To explore the association of maternal cardiovascular function at mid-gestation with uterine artery pulsatility index and biomarkers of placental function and the impact on birthweight.

Key findings

Lower birthweight was associated with reduced maternal systolic function and left ventricular mass and increased peripheral vascular resistance but the association was weak.

What does this add to what is known?

At mid-gestation maternal cardiac function assessment provides little contribution in the prediction of low birthweight.

and assess its relationship with birthweight after accounting for pregnancy complications.

Methods

Study design and participants

This was a prospective observational study of women attending for a routine hospital visit at 19+1 to 23+3 weeks of gestation at King's College Hospital, London, UK, between August 2019 and December 2021. This visit included recording of maternal demographic characteristics and medical history; ultrasound examination for fetal anatomy; transvaginal color Doppler ultrasound of the left and right uterine arteries, and calculation of the mean UtA-PI,[25] which was used as a marker of placental perfusion, assessment of maternal cardiovascular function; measurement of mean arterial pressure (MAP), using validated automated devices (Microlife BPA2-B; Microlife AG Swiss Corporation, Widnau, Switzerland) and a standardized protocol, in which 2 blood pressure recordings were made in the right and left arms and the average of the 4 measurements was used for analysis[26]; and measurement of serum concentration of PlGF, as a marker of placental function and angiogenesis, was carried out using an automated biochemical analyzer (BRAHMS KRYPTOR compact PLUS; Thermo Fisher Scientific, Hennigsdorf, Germany). At a PlGF concentration of 20 pg/mL, the coefficient of variation for reproducibility is 7.4%, and at a concentration of 894 pg/mL the coefficient of variation is 4.6%. The cohort was followed up longitudinally until delivery and pregnancy complications were reported.

Gestational age was determined by the measurement of fetal crown-rump length at 11 to 13 weeks of gestation or fetal head circumference at 19 to 24 weeks.[27,28] The women gave written informed consent to participate in the study, which was approved by the National Health System Research Ethics Committee (REC No 18/NI/0013, 2018 IRAS ID:237,936).

The inclusion criteria for this study were singleton pregnancy delivering a nonmalformed live-born or stillborn baby. Exclusion criteria for the study were the presence of major fetal abnormality and inability to provide informed written consent. Additionally, women were excluded if they had breast implants, as these obscure echocardiographic windows.

Maternal cardiovascular assessment

Cardiovascular assessment was performed using 2-dimensional and Doppler transthoracic echocardiography. Measurements were performed in the parasternal and apical views using a Canon Aplio i900 scanner (Canon Medical Systems Europe BV, Zoetermeer, The Netherlands) as per American Society of Echocardiography and European Society Cardiovascular imaging recommendations.[29]

The systolic function of the left ventricle was assessed using a variety of techniques (Supplemental Figure); (a) M-mode in the parasternal long-axis view to calculate fraction shortening and ejection fraction, (b) tissue Doppler to assess the average of the lateral and septal myocardial left ventricular myocardial wall systolic (s') velocity at the level of the mitral valve, and (c) speckle-tracking analysis in the 4-chamber, 2-chamber, and 3-chamber views to calculate left ventricular global longitudinal systolic function. Increased negative values denote increased deformation and improved myocardial strain.

Diastolic function of the left ventricle was assessed using a variety of methods[30] (Supplemental Figure): (a) pulsed Doppler to measure mitral valve early (E) and late (A) inflow and calculate E/A ratio and (b) tissue Doppler diastolic filling pressure was estimated by using E/e' index. Left atrial volume was assessed as previously described. Global myocardial contractility was assessed by calculating myocardial performance index.

Structural left ventricular parameters which were calculated included relative wall thickness (RWT) and left ventricular mass. RWT was estimated using the formula (2 × posterior wall thickness)/(left ventricular internal diameter at end-diastole). Left ventricular mass was indexed to body surface area.

Hemodynamic measurements included assessment of cardiac output, which was calculated using the formula (stroke volume * heart rate) and peripheral vascular resistance, which was calculated using the formula (MAP*80/cardiac output).[13] The reproducibility of the maternal echocardiographic assessment in our unit has been previously reported.[24]

Pregnancy complications

Information on pregnancy complications of PE or gestational hypertension, grouped as hypertensive disorders of pregnancy (HDP), and gestational diabetes mellitus (GDM) were obtained in all women. Diagnosis of HDP was made according to the definitions of the American College of Obstetricians and Gynecologists.[31] The diagnosis of GDM

was based on a 75-g oral glucose tolerance test (OGTT); the diagnostic criteria were fasting plasma glucose level ≥5.6 mmol/L and/or 2-hour plasma glucose level ≥7.8 mmol/L.[32] There was a 2-stage screening policy for GDM. First, women with at least 1 risk factor (body mass index >30 kg/m^2, previous birth of a macrosomic baby weighing >4.5 kg, previous GDM, first-degree relative with diabetes or persistent glucosuria) were offered measurement of glycosylated hemoglobin at booking and, if the value was ≥5.7%, then they had an OGTT, usually at around 12 weeks of gestation. Second, in all women at 26 to 28 weeks of gestation, plasma glucose level was measured 1 to 2 hours after eating ≥50 g of carbohydrate, and, if the concentration was ≥6.7 mmol/L, an OGTT was carried out. An OGTT was also performed if there was polyhydramnios or the fetus became macrosomic.

The Fetal Medicine Foundation (FMF) fetal and neonatal population weight charts were used to convert birth weight to percentiles and Z scores.[33]

Statistical analysis

Continuous variables were presented as the median (interquartile range) if they were departing Gaussian distribution. Nominal variables were summarized as counts and percentages. We fitted multivariate regression models to describe the association of UtA-PI, with maternal cardiovascular indices, adjusting for maternal characteristics and occurrence of GDM and HDP. We subsequently developed multivariate regression models to describe the association of birthweight, expressed in Z scores, with maternal cardiovascular indices and multiple of the median (MoM) values of UtA-PI and PlGF, adjusting for maternal characteristics and occurrence of GDM and HDP. MoM values and Z scores were obtained by using previously published equations.[33,34] The process for model construction was carried out as follows. Initially, we explored the distributional properties of each variable to define the need for transformation, to achieve homogeneity of variance and approximate Gaussian distribution. Data were partitioned into intervals to identify functional forms between dependent and independent variables that departed from linearity. We factored in a prespecified set of confounders, including maternal age, weight and height,

TABLE 1
Maternal and pregnancy characteristics of the study population

Variable	(*n*=4006)
Age (y)	33.2 (30.2–36.4)
Weight (kg)	71.0 (63.6–80.0)
Height (cm)	166 (162–170)
Body mass index (kg/m^2)	25.5 (23.1–28.8)
Gestational age at assessment (wk)	21.2 (20.6–21.4)
Ethnicity	
White	2960 (73.9)
Black	550 (13.1)
South Asian	237 (5.9)
East Asian	111 (2.8)
Mixed	148 (3.7)
Conception	
Natural	3737 (93.3)
Ovulation induction	28 (0.7)
In vitro fertilization	241 (6.0)
Medical history	
Chronic hypertension	68 (1.7)
Diabetes mellitus type I or II	40 (0.9)
SLE/APS	4 (0.1)
Cigarette smoker	51 (1.3)
Family history of preeclampsia	163 (4.1)
Parity	
Nulliparous	1562 (39.0)
Parous with previous small for gestational age <3rd percentile	117 (2.9)
Parous with previous preeclampsia	84 (2.1)
Interpregnancy interval (y)	2.7 (1.6–5.3)
Pregnancy outcome	
Preeclampsia	94 (2.4)
Gestational hypertension	85 (2.1)
Gestational diabetes mellitus	421 (10.5)
Gestational age at birth in wk	39.6 (39.0–40.6)
Birth weight in grams	3400 (3070–3710)
Birth weight in Z-scores	0.02 (−0.7–0.63)

Data are given as median (interquartile range) or *n* (%).

APS, antiphospholipid syndrome; *SLE*, systemic lupus erythematosus.

TABLE 2
Distribution of placental perfusion and function, and echocardiographic indices

Variable	Estimate
Uterine artery pulsatility Index	0.99 (0.81–1.21)
Placental growth factor in pg/mL	256.2 (188.1–356.3)
Mean arterial pressure in mmHg	84.7 (79.9–90.2)
Heart rate in beats per minute	72 (65–79)
Cardiac output in L/min	5.5 (4.8–6.4)
Peripheral vascular resistance in dynes/sec/cm^{-5}	1222 (1057–1424)
Mitral valve E/A	2.3 (1.8–3.0)
Myocardial performance index	0.37 (0.33–0.43)
Mitral valve E/e'	6.2 (5.4–7.1)
Mitral valve s' mean in cm/s	10.4 (9.5–11.5)
Left atrial volume in mL	14.2 (12.2–16.5)
Left ventricular mass indexed to body surface area	58.9 (52.9–65.5)
Relative wall thickness	0.36 (0.32–0.41)
Global longitudinal strain (%)	−24.0 (−25.6 to −22.4)

Values are given as median (interquartile range).

ethnicity, method of conception, medical history of diabetes mellitus, chronic hypertension, systemic lupus erythematosus or antiphospholipid syndrome, aspirin administration, parity, gestational age at delivery in previous pregnancy, previous birthweight, interpregnancy interval, previous GDM, previous PE, family history of PE or diabetes mellitus, smoking status, heart rate and MAP, and development of HDP or GDM in the current pregnancy. Backward elimination was used for variable selection in the regression models. We examined the correlation among the cardiovascular indices avoiding inflation of *P* values due to collinearity. Collinearity among independent variables was further assessed by calculating the variance inflation factor. We checked for significant interactions and the final models were chosen on the basis of parsimony. Residual diagnostics were used to examine model fitting and refine the parameter's inferences. Standardized regression parameters were calculated to compare the effect size of each variable on mean birthweight Z scores. Finally, to assess the contribution of maternal characteristics, cardiovascular indices, UtA-PI and PlGF on birthweight's variance we obtained the distributions of adjusted R squared values after bootstrapping with 1000 replicates for each multivariate regression model.

The statistical software package R was used for data analyses.[35]

Results

Study population

Maternal and pregnancy characteristics of the study population of 4006 singleton pregnancies are summarized in Table 1. The median age of women was 33.2 (30.2–36.4) years. HDP occurred in 4.5% of women and GDM occurred in 10.5%.

Maternal cardiovascular indices and placental perfusion at mid-gestation

The distributions of UtA-PI, PlGF, and maternal cardiovascular indices are presented in Table 2.

Higher UtA-PI values were associated with lower MAP, heart rate, and lower left ventricular systolic function, as assessed by mitral valve s' after adjustment for maternal characteristics and subsequent development of HDP or GDM (Table 3).

Maternal cardiovascular indices and birthweight

In a multivariable approach that combined cardiovascular indices, MAP, UtA-PI, and PlGF, birthweight was positively associated with mitral valve s' (P=.0004) and left ventricular mass indexed for body surface area (P=.002) and inversely related to peripheral vascular resistance (P=.0088), after adjustment for maternal demographic characteristics and development of HDP and GDM (Table 4). The full model explained 17.9% of the birthweight variance (R^2=0.179). The proportions of birthweight variance explained by the maternal factors and the incremental increase by the cardiovascular indices, UtA-PI and PlGF are provided in Figure 1. The standardized effect size of cardiovascular and hemodynamic indices, UtA-PI and PlGF on birthweight are given in Figure 2.

Comment

Main findings

This study has demonstrated that UtA-PI, measured at mid-gestation, is associated with maternal cardiac function. Specifically, increased impedance to flow in the uteroplacental circulation was related to a lower systolic cardiac function. Maternal cardiac indices at mid-gestation were also associated with birthweight, so that women destined to deliver smaller babies had progressively lower systolic function and left ventricular mass and higher peripheral vascular resistance. This association remained even after accounting for the development of pregnancy complications. However, in a multivariable framework, our analysis also revealed that despite the noted associations the impact of cardiovascular indices in the determination of mean and spread of birthweight was small, which suggests that routine maternal echocardiography is not recommended for the prediction of birthweight (Figures 1 and 2).

TABLE 3
Inferences for the parameters of the multivariable regression model on maternal echocardiographic variables

log_{10} uterine artery pulsatility index

Model structure	Estimate (standard error), *P* value
Intercept	0.480 (0.081), *P*<.0001
Maternal factors and history	
Gestational age at assessment	−0.013 (0.004), *P*=.0003
Black ethnicity	0.020 (0.006), *P*=.0006
Chronic hypertension	0.048 (0.016), *P*=.002
Pregnancy complications	
Hypertensive disorders of pregnancy	0.038 (0.010), *P*<.0001
Gestational diabetes mellitus	NS
Maternal cardiovascular indices	
Mean arterial pressure (mmHg)	−0.0008 (0.0003), *P*=.0057
Heart rate (beats/min)	−0.001 (0.0002), *P*<.0001
log_{10} mitral valve E/A	NS
Myocardial performance index	NS
log_{10} mitral valve E/e'	NS
Mitral valve s' (cm/s)	−0.004 (0.001), *P*=.0007
Left atrial volume (mL)	NS
log_{10} cardiac output (L/min)	NS
log_{10} peripheral vascular resistance (dynes/sec/cm^{-5})	NS
Left ventricular mass indexed to body surface area	NS
log_{10} relative wall thickness	NS
Global longitudinal strain (%)	NS
Model specifications	
R^2	0.031
Residual standard deviation	0.125
F-statistic	18.3
F-test	*P*<.0001

The models are adjusted for maternal factors, obstetrical and medical history, and the pregnancy complications of hypertensive disorders and gestational diabetes mellitus.

NS, nonsignificant.

Interpretation of results and comparison with existing literature

This study elucidates the association between maternal cardiovascular functional indices, maternal hemodynamics and markers of placental perfusion and function as well as birthweight at mid-gestation in an unselected cohort. We found that lower birthweight was associated with increased Ut-A PI, lower serum PLGF, reduced maternal left ventricular systolic function, lower left ventricular mass, and higher peripheral vascular resistance.

Previous groups have reported that in fetal growth restriction maternal cardiac output is reduced whilst peripheral vascular resistance is increased in the absence of PE.[3,5] In the current study, we expand our understanding including placental perfusion and fetal indices attempting an integrated exploratory study for the determinants of neonatal size and confirm the multifactorial nature of this outcome. The pattern of association in the current study is in alignment with previous studies from our group conducted near term in which we reported a linear association between maternal cardiovascular function and hemodynamics with placental angiogenesis.[10,24]

Increased impedance to flow in the uterine arteries is associated with gradually lower systolic function (Table 2). In terms of hemodynamic status, we found that lower maternal heart rate and MAP were associated with higher impedance to flow in the uterine arteries (Table 2). Indeed, the latter association was evident in all studies pertinent to placental related problems, that examined the correlation between UtA-PI and MAP, at mid-gestation.[16,36] Increased impedance to flow in the uterine arteries was accompanied with lower heart rate and MAP suggesting maternal maladaptation to increase in volume loading. However, it remains unknown whether lower heart rate suggests compensatory mechanism to reduced volume or fetal demands. As far as MAP is concerned, we can speculate that at mid-gestation maternal blood pressure is not yet already affected by placental dysfunction, and on the contrary, higher impedance in the uterine flow accompanied by a poorer maternal cardiac function might be countered by lower MAP. In the current study, peripheral vascular resistance, rather than cardiac output, appeared to provide more information about birthweight. In particular, the higher the peripheral vascular resistance the lower the birthweight, suggesting a pathological maternal adaptation at mid-gestation.

Taking a step forward we modeled altogether individual characteristics, PlGF, UtA-PI, and maternal cardiovascular indices in relation to neonatal size, expressed as birth weight Z scores adjusted for gestational age at delivery. Women who delivered smaller babies had cardiac alterations with a trend to lower systolic tissue Doppler functional indices, worst hemodynamic status with higher peripheral resistance and lower left ventricular mass (Table 3).

TABLE 4
Inferences for the parameters of the multivariable regression models of birthweight on maternal cardiovascular indices and biophysical and biochemical indices of placental function

Birthweight Z scores	
Model structure	**Estimate (standard error), *P* value**
Intercept	−1.926 (0.171), *P*<.0001
Pregnancy complications	
Hypertensive disorders of pregnancy	−0.242 (0.074), *P*=.0012
Gestational diabetes mellitus	NS
Maternal cardiovascular indices	
Mean arterial pressure (mmHg)	NS
Heart rate (beats/min)	NS
log_{10} mitral valve E/A	NS
Myocardial performance index	NS
log_{10} E/e'	NS
Mitral valve s' (cm/s)	0.034 (0.009), *P*=.0004
Left atrial volume (ml)	NS
log_{10} cardiac output (L/min)	NS
log_{10} peripheral vascular resistance	−0.428 (0.163), *P*=.0088
Left ventricular mass indexed	0.004 (0.001), *P*=.0020
log_{10} relative wall thickness	NS
Global longitudinal strain (%)	NS
Placental perfusion and function	
log_{10} MoM UtA-PI	−1.012 (0.124), *P*<.0001
log_{10} MoM UtA-PI-2	−4.627 (0.656), *P*<.0001
log_{10} MoM Placental growth factor	0.849 (0.075), *P*<.0001
Model specifications	
R^2	0.179
Residual standard deviation	0.944
F-statistic	61.3
P value	*P*<.0001

The models are adjusted for maternal factors, obstetrical and medical history, and pregnancy complications.

MoM, multiple of the median; *NS*, nonsignificant; *UtA-PI*, uterine artery pulsatility index.

Clinical implications

Maternal systolic cardiac function and hemodynamic status are associated with neonatal size but the magnitude of association is small (Figures 1 and 2). From various cardiac indices maternal hemodynamics had the most pronounced changes. Previously, routine assessment of maternal hemodynamics was suggested as a means to identify mothers at risk to develop pregnancy complications[5,6] and other groups reported the value of optimizing maternal cardiac function before conception for better pregnancy outcome.[37,38] However, in our large cohort the contribution of maternal cardiac indices in the prediction of birthweight was small in comparison to that of other markers, such as Ut-A-PI and PLGF.

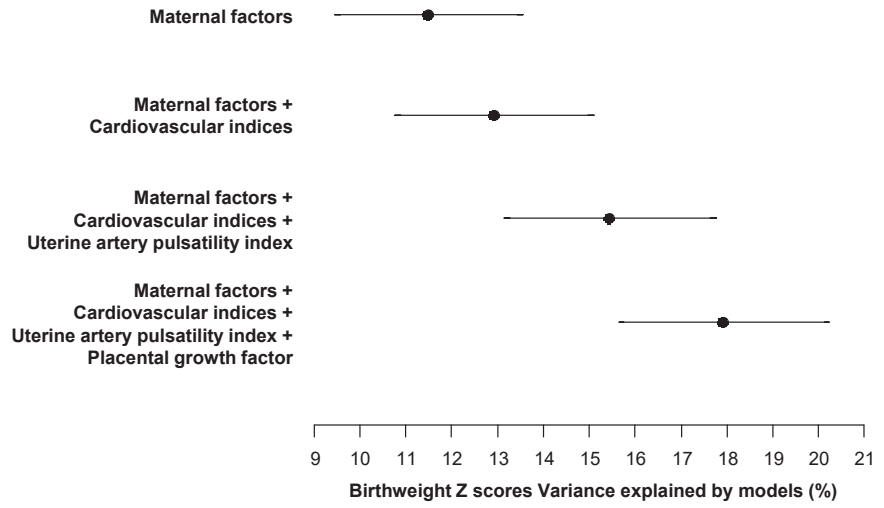
Although in the current study we elected to use echocardiography to assess maternal cardiac function and hemodynamics, a variety of other noninvasive modalities are available that can provide information about maternal hemodynamics alone or in conjunction with arterial functional indices that are less operator independent and require minimal training.[4,39]

An extensive echocardiographic assessment, however, has additional merits beyond a simple evaluation of maternal hemodynamics, as a tool complementary to placental profiling and fetal assessment. Detailed analysis of maternal left ventricular systolic and diastolic function is felt to be beyond the knowledge of obstetricians, but it may provide detailed information on the adaptation of maternal cardiovascular system to the volume loading of pregnancy. A detailed evaluation of the maternal heart could be useful to identify abnormal findings over and above the mild associations found in this large-scale population study. This may be of paramount importance in several pathological conditions, such as hypertension, glucose intolerance or growth restriction, as we have demonstrated in this and in previous research endeavors.[7,9,40,41] However, information obtained with echocardiography should be balanced against the extensive training, the time, and cost related to the methodology.

Strengths and limitations

A major advantage of this study is its prospective nature and the large unselected population of pregnant women undergoing a routine assessment at mid-gestation. Another important strength is that we had in our disposal data for important known or potential determinants of birth weight such as UtA-PI, PlGF, and individual characteristics, allowing to remove confounding effects or overlapping associations. We used automated machines to provide accurate measurement within 40 minutes of sampling of maternal serum concentration of PlGF, minimizing the bias due to sample transfer or different laboratories. Fetal variables and UtA-PI were measured by sonographers with appropriate training according to the FMF standards. Another important strength is

FIGURE 1
Proportion of birthweight Z scores variance explained by different sets of variables



Coefficients of determination (adjusted R square values) with 95% confidence limits, are provided.

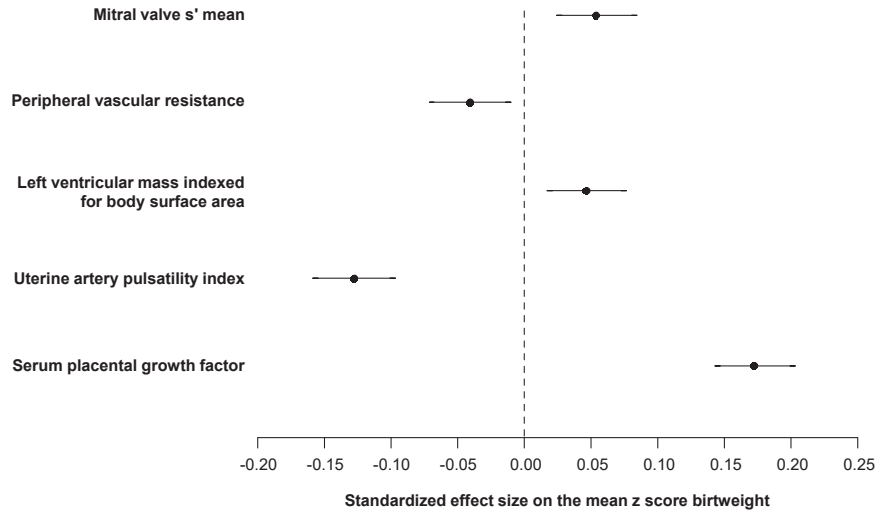
the extensive training of the personnel that took the echocardiographic measurements and the adherence to a strict quality control by means of reproducibility studies and validation against the measurements performed by a cardiologist.

An inherent limitation of all phenotype studies is the inability to deduct causal or unidirectional relations. Also, we can neither expand our results to include twins nor inform a proper cost-benefit analysis for the implementation of standardized echocardiography.

Conclusion

This is the largest phenotype study combining information regarding maternal factors, medical and obstetrical history, maternal cardiovascular function, and biomarkers of placentation, at mid-gestation. We describe the association between indices of maternal cardiac and placental function as well as birthweight. In our modeling, placental perfusion and function remain the main drivers of birthweight whereas maternal cardiac function at mid-gestation has a relatively small yet significant contribution in this process. ■

FIGURE 2
Effect size on the mean Z scores birthweight of the cardiovascular and placental function indices



The inferred standardized regression parameters with 95% confidence limits are provided.

Acknowledgments

The ultrasound machines for echocardiography and the software for speckle tracking analysis were provided free of charge by Canon Medical. The reagents and equipment for the measurement of serum placental growth factor were provided by Thermo Fisher Scientific. These bodies had no involvement in the study design, in the collection, analysis and interpretation of data, and in the writing of the report.

References

1. Bamfo JE, Kametas NA, Nicolaides KH, Chambers JB. Maternal left ventricular diastolic and systolic long-axis function during normal pregnancy. Eur J Echocardiogr 2007;8:360–8.

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

3. Vasapollo B, Novelli GP, Maellaro F, et al. Maternal cardiovascular profile is altered in the preclinical phase of normotensive early and late intrauterin growth restriction. Am J Obstet Gynecol 2024. https://doi.org/10.1016/j.ajog.2024.05.015.

4. Szczepkowska A, Adjahou S, Papastefanou I, De Pauli M, Nicolaides KH, Charakida M. Maternal vascular indices at 36 weeks' gestation in small and growth restricted fetuses. Ultrasound Obstet Gynecol 2024;64:480–5.

5. Vasapollo B, Zullino S, Novelli GP, et al. Maternal hemodynamics from preconception to delivery: research and potential diagnostic and therapeutic implications: position statement by Italian association of pre-eclampsia and Italian society of perinatal medicine. Am J Perinatol 2024;41:1999–2013.

6. Bernstein IM, Badger GJ, McBride CA. Pre-pregnancy physiology and subsequent preterm preeclampsia. Am J Obstet Gynecol 2024. https://doi.org/10.1016/j.ajog.2024.05.031.

7. Gibbone E, Huluta I, Wright A, Nicolaides KH, Charakida M. Maternal cardiac function at midgestation and development of preeclampsia. J Am Coll Cardiol 2022;79:52–62.

8. Thilaganathan B. Maternal cardiac dysfunction precedes development of preeclampsia. Hypertension 2020;76:321–2.

9. Garcia-Gonzalez C, Georgiopoulos G, Azim SA, et al. Maternal cardiac assessment at 35 to 37 Weeks improves prediction of

development of preeclampsia. Hypertension 2020;76:514–22.
10. Papastefanou I, Szczepkowska A, Tezhaeva M, De Pauli M, Charakida M, Nicolaides KH. Maternal cardiovascular function at mid-gestation is related to placental angiogenesis. Ultrasound Obstet Gynecol 2024;64:180–6.
11. Reijnders IF, Mulders A, Koster M, et al. First-trimester maternal haemodynamic adaptation to pregnancy and placental, embryonic and fetal development: the prospective observational Rotterdam Periconception cohort. BJOG 2022;129:785–95.
12. Mahendru AA, Foo FL, McEniery CM, Everett TR, Wilkinson IB, Lees CC. Change in maternal cardiac output from preconception to mid-pregnancy is associated with birthweight in healthy pregnancies. Ultrasound Obstet Gynecol 2017;49:78–84.
13. Mansukhani T, Wright A, Arechvo A, et al. Maternal vascular indices at 36 weeks gestation in the prediction of preeclampsia. Am J Obstet Gynecol 2024;230:448.e1–15.
14. Tay J, Masini G, McEniery CM, et al. Uterine and fetal placental Doppler indices are associated with maternal cardiovascular function. Am J Obstet Gynecol 2019;220:96.e1–8.
15. O'Gorman N, Wright D, Syngelaki A, et al. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks gestation. Am J Obstet Gynecol 2016;214:103.e1–12.
16. Gallo DM, Wright D, Casanova C, Campanero M, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 19–24 weeks' gestation. Am J Obstet Gynecol 2016;214:619.e1–17.
17. Tsiakkas A, Saiid Y, Wright A, Wright D, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 30–34 weeks' gestation. Am J Obstet Gynecol 2016;215:87.e1–17.
18. Ciobanu A, Wright A, Panaitescu A, Syngelaki A, Wright D, Nicolaides KH. Prediction of imminent preeclampsia at 35-37 weeks gestation. Am J Obstet Gynecol 2019;220:584.e1–11.
19. Papastefanou I, Wright D, Syngelaki A, Souretis K, Chrysanthopoulou E, Nicolaides KH. Competing-risks model for prediction of small-for-gestational-age neonates from biophysical and biochemical markers at 11-13 weeks' gestation. Ultrasound Obstet Gynecol 2021;57:52–61.
20. Nowacka U, Papastefanou I, Bouariu A, Syngelaki A, Akolekar R, Nicolaides KH. Second-trimester contingent screening for small-for-gestational-age neonate. Ultrasound Obstet Gynecol 2022;59:177–84.
21. Nowacka U, Papastefanou I, Bouariu A, Syngelaki A, Nicolaides KH. Competing risks model for prediction of small for gestational age neonates and the role of second trimester soluble fms-like tyrosine kinase-1. J Clin Med 2021;10:3786.
22. Papastefanou I, Menenez M, Szczepkowska A, Gungil B, Syngelaki A, Nicolaides KH. Comparison of competing-risks model with angiogenic factors in midgestation screening for preterm growth-related neonatal morbidity. Ultrasound Obstet Gynecol 2024;63:613–8.
23. Papastefanou I, Nobile Recalde A, Silva Souza Y, Syngelaki A, Nicolaides KH. Evaluation of angiogenic factors in prediction of growth related neonatal morbidity at term and comparison with competing risks model. Ultrasound Obstet Gynecol 2024;63:457–65.
24. Garcia-Gonzalez C, Abdel-Azim S, Galeva S, Georgiopoulos G, Nicolaides KH, Charakida M. Placental function and fetal weight are associated with maternal hemodynamic indices in uncomplicated pregnancies at 35-37 weeks of gestation. Am J Obstet Gynecol 2020;222:604.e1–10.
25. Papageorghiou AT, Yu CK, Bindra R, Pandis G, Nicolaides KH. Multicenter screening for pre-eclampsia and fetal growth restriction by transvaginal uterine artery Doppler at 23 weeks of gestation. Ultrasound Obstet Gynecol 2001;18:441–9.
26. Poon L, Zymeri N, Zamprakou A, Syngelaki A, Nicolaides K. Protocol for measurement of mean arterial pressure at 11-13 weeks' gestation. Fetal Diagn Ther 2012;31:42–8.
27. Robinson HP, Fleming JE. A critical evaluation of sonar crown rump length measurements. Br J Obstet Gynaecol 1975;82:702–10.
28. Snijders RJ, Nicolaides KH. Fetal biometry at 14-40 weeks' gestation. Ultrasound Obstet Gynecol 1994;4:34–48.
29. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233–71.
30. Othman F, Abushahba G, Salustri A. Adherence to the American society of echocardiography and European association of cardiovascular imaging recommendations for the evaluation of left ventricular diastolic function by echocardiography: a quality improvement project. J Am Soc Echocardiogr 2019;32:1619–21.
31. American College of Obstetricians and Gynecologists. ACOG practice bulletin No. 202: gestational hypertension and preeclampsia. Obstet Gynecol 2019;133:e1–25.
32. World Health Organisation. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Part 1, diagnosis and classification of diabetes mellitus. Geneva: World Health Organization; 1999.
33. Nicolaides KH, Wright D, Syngelaki A, Wright A, Akolekar R. Fetal Medicine Foundation fetal and neonatal population weight charts. Ultrasound Obstet Gynecol 2018;52:44–51.
34. Ciobanu A, Wright A, Syngelaki A, Wright D, Akolekar R, Nicolaides KH. Fetal Medicine Foundation reference ranges for umbilical artery and middle cerebral artery pulsatility index and cerebroplacental ratio. Ultrasound Obstet Gynecol 2019;53:465–72.
35. R Development Core Team. R: a language and environment for statistical computing: R Foundation for Statistical Computing, Vienna, Austria. Available at: https://www.r-project.org. Accessed December 15, 2023.
36. Papastefanou I, Nowacka U, Syngelaki A, et al. Competing risks model for prediction of small-for-gestational-age neonates from biophysical markers at 19 to 24 weeks' gestation. Am J Obstet Gynecol 2021;225:530.e1–19.
37. Foo FL, Mahendru AA, Masini G, et al. Association between prepregnancy cardiovascular function and subsequent preeclampsia or fetal growth restriction. Hypertension 2018;72:442–50.
38. Osman MMA, Mullins E, Kleprlikova H, Wilkinson IB, Lees C. Beetroot juice, exercise, and cardiovascular function in women planning to conceive. J Hypertens 2024;42:101–8.
39. Vinayagam D, Thilaganathan B, Stirrup O, Mantovani E, Khalil A. Maternal hemodynamics in normal pregnancy: reference ranges and role of maternal characteristics. Ultrasound Obstet Gynecol 2018;51:665–71.
40. DeVore GR, Polanco B. Assessing maternal cardiac function by obstetricians: technique and reference ranges. Am J Obstet Gynecol 2023;229:155.e1–18.
41. Anzoategui S, Gibbone E, Wright A, Nicolaides KH, Charakida M. Midgestation cardiovascular phenotype in women who develop gestational diabetes and hypertensive disorders of pregnancy: comparative study. Ultrasound Obstet Gynecol 2022;60:207–14.

Author and article information

From the Department of Women and Children's Health, School of Life Course and Population Sciences, Faculty of Life Sciences & Medicine, King's College London, London, UK (Papastefanou and Nicolaides); Harris Birthright Research Centre for Fetal Medicine, Fetal Medicine Research Institute, King's College Hospital, London, UK (Mesaric, Gomes Castello, Nicolaides and Charakida); and School of Biomedical Engineering and Imaging Sciences, King's College London, London, UK (Charakida).

Received April 10, 2024; revised Dec. 24, 2024; accepted Jan. 10, 2025.

The authors report no conflict of interest.

This study was funded by a grant from the Fetal Medicine Foundation (Charity No: 1037116).

Corresponding author: Kypros H. Nicolaides, MD. kypros@fetalmedicine.com