Fetal Cardiac Function at Midgestation and Subsequent Development of Preeclampsia

Iulia Huluta, MD, Alan Wright, PhD, Livia Mihaela Cosma, MD, Karam Hamed, MD, Kypros H. Nicolaides, MD, and Marietta Charakida, MD, PhD, *London and Exeter, United Kingdom*

Objective: To assess differences in cardiac morphology and function at midgestation in fetuses from pregnancies that subsequently developed preeclampsia (PE) or gestational hypertension (GH).

Methods: This was a prospective study in 5,801 women with singleton pregnancies attending for a routine ultrasound examination at midgestation, including 179 (3.1%) who subsequently developed PE and 149 (2.6%) who developed GH. Conventional and more advanced echocardiographic modalities, such as speckle-tracking, were used to assess fetal cardiac function in the right and left ventricle. The morphology of the fetal heart was assessed by calculating the right and left sphericity index.

Results: In fetuses from the PE group (vs the no PE or GH group) there was a significantly higher left ventricular global longitudinal strain and lower left ventricular ejection fraction that could not be accounted for by fetal size. All other indices of fetal cardiac morphology and function were comparable between groups. There was no significant correlation between fetal cardiac indices and uterine artery pulsatility index multiple of the median or placental growth factor multiple of the median.

Conclusion: At midgestation, fetuses of mothers at risk of developing PE, but not those at risk of GH, have mild reduction in left ventricular myocardial function. Although absolute differences were minimal and most likely not clinically relevant, these may suggest an early programming effect on left ventricular contractility in fetuses of mothers who develop PE. (J Am Soc Echocardiogr 2023;36:1110-5.)

Keywords: Fetal echocardiography, Cardiac function, Deformation, Speckle-tracking, Sphericity index

INTRODUCTION

Epidemiological studies have reported consistently that hypertensive disorders of pregnancy (HDP) can have long-lasting adverse cardiovascular effects not only for mothers but also for their offspring.[1-4] Infants as well as adolescents from a hypertensive pregnancy, in particular those with preeclampsia (PE), have higher reported blood pressure, metabolic abnormalities, and cardiac functional and structural alterations.[5-10] However, the etiology of this relationship remains unclear. It is possible that PE per se, adverse maternal risk factor profile, placental and fetal hemodynamic changes, or the postdelivery environment may contribute.

In utero assessment of fetal cardiac function provides an opportunity to establish pathophysiologic links as it eliminates the impact of the postdelivery environment. For instance, our group has previously demonstrated that hemodynamic changes that occur even prior to the development of PE may contribute to fetal cardiac remodeling[11]; we showed that at 35 to 36 weeks of gestation, in women at risk of developing PE there is evidence of impaired placentation, placental ischemia, and fetal hypoxia-induced redistribution in the fetal circulation and that all these would potentially contribute to more globular hearts and biventricular dysfunction in the fetuses.[11]

In the current prospective study, we phenotyped a large unselected group of women at midgestation and performed detailed fetal cardiovascular assessment with the aim to assess whether in pregnancies at risk for subsequent development of PE and gestational hypertension (GH) there is evidence of fetal cardiac remodeling.

From the Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, United Kingdom (I.H., L.M.C., K.H., K.H.N., M.C.); Institute of Health Research, University of Exeter, Exeter, United Kingdom (A.W.); and School of Biomedical Engineering and Imaging Sciences, King's College London, London, United Kingdom (M.C.).

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Reprint requests: Marietta Charakida, MD, PhD, Fetal Medicine Research Institute, King's College Hospital, 16-20 Windsor Walk, Denmark Hill, London SE5 8BB, United Kingdom (E-mail: *charakidadoc@googlemail.com*).

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Abbreviations
GDM = Gestational diabetes mellitus
GH = Gestational hypertension
HDP = Hypertensive disorders of pregnancy
MAP = Mean arterial pressure
PE = Preeclampsia
PlGF = Placental growth factor
MoM = Multiple of the median
SGA = Small for gestational age
UtA-PI = Uterine artery pulsatility index

METHODS

Study Design and Participants

This was a prospective observational cohort study of women who attended a routine hospital visit at 19 + 0 to 23 + 6 weeks of gestation at King's College Hospital, London, United Kingdom, between August 2019 and December 2021. Gestational age was determined from the measurement of fetal crown-rump length at 11 to 13 weeks of gestation.[12]

The visit included, first, recording of maternal demographic characteristics and medical history; second, ultrasound examination for fetal anatomy and growth; third, measurement of the left and right uterine artery pulsatility index (UtA-PI) either by transvaginal or transabdominal color Doppler ultrasound and calculation of the mean value of the 2 arteries[13]; fourth, measurement of the mean arterial pressure (MAP) by validated automated devices and a standardized protocol[14]; fifth, measurement of maternal serum placental growth factor (PlGF) in units of pg/mL by an automated biochemical analyzer (Brahms Kryptor Compact Plus; Thermo Fisher Scientific); and sixth, fetal cardiac functional assessment.

Participants completed a questionnaire, which was then reviewed by a doctor together with the woman. Patient characteristics included maternal age; race (White, Black, South Asian, East Asian, and mixed); method of conception (natural or assisted by in vitro fertilization or ovulation induction); cigarette smoking during pregnancy; medical history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus, or antiphospholipid syndrome; family history of PE in the woman's mother; and obstetric history that included parity (parous or nulliparous if no previous pregnancies at ≥24 weeks of gestation); for parous women characteristics included previous pregnancy with PE and interpregnancy interval. The maternal weight and height were measured, and the body mass index was calculated in units of kg/m^2.

The women gave written informed consent to participate in the study, which was approved by the National Health Service Research Ethics Committee. The inclusion criteria for this study were singleton pregnancies delivering a nonmalformed liveborn or stillborn infant at ≥24 weeks' gestation. We excluded pregnancies with aneuploidies and major fetal abnormalities.

Outcome Measures

Outcome measure was delivery with PE and GH. Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The obstetric records of all women with chronic hypertension or pregnancy-associated hypertension were examined to determine the diagnosis of PE or GH. Diagnosis of GH was based on the finding of hypertension (systolic blood pressure of ≥140 mm Hg or diastolic blood pressure of ≥90 mm Hg on at least 2 occasions 4 hours apart developing after 20 weeks' gestation in previously normotensive women). Diagnosis of PE was based on the finding of new-onset hypertension or chronic hypertension and at least 1 of the following: proteinuria (≥300 mg/24 hour or protein to creatinine ratio ≥30 mg/mmoL or ≥2+ on dipstick testing), renal insufficiency with serum creatinine >97 μmol/L in the absence of underlying renal disease, hepatic dysfunction with blood concentration of transaminases more than twice the upper limit of normal (≥65 IU/L for our laboratory), thrombocytopenia (platelet count <100,000/μL), neurological complications (e.g., cerebral or visual symptoms), or pulmonary edema.[15] Information was also collected on gestational age of delivery with PE and GH as well as on birthweight. Small for gestational age (SGA) fetuses were defined as those whose birthweight was <10th centile for gestational age at birth.[16]

Fetal Cardiac Functional Analysis

A comprehensive fetal cardiac functional assessment was carried out using Canon Aplio i900 machines with a convex transducer (i8CX1) (Canon Medical Systems Europe BV, Zoetermeer). Measurements were performed using conventional pulsed-wave Doppler and M mode as well as more advanced imaging modalities, such as tissue Doppler imaging and speckle-tracking echocardiography. Right systolic ventricular function was assessed by measuring tricuspid annular plane systolic excursion and right ventricular global longitudinal strain using speckle-tracking. Left ventricular systolic function was assessed by calculating myocardial performance index and left ventricular global longitudinal strain. Higher left ventricular global longitudinal strain (less negative) signifies lower myocardial contractility.

Image acquisition for speckle-tracking analysis was performed in a 4-chamber view at an "apex up or down" projection. A clip of 3 to 5 seconds with a minimum of 100 frames per second was obtained for each case in accordance with recent guidelines,[17] and analysis was carried out using proprietary software (Vitrea, Canon Medical Systems) as described elsewhere.[11,18] Left ventricular diastolic function was assessed by calculating the E/A ratio by measuring the mitral valve early (E) and late (A) diastolic filling peak Doppler velocities and E/e' from tissue Doppler as described elsewhere.[19] The morphology of the left and right ventricle was assessed in an apical or basal 4-chamber view, and the length and width of the left and right ventricles were measured in end diastole. The sphericity index was calculated by dividing base-to-apex length by transverse diameter. Fetal cardiac examinations were carried out by 7 trained fetal medicine fellows who also performed the analysis of the Doppler indices. Analysis of speckle-tracking was carried out by 2 operators. Inter- and intra-analyzer reproducibility for the Doppler indices was assessed in 20 fetuses from uncomplicated pregnancies. We have previously reported on reproducibility of speckle-tracking analysis in our group.[11,18]

Statistical Methods

Data were expressed as median (interquartile range) for continuous variables and *n* (%) for categorical variables. Student's *t* test and chi-squared test or Fisher's exact test were used for comparing outcome groups for continuous and categorical data, respectively.

Multiple linear regression models were fitted to each of the 12 cardiac indices, with terms for gestational age at measurement, maternal age, weight, height, racial origin, heart rate, method of conception, diabetes, history of gestational diabetes mellitus (GDM), history of chronic hypertension or antiphospholipid syndrome, and development of GDM, PE, or GH. Histograms were

HIGHLIGHTS

- Fetuses of mothers with PE have mild reduction in their cardiac function.
- Placental function was not associated with fetal cardiac function.
- Gestational age of PE development was not associated with fetal cardiac function.

used to identify suitable transformations where appropriate, and backward elimination was used for model selection. Variables were preselected on the basis of previous knowledge.[11,20,21]

These regression models were used, first, to assess the effects of gestational age, maternal characteristics and medical history, and maternal complications including GDM, GH, and PE on each of the cardiac markers. Second, the partial residuals from the fitted models were created after excluding the contribution of PE or GH. These comprised either the log10 multiple of the median (MoM) values or the deviations from the median (deltas) depending on the transformation of the cardiac outcome variable in the original model fitting. Standardizing the indices into MoMs or deltas allows us to observe the contribution of PE and GH to each of the indices over and above effects of gestational age and maternal characteristics and medical history. Median MoMs or deltas with 95% CIs by PE status were calculated and compared. Terms with P values $< .05$ were included in the final models.

Analysis of the fetal cardiac indices in the PE and GH groups was also stratified by gestational age at delivery and SGA.

The statistical software package R was used for all data analyses.[22]

RESULTS

Study Population

The study population of 5,801 women with singleton pregnancies included 179 (3.1%) who subsequently developed PE and 149 (2.6%) who developed GH. Among them, 50 in the former group and 34 in the latter group were born SGA. A small proportion of women (17%) were treated with aspirin. The PE (vs no PE or GH) group had higher mean body mass index; higher proportion of Black race, chronic hypertension and diabetes mellitus, family history of PE, conception by in vitro fertilization, nulliparity, and previous pregnancy complicated by PE; and longer interpregnancy interval (Table 1). Similarly, in the GH (vs no PE or GH) group, there was a higher mean body mass index; higher proportion of Black race, nulliparity, and previous pregnancy complicated by PE; and longer interpregnancy interval (Table 1).

In terms of biomarkers of PE, in both the PE and GH groups (vs no PE or GH group), mean MAP and UtA-PI were higher and serum PlGF was lower (Table 1).

Fetal Cardiac Changes in the PE, GH and No PE or GH Groups

In fetuses from the PE group (vs no PE or GH group) there was a significantly higher left ventricular global longitudinal strain and lower left ventricular ejection fraction, although absolute differences were minimal between groups (Table 2 and Supplemental Tables 1 and 2). All other indices of fetal cardiac morphology and function were not significantly different between the 2 groups apart from the diastolic index E/e′, which was marginally reduced in the PE group. There were no significant differences between the GH and no PE or GH groups in any of the fetal cardiac indices. Separate analysis of data from pregnancies that were not treated with aspirin showed no significant differences from the total population (data not shown).

Fetuses whose mother developed preterm PE compared with those with term PE had reduced left ventricular E/e′, and no other differences were detected when the analysis was stratified according to the gestational age at delivery with PE and GH (Supplemental Table 3). Similarly, when the analysis was stratified by SGA, there were no significant differences in fetal cardiac indices between the SGA and non-SGA groups, with the exception of E/e′ and left ventricular global longitudinal strain, which were lower in the SGA groups (Supplemental Table 4).

There were no significant associations between higher left ventricular global longitudinal strain MoM and UtA-PI MoM ($r = 0.013$, $P = .381$) or PlGF MoM ($r = 0.007$, $P = .661$). There was a small but significant correlation between higher left ventricular global longitudinal strain MoM and MAP MoM ($r = 0.035$, $P = .009$). There were no significant associations between higher left ventricular ejection fraction delta and UtA-PI MoM ($r = -0.022$, $P = .142$) or PlGF MoM ($r = 0.088$, $P = .088$). There was a small but significant correlation between higher left ventricular ejection fraction delta and MAP MoM ($r = -0.038$, $P = .013$).

DISCUSSION

In this large prospective study, we demonstrated that at midgestation women who subsequently develop HDP, irrespective of the severity of phenotype, that is, PE or GH, have an adverse cardiovascular risk factor profile with increased weight, non-White ethnicity, and higher blood pressure compared with women with normotensive pregnancy. In addition, in the affected pregnancies, UtA-PI and PlGF, which are markers of placental perfusion and function, were also impaired. Detailed assessment of fetal cardiac function, however, demonstrated that, first, mild reduction in left ventricular function was apparent only in fetuses whose mothers subsequently developed PE and not in those with GH and, second, that these changes were not accounted for by gestational age of delivery with PE or the presence of SGA. Although absolute differences between groups were minimal, these findings are novel and suggest an early programming effect in the fetuses of PE mothers, which primarily affects left ventricular myocardial contractility.

The association between HDP and altered fetal and offspring cardiac function and structure remains an unresolved puzzle. Epidemiological studies have consistently reported that offspring of hypertensive mothers are likely to become hypertensive themselves, with increases in blood pressure being evident from childhood and further progression noted in adolescence and adulthood.[3,5,10] Cardiac structural and functional changes with increases in left ventricular mass and reduced chamber volume have also been seen in the offspring of women with HDP.[3,23] However, from these studies, it remains unclear how much myocardial or vascular changes are driven by maternal hypertension before birth versus being a postnatal response.

Previous studies have demonstrated fetal cardiac remodeling, that is, globular hearts and reduced fetal myocardial function in pregnancies complicated by PE, and this pattern of fetal cardiac change was

Table 1 Maternal characteristics and medical history of the study population

Characteristic	No PE or GH (*n* = 5,473)	PE (*n* = 179)	GH (*n* = 149)
Maternal age, years	33.2 (30.1, 36.3)	33.8 (30.5, 37.8)	33.5 (30.4, 36.8)
Maternal weight, kg	70.7 (63.6, 80.0)	77.0 (68.0, 87.8)*	78.0 (69.5, 87.0)*
Maternal height, cm	166 (161, 170)	165 (162, 170)	168 (163, 172)*
Body mass index, kg/m^2	25.6 (23.1, 28.8)	28.3 (24.6, 31.6)*	28.2 (24.6, 31.6)*
Gestational age, weeks	21.3 (20.9, 21.6)	21.4 (21.0. 21.6)	21.3 (20.9, 21.6)
Race:		*	
White	3,983 (72.8)	114 (63.7)	102 (68.5)
Black	794 (14.5)	48 (26.8)	33 (22.2)
South Asian	345 (6.3)	9 (5.0)	8 (5.4)
East Asian	154 (2.8)	4 (2.2)	1 (0.7)
Mixed	197 (3.6)	4 (2.2)	5 (3.4)
Medical history:			
Chronic hypertension	83 (1.5)	19 (10.6)*	0 (0.0)
Diabetes mellitus type 1	11 (0.2)	4 (2.2)*	0 (0.0)
Diabetes mellitus type 2	16 (0.3)	1 (0.6)*	1 (0.7)
Systemic lupus erythematosus/antiphospholipid syndrome	13 (0.2)	0 (0.0)	3 (2.0)*
Smoker	62 (1.1)	5 (2.8)	2 (1.3)
Family history of PE	167 (3.1)	16 (8.9)*	9 (6.0)
Method of conception:		*	
Spontaneous	5,134 (93.8)	153 (85.5)	136 (91.3)
In vitro fertilization	306 (5.6)	25 (14.0)	12 (8.1)
Ovulation drugs	33 (0.6)	1 (0.6)	1 (0.7)
Parity:		*	*
Nulliparous	2,945 (53.8)	112 (62.6)	96 (64.4)
Parous, no previous PE	2,406 (44.0)	44 (24.6)	45 (30.2)
Parous, previous PE	122 (2.2)	23 (12.9)	8 (5.4)
Interpregnancy interval, years	2.5 (1.5, 4.3)	3.5 (2.1, 5.8)*	3.9 (2.3, 6.6)*
Biomarkers of PE			
Mean arterial pressure MoM	1.00 (0.95, 1.05)	1.06 (1.00, 1.11)*	1.08 (1.03, 1.14)*
Uterine artery PI MoM	1.00 (0.82, 1.20)	1.10 (0.87, 1.57)*	1.07 (0.88, 1.33)*
PlGF MoM	1.00 (0.74, 1.35)	0.85 (0.54, 1.13)*	0.87 (0.67, 1.21)*

Values are given as median (interquartile range) and *n* (%).
*$P < .001$ comparisons were made using analysis of variance with the no PE GH group.

independent of fetal growth pattern.[24] Our group has also demonstrated in the third trimester fetal cardiac remodeling prior to development of PE and identified both placental as well as hemodynamic parameters as potential contributors of these alterations.[11] In the current study, we assessed fetal myocardial function and morphology at a much earlier phase during pregnancy. We showed no difference in ventricular morphology and mild alterations in left ventricular function in fetuses of women who subsequently developed PE. The etiology of these observations is unclear. In our analysis, only maternal MAP was associated with left ventricular dysfunction, but the magnitude of the association was very small; there were no associations with UtA-PI and PlGF, markers of placental perfusion and function.

The etiology of PE and GH, despite many years of research, remains unclear.[25] The involvement of the placenta in these conditions has been well established as the delivery of the fetus and placenta reverses the hypertensive condition. In addition, preexisting maternal vascular disease as well as genetic and environmental influences have been implicated in the development of both PE and GH.[26-28] Although women with GH had similar maternal and hemodynamic characteristics to those with PE, fetal cardiac changes had similar trends in the groups but reached statistical significance only in the latter. The noted alterations, however, are small; thus it remains unclear whether these are of clinical significance in fetal life or whether these might persist and have any postnatal implications.

Strengths and Limitations

The main strengths of this study are, first, the prospective study design and large cohort, which provided us with adequate power to examine differences in fetal cardiac function between pregnancies at risk of HDP and those not at risk. In addition, we had the opportunity to decipher early fetal cardiac changes in pregnancies complicated by PE versus those with GH. We used novel and established techniques

Table 2 Unstandardized raw values of fetal cardiac indices in pregnancies with and without hypertensive disorders

Cardiac index	PE (*n* = 179)	GH (*n* = 149)	No PE or GH (*n* = 5,473)
Morphometry:			
RV sphericity index	1.86 (1.80, 1.91)	1.85 (1.79, 1.91)	1.88 (1.87, 1.89)
LV sphericity index	2.0 (2.1, 2.3)	2.1 (2.0, 2.2)	2.27 (2.15, 2.18)
Diastolic indices:			
Mitral valve E cm/sec	29.9 (29.0, 30.8)	30.4 (29.7, 31.1)	30.3 (30.2, 30.5)
Mitral valve A cm/sec	46.2 (45.1, 47.4)	46.6 (45.5, 47.7)	46.9 (46.7, 47.2)
Mitral valve E/A	0.653 (0.632, 0.675)	0.651 (0.627, 0.675)	0.659 (0.655, 0.663)
Mitral valve E/e'	10.1 (9.8, 10.5)	10.5 (10.1, 10.9)	10.5 (10.5, 10.6)
Systolic indices:			
Myocardial performance index	0.403 (0.392, 0.414)	0.406 (0.394, 0.418)	0.403 (0.401, 0.405)
Tricuspid annular plane systolic excursion, mm	4.1 (4.0. 4.2)	4.126 (4.005, 4.248)	4.069 (4.049, 4.089)
Speckle-tracking:			
RV global longitudinal strain, %	−21.1 (−21.7, −20.4)	−20.2 (−21.0. −19.4)	−20.5 (−20.7, −20.4)
LV global longitudinal strain, %	−22.2 (−23.3, −21.1)	−22.5 (−23.9, −21.2)	−23.9 (−24.117, −23.688)
RV ejection fraction, %	0.546 (0.540, 0.552)	0.565 (0.550, 0.580)	0.555 (0.553, 0.557)
LV ejection fraction, %	0.692 (0.667, 0.718)	0.704 (0.671, 0.737)	0.723 (0.719, 0.728)

Values are given as mean (95% CI).
LV, Left ventricular; *RV*, right ventricular.

to accurately define fetal cardiac function and structure, and we had the opportunity to establish associations with maternal characteristics as well as hemodynamic parameters. We stratified our analysis according to gestational age at delivery with PE and GH and birth of SGA neonates, and this provides further evidence that the noted fetal cardiac changes are not related to prematurity or fetal size. The major limitation of the study is that we did not perform serial cardiac functional assessment during pregnancy, which would enable us to document differences with advancing gestation. In addition, the study is cross-sectional; thus, no causal inferences can be made.

CONCLUSION

We have demonstrated that at midgestation fetuses of mothers at risk of developing PE, but not those at risk of GH, have mild reduction in left ventricular myocardial function, and this finding cannot be explained by the presence of SGA or time of delivery with PE. Although the etiology and clinical significance of this finding remain unclear, our data support an early fetal cardiac programming effect in fetuses whose mothers later develop PE.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2023.05.008.

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