Ultrasound Obstet Gynecol 2021; **57**: 417–422
Published online 10 February 2021 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.23521

Fetal cardiac function at 35–37 weeks' gestation in pregnancies that subsequently develop pre-eclampsia

J. SEMMLER[1], C. GARCIA-GONZALEZ[1], A. SANCHEZ SIERRA[1], M. GALLARDO AROZENA[1], K. H. NICOLAIDES[1] and M. CHARAKIDA[1,2]

[1]*Harris Birthright Research Centre for Fetal Medicine, Fetal Medicine Research Institute, King's College Hospital, London, UK;* [2]*School of Biomedical Engineering and Imaging Sciences, King's College London, London, UK*

KEYWORDS: fetal cardiac function; pre-eclampsia; third trimester

CONTRIBUTION

What are the novel findings of this work?
In pregnancies that subsequently develop pre-eclampsia, there is evidence of mild fetal biventricular dysfunction.

What are the clinical implications of this work?
The etiology and clinical significance of fetal cardiac changes in pregnancies that subsequently develop pre-eclampsia are not certain. However, our findings imply that postnatal follow-up of these children might be useful to assess whether the subtle cardiac functional changes deteriorate with time and contribute to their increased long-term cardiovascular risk.

ABSTRACT

Objective *To compare fetal cardiac morphology and function between pregnancies that subsequently developed pre-eclampsia (PE) and those that remained normotensive.*

Methods *This was a prospective observational study in 1574 pregnancies at 35–37 weeks' gestation, including 76 that subsequently developed PE. We carried out comprehensive assessment of fetal cardiac morphology and function including novel imaging modalities, such as speckle-tracking echocardiography, and measured uterine artery pulsatility index, mean arterial pressure (MAP), serum placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1) and cerebroplacental ratio (CPR). The findings in the group that subsequently developed PE were compared to those in pregnancies that remained normotensive.*

Results *In fetuses of mothers who subsequently developed PE, compared to those from normotensive pregnancies, there was a more globular right ventricle, as shown by reduced right ventricular sphericity index, reduced right ventricular systolic contractility, as shown by reduced global longitudinal strain, and reduced left ventricular diastolic function, as shown by increased E/A ratio. On multivariable regression analysis, these indices demonstrated an association with PE, independent of maternal characteristics and fetal size. In pregnancies that subsequently developed PE, compared to those that remained normotensive, MAP, sFlt-1 and the incidence of low birth weight were higher, whereas serum PlGF, CPR and the interval between assessment and delivery were lower. These findings demonstrate that, in pregnancies that develop PE, there is evidence of impaired placentation, reflected in low PlGF and reduced birth weight, placental ischemia, evidenced by increased sFlt-1 which becomes apparent in the interval of 2–4 weeks preceding the clinical onset of PE, and consequent fetal hypoxia-induced redistribution in the fetal circulation, reflected in the low CPR.*

Conclusion *Although the etiology of the observed fetal cardiac changes in pregnancies that subsequently develop PE remains unclear, it is possible that the reduction in right-heart systolic function is the consequence of high afterload due to increased placental resistance, whilst the early left ventricular diastolic changes could be due to fetal hypoxia-induced redistribution in the fetal circulation.* © *2020 International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Fetal echocardiographic studies in pregnancies with pre-eclampsia (PE), compared to normotensive controls, have reported impairment in fetal cardiac function, which has been attributed to placental vascular resistance and

Correspondence to: Prof. K. H. Nicolaides, Fetal Medicine Research Institute, King's College Hospital, 16–20 Windsor Walk, Denmark Hill, London SE5 8BB, UK (e-mail: kypros@fetalmedicine.com)

Accepted: 22 September 2020

increased cardiac afterload[1–7]. However, it is uncertain whether this dysfunction precedes or coincides with the clinical onset of the disease.

There is extensive evidence that PE is preceded by increased uterine artery (UtA) pulsatility index (PI), mean arterial pressure (MAP) and soluble fms-like tyrosine kinase-1 (sFlt-1) and reduced serum placental growth factor (PlGF)[8–21]. Additionally, the impaired placentation is often associated with birth of a small-for-gestational-age neonate and fetal hypoxia with redistribution in the fetal circulation, reflected in reduced cerebroplacental ratio (CPR)[22–25].

The objective of this large screening study at 35–37 weeks' gestation was to compare fetal cardiac morphology and function between pregnancies that subsequently developed PE and those that remained normotensive.

METHODS

Study design

This was a prospective observational study. The study population included two groups of women with singleton pregnancy attending King's College Hospital, London, UK, at 35 + 0 to 36 + 6 weeks' gestation: first, women attending a routine hospital visit between April 2018 and November 2019; and, second, women identified as being at high risk for PE by routine screening using maternal history, MAP, PlGF and sFlt-1 between November 2019 and October 2020. The first group included 1498 women without diabetes or hypertensive disorders, who have been reported on previously[26], and 41 who subsequently developed PE, and the second group included 35 women who subsequently developed PE.

Women were not eligible to participate in this study if they were < 16 years of age or unable to provide informed consent or if the fetus had a chromosomal abnormality or anatomical defect, including congenital heart defect. To minimize the possible confounding effect of maternal conditions on the fetal heart, women with pregestational or gestational diabetes, chronic hypertension or pregnancy-induced hypertension who did not develop PE were also excluded from the analysis. The study protocol was approved by the National Research Ethics Committee (REC No, 18/NI/0013; IRAS ID, 237936) and all patients provided written informed consent prior to participation.

Maternal characteristics

Maternal characteristics recorded during the clinic visit included age, height, weight, racial origin (white, black or Asian), and method of conception (natural or assisted by *in-vitro* fertilization or use of ovulation drugs). MAP was measured using validated automated devices and a standardized protocol[27]. Serum concentrations of PlGF and sFlt-1 were measured using an automated biochemical analyzer (Brahms Kryptor compact Plus, Thermo Fisher Scientific, Hennigsdorf, Germany).

Diagnosis of pre-eclampsia

Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. Diagnosis of PE was based on the finding of new-onset hypertension (systolic blood pressure of > 140 mmHg or diastolic blood pressure of > 90 mmHg on at least two occasions 4 h apart developing after 20 weeks' gestation in a previously normotensive woman) or chronic hypertension and at least one of the following: proteinuria (≥ 300 mg/24 h 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 (for example, cerebral or visual symptoms); or pulmonary edema[28].

Fetal ultrasound and echocardiography

Transabdominal ultrasound examination was carried out (Canon Aplio i900 scanner, Canon Medical Systems Europe BV, Zoetermeer, The Netherlands) for estimation of fetal weight from head circumference, abdominal circumference and femur length[29,30] and Doppler ultrasound was used for measurement of PI in the UtAs, umbilical artery (UA) and fetal middle cerebral artery (MCA)[31,32]. CPR was calculated by dividing MCA-PI by UA-PI. All values were converted to *Z*-scores based on Fetal Medicine Foundation calculators[31]. Birth weight for gestational age was converted to a *Z*-score based on the Fetal Medicine Foundation birth-weight chart[33].

The fetal heart was assessed using a Canon Aplio i900 machine equipped with a convex transducer (i8CX1). Cardiac function was assessed in the right and left ventricles as described previously[34]. Indices which were used to assess systolic cardiac function included tricuspid annular plane systolic excursion, right and left ventricular global longitudinal strain (Figure 1) and myocardial performance index. Diastolic function was assessed in the left ventricle by calculating E/A ratio (ratio of mitral valve peak early to late diastolic flow velocities) and E/e′ ratio from tissue Doppler imaging[35,36]. The morphology of the right and left ventricles was assessed by calculating the sphericity index by dividing base-to-apex length by transverse diameter[37].

Statistical analysis

Normally distributed continuous variables are presented as mean ± SD and non-normally distributed variables are presented as median (interquartile range). Variables were compared between women who subsequently developed PE and those who did not using the independent-samples Student's *t*-test or Mann–Whitney *U*-test and the chi-squared test for continuous and categorical variables, respectively.

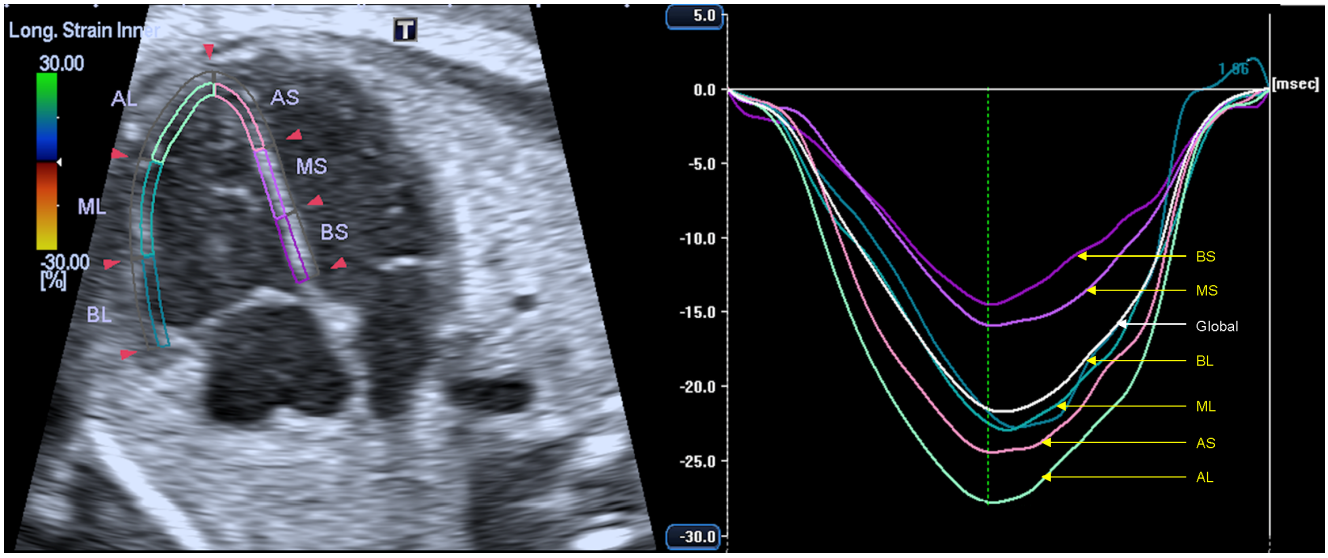

Figure 1 Fetal speckle-tracking echocardiography of right ventricle in normal pregnancy at 36 weeks' gestation. AL, apical lateral; AS, apical septal; BL, basal lateral; BS, basal septal; ML, middle lateral; MS, middle septal.

Multivariable linear regression models were employed to assess the influence of maternal characteristics and birth weight on the fetal echocardiographic parameters which differed in our primary comparisons between fetuses whose mother developed PE and those whose mother did not. To ensure normality assumptions in regression analyses, we employed inverse-ranking normalization for all continuous cardiac variables used as dependent variables.

Statistical analyses were conducted using Stata package, version 13.1 (StataCorp, College Station, TX, USA). We deemed statistical significance as $P < 0.05$.

RESULTS

The demographic characteristics and biochemical, ultrasonographic and cardiac indices of the study population of 1574 pregnancies, including 76 that subsequently developed PE, are summarized in Table 1. In the PE group, compared to the non-PE group, body mass index, MAP multiples of the median (MoM), sFlt-1 MoM, sFlt-1/PlGF ratio and the incidence of birth weight $< 10^{th}$ percentile were higher, whereas CPR *Z*-score, PlGF MoM, gestational age at delivery, the interval between assessment and delivery and birth-weight *Z*-score were lower. There was no significant difference between the two groups in maternal age, distribution of racial origin, method of conception, UtA-PI *Z*-score or fetal heart rate.

In the PE group, compared to the non-PE group, there was reduced fetal right ventricular global longitudinal systolic strain, increased E/A ratio and a more globular right ventricle with reduced right ventricular sphericity index (Table 1). There were no significant differences between the two groups in left ventricular systolic parameters, E/e′ ratio or left ventricular sphericity index.

Multivariable regression analysis demonstrated a persistence in the difference between the PE and non-PE groups in right ventricular sphericity index and global longitudinal systolic strain and in left ventricular diastolic function; these differences were independent of maternal characteristics and fetal size (Table 2).

DISCUSSION

Main findings of study

In this large prospective screening study, comprehensive assessment of fetal cardiac morphology and function at 35–37 weeks' gestation showed that cardiac changes can be detected in both the right and left ventricles in fetuses from mothers who subsequently develop the clinical symptoms of PE. Right ventricular sphericity index and systolic contractility were reduced and there was also a reduction in left ventricular diastolic function, as shown by an increase in E/A Doppler velocities. Although the noted differences were small and their long-term clinical significance remains unclear, these findings are novel as they demonstrate that the fetal heart is sensitive to changes in placental resistance and function that occur prior to the clinical development of PE.

In pregnancies that subsequently developed PE, compared to those that remained normotensive, MAP, sFlt-1, UA-PI and the incidence of low birth weight were higher, whereas, serum PlGF, MCA-PI, CPR and the interval between assessment and delivery were lower; there was no significant difference between the two groups in UtA-PI, which is consistent with the findings of previous studies investigating term PE[19,20]. These findings demonstrate that, in pregnancies that develop PE, there is evidence of impaired placentation, reflected in low PlGF and reduced birth weight, placental ischemia, evidenced by increased sFlt-1 which becomes apparent in the interval of 2–4 weeks preceding the clinical onset of PE, and consequent fetal hypoxia-induced redistribution

in the fetal circulation, reflected in high UA-PI and low MCA-PI and CPR[10,11,19–24]. Although the etiology of the observed fetal cardiac changes remains unclear, it is possible that the reduction in right-heart sphericity index and systolic function is the consequence of high afterload due to increased placental resistance, whilst the early left ventricular diastolic changes could be due to fetal hypoxia-induced redistribution in the fetal circulation.

Comparison with results of previous studies

Our study is the only screening study investigating fetal cardiac morphometry and function before the development of the clinical features of PE. The study was confined to the gestational-age window of 35–37 weeks and used both conventional and speckle-tracking echocardiography to assess both the left and right ventricles. Several previous case–control studies compared fetal echocardiographic findings in pregnancies with established PE in comparison with those in normotensive pregnancies[1–7,38]. These studies varied in the number of included patients with PE, which ranged from 19[1] to 65[4], gestational age at testing, which ranged from 20 weeks[3] to 40 weeks[4,38], type of PE, which was early[1,2], late[5,6] or a mixture of the two[3,4,38], techniques used for fetal assessment, which varied from conventional

Table 1 Demographic characteristics and biochemical, ultrasonographic and cardiac indices of study population of 1574 singleton pregnancies, according to development of pre-eclampsia (PE)

Variable	*Controls* (n = *1498)*	*PE* (n = *76)*	P
Age (years)	33.0 ± 4.95	33.5 ± 5.9	0.448
Body mass index (kg/m^2)	28.2 (25.8–31.4)	30.4 (28.4–33.7)	< 0.001
Racial origin			0.214
White	1072 (71.6)	53 (69.7)	
Black	245 (16.4)	18 (23.7)	
Asian	118 (7.9)	4 (5.3)	
Mixed	63 (4.2)	1 (1.3)	
GA at scan (weeks)	36.0 (35.9–36.4)	36.0 (35.7–36.3)	0.009
Method of conception			0.054
Natural	1421 (94.9)	68 (89.5)	
In-vitro fertilization	69 (4.6)	8 (10.5)	
Ovulation drugs	8 (0.5)	0 (0)	
Chronic hypertension	—	4 (5.3)	
Pre- or gestational diabetes mellitus	—	6 (7.9)	
Uterine artery PI *Z*-score	−0.14 (−0.81 to 0.62)	0.17 (−0.90 to 1.06)	0.075
Mean arterial pressure MoM	1.00 ± 0.07	1.11 ± 0.09	< 0.001
Umbilical artery PI *Z*-score	−0.022 (−0.72 to 0.67)	0.202 (−0.58 to 0.95)	0.018
Middle cerebral artery PI *Z*-score	−0.284 (−0.92 to 0.45)	−0.579 (−1.05 to −0.20)	0.002
Cerebroplacental ratio *Z*-score	−0.15 (−0.78 to 0.57)	−0.58 (−1.278 to 0.211)	0.015
PlGF MoM	0.91 (0.49–1.67)	0.35 (0.20–0.53)	< 0.001
sFlt-1 MoM	1.07 (0.77–1.66)	2.51 (1.71–3.78)	< 0.001
sFlt-1/PlGF ratio	1.04 (0.49–2.7)	8.0 (4.1–15.3)	< 0.001
Fetal heart rate (bpm)	140 ± 14	142 ± 13.3	0.323
GA at delivery (weeks)	40 (39.1–40.9)	39.4 (38.4–40.3)	< 0.001
Interval between examination and delivery (days)	27.5 (21.0–33.0)	25.0 (17.0–29.5)	0.001
Birth-weight *Z*-score	−0.03 (−0.72 to 0.59)	−0.59 (−1.56 to 0.13)	< 0.001
Birth weight < 10th percentile	146 (9.7)	24 (31.6)	< 0.001
Fetal cardiac parameters			
Systolic parameters			
LV myocardial performance index	0.58 (0.50–0.66)	0.57 (0.47–0.65)	0.223
LV GLS (%)	−20.5 (−22.8 to −18.3)	−19.25 (−22.55 to −17.35)	0.187
RV GLS (%)	−19 (−21.1 to −17.2)	−16.9 (−18.4 to −15.2)	< 0.001
TAPSE (mm)	7.4 (6.4–8.5)	7.2 (6.2–8.4)	0.327
Isovolumic contraction time (s)	0.04 (0.03–0.05)	0.038 (0.03–0.04)	0.007
Ejection time (s)	0.163 (0.15–0.17)	0.165 (0.15–0.18)	0.391
LV diastolic parameters			
E/A ratio	0.82 (0.72–0.92)	0.84 (0.77–1.02)	0.010
E/e′ ratio	9.12 (7.8–10.8)	8.93 (8.0–10.3)	0.872
Isovolumic relaxation time (ms)	0.052 (0.05–0.06)	0.054 (0.05–0.06)	0.391
Morphology			
LV sphericity index	1.94 (1.75–2.11)	1.98 (1.67–2.08)	0.401
RV sphericity index	1.72 (1.56–1.88)	1.64 (1.45–1.83)	0.022

Data are given as mean ± SD, median (interquartile range) or *n* (%). A, mitral valve peak late diastolic flow velocity; E, mitral valve peak early diastolic flow velocity; e′, tissue Doppler early diastolic flow velocity; GA, gestational age; GLS, global longitudinal strain; LV, left ventricular; MoM, multiples of the median; PlGF, placental growth factor; PI, pulsatility index; RV, right ventricular; sFlt-1, soluble fms-like tyrosine kinase-1; TAPSE, tricuspid annular plane systolic excursion.

Table 2 Multivariable linear regression analysis of influence of maternal characteristics and birth weight on fetal echocardiographic parameters

Variable	*Coefficient (95% CI)*	P
RV GLS		
Pre-eclampsia	0.783 (0.473 to 1.093)	< 0.001
Birth-weight *Z*-score	−0.134 (−0.199 to −0.069)	< 0.001
Age (in years)	0.007 (−0.006 to 0.020)	0.311
Racial origin		
White (reference)	—	—
Black	0.096 (−0.083 to 0.274)	0.292
Asian	0.041 (−0.195 to 0.277)	0.735
Mixed	−0.039 (−0.351 to 0.291)	0.853
Method of conception		
Natural (reference)	—	—
IVF	0.705 (−0.031 to 1.441)	0.425
Ovulation drugs	−0.135 (−0.200 to 0.470)	0.061
BMI (in kg/m^2)	−0.002 (−0.017 to 0.014)	0.817
GA at scan (in weeks)	0.129 (0.011 to 0.269)	0.072
Chronic hypertension	−0.095 (−1.410 to 1.219)	0.887
Pre- or gestational diabetes	−0.996 (−2.302 to 0.311)	0.135
LV E/A ratio		
Pre-eclampsia	0.301 (0.049 to 0.566)	0.020
Birth-weight *Z*-score	−0.081 (−0.135 to −0.026)	0.004
Age (in years)	−0.001 (−0.007 to 0.012)	0.833
Racial origin		
White (reference)	—	—
Black	0.089 (−0.054 to 0.234)	0.222
Asian	−0.191 (−0.384 to 0.002)	0.053
Mixed	0.251 (−0.011 to 0.512)	0.060
Method of conception		
Natural (reference)	—	—
IVF	0.233 (−0.464 to 0.931)	0.811
Ovulation drugs	0.029 (−0.274 to 0.214)	0.815
BMI (in kg/m^2)	−0.004 (−0.016 to 0.007)	0.504
GA at scan (in weeks)	0.073 (−0.040 to 0.186)	0.207
Chronic hypertension	0.251 (−0.767 to 1.269)	0.629
Pre- or gestational diabetes	−0.221 (−1.064 to 0.622)	0.608
RV sphericity index		
Pre-eclampsia	−0.326 (−0.636 to 0.016)	0.039
Birth-weight *Z*-score	0.080 (0.013 to 0.148)	0.020
Age (in years)	−0.006 (−0.020 to 0.008)	0.420
Racial origin		
White (reference)	—	—
Black	−0.146 (−0.329 to 0.038)	0.120
Asian	−0.161 (−0.409 to 0.088)	0.204
Mixed	0.169 (−0.158 to 0.496)	0.311
Method of conception		
Natural (reference)	—	—
IVF	−0.211 (−0.993 to 0.571)	0.597
Ovulation drugs	−0.211 (−0.543 to 0.122)	0.214
BMI (in kg/m^2)	−0.002 (−0.018 to 0.014)	0.805
GA at scan (in weeks)	−0.100 (−0.245 to 0.045)	0.175
Chronic hypertension	1.220 (−0.171 to 2.611)	0.085
Pre- or gestational diabetes	−0.132 (−1.515 to 1.250)	0.851

A, mitral valve peak late diastolic flow velocity; BMI, body mass index; E, mitral valve peak early diastolic flow velocity; GA, gestational age; GLS, global longitudinal strain; IVF, *in-vitro* fertilization; LV, left ventricular; RV, right ventricular.

echocardiography[1,2,7,38] to more advanced methods, such as tissue Doppler imaging or speckle-tracking echocardiography[3,5,6], and type of cardiac indices that were assessed[1–7,38].

Many, but not all, previous studies on fetal cardiac function in pregnancies complicated by PE reported changes in a few cardiac indices and suggested the presence of a mild degree of cardiac dysfunction, but most indices were not significantly different from those in normotensive pregnancies[1–7]. In accordance with previous studies, our data showed that, in the PE group, the right ventricles were more globular[7] and had less longitudinal contractility, as measured by global longitudinal strain[6], and the left ventricles had increased diastolic filling ratios[2]. In agreement with the findings of Api *et al.*[38], but in contrast to other previous reports[2,4,7], we found similar values of myocardial performance index in PE and normotensive pregnancies. Previous studies reported that fetal cardiac changes observed in PE pregnancies are similar to those found in growth-restricted fetuses[2,7]. In our study, fetal cardiac morphological and functional changes observed in the PE group persisted after accounting for differences in maternal characteristics and birth weight as a continuous variable.

Strengths and limitations

The main strengths of this study are, first, the prospective study design and large cohort in which the effects of PE on the cardiac function of fetuses at a gestational age of 35–37 weeks were evaluated, second, application of a strict comprehensive imaging protocol which included novel imaging modalities, such as speckle-tracking echocardiography, and, third, adjustment for the confounder fetal size, to investigate the influence of PE alone on fetal cardiac function. The major limitation of the study is that it was conducted exclusively in the third trimester and included patients with late PE, allowing no conclusions to be drawn on fetal cardiac function before the development of early PE.

Conclusions

We have demonstrated that, at 35–37 weeks' gestation, fetuses of mothers at risk of developing PE have biventricular functional changes. Although the etiology and clinical significance of these findings remain unclear, our data imply that postnatal follow-up of these children might be useful to assess whether these subtle cardiac functional changes deteriorate with time and contribute to their increased long-term cardiovascular risk.

ACKNOWLEDGMENTS

This study was supported by a grant from The Fetal Medicine Foundation (Charity No: 1037116). The reagents and equipment for the measurement of serum PlGF and soluble sFlt-1 were provided by Thermo Fisher

Scientific. These bodies had no involvement in the study design, in the collection, analysis and interpretation of data, in the writing of the report or in the decision to submit the article for publication.

REFERENCES

1. Mari G, Hanif F, Kruger M. Sequence of cardiovascular changes in IUGR in pregnancies with and without preeclampsia. *Prenat Diagn* 2008; **28**: 377–383.
2. Crispi F, Comas M, Hernández-Andrade E, Eixarch E, Gómez O, Figueras F, Gratacós E. Does pre-eclampsia influence fetal cardiovascular function in early-onset intrauterine growth restriction? *Ultrasound Obstet Gynecol* 2009; **34**: 660–665.
3. Zhou Q, Ren Y, Yan Y, Chu C, Gui Y, Li X. Fetal tissue Doppler imaging in pregnancies complicated with preeclampsia with or without intrauterine growth restriction. *Prenat Diagn* 2012; **32**: 1021–1028.
4. Balli S, Kibar AE, Ece I, Oflaz MB, Yilmaz O. Assessment of fetal cardiac function in mild preeclampsia. *Pediatr Cardiol* 2013; **34**: 1674–1679.
5. Yu L, Zhou Q, Peng Q, Yang Z. Left ventricular function of patients with pregnancy-induced hypertension evaluated using velocity vector imaging echocardiography and N-terminal pro-brain natriuretic peptide. *Echocardiography* 2018; **35**: 459–466.
6. Yu L, Zhou Q, Peng Q, Zeng S, Yang Z. Velocity vector imaging echocardiography and NT-proBNP study of fetal cardiac function in pregnancy-induced maternal hypertension. *J Clin Ultrasound* 2019; **47**: 285–291.
7. Youssef L, Miranda J, Paules C, Garcia-Otero L, Vellvé K, Kalapotharakos G, Sepulveda-Martinez A, Crovetto F, Gomez O, Gratacós E, Crispi F. Fetal cardiac remodeling and dysfunction is associated with both preeclampsia and fetal growth restriction. *Am J Obstet Gynecol* 2020; **222**: 79.e1–9.
8. O'Gorman N, Tampakoudis G, Wright A, Wright D, Nicolaides KH. Uterine artery pulsatility index at 12, 22, 32 and 36 weeks' gestation in screening for pre-eclampsia. *Ultrasound Obstet Gynecol* 2016; **47**: 565–572.
9. Tayyar A, Krithinakis K, Wright A, Wright D, Nicolaides KH. Mean arterial pressure at 12, 22, 32 and 36 weeks' gestation in screening for pre-eclampsia. *Ultrasound Obstet Gynecol* 2016; **47**: 573–579.
10. Tsiakkas A, Cazacu R, Wright A, Wright D, Nicolaides KH. Maternal serum placental growth factor at 12, 22, 32 and 36 weeks' gestation in screening for pre-eclampsia. *Ultrasound Obstet Gynecol* 2016; **47**: 472–477.
11. Tsiakkas A, Mendez O, Wright A, Wright D, Nicolaides KH. Maternal serum soluble fms-like tyrosine kinase-1 at 12, 22, 32 and 36 weeks' gestation in screening for pre-eclampsia. *Ultrasound Obstet Gynecol* 2016; **47**: 478–483.
12. O'Gorman N, Wright D, Syngelaki A, Akolekar R, Wright A, Poon LC, Nicolaides KH. 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.
13. Tan MY, Syngelaki A, Poon LC, Rolnik DL, O'Gorman N, Delgado JL, Akolekar R, Konstantinidou L, Tsavdaridou M, Galeva S, Ajdacka U, Molina FS, Persico N, Jani JC, Plasencia W, Greco E, Papaioannou G, Wright A, Wright D, Nicolaides KH. Screening for pre-eclampsia by maternal factors and biomarkers at 11–13 weeks' gestation. *Ultrasound Obstet Gynecol* 2018; **52**: 186–195.
14. 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.
15. Litwinska M, Syngelaki A, Wright A, Wright D, Nicolaides KH. Management of pregnancies after combined screening for pre-eclampsia at 19–24 weeks' gestation. *Ultrasound Obstet Gynecol* 2018; **52**: 365–372.
16. 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.
17. Wright D, Dragan I, Syngelaki A, Akolekar R, Nicolaides KH. Proposed clinical management of pregnancies after combined screening for pre-eclampsia at 30–34 weeks' gestation. *Ultrasound Obstet Gynecol* 2017; **49**: 194–200.
18. Andrietti S, Silva M, Wright A, Wright D, Nicolaides KH. Competing-risks model in screening for pre-eclampsia by maternal factors and biomarkers at 35–37 weeks' gestation. *Ultrasound Obstet Gynecol* 2016; **48**: 72–79.
19. Panaitescu A, Ciobanu A, Syngelaki A, Wright A, Wright D, Nicolaides KH. Screening for pre-eclampsia at 35–37 weeks' gestation. *Ultrasound Obstet Gynecol* 2018; **52**: 501–506.
20. 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.
21. Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, Schisterman EF, Thadhani R, Sachs BP, Epstein FH, Sibai BM, Sukhatme VP, Karumanchi SA. Circulating angiogenic factors and the risk of pre-eclampsia. *N Engl J Med* 2004; **350**: 672–683.
22. Nicolaides KH, Bilardo KM, Soothill PW, Campbell S. Absence of end diastolic frequencies in the umbilical artery a sign of fetal hypoxia and acidosis. *BMJ* 1988; **297**: 1026–1027.
23. Vyas S, Nicolaides KH, Bower S, Campbell S. Middle cerebral artery flow velocity waveforms in fetal hypoxaemia. *Br J Obstet Gynaecol* 1990; **97**: 797–803.
24. Bahado-Singh RO, Kovanci E, Jeffres A, Oz U, Deren O, Copel J, Mari G. The Doppler cerebroplacental ratio and perinatal outcome in intrauterine growth restriction. *Am J Obstet Gynecol* 1999; **180**: 750–756.
25. Akolekar R, Ciobanu A, Zingler E, Syngelaki A, Nicolaides KH. Routine assessment of cerebroplacental ratio at 35–37 weeks' gestation in the prediction of adverse perinatal outcome. *Am J Obstet Gynecol* 2019; **221**: 65.e1–18.
26. Semmler J, Abdel-Azim S, Anzoategui S, Zhang H, Nicolaides KH, Charakida M. The influence of birth weight on fetal cardiac indices at 35–37 weeks' gestation. *Ultrasound Obstet Gynecol* 2021; **57**: 266–272.
27. 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**: 42–48.
28. ACOG Practice Bulletin No. 202 Summary: Gestational Hypertension and Preeclampsia. *Obstet Gynecol* 2019; **133**: 211–214.
29. Hadlock FP. Harrist RB. Sharman RS. Deter RL. Park SK. Estimation of fetal weight with the use of head, body, and femur measurements–a prospective study. *Am J Obstet Gynecol* 1985; **151:** 333–337.
30. Hammami A, Mazer Zumaeta A, Syngelaki A, Akolekar R, Nicolaides KH. Ultrasonographic estimation of fetal weight: development of new model and assessment of performance of previous models. *Ultrasound Obstet Gynecol* 2018; **52**: 35–43.
31. 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**: 465–472.
32. Albaiges G, Missfelder-Lobos H, Lees C, Parra M, Nicolaides KH. One-stage screening for pregnancy complications by color Doppler assessment of the uterine arteries at 23 weeks' gestation. *Obstet Gynecol* 2000; **96**: 559–564.
33. Nicolaides K, 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. Aguilera J, Semmler J, Coronel C, Georgiopoulos G, Simpson J, Nicolaides KH, Charakida M. Paired maternal and fetal cardiac functional measurements in women with gestational diabetes mellitus at 35–36 weeks' gestation. *Am J Obstet Gynecol* 2020; **223**: 574.e1–15.
35. Hernandez-Andrade E, Benavides-Serralde JA, Cruz-Martinez R, Welsh A, Mancilla-Ramirez J. Evaluation of conventional Doppler fetal cardiac function parameters: E/A ratios, outflow tracts, and myocardial performance index. *Fetal Diagn Ther* 2012; **32**: 22–29.
36. Comas M, Crispi F, Gomez O, Puerto B, Figueras F, Gratacos E. Gestational age- and estimated fetal weight-adjusted reference ranges for myocardial tissue Doppler indices at 24–41 weeks' gestation. *Ultrasound Obstet Gynecol* 2011; **37**: 57–64.
37. Schneider C, McCrindle BW, Carvalho JS, Hornberger LK, McCarthy KP, Daubeney PEF. Development of *Z*-scores for fetal cardiac dimensions from echocardiography. *Ultrasound Obstet Gynecol* 2005; **26**: 599–605.
38. Api O, Balcin Emeksizm M, Api M, Ugurel V, Unal O. Modified myocardial performance index for evaluation of fetal cardiac function in pre-eclampsia. *Ultrasound Obstet Gynecol* 2009; **33**: 51–57.

