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

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What are the novel findings of this work

In pregnancies that subsequently develop preeclampsia there is evidence of fetal mild biventricular dysfunction.

What are the clinical implications of this work

The etiology and clinical significance of fetal cardiac changes in pregnancies that subsequently develop preeclampsia is not certain. However, the 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 the increased long term cardiovascular risk of these children.

ABSTRACT

Objective: To compare fetal cardiac morphology and function in pregnancies that subsequently developed preeclampsia (PE) with those that remained normotensive.

Methods: Prospective observational study at 35-37 weeks' gestation in 1,574 pregnancies, 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 the uterine artery pulsatility index (UtA-PI), 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 the pregnancies that remained normotensive.

Results: In the fetuses of mothers who subsequently developed PE, compared to normotensive pregnancies, there was a more globular right ventricle (reduced right ventricular sphericity index), reduced right ventricular systolic contractility and reduced left ventricular diastolic function as shown by an increase in E/A Doppler velocities; in a 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 incidence of low birthweight were higher, whereas, serum PlGF, CPR and interval between assessment and delivery were lower. These findings demonstrate that in pregnancies that develop PE there is evidence of impaired placentation, reflected in the low PlGF and reduced birthweight, 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.

INTRODUCTION

Fetal echocardiographic studies in pregnancies with preeclampsia (PE), compared to normotensive controls, have reported impairment in fetal cardiac function, which has been attributed to placenta vascular resistance and increased cardiac afterload [1-7]. But 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 pulsatility index (UtA-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 small for gestational age (SGA) neonates 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 is to compare fetal cardiac morphology and function in pregnancies that subsequently developed PE with those that remained normotensive.

METHODS

Study design

The study population included two groups of women with singleton pregnancies attending King's College Hospital, London, UK at 35^{+0} - 36^{+6} weeks' gestation: first, women having a routine hospital visit between April 2018 and November 2019, and second, women identified by routine screening using maternal history, MAP, PlGF and sFLT-1 between November 2019 and October 2020 as being at high risk for PE. The first group included 1,498 women without diabetes and hypertensive disorders that was previously reported [26] and 41 that subsequently developed PE, and the second group included 35 women that subsequently developed PE.

Women were not eligible to participate in this study if they were: <16 years, 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 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 and Asian), and method of conception (natural or assisted by *in-vitro* fertilization or use of ovulation drugs). Mean arterial pressure was measured using validated automated devices and 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 preeclampsia

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 mm Hg or diastolic blood pressure of >90 mmHg on at least two occasions four hours apart developing after 20 weeks' gestation in previously normotensive women) or chronic hypertension and at least one of the following: proteinuria (≥300 mg/24h 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 [28].

Fetal ultrasound and echocardiogram

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

Fetal heart was assessed using Canon Aplio i900 machines equipped with a convex transducer (i8CX1). Cardiac function was assessed in the right and left ventricle as previously described [34]. Indices which were used to assess systolic cardiac function included: tricuspid annular plane systolic excursion (TAPSE), global longitudinal right and left ventricular strain (figure 1) and myocardial performance index . Diastolic function was assessed in the left ventricle by calculating E/A ratio and E/e' [35,36]. The morphology of the right and left ventricle was assessed through the sphericity index by dividing base-to-apex length by transverse diameter [37,

Statistical analysis

Normally distributed continuous variables are presented as mean (standard deviation) and variables not normally distributed as median (interquantile range). Comparisons of variables between women who subsequently developed PE and those who did not were made using independent samples Student's T Test or the Mann-Whitney U Test and the chi-squared test for continuous and categorical variables, respectively.

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

Statistical analyses were conducted with STATA package, version 13.1 (StataCorp, College Station, Texas USA). We deemed statistical significance at $p < 0.05$.

RESULTS

The demographic characteristics, biochemical, ultrasonographic and cardiac indices of the study population of 1,574 pregnancies, including the 76 that subsequently developed PE are summarized in Table 1. In the PE group, compared to the non-PE group, the body mass index and MAP MoM, sFLT-1 MoM, sFLT-1 / PlGF ratio and incidence of birthweight <10th percentile were higher, whereas, CPR z-score, PlGF MoM, gestational age at delivery, interval between assessment and delivery and birthweight z-score were lower. There was no significant difference between the two groups, in maternal age, distribution of racial origin, method of conception, Ut-PI z-score and fetal heart rate.

In the PE group, compared to the non-PE group, there was reduced right ventricular global systolic strain, increased E/A and 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' or left ventricular sphericity index.

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

DISCUSSION

Main findings of the study

This large prospective screening study of 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 that 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 incidence of low birthweight were higher, whereas, serum PlGF, MCA-PI, CPR and interval between assessment and delivery were lower; there was no significant difference between the two groups in UtA-PI, which is consistent with previous studies investigating term-PE [19,20]. These findings demonstrate that in pregnancies that develop PE there is evidence of impaired placentation, reflected in the low PlGF and reduced birthweight, 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 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 was the only screening study investigating fetal cardiac morphometry and function before the development of the clinical features of PE, it 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 have varied in included number of patients with PE, which ranged from 19 [1] to 65 [4], gestational age at testing, which ranged from 20 [3] to 40 [4,38] weeks, 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 echocardiography [1,2,7,38] to more advanced methods, such as tissue Doppler imaging or speckle tracking echocardiography [3,5,6], and in the type of cardiac indices that were assessed [1-7,38].

Many, but not all, of the previous studies reported changes in a few cardiac indices in pregnancies complicated with PE 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 measured in GLS [6] and the left ventricles had increased diastolic filling ratios [2]. In agreement with Api *et al.*[38] , but in contrast to other previous reports [2,4,7], we found similar values of the myocardial performance index in the 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 birthweight as a continuous variable.

Strengths and limitations

The main strengths of this study are: first, 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, a strict comprehensive imaging protocol was applied which included novel imaging modalities, such as speckle tracking echocardiography; third, we adjusted 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 includes patients with late PE, allowing no conclusions to be drawn on fetal cardiac function before the development of early PE.

Conclusion

In summary we demonstrated that at 35-37 weeks' gestation, fetuses of mothers at risk to develop PE have biventricular functional changes. Although the etiology and the 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 the increased long term cardiovascular risk of these children.

Conflict of interest: The authors report no conflict of interest

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Figure legend

Figure 1. Fetal speckle tracking of the right ventricle in a normal pregnancy at 36 weeks' gestation.

Table 1. Demographic characteristics, biochemical, ultrasonographic and cardiac indices of the study population.

Variable	Controls (n = 1,498)	PE (n = 76)	P value
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 White Black Asian Mixed	 1,072 (71.6) 245 (16.4) 118 (7.9) 63 (4.2)	 53 (69.7) 18 (23.7) 4 (5.3) 1 (1.3)	0.214
Gestational age at scan (weeks)	36 (35.9, 36.4)	36 (35.7, 36.3)	0.009
Conception Natural *In vitro* fertilization Ovulation drugs	 1,,421 (94.9) 69 (4.6) 8 (0.5)	 68 (89.5) 8 (10.5) 0 (0.0)	0.054
Chronic hypertension	0 (0)	4 (5%)	<0.001
Pregestational or gestational diabetes mellitus	0(0)	6 (7.9)	<0.001
Uterine artery pulsatility index (z-score)	-0.14 (-0.81, 0.62)	0.17 (-0.9, 1.06)	0.075
Mean arterial pressure (MoM)	1.0 (0.07)	1.11(0.09)	<0.001
Umbilical artery pulsatility index (z-score)	-0.022 (-0.72, 0.67)	0.202 (-0.58, 0.95)	0.018
Middle cerebral artery pulsatility index (z-score)	-0.284 (-0.92, 0.45)	-0.579 (-1.05, -0.20)	0.002
Cerebroplacental ratio (z-score)	-0.15 (-0.78, 0.57)	-0.58 (-1.278, 0.211)	0.015
Placental growth factor (MoM)	0.91 (0.49, 1.67)	0.35 (0.199, 0.53)	<0.001
soluble fms-like tyrosine kinase-1 (MoM)	1.07 (0.77, 1.66)	2.51 (1.71, 3.78)	<0.001
soluble fms-like tyrosine kinase-1 / Placental growth factor	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
Gestational age at delivery (weeks)	40 (39.1, 40.9)	39.4 (38.4, 40.3)	<0.001
Interval to delivery (days)	27.5 (21,33)	25 (17, 29.5)	0.0012
Birthweight (z-score)	-0.03 (-0.72, 0.59)	-0.59 (-1.56, 0.13)	<0.001
Birthweight <10th percentile	146 (9.7%)	24 (31.6%)	<0.001
Fetal cardiac parameters			
Systolic parameters			
Left ventricular myocardial performance index	0.58 (0.5, 0.66)	0.57 (0.47, 0.65)	0.223
Left ventricular global longitudinal strain	-20.5 (-22.8, -18.3)	-19.25 (-22.55, -17.35)	0.187
Right ventricular global longitudinal strain	-19 (-21.1, -17.2)	-16.9 (-18.4, -15.2)	<0.001
Tricuspid annular plane systolic excursion	7.4 (6.4, 8.5)	7.2 (6.2, 8.4}	0.327
Isovolumic contraction time (sec)	0.04 (0.03, 0.05)	0.038 (0.03, 0.04)	0.007

Ejection time (sec)	0.163 (0.15, 0.17)	0.165 (0.15, 0.18)	0.391
Left ventricular diastolic parameters			
E/A	0.82 (0.72, 0.92)	0.84 (0.77, 1.02)	0.010
E/e'	9.12 (7.8, 10.8)	8.93 (8, 10.3)	0.872
Isovolumic relaxation time (msec)	0.052 (0.05, 0.06)	0.054 (0.05, 0.06)	0.391
Morphology			
Left ventricular sphericity index	1.94 (1.75, 2.11)	1.98 (1.67, 2.08)	0.401
Right ventricular sphericity index	1.72 (1.56, 1.88)	1.64 (1.45, 1.83)	0.022

Table 2. Multivariable linear regression analysis to assess the influence of maternal characteristics and birthweight on fetal echocardiographic parameters.

	Coefficient (95% Confidence interval)	**P value**
Right ventricular global longitudinal strain		
Preeclampsia	0.783 (0.473 to 1.093)	<0.001
Birthweight (z-score)	-0.134 (-0.199 to -0.069)	<0.001
Age (years)	0.007 (-0.006 to 0.020)	0.311
Racial origin White (reference) Black Asian Mixed	 0.096 (-0.083 to 0.274) 0.041 (-0.195 to 0.277) -0.039 (-0.351 to 0.291)	 0.292 0.735 0.853
Method of conception Natural (reference) *In vitro* fertilization Ovulation drugs	 0.705 (-0.031 to 1.441) -0.135 (-0.200 to 0.470)	
Body mass index (kg/m^2)	-0.002 (-0.017 to 0.014)	0.817
Gestational age at entry (weeks)	0.129 (0.011 to 0.269)	0.072
Chronic hypertension	-0.095 (-1.410 to 1.219)	0.887
Pregestational or gestational diabetes	-0.996 (-2.302 to 0.311)	0.135
Left ventricular diastolic index EA		
Preeclampsia	0.301 (0.049 to 0.566)	0.020
Birthweight (z-score)	-0.081 (-0.135 to -0.026)	0.004
Age (years)	-0.001 (-0.007 to 0.012)	0.833
Racial origin White (reference) Black Asian Mixed	 0.089 (-0.054 to 0.234) -0.191 (-0.384 to 0.002) 0.251 (-0.011 to 0.512)	 0.222 0.053 0.060
Method of conception Natural (reference) *In vitro* fertilization Ovulation drugs	 0.233 (-0.464 to 0.931) 0.029 (-0.274 to 0.214)	 0.811 0.815
Body mass index (kg/m^2)	-0.004 (-0.016 to 0.007)	0.504
Gestational age at entry (weeks)	0.073 (-0.040 to 0.186)	0.207
Chronic hypertension	0.251 (-0.767 to 1.269)	0.629
Pregestational or gestational diabetes	-0.221 (-1.064 to 0.622)	0.608

Right ventricular sphericity index		
Preeclampsia	-0.326 (-0.636 to 0.016)	0.039
Birthweight (z-score)	0.080 (0.013 to 0.148)	0.020
Age (years)	-0.006 (-0.020 to 0.008)	0.420
Racial origin White (reference) Black Asian Mixed	 -0.146 (-0.329 to 0.038) -0.161 (-0.409 to 0.088) 0.169 (-0.158 to 0.496)	 0.120 0.204 0.311
Method of conception Natural (reference) *In vitro* fertilization Ovulation drugs	 -0.211 (-0.993 to 0.571) -0.211 (-0.543 to 0.122)	 0.597 0.214
Body mass index (kg/m^2)	-0.002 (-0.018 to 0.014)	0.805
Gestational age at entry (weeks)	-0.100 (-0.245 to 0.045)	0.175
Chronic hypertension	1.220 (-0.171 to 2.611)	0.085
Pregestational or gestational diabetes	-0.132 (-1.515 to 1.250)	0.851

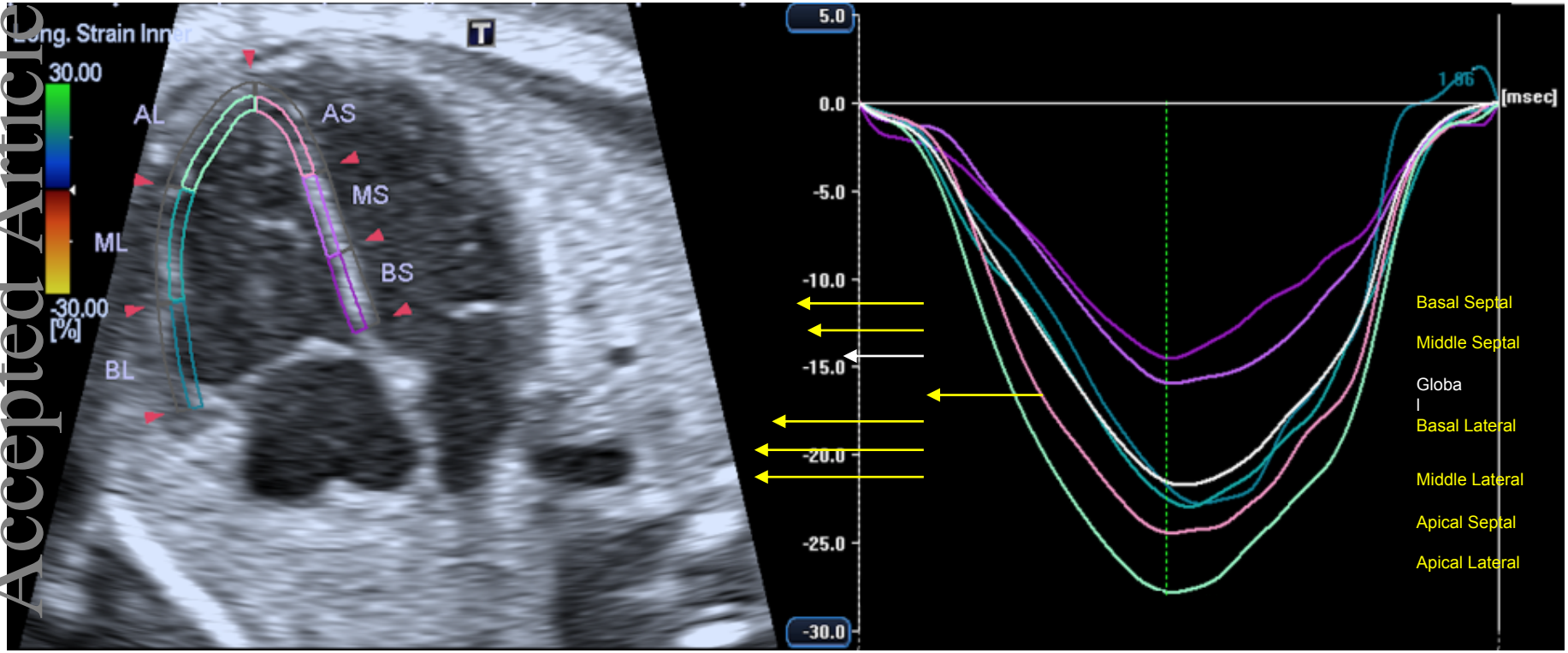

Figure 1