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Impaired placental perfusion and major fetal cardiac defects

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KEYWORDS: congenital heart defect; pre-eclampsia; ultrasound screening; uterine artery pulsatility index

ABSTRACT

Objective *To investigate the relationship between fetal congenital heart defects (CHD) and placental perfusion assessed by uterine artery pulsatility index (UtA-PI), in relation to development of pre-eclampsia (PE).*

Methods *This was a prospective screening study of singleton pregnancies at 19–24 weeks' gestation. Transvaginal ultrasound was used to measure UtA-PI and the values were converted into multiples of the normal median (MoM). Median MoM values in pregnancies with a fetus with isolated major CHD were compared to those without CHD, in relation to development of PE.*

Results *The 91 407 singleton pregnancies fulfilling the entry criteria included 206 (0.23%) with isolated major fetal CHD and 91 201 without CHD. The prevalence of PE was 4.4% in pregnancies with fetal CHD and 2.7% in those without CHD (relative risk (RR), 1.6 (95% CI, 0.84–3.04);* $P = 0.150$*); the respective values for preterm PE with delivery at < 37 weeks' gestation were 2.4% and 0.7% (RR, 3.4 (95% CI, 1.42–8.09);* $P = 0.006$*). In the total population, median UtA-PI MoM was significantly higher in those that developed PE compared to those without PE (1.22 (interquartile range (IQR), 0.94–1.57)* vs *1.00 (IQR, 0.84–1.19);* $P < 0.0001$*) and, in the PE group, the median UtA-PI MoM was inversely related to gestational age at delivery (*$r = -0.458$*;* $P < 0.0001$*). The same pattern of inverse relationship between UtA-PI MoM and gestational age at delivery with PE was observed in pregnancies with and those without CHD, but, in the CHD group, compared to those without CHD, UtA-PI was significantly higher both in pregnancies with and in those without PE.*

Conclusions *In pregnancies both with and without fetal CHD that develop PE, impedance to flow in the UtAs is increased and this increase is particularly marked in those with preterm PE. The prevalence of preterm PE is more than three times higher in pregnancies with than those without fetal major CHD, and the prevalence of major CHD in pregnancies with preterm PE is also more than three times higher than in those without PE. However, > 97% of pregnancies with fetal CHD do not develop preterm PE and > 99% of pregnancies with preterm PE are not associated with fetal CHD.* Copyright © 2018 ISUOG. Published by John Wiley & Sons Ltd.

INTRODUCTION

A common pathophysiological mechanism for maternal pre-eclampsia (PE) and fetal congenital heart defects (CHD) is suggested by the findings that, first, in both conditions there is evidence of impaired placental angiogenesis and, second, there is epidemiological evidence of an association between PE and CHD. In pregnancies that develop PE, the maternal serum level of the proangiogenic placental growth factor (PlGF) at 11–13 weeks' gestation is reduced and the deviation from normal is greater for early than late PE[1–3]. A study of 68 pregnancies with isolated major fetal CHD and 340 normal controls at 11–13 weeks' gestation reported that, in the CHD group, compared to the controls, maternal serum levels of PlGF were lower[4]. This finding was confirmed in a prospective screening study in 50 094 singleton pregnancies at 11–13 weeks, which demonstrated that, in the group of 196 pregnancies with isolated major fetal CHD, serum PlGF was reduced[5]. A study of 1 942 072 neonates born in Canada between 1989 and 2012, reported that the prevalence of CHD was higher in infants from pregnancies with than those from pregnancies without PE, and this was particularly so for early PE < 34 weeks' gestation (relative risk (RR), 5.5 (95% CI, 5.0–6.2))[6]. A study of 914 703 singleton births without chromosomal abnormalities in Norway between 1994 and 2009, reported that the prevalence of severe CHD was higher in infants of pregnancies with than those of pregnancies without PE, and this was particularly so for early PE (RR, 2.8 (95% CI,

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1.8–4.4))[7]. A study of 1 972 857 singleton births without chromosomal abnormalities in Denmark between 1978 and 2011, reported that, in the presence of fetal CHD, there is a seven-fold increased risk of early PE[8].

In PE, particularly preterm PE, there is evidence from Doppler studies of impaired uteroplacental perfusion, reflected in increased uterine artery pulsatility index (UtA-PI)[2,9–11]. The objective of this study is to investigate further the association between fetal CHD and maternal PE by examining second-trimester UtA-PI in pregnancies with and those without major CDH.

METHODS

Study population

This was a prospective observational study in women with a singleton pregnancy attending for a routine hospital visit at 19 + 0 to 24 + 6 weeks' gestation at King's College Hospital, London, UK or Medway Maritime Hospital, Gillingham, UK, between April 2006 and October 2017. This visit included recording of maternal demographic characteristics and medical history, measurement of maternal weight and height, ultrasound examination for fetal anatomy and growth, and measurement of the left and right UtA-PI by transvaginal color Doppler ultrasound and calculation of the mean value of the two arteries[12]. The ultrasound examination of the fetus was carried out transabdominally and included a sweep through the heart in the transverse plane for assessment of the four-chamber view, outflow tracts and three-vessel view of the heart and great vessels. The scans were carried out by sonographers who had obtained the appropriate Fetal Medicine Foundation certificate of competence in ultrasound scanning, and all cases of suspected fetal abnormality were examined by a fetal medicine specialist. Likewise, all cases of suspected fetal cardiac defect were examined by a fetal cardiologist. Gestational age was determined by the measurement of fetal crown–rump length at 11–13 weeks or fetal head circumference at 19–24 weeks[13,14]. The women gave written informed consent to participate in the study, which was approved by the NHS Research Ethics Committee.

All neonates were examined by a pediatrician. Prenatal and neonatal findings were recorded in computerized databases. Data on pregnancy outcome from women who booked for obstetric care in our hospitals but delivered in other hospitals were obtained from either the maternity computerized records of these hospitals or the general medical practitioners of the women.

The obstetric records of all women with pre-existing or pregnancy-associated hypertension were examined to determine if the condition was chronic hypertension, PE or non-proteinuric gestational hypertension. The definition of PE was that of the International Society for the Study of Hypertension in Pregnancy[15]. Preterm PE and early PE were defined as delivery with PE at < 37 and < 34 weeks' gestation, respectively.

Inclusion and exclusion criteria

In this study, we compared the measurements of UtA-PI in pregnancies with and those without major fetal cardiac defects. The inclusion criterion for the control group was pregnancy delivering a non-malformed liveborn or stillborn infant at > 24 weeks' gestation. We excluded pregnancies with aneuploidy or major fetal abnormality. In the group with cardiac defects, we included all cases with major cardiac defects diagnosed by pediatric cardiologists antenatally and/or in the neonatal period. Abnormalities suspected antenatally but not confirmed in the neonates were not included. In contrast, the prenatal diagnosis in cases of stillbirth were assumed to be correct because, in these cases, postmortem examination was not performed systematically. We excluded all cases with aneuploidy and non-cardiac defects diagnosed prenatally or in the neonatal period. The following fetal cardiac defects were not included: first, ventricular septal defect not requiring surgery; second, right aortic arch, persistent left superior vena cava and aberrant right subclavian artery, because these are variants of normal rather than true defects; and, third, ventricular aneurysm or cardiac tumor developing during the second or third trimester of pregnancy.

Patient characteristics

Recording of patient characteristics included maternal age, racial origin (white, black, South Asian, East Asian or mixed), method of conception (spontaneous or assisted conception requiring the use of ovulation drugs or *in-vitro* fertilization), cigarette smoking during pregnancy, medical history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus or antiphospholipid syndrome, family history of PE in the mother of the patient and obstetric history including parity (parous or nulliparous if no previous pregnancy at or after 24 weeks), previous pregnancy with PE, and interval in years between birth of the last child and estimated date of conception of the current pregnancy. Maternal weight and height were measured and body mass index was calculated.

Statistical analysis

Comparison of the maternal characteristics between the outcome groups was by the χ^2 test or Fisher's exact test for categorical variables and Mann–Whitney *U*-test for continuous variables. The measured values of UtA-PI were expressed as multiples of the normal median (MoM) after adjustment for those characteristics that provide a substantial contribution to their $\log_{10}$ transformed value[16]. Median UtA-PI MoM values were compared between outcome groups by Mann–Whitney *U*-test. Regression analysis was used to examine the association of UtA-PI MoM with gestational age at delivery. The statistical software package SPSS 22.0 (IBM Corp., Armonk, NY, USA) was used for data analyses.

RESULTS

The 91 407 singleton pregnancies fulfilling the entry criteria included 206 (0.23%) with isolated major fetal CHD and 91 201 without CHD. The median gestational age at ultrasound examination was 22.1 (interquartile range (IQR), 20.6–22.6) weeks. The maternal and pregnancy characteristics in the outcome groups are compared in Table 1. There were no significant differences between the groups in maternal characteristics and medical history but, in the CHD group, the gestational age at delivery was lower and the incidence of preterm PE was higher.

Table 1 Maternal and pregnancy characteristics of study population of 91 407 singleton pregnancies, according to presence of fetal congenital heart defect (CHD)

Characteristic	*No CHD* (n = *91 201*)	*CHD* (n = *206*)
Age (years)	30.8 (27.3–34.7)	31.4 (25.9–34.7)
Weight (kg)	71.4 (63.8–82.0)	70.0 (60.8–82.0)
Height (cm)	165 (160–169)	165 (160–169)
Racial origin		
White	65 076 (71.4)	156 (75.7)
Black	18 005 (19.7)	33 (16.0)
South Asian	3871 (4.2)	9 (4.4)
East Asian	1837 (2.0)	4 (1.9)
Mixed	2412 (2.6)	4 (1.9)
Conception		
Natural	88 232 (96.7)	197 (95.6)
Ovulation drugs	822 (0.9)	4 (1.9)
In-vitro fertilization	2147 (2.4)	5 (2.4)
Cigarette smoker	8866 (9.7)	16 (7.8)
Chronic hypertension	1246 (1.4)	0 (0.0)
SLE/APS	183 (0.2)	0 (0.0)
Diabetes mellitus	790 (0.9)	1 (0.5)
Parity		
Nulliparous	44 303 (48.6)	97 (47.1)
Parous, no previous PE	44 089 (48.3)	103 (50.0)
Parous, previous PE	2809 (3.1)	6 (2.9)
Family history of PE	3541 (3.9)	3 (1.5)
Interpregnancy interval (years)*	3.0 (2.0–5.1)	3.0 (2.4–4.0)
Gestational age at delivery (weeks)	40.0 (39.0–40.9)	38.6 (37.4–39.3)†
PE		
Any	2490 (2.7)	9 (4.4)
Delivery < 37 weeks	653 (0.7)	5 (2.4)‡
Delivery < 34 weeks	300 (0.3)	1 (0.5)

Data are given as median (interquartile range) or *n* (%). *Calculated for parous women. For comparison with no CHD group: †$P < 0.0001$; ‡$P < 0.01$. APS, antiphospholipid syndrome; PE, pre-eclampsia; SLE, systemic lupus erythematosus.

The major cardiac defects included tetralogy of Fallot ($n = 50$), transposition of the great arteries ($n = 29$), coarctation of the aorta ($n = 27$), pulmonary atresia or stenosis ($n = 22$), atrioventricular septal defect ($n = 19$), left atrial isomerism ($n = 11$), hypoplastic left or right heart ($n = 10$), tricuspid atresia or stenosis ($n = 8$), double outlet right ventricle ($n = 6$), aortic stenosis ($n = 5$), large ventricular septal defect requiring surgery ($n = 4$), common arterial trunk ($n = 3$) and complex CHD ($n = 12$).

The prevalence of PE was 4.4% (9 of 206) in those with CHD and 2.7% (2490 of 91 201) in those without CHD (RR, 1.6 (95% CI, 0.84–3.04); $P = 0.150$); the respective values for preterm PE were 2.4% (5 of 206) and 0.7% (653 of 91 201) (RR, 3.4 (95% CI, 1.42–8.09); $P = 0.006$). Therefore, the prevalence of major CHD was 0.36% (9 of 2499) in pregnancies with PE and 0.22% (197 of 88 908) in those without PE (RR, 1.6 (95% CI, 0.83–3.17); $P = 0.153$); the respective values for preterm PE were 0.76% (5 of 658) and 0.22% (201 of 90 749) (RR, 3.4 (95% CI, 1.42–8.31); $P = 0.006$).

In the total population, the median UtA-PI MoM was significantly higher in those that developed PE compared to those without PE (1.22 (IQR, 0.94–1.57) *vs* 1.00 (IQR, 0.84–1.19); $P < 0.0001$) and, in the PE group, the median UtA-PI MoM was inversely related to gestational age at delivery ($r = -0.458$; $P < 0.0001$). The same pattern was observed in pregnancies with and those without CHD but, in the CHD group, compared to those without CHD, UtA-PI was significantly higher both in pregnancies with and in those without PE (Table 2).

DISCUSSION

Main findings of study

The findings of this study, that the prevalence of preterm PE is more than three times higher in pregnancies with than those without major fetal CHD, and that the prevalence of major CHD in pregnancies with preterm PE is also more than three times higher in pregnancies with than in those without PE, are consistent with those of large epidemiological studies. However, the study has also highlighted that > 97% of pregnancies with fetal

Table 2 Median uterine artery pulsatility index (UtA-PI) multiples of the median (MoM) in pregnancies with and those without fetal congenital heart defect (CHD), according to development of pre-eclampsia

	CHD (n = *206*)		*No CHD* (n = *91 201*)		
Outcome	n	*UtA-PI MoM*	n	*UtA-PI MoM*	P
Pre-eclampsia					
Any	9	1.82 (1.25–2.03)	2490	1.22 (0.94–1.57)	0.017
Preterm (delivery < 37 weeks)	5	1.88 (1.35–2.03)	653	1.59 (1.28–1.93)	0.482
Early (delivery < 34 weeks)	1	1.87 (1.77–1.87)	300	1.74 (1.47–2.07)	0.721
No pre-eclampsia	197	1.05 (0.88–1.31)	88 711	1.00 (0.84–1.19)	0.001

Values in parentheses are interquartile range.

CHD do not develop preterm PE and > 99% of pregnancies with preterm PE are not associated with fetal CHD. There is coincidence of both CHD and preterm PE in about five per 100 000 pregnancies.

The epidemiological studies highlighting the association between fetal CHD and PE reported that the increased risk affected mainly the rate of early PE with delivery at < 34 weeks' gestation[6–8]. However, the incidence of such early PE in the general population is very low (0.2–0.3%)[7,8] and, even with a seven-fold increased incidence of cases of fetal CHD[8], the expected incidence in such cases would be only 1–2%.

We found that in pregnancies both with and without CHD that develop PE, impedance to flow in the uterine arteries is increased and this increase is particularly marked in those with preterm PE. Several previous studies have reported that, in pregnancies that develop PE, UtA-PI MoM is increased in the first, second and third trimesters and that the increase is related inversely to the gestational age at which delivery is undertaken for maternal and/or fetal indications[2,3,9–11,17–23]. These Doppler ultrasound findings have been interpreted as supportive evidence for the results of histological studies that PE is associated with impairment of the physiological process of trophoblastic invasion of the maternal spiral arteries and their conversion from narrow muscular vessels to dilated non-muscular channels[24–26].

In a small number of pregnancies, there is coincidence of CHD and impaired placentation, which is reflected in low first-trimester serum PlGF[4,5] and high second-trimester UtA-PI. The pathophysiological mechanism for such an association is uncertain. There is emerging evidence that the placenta and fetal heart share several developmental pathways and they consequently share a common vulnerability to genetic defects and early environmental insults, a phenomenon known as the heart–placenta axis[27]. There is also evidence from animal studies that placental insufficiency can cause CHD, but what is not so evident is how the interaction between genetic defects and placental insufficiency alters heart development and how that interaction contributes to CHD[28]. In our study, there were no significant differences in maternal characteristics between the CHD and non-CHD groups but, in the CHD group, even in the absence of PE, UtA-PI was increased; it is therefore possible that, in a small number of cases, there is an underlying genetic abnormality that affects both the development of the heart and that of the placenta, and, in such cases, reduced placental perfusion with consequent hypoxia could result in CHD.

Strengths and limitations

The strengths of this study are, first, screening of a large population of pregnant women attending for routine assessment at 19–24 weeks' gestation, second, routine screening for cardiac defects based on a standardized protocol, examination of all cases with suspected CHD by a fetal cardiologist and examination of all neonates by a pediatrician, and, third, use of a specific methodology and appropriately trained doctors to obtain measurements of UtA-PI and expression of the values as MoMs after adjustment for factors that affect the measurements. A limitation of the study is that, although we examined 91 407 pregnancies, the number of isolated major cardiac defects was small; nevertheless, the sample size was sufficient to demonstrate that the association between fetal CHD and preterm PE was significant. We did not investigate minor cardiac defects, such as ventricular septal defects not requiring surgery, because prenatal detection during routine screening is likely to underestimate the true incidence of the defect.

Comparison with other studies

In a previous screening study at 11–13 weeks' gestation, there was no significant difference in median UtA-PI MoM between 196 pregnancies with and 49 898 without major fetal CHD, but, in that study, the values in pregnancies with PE were not reported[5]. Another study at 18–37 weeks' gestation, involving 65 pregnancies with isolated major CHD that did not develop PE and 204 uncomplicated pregnancies delivering phenotypically normal neonates, reported no significant differences in UtA-PI between the two groups[29].

Implications for clinical practice

In the presence of CHD, there is a three-to-four-fold increase in risk of preterm PE and such increase is similar to that of other risk factors, such as black racial origin, family history of PE and diabetes mellitus, but less than the 13-fold increase in women with chronic hypertension and the six-fold increase in those with previous PE[9]. In screening for preterm PE by the competing risks model, the finding of isolated major CHD, observed in about 0.2% of pregnancies, could be included in the algorithm for calculation of the prior risk, which is then combined with the results of biomarkers for estimation of the patient-specific posterior risk[30]. This would be particularly useful in the assessment of risk for preterm PE because the high-risk group would benefit from prophylactic use of aspirin[31]. In the case of second-trimester diagnosis of CHD, the pregnancies would benefit from close monitoring for development of PE, which would be useful in deciding the best time and method of delivery.

Conclusion

In pregnancies both with and without fetal CHD that develop PE, impedance to flow in the uterine arteries is increased and this increase is particularly marked in those with preterm PE. The prevalence of preterm PE is more than three times higher in pregnancies with than those without fetal major CHD and the prevalence of major CHD in pregnancies with preterm PE is also more than three times higher than in those without PE.

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