Impaired placental perfusion and major fetal cardiac defects

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Abstract

Objectives: 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 preeclampsia (PE).

Methods: This was a prospective screening study in singleton pregnancies at 19-24 weeks' gestation. Transvaginal ultrasound was used to measure the UtA-PI and the values were converted into multiples of the normal median (MoM). Median MoM values in pregnancies with fetuses 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 those with CHD and 2.7% in those without CHD (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, 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 of inverse relationship between UtA-PI MoM and gestational age at delivery with PE was observed in pregnancies with and 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 both pregnancies 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 3 times higher in pregnancies with than without fetal major CHD and the prevalence of major CHD in pregnancies with preterm-PE is also more than 3 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.

Introduction

A common pathophysiological mechanism for maternal preeclampsia (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 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 without PE and this was particularly so for early-PE <34 weeks' gestation (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 without PE and this was particularly so for early-PE (RR 2.8, 95% CI 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 7-fold increase of 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 without major CDH.

Methods

Study population

This was a prospective observational study in women with singleton pregnancies attending for a routine hospital visit at 19^{+0} - 24^{+6} weeks' gestation at King's College Hospital, London 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 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 abnormalities 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 the 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 computerised databases. Data on pregnancy outcome from women who booked for obstetric care in our hospitals but delivered in other hospitals were obtained either from the maternity computerised records in 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-E 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 without major fetal cardiac defects. The inclusion criterion for the control group was pregnancy delivering a non-malformed live birth or stillbirth at >24 weeks' gestation. We excluded pregnancies with aneuploidies and major fetal abnormalities. In the group with cardiac defects we included all cases with major cardiac defects diagnosed by pediatric cardiologists either 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 stillbirths were assumed to be correct because in these cases post mortem examination was not performed systematically. We excluded all aneuploidies and non-cardiac defects diagnosed prenatally or in the neonatal period. The following fetal cardiac defects were not included: first, ventricular septal defects 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 aneurysms or cardiac tumors developing during the second and third trimesters of pregnancy.

Patient characteristics

Recording of patient characteristics included maternal age, racial origin (White, Black, South Asian, East Asian and 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 anti-phospholipid syndrome, family history of PE in the mother of the patient and obstetric history including parity (parous or nulliparous if no previous pregnancies 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 the BMI was calculated.

Statistical analysis

Comparison of the maternal characteristics between the outcome groups was by the $\chi 2$-square test or Fisher's exact test for categorical variables and Mann-Whitney U-test for continuous variables, respectively. The measured values of UtA-PI were expressed as a multiple 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 SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp, 2013) was used for the 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 (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.

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 (n=12).

The prevalence of preeclampsia (PE) was 4.4% (9 of 206) in those with CHD and 2.7% (2,490 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 2,499) 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 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 the study

The findings of the study, that the prevalence of preterm-PE is more than 3 times higher in pregnancies with than without major fetal CHD and the prevalence of major CHD in pregnancies with preterm-PE is also more than 3 times higher 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 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 5 per 100,000 pregnancies.

The epidemiological studies highlighting the association between fetal CHD and PE reported that the increased risk was mainly affecting 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 7-fold increase in the case of fetal CHD[8] the expected incidence in such cases would be only 1-2%.

We found that both in pregnancies with and in those 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 inversely related to the gestational age at which delivery is undertaken for maternal and / or fetal indications.[2,3,9-11,17-24] 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. [25-27]

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.[28] 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.[29] 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.[30]

Implications for clinical practice

In the presence of CHD there is a 3-4 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 6-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.[32] 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.[33] 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 both pregnancies 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 3 times higher in pregnancies with than without fetal major CHD and the prevalence of major CHD in pregnancies with preterm-PE is also more than 3 times higher than in those without PE.

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Table 1. Maternal and pregnancy characteristics of the study population.

Maternal characteristics	**No cardiac defects (n=91,201)**	**Cardiac defects (n=206)**
Age in years, median (IQR)	30.8 (27.3-34.7)	31.4 (25.9-34.7)
Weight in Kg, median (IQR)	71.4 (63.8-82.0)	70.0 (60.8-82.0)
Height in cm, median (IQR)	165 (160-169)	165 (160-169)
Racial origin		
White, n (%)	65,076 (71.4)	156 (75.7)
Black, n (%)	18,005 (19.7)	33 (16.0)
South Asian, n (%)	3,871 (4.2)	9 (4.4)
East Asian, n (%)	1,837 (2.0)	4 (1.9)
Mixed, n (%)	2,412 (2.6)	4 (1.9)
Conception		
Natural, n (%)	88,232 (96.7)	197 (95.6)
Use of ovulation drugs, n (%)	822 (0.9)	4 (1.9)
In vitro fertilization, n (%)	2,147 (2.4)	5 (2.4)
Cigarette smoking, n (%)	8,866 (9.7)	16 (7.8)
Chronic hypertension, n (%)	1,246 (1.4)	0 (0.0)
SLE / APS, n (%)	183 (0.2)	0
Diabetes mellitus, n (%)	790 (0.9)	1 (0.5)
Parity		
Nulliparous, n (%)	44,303 (48.6)	97 (47.1)
Parous no previous PE, n (%)	44,089 (48.3)	103 (50.0)
Parous previous PE, n (%)	2,809 (3.1)	6 (2.9)
Family history of PE, n (%)	3,541 (3.9)	3 (1.5)
Pregnancy interval in years, median (IQR)*	3.0 (2.0-5.1)	3.0 (2.4-4.0)
Gestation at delivery in weeks, median (IQR)	40.0 (39.0-40.9)	38.6 (37.4-39.3) [a]
Preeclampsia		
Any	2,490 (2.7)	9 (4.4)
Delivery at <37 w, n (%)	653 (0.7)	5 (2.4) [b]
Delivery at <34 w, n (%)	300 (0.3)	1 (0.7)

***** Calculated for parous women

[a] = p <0.0001, [b] = p <0.01,

PE = preeclampsia; IQR = interquartile range; SLE = systemic erythematosus lupus; APS = antiphospholipid syndrome.

Table 2. Median uterine artery pulsatility index multiple of the median, with interquartile range in the pregnancies with and without congenital heart defects.

Outcome	Heart defects (n=206)		No heart defects (n=91,201)		P value
	n	UtA-PI MoM (IQR)	n	UtA-PI MoM (IQR)	
Preeclampsia					
All	9	1.82 (1.25-2.03)	2,490	1.22 (0.94-1.57)	0.017
Preterm	5	1.88 (1.35-2.03)	653	1.59 (1.28-1.93)	0.482
Early	1	1.87 (1.77-1.87)	300	1.74 (1.47-2.07)	0.721
No preeclampsia	197	1.05 (0.88-1.31)	88,711	1.00 (0.84-1.19)	0.001