Major cardiac defects and placental dysfunction at 11-13 weeks' gestation

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Abstract

Objectives: To investigate the relationship between fetal major cardiac defects and markers of placental perfusion and function.

Methods: This was a prospective screening study in singleton pregnancies at 11-13 weeks' gestation. Uterine artery pulsatility index (UTPI), serum pregnancy associated plasma protein-A (PAPP-A) and placental growth factor (PLGF) were measured and the values were converted into multiples of the normal median (MoM). Median MoM values in fetuses with isolated major cardiac defects were compared to those in fetuses without major defects.

Results: The 50,094 singleton pregnancies fulfilling the entry criteria included 49,898 pregnancies with a normal cardiac anatomy and 196 (0.39%) with major congenital cardiac defects; 73 (37.2%) with conotruncal defects, 63 (32.1%) with left ventricular outflow tract (LVOT) defects and 60 (30.6%) with valvular defects. In the group of cardiac defects, compared to controls, there was lower median PAPP-A MoM (0.81 vs 1.00, $p<0.0001$) and PLGF MoM (0.78 vs 1.00, $p<0.0001$) but no significant difference in UTPI MoM (1.01 vs 1.00, $p=0.162$).

Conclusions: In pregnancies with isolated major cardiac defects there is evidence of placental dysfunction in the absence of impaired placental perfusion.

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Introduction

Congenital heart defects (CHD) are considered to be major if they require surgery or interventional cardiac catheterization within the first year of life, and such defects are often associated with fetal growth restriction (FGR).[1-4] It is uncertain whether the cause of FGR is of placental origin or genetic as is the case with many fetal abnormalities.[5-8] A study of 68 cases of isolated major CHDs and 340 normal controls at 11-13 weeks' gestation reported that in the CHD group maternal serum levels of placental growth factor (PLGF) were decreased, but there was no significant change in the levels of pregnancy associated plasma protein-A (PAPP-A) or uterine artery pulsatility index (UTPI); these findings suggested that in CHD there is evidence of impaired placental angiogenesis in the absence of impaired placental perfusion and function.[9]

The objective of this study is to investigate further the relationship between isolated major CHDs and markers of placental perfusion and function.

Methods

Study population

The data for this study were derived from prospective screening for adverse obstetric outcomes in women attending for routine pregnancy care at 11^{+0}-13^{+6} weeks' gestation at King's College Hospital and Medway Maritime Hospital, United Kingdom. This visit, included recording of maternal demographic characteristics and obstetric and medical history, measurement of maternal weight and height, ultrasound examination for the measurement of the fetal crown-rump length (CRL) to determine gestational age,[10] measurement of the fetal nuchal translucency (NT) thickness, maternal serum PAPP-A and free ß-human chorionic gonadotropin for combined screening for fetal aneuploidies,[11] examination of the fetal anatomy for the diagnosis of major fetal defects,[12] and transabdominal colour Doppler ultrasound for the measurement of UTPI.[13] The women were screened between March 2006 and October 2015 and gave written informed consent to participate in the study, which was approved by the Ethics Committee.

The policy in our hospitals was to offer routinely a second ultrasound examination at 20^{+0}-23^{+6} weeks. This scan was performed transabdominally and involved systematic detailed examination of the fetus, including a sweep through the heart in transverse plane to include the four-chamber view, outflow tracts and three vessel view of the heart and great vessels. 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. In addition, the cardiologists carried out fetal echocardiography at 11-14 weeks in those with nuchal translucency above the 99th centile and at 20 weeks in those with nuchal translucency between the 95th and 99th centiles.

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.

Inclusion and exclusion criteria

In this study we compared the measurements of serum PAPP-A and PLGF, fetal NT and UTPI at 11-13 weeks in pregnancies with major fetal cardiac defects and those resulting in live birth of phenotypically normal babies. We excluded all aneuploidies and non-cardiac defects diagnosed prenatally or in the neonatal period.

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 terminations and miscarriages at < 24 weeks or stillbirths at $\geq$ 24 weeks were assumed to be correct because in these cases postmortem examination was not performed systematically. The following fetal cardiac defects were not included: firstly, ventricular septal defects because they are generally not considered to be major defects, secondly, right aortic arch, persistent left superior vena cava and aberrant right subclavian artery because these are variants of normal rather than true defects and thirdly, cardiac tumors developing during the second and third trimesters of pregnancy because these defects would not be expected to have any manifestations during the 11-13 weeks scan.

We excluded all aneuploidies and non-cardiac defects diagnosed prenatally or in the neonatal period. We also excluded pregnancies with no abnormal fetal findings at the 11-13 weeks scan and / or the 20-23 weeks scan which resulted in termination, miscarriage or

stillbirth and those lost to follow up.

Classification of cardiac defects

Major cardiac defects were subdivided into three groups as in a previous publication.[9] First, conotruncal cardiac defects, which included tetralogy of Fallot, transposition of great arteries, double outlet right ventricle, and common arterial trunk. Second, left ventricular outflow tract (LVOT) defects, which included hypoplastic left heart syndrome, aortic stenosis, coarctation of aorta, and interrupted aortic arch. Third, valvular defects, which included atrioventricular septal defects, tricuspid stenosis, dysplasia or atresia, pulmonary stenosis or atresia, and Ebstein's anomaly.

Statistical analysis

Data from continuous variables were expressed as medians and interquartile ranges and from categorical data as n (%). 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. A p value of < 0.05 was considered significant. *Post-hoc* Bonferroni correction was used for multiple comparisons.

The measured values of PAPP-A, PLGF and UTPI were $\log_{10}$ transformed to make their distributions Gaussian and each value was expressed as a multiple of the normal median (MoM) after adjustment for those characteristics that provide a substantial contribution to the $\log_{10}$ transformed value.[14-16] The measured fetal NT was expressed as a difference from the expected normal mean for fetal CRL (delta value).[17] Median MoM values of biomarkers were compared between outcome groups. We divided congenital cardiac defects into those with fetal NT< 3.5 and those with measurements ≥ 3.5 and compared the significant of difference in the biomarkers in each group. Non-parametric bivariate correlation analysis was used to examine the association between biomarkers in pregnancies with congenital cardiac defects and those with normal cardiac anatomy.

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

Study population

The 50,094 singleton pregnancies fulfilling the entry criteria included 49,898 pregnancies with a normal cardiac anatomy and 196 (0.4%) with major congenital cardiac defects; 73 (37.2%) with conotruncal defects, 63 (32.1%) with LVOT defects and 60 (30.6%) with valvular abnormalities. The maternal and pregnancy characteristics in the outcome groups are compared in Table 1.

Biomarkers in outcome groups

In the cardiac defect group, compared to the normal cardiac anatomy group, the median PlGF MoM and PAPP-A MoM were lower, fetal delta NT was higher and UTPI MoM was not significantly different. In all the sub-groups of congenital cardiac defects, this trend was maintained with lower PLGF and PAPP-A MoMs, higher delta fetal NT but no significant difference in UTPI MoM (Table 2, Figure 1).

A significant association between PlGF MoM and delta fetal NT was found in the group with cardiac defects but not in those without defects (Table 3). In fetuses with cardiac defects and increased NT PLGF MoM was significantly lower in those with increased NT, compared to those with normal NT (0.56 vs 0.83 MoM; p=0.007) (Figure 2); there was no significant difference in PAPP-A MoM between the two groups (0.84 vs 0.79 MoM; p=0.586).

Discussion

Main findings of the study

The findings of the study demonstrate that in pregnancies with major cardiac defects, compared to those with normal cardiac anatomy, serum PAPP-A and PlGF are significantly lower, but there is no significant difference in UTPI. These findings suggest that in fetal cardiac defects there is evidence of placental dysfunction in the absence of impairment in placental perfusion. In pregnancies with major cardiac defects, compared to those without, fetal NT is increased and in those with high NT serum PLGF is lower than in those with normal NT; this finding is compatible with that of a previous study which suggested a common pathophysiological mechanism for high NT and low PLGF.[9]

The suggestion that in pregnancies with major cardiac defects there is placental dysfunction in the absence of impaired perfusion is supported by evidence from placental histological studies that in pregnancies with heart defects, compared to matched controls, there is significantly reduced placental weight, decreased number of terminal chorionic villi due with reduced proliferation and branching of fetal vasculature within the villi.[18] This is different from pregnancies complicated by preeclampsia and fetal growth restriction where low serum PAPP-A and PLGF is accompanied by increased UTPI.[19-22]

Strengths and limitations

The strengths of this screening study are first, examination of a large population of pregnant women attending for routine assessment at 11-13 weeks' gestation, second, prospective recording of data regarding cardiac defects based on a specific protocol which includes a detailed screening examination, review by fetal cardiologist in those with suspected abnormalities and neonatal examination by a pediatrician in all cases; third, use of a specific methodology and appropriately trained doctors to obtain measurements of UTPI, fourth, availability of accurate measurements of PAPP-A and PlGF in the study population and fifth, expression of the values of biomarkers as MoMs after adjustment for factors that affect the measurements.

Comparison with other studies

Our findings that in pregnancies with fetal cardiac defects first, serum PLGF is reduced, fetal NT is increased and UTPI is not significantly altered and second, there is a significant association between PLGF and NT are similar to those of a previous case-control study of 68 pregnancies with major cardiac defects and 340 controls.[9] In the previous study serum PAPP-A was reduced but not significantly so, presumably because of the small number of cases. Another difference between the studies is that we found PLGF to be reduced in all three types of cardiac defects, whereas in the previous study it was reduced in conotruncal and valvular defects but not in LVOT defects.[9]

Conclusion

The findings of our study suggest that in pregnancies with major cardiac defects there is placental dysfunction from as early as 11-13 weeks' gestation in the absence of impaired placental perfusion.

Figure legend

Figure 1. Maternal serum placental growth factor in pregnancies with major congenital cardiac defects compared to those without defects. The cardiac defect group is subdivided according to high or normal NT and according to type of defect.

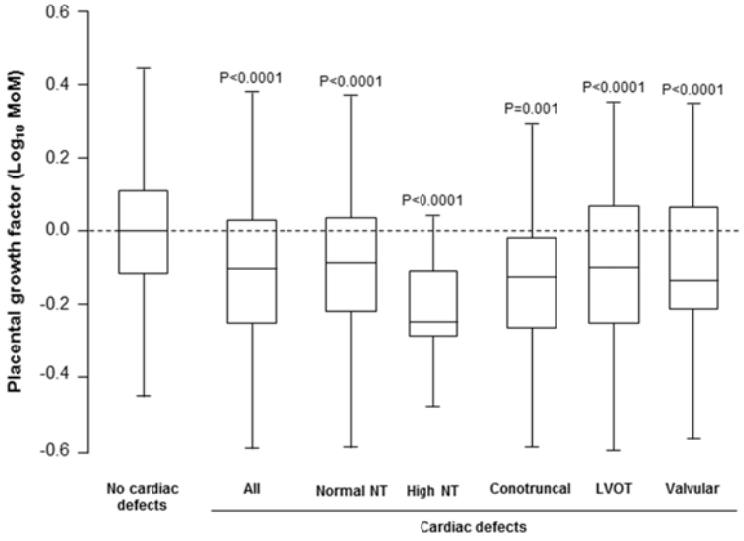

Figure 1

Table 1. Maternal and pregnancy characteristics in fetuses with congenital cardiac defect, stratified according to sub-groups, compared to those with normal cardiac anatomy.

Maternal characteristics	No cardiac defect (n=49,898)	All cardiac defects (n=196)	Conotruncal defects (n=73)	LVOT defects (n=63)	Valvular defects (n=60)
Age, median (IQR)	31.2 (26.7-34.8)	31.7 (26.1-36.1)	30.1 (24.7-35.2)	32.3 (28.9-36.3)	32.6 (26.5-36.5)
Weight, median (IQR)	66.9 (59.1-77.7)	67.0 (58.5-78.9)	68.0 (59.0-86.0)	67.0 (57.2-77.6)	65.6 (59.9-76.9)
Height, median (IQR)	1.65 (1.60-1.69)	1.65 (1.59-1.70)	1.65 (1.58-1.70)	1.67 (1.57-1.70)	1.65 (1.60-1.70)
Racial origin					
Caucasian, n (%)	36,327 (72.8)	146 (74.5)	53 (72.6)	49 (77.8)	44 (73.3)
Afro-Caribbean, n (%)	8,823 (17.7)	33 (16.8)	11 (15.1)	9 (14.3)	13 (21.7)
South Asian, n (%)	2,296 (4.6)	9 (4.6)	3 (4.1)	3 (4.8)	3 (5.0)
East Asian, n (%)	1,123 (2.3)	5 (2.6)	4 (5.5)	1 (1.6)	0
Mixed, n (%)	1,329 (2.7)	3 (1.5)	2 (2.7)	1 (1.6)	0
Method of conception					
Spontaneous, n (%)	48,317 (96.8)	189 (96.4)	73 (100.0)	61 (96.8)	55 (91.7)
Assisted conception, n (%)	1,581 (3.2)	7 (3.6)	0	2 (3.2)	5 (8.3)
Cigarette smoking, n (%)	4,595 (9.2)	16 (8.2)	7 (9.6)	5 (7.9)	4 (6.7)
Chronic hypertension, n (%)	735 (1.5)	2 (1.0)	1 (1.4)	0	1 (1.7)
SLE / APS, n (%)	114 (0.2)	0	0	0	0
Diabetes mellitus, n (%)	435 (0.9)	5 (2.6) *	3 (4.1)	2 (3.2)	0
Nulliparous, n (%)	25,003 (50.1)	101 (51.5)	40 (54.8)	32 (50.8)	29 (48.3)
Inter-pregnancy interval, median (IQR)	3.0 (2.0-4.9)	2.8 (1.8-3.9)	2.2 (1.6-3.8)	2.8 (1.9-3.3)	3.2 (1.9-5.0)

Post hoc Bonferroni correction for multiple comparisons; * = p< 0.0167; LVOT = left ventricular outflow tract; IQR = interquartile range; SLE = systemic lupus erythematosus; APS = antiphospholipid syndrome.

Table 2. Median and interquartilie range of biomarkers in fetuses with congenital cardiac defects compared to those with a normal cardiac anatomy.

Marker	No cardiac defect (n=49,898)	All cardiac defects (n=196)	Conotruncal defects (n=73)	LVOT defects (n=63)	Valvular defects (n=60)
Serum PAPP-A MoM	1.00 (0.69-1.42)	0.81 (0.52-1.27)**	0.73 (0.57-1.18)*	0.73 (0.44-1.29)*	0.90 (0.55-1.32)
Serum PlGF MoM	1.00 (0.77-1.29)	0.78 (0.56-1.07)**	0.75 (0.55-0.97)**	0.80 (0.56-1.19)*	0.74 (0.61-1.17)*
UTPI MoM	1.00 (0.81-1.22)	1.01 (0.83-1.26)	0.97 (0.81-1.28)	1.05 (0.84-1.29)	1.00 (0.89-1.25)
Delta fetal NT	0.00 (-0.20-0.22)	0.28 (-0.06-0.86)**	0.19 (-0.11-0.68)**	0.47 (-0.02-0.89)**	0.24 (-0.04-0.96)**

Significance value * p<0.01; ** p<0.001; *post hoc* Bonferroni correction for multiple comparisons; LVOT = Left ventricular outflow tract; PAPP-A = pregnancy associated plasma protein-A; PLGF = placental growth factor; UTPI = uterine artery pulsatility index ; NT = nuchal translusency; MoM = Multiple of normal median.

Table 3. Correlations between biophysical and biochemical markers in fetuses with and without congenital cardiac defects.

Marker	Congenital cardiac defects			
	Serum PIGF MoM	Serum PAPP-A MoM	Uterine artery PI MoM	Delta fetal NT
Serum PIGF MoM	-	r = 0.340; p<0.0001	r = -0.232; p = 0.001	r = -0.151; p = 0.035
Serum PAPP-A MoM		-	r = -0.217; p = 0.002	r = -0.010; p = 0.893
Uterine artery PI MoM			-	r = -0.078; p = 0.278
Delta fetal NT				-
	Normal cardiac anatomy			
	Serum PIGF MoM	Serum PAPP-A MoM	Uterine artery PI MoM	Delta fetal NT
Serum PIGF MoM	-	r = 0.287; p<0.0001	r = -0.135; p<0.0001	r = 0.004; p = 0.358
Serum PAPP-A MoM		-	r = -0.152; p<0.0001	r = 0.020; p <0.0001
Uterine artery PI MoM			-	r = -0.006; p = 0.203
Delta fetal NT				-

PAPP-A = pregnancy associated plasma protein-A; PLGF = placental growth factor; UTPI = uterine artery pulsatility index ; NT = nuchal translusency; MoM = Multiple of normal median.

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