

# Cardiac defects in chromosomally normal fetuses with abnormal ductus venosus blood flow at 10–14 weeks

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## ABSTRACT

**Objective** To assess a possible relationship between ductus venosus blood flow abnormalities and cardiac defects in chromosomally normal fetuses with increased nuchal translucency thickness at 10–14 weeks of gestation.

**Methods** Ductus venosus Doppler ultrasound blood flow velocity waveforms were obtained at 10–14 weeks' gestation immediately before fetal karyotyping in 200 consecutive singleton pregnancies with increased nuchal translucency. Fetal echocardiography was subsequently carried out in those with normal fetal karyotype.

**Results** Reverse or absent flow during atrial contraction was observed in 11 of the 142 chromosomally normal fetuses with increased nuchal translucency. Major defects of the heart and/or great arteries were present in seven of the 11 with abnormal ductal flow and increased nuchal translucency, but in none of the 131 with normal flow.

**Conclusion** These preliminary results suggest that abnormal ductus venosus blood flow in chromosomally normal fetuses with increased nuchal translucency identifies those with an underlying major cardiac defect.

## INTRODUCTION

Fetal nuchal translucency above the 95th centile for crown–rump length at 10–14 weeks of gestation is associated with an increased risk for trisomy 21 and other chromosomal abnormalities<sup>1,2</sup>. In chromosomally normal fetuses, increased nuchal translucency thickness is associated with cardiac defects<sup>3,4</sup> and a wide range of skeletal dysplasias and genetic syndromes<sup>5</sup>. In about 90% of chromosomally abnormal fetuses with increased nuchal translucency thickness, there is evidence of cardiac

dysfunction, as documented by Doppler studies of flow in the ductus venosus with absence or reversal of flow during atrial contraction<sup>6–8</sup>.

The aim of this study was to determine if abnormal ductus venosus blood flow in chromosomally normal fetuses with increased nuchal translucency thickness at 10–14 weeks of gestation was associated with cardiac defects.

## METHODS

Ductus venosus blood flow velocity waveforms were obtained immediately before chorionic villus sampling for fetal karyotyping in 200 consecutive singleton pregnancies with fetal nuchal translucency thickness above the 95th centile for crown–rump length at 10–14 weeks of gestation (2.2 mm at 38 mm to 2.8 mm at 84 mm<sup>9</sup>). The first 50 patients were examined at the Ultrasound Unit (Department of Obstetrics and Gynecology), S. João Hospital, Porto and the study was then transferred to the Fetal Medicine Unit of King's College Hospital, London.

For the Doppler studies, a right ventral mid-sagittal plane of the fetal trunk was first obtained during fetal quiescence. The pulsed Doppler gate was placed in the distal portion of the umbilical sinus with an angle of insonation kept to a minimum and always less than 60°<sup>10,11</sup>. The Doppler wall filter was set at 50 Hz. The waveforms were classified as normal or abnormal depending on whether the A-wave lowest forward velocity during atrial contraction in late diastole was positive or absent/negative, respectively. In London, the studies were carried out transabdominally using a 5-MHz curvilinear probe (Ecocee, Toshiba, Japan), whereas in Porto the transvaginal route was used (SSD 2000, Aloka, Japan).

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In the chromosomally normal pregnancies, follow-up scans, including detailed fetal echocardiography, were carried out at 14–16 weeks of gestation and again at 19–21 weeks of gestation. Fetal echocardiography included assessment of the position of the heart, the four-chamber view, the outflow tracts and the venous return to the heart. The transabdominal approach was preferentially used, but, whenever the views were suboptimal, transvaginal scanning was carried out.

## RESULTS

The median gestational age at the time of Doppler studies was 12 weeks. The fetal karyotype was normal in 142 cases and abnormal in 58. Absent or reverse flow during atrial contraction was observed in 54 of the 58 chromosomally abnormal fetuses and in 11 of the 142 chromosomally normal fetuses.

Fetal echocardiography at 14–16 weeks gestation revealed cardiac abnormalities in six of 11 fetuses with abnormal ductal flow and normal karyotype at 10–14 weeks. A seventh cardiac abnormality was identified at autopsy in a fetus that was found to have died spontaneously at the time of the proposed cardiac scan. The abnormalities are detailed in Table 1. Three of the fetuses had normal echocardiograms and no cardiac assessment was available in one pregnancy terminated at 12 weeks because of a skeletal dysplasia. In two of the fetuses with cardiac defects, in which ductus venosus Doppler was repeated at the time of the cardiac scan, the flow pattern had returned to normal. The parents elected to continue the pregnancy in only one of the six cases, the others opting for termination. The continuing pregnancy was complicated by prolonged rupture of membranes, preterm labor and an additional postnatal finding of tracheoesophageal fistula, but the infant has subsequently survived repair of his tetralogy of Fallot. No cardiac abnormality was identified amongst the 131

fetuses with normal ductus venosus flow, increased translucency and normal karyotype.

## DISCUSSION

In the second and third trimesters of pregnancy, abnormal ductus venosus flow has generally been noted in association with cardiac dysfunction resulting from structural heart defects, post-tachycardia cardiomyopathy and end-stage fetal hypoxia<sup>12–14</sup> or increased right ventricular afterload<sup>15</sup>. It is well recognized, however, that, in most forms of major structural heart defect, fetal well-being is not markedly affected and overt evidence of cardiac dysfunction is not a usual finding. In the first trimester, reversed ductus venosus flow has been shown in chromosomally abnormal fetuses<sup>8</sup> and we have now demonstrated its occurrence in fetuses with cardiac defects but normal karyotype.

In hearts with markedly impaired diastolic function, atrial contraction occurs against increased impedance to forward flow. The proportion of blood ejected retrogradely into the great veins is greater than when ventricular filling is unimpaired and this explains the transient flow reversal in the ductus venosus that constitutes the negative A-wave. Previous studies indicate that the reversed flow in the ductus corresponds to similar abnormalities in inferior caval vein blood flow<sup>7</sup>. However, the normal inferior caval vein blood flow is reversed, corresponding to atrial contraction, and abnormality will be manifest as a quantitative rather than a qualitative change. In contrast, in the ductus venosus, forward flow throughout the cardiac cycle is normal and any flow reversal is evidently abnormal. A wide variety of different cardiac structural abnormalities have been associated with increased nuchal translucency<sup>3,4</sup> and, in this study, with the absence or reversal of ductal flow between 10 and 14 weeks of gestation. Included in both situations are heart defects not generally associated with overt heart failure, such as tetralogy of Fallot and other

**Table 1** Characteristics of the 11 fetuses with abnormal ductus venosus flow. Increased nuchal translucency and normal karyotype

Case	Gestational age (weeks)	Crown–rump length (mm)	Nuchal translucency (mm)	Ductus venosus A-wave (cm/s)	Cardiac or other defects
1	11	44.8	2.7	reversed 6	tetralogy of Fallot
2	13	81	3.4	reversed 10	chondrodysplasia punctata
3	11	55	3.9	zero	normal heart
4	13	78	4.0	reversed 8.7	tricuspid atresia
5	11	43	5.4	reversed 7	normal heart
6	11	43	6.8	reversed 15	pulmonary atresia with ventricular septal defect
7	11	50	7.1	reversed 5	pulmonary atresia with intact ventricular septum
8	11	55	7.7	reversed 11	intrauterine death, agenesis of the aortic and pulmonary valves
9	11	53	8.9	reversed 11	aortic atresia with ventricular septal defect
10	13	84	13.2	reversed 9	double-inlet left ventricle with discordant arterial connection
11	13	80	4.0	zero	normal heart

conditions in which heart failure develops only following the fall in pulmonary vascular resistance after birth. Important differences in normal cardiovascular function between the first and second trimesters can, nevertheless, account for the observed response to cardiac defects.

Detailed information about differences in myocardial mechanics between early and late gestations is lacking, though there are major differences between the fetus and neonate. The immature ventricles of the fetus are disadvantaged from the point of view of filling because they have a less organized myocardial arrangement, fewer sarcomeres per unit mass, smaller diameter and operate at a significantly higher heart rate, allowing less time for inactivation of contraction<sup>17,18</sup>. Fetal myocardium develops a considerably greater tension at rest when stretched and develops less tension at any resting length when compared to the adult myocardium<sup>19,20</sup>. Therefore, in the fetus, there is an upward displacement of the end-diastolic pressure–volume relation with a higher pressure at any volume. The lower compliance of the fetal heart compared with the adult heart is demonstrated on ventricular filling Doppler traces by the predominance of the atrial contraction wave, the A-wave in the fetus, but the early ventricular filling wave, the E-wave, in the adult. The predominance of the atrial contraction wave is greater in normal first-trimester hearts, compared with those of later gestations<sup>21</sup>. This suggests that the developmental improvement in diastolic function demonstrated between fetal and adult hearts may begin in the first trimester and that diastolic function in the first trimester is impaired, compared with later gestations. In addition, in the first trimester, cardiac afterload is significantly greater than that in later gestation because of higher placental resistance<sup>21</sup>. Also, the fetus has not yet developed intrinsic renal function to counteract any tendency to fluid retention.

Thus, in the first trimester, only a small additional impairment of cardiac diastolic function may be necessary in order for cardiac dysfunction to become evident, as an increase in the nuchal translucency and reversal of A-wave flow in the ductus venosus<sup>6–8</sup>. The fluid dynamics within the fetal atria are complex, because of selective streaming of blood flow originating from the ductus venosus into the left atrium. However, the fact that the atria are connected by a non-restrictive communication at the oval foramen, for at least part of the cardiac cycle, implies that venous flow from the ductus venosus may be influenced by both left and right ventricular compliance in a normally connected heart. Ventricular filling is itself a complex phenomenon related to atrial pressure and ventricular relaxation and compliance, right/left ventricular interactions and the influences of the lungs and pericardium<sup>13</sup>. When filling of one ventricle is impaired because of a structural defect, the other ventricle may be larger in compensation, but the overall dynamics of combined ventricular filling is unlikely to be completely normal.

The data in this study suggest that, in chromosomally normal fetuses with increased nuchal translucency, absence or reversal of the A-wave from the ductus venosus blood flow identifies a group with a high probability of an under-

lying major cardiac defect. Abnormal flow was observed in all fetuses with cardiac defect irrespective of whether the defect was primarily affecting the left or the right side of the heart.

The observation, that fetuses with cardiac defects as well as those with chromosomal abnormalities may manifest both increased nuchal translucency and abnormal ductus venosus flow, invites a common hemodynamic hypothesis to explain the nuchal translucency in both conditions. In fetuses with structurally normal hearts but abnormal chromosomes, increased placental resistance or intrinsically less compliant myocardium are potential factors precipitating fluid retention at the critically vulnerable gestational age.

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