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Ductus venosus Doppler in fetuses with cardiac defects and increased nuchal translucency thickness

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KEYWORDS: cardiac defects; Doppler ultrasound; ductus venosus; first-trimester screening; nuchal translucency thickness

ABSTRACT

Objective *To examine the possible role of Doppler ultrasound assessment of ductus venosus blood flow in screening for major cardiac defects in chromosomally normal fetuses with increased nuchal translucency (NT) thickness at 11 + 0 to 13 + 6 weeks' gestation.*

Methods *Ductus venosus blood flow velocity waveforms were obtained immediately before chorionic villus sampling for fetal karyotyping in fetuses with NT thickness of 3.5 mm or more at 11 + 0 to 13 + 6 weeks of gestation. In the chromosomally normal group fetal echocardiography was performed by a specialist pediatric cardiologist at 11 + 0 to 13 + 6 weeks and/or 18–22 weeks' gestation.*

Results *Major cardiac defects were diagnosed in 16 (8.4%) of the 191 chromosomally normal fetuses. Reversed or absent flow in the ductus venosus during atrial contraction was observed in 11 of the 16 (68.8%) fetuses with cardiac defects and in 40 of the 175 (22.9%) with no cardiac defects. Multivariate analysis demonstrated that the prevalence of an abnormal A-wave in the ductus venosus in fetuses without major cardiac defects increased with fetal NT thickness (odds ratio (OR), 1.463; 95% CI, 1.183–1.809;* $P < 0.0001$*) but in those with cardiac defects it did not change significantly with NT thickness (OR, 2.054; 95% CI, 0.573–7.360;* $P = 0.269$*). The likelihood ratio for a major cardiac defect when the ductus venosus flow was abnormal decreased with fetal NT thickness from 4.58 at NT 3.5 mm to 2.47 for NT 5.5 mm, and the likelihood ratio when the ductus venosus flow was normal increased from 0.37 at NT 3.5 mm to 0.43 for NT 5.5 mm.*

Conclusion *In chromosomally normal fetuses with increased NT the finding of an absent or reversed A-wave in the ductus venosus is associated with a three-fold increase in the likelihood of a major cardiac defect, whereas the finding of normal ductal flow is associated with a halving in risk for such defects. Copyright © 2008 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Abnormal flow in the ductus venosus at 11 + 0 to 13 + 6 weeks of gestation is associated with an increased risk for chromosomal abnormalities and cardiac defects[1–9]. In the combined data from seven studies that examined ductus venosus waveforms in 600 chromosomally normal fetuses with increased nuchal translucency (NT) thickness (above the 95th centile) a major cardiac defect was observed in 29 (4.8%) fetuses, and 28 (96.6%) of these had abnormal Doppler waveforms in the ductus venosus (Table 1)[3–9]. However, there were wide variations between the individual studies in the number of cases examined (16–142), the prevalence of cardiac defects (1.7–9.5%), and the incidence of abnormal ductus venosus waveforms in those without cardiac defects (0–40%).

The aim of this study was to examine further the possible role of Doppler ultrasound assessment of ductus venosus blood flow in screening for major cardiac defects in chromosomally normal fetuses with increased NT thickness at 11 + 0 to 13 + 6 weeks' gestation.

METHODS

In this prospective study ductus venosus blood flow velocity waveforms were obtained immediately before chorionic villus sampling for fetal karyotyping in fetuses with NT thickness of 3.5 mm or more at 11 + 0 to 13 + 6 weeks of gestation, between November 2005 and August 2007. The Doppler studies were undertaken by

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Table 1 Previous studies that examined the relationship between ductus venosus waveforms and major cardiac defects in chromosomally normal fetuses with nuchal translucency thickness above the 95th centile

			Abnormal ductus venosus flow	
Reference	*Total* (n)	*Cardiac defects* (n (%))	*No cardiac defects* (n (%))	*Cardiac defects* (n (%))
Matias *et al.* 1999[3]	142	7 (4.9)	4/135 (3.0)	7/7 (100)
Bilardo *et al.* 2001[4]	69	4 (5.8)	19/65 (29.2)	4/4 (100
Murta *et al.* 2002[5]	16	1 (6.3)	0/15 (0.0)	1/1 (100)
Zoppi *et al.* 2002[6]	115	2 (1.7)	30/113 (26.5)	2/2 (100)
Haak *et al.* 2003[7]	22	2 (9.1)	8/20 (40.0)	2/2 (100)
Favre *et al.* 2003[8]	95	9 (9.5)	20/86 (23.3)	9/9 (100)
Toyama *et al.* 2004[9]	141	4 (2.8)	23/137 (16.8)	3/4 (75)
Total	600	29 (4.8)	104/571 (18.2)	28/29 (96.6)

sonographers with experience in this technique and the following criteria were fulfilled: (a) the examinations were undertaken during fetal quiescence; (b) the magnification of the image was such that the fetal thorax and abdomen occupied the whole screen; (c) a right ventral mid-sagittal view of the fetal trunk was obtained and color flow mapping was used to demonstrate the umbilical vein, ductus venosus and fetal heart; (d) the pulsed Doppler sample was small (0.5–1.0 mm) to avoid contamination from the adjacent veins and it was placed in the yellowish aliasing area, which is the portion immediately above the umbilical sinus; (e) the insonation angle was less than 30°; (f) the filter was set at a low frequency (50–70 Hz) to allow visualization of the whole waveform; and (g) the sweep speed was high (2–3 cm/s) so that the waveforms were widely spread, allowing better assessment of the A-wave[10]. Waveforms were assessed qualitatively and considered to be abnormal if the A-wave was absent or reversed (Figure 1).

In this study we report the findings in fetuses with a normal karyotype. In these cases fetal echocardiography was performed transabdominally by a specialist pediatric cardiologist at 11 + 0 to 13 + 6 weeks and/or 18–22 weeks. Fetal echocardiography included assessment of the position of the heart, the four-chamber view, the outflow tracts, the duct and the arch.

Statistical analysis

Logistic regression analysis was performed to determine the significance of the contribution of fetal NT thickness and crown–rump length (CRL) in the prediction of the prevalence of an abnormal A-wave in the ductus venosus in fetuses with and without major cardiac defects.

RESULTS

Successful visualization of the ductus venosus and assessment of the A-wave was achieved in 191 (98.5%) of the 194 chromosomally normal fetuses examined. The median maternal age was 32 (range, 17–44) years, the median CRL was 65.3 (range, 45–84) mm and the median NT thickness was 4.0 (range 3.5–13.0) mm. An absent or reversed A-wave was observed in 51 (26.7%) of the fetuses, and the prevalence increased with fetal NT ($P < 0.0001$) and decreased with CRL ($P = 0.004$). The median pulsatility index for veins in those with an abnormal A-wave was 1.97 (range, 1.45–2.86) and

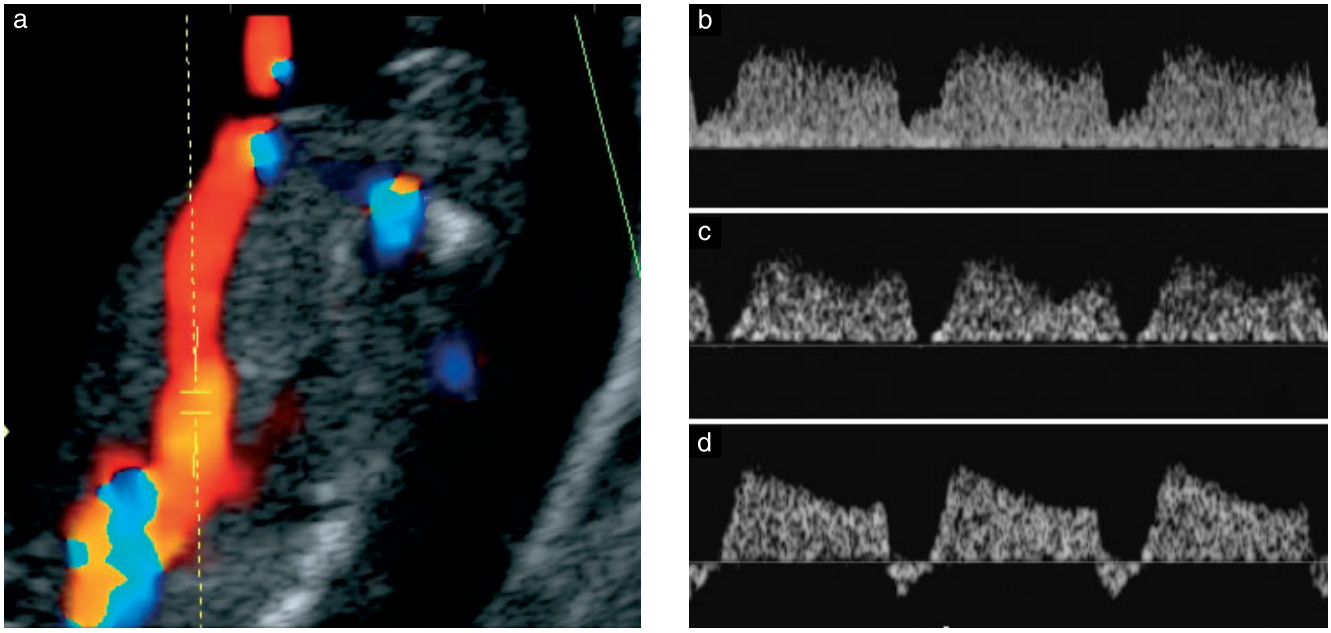

Figure 1 Mid-sagittal view of the fetal trunk demonstrating, with color flow mapping, the umbilical vein, ductus venosus and fetal heart (a) and ductus venosus flow velocity waveforms showing a normal waveform (b), absent A-wave (c) and reversed A-wave (d).

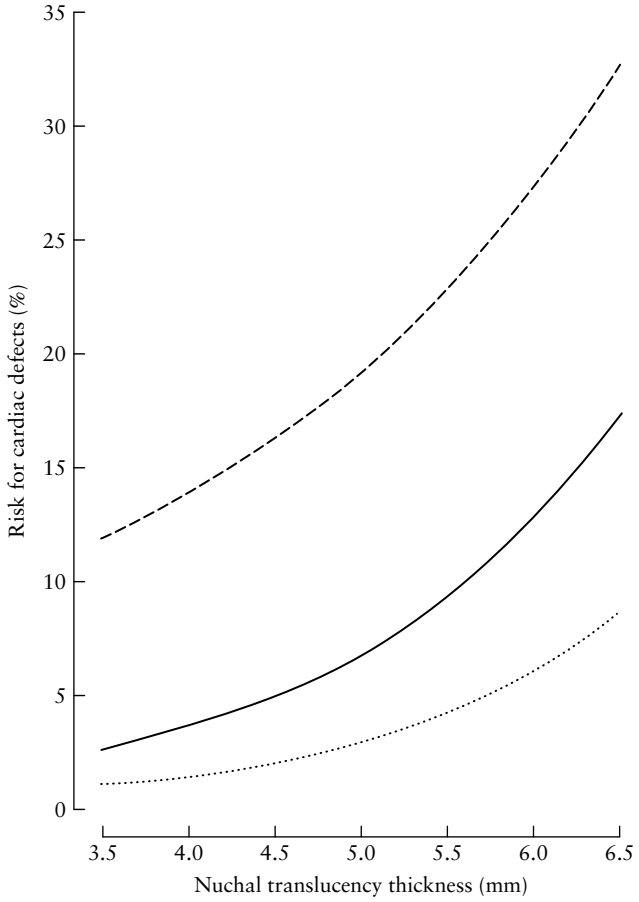

Figure 2 Relationship between nuchal translucency (NT) thickness in chromosomally normal fetuses and risk of major cardiac defects. The *a priori* NT-related risk[11] (———) is multiplied by the positive and negative likelihood ratios for abnormal (– – – – –) and normal (·····) A-waves in the ductus venosus, respectively, to derive the adjusted risk.

Table 2 Ductus venosus Doppler findings in fetuses with cardiac defects

Cardiac defect	*Ductus venosus A-wave*	*CRL (mm)*	*NT (mm)*
Tricuspid atresia	Reversed	54.5	9.1
Tricuspid atresia	Reversed	69.0	13.0
Tricuspid dysplasia	Reversed	53.2	4.3
Hypoplastic left heart syndrome	Reversed	45.3	3.5
Double outlet right ventricle	Reversed	81.0	5.5
Double outlet right ventricle	Reversed	55.4	3.8
Double outlet right ventricle	Reversed	70.2	5.8
Pulmonary atresia	Reversed	66.9	4.6
Pulmonary atresia, tricuspid dysplasia	Positive	64.2	5.5
Pulmonary stenosis	Positive	74.4	4.7
Tetralogy of Fallot, pulmonary atresia	Positive	77.0	3.8
Coarctation of the aorta	Positive	51.1	3.5
Coarctation of the aorta	Positive	69.8	4.0
Left atrial isomerism (heart block, VSD)	Reversed	60.7	4.0
Atrioventricular septal defect	Reversed	49.0	6.1
Transposition of the great arteries	Reversed	47.1	5.1

CRL, crown–rump length; NT, nuchal translucency thickness; VSD, ventricular septal defect.

in those with a normal A-wave it was 1.03 (range, 0.54–1.49).

Fetal echocardiography was performed both at 11 + 0 to 13 + 6 weeks and at 18–22 weeks in 127 cases. There was agreement between the two scans for absence of cardiac defects in 121 cases and presence of cardiac defects in five cases (coarctation of the aorta in two, double outlet right ventricle in one, pulmonary stenosis in one and tricuspid atresia in one). There was an additional case where the heart was thought to be normal at 13 weeks, coarctation of the aorta was suspected at 20 weeks but the heart was found to be normal at birth. There were 14 cases in which fetal echocardiography was carried out only in the first trimester because the pregnancies resulted in fetal death or termination at the request of the parents. In this group, major cardiac defects were suspected in six cases (hypoplastic left heart in one, pulmonary atresia in two, tricuspid atresia in one, tricuspid dysplasia in one, ventricular septal defect with left isomerism and heart block in one). There were 50 cases in which fetal echocardiography was carried out only in the second trimester, and in this group a major cardiac defect was diagnosed in five cases (double outlet right ventricle in two, transposition of the great arteries in one, atrioventricular septal defect in one and tetralogy of Fallot in one).

In total, major cardiac defects were diagnosed in 16 (8.4%) of the 191 fetuses (Table 2). An abnormal A-wave in the ductus venosus was identified in 11 of the 16 (68.8%) fetuses with cardiac defects and in 40 of the 175 (22.9%) with no cardiac defects.

Multivariate analysis demonstrated that in fetuses with major cardiac defects the prevalence of an abnormal A-wave in the ductus venosus was not significantly associated with fetal NT thickness (odds ratio (OR), 2.054; 95% CI, 0.573–7.360; $P = 0.269$) or CRL (OR, 0.930; 95% CI, 0.834–1.038; $P = 0.196$). In fetuses without major cardiac defects the prevalence of an abnormal A-wave in the ductus venosus was significantly associated with fetal NT thickness (OR, 1.463; 95% CI, 1.183–1.809; $P < 0.0001$) but not CRL (OR, 0.962, 95% CI, 0.925–1.0; $P = 0.053$).

The likelihood ratio for cardiac defects with an abnormal A-wave in the ductus venosus was derived by dividing the prevalence of abnormal Doppler findings in fetuses with cardiac defects by that in fetuses without cardiac defects. In fetuses with cardiac defects

Table 3 Relationship between fetal nuchal translucency (NT) thickness and likelihood ratios (LR) for major cardiac defects depending on the findings of ductus venosus Doppler ultrasonography

	Prevalence (%) of abnormal A-wave when cardiac defect is:		*Major cardiac defect*		
NT (mm)	*Present*	*Absent*	*LR positive*	*LR negative*	a priori *risk (%)*
3.5	68.8	15.0	4.58	0.37	2.6
4.0	68.8	17.7	3.89	0.38	3.5
4.5	68.8	20.7	3.32	0.39	4.9
5.0	68.8	24.1	2.85	0.41	6.7
5.5	68.8	27.9	2.47	0.43	9.2

To derive the patient-specific risk for cardiac defects the appropriate LR was multiplied by the *a priori* risk reported in a previous study on the relationship between fetal NT and major cardiac defects[11].

the prevalence of an abnormal A-wave was 68.8%. In fetuses without cardiac defects the prevalence (%) of an abnormal A-wave was: $(\text{odds}/1 + \text{odds}) \times 100$, where $\text{odds} = \exp Y$ or $Y = \text{Log}_e(\text{odds})$, $= -3.104 + (0.391 \times \text{NT in mm})$. In chromosomally normal fetuses with increased NT when the A-wave in the ductus venosus is abnormal the risk that the fetus has a major cardiac defect is derived by multiplying the *a priori* prevalence of cardiac defects, which increases with fetal NT[11], by the positive likelihood ratio (Figure 2, Table 3). When the A-wave in the ductus venosus is normal the risk that the fetus has a major cardiac defect is derived by multiplying the *a priori* prevalence of cardiac defects by the negative likelihood ratio (Figure 2, Table 3)[10].

DISCUSSION

The findings of this study confirm the high association between abnormal ductus venosus flow at $11 + 0$ to $13 + 6$ weeks' gestation and major cardiac defects. In chromosomally normal fetuses with increased NT the finding of an absent or reversed A-wave in the ductus venosus is associated with a three-fold increase in the likelihood of a major cardiac defect, whereas the finding of normal ductal flow is associated with a halving in risk for such defects.

The prevalence of major cardiac defects in our chromosomally normal fetuses with NT of 3.5 mm or more (8.4%) was 17 times higher than the estimated 0.5% in chromosomally normal fetuses at this gestation[12], confirming that high NT is associated with increased risk for cardiac defects[13–17]. A fetal echocardiographic study of 6921 chromosomally normal fetuses reported that the prevalence of major cardiac defects increases with fetal NT thickness from about 0.5% in those with NT below the median, to 1% for NT between the median and less than the 95th centile, 2% for NT between the 95th and 99th centiles, and exponentially thereafter to 3.5, 6.5 and 12.5 for NT of 3.5–4.4, 4.5–5.4 and ≥ 5.5 mm, respectively (Figure 2)[11].

In the assessment of individual risk for major cardiac defects the *a priori* NT-dependent risk can be multiplied by the appropriate likelihood ratio depending on whether the A-wave in the ductus venosus is normal or abnormal. For example, in a fetus with NT thickness of 3.5 mm the risk for major cardiac defects is 2.6%, and this is increased to 11.9% if the a-wave is abnormal and reduced to 1.0% if the flow is normal, and in a fetus with NT thickness of 5.5 mm the *a priori* risk is 9.2%, and this is increased to 22.7% if the a-wave is abnormal and reduced to 4.0% if the flow is normal.

A meta-analysis of studies examining the screening performance of NT thickness for the detection of cardiac defects in fetuses with normal karyotype reported that the detection rates were about 37% and 31% for the respective NT cut-offs of the 95th and 99th centiles[17]. This compares favorably with the less than 10% detection associated with a policy of screening by maternal factors, such as diabetes mellitus, exposure to teratogens or family history of cardiac defects[18]. The findings of our study and those of previous reports[3–9] that 68.8 and 96.6%, respectively, of fetuses with major cardiac defects have abnormal flow in the ductus venosus suggest that Doppler assessment of this vessel may provide an effective method for early screening for such defects. However, the studies examining the association between ductus venosus flow and cardiac defects are essentially confined to fetuses with increased NT, and it is therefore uncertain whether in fetuses with cardiac defects and normal NT the A-wave in the ductus venosus is also abnormal. Consequently, population-based studies in which there is no preselection by measurement of the NT thickness are needed to assess the true effectiveness of first-trimester screening for major cardiac defects by Doppler assessment of the ductus venosus.

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