

Screening for chromosomal abnormalities at 10–14 weeks: the role of ductus venosus blood flow

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ABSTRACT

Objective To assess the possible role of Doppler ultrasound assessment of ductus venosus blood flow in screening for chromosomal abnormalities at 10–14 weeks of gestation.

Methods Ductus venosus flow velocity waveforms were obtained immediately before fetal karyotyping in 486 consecutive singleton pregnancies at 10–14 weeks of gestation. All cases were screened for chromosomal defects by a combination of maternal age and fetal nuchal translucency thickness. The peak systolic and diastolic velocities, the velocity during atrial contraction and the pulsatility index were measured.

Results There were 63 chromosomal defects (38 cases of trisomy 21, 12 cases of trisomy 18, seven cases of trisomy 13, three cases of Turner's syndrome and three cases of triploidy). In 57 (90.5%) cases there was reverse or absent flow during atrial contraction. Abnormal ductus venosus flow was also observed in 13 (3.1%) of the 423 chromosomally normal fetuses. In the chromosomally abnormal group, compared to the normal group, the median heights of the S and D waves were significantly lower and the pulsatility index was significantly higher. However, multivariate regression analysis demonstrated that only the height of the A wave provided a significant independent contribution in distinguishing between the chromosomally normal and abnormal groups.

Conclusion These preliminary results suggest that assessment of ductus venosus blood flow in pregnancies considered to be at high risk for chromosomal defects may result in a major reduction in the need for invasive testing, with only a small decrease in sensitivity.

INTRODUCTION

Screening for chromosomal defects by a combination of maternal age and fetal nuchal translucency thickness at 10–14 weeks of gestation can identify about 75–80% of affected pregnancies for a false-positive rate of 5%^{1,2}. Increased nuchal translucency is also a marker of cardiac and other defects as well as a wide range of genetic syndromes³. Possible mechanisms for this transient ultrasound marker include cardiac failure, superior mediastinal compression found in diaphragmatic hernia or narrow chest in skeletal dysplasia, abnormal or delayed development of the lymphatic system, failure of lymphatic drainage due to impaired fetal movements in various neuromuscular disorders, and altered composition of the subcutaneous connective tissue³.

The association between increased nuchal translucency and cardiac failure is based on the demonstration that a high proportion of both chromosomally abnormal and normal fetuses with increased translucency have abnormalities of the heart and great arteries^{4,5}. *In vivo* evidence of heart failure has been provided by case reports of abnormal flow in the ductus venosus during atrial contraction at 11–13 weeks in chromosomally abnormal fetuses with increased nuchal translucency thickness^{6–8}. The ductus venosus is a unique shunt that carries well-oxygenated blood from the umbilical vein to the right atrium and across the foramen ovale into the left atrium. It appears to be the most useful vessel in assessing disturbed cardiac function⁹.

The aim of this study was to assess the possible role of Doppler ultrasound assessment of ductus venosus blood flow in screening for chromosomal abnormalities at 10–14 weeks of gestation.

METHODS

Ductus venosus flow velocity waveforms were obtained immediately before fetal karyotyping in 486 consecutive singleton pregnancies, at 10–14 weeks of gestation, examined at the Fetal Medicine Units of King's College Hospital, London or S. Joao Hospital, Porto. In all cases, screening was performed for chromosomal defects by a combination of maternal age and fetal nuchal translucency thickness^{1,2} and, after counselling, the parents elected to have invasive testing.

For the Doppler studies, a right ventral mid-sagittal plane of the fetal trunk was first obtained during fetal quiescence and the pulsed Doppler gate was placed in the distal portion of the umbilical sinus (Figure 1); care was taken to avoid contamination from the intrahepatic portion of the umbilical vein, the left hepatic vein and inferior vena cava¹⁰. An average of five consecutive high-quality waveforms was used to measure the peak velocity during ventricular systole (*S* wave) and diastole (*D* wave), the lowest forward velocity during atrial contraction in late diastole (*A* wave) and the pulsatility index (PI). In London, the studies were carried out transabdominally (5-MHz curvilinear probe, Ecocee, Toshiba, Japan), whereas in Porto the transvaginal route was used (SSD 2000, Aloka, Japan).

In all cases where the nuchal translucency was above the 95th centile for the crown–rump length (2.2 mm at 38 mm, increasing linearly to 2.8 mm at 84 mm)², and, in those with translucency below the 95th centile but abnormal ductus venosus flow, a follow-up scan, including specialist echocardiography, was carried out at 14–16 weeks of gestation.

The Mann–Whitney *U* test was used to determine the significance of differences in the median values in PI, *S*, *D* and *A* in the chromosomally normal and abnormal groups. Multivariate regression analysis was used to determine those variables that provided a significant independent contribution in distinguishing between the two groups.

RESULTS

The median maternal age was 35 years (range 17–46 years), the median fetal crown–rump length was 61 mm (38–84 mm) and the median gestation was 12 weeks (10–14 weeks). The fetal nuchal translucency was less than the 95th centile in 288 cases, between the 95th centile and 3.4 mm in 96 cases, 3.5–4.4 mm in 62 cases, and 4.5 mm or more in 40 cases. The fetal karyotype was normal in 423 cases and abnormal in 63 (12.9%), including 38 cases of trisomy 21, 12 cases of trisomy 18, seven cases of trisomy 13, three cases of Turner's syndrome and three cases of triploidy. The incidence of chromosomal defects increased with fetal nuchal translucency thickness from 1.7% (5/288) for translucency of less than the 95th centile, to 11.5% (11/96) for translucency from the 95th centile to 3.4 mm, 29.0% (18/62) at 3.5–4.4 mm and 72.5% (29/40) at 4.5 mm or more (Table 1).

Flow velocity waveforms were successfully obtained in all cases. Although in most fetuses satisfactory waveforms were obtained within 3 min of the onset of the scan, in some cases it took up to 10 min before the appropriate sagittal plane of the fetal trunk during fetal quiescence could be obtained. In the chromosomally abnormal group, compared to the normal group, the median heights of the *A*, *S* and *D* waves were significantly lower and the PI was significantly higher (Table 2, Figures 2–6). However, multivariate regression analysis demonstrated that only the height of the *A* wave provided a significant independent contribution in distinguishing between the chromosomally normal and abnormal groups.

Absent or reversed flow during atrial contraction was observed in 90.5% (57/63) of chromosomally abnormal fetuses and in 3.1% (13/423) of chromosomally normal fetuses (Table 1). In seven of the 13 chromosomally normal fetuses with absent or reversed flow, an ultrasound scan at 14–16 weeks demonstrated a major cardiac defect. In all but one of the chromosomally abnormal fetuses, the parents elected to have termination of pregnancy. In one case of trisomy 21 with nuchal translucency thickness of

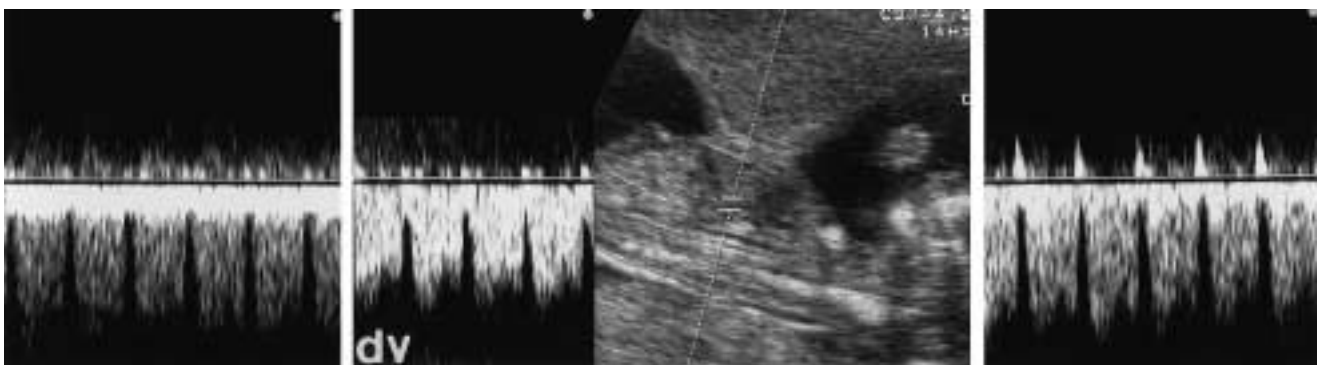


Figure 1 Right ventral mid-sagittal plane of the fetal trunk demonstrating the position of the pulsed Doppler gate for the study of ductus venosus blood flow (middle). The flow waveform on the far left demonstrates contamination by the umbilical vein and the waveform on the far right demonstrates contamination by the inferior vena cava

Table 1 Ductus venosus flow velocity waveform in chromosomally normal and abnormal fetuses according to nuchal translucency thickness at 10–14 weeks of gestation. Flow is classified according to the presence (normal) and absence or reversal (abnormal) of frequencies during atrial contraction

Nuchal translucency	Normal karyotype		Abnormal karyotype		Type
	Normal flow	Abnormal flow	Normal flow	Abnormal flow	
< 95th centile	280	3 (1a)	2b	3	trisomy 21, 2 trisomy 13, 1 trisomy 18, 1 triploidy, 1
95th centile–3.4 mm	84	1	2b	9	trisomy 21, 8 trisomy 13, 2 triploidy, 1
3.5–4.4 mm	41	3 (1a)	2c	16	trisomy 21, 16 trisomy 13, 1 Turner, 1
≥ 4.5 mm	5	6 (5a)	0	29	trisomy 21, 12 trisomy 18, 11 trisomy 13, 3 Turner, 2 triploidy, 1
Total	410	13	6	57	

a, major cardiac defect; b, one case each of trisomy 21 and trisomy 13; c, one case each of trisomy 21 and Turner’s syndrome

Table 2 Median (range) values for maternal age, ultrasound and ductus venosus Doppler findings in chromosomally normal and abnormal fetuses

	Normal karyotype	Abnormal karyotype	p
Maternal age (years)	35 (17–46)	36 (22–45)	NS
Crown–rump length (mm)	61 (38–84)	59 (40–84)	NS
Gestational age (weeks)	12 (10–14)	12 (10–14)	NS
Nuchal translucency (mm)	2.0 (0.7–13.2)	4.4 (1.4–16.2)	< 0.0001
S wave (cm/s)	31 (7–57)	28.1 (15–48)	< 0.05
D wave (cm/s)	26 (5–48.1)	21 (10–41.5)	< 0.01
A wave (cm/s)	5 (–15–21)	–6.2 (–16–15)	< 0.0001
Pulsatility index	1.2 (0.6–3.3)	2.3 (0.8–7.7)	< 0.0001

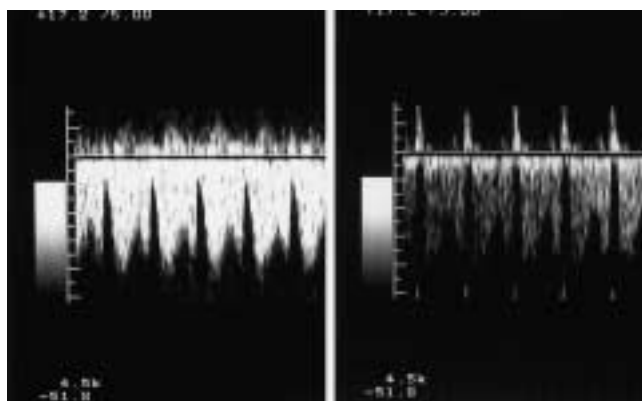


Figure 2 Flow velocity waveforms from the ductus venosus in 12-week fetuses. On the left is the waveform from a normal fetus demonstrating forward flow during atrial contraction. On the right is the waveform from a trisomy 21 fetus demonstrating reversed flow during atrial contraction

5.5 mm at 13 weeks, the parents chose to continue with the pregnancy; repeat ultrasound examination at 15 weeks

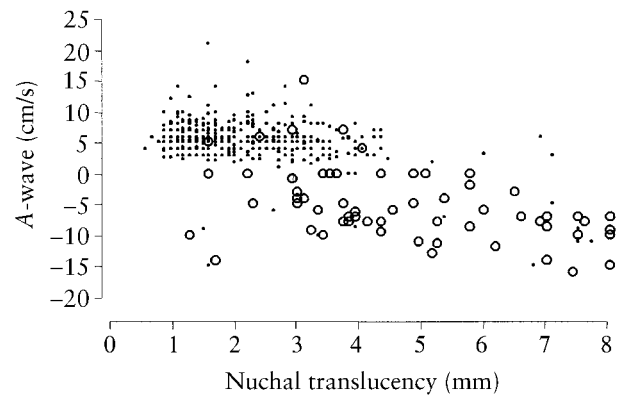


Figure 3 Relation between the height of the A wave in the ductus venosus flow velocity waveform and nuchal translucency thickness at 10–14 weeks of gestation in chromosomally normal (dots) and abnormal (o) fetuses

demonstrated resolution of the translucency, normal heart and great arteries and normal waveforms in the ductus venosus.

DISCUSSION

The findings of this study have demonstrated the feasibility of assessing ductus venosus blood flow at 10–14 weeks of gestation by Doppler ultrasound, both transabdominally and transvaginally. The studies were carried out by experienced sonographers in fetal medicine units and it is unlikely that this assessment will be incorporated into the routine first-trimester scan. However, the data suggest that assessment of ductus venosus blood flow may provide a useful method for a major reduction in the false-positive rate of screening for chromosomal abnormalities by a combination of maternal age and fetal nuchal translucency thickness at 10–14 weeks of gestation.

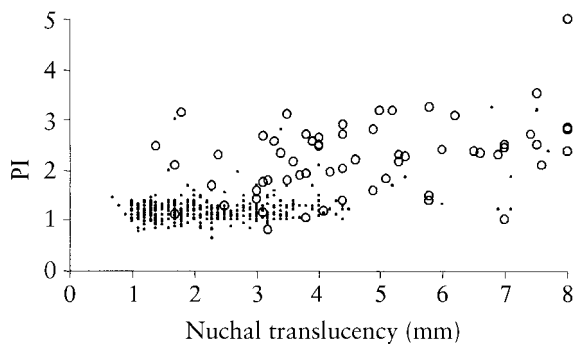


Figure 4 Relation between the pulsatility index in the ductus venosus flow velocity waveform and nuchal translucency thickness at 10–14 weeks of gestation in chromosomally normal (dots) and abnormal (○) fetuses

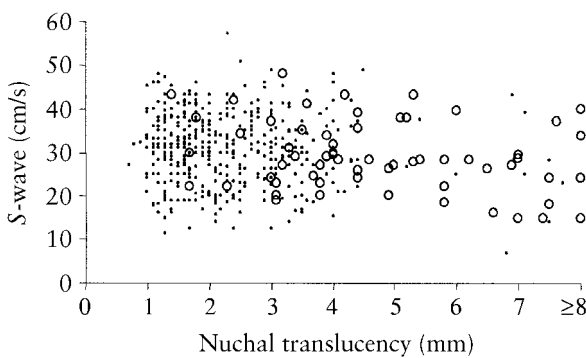


Figure 5 Relation between the height of the S wave in the ductus venosus flow velocity waveform and nuchal translucency thickness at 10–14 weeks of gestation in chromosomally normal (dots) and abnormal (○) fetuses

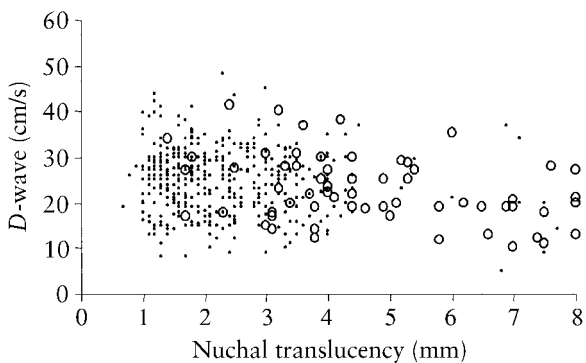


Figure 6 Relation between the height of the D wave in the ductus venosus flow velocity waveform and nuchal translucency thickness at 10–14 weeks of gestation in chromosomally normal (dots) and abnormal (○) fetuses

The sphincter-like ductus venosus is an important regulator of the fetal circulation; it directs well-oxygenated umbilical venous blood to the coronary and cerebral circulation, by preferential streaming through the foramen ovale into the left atrium. Blood flow in the ductus is characterized by high velocity during ventricular systole (S wave)

and diastole (D wave) and the presence of forward flow during atrial contraction (A wave). In contrast, in both the inferior vena cava and the hepatic veins, with their low pressure, low velocity and compliant walls, there is reversed flow during atrial contraction. In cardiac failure, with or without cardiac defects, reversed flow during atrial contraction is also observed in the ductus venosus^{11–14}. The inferior vena cava, left and medial hepatic veins and the ductus venosus drain into a common subdiaphragmatic vestibulum and, therefore, when attempting to obtain flow velocity waveforms from the ductus, care should be taken to avoid contamination from the other veins (Figure 1).

The finding of absent or reversed A wave in the chromosomally abnormal group could be attributed to cardiac failure, possibly due to an underlying cardiac defect. This is supported by the finding that, in seven chromosomally normal fetuses with cardiac defects, there was also an abnormal A wave. However, a pathological study of 60 trisomy 21 fetuses, presenting with increased nuchal translucency, reported that, although a high proportion of the fetuses had an abnormality in the heart and great arteries, this is not always the case⁴.

In our study, in all but one of the cases with chromosomal defects, the parents requested termination of pregnancy and no pathological studies were carried out. However, in one case of trisomy 21 with abnormal ductus venosus flow and increased nuchal translucency at 13 weeks, the parents decided to continue with the pregnancy; in this case there was no cardiac defect and at 15 weeks both the translucency and the abnormal A wave resolved. We had another case of trisomy 21 and increased nuchal translucency at 13 weeks but this fetus had a major atrio-ventricular septal defect; this case is not included in the present series because we did not examine ductus venosus flow in the first trimester, but at 16 weeks ductus venosus flow was normal. Similarly, Huisman and Bilardo⁸ reported a case of trisomy 18 with a small membranous septal defect presenting at 13 weeks with increased nuchal translucency and reversed A wave in the ductus; with advancing gestation there was resolution in both the nuchal translucency and the abnormal ductal flow.

These findings suggest that, in chromosomally abnormal fetuses with increased nuchal translucency, first, abnormal ductal flow can be found in the absence of cardiac defects and, second, the abnormal ductal flow may be a temporary phenomenon. It is hypothesized that, in fetuses with certain cardiac defects and in those with chromosomal abnormalities, with or without cardiac defects, there is a temporary functional abnormality either in the ventricles and/or the ductus itself^{5–7}. This hypothesis would require further investigation from the study of a larger number of chromosomally normal fetuses with cardiac defects (both with increased and normal nuchal translucency) and the study of chromosomally abnormal fetuses with normal translucency (both with and without cardiac defects).

Our population was preselected because the patients had undergone assessment of risk by maternal age and fetal nuchal translucency thickness, and consequently the majority of chromosomally abnormal fetuses had increased

nuchal translucency. It is, therefore, not possible from our results to define the role of ductal flow as a primary method of screening for chromosomal defects. However, the data suggest the assessment of ductal flow can potentially play a major role as a secondary method of screening.

There is substantial evidence to suggest that the most sensitive method of screening for trisomy 21 is by a combination of maternal age, maternal serum free β -hCG and PAPP-A levels and fetal nuchal translucency thickness at 10–14 weeks of gestation; for a 5% invasive testing rate, it is estimated that about 90% of trisomy 21 pregnancies would be identified¹⁵.

In the USA and most western European countries, the median maternal age is about 27 years and the prevalence of trisomy 21 at 12 weeks of gestation is about one in 400¹⁶. In a representative sample of 20 000 pregnancies, assessment of risk by a combination of maternal age, maternal biochemistry and fetal nuchal translucency would classify 1000 such pregnancies as being at high risk and this group would contain 45 (90%) of the estimated 50 cases of trisomy 21. One option in the management of this high-risk group of 1000 pregnancies is to carry out an invasive test, such as chorionic villus sampling, which would diagnose all 45 cases of trisomy 21 but such a policy would be associated with a procedure-related miscarriage of ten pregnancies.

An alternative policy would be to carry out Doppler assessment of ductus venosus flow in the 1000 high-risk pregnancies and reserve chorionic villus sampling only for those cases with abnormal flow. According to our preliminary results, such a policy could reduce the need for invasive testing to less than 0.5% of the whole population of 20 000 pregnancies (about 3% or 29 of the 955 high-risk but chromosomally normal pregnancies and about 90% or 41 of the 45 trisomy 21 pregnancies) with a small loss in sensitivity (a decrease by about 10% from the estimated 90% to 80%) for detection of trisomy 21.

In conclusion, examination of flow velocity waveforms from the ductus venosus is likely to be useful as a method of selecting for invasive testing those pregnancies considered to be high risk after first-trimester screening. Such a policy could identify about 80% of trisomy 21 pregnancies after invasive testing in less than 0.5% of the pregnant population.

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