Ultrasound Obstet Gynecol 2005; **26**: 22–27
Published online 6 June 2005 in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/uog.1922

Likelihood ratio for trisomy 21 in fetuses with tricuspid regurgitation at the 11 to 13 + 6-week scan

S. FAIOLA, E. TSOI, I. C. HUGGON, L. D. ALLAN and K. H. NICOLAIDES
Harris Birthright Research Centre for Fetal Medicine, King's College Hospital Medical School, London, UK

KEYWORDS: echocardiography; first trimester; nuchal translucency; screening; tricuspid regurgitation; trisomy 21; ultrasound

ABSTRACT

Objective *To determine the likelihood ratio for trisomy 21 in fetuses with tricuspid regurgitation at the 11 to 13 + 6-week scan.*

Methods *Fetal echocardiography was carried out by specialist pediatric cardiologists in 742 singleton pregnancies at 11 to 13 + 6 weeks' gestation and pulsed wave Doppler was used to ascertain the presence or absence of tricuspid regurgitation. To avoid confusion with other adjacent signals, a strict definition of tricuspid regurgitation was used, in that it had to occupy at least half of systole and reach a velocity of over 80 cm/s. The fetal crown–rump length (CRL) and the nuchal translucency (NT) thickness were measured and the presence of any congenital heart abnormality noted. Follow-up of the pregnancy was carried out to determine the presence of chromosomal abnormalities. The likelihood ratio for trisomy 21 in fetuses with and without tricuspid regurgitation was determined.*

Results *The tricuspid valve was successfully examined in 718 (96.8%) cases. Tricuspid regurgitation was present in 39 (8.5%) of the 458 chromosomally normal fetuses, in 82 (65.1%) of the 126 with trisomy 21, in 44 (53.0%) of the 83 with trisomy 18 or 13, and in 11 (21.6%) of the 51 with other chromosomal defects. The prevalence of tricuspid regurgitation was also associated with fetal CRL, delta NT and the presence of cardiac defects. Logistic regression analysis, irrespective of cardiac defects, demonstrated that in the chromosomally normal fetuses significant independent prediction of the likelihood of tricuspid regurgitation was provided by fetal delta NT (odds ratio (OR), 1.26; 95% CI, 1.34–1.41;* $P < 0.0001$*), while in trisomy 21 fetuses prediction was provided by CRL (OR, 0.94; 95% CI, 0.89–0.99;* $P = 0.021$*). The likelihood ratio for trisomy 21 for tricuspid regurgitation was derived by dividing the likelihood in trisomy 21 by that in normal fetuses. In the chromosomally normal fetuses, the prevalence of tricuspid regurgitation in those with cardiac defects was 46.9% and 5.6% in those without cardiac defects, and the likelihood ratio of tricuspid regurgitation for cardiac defects was 8.4.*

Conclusion *At 11 to 13 + 6 weeks' gestation, there is a high association between tricuspid regurgitation and trisomy 21, as well as other chromosomal defects. The prevalence of tricuspid regurgitation increases with fetal NT thickness and is substantially higher in those with, than those without, a cardiac defect. Copyright © 2005 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Increased fetal nuchal translucency (NT) thickness at 11 to 13 + 6 weeks of gestation is associated with chromosomal anomalies and a wide range of fetal malformations and genetic syndromes[1–3]. The association with major cardiac defects has led to attempts at specialist fetal echocardiography in early pregnancy, and several studies have reported that early cardiac scanning provides reliable diagnosis[4]. During this experience, it was noticed that tricuspid regurgitation, even in the absence of other abnormal cardiac findings, was associated with an increased prevalence of chromosomal defects. Thus, in a population at high risk for chromosomal abnormality, Huggon *et al.* found tricuspid regurgitation in 38 of 64 (59.4%) fetuses with trisomy 21 and in 12 of 136 (8.8%) chromosomally normal fetuses at 11 to 13 + 6 weeks' gestation[5]. However, the utility and application of tricuspid regurgitation in modifying the risk estimate for trisomy 21 will relate to its dependence on or independence from other risk factors, in particular fetal NT thickness.

The aim of this study was to determine the likelihood ratio for trisomy 21 in fetuses with and without tricuspid regurgitation at 11 to 13 + 6 weeks' gestation.

Correspondence to: Prof. K. H. Nicolaides, Harris Birthright Research Centre for Fetal Medicine, King's College Hospital Medical School, Denmark Hill, London SE5 9RS, UK (e-mail: fmf@fetalmedicine.com)

Accepted: 4 April 2005

Copyright © 2005 ISUOG. Published by John Wiley & Sons, Ltd.

METHODS

In our center, fetal echocardiography is performed by specialist pediatric cardiologists, with a common indication for such an examination being increased risk for chromosomal defects arising from our NT screening program at 11 to 13 + 6 weeks of gestation[1]. All examinations are carried out transabdominally using a 7-MHz curvilinear transducer (Acuson Aspen system, Mountain View, CA, USA). The four-chamber view, outflow tracts, arterial duct and aortic arch are assessed on cross-sectional imaging and color-flow mapping. The presence or absence of tricuspid regurgitation is determined by pulsed wave Doppler. The sample volume is positioned across the tricuspid valve in an apical four-chamber view such that the angle to the direction of flow is less than 30° (Figure 1). Tricuspid regurgitation at this gestation is diagnosed if it is found during at least half of systole with a velocity of over 80 cm/s (Figure 2). The scan is abandoned if a satisfactory study is not obtained within 20 min.

Crown–rump length (CRL), nuchal translucency (NT) thickness and presence or absence of cardiac defects are recorded in a fetal database at the time of the examination. Follow-up consisted of the results of fetal karyotype or information from the mother postnatally in the continuing pregnancies, if a karyotype had not been obtained. The inclusion criteria for this study were patients referred for specialist fetal echocardiography between May 2001 and December 2004 with singleton pregnancies, fetal CRL between 45 and 84 mm and known fetal karyotype, or the birth of a phenotypically normal baby.

Statistical analysis

Univariate analysis was performed to assess the association between tricuspid regurgitation and fetal karyotype, fetal CRL expressed in mm, fetal delta NT, which is the difference in mm between the observed NT and the normal mean for the same CRL[1], and the presence or absence of cardiac defects. Subsequently, logistic regression analysis was performed to determine the significant independent contribution of these variables to the prevalence of tricuspid regurgitation in chromosomally normal and trisomy 21 fetuses. The likelihood of having tricuspid regurgitation in the chromosomally normal and trisomy 21 fetuses was calculated from the regression equation.

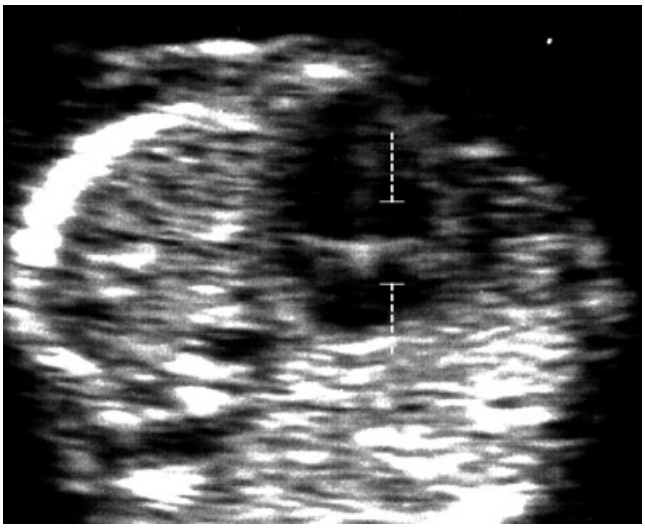

Figure 1 Apical four-chamber view of the heart at 12 weeks. The Doppler sample volume is positioned in the tricuspid valve orifice, including the right atrium and ventricle. The alignment of the atrioventricular valve flow is parallel to the ultrasound beam.

RESULTS

Specialist fetal echocardiography at 11 to 13 + 6 weeks of gestation was performed in 742 fetuses. An acceptable Doppler flow profile was obtained in 718 (96.8%) of the 742 cases; in the 24 cases without a satisfactory profile the fetus remained in a lateral position throughout the duration of the examination. In 648 of the 718 cases, fetal echocardiography was carried out before chorionic villus sampling for fetal karyotyping. In the remaining 70 cases with no antenatal karyotyping, a phenotypically normal baby was delivered and was assumed to have a normal karyotype. The indications for fetal echocardiography in these cases was family history of cardiac defects ($n = 35$) or parental anxiety ($n = 35$).

In the 718 fetuses for which an acceptable Doppler flow profile was obtained, the median CRL was 63 (range, 45–84) mm, and the median delta NT was 2.8 (range, −1.4 to 20.8) mm. The fetal NT was equal to or above the 95th centile for CRL in 596 (83.0%) of the cases. The fetal karyotype was normal in 458 and abnormal in 260 (Table 1). Cardiac defects were detected in 32 of the chromosomally normal and in 117 of the chromosomally abnormal fetuses (Table 1). Tricuspid regurgitation at 11 to 13 + 6 weeks was found in 176 fetuses (24.5%), including 39 of the 458 (8.5%) chromosomally normal and in 137 of the 260 (52.7%) chromosomally abnormal fetuses. Table 2 summarizes the types of cardiac defects in the chromosomally normal and abnormal fetuses.

In 294 cases the final diagnosis of presence ($n = 118$) or absence ($n = 176$) of a cardiac defect was based on the findings at the 11 to 13 + 6-week scan, because the pregnancies are ongoing ($n = 32$) or they were terminated ($n = 251$) or they resulted in fetal death ($n = 11$). In 424 cases the final diagnosis of presence ($n = 31$) or absence ($n = 393$) of a cardiac defect was based on the findings of the 20-week scan and/or postnatal examination. At 11 to 13 + 6 weeks' gestation the correct diagnosis of absence of a cardiac defect was made in 391 of the 393 (99.5%) cases, and the presence of a cardiac defect was diagnosed in 25 of the 31 (80.6%) cases. In 29 of the cases with tricuspid regurgitation at 11 to 13 + 6 weeks (24 with normal karyotype, four with trisomy 21 and one with trisomy 18), fetal echocardiography was repeated at 20 weeks' gestation and none of the cases demonstrated persistence of tricuspid regurgitation.

Univariate analysis showed that the prevalence of tricuspid regurgitation was significantly associated with fetal karyotype (odds ratio (OR), 11.97; 95% CI,

Copyright © 2005 ISUOG. Published by John Wiley & Sons, Ltd.

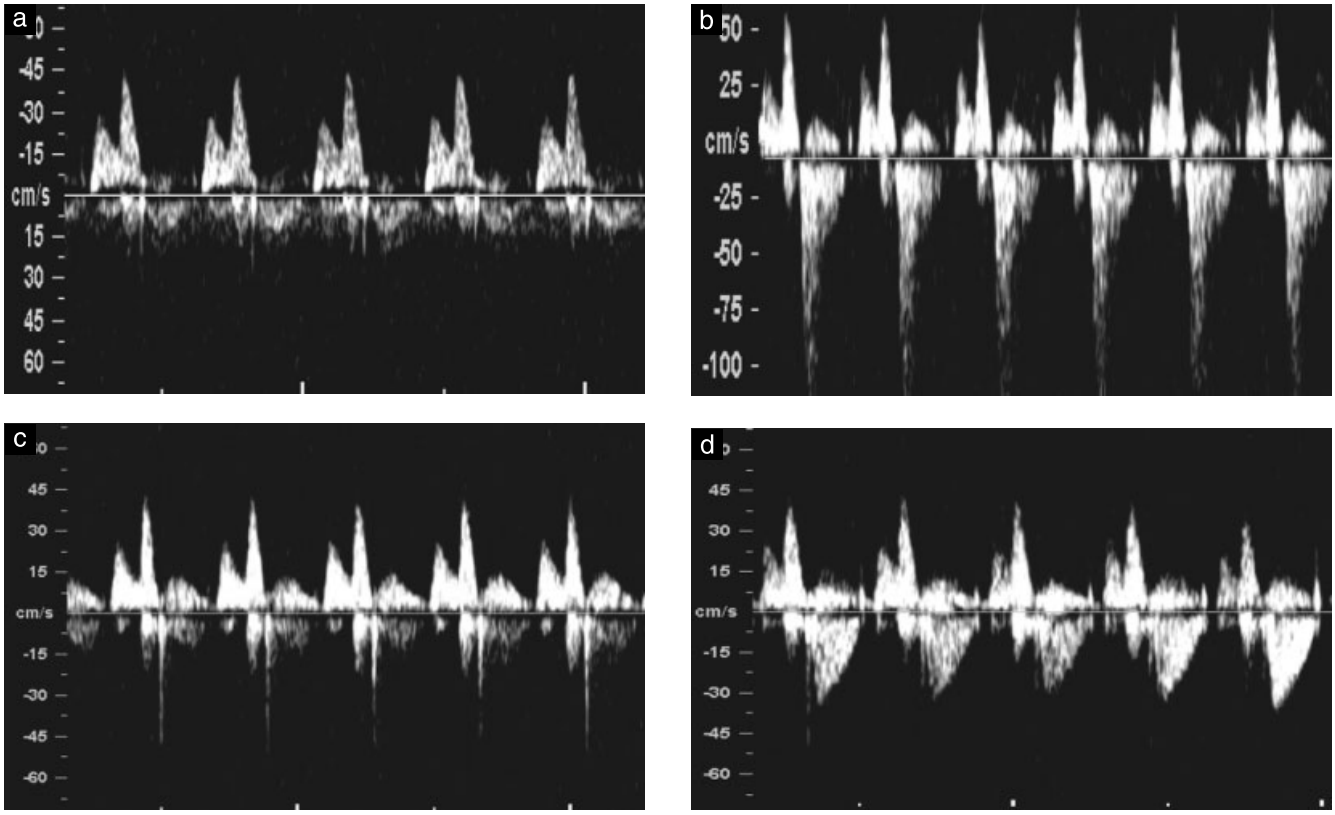

Figure 2 Doppler flow profile in the tricuspid valve with no regurgitation during systole (a), and regurgitation during approximately half of systole and with a velocity more than 80 cm/s (b). The short reverse 'spike' generated by the closure of the valve cusp (c) and the jet produced by aortic or pulmonary arterial blood flow, which at this gestation can produce a maximum velocity of 50 cm/s (d), should not be mistaken for tricuspid regurgitation.

Table 1 Prevalence of tricuspid regurgitation in chromosomally normal and abnormal fetuses in the presence or absence of a cardiac defect

			Tricuspid regurgitation		
Karyotype	*Total*	*Cardiac defect* (n (%))	*Total* (n (%))	*Cardiac defect* (n (%))	*No cardiac defect* (n (%))
Normal	458	32 (7.0)	39 (8.5)	15 (46.9)	24 (5.6)
Trisomy 21	126	40 (31.7)	82 (65.1)	39 (97.5)	43 (50.0)
Trisomy 18	68	41 (60.3)	37 (54.4)	28 (68.3)	9 (33.3)
Trisomy 13	15	9 (60.0)	7 (46.6)	5 (55.6)	2 (33.3)
Turner	28	16 (57.1)	4 (14.3)	4 (25.0)	—
Other	23	11 (47.8)	7 (30.4)	5 (45.5)	2 (16.7)

7.95–18.01; $P < 0.0001$), fetal CRL (OR, 0.97; 95% CI, 0.95–0.98; $P < 0.001$; Table 3), fetal delta NT (OR, 1.22; 95% CI, 1.15–1.29 $P < 0.0001$; Table 4) and the presence of a cardiac defect (OR, 11.07; 95%, CI 7.34–16.69 $P < 0.0001$).

Multivariate analysis demonstrated that in the trisomy 21 fetuses significant independent prediction of the likelihood of tricuspid regurgitation was provided by the presence of cardiac defects (OR, 38.99; 95% CI, 5.12–296.58) and in the chromosomally normal fetuses prediction was provided by delta NT (OR, 1.18; 95% CI, 1.05–1.34, $P = 0.006$) and the presence of cardiac defects (OR, 10.44; 95% CI, 4.47–24.37, $P < 0.0001$). The likelihood ratio for trisomy 21 with tricuspid regurgitation is derived by dividing the likelihood (%) in trisomy 21 by that in normal fetuses. In trisomy 21 fetuses, the likelihood of having tricuspid regurgitation (%) is: (odds/1 + odds) × 100, where odds = e^y and $Y = \text{Log}_e$ (odds) = 3.663 × (0 for no cardiac defect or 1 for cardiac defect). In chromosomally normal fetuses, the likelihood of having tricuspid regurgitation (%) is: (odds/1 + odds) × 100, where odds = e^y and $Y = \text{Log}_e$ (odds) = −3.267 + 0.169 × delta NT in mm + 2.346 × (0 for no cardiac defect or 1 for cardiac defect).The likelihood ratios at different values of delta NT and the presence or absence of a cardiac defect are shown in Table 5.

Logistic regression analysis, irrespective of cardiac defects, demonstrated that in trisomy 21 fetuses significant independent prediction of the likelihood of tricuspid

Copyright © 2005 ISUOG. Published by John Wiley & Sons, Ltd.

Table 2 Prevalence of tricuspid regurgitation with specific cardiac defects in the chromosomally normal and abnormal fetuses

	Karyotype					
Cardiac defect	*Normal*	*Trisomy 21*	*Trisomy 18*	*Trisomy 13*	*Turner*	*Other*
Atrioventricular septal defect	5	30	12	2	1	—
Coarctation of the aorta	9	5	10	2	8	1
Tetralogy of Fallot	3	1	4	—	—	3
Ventricular septal defect	3	1	5	—	—	—
Tricuspid dysplasia	1	2	1	—	—	2
Pulmonary stenosis/atresia	4	1	4	3	—	—
Double outlet right ventricle	2	—	2	1	—	—
Hypoplastic left heart	3	—	3	—	7	1
Transposition of great arteries	2	—	—	—	—	—
Truncus arteriosus	—	—	—	1	—	2
Interrupted aortic arch	—	—	—	—	—	1
Right aortic arch	—	—	—	—	—	1
Total	32	40	41	9	16	11

Table 3 Prevalence of tricuspid regurgitation in trisomy 21 and normal fetuses and likelihood ratio according to crown–rump length

CRL	*Trisomy 21*	*Normal*	*Likelihood ratio for trisomy 21*	
(range (mm))	(n *(%)*)	(n *(%)*)	*TR positive*	*TR negative*
45–54	8/10 (80.0)	8/72 (11.1)	7.2	0.22
55–64	33/43 (76.7)	17/179 (9.5)	8.1	0.25
65–74	32/53 (60.4)	9/151 (6.0)	10	0.42
75–84	9/20 (45.0)	5/56 (8.9)	5.0	0.60
Total	82/126 (65.1)	39/458 (8.5)	7.7	0.38

CRL, crown–rump length; TR, tricuspid regurgitation.

Table 4 Prevalence of tricuspid regurgitation in trisomy 21 and normal fetuses and likelihood ratio according to delta nuchal translucency thickness

	Trisomy 21	*Normal*	*Likelihood ratio for trisomy 21*	
Delta NT	(n *(%)*)	(n *(%)*)	*TR positive*	*TR negative*
< 1.0	1/2 (50.0)	4/130 (3.1)	16.1	0.51
1.0–2.9	24/41 (58.5)	13/191 (6.8)	8.6	0.44
3.0–4.9	26/34 (76.5)	11/92 (12.0)	6.4	0.27
⩾ 5.0	31/49 (63.3)	11/45 (24.4)	2.6	0.49
Total	82/126 (65.1)	39/458 (8.5)	7.7	0.38

NT, nuchal translucency; TR, tricuspid regurgitation.

regurgitation was provided by CRL (OR, 0.94; 95% CI, 0.89–0.99; $P = 0.021$) while in chromosomally normal fetuses prediction was provided by fetal delta NT (OR, 1.26; 95% CI, 1.34–1.41, $P < 0.0001$). In trisomy 21 fetuses, the likelihood of having tricuspid regurgitation (%) is: (odds/1 + odds) × 100, where odds = e^y and $Y = \text{Log}_e$ (odds) = 4.507 − 0.058 × CRL (in mm). In chromosomally normal fetuses, the likelihood of having tricuspid regurgitation (%) is: (odds/1 + odds) × 100, where odds = e^y and $Y = \text{Log}_e$ (odds) = −3.089 + 0.236 × delta NT (in mm). The likelihood ratios at different values of delta NT are shown in Table 6.

In the chromosomally normal fetuses, with and without tricuspid regurgitation, the prevalence of cardiac defects increased with fetal NT (Table 7). The prevalence of tricuspid regurgitation was 46.9% (15 of 32) in those with cardiac defects and 5.6% (24 of 426) in those without cardiac defects. Therefore, the positive and negative likelihood ratios for cardiac defects were 8.4 and 0.56, respectively.

DISCUSSION

In this study, where more than 80% of the fetuses had increased NT and 20% had cardiac defects, tricuspid regurgitation was found in 8.5% of chromosomally normal fetuses, in 65.1% of trisomy 21 fetuses and in about 50% of those with trisomy 18 or 13. The study has

Copyright © 2005 ISUOG. Published by John Wiley & Sons, Ltd.

Table 5 Prevalence of tricuspid regurgitation in chromosomally normal and trisomy 21 fetuses and likelihood ratio according to delta nuchal translucency and presence or absence of a cardiac defect

	Cardiac defect present				*Cardiac defect absent*			
Delta	*Tricuspid regurgitation (%)*				*Tricuspid regurgitation (%)*			
NT (mm)	*Trisomy 21*	*Normal*	*LR +ve*	*LR −ve*	*Trisomy 21*	*Normal*	*LR +ve*	*LR −ve*
−1	92.9	25.2	3.7	0.095	47.2	3.1	15.1	0.544
0	92.9	28.4	3.3	0.099	47.2	3.7	12.8	0.548
1	92.9	32.0	2.9	0.104	47.2	4.3	10.9	0.551
2	92.9	35.8	2.6	0.110	47.2	5.1	9.3	0.556
3	92.9	39.8	2.3	0.117	47.2	5.6	7.9	0.561
4	92.9	43.9	2.1	0.126	47.2	7.0	6.8	0.567
5	92.9	48.1	1.9	0.136	47.2	8.2	5.8	0.575
6	92.9	52.3	1.8	0.149	47.2	9.5	4.9	0.583
7	92.9	56.5	1.6	0.163	47.2	11.1	4.3	0.594
8	92.9	60.6	1.5	0.180	47.2	12.8	3.7	0.605

LR, likelihood ratio; NT, nuchal translucency.

Table 6 Prevalence of tricuspid regurgitation in chromosomally normal and trisomy 21 fetuses and likelihood ratio according to delta nuchal translucency regardless of presence of cardiac defect

	Prevalence of tricuspid regurgitation (%)			
Delta NT (mm)	*Trisomy 21*	*Normal karyotype*	*LR +ve*	*LR −ve*
−1	65.1	3.5	18.7	0.361
0	65.1	4.4	14.9	0.364
1	65.1	5.4	11.9	0.369
2	65.1	6.8	9.6	0.374
3	65.1	8.4	7.7	0.381
4	65.1	10.5	6.2	0.389
5	65.1	12.9	5.0	0.401
6	65.1	15.8	4.1	0.414
7	65.1	19.2	3.4	0.431
8	65.1	23.1	2.8	0.454

LR; likelihood ratio; NT, nuchal translucency.

Table 7 Prevalence of cardiac defects in chromosomally normal fetuses with and without tricuspid regurgitation according to nuchal translucency

	Cardiac defect (n *(%))*		
NT (mm)	*Total*	*TR +ve*	*TR −ve*
< 3.5	4/181 (2.2)	2/8 (25.0)	2/173 (1.2)
3.5–4.4	6/130 (4.6)	3/9 (33.3)	3/121 (2.5)
⩾ 4.5	22/147 (15.0)	10/22 (45.5)	12/125 (9.6)
Total	32/458 (7.0)	15/39 (38.5)	17/419 (4.1)

NT, nuchal translucency; TR, tricuspid regurgitation.

also demonstrated that firstly, the prevalence of tricuspid regurgitation decreases with gestation, increases with fetal NT thickness and is substantially higher in those with than those without a cardiac defect and secondly, in chromosomally normal fetuses the finding of tricuspid regurgitation is associated with an 8-fold increase in risk for cardiac defects.

An experienced fetal echocardiographer can obtain adequate views for evaluation of the tricuspid valve in more than 95% of cases at 11 to 13 + 6 weeks' gestation. At this gestational age the fetus is very mobile and it is usually possible during a 3–5-min period of fetal cardiac scanning to obtain an apical four-chamber view, with the spine either anterior or posterior. However, an adequate flow profile cannot be obtained when the fetus remains fixed in an unfavorable position, with the four-chamber view in a lateral orientation.

The diagnosis of tricuspid regurgitation was based on firstly, the use of pulsed-wave Doppler, rather than color-flow mapping, and secondly, the presence of regurgitation during at least half of systole and with a minimum velocity of 80 cm/s. We have found that, at 11 to 13 + 6 weeks' gestation, color-flow mapping, which is useful in identifying cardiac structures, is unreliable for the detection of tricuspid regurgitation and is highly variable between ultrasound machines[5]. Although color-flow mapping is the most reliable way of detecting valvar regurgitation in postnatal life and even at 20 weeks' gestation, this does not appear to be true – at least in our experience – for the transabdominal route at 11 to 13 + 6 weeks' gestation. This is probably related to the small size of the tricuspid orifice (mean of 2 mm) coupled with the heart rate (mean 165 beats per min) at this time. The criteria for the minimum duration and velocity were used to avoid the erroneous diagnosis of tricuspid regurgitation in the presence of a jet produced by the relatively large Doppler sample volume picking up overlying aortic or pulmonary arterial blood flow, which at this gestation can produce a maximum velocity of 50 cm/s, or by the short reverse 'spike' generated by the closure of the valve cusp itself (valve click; Figure 2c).

Trisomy 21 and other chromosomal defects are associated with a high prevalence of tricuspid regurgitation. This association has also been reported in an echocardiographic study in mice at 11–14 days of gestation, where tricuspid regurgitation was found in 25% of 20 embryos with trisomy 16, which is the animal model of

Copyright © 2005 ISUOG. Published by John Wiley & Sons, Ltd.

human trisomy 21, but in none of 129 chromosomally normal embryos[6].

The prevalence of tricuspid regurgitation, in both chromosomally normal and abnormal fetuses, decreases with gestation (Table 3). Thus, within the gestational range of 11 + 0 to 13 + 6 weeks, we found a CRL-related decrease in the prevalence of tricuspid regurgitation. In addition, none of those 29 fetuses with tricuspid regurgitation at 11 to 13 + 6 weeks' gestation and a repeated fetal echocardiography at 20 weeks demonstrated persistence of the tricuspid regurgitation. Consistent with our findings are the results of a previous study at 15–25 weeks' gestation, which reported tricuspid regurgitation in only 28% of 80 fetuses with trisomy 21 and in 1.7% of controls[7]. Furthermore, a longitudinal study of 22 normal fetuses with tricuspid regurgitation demonstrated resolution of this finding in all cases within 7 weeks of the initial diagnosis at 15–35 weeks' gestation[8].

The prevalence of tricuspid regurgitation, in both chromosomally normal and abnormal fetuses, increases with fetal NT thickness (Table 4). Since the prevalence of both chromosomal abnormalities and cardiac defects increases with fetal NT[1,3,9], the high prevalence of tricuspid regurgitation in the chromosomally abnormal fetuses can be partly attributed to the coincidence of cardiac defects. However, we found that even in fetuses with apparently normal hearts there was an increased prevalence of tricuspid regurgitation. For example, in fetuses with no cardiac defects the prevalence of tricuspid regurgitation was 50% in those with trisomy 21, compared to 5.6% in the chromosomally normal fetuses. Possible mechanisms underlying the association between high NT and tricuspid regurgitation include increased cardiac preload or afterload. Previous studies have reported tricuspid regurgitation in a wide range of pathological conditions characterized by increased cardiac preload, such as non-immune hydrops, arteriovenous fistulae and the recipient fetus in twin-to-twin transfusion syndrome, or increased cardiac afterload, such as severe fetal growth restriction and indomethacin-induced ductal constriction[10–14]. In addition, it can occur where there is a dysplastic atrioventricular valve, as in a common atrioventricular valve or Ebstein's anomaly[15].

This study cannot be used to define the screening performance of tricuspid regurgitation for the detection of chromosomal abnormalities and cardiac defects because it was not a screening study of an unselected population but one with a high prevalence of increased NT. However, the findings clearly demonstrate that, certainly in such a group of fetuses, the presence or absence of tricuspid regurgitation can be used to modify firstly, the maternal age- and fetal NT-related risk for chromosomal defects (Tables 5 and 6) and secondly, the fetal NT-related risk for cardiac defects in chromosomally normal fetuses (Table 7). In the case of screening for trisomy 21, the implications of tricuspid regurgitation are quantitatively different in the presence or absence of a cardiac defect (Table 5). However, knowledge of cardiac structure and therefore expertise in fetal echocardiography is not essential to the application of tricuspid regurgitation in order to modify risk (Table 6). In the case of chromosomally normal fetuses, the finding of tricuspid regurgitation substantially increases the risk for cardiac defects and such pregnancies should be referred for early specialist fetal echocardiography.

ACKNOWLEDGMENT

This study was supported by a grant from The Fetal Medicine Foundation (Charity No: 1037116).

REFERENCES

1. Snijders RJ, Noble P, Sebire N, Souka A, Nicolaides KH. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal translucency thickness at 10–14 weeks of gestation. *Lancet* 1998; **351**: 343–346.
2. Souka AP, Krampl E, Bakalis S, Heath V, Nicolaides KH. Outcome of pregnancy in chromosomally normal fetuses with increased nuchal translucency in the first trimester. *Ultrasound Obstet Gynecol* 2001; **18**: 9–17.
3. Hyett J, Perdu M, Sharland G, Snijders R, Nicolaides KH. Using fetal nuchal translucency to screen for major congenital cardiac defects at 10–14 weeks of gestation: population based cohort study. *BMJ* 1999; **318**: 81–85.
4. Haak MC, Van Vugt JMG. Echocardiography in early pregnancy. Review of literature. *J Ultrasound Med* 2003; **22**: 271–280.
5. Huggon IC, DeFigueiredo DB, Allan LD. Tricuspid regurgitation in the diagnosis of chromosomal anomalies in the fetus at 11–14 weeks of gestation. *Heart* 2003; **89**: 1071–1073.
6. Gui Y, Linask K, Khowsathit P, Huhta J. Doppler echocardiography of normal and abnormal embryonic mouse heart. *Pediatr Res* 1996; **40**: 633–642.
7. De Vore G. Trisomy 21: 91% detection rate using second-trimester ultrasound markers. *Ultrasound Obstet Gynecol* 2000; **16**: 133–141.
8. Smrcek JM, Gembruch U. Longitudinal observations in normally grown fetuses with tricuspid valve regurgitation: report of 22 cases. *Prenat Diagn* 1999; **19**: 197–204.
9. Atzei A, Gajewska K, Huggon IC, Allan L, Nicolaides KH. Relation between nuchal translucency thickness and prevalence of major cardiac defects in fetuses with normal karyotype. *Ultrasound Obstet Gynecol* 2005; (in press).
10. Respondek M, Kammermeir M, Ludomirsky A, Weil S, Huhta J. The prevalence and clinical significance of fetal tricuspid valve regurgitation with normal heart anatomy. *Am J Obstet Gynecol* 1994; **171**: 1265–1270.
11. Gembruch U, Bald R, Fahnenstich H, Hansmann M. Chronic twin-twin transfusion syndrome: a Doppler sonographic and Doppler echocardiographic longitudinal study. *J Matern Fetal Invest* 1993; **3**: 201.
12. Gudmundsson S, Huhta J, Wood D, Tulzer G, Cohen A, Weiner S. Venous Doppler ultrasonography in the fetus with nonimmune hydrops. *Am J Obstet Gynecol* 1991; **164**: 33–37.
13. Tulzer G, Gudmundsson S, Rotondo K, Wood D, Cohen A, Huhta J. Doppler in the evaluation and prognosis of fetuses with tricuspid regurgitation. *J Matern Fetal Invest* 1991; **1**: 15–18.
14. Rizzo G, Arduini D. Fetal cardiac function in intrauterine growth retardation. *Am J Obstet Gynecol* 1991; **165**: 876–882.
15. Oberhoffer R, Cook A, Lang D, Sharland G, Allan L, Fagg N, Anderson R. Correlation between echo-cardiographic and morphological investigation of lesions of tricuspid valve diagnosed during fetal life. *Br Heart J* 1992; **68**: 580–585.

Copyright © 2005 ISUOG. Published by John Wiley & Sons, Ltd.