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Fetal tricuspid regurgitation at the 11 + 0 to 13 + 6-week scan: association with chromosomal defects and reproducibility of the method

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KEYWORDS: first trimester; nuchal translucency; screening; tricuspid regurgitation; trisomy 18; trisomy 21; ultrasound

ABSTRACT

Objective *To determine the reproducibility of diagnosing tricuspid regurgitation (TR) at 11 + 0 to 13 + 6 weeks' gestation, to examine further the relationship between TR and the presence of chromosomal defects and to calculate the likelihood ratios for trisomy 21 and trisomy 18 in fetuses with TR.*

Methods *Pulsed wave Doppler of flow across the tricuspid valve was carried out by 12 obstetricians, trained in fetal echocardiography, to ascertain the presence or absence of TR in 1557 fetuses at 11 + 0 to 13 + 6 weeks. The assessment was carried out immediately before chorionic villus sampling for fetal karyotyping. In 128 cases, assessment of tricuspid flow was also performed by experienced fetal cardiologists to examine the reproducibility of the method.*

Results *Tricuspid flow was successfully assessed in 1538 (98.8%) cases and TR was present in 58 (4.4%) of the 1323 chromosomally normal fetuses, 77 (67.5%) of the 114 cases with trisomy 21, and 14 (33.3%) of the 42 cases with trisomy 18. The kappa coefficient of agreement between obstetricians and cardiologists was 0.872 (*$P < 0.0001$*). Logistic regression analysis demonstrated that, in chromosomally normal fetuses, significant prediction of the likelihood of TR was provided by delta nuchal translucency (NT). The likelihood ratio for trisomy 21 and trisomy 18 for TR, derived by dividing the likelihood (%) of TR in trisomy 21 by the likelihood (%) in normal fetuses, decreased with delta NT.*

Conclusion *At 11 + 0 to 13 + 6 weeks, TR is a common finding in fetuses with trisomies 21 and 18. Assessment of the tricuspid flow can be performed by sonographers trained in fetal echocardiography. Copyright © 2006 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Tricuspid regurgitation (TR), determined by pulsed wave Doppler, is a common finding in trisomy 21 fetuses at 11 + 0 to 13 + 6 weeks of gestation[1,2]. A study, performed by experienced fetal cardiologists, reported the presence of TR in 8.5% of 458 chromosomally normal fetuses and in 65.1% of 126 fetuses with trisomy 21[2]. In the normal fetuses, the prevalence of TR increased with nuchal translucency (NT) and the study established likelihood ratios for trisomy 21 in fetuses with and without TR at the 11 + 0 to 13 + 6-week scan[2]. However, the inclusion of TR in first-trimester sonographic screening for chromosomal defects necessitates the training of a large number of sonographers.

The aims of this study were firstly, to examine the degree of agreement in the diagnosis of TR between obstetricians trained in fetal echocardiography and experienced fetal cardiologists, and secondly, to examine further the association between TR and chromosomal defects, and to establish likelihood ratios for trisomy 18 in addition to those for trisomy 21.

METHODS

In this prospective study, we examined 1557 fetuses for the presence or absence of TR during the routine ultrasound examination at 11 + 0 to 13 + 6 weeks carried out before chorionic villus sampling for fetal karyotyping between September 2004 and October 2005. The inclusion criteria were singleton pregnancy at 11 + 0 to 13 + 6 weeks of gestation with fetal crown–rump length (CRL) between 45 and 84 mm. In all cases there was prior screening for chromosomal defects by a combination of maternal age and fetal NT[3] and, after

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counseling, the parents opted for fetal karyotyping by chorionic villus sampling. All scans were carried out by a total of 12 obstetricians with training in first-trimester echocardiography. The process of training involves both theoretical and practical examinations in which the sonographers must demonstrate their ability to identify the normal and the abnormal anatomy of the heart and to obtain standard views of the four chambers, outflow tracts, arterial duct and aortic arch on cross-sectional imaging, and to use color-flow mapping and pulsed wave Doppler in the assessment of the fetal heart.

All scans were carried out transabdominally using either a RAB 4-8L probe (Voluson 730 Expert, GE Medical Systems, Milwaukee, WI, USA) or a 5-MHz curvilinear probe (Aloka Prosound 5000, Tokyo, Japan). The presence or absence of TR was determined by pulsed wave Doppler. A sample volume of 2–3 mm was positioned across the tricuspid valve in an apical four-chamber view such that the angle to the direction of flow was less than 20° (Figure 1). A minimum of three attempts were made since the regurgitation jet, when present, may vary its direction towards the right atrium. TR was diagnosed if it was found during at least half of systole and with a velocity of over 60 cm/s, since aortic or pulmonary arterial blood flow at this gestation can produce a maximum velocity of 50 cm/s (Figure 2). When TR was diagnosed, its peak systolic velocity (PSV) was also recorded. The scan was abandoned if a satisfactory evaluation was not obtained within the 20 min dedicated to the routine 11 + 0 to 13 + 6-week scan.

Demographic characteristics and ultrasound findings were recorded in a fetal database at the time of the examination. The results of fetal karyotyping were also entered in the database when they became available.

In 128 cases, assessment of the tricuspid valve was firstly performed by an obstetrician and immediately afterwards by one of two experienced fetal cardiologists, who were not aware of the findings by the obstetricians.

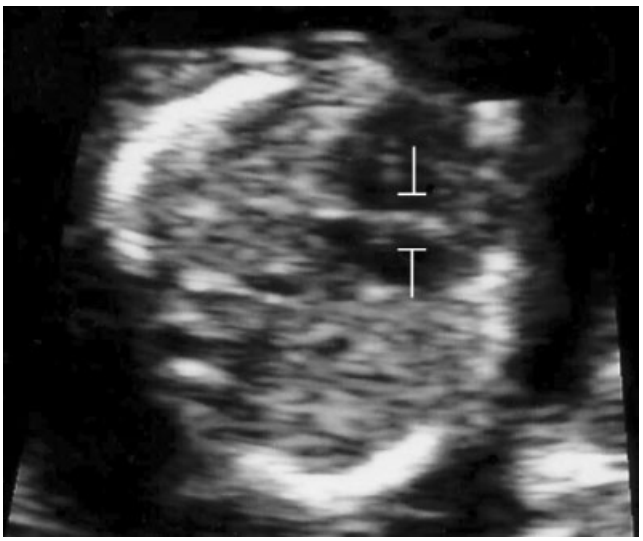

Figure 1 Ultrasound image showing the apical four-chamber view of the heart at 12 weeks. The Doppler sample volume is positioned across the tricuspid valve.

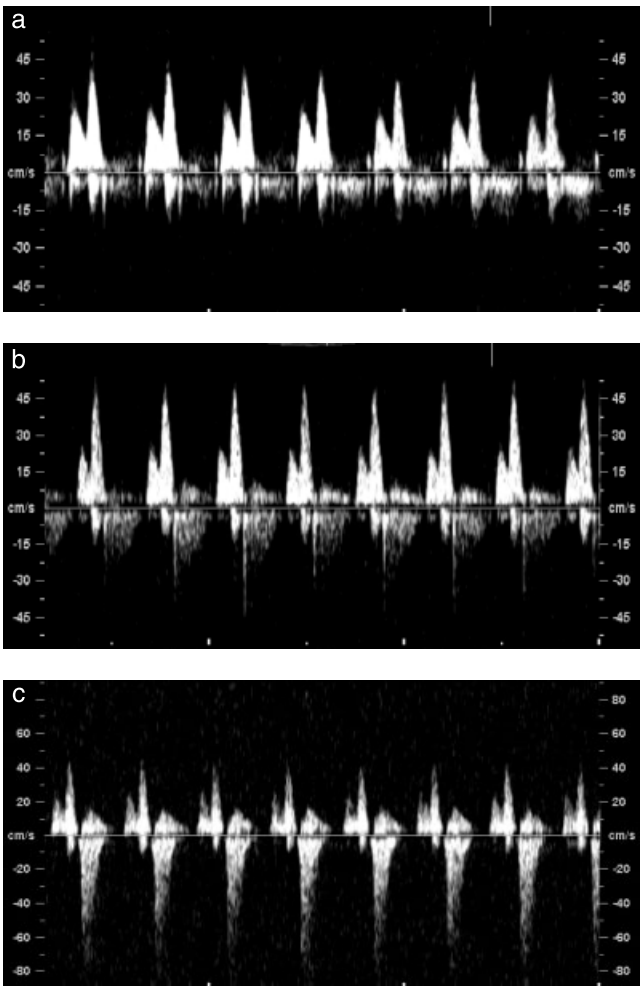

Figure 2 Ultrasound images showing the Doppler flow profile in the tricuspid valve with (a) no regurgitation during systole, (b) a short reverse 'spike' generated by the closure of the valve cusp and the jet produced by aortic or pulmonary arterial blood flow, and (c) regurgitation during approximately half of systole and with a velocity of more than 60 cm/s.

Statistical analysis

The delta NT (difference between the observed NT measurement and its normal mean for CRL) was calculated and logistic regression analysis was used to examine the effect of fetal CRL and delta NT on the prevalence of TR in the chromosomally normal and abnormal fetuses. The likelihood of having TR in the chromosomally normal, trisomy 21, and trisomy 18 fetuses was calculated from the regression equation. The Shapiro–Wilk test demonstrated that not all of the study groups had a normal distribution of their PSV values when TR was present, and therefore, the Mann–Whitney *U*-test was used to determine the significance of differences between the chromosomally normal and abnormal groups. The kappa coefficient was used to determine the degree of agreement between the obstetricians and cardiologists in assessing the presence or

Table 1 Positive and negative likelihood ratios for tricuspid regurgitation for trisomy 21 and trisomy 18 according to delta nuchal translucency

	Trisomy 21		*Trisomy 18*	
Delta NT	*LR* +ve *(mean (95% CI))*	*LR* −ve *(mean (95% CI))*	*LR* +ve *(mean (95% CI))*	*LR* −ve *(mean (95% CI))*
< 1.0	18.6 (18.5–18.7)	0.337 (0.337–0.337)	9.2 (9.1–9.2)	0.692 (0.692–0.692)
1.0–2.9	13.9 (13.7–14.0)	0.342 (0.342–0.342)	6.8 (6.8–6.9)	0.702 (0.701–0.702)
3.0–4.9	8.8 (8.6–9.0)	0.353 (0.352–0.353)	4.3 (4.2–4.4)	0.723 (0.722–0.725)
≥ 5.0	4.3 (4.0–4.6)	0.405 (0.388–0.421)	2.1 (2.0–2.3)	0.830 (0.797–0.863)

LR, likelihood ratio; NT, nuchal translucency.

absence of TR. The data were analyzed using the statistical software SPSS 13.0 (SPSS, Chicago, Illinois, USA), and $P < 0.05$ was considered statistically significant.

RESULTS

The median maternal age was 37 (range, 16–47) years, the median CRL was 66 (range, 45–84) mm, and the median gestation was 12 (range, 11 + 0 to 13 + 6) weeks. The tricuspid valve was successfully examined in 1538 (98.8%) of the 1557 cases. In the 19 cases without a satisfactory Doppler flow profile the fetus remained in a lateral position throughout the duration of the examination. TR was present in 58 (4.4%, 95% CI, 3.3–5.5%) of the 1323 chromosomally normal fetuses, 77 (67.5%, 95% CI, 58.8–76.3%) of the 114 with trisomy 21, 14 (33.3%, 95% CI, 18.5–48.2%) of the 42 with trisomy 18, and in 9 (15.3%, 95% CI, 5.8–24.7%) of the 59 with other chromosomal defects.

When present, the median PSV of TR was 80 (range, 65–123) cm/s in the chromosomally normal group, 83 (range, 65–175) cm/s in the fetuses with trisomy 21, and 93 (range, 70–120) cm/s in the fetuses with trisomy 18. There were no significant differences between the normal and the abnormal groups ($P = 0.968$ for trisomy 21 and $P = 0.402$ for trisomy 18).

Likelihood ratios

Logistic regression analysis demonstrated that, in chromosomally normal fetuses, significant prediction of the likelihood of TR was provided by fetal delta NT (odds ratio 1.259, 95% CI, 1.106–1.433, $P = 0.001$), but not by fetal CRL (odds ratio 1.018, 95% CI, 0.986–1.051, $P = 0.277$). In trisomy 21, prediction was not provided by either CRL (odds ratio 0.964, 95% CI, 0.907–1.024, $P = 0.235$) or delta NT (odds ratio 1.234, 95% CI, 0.984–1.548, $P = 0.069$). Similarly, in trisomy 18 fetuses prediction of the likelihood of TR was not provided by either CRL (odds ratio 0.906, 95% CI, 0.802–1.024, $P = 0.116$) or delta NT (odds ratio 0.995, 95% CI, 0.757–1.309, $P = 0.973$). In chromosomally normal fetuses, the likelihood of having TR (%) is: (odds/1 + odds) × 100, where odds = e^y, and Y = ln (odds) = −3.334 + 0.230 × delta NT (in mm).

Table 2 Agreement between obstetricians and cardiologists in the diagnosis of tricuspid regurgitation

	Cardiologists' diagnosis of TR	
	Negative n *(%)*	*Positive* n *(%)*
Obstetricians' diagnosis of TR		
Negative *n* (%)	85 (97.7)	5 (12.2)
Positive *n* (%)	2 (2.3)	36 (87.8)
Total no. of cases	87	41

TR, tricuspid regurgitation.

The likelihood ratio for trisomy 21 or trisomy 18 in the presence of TR is derived by dividing the likelihood (%) of TR in trisomy 21 (67.5%) or trisomy 18 (33.3%), respectively, by the likelihood (%) of TR in normal fetuses, which is dependent on fetal delta NT (Table 1).

Agreement between obstetricians and cardiologists

In the 128 cases examined by both obstetricians and fetal cardiologists, there was agreement in 36 (87.8%) of the 41 cases in which TR was present and in 85 (97.7%) of the 87 in which it was absent (Table 2). The kappa coefficient of agreement was 0.872 ($P < 0.0001$).

DISCUSSION

The findings of this study provide further evidence for the high association between TR at the 11 + 0 to 13 + 6-week scan and chromosomal defects. Thus, TR is found in less than 5% of chromosomally normal fetuses, in more than 65% of fetuses with trisomy 21, and in more than 30% of fetuses with trisomy 18.

In chromosomally normal fetuses the prevalence of TR increases with NT, which has been attributed to increased cardiac preload or afterload[2]. We have previously reported that both in chromosomally normal and trisomy 21 fetuses there is a high association between TR and cardiac defects, and suggested that the high prevalence of TR in the chromosomally abnormal fetuses can be partly attributed to the coincidence of cardiac defects[2]. In this study we wanted to investigate the feasibility of the

inclusion of TR in first-trimester sonographic screening for chromosomal defects by a large number of obstetricians who had received training in this technique. We did not investigate the accuracy of the first-trimester scan in the diagnosis of cardiac defects. However, since in the case of chromosomally normal fetuses the finding of TR substantially increases the risk for cardiac defects[2], such pregnancies should be referred for early echocardiography by experienced cardiologists.

The likelihood ratios for absent or present TR can be used in the calculation of patient-specific risks for chromosomal defects. In a previous study we demonstrated that there are no significant differences in median values of free beta-human chorionic gonadotropin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A) in trisomy 21 fetuses with and without TR, and Doppler examination of tricuspid flow can be incorporated into routine first-trimester screening for chromosomal defects by a combination of fetal NT and maternal serum biochemistry[4]. Examination of tricuspid flow, either in all cases or in about one sixth of the population that constitute the intermediate-risk group (between 1 in 101 and 1 in 1000) after screening by fetal NT and serum free β-hCG and PAPP-A, can improve the performance of screening by reducing the false-positive rate from 5% to less than 3%, while retaining the high detection rate of 90%[4,5].

Examination of the fetal heart and assessment of tricuspid flow necessitates specialist training. As demonstrated in this study, appropriately trained obstetricians can become highly competent in performing this examination and obtaining adequate views for accurate assessment of tricuspid flow at 11 + 0 to 13 + 6 weeks in about 99% of cases.

ACKNOWLEDGMENT

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