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First trimester tricuspid regurgitation and fetal abnormalities

Abstract

Background: Tricuspid regurgitation (TR) is a common sonographic finding during the fetal life. It has been reported in 7% of normal fetuses. It may be associated with aneuploidy and with both cardiac and extracardiac defects.
Objectives: In this study, we have looked at the characteristics of fetuses with and without TR at 11^{+0} to 13^{+6} weeks' gestation. Groups were compared with respect to the following variables: prevalence of chromosomal defects; other markers of aneuploidy; fetal cardiac; and extracardiac anomalies.
Methods: The study group included women, who underwent an ultrasound examination at 11–13^{+6} weeks' gestation between 2009 and 2012. The inclusion criteria were singleton pregnancies with crown-rump length measurements of 45–84 mm where the pregnancy outcome was known.
Results: Some 1075 patients met our inclusion criteria including 979 fetuses without TR and 96 with TR. There were 72 cases of aneuploidy diagnosed (6.7%). Isolated TR was found in 53 euploid fetuses (5.2%). All of the TR(+) aneuploid fetuses (n=40) had additional ultrasound markers present. Extracardiac anatomy showed a higher prevalence of abnormalities in the group of TR positives (12.5%) vs. TR negatives (1.6%). Abnormal cardiac findings were more frequent in the TR-positive group independently of chromosomal status and were found in 18.8% of fetuses with TR and in 1.9% with a normal tricuspid flow.
Conclusions: TR in combination with other markers is the strongest predictor for aneuploidy. TR, as an isolated parameter, is a poor screening tool both for all and for each individual chromosomal abnormality and congenital cardiac defects.

Keywords: Fetal heart; first trimester; tricuspid flow.

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Introduction

Tricuspid regurgitation (TR) is a fairly common sonographic finding during fetal life. It has been reported in as many as 7% of normal fetuses. However, it may also be associated with aneuploidy and with both cardiac and extracardiac structural defects [5, 12].

The exact reason for the association between TR and aneuploidy in the absence of a cardiac structural defect is not completely clear. It may be a result of dilation of the tricuspid valve (TCV) annulus secondary to right ventricular dilation. It may also be related to a primary defect in the valve due to microscopic changes that may be seen in association with aneuploidy. For example, the BMPR2 mutation that can be seen more commonly in fetuses with trisomy 21 is associated with TCV insufficiency in postnatal life [1, 9, 11]. The relationship between TR and cardiac structural anomalies is relatively straightforward as valvular disease accompanies many of these abnormalities.

The examination of TCV with pulsed Doppler has become an accepted part of the first trimester (11–13+6 weeks' gestation) fetal examination and significantly contributes to establishing an individualized aneuploidy risk assessment for the patient [6]. If TR is detected at the time of the first trimester scan, a detailed early, standard fetal cardiac examination should be performed as the presence of TR appears to increase the risk of cardiac structural defects, even in the absence of aneuploidy.

In our unit, we have been using Doppler evaluation of TCV as a part of the first trimester ultrasound for a number of years. In this study, we have looked at the characteristics of fetuses with and without TR at 11–13+6 weeks' gestation. These two groups were compared with respect to the following variables: prevalence of chromosomal defects; presence or absence of other markers of aneuploidy; and presence or absence of fetal cardiac and extracardiac structural anomalies.

Methods

The study group included women, who underwent an ultrasound examination at 11^{+0} to 13^{+6} weeks' gestation at the Ultrasound Lab of Gynecology and Obstetrics Chair, Jagiellonian University between January 2009 and June 2012. The local Ethics Committee approved the study protocol and all participating subjects gave written consent. The electronic records of the ultrasound images and reports were retrospectively analyzed. The inclusion criteria were singleton pregnancies with crown-rump length (CRL) measurements of 45–84 mm (11^{+0} to 13^{+6} weeks' gestation) of which the pregnancy outcome was known. The study population included all women irrespective of their risk for aneuploidy. All subjects were Caucasian.

The pregnancy outcome data were obtained from medical records, including post-mortem examinations. The patients were contacted to provide additional information if necessary. The presence or absence of aneuploidy and structural defects was recorded for each patient. The fetal karyotype was determined based on amniocentesis (159 cases). The remainder of the fetuses (916 cases) was considered to be euploid based on a normal neonatal examination. Aneuploidy other than trisomies 21, 18, and 13 and monosomy X were excluded from the study. All examinations were performed using the Voluson E6 ultrasound system (GE Healthcare, Zipf, Austria). Most examinations were done transabdominally, nevertheless in selected cases, transvaginal ultrasound was employed in order to complete the examination. Our first trimester ultrasound examination protocol includes a systematic evaluation of the entire fetus including a detailed cardiac examination. The following markers of aneuploidy are assessed using gray scale: nuchal translucency (NT) measurement, nasal bone (NB) ossification, and fronto-maxillary facial angle (FA) measurement. Doppler is employed to evaluate the ductus venosus and the flow across the TCV. The methods used adhered strictly to those recommended by the Fetal Medicine Foundation (FMF). Specifically, the evaluation of the TCV was done using the four-chamber cardiac view with the angle between the pulsed Doppler beam and the longitudinal axis of the ventricular septum being less than 30°. In order for the diagnosis of TR to be made, the regurgitant jet velocity had to exceed 60 cm/s and its duration had to be greater than 50% of the systole. All examinations were performed by the physicians (MW and AN have been certified by the FMF in NT measurements as well as additional ultrasound markers for over 5 years).

The subjects were divided into two groups based on the presence or absence of TR. The prevalence and types of chromosomal defects were determined in each group. The presence of additional markers in each fetus was determined and recorded. The configuration of primary and secondary markers of aneuploidy among TR positives and TR negatives was analyzed. Due to the potentially high number of coincidences of these markers, major core patterns were defined in Table 1 and coded in our databases as nonparametric variables. Normality of continuous variable distribution was validated (using the Kolmogorov-Smirnov test). The distribution of categorized variables was presented in multi-way tables. The χ^2 test was used to present differences. For variables presenting Gaussian distribution, parametric tests were applied. Here two groups of independent variables were compared using the Student's *t*-test. For continuous variables not presenting Gaussian distribution nonparametric tests were utilized. Two groups of independent variables were compared in this case by the Mann-Whitney *U* test. SPSS Statistics v.17 (IBM Corporation, USA) software was utilized in this study. Values of $P<0.05$ were considered significant.

Table 1 List of core patterns of aneuploidy markers that were used in this study.

Code	Configuration of markers
0	No markers
1	Isolated NT>95th per
2	NT>95th per+TR+eventual other markers excluding NB(–)
3	NT>95th per+NB(–)+eventual other markers
4	Isolated abn. DV or abn. DV+eventual other markers excluding NT>95th per
5	NB(–)+TR+eventual other markers
6	NB(–)+FA>85°
7	NT>95th per+absent DV
8	Isolated FA>85°
9	Isolated TR
10	Isolated SUA
11	Isolated NB(–)
12	NT>95th per+SUA
13	TR+FA>85°
14	NT>95th per+FA>85+SUA

DV=ductus venosus, abn. DV=Negative a wave in ductus venosus flow, NB(–)=negative nasal bone, NT=nuchal translucency, FA=facial angle, SUA=single umbilical artery, and TR=tricuspid regurgitation.

Results

A total of 1075 patients met our inclusion criteria. There were 979 fetuses without TR [TR(–)] and 96 with TR [TR(+)]. The CRL measurements did not differ between the two groups (TR(–)=62.67 mm (95%CI: ±9.90 mm); TR(+)=63.69 mm (95%CI: ±10.33 mm) (P=0.34). However, maternal age (MA), fetal heart rate (FHR), and NT measurements were all statistically different between the two groups (P<0.05) (Table 2).

Overall, there were 72 cases of aneuploidy diagnosed, which represents 6.7% of the total population. Thirty-two were in the TR(+) group (prevalence=33.33%) and 40 were

Table 2 Comparison of TR(–) and TR(+) groups with respect to maternal age (MA), fetal heart rate (FHR), nuchal translucency (NT) measurement, and crown-rump length (CRL).

	Tricuspid flow	n	Mean	Standard deviation (SD)	Statistical significance P<0.05
MA (years)	TR(–)	979	30.41	4.489	0.03
	TR(+)	96	31.51	4.821	
FHR (bpm)	TR(–)	979	161.02	7.411	0.03
	TR(+)	96	158.96	9.333	
NT (mm)	TR(–)	979	1.880	0.9942	0.00
	TR(+)	96	2.974	2.0118	
CRL (mm)	TR(–)	979	62.671	9.8981	0.34
	TR(+)	96	63.691	10.3253	

in the TR(–) group (prevalence=4.09%), which is statistically different (P<0.05). Conversely, the prevalence of TR was 6.38% in euploid fetuses and 44.44% in those with aneuploidy, which is also significantly different (P<0.05). Among the chromosomal abnormalities, the highest prevalence of TR was found in trisomy 18 at 63.6%. In trisomy 21, trisomy 13 and Turner syndrome, TR was seen in 44.4%, 42.9%, and 22.2% of the fetuses, respectively. All of these were statistically different from the euploid population (P<0.05).

The fetuses were grouped according to their chromosomal status. Within each group, a comparison of the NT measurement was made according to the presence or absence of TR (Figure 1 and Table 3). In the trisomy 21 and trisomy 13 groups, the presence of TR was associated with a tendency of increase in NT measurements; however, due to a small number of cases it was statistically not significant (P>0.05). In the larger subgroup of euploid fetuses the relation between the presence of TR and increased NT was also not statistically significant (P=0.133). In Turner syndrome, there were no statistically significant differences found in NT measurements between TR(–) and TR(+) fetuses (P=0.667). In cases of trisomy 18 there was a trend towards smaller NT measurements in fetuses with TR (P=0.029).

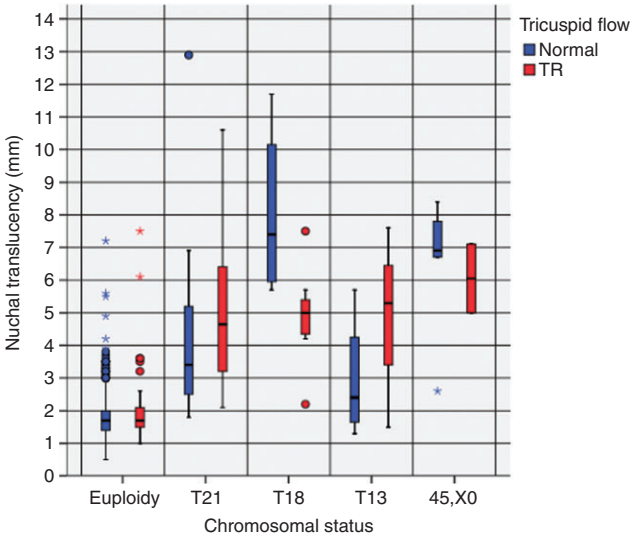

Figure 1 In this chart the relationship between TR, nuchal translucency measurements and chromosomal status is shown.

Table 3 Mean NT measurements, their standard deviations, and statistical significances (P) among TR positive and normal tricuspid flow [TR(–)] cases with normal karyotype and chromosomal abnormalities.

Group	Tricuspid flow	n	Mean NT	SD	P value
Euploidy	TR(+)	64	1.984	1.0336	0.133
	TR(–)	939	1.752	0.5747	
Trisomy 21	TR(+)	20	4.890	2.1766	0.150
	TR(–)	25	4.160	2.3805	
Trisomy 18	TR(+)	7	4.886	1.6015	0.029
	TR(–)	4	8.050	2.7429	
Trisomy 13	TR(+)	3	4.800	3.0806	0.629
	TR(–)	4	2.950	1.9330	
45 X0	TR(+)	2	6.050	1.4849	0.667
	TR(–)	7	6.700	1.9296	

Isolated TR was found in 53 euploid fetuses (5.2%). There were 6 (0.6%) euploid fetuses that had a combination of TR(+) and an increased NT (>95th percentile). All of the TR(+) aneuploid fetuses (n=40) had additional ultrasound markers present. The combination of TR(+) and an increased NT was found in 12 (26.7%) cases of trisomy 21, 4 (36.4%) cases of trisomy 18, and 2 (22.2%) cases of monosomy X0. The combination of TR, increased NT, and delayed nasal ossification was found in only one case of euploidy (0.1%), in 6 cases (13.3%) of trisomy 21, in two cases of trisomy 18 (18.2%), and in two cases of trisomy 13 (28.6%). Additionally, in TR positives, combinations of TR and DV abnormalities, TR and NB(–), and TR and increased FA were found. A detailed configuration of markers in TR positive and negative cases is shown in Figures 2 and 3.

In the euploid population, most fetuses that were TR(–) also lacked additional ultrasound markers [804 (85.9%)]. In the aneuploidy population there were only two fetuses in which no markers were observed (two cases of trisomy 13 out of 7).

The analysis of extracardiac anatomy showed a higher prevalence of structural abnormalities in the group of TR positives (12.5%) vs TR negatives (1.6%) and is summarized in Tables 4 and 5. In euploidy, trisomy 21 and trisomy 18, TR-positive cases were more prevalent with extracardiac anomalies, whereas in trisomy 13 and monosomy 45 X0, these abnormalities were noted more often in tricuspid normal flow cases. However, the incidence of extracardiac anomalies was not found statistically significant among TR-positive cases of euploidy (P=0.08) and aneuploidy (P>0.05).

Abnormal cardiac findings were more frequent in the TR-positive group independently of chromosomal status and were found in 18.8% of fetuses with TR and in 1.9% with a normal tricuspid flow. We found that the cases with insufficient TCV presented higher values of NT in euploidy cases affected by congenital heart defect (CHD) (Figure 4).

The coincidence between the TR and the presence of CHD in euploidy subjects was not found statistically significant (P=0.06). Cardiac abnormalities identified in our study population based on mid-trimester ultrasound and

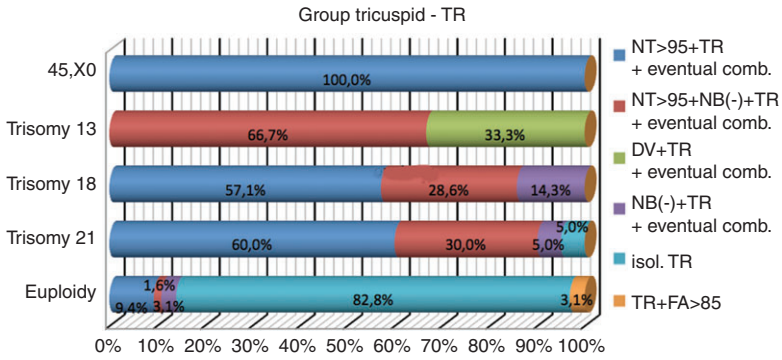

Figure 2 The configuration and prevalence of isolated and combined markers of aneuploidy in TR positive cases in terms of chromosomal status.

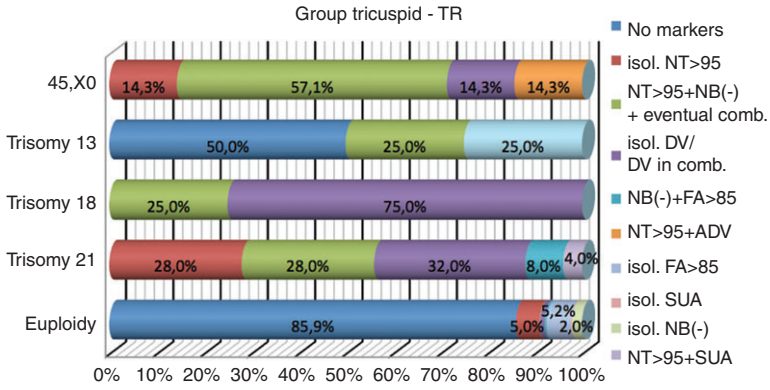

Figure 3 The configuration and prevalence of isolated and combined markers of aneuploidy in TR negative cases in terms of chromosomal status.

Table 4 Prevalence of structural abnormalities among cases of euploidy, trisomy 21, trisomy 18, trisomy 13, and Turner syndrome in terms of tricuspid flow.

Groups				Tricuspid flow	
				TR(–)	TR(+)
Euploidy	Extracardiac anomaly	Absent	n	930	61
			% of total	92.7%	6.1%
		Present	n	9	3
			% of total	0.9%	0.3%
Trisomy 21	Extracardiac anomaly	Absent	n	24	17
			% of total	53.3%	37.8%
		Present	n	1	3
			% of total	2.2%	6.7%
Trisomy 18 and trisomy 13	Extracardiac anomaly	Absent	n	4	5
			% of total	22.2%	27.8%
		Present	n	4	5
			% of total	22.2%	27.8%
45 X0	Extracardiac anomaly	Absent	n	6	2
			% of total	66.7%	22.2%
		Present	n	1	0
			% of total	11.1%	0%

postnatal findings according to tricuspid flow and chromosomal statuses are summarized in Table 6.

In euploidy group presenting normal tricuspid flow, we identified: one case of atrio-ventricular septal defect (AVSD), two cases of tetralogy of Fallot (ToF), two cases of d-transposition of great arteries, three cases of hypoplastic left heart syndrome (HLHS), and one case of pulmonary atresia with intact interventricular septum. There

Table 5 Total number of diagnosed extracardiac structural abnormalities summarized according to tricuspid flow.

Anatomic defects	n	Groups according to tricuspid flow	Chromosomes				All
			Euploidy	Trisomy 21	Trisomy 18	Trisomy 13	45 X0	
None	1052	TR(+)	61	20	4	1	2	88 (91.6%)
		TR(–)	930	24	3	1	6	964 (98.5%)
Hydrops	5	TR(+)	–	–	2	1	–	3 (3.1%)
		TR(–)	–	1	–	–	1	2 (0.2%)
Holoprosencephaly	1	TR(+)	–	–	–	1	–	1 (1%)
		TR(–)	–	–	–	–	–	0 (0%)
Facial nomalies	6	TR(+)	1	–	–	1	–	2 (2.1%)
		TR(–)	2	–	–	2	–	4 (0.4%)
Abdominal anomalies	12	TR(+)	1	–	1	2	–	4 (4.2%)
		TR(–)	4	–	1	3	–	8 (0.8%)

The number of patients is listed and in brackets percentages are presented in analyzed TR-positive or TR-negative subjects.

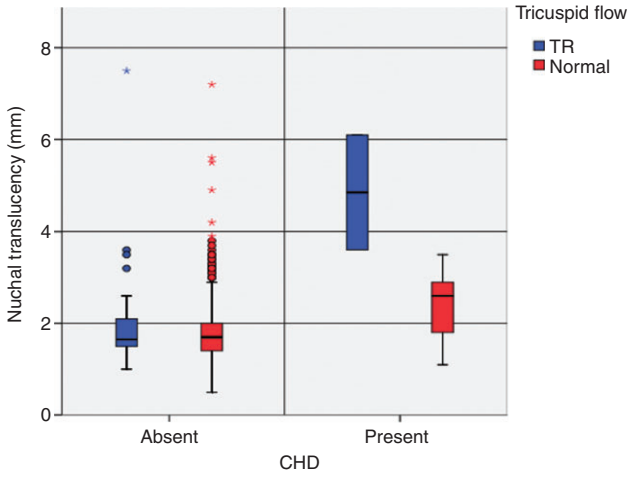

Figure 4 Mean nuchal translucency values in the group of euploidy according to tricuspid flow and the presence or absence of congenital heart defect are presented.

were no additional cases of these anomalies in the total group of euploidy.

We also checked detection rates and false-positive rates (FPRs) of TR for aneuploidy and cardiac defects irrespective of the presence or absence of other markers (Table 7).

Discussion

After the relationship of TR with aneuploidy and cardiac defects was raised, we noted a high number of referrals to our tertiary center because of incompetent tricuspid flow and subsequently increased risk of aneuploidy in the first trimester [3, 6]. This prompted us to analyze the significance of TR in terms of chromosomal status as well as congenital defects. The general prevalence of TR in our analyzed group was comparable with other observations and was 8.9%. An initial report by Faiola et al. based on 742 singleton pregnancies, showed tricuspid insufficiency in 8.5% of euploidy, 65.1% of trisomy 21, and 53% of trisomy 18, or 13 cases [3]. A later study from the same group based on 1557 cases demonstrated a lower incidence of TR, 4.4% in the euploidy group, 67.5% in trisomy 21, and 33.3% in trisomy 18 [4]. In 2009 Kagan et al. examined 19,800 subjects and noted the incidence of TR in 0.9% in the euploidy group, 55.7%, 33%, and 30% of the fetuses with trisomy 21, 18, and 13, respectively, and 30.5% of those with Turner syndrome [7]. For comparison our study demonstrated the following prevalence of TR based on chromosomal status: 6.4% of the euploidy group, 44.4% in cases of trisomy 21, 63.6% in cases of trisomy 18, 42.9% trisomy 13, and 22.2% of monosomy 45 X0.

In literature reviews we noted that investigators focused on isolated markers of aneuploidy rather than on their distribution and combinations. Molina Garcia et al. who analyzed secondary markers of aneuploidy before chorionic villus sampling highlighted the need for secondary markers assessment [10]. In our group, only 29.2% of cases of aneuploidy (NT>95th percentile – 8 cases; abnormal DV – 12 cases; TR – 1 case) and almost 14.8% of euploidy (TR – 53 cases, FA>85^{o} – 49 cases, and NT>95th percentile – 47 cases) presented isolated markers. The remainder of chromosomal abnormalities demonstrated ultrasound markers in arrangements. In this "combination of markers" group, TR plus at least one other marker is the most frequent indicator of aneuploidy in 58.8% (NT>95th percentile+TR=18 cases; NT>95th percentile+NB(–)+TR=10 cases; NB(–)+TR=2 cases), which constitutes 43.1% of all aneuploidy cases. Some 42.2% of trisomy 21 and 64% of trisomy 18 cases also presented a combination of markers

Table 6 Abnormal cardiac findings summarized according to tricuspid flow and chromosomal status.

Chromosomal status				Tricuspid flow	
				TR(+)	TR(–)
Euploidy	Fetal heart	Normal	n	62	930
			% of total	6.2%	92.7%
		Septal defects	n	0	1
			% of total	0%	0.1%
		Left heart defects	n	1	3
			% of total	0.1%	0.3%
		Conotruncal defects	n	0	4
			% of total	0%	0.4%
		Right heart defects	n	1	1
			% of total	0.1%	0.1%
Aneuploidy	Fetal heart	Normal	n	16	30
			% of total	21.6%	40.5%
		Septal defects	n	8	1
			% of total	10.8%	1.4%
		Left heart defects	n	5	3
			% of total	6.8%	4.1%
		Conotruncal defects	n	1	4
			% of total	1.4%	5.4%
		Functional abnormalities	n	3	2
			% of total	4.1%	2.7%
		Single ventricle	n	0	1
			% of total	0%	1.4%

rather than their isolated prevalence. This indicates that TR in combination with other markers is the strongest predictor for aneuploidy. In the first high-risk series based mainly on thickened NT cases authors demonstrated 83% of aneuploidy in TR positives compared to 35% in TR negatives [6]. Comparatively, we found that isolated TR does not increase the risk of aneuploidy as only 1 out of 54 cases was aneuploid in our group. In this subject, however, the NT was at the 95th percentile. This observation is similar to that as found in the study by DeVore who did not find any Down syndrome subjects presenting with isolated TR [2].

With regard to structural findings, TR-positive cases demonstrated a 5.72 times higher incidence of abnormalities than TR-negative cases. However, normal tricuspid flow did not assure normal extracardiac fetal anatomy. We identified cases of cleft lip/palate, diaphragmatic hernia, and omphaloceles that did not present with TR. In terms of cardiac abnormalities, anomalies were identified 9.89 times more often in TR-positive cases than in TR-negative cases. Among the TR-positive cases we identified cases of ventricular septal defects, AVSD, double outlet right ventricle, Ebstein's anomaly, right dominant heart, and cardiomegaly. Abnormal cardiac findings were also observed in the group with normal tricuspid flow including ToF, d-transposition of the great arteries, AVSDs, and HLHS. Among TR-positive euploidy, normal extracardiac anatomy was found in 93.8% of cases and showed normal cardiac findings in 96.9%. Surprisingly we did not identify any case of cardiac malformation in the group of subjects with isolated TR. This observation means that isolated TR can be considered as a cardiovascular phenomenon rather than an indicator of abnormality, if the additional markers are not found and early fetal anatomy is not suspicious. Our results showed that the detection rates of TR for trisomies 21, 18, 13 and monosomy 45 X0 are comparable with results presented by Karadzov-Orlic et al. They demonstrated higher detection rates of TR for trisomy 21 (57.7%) with lower FPRs, i.e., 2.1%, but not for other chromosomal aberrations [8]. Likewise we noted a low detection rate of TR for congenital cardiac defects in euploidy of less than 20%. The above results indicate that TR, as

Table 7 Detection rates (DR) and false-positive rates (FPRs) of TR for aneuploidies and cardiac defects.

	All aneuploidy	T21	T18	T13	45 X0	All CHD	CHD in euploidy
DR	44.4%	44.4%	63.6%	42.9%	22.2%	48.6%	18.2%
FPR	6.4%	7.4%	8.4%	8.7%	8.8%	7.5%	6.3%

an isolated parameter, is a poor screening tool both for all and for each individual chromosomal abnormality and congenital cardiac defects.

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