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First trimester severe ductus venosus flow abnormalities in isolation or combination with other markers of aneuploidy and fetal anomalies

Abstract

Background: Altered flow in ductus venosus (DV) may be caused by the changes in preload or afterload. Its association with aneuploidy and congenital heart defects (CHDs) was widely described.

Objectives: The aim of this study was to examine the incidence of a reversed a-wave in DV flow (revDV) and the absence of DV (noDV), their coincidences with other markers of aneuploidy or fetal abnormalities in a mixed-risk population.

Methods: The study group covered women who underwent an ultrasound scan between 11+0 and 13+6 weeks' gestation.

Applied inclusion criteria: Singleton pregnancies with known pregnancy outcome and a crown-rump length of 45–84 mm.

Results: A total of 5811 cases, including 137 aneuploidies, met the inclusion criteria: 35 subjects of noDV, 189 of revDV and 5587 of normal DV flow. The incidence of noDV in euploidy was 0.47%, and in aneuploidy 5.8%. The incidence of revDV in euploidy was 2.46%, and in aneuploidy 35.7%. Among aneuploidy, the highest prevalence of noDV was found in monosomy 45X. revDV showed the highest prevalence in trisomy 18. Isolated noDV was only found in euploidy. Isolated revDV subjects were only observed in euploidy and trisomy 21. Any combination of revDV with additional markers showed high incidence in major trisomies. Extracardiac anatomy and abnormal cardiac findings showed a higher prevalence in noDV and revDV cases.

Conclusions: The presence of noDV might be useful in suspicion of monosomy X among cases with increased nuchal translucency, as well as in differentiating them from other aneuploidies. The combinations of aneuploidy markers with revDV are strong indicators of aneuploidy. revDV alone is a poor screening tool for aneuploidy and euploidy with CHD.

Keywords: Chromosomal aberrations; ductus venosus; first trimester.

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Introduction

A flow velocity pattern in ductus venosus (DV) reveals the pressure gradient between the fetal umbilical vein and the right atrium. An altered flow in DV may be caused by the changes in preload or afterload. Abnormal patterns of flow observed in fetal DV and their connection with cardiac insufficiency and severe fetal conditions were widely described in the literature [1–4]. The majority of reports refer to the second and third trimester cases, but for more than 15 years their association in the first trimester with increased nuchal translucency (NT), tricuspid regurgitation (TR), aneuploidy and congenital heart defects (CHDs) has been well documented [5–7]. The most critical part of the DV waveform is the "a-wave", which demonstrates augmentation and, in most severe circumstances, a reversed pattern of flow, which reflects deterioration of cardiac function [8]. The first trimester reversed a-wave in DV flow (revDV) was observed in 28.2% of the fetuses with cardiac defects (CHDs) and in 2.1% of those without cardiac anomalies [9]. revDV also shows high incidence in cases of aneuploidy up to 86.7% [10]. It was also noticed that the absence of DV (noDV), which has a prevalence of 1 in 2500 pregnancies, may be linked with unfavorable outcome and its prognosis is dependent on the first trimester NT thickness and associated abnormalities [11].

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In our ultrasound lab, we have been routinely using Doppler evaluation of DV as a part of the first trimester ultrasound for a number of years.

The aim of this study was to examine the incidence of revDV and noDV, their coincidences with other markers of aneuploidy or fetal abnormalities in a mixed-risk population of pregnant women undergoing ultrasound evaluation at our tertiary center.

Methods

This retrospective study was based on pregnant women who underwent an ultrasound examination at 11+0 to 13+6 weeks' gestation at our tertiary center between January 2009 and June 2012. The study protocol was approved by the local ethics committee, and all participating subjects signed a written consent. The electronic records of the ultrasound images and reports were studied. The inclusion criteria were singleton pregnancies with crown-rump length (CRL) measurements of 45–84 mm of which the pregnancy outcome was evident. All examined women were Caucasian. The outcome data were acquired from medical records, including 18–21 and 28–32 weeks' sonography, autopsy examinations and neonatal evaluation. The subjects were contacted to provide supplementary information if essential. The study population is depicted in Figure 1.

The incidence of aneuploidy or structural defects was recorded for each patient. Fetal karyotyping was obtained from amniotic fluid samples (652 cases). The rest of the fetuses (5641 cases) were considered to be euploid based on a normal neonatal examination. Aneuploidy other than trisomies 21, 18 and 13 and Turner syndrome were excluded from the study. All examinations were performed using the Voluson E6 ultrasound system (GE Healthcare, Zipf, Austria). Most examinations were conducted transabdominally, nevertheless, in selected cases; transvaginal ultrasound had to be applied in order to complete the examination. Our late first-trimester scan protocol included a systematic evaluation of the entire fetus, which further included a detailed cardiac examination. The following markers of aneuploidy were assessed using B-mode: NT measurement and nasal bone (NB) ossification. Doppler ultrasound was utilized to evaluate the DV and the flow across the tricuspid valve. The methods used followed the Fetal Medicine Foundation (FMF) guidelines. Particularly, the evaluation of the DV was carried out using the right ventral mid-sagittal view of the fetal trunk in color mapping with the angle between the pulsed Doppler beam and the longitudinal axis of DV being <30°. Sampling of DV was performed three times in each case. The cases showing transient, short-lasting episodes of revDV in the predominance of a positive a-wave in DV flow (posDV) were classified as posDV, and vice versa, if episodes of posDV were observed in the predominance of revDV, they were classified as revDV. The decision to use a qualitative evaluation of DV in all examined cases was made because at the beginning of the study, a quantitative method by using DV pulsatility index for veins (DV PIV) was not applied. In order for the diagnosis of revDV to be made, the clear negative wave without contamination from surrounding vessels had to be shown in pulsed wave Doppler (PWD) reading. In order for the diagnosis noDV to be made, color Doppler mapping was unable to define aliasing above the umbilical sinus, which was confirmed by means of PWD (Figure 2).

All examinations were performed by the physicians (MW and AN) and have been certified by the FMF in NT measurements as well as additional ultrasound markers for over 5 years. The subjects were divided into three groups: posDV, revDV and noDV, depending on the profile of flow. 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 posDV, revDV and noDV was analyzed. Due to the potentially high number of coincidences of these markers, major core patterns were defined and coded in our databases as nonparametric variables.

Normality of the continuous variable distribution was validated (using the Kolmogorov-Smirnov test). The χ^2 test was used to show differences. For variables presenting the Gaussian distribution, parametric tests were performed. Here, two groups of independent variables were contrasted using Student's *t*-test. For continuous variables, which did not present the Gaussian distribution, nonparametric tests were performed. Three groups of independent variables were compared in this case by the Mann-Whitney *U*-test. The SPSS Statistics v.17 software (IBM Co., New York, USA) was applied in this study. The values of $P<0.05$ were considered significant.

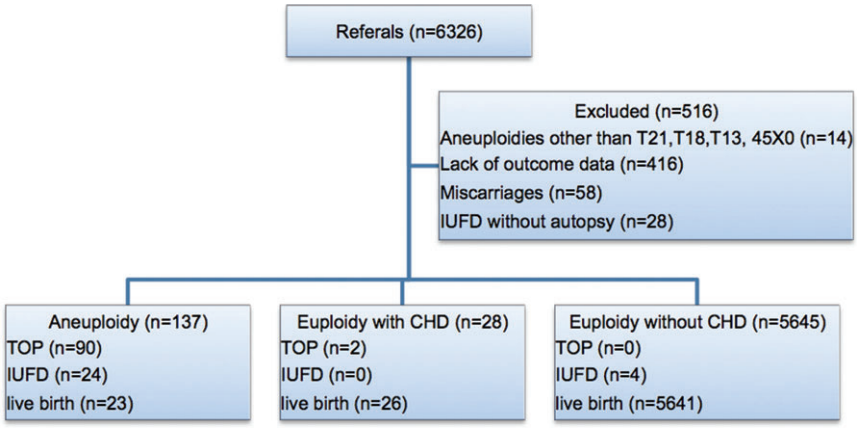

Figure 1 Study population description. T21=trisomy 21; T18=trisomy 18; T13=trisomy 13; 45X0=Turner syndrome; IUFD=intrauterine fetal demise; TOP=termination of pregnancy.

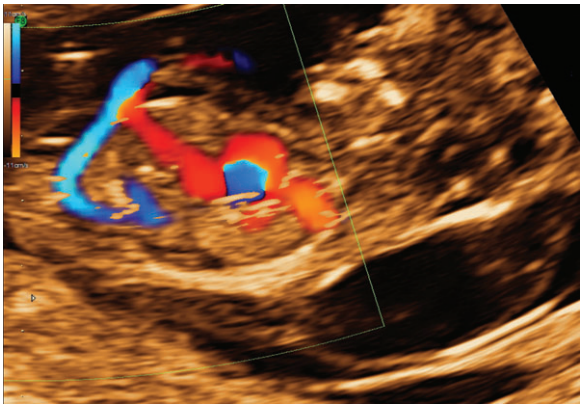

Figure 2 Lack of aliased flow at the connection between umbilical vein and hepatic venous system in a case diagnosed with Turner syndrome classified as noDV.

Table 1 Ductus venosus (DV) profiles of flow in the analyzed group according to the fetal chromosomal status.

Karyotype	DV profile	n	%
Euploidy	noDV	27	0.47
	posDV	5506	97.05
	revDV	140	2.46
Trisomy 21	noDV	1	1.19
	posDV	55	65.47
	revDV	28	33.33
Trisomy 18	posDV	12	52.17
	revDV	11	47.82
Trisomy 13	noDV	1	7.14
	posDV	7	50.00
	revDV	6	42.85
Turner syndrome	noDV	6	37.50
	posDV	6	37.50
	revDV	4	25.00

Results

In all 5810 cases, subjects underwent successful sampling of DV, which demonstrated the following profiles of flow: 35 subjects of noDV, 5587 of posDV and 189 of revDV. In the analyzed group, 137 cases of aneuploidy (2.35%) and 28 of euploidy with CHD (0.48%) were diagnosed. The incidence of noDV in euploidy was estimated at 0.47%, while in aneuploidy at 5.8%. The incidence of revDV in euploidy was estimated at 2.46%, while in aneuploidy at 35.7%. Among chromosomal abnormalities, the highest prevalence of noDV was found in monosomy 45X at 37.5%, but it was not observed in trisomy 18; furthermore, it was not frequent in the remaining trisomies: 21 (1.19%) and 13 (7.14%). On the other hand, revDV showed the highest prevalence in trisomy 18 (47.8%), but it was also common in other aberrations: trisomy 21 – 33.3%, trisomy 13 – 42.8% and in monosomy X (25%). The details are presented in Table 1.

Statistical significance of maternal age, CRL, fetal heart rate and NT between fetuses with various profiles of flow in DV was examined. Table 2 shows that out of the four depicted parameters, only the NT was statistically significant with the use of the Kruskal-Wallis test. This means that the three subgroups of DV patterns differed only in terms of NT thickness (P<0.000). Mean NT values in all three subgroups of DV flow were dependent on the karyotyping result (Figure 3).

Regarding nonparametric variables, the statistical significance of coincidences of revDV with TR was confirmed by means of the χ^2 test (P=0.000).

The distribution of markers of aneuploidy in subgroups divided by the DV profile was also examined. noDV cases showed only two configurations: noDV in isolation and combined with increased NT above the 95th percentile (Figure 4). Isolated noDV was only found in euploidy (0.4%), but combined it was observed in three cases of euploidy, six subjects of monosomy X (37.5%) and singular cases of trisomies 21 and 13.

Cases of posDV included predominantly subjects without any markers of aneuploidy in euploidy (5120 cases=90.2%) and trisomy 13 (3 cases=21.4%). This subgroup also included a few isolated positive markers: NT>95th percentile, delayed nasal ossification (NB-), isolated TR, their combinations and NT>95th percentile plus single umbilical artery. The majority of these coincidences were noted in euploidy. However, isolated increased NT was also found in 16 cases of trisomy 21 (19%), 2 cases of

Table 2 Fetuses with three profiles of flow in DV were compared against 4 parameters.

	MA	FHR	CRL	NT
noDV				
n	35	35.0	35.0	35.0
Mean	30.5	164.8	61.7	4.4
Median	31.0	163.0	59.8	2.0
Standard deviation	4.0	11.1	8.9	5.1
posDV				
n	5587.0	5587.0	5587.0	5587.0
Mean	30.5	160.4	63.3	1.7
Median	30.0	160.0	62.9	1.6
Standard deviation	4.2	7.3	9.1	0.8
revDV				
n	189.0	189.0	189.00	189.00
Mean	31.0	159.9	62.2	3.3
Median	30.0	161.0	61.3	2.3
Standard deviation	4.9	11.3	8.8	2.6
Statistical significance	0.715	0.114	0.176	0.000

MA=maternal age, FHR=fetal heart rate, CRL=crown-rump length, NT=nuchal translucency.

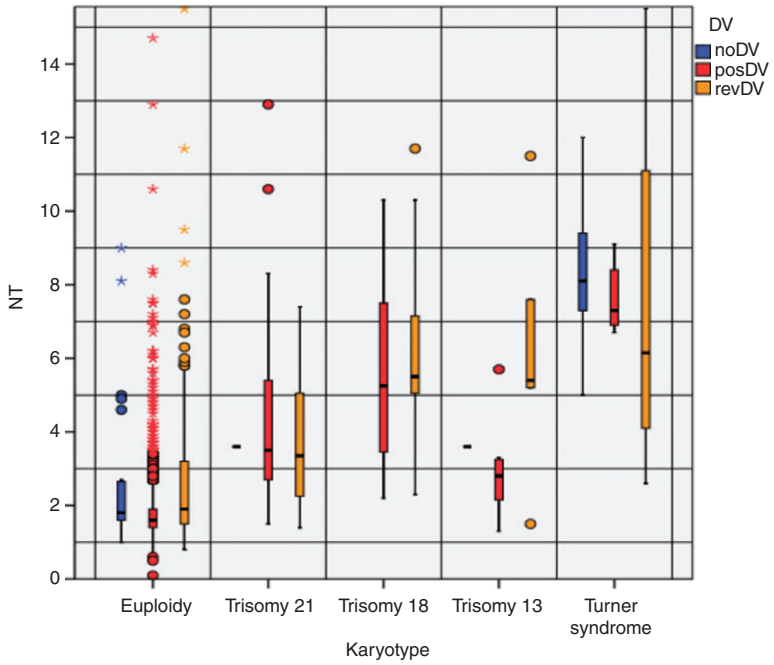

Figure 3 The relationship between DV profiles of flow, nuchal translucency thickness and chromosomal status.

Turner syndrome and singular cases of trisomies 18 and 13. The combination of increased NT and TR was observed in 0.3% cases of euploidy, 15.5% of trisomy 21, 21.7% of trisomy 18 and in one case of monosomy X. The combination of thickened NT and NB(-) was seen in 0.2% of euploidy, 11.2% of trisomy 21, 18.8% of Turner syndrome and singular cases of trisomies 18 and 13.

Cases of revDV included isolated subjects of revDV, which were only observed in euploidy (1.7%) and trisomy 21 (6%). Increased NT combined with revDV was observed in 0.5% of euploidy, 7.1% of trisomy 21, 21.7% of trisomy 18, 14.3% of trisomy 13 and 12.5% of Turner syndrome. The combination of thickened NT, revDV and TR was seen in 0.1% of euploidy, 7.1% of trisomy 21 and 13% of trisomy 18.

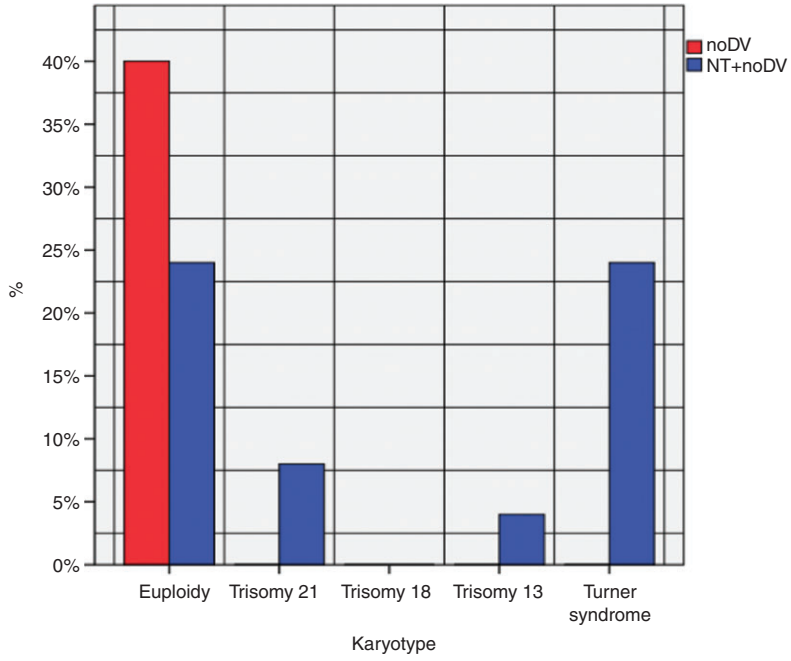

Figure 4 The configuration and prevalence of isolated and combined markers of aneuploidy in noDV cases in terms of chromosomal status.

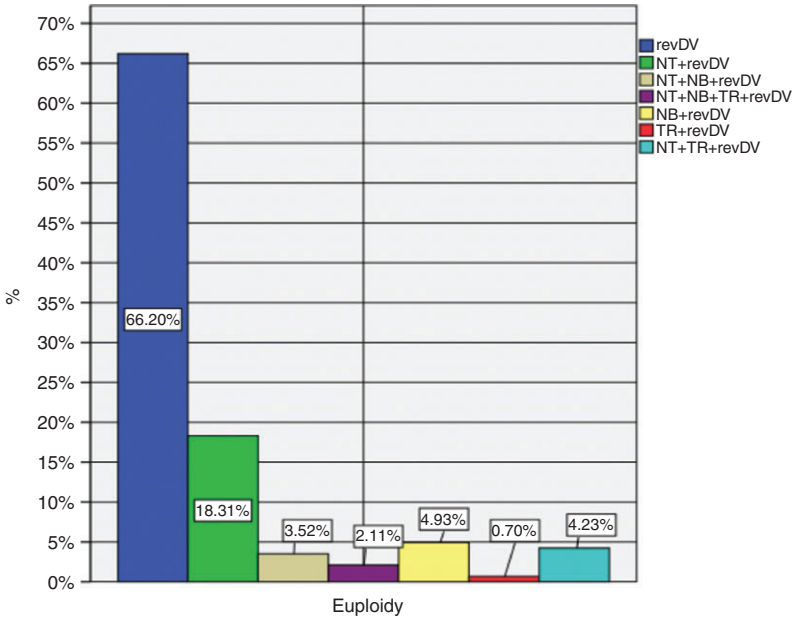

Figure 5 The configuration and prevalence of isolated and combined markers of aneuploidy in revDV cases of euploidy.

Other combinations of revDV were less common, but also more frequent in aneuploidy (Figures 5 and 6).

An analysis of extracardiac anatomy showed a higher prevalence of structural abnormalities in the group of noDV (14.3%) and in revDV (15.3%) vs. posDV (1%), which was statistically significant (P<0.05). In euploidy, trisomy 13 and monosomy X, noDV cases were more prevalent with extracardiac anomalies. Similarly, in euploidy, major trisomies and Turner syndrome, these abnormalities were noted more often in revDV cases. The incidence and type of abnormalities are shown in detail in Table 3.

It was noted that revDV euploidy cases affected by CHD presented higher values of NT (Figure 7).

Abnormal cardiac findings were more frequent in groups: noDV (14.3%) and revDV (11.1%) compared with posDV (0.8%), which is statistically significant (P<0.05). The details regarding particular abnormalities and cardiac findings are presented in Table 4.

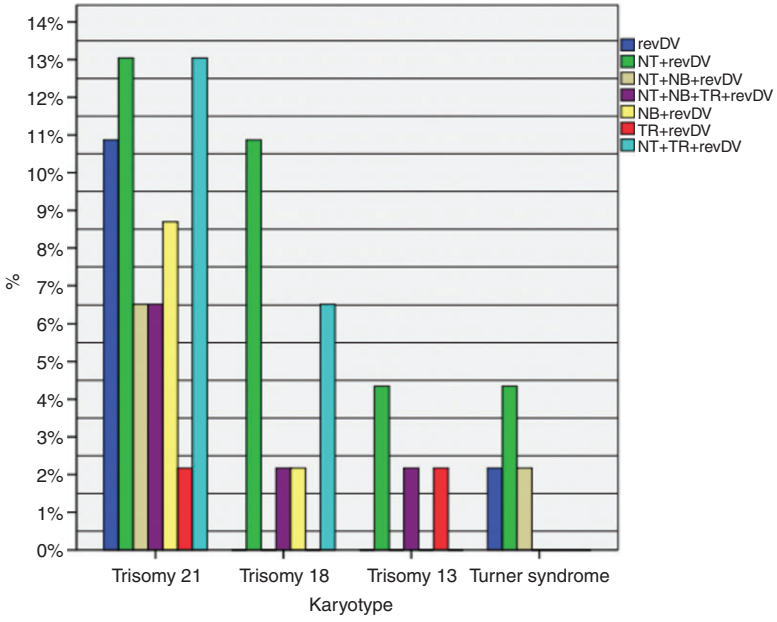

Figure 6 The configuration and prevalence of isolated and combined markers of chromosomal aberrations in revDV cases of aneuploidy.

Table 3 Extracardiac structural abnormalities summarized in terms of ductus venosus (DV) profiles of flow. Listed number of patients and percentages presented in parentheses in analyzed subgroups of subjects.

			Karyotype				
			Euploidy	Trisomy 21	Trisomy 18	Trisomy 13	Turner syndrome
Normal	DV						
	noDV	n (%)	25 (0.40%)	1 (1.19%)	0 (0.0%)	0 (0.0%)	4 (25.0%)
	posDV	n (%)	5470 (96.40%)	47 (55.9%)	7 (30.4%)	2 (14.3%)	4 (25.0%)
	revDV	n (%)	122 (2.10%)	25 (29.7%)	8 (34.7%)	3 (21.4%)	2 (12.5%)
Hydrops	DV						
	noDV	n (%)	0 (0.00%)	0 (0.0%)	0 (0.0%)	–	1 (6.2%)
	posDV	n (%)	5 (0.08%)	2 (2.4%)	1 (4.3%)	–	1 (6.2%)
	revDV	n (%)	2 (0.03%)	0 (0.0%)	1 (4.3%)	–	0 (0.0%)
Brain anomalies	DV						
	noDV	n (%)	0 (0.0%)	–	–	1 (7.1%)	–
	posDV	n (%)	11 (0.19%)	–	–	0 (0.0%)	–
	revDV	n (%)	3 (0.05%)	–	–	0 (0.0%)	–
Abdominal anomalies	DV						
	posDV	n (%)	15 (0.26%)	1 (1.2%)	2 (8.7%)	6 (42.8%)	–
	revDV	n (%)	4 (0.07%)	0 (0.0%)	3 (13.0%)	5 (35.7%)	–
Urinary tract anomalies	DV						
	posDV	n (%)	3 (0.05%)	–	1 (4.3%)	–	–
	revDV	n (%)	3 (0.05%)	–	0 (0.0%)	–	–
Limb anomalies	DV						
	noDV	n (%)	2 (0.03%)	–	0 (0.0%)	–	–
	posDV	n (%)	5 (0.08%)	–	1 (4.3%)	–	–
	revDV	n (%)	2 (0.03%)	–	0 (0.0%)	–	–
Head/neck anomalies	DV						
	posDV	n (%)	4 (0.07%)	1 (1.2%)	–	5 (35.7%)	0 (0.0%)
	revDV	n (%)	2 (0.03%)	0 (0.0%)	–	0 (0.0%)	1 (6.2%)
Thoracic anomalies	DV						
	PosDV	n (%)	3 (0.05%)	–	–	–	–
	revDV	n (%)	3 (0.05%)	–	–	–	–

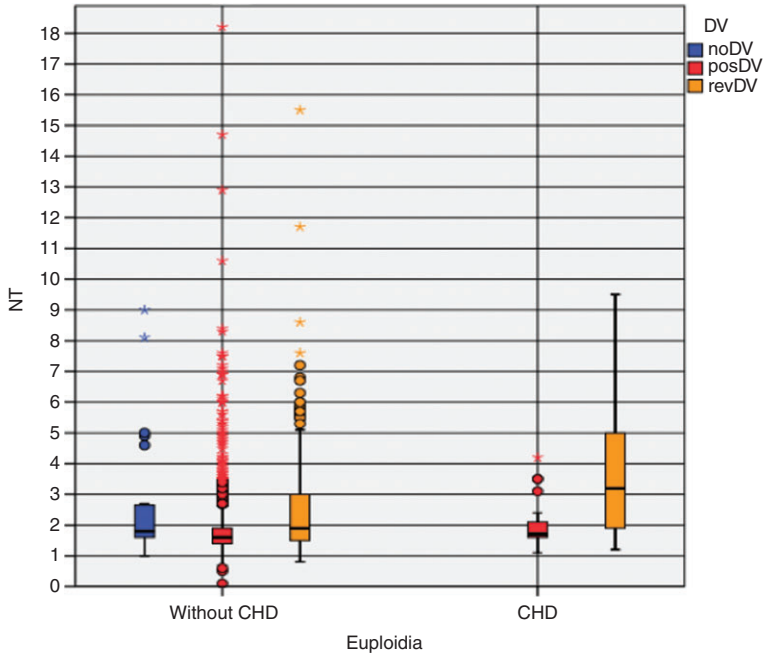

Figure 7 The relationship between ductus venosus flow patterns, nuchal translucency measurements and the presence or absence of CHD in the group of euploidy.

Table 4 Cardiac anomalies summarized depending on the ductus venosus (DV) flow patterns and chromosomal status. Listed number of patients and percentages presented in parentheses for analyzed noDV, posDV and revDV subjects.

Karyotype	Cardiac anatomy	DV		
		noDV	posDV	revDV
Euploidy	Normal	27 (0.5%)	5483 (96.70%)	135 (2.40%)
	Septal defects	0 (0.0%)	2 (0.03%)	0 (0.00%)
	Conotruncal anomalies	0 (0.0%)	9 0.20%)	2 (0.03%)
	Left heart defects	0 (0.0%)	6 (0.10%)	1 (0.01%)
	Right heart defects	0 (0.0%)	4 (0.07%)	3 (0.05%)
	Aortic arch anomalies	0 (0.0%)	1 (0.01%)	0 (0.00%)
Trisomy 21	Normal	1 (1.2%)	45 (53.60%)	23 (27.30%)
	Septal defects	0 (0.0%)	7 (8.30%)	6 (7.10%)
	Conotruncal anomalies	0 (0.0%)	2 (2.40%)	1 (1.20%)
	Right heart defects	0 (0.0%)	1 (1.20%)	0 (0.00%)
Trisomy 18	Normal	–	4 (17.30%)	5 (21.70%)
	Septal defects	–	4 (17.30%)	3 (13.00%)
	Conotruncal anomalies	–	1 (4.30%)	2 (8.70%)
	Left heart defects	–	2 (8.70%)	1 (4.30%)
	Cardiomegaly	–	1 (4.30%)	1 (4.30%)
	Right heart defects	–	0 (0.00%)	1 (4.30%)
Trisomy 13	Normal	0 (0.0%)	4 (28.60%)	4 (28.60%)
	Conotruncal anomalies	1 (7.1%)	3 (21.40%)	3 (21.40%)
	Left heart defects	0 (0.0%)	1 (7.10%)	0 (0.00%)
Turner syndrome	Normal	2 (12.5%)	5 (31.30)	1 (6.30%)
	Left heart defects	4 (25.0%)	1 (6.30%)	3 (18.80%)

The effectiveness of abnormal DV flow patterns in screening for trisomy 21, aneuploidy and euploidy with CHD was analyzed (Table 5). Regarding trisomy 21, the lowest sensitivity was obtained by using revDV positives excluding combinations with increased NT above the 95th percentile. In this method, the detection rate reached 10.7% and demonstrated a low positive predictive value (PPV) of 8.7. On the other hand, all positive revDV combinations of markers including isolated revDV cases demonstrated a higher sensitivity of 33.3% for trisomy 21 with a higher PPV of 16.7. Screening for CHDs by using all revDV positive combinations showed low sensitivity at the level of 17.9% with a PPV of 3.5. By excluding combinations with NT above the 95th percentile, the sensitivity was much lower and reached 9.5% with a PPV of 2.1. Additionally, the screening performance of noDV positives for monosomy X was checked, which showed a sensitivity of 37.5% with a PPV of 18.2 (Table 5).

Table 5 Summarized screening performance for trisomy 21 (T21), aneuploidy (AN) and congenital heart defects in euploidy of each method used in this study.

Method	revDV for T21	revDV for AN	revDV for euploidy with CHD	revDV without NT>95th percentile for T21	revDV without NT>95th percentile for EU with CHD	noDV for Turner syndrome
Sensitivity	33.3	35.8	17.9	10.7	9.5	37.5
FPR	2.5	2.5	2.4	1.8	1.7	0.5
Specificity	97.5	97.5	97.6	98.2	98.3	99.5
PPV	16.7	25.9	3.6	8.7	2.1	18.2
NPV	99.0	98.4	99.6	98.6	99.6	99.8
Diagnostic accuracy	96.6	96.1	97.2	98.1	97.9	99.3

FPR=false positive rate; PPV=positive predictive value; NPV=negative predictive value; NT=nuchal translucency; EU=euploidy; CHD=congenital heart defect.

Discussion

The first trimester assessment of DV flow is considered in the number of studies as a reliable element of screening for CHDs in euploidy [8, 11]. It is also used as a secondary parameter in the risk calculation protocols for aneuploidy [12]. These two major reasons draw the attention of physicians and sonographers to DV Doppler velocimetry in the first trimester. The incidence of revDV in euploidy is estimated to be 3.2%, which is comparable with our results (2.46%) [12]. However, our data demonstrated a lower prevalence of revDV in total aneuploidy (35.7%) and in particular chromosomal aberrations (33.3% in trisomy 21, 47.8% in trisomy 18, 42.8% in trisomy 13 and 25% in Turner syndrome) compared with the published data (66.4% in trisomy 21, 58.3% in trisomy 18, 55% in trisomy 13 and 75% in monosomy X) [12]. In our series, revDV was identified in 17.8% of fetuses with CHD, which is consistent with the study of Martinez (15.6%) [11]. However, Pereira observed a higher prevalence of revDV in euploidy with CHD cases at the level of 28.2% and 2.1% in euploidy without CHD [9]. We demonstrated a similar prevalence of revDV at the level of 2.4% in cases of euploidy without CHD. A lower prevalence of noDV at the level of 22.8% was observed in our series among cases of aneuploidy compared with the literature (42.3%) [13]. Zoppi et al. found the differences in NT thickness between cases with and without abnormal DV flow [14]. In our series, these differences were dependent on the chromosomal status and revDV euploidy cases demonstrated comparable mean NT values as posDV euploidy subjects.

The strength of our study is the fact that the evaluation of the DV flow was performed in a large number of patients who underwent ultrasound scans performed by experienced examiners without any input of trainees. This policy limited the risk of DV flow erroneous, which may be the case if trainees and research fellows are involved. As was examined in our previous study on TR, we also concentrated in this series on coincidences of aneuploidy markers, which was not highlighted before in the literature [7]. As an example, we found isolated noDV subjects only among euploidy cases, which is consistent with the observations of Staboulidou, who demonstrated a good obstetric outcome in cases of noDV with normal NT [13]. We observed that the presence of noDV might be useful in suspicion of monosomy X among cases with increased NT, as well as in differentiating them from other aneuploidies. Isolated revDV was identified only in euploidy and trisomy 21. We also observed that any combination of revDV with additional markers was found in 27.4% cases of trisomy 21, 43.5% cases of trisomy 18 and 28.6% cases of trisomy 13. As was raised in our previous study, we confirmed in this series that the combination of increased NT and TR is a strong combination in trisomies 21 and 18 [7]. In our series, revDV as a singular marker demonstrated low sensitivity for trisomy 21, total aneuploidy and CHD in euploidy, which was also proven by other authors [5, 9]. It is insufficient especially in cases without increased NT. The possible weakness of the study might be the fact that due to the mixed-risk population, the frequency of aneuploidy in our series was unnaturally high. Thus, the predictive values we realized may or may not be reproducible in a screening setting.

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