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First-trimester presentation of ultrasound findings in trisomy 13 and validation of multiparameter ultrasound-based risk calculation models to detect trisomy 13 in the late first trimester

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Abstract

Objectives: To identify the most common ultrasound patterns of markers and anomalies associated with Patau syndrome (PS), to explore the efficacy of multiparameter sonographic protocols in detecting trisomy 13 (T13) and to analyze the influence of maternal age (MA) on screening performance. Methods: The project was a prospective study based on singleton pregnancies referred for a first-trimester screening examination. The scan protocol included nuchal translucency (NT), fetal heart rate (FHR), secondary ultrasound markers [nasal bone (NB), tricuspid regurgitation (TR), ductus venosus reversed a-wave (revDV)] and major anomaly findings. Results: The study population comprised 6133 pregnancies: 6077 cases of euploidy and 56 cases of T13. Statistically significant differences were found in MA, FHR, NT, absence of NB, presence of revDV, TR and single umbilical artery. Fourteen cases of T13 (25%) demonstrated no markers of aneuploidy. The best general detection rate (DR) (DR of 78.6% with an false positive rate (FPR) of 1.2%) was obtained for a cutoff of 1/300 utilizing the "NT+T13" algorithm. The logistic regression model revealed that the central nervous system (CNS) anomalies had the greatest odds ratio (of 205.4) for T13. Conclusions: The effectiveness of the multiparameter sonographic protocol used for T13 screening showed promising results in patients older than 36 years and suboptimal results in patients between 26 and 36 years old. When screening for T13 left heart defects, CNS anomalies, abdominal anomalies, FHR above the 95th percentile, increased NT, revDV and lack of NB should receive specific attention.

Keywords: first-trimester; first trimester screening; mesocardia; patau syndrome; trisomy 13.

Introduction

Trisomy 13 (T13), also known as Patau syndrome (PS), is the third most common autosomal trisomy following trisomies 21 (T21) and 18 (T18) [1]. The incidence of PS is 1 in 5000–20.000 live births [2]. According to data collected by EUROCAT (European surveillance of congenital anomalies), the T13 prevalence slowly increased from 2.0/10.000 in 2011 to above 2.5/10.000 in 2017 [3].

T13 is associated with numerous congenital anomalies, including central nervous system (CNS) defects, cleft lip and palate, other craniofacial, limb and cardiac defects, and is characterized by a high intrauterine fetal mortality rate of 46% [1, 4, 5].

Considering the data described in the literature regarding the different methods of T13 screening, the

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conclusion is that T13 generally presents a lower detection rate (DR) than other major trisomies. First-trimester screening for T13 based on the combined screening test (CST) shows DRs of 75–92.3% [6–8], whereas for T21, obtainable published DRs were between 90 and 95% [9–11]. One of the latest larger studies, conducted by the Danish Fetal Medicine Study Group, reported a DR of 80% by using CST in screening for T13 [12]. In contrast, Santorum et al. obtained higher DRs for T13 than for T21, 92 vs 90%, respectively, at 4% false positive rate (FPR), in a large study focused on the accuracy of first trimester CST in screening for major trisomies [13]. These reports demonstrate inconsistent results among various studies in the context of screening for T13. Noninvasive prenatal screening (NIPT) for T13 showed DRs of 80–91% with FPR below 1% compared to a DR above 99% with an FPR of below 1% for T21 [14–15].

After conducting our first study comparing the effectiveness of multiparameter ultrasound-only protocols with that of CST in detecting T13, we decided to conduct another series on a larger number of cases focused on the most common T13-related sonographic findings and the screening performance of a multiparameter ultrasound-only protocol [8]. Other studies in this area presented different methodology or were not focused specifically on T13 [16, 17]. Therefore, we decided to conduct this second T13 study.

The first aim was to identify the most common ultrasound patterns of markers and anomalies associated with PS in our population and to develop a logistic regression model determining the odds ratios of these markers. The second aim was to explore the efficacy of multiparameter ultrasound-only methodology in detecting T13 using protocols based on background risk and all available ultrasound parameters of the FMF algorithm without adding biomarkers. Our previous papers on screening for T21 and T18 showed surprisingly high screening performance of this methodology, which we called “NT+” and decided to use this term also for the purposes of this study [18, 19]. The major difference in “NT+” is that the individual risk figure is obtained by correcting risk figures based on background risk, nuchal translucency (NT) and fetal heart rate (FHR) by secondary ultrasound markers such as nasal bone (NB), tricuspid flow (TF), ductus venosus (DV) velocimetry and major anomaly findings included in the FMF risk calculation algorithm (holoprosencephaly, atrioventricular septal defect, omphalocele, diaphragmatic hernia, and megacystis) without using the levels of serum biochemical markers [6]. The third aim was to analyze the influence of maternal age (MA) on screening performance by using the methodology proposed by us.

Materials and methods

This was a prospective study based on singleton pregnancies examined at 11+0 to 13+6 weeks at our institution. The study group consisted of low-risk patients (5901) and a considerable number of high-risk cases (758), including subjects presenting suspicious ultrasound findings on initial scan performed by antenatal care services not qualified for first-trimester screening (306) and those with an MA above 35 years (452). Karyotyping results and postnatal evaluation findings were recorded in the database as soon as they were available. Patients examined between January 2016 and September 2018 were included. The sonography reports and the digital data were reviewed taking into account the following inclusion criteria: singleton pregnancy, crown-rump length (CRL) measurement of 45–84 mm and known pregnancy outcome. The patient’s body mass index (BMI) was measured immediately before the first trimester ultrasound scan. Cases of aneuploidies other than trisomy 13 were excluded from the study. Professionals qualified to obtain the complete set of sonographic markers based on the Fetal Medicine Foundation (FMF) certification and who could conduct early fetal cardiac scan studies were involved in data collection. All examiners had more than 10 years of experience in first-trimester aneuploidy screening, early anomaly screening and early fetal echocardiography. Almost all scans were performed with a transabdominal approach applying the Voluson E6 ultrasound scanner (GE Healthcare, Zipf, Austria) and WS80 Elite (Samsung, Seoul, Korea). In only 3.9% of cases, a transvaginal probe was applied for better visualization of fetal anatomy. The scan protocol comprised the entire early extracardiac fetal anatomy, accompanied by fetal cardiac evaluation based on the following parameters: visceral situs, four-chamber view (4CV), outflow tracts, three-vessel and trachea view (3VTV) in B-mode and color mapping, which is in line with the protocol described by Springhall et al. [20]. The sonographic markers of chromosomal aberrations (NT, NB, TF, DV) were checked in accordance with FMF recommendations. For the purpose of this study NT and FHR were recognized as primary ultrasound markers of aneuploidy; and nasal bone, tricuspid flow, ductus venosus velocimetry, and number of umbilical arteries as secondary markers. DV was evaluated by a quantitative method (pulsatility index=PI), and the abnormal profiles of reversed a-wave (revDV) or absent DV were also recorded. The term “major anomalies” was applied to five major structural abnormalities included in the FMF risk calculation model: atrioventricular septal defect (AVSD), holoprosencephaly (HPE), megacystis (MC), congenital diaphragmatic hernia (CDH), and omphalocele (OMPH). Other structural findings were also reported in our detailed analysis of extracardiac and cardiac fetal anatomy assessment. The risk calculations for major trisomies were made with the use of FMF 2.8.0_3 algorithm software (Astraia Gmbh, Munich, Germany). In order to validate the efficacy of ultrasound-only approach in detecting T13 screening tests as shown in Table 1 were applied. The study findings were used for research purposes only and did not influence management, which is based on CST according to local screening policy [21]. All subjects who continued pregnancy

Table 1: Screening tests used in the study.

Screening test	Parameters used in the protocol	Positive if,
T13 NT+ with cut offs 1/50, 1/100, and 1/300	MA, NT, FHR, NB, DV, TR, and major anomalies*	Individual risk for T13 is higher than the cut off value
T21 NT+ with cut offs 1/50, 1/100, and 1/300	MA, NT, FHR, NB, DV, TR, and major anomalies*	Individual risk for T21 is higher than the cut off value
T18 NT+ with cut offs 1/50, 1/100, and 1/300	MA, NT, FHR, NB, DV, TR, and major anomalies*	Individual risk for T18 is higher than the cut off value

*major anomalies, five major anomalies included in FMF risk calculation (atrioventricular septal defec, AVSD; holoprosencephaly, HPE; megacystis, MC; congenital diaphragmatic hernia, CDH; and omphalocele, OMPH). NT, nuchal translucency above the 95th percentile; TR, tricuspid regurgitation; NB, negative nasal bone; DV, ductus venosus pulsatility index; MA, maternal age; FHR, fetal heart rate above the 95th percentile.

underwent anomaly scans between 18 and 21 weeks according to the protocol published by Bethune M et al., which included fetal cardiac assessment [22]. The outcome data were collected from medical records and included karyotyping, 18–21 and 28–32 weeks sonography, autopsy and neonatal findings. The local Ethics Committee approved the study protocol, and all subjects provided written consent.

Statistical analysis

In the statistical data assessment, the Kolmogorov-Smirnov test was applied to assess continuous variable distribution. The χ^2-test was used to demonstrate the differences. Groups of independent variables were compared using Student's t-test. Nonparametric tests were also utilized. SPSS Statistics v.17 (IBM Co., New York, USA) software was applied in this study. The findings with $p<0.05$ were considered significant. Based on the most common ultrasound findings presenting OR>1 in T13, a logistic regression model was developed.

Results

Study population

A screening ultrasound was carried out in 6659 singleton pregnancies. Fetal karyotyping was performed in 6.2% of subjects from chorionic villus sampling (123) and amniotic fluid samples (243 cases). The rest of the subjects were assumed to be euploid based on normal postnatal evaluation. Five hundred twenty-six (7.9%) cases were excluded from further analysis because in 391 (5.9%) cases, it was impossible to establish the fetal karyotype due to loss to follow-up, 32 (0.5%) cases resulted in miscarriages not related to invasive testing and 16 (0.2%) resulted in intrauterine fetal demise (IUFD) without subsequent karyotyping. In 87 (1.3%) cases, there was a chromosomal abnormality other than trisomy 13. Therefore, our study population comprised 6133 pregnancies: 6,077 with a normal karyotype or delivery of a neonate presenting no features of chromosomal aberrations (euploid group) and 56 cases of trisomy 13. One live birth at 37th weeks of gestation was noted. In this case, after first-trimester screening, PS was confirmed with amniotic fluid sampling in early second trimester, nonetheless, the patient decided to continue the pregnancy. The characteristics of the study population are summarized in Figure 1 and Table 2. The median maternal BMI was 22.6 kg/m^2 (range 17.7–34.9). All women participating in this study were Caucasian.

Euploid and T13 fetal characteristics

The mean NT thickness in the euploidy subgroup was 1.7 mm (range 0.8–4.9 mm), and in the T13 subgroup, it was 4.1 mm (range 1.3–11.5 mm) ($p<0.000$). The mean MA in the euploid group was 30.6 years (range 16–46 years) compared to 32.7 years (range 17–42 years) in the trisomy 13 group ($p=0.001$). The mean CRL at the time of examination was 63.5 mm in the euploid group vs. 63.1 mm in the T13 group. The mean FHR was 160.2 bpm in euploidy (range 109–190 bpm) vs 170 bpm in the T13 group (range 148–201 bpm), ($p<0.000$). FHR above the 95th percentile was noted in 735 cases in the euploidy group (12.1%) and in 35 cases in the T13 group (62.5%). No statistically significant differences were found between the euploidy and trisomy 13 groups in terms of CRL, but all other basic parameters disclosed statistical significance (Table 3).

NT thickness above the 95th percentile was observed in 237 euploid fetuses (3.9%) and in 19 fetuses (33.9%) affected by trisomy 13 ($p=0.000$). By using the $\chi 2$ Pearson test, significant differences were found between the

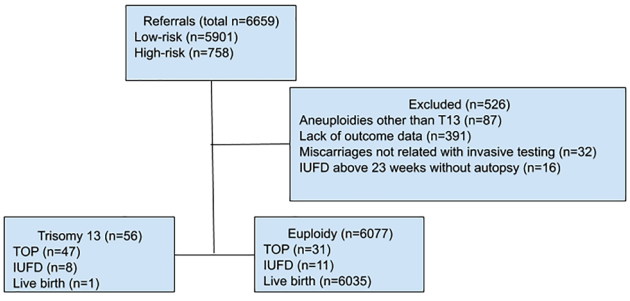

Figure 1: Study population diagram. T13 = trisomy 13, IUFD = intrauterine fetal demise, TOP = termination of pregnancy.

Table 2: Presentation of trisomy 13 fetuses.

Case #	MA	Anomalies detected during first trimester scan			Anomalies detected during second trimester scan	Week of TOP or delivery	Additional autopsy or postnatal findings
1	36	TR+SUA	face/neck anomalies	Left heart defects/ mesocardia	–	TOP 16	–
2	27	NB+revDV+FHR	Abdominal anomalies/CNS anomalies	Conotruncal anomalies	–	TOP 16	–
3	30	NT+NB+TR+revDV+SUA	Abdominal anomalies/CNS anomalies	Left heart defects	–	TOP 18	–
4	34	NT+NB+TR+revDV+FHR	Abdominal anomalies	Left heart defects	–	TOP 17	–
5	25	NT+NB+TR+FHR	–	Left heart defects	–	IUFD 14	–
6	36	NT+NB+FHR	–	Conotruncal anomalies/rare anomalies	–	TOP 18	–
7	30	No markers	face/neck anomalies	Left heart defects	–	TOP 19	–
8	33	revDV+FHR	face/neck anomalies	Left heart defects	Polydactyly, micrognathia, microphthalmia	Live birth 37th week	Low-set ears, missing skin
9	32	No markers	Abdominal anomalies/CNS anomalies	Left heart defects	–	TOP 17	–
10	32	FHR	–	Left heart defects	–	TOP 17	–
11	42	No markers	Urinary tract anomalies	Left heart defects	–	IUFD 14	–
12	33	No markers	CNS anomalies	Left heart defects	–	TOP 16	–
13	20	NT+noDV+FHR	CNS anomalies/urinary tract anomalies	Conotruncal anomalies	Polydactyly	TOP 20	–
14	42	NT+FHR	Abdominal anomalies	Conotruncal anomalies	–	TOP 18	–
15	35	No markers	Abdominal anomalies/CNS anomalies	Conotruncal anomalies	–	TOP 16	–
16	33	NT+revDV+FHR	Abdominal anomalies/CNS anomalies	Conotruncal anomalies	–	TOP 17	–
17	41	NT+revDV+FHR	–	Conotruncal anomalies/rare anomalies	VSD, fetal growth restriction	IUFD 29	Scalp defects
18	40	NT+revDV+FHR	CNS anomalies	Septal defects	–	TOP 16	–
19	40	NT+FHR	–	Septal defects	–	TOP 17	–
20	32	FHR	Upper and lower limbs/CNS anomalies	Left heart defects/ mesocardia	–	TOP 16	–
21	36	TR+DV+FHR	–	Septal defects	–	TOP 16	–
22	40	No markers	–	Septal defects/ mesocardia	–	TOP 18	–
23	41	revDV	Abdominal anomalies/upper and lower limbs	Septal defects	–	IUFD 14	–
24	36	NB+TR+revDV+FHR	CNS anomalies	–	–	TOP 16	–
25	40	TR+SUA+FHR	Urinary tract anomalies	–	–	TOP 16	–
26	29	NT+NB+FHR	Upper and lower limbs	–	Polydactyly, VSD, microcephaly	IUFD 30	Close-set eyes
27	32	FHR	Upper and lower limbs	–	–	TOP 16	–
28	35	No markers	CNS anomalies	–	–	TOP 17	–
29	37	NB+TR+FHR	face/neck anomalies	–	–	TOP 17	–

Table 2: (continued)

Case #	MA	Anomalies detected during first trimester scan			Anomalies detected during second trimester scan	Week of TOP or delivery	Additional autopsy or postnatal findings
30	26	NT+NB+TR+revDV+FHR	CNS anomalies	–	–	TOP 16	–
31	27	NB+FHR	CNS anomalies	–	–	TOP 16	–
32	29	NT+SUA+FHR	face/neck anomalies	–	–	TOP 17	–
33	33	FHR	CNS anomalies/urinary tract anomalies	Mesocardia	–	TOP 17	–
34	36	NT	Abdominal anomalies	–	–	TOP 19	–
35	27	NT+NB+TR+revDV+FHR	Abdominal anomalies/CNS anomalies	–	–	TOP 15	–
36	33	No markers	Abdominal anomalies/upper and lower limbs	Mesocardia	–	TOP 16	–
37	39	No markers	Abdominal anomalies/upper and lower limbs	–	–	TOP 18	–
38	28	NB+revDV+FHR	–	–	–	TOP 17	–
39	27	No markers	–	–	–	TOP 17	–
40	32	FHR	–	–	–	TOP 17	–
41	39	No markers	–	–	Cleft lip	TOP 20	–
42	28	NT+FHR	–	–	–	TOP 18	–
43	38	NT+SUA	–	–	VSD, coarctation of aorta	IUFD 27	Polydactyly
44	38	No markers	–	–	–	TOP 17	–
45	25	FHR	–	–	–	TOP 17	–
46	33	NT+NB+TR+FHR	–	Mesocardia	–	TOP 19	–
47	22	No markers	–	–	–	TOP 17	–
48	24	revDV	–	–	–	TOP 16	–
49	17	noDV+FHR	–	–	–	TOP 16	–
50	30	FHR	–	–	–	TOP 19	–
51	23	No markers	–	–	–	IUFD 18	–
52	35	TR+revDV+SUA+FHR	–	–	–	TOP 18	–
53	39	TR+revDV+SUA+FHR	–	–	–	TOP 15	–
54	41	NB+TR+SUA	–	–	Polydactyly, VSD, cleft lip	IUFD 25	Missing skin
55	30	NB+TR+SUA+FHR	–	–	–	TOP 16	–
56	39	NT+FHR	–	–	–	TOP 16	–

NT, nuchal translucency above the 95th percentile; TR, tricuspid regurgitation; NB, negative nasal bone; revDV, reversed a wave in ductus venosus flow; noDV, absent ductus venosus; SUA, single umbilical artery, FHR, fetal heart rate above the 95th percentile; CNS, central nervous system; VSD, ventricular septal defect; MA, maternal age.

euploidy and T13 groups in the absence of NB (p=0.000), 85 cases (1.4%) vs 15 (26.8%); presence of tricuspid regurgitation (TR) (p=0.000), 92 cases (1.5%) vs 15 (26.8%); reverse a-wave in DV (revDV) flow (p=0.000), 108 cases (1.8%) vs 16 (28.6%); and the presence of single umbilical artery (SUA) (p=0.000), 4 cases (0.07%) vs 9 cases (16.1%). The mean DV PI in the T13 group was 1.2 (range 0.8–1.6) vs 0.9 (range 0.3–1.5) in the euploidy group (p=0.000).

Fourteen trisomy 13 cases (25%) demonstrated no markers of aneuploidy, as opposed to 4903 euploidy cases (80.7%). Isolated markers were identified in 10 cases of trisomy 13 (17.9%), including seven cases of increased FHR above the 95th percentile, one case of increased NT above the 95th percentile, 2 cases of reversed a-wave in DV (revDV). On the other hand, isolated markers were identified in 1046 cases of euploidy (17.2%), including subjects with increased FHR above the 95th percentile (679 cases), NT above the 95th percentile (153 cases), delayed nasal ossification (51 cases), TR (66 cases), reversed a-wave in DV flow (78 cases) and absent DV (19 cases).

Table 3: Comparison of fetuses with euploidy and trisomy 13 according to four parameters: CRL, crown-rump length; NT, nuchal translucency; FHR, fetal heart rate and MA, maternal age; SD, standard deviation, mm, millimeters, bpm, beats per minute.

Karyotype		CRL (mm)	NT (mm)	FHR (bpm)	MA (years)
Euploidy	n	6077.0	6077.0	6077.0	6077.0
	Mean	63.5	1.7	160.2	30.6
	Median	63.0	1.6	160.0	30.0
	SD	9.1	0.5	7.3	4.2
Trisomy 13	n	56.0	56.0	56.0	56.0
	Mean	63.1	4.1	170.0	32.7
	Median	61.6	3.3	170.0	33.0
	SD	10.1	2.5	10.8	5.9
Statistical significance		0.747	0.000	0.000	0.001

The most common core coincidences of aneuploidy ultrasound markers in trisomy 13 cases were FHR above the 95th percentile with NT above the 95th percentile, noted in 16 cases (28.6%); FHR above the 95th percentile and revDV, found in 13 cases (23.2%); FHR above the 95th percentile with absent NB, found in 13 cases (23.2%) and FHR above the 95th percentile with TR, noted in 12 cases (21.4%). These core combinations were observed in only 30 (0.5%), 11 (0.2%), 6 (0.1%) and 9 (0.15%) euploidy cases, respectively. The details showing the configuration of ultrasound markers of aneuploidy in the euploidy and T13 groups are summarized in Table 4.

Extracardiac malformations (ECMs) were identified in 30 cases of trisomy 13 (53.6%) and in 45 cases of euploidy (0.7%). This difference was statistically significant (p=0.000). ECMs were isolated among euploidy cases except in three cases presenting combinations of central nervous system (CNS) and urinary tract anomalies (2 cases) and CNS and facial anomalies (1 case). Twelve trisomy 13 cases presented multiple anomalies (21%). The most common combination included central nervous system and abdominal anomalies (6 cases) followed by abdominal and limb anomalies (3 cases), CNS and urinary tract anomalies (2 cases), and CNS and limb anomalies (1 case). The distribution of anomalies is shown in Table 5.

Regarding congenital heart defects (CHDs), we observed these defects in 23 cases of trisomy 13 (41.1%) and in 32 cases of euploidy (0.5%). The largest fractions of CHDs in trisomy 13 were left heart defects (19.6%) and conotruncal anomalies (12.5%) (details are depicted in Table 6). In addition, we found mesocardia in six cases of trisomy 13 (10.7%) and 1 case of euploidy (0.02%) (p=0.000).

Table 4: The configuration and prevalence of isolated and combined markers of aneuploidy in euploid and trisomy 13 fetuses.

Karyotype	configuration of US markers	n	%
Euploidy	No markers	4903	80.68
	FHR	679	11.17
	NT	153	2.52
	NT+FHR	23	0.38
	NB	51	0.84
	NB+FHR	11	0.18
	TR	66	1.09
	TR+FHR	9	0.15
	revDV	78	1.28
	revDV+FHR	5	0.08
	noDV	19	0.31
	NT+NB	4	0.07
	NT+TR	7	0.12
	NT+revDV	12	0.20
	NT+NB+revDV	2	0.03
	NT+NB+TR+revDV	1	0.02
	NB+ revDV	5	0.08
	NT+noDV	24	0.39
	NT+noDV+FHR	7	0.12
	NB+TR	2	0.03
	NT+TR+revDV	1	0.02
	NT+SUA	2	0.03
	NT+NB+TR+noDV	1	0.02
	NB+TR+revDV	2	0.03
	NB+revDV+SUA	1	0.02
	revDV+SUA+FHR	1	0.02
	NB+noDV	5	0.08
	noDV+TR	3	0.05
Trisomy 13	No markers	14	25.00
	FHR	7	12.50
	NT	1	1.79
	NT+FHR	4	7.14
	NB+FHR	1	1.79
	revDV+FHR	1	1.79
	revDV	2	3.57
	noDV+FHR	1	1.79
	NT+NB+FHR	2	3.57
	NT+revDV+FHR	3	5.36
	NT+NB+TR+FHR	2	3.57
	NT+NB+TR+revDV+FHR	3	5.36
	NB+revDV+FHR	2	3.57
	NT+noDV+FHR	1	1.79
	NB+TR+FHR	1	1.79
	NT+SUA	1	1.79
	NT+SUA+FHR	1	1.79
	NT+NB+TR+revDV+SUA	1	1.79
	NB+TR+revDV+FHR	1	1.79
	TR+revDV+SUA+FHR	2	3.57
	NB+TR+SUA	1	1.79
	NB+TR+SUA+FHR	1	1.79
	TR+SUA	1	1.79
	TR+SUA+FHR	1	1.79
	TR+revDV+FHR	1	1.79

NT, nuchal translucency above the 95th percentile; TR, tricuspid regurgitation; NB(–), negative nasal bone; revDV, reversed a wave in ductus venosus flow; noDV, absent ductus venosus; SUA, single umbilical artery; FHR, fetal heart rate above the 95th percentile; US, ultrasound.

Logistic regression

A logistic regression model was developed based on the most common ultrasound findings in T13 presenting OR>1. The following parameters were obtained: lack of NB, NT≥3 mm, central nervous system anomalies, abdominal anomalies, left heart defects, and the presence of revDV (Table 7).

Table 5: Extracardiac structural abnormalities summarized in terms of chromosomal status.

Karyotype		Euploidy		T13	
Frequency		**n**	**%**	**n**	**%**
Type of extracardiac anomaly	No ECM	6032	99.4	26	46.4
	Hydrops	4	0.1	0	0.0
	Central nervous system anomalies	10	0.2	15	26.8
	Abdominal anomalies	9	0.2	12	21.4
	Urinary tract anomalies	8	0.1	4	7.1
	Limb anomalies	7	0.1	6	9.5
	Facial and neck anomalies	7	0.1	5	7.9
	Thoracic anomalies	3	0.0	0	0.0

ECM, extracardiac malformation.

Table 6: Cardiac anomalies summarized in the euploidy and trisomy 13 groups.

Karyotype	Euploidy		T13	
	n	**%**	**n**	**%**
No CHD	6045	99.5	33	58.9
Septal defects	18	0.3	5	8.9
Conotruncal anomalies	4	0.1	7	12.5
Left heart defects	5	0.1	11	19.6
Right heart defects	4	0.1	0	0.0
Rare anomalies	1	0.0	2	3.6

CHD, congenital heart defect

Table 7: Odds ratios (ORs) for the most common features found in T13 fetuses based on a logistic regression model.

			95% CI for OR	
	P	**OR**	**Lower limit**	**Upper limit**
Lack of NB	0.000	6.3	2.4	16.2
RevDV	0.040	3.1	1.1	8.9
Abdominal anomaly	0.000	24.3	7.4	79.3
Left heart defects	0.001	18.2	3.4	98.3
CNS anomaly	0.000	205.4	63.2	667.7
NT>=3 mm	0.000	36.5	17.0	78.1

NB, nasal bone; RevDV, reversed a wave in ductus venosus flow; CNS, central nervous system; NT, nuchal translucency.

Screening performance

The actual screening efficacy for detecting trisomy 13 using the T13, T21, and T18 NT+protocols (consisting of NT, FHR, NB, TF, DV PI, and major anomaly findings: AVSD, HPE, MC, CDH, and OMPH) with cut-offs of 1/50, 1/100, and 1/300 is shown in Table 8.

T13 detection rate in relation to maternal age (MA)

We noted seven cases of T13 in the MA range below 26 years, 13 cases between 26 and 30 years, 16 cases in the MA range between 31 and 35 years, 15 cases in the MA range from 36–40 years and five cases in the range above 40 years. The influence of MA on DR and FPR depending on the NT+screening protocol is shown in Figure 2.

Discussion

As previously published, in our series, we observed an increased incidence of primary and secondary ultrasound markers in T13 cases. Regarding NT thickening, our results demonstrate data comparable to those of other authors. The median CRL-independent NT thickness in the subgroup of euploidy was 1.6 mm, and in the subgroup of PS, it was 3.3 mm, which is in line with the findings of Nicolaides et al., who obtained values of 2.0 vs. 4.0 mm, respectively [23]. We obtained also comparable results regarding FHR values above the 95th percentile among T13 fetuses (62.5%) as Papageorghiou et al. who reported FHR above the 95th and 99th percentiles of the normal range for CRL in 71.3 and 51.4% of the T13 cases [16]. However in our series, a wider range of FHR values was observed both in euploidy and T13 groups than published by Wright et al. who obtained values of 159 (155–164) bpm in the euploidy group vs. 179 (172–184) bpm in the PS subgroup [24]. We observed a 1.5% prevalence of TR in the euploidy group compared to 26.8% in the T13 group what turned out to be much less than in the study by Faiola et al.: 8.5% for euploidy vs. 46.6% for T13 [25], absent nasal bone in 1.4% in the euploidy group vs. 26.8% in the T13 group (comparable to the study by Cicero et al.: 2.8% for euploidy vs. 31.8% for T13) [26], and reverse ductus venosus flow in 1.8% in the euploidy group compared to 28.6% in the T13 group which is much lower than the values obtained by Maiz et al.: 3.2% for euploidy vs. 55% for T13 [27], but comparable to the findings of our

Table 8: Screening performance summary of the methods used in this study.

Screening method	NT+T13 1/50	NT+T13 1/100	NT+T13 1/300	NT+T21 1/50	NT+T21 1/100	NT+T21 1/300	NT+T18 1/50	NT+T18 1/100	NT+T18 1/300
Sensitivity	64.3% (51.2 – 75.5)	69.6% (56.6 – 80.1)	78.6% (66.2 – 87.3)	53.6% (40.7 – 65.9)	58.9% (45.8 – 70.8)	66.1% (53.0 – 77.1)	60.7% (47.6 – 72.4)	62.5% (49.4 – 73.9)	69.6% (56.7 – 80.1)
Specificity	99.3% (99.1 – 99.5)	99.2% (98.9 – 99.4)	98.8% (98.5 – 99.1)	98.0% (97.6 – 98.3)	96.9% (96.5 – 97.3)	96.2% (95.6 – 96.6)	99.1% (98.8 – 99.3)	98.9% (98.6 – 99.1)	97.9% (97.5 – 98.2)
PPV	47.4% (36.5 – 58.4)	44.8% (34.8 – 55.3)	37.9% (29.6-47.0)	20.0% (14.4 – 27.1)	15.1% (10.9 – 20.4)	13.7% (10.1 – 18.3)	39.1% (29.5 – 49.6)	34.6% (26.1 – 44.3)	23.3% (17.6 – 30.3)
NPV	99.7% (99.5 – 99.8)	99.7% (99.5 – 99.8)	99.8% (99.6 – 99.9)	99.6% (99.4 – 99.7)	99.6% (99.4 – 99.7)	99.7% (99.5 – 99.8)	99.6% (99.45–99.8)	99.6% (99.5 – 99.7)	99.7% (99.5 – 99.8)
Diagnostic accuracy	99.0 (98.7 – 99.2)	98.9% (98.6 – 99.2)	98.6% (98.3 – 98.9)	97.6% (97.2 – 97.9)	96.6% (96.1 – 97.0)	95.9% (95.4 – 96.4)	98.8% (98.5 – 99.0)	98.6% (98.2 – 98.8)	97.6% (97.2 – 97.9)

T13, trisomy 13; T18, trisomy 18; T21, trisomy 21; PPV, positive predictive value; NPV, negative predictive value. In brackets, the estimates of lower to upper 95% confidence intervals (CIs) are shown.

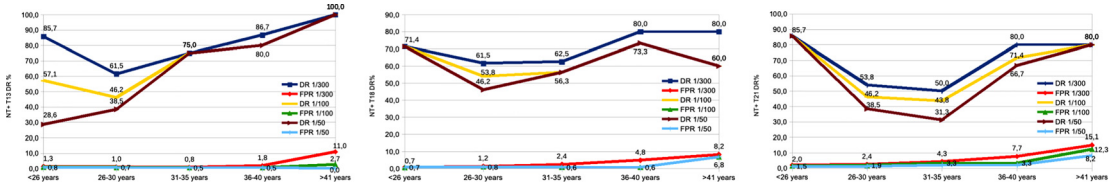

Figure 2: From the left: detection rates (DRs) and false-positive rates (FPRs) of the "NT+T13", "NT+T18" and "NT+T21" for cutoffs of 1/300, 1/100, 1/50 depending on maternal age (MA) ranges.

previous studies: 2.5% for euploidy compared to 25% for T13 [28].

Regarding the presentation of the ultrasound markers, at least one marker was observed in 75% of fetuses with T13 compared to 19.3% of fetuses with normal karyotypes. This means that a considerable group of T13 subjects (25%) showed normal FHR and a lack of NT thickening or the presence of absent NB, revDV, noDV, TR or SUA. Isolated ultrasound markers were identified in 17.9% of these fetuses. Only the remaining 57.1% of T13 cases presented with more than one of the abovementioned markers concomitantly. In our opinion, the fact that the significant number of T13 fetuses did not present any markers or presented only isolated markers is another reason that screening for T13 is challenging at the time of first-trimester sonography esp. basing on ultrasound-only strategy. In our previous studies, concomitant findings of ultrasound markers (primary or secondary) were observed in 71.4, 91.9, and 74.2% of T21, T18, and Turner syndrome cases, respectively, which increased the effectiveness of multiparameter ultrasound-only screening for these aberrations [18, 19, 29]. Additionally, isolated ultrasound markers were observed in 7.7, 5.4, and 25.8% of T21, T18, and Turner syndrome cases, respectively, but in the context of Turner syndrome, no cases without any ultrasound marker presentation were identified [18, 19, 29].

The most common congenital anomalies in the group of fetuses with PS were cardiac defects (41.1%), which is in agreement with other authors. However, this value is much lower than that described by Watson et al. (58%), or Chen (80%) [1, 30]. Among all anomalies, left heart defects were the most common. This observation was not raised before by other authors. This also refers to mesocardia, which we found statistically significant among T13 fetuses in our series.

Comparing the frequency of extracardiac ultrasound findings in T13 cases with the available literature, we obtained diversified results. Most studies describing fetal anatomy were conducted during the second trimester screening. Facial and neck anomalies were visualized in 7.9% of fetuses in our study, compared to 16–52% reported by other authors [31–33]. CNS anomalies were present in our study in 26.8% of cases vs. 52.0–64.3% described in the literature, and these anomalies increased the OR for T13 by 205.4 according to our regression model [32, 34]. Abdominal anomalies were found in 21.4% of cases vs 9.1% of cases reported by Snijders et al., with an OR for T13 of 24.3 [34]. Urinary tract anomalies were found in 7.1% of cases in

comparison to 42.9% reported by Papp et al. [32]. Limb anomalies were detected in 9.5% of cases in our study, whereas other authors reported rates of 3.0–7.1% [31, 32]. Szigeti et al. pointed out the difficulties in sonographic assessment of the limbs; in their study, limb defects were visible in 8% of T13 fetuses, while in the postmortem examination, such defects were present in as many as 64% of fetuses [33]. Witters et al. described postaxial polydactyly with small hyperconvex nails as typical for T13 [4].

Regarding screening performance, the best general DR in our study (DR of 78.6% with a FPR of 1.2%) was obtained for a cut off of 1/300 utilizing the "NT+T13 " algorithm, whose DR was comparable to the CST DR of 80% obtained by the Danish Fetal Medicine Study Group presenting the leading national wide screening setup in Europe [12]. The Danish group utilized CST risk for T21>1:300 or for T13/18 risk>1:150 for detecting T13. This means that PS remains one of the challenges of first trimester screening independent of the methodology. EUROCAT data, collected between 2013 and 2017, covered 610 T13 cases, of which 578 (94.75%) were detected prenatally. Only 249 (40.82%) of these cases were detected in the first trimester, whereas 224 (36.55%) cases were detected after 14 weeks of gestation; however, the data were incomplete; in 106 (17.38%) cases, no information was provided. Nonetheless, the T13 detection rate in the first trimester was rather low across the population in comparison with the DRs of T21 and T18 [3].

According to ROC curves for fixed FPRs of 3 and 5%, the T13 detection rates reached 86 and 91%, respectively, in the "NT+T13" algorithm. It should be noted, however, that these results come with cutoffs read from ROC curves of 1/1512 and 1/3427, respectively (Table 9). In the available literature, some authors fail to mention cutoff points read from the ROC curves, and the results are given only in the "DR at fixed FPR" format [35]. In our opinion, from a clinical point of view, the effectiveness of the cutoff points seems to be a crucial matter for the screening practitioner. We reached a similar conclusion in our previous study [8].

Regarding our analysis, it should be noted that taking into account the DRs depending on MA, the obtained DR level was rather suboptimal, generally speaking, in younger patients. In the MA ranges of 26–30 and 31–35 years, the "1/300 T13 NT+" model showed DRs only of 61.5 and 75%, respectively, with an FPR of 1 and 0.8%, respectively, which would suggest avoiding this test in the abovementioned MA groups. However, in the youngest group of patients (MA<26 years), the results of this model were promising (DR of 85.7% with an FPR of 1.3%). The best screening performance was obtained by using our "1/300 T13 NT+" model in patients older than 36 years, reaching a DR of 86.7% with an FPR of 1.8% in the group of patients with a MA between 36 and 40 years and even a DR of 100% with an FPR of 11% in patients older than 40 years. In this advanced MA group, our results even outperform the T13 general DR figure from the Danish study. However, that study did not focus on the influence of MA on screening performance [12].

Table 9: Detection rates (DR) and 95% confidence intervals (CI) at fixed false positive rates (FPR) of 3 and 5% in screening methods used in the study.

Screening test	AUC	DR% (95% CI) at 3% FPR	ROC calculated cut-off	DR% (95% CI) at 5% FPR	ROC calculated Cut-off
NT+T13	0.975	86.0% (81,6–91,4)	1/1512	91.0% (85,4–96,6)	1/3427
NT+T21	0.904	59.0% (54.5–63.5)	1/97	70% (65.1–74.9)	1/731
NT+T18	0.906	73.0% (68.0–78.0)	1/409	77% (71.9–82.1)	1/830

AUC, area under the curve.

The results obtained with the "NT+T18" and the "NT+T21" protocols were generally worse, although in the group of younger patients, using the "NT+T18" algorithm with a cutoff of 1/300 resulted in slightly better DRs (DRs for patients in the MA range of 26–30 years and 31–35 years were 62.5 and 80%, respectively, with an FPR of 2.4 and 4.8%, respectively). A significant decrease in DR for patients with an MA below 36 years was noticeable for cutoff points of 1/100 and 1/50, especially for the "NT+T13" algorithm, though the DR reduction was not as marked for the "NT+T21" algorithm (Figure 2). These results correspond to the data published by Tonks et al., where it was shown that the DR for T13 was higher in the group of patients older than 35 [2]. Thus, if multiparameter ultrasound-only screening was performed in this group using the "NT+T13" protocols, a significant proportion of fetuses with PS in subjects younger than 36 years of age may be missed. To maintain DR at the level of 80% in subjects between 31 and 35 years old, "NT+T18" with a cutoff of 1/300 may be of help if the proposed multiparameter ultrasound-only screening model is aiming to detect T13.

Our results for a multiparameter ultrasound protocol in detecting T13 are weaker than the results obtained in similar studies performed by our team and other investigators in the context of trisomy 21 and trisomy 18 using the "NT+T18" and "NT+T21" algorithms [17–19, 35]. This is probably because the FMF risk calculation software takes into account only such anatomical abnormalities as AVSD,

HPE, MC, CDH, and OMPH and does not include abnormalities such as upper limb defects (polydactyly), craniofacial defects (cleft lip/palate, proboscis, cyclopia, micrognathia) or non-AVSD cardiac defects that are quite common in fetuses with PS [1, 4, 31–34]. Thus, second trimester screening gives much better results in detecting T13. Benacerraf reported the sensitivity to be 90–100% when a detailed second trimester scan was performed [36]. Moreover, the influence of the maternal age factor in women aged younger than 35 is probably less notable in the risk calculation program. A weaker correlation between the incidence of T13 and maternal age was reported in a study by Savva et al., who observed a smaller increase in T13 prevalence over the years, despite the MA increase, in comparison to other major trisomies [37]. Analyzing the EUROCAT data regarding maternal age, 275 (45.08%) cases of T13 were diagnosed in the group with an MA younger than 35 years vs. 303 (49.67%) cases in the group older than 35 years; for the remaining 32 (5.25%) cases, no information was provided. For comparison, the percentages of T21 and T18 cases detected in the MA younger than 35 group were only 23.12 and 31.55%, respectively [3].

The strengths of our study include the large number of patients enrolled with a considerable number of T13 cases and the fact that it was a prospective study. Screening model evaluation was performed by highly competent professionals in the field of first trimester sonography, which is representative for analyzing the power of ultrasound-only methods in first trimester screening for T13. Regarding weaknesses, the incidence of T13 in our study was 1/110, which is much higher than in the general population [1]. The reason for this prevalence is that the material was collected partially from high-risk patients and from subjects referred for screening with initial suspicion. In addition, the patients were of Caucasian origin, so the results of the study may not be relevant to other ethnic groups.

Taking into account the abovementioned results in the context of T13, inclusion of PAPP-A and free beta-HCG into the FMF risk calculation seems to be unavoidable if the examiner qualifies the patient for invasive testing based only on the individual risk figures from FMF algorithm [8]. This applies even, if the screening is carried out by unquestioned experts in the field of first-trimester ultrasound as was done in our study. However, if a combination of ultrasound markers of aneuploidy and a wider scope of early anomaly findings indicative of T13, including limb, craniofacial, CNS, and left heart anomalies or mesocardia, are considered in addition to the risk results, the examiner may minimize the chance of missing T13.

In our previous research, we obtained a DR of 92.3% with an FPR of 2.5% for CST in screening for T13 [8]. Other authors reported DRs in the range of 75–92% with FPRs of 0.5–4.0% for CST [6, 7, 13], but the most reliable screening method seems to be that from the Danish study based on national data presenting the abovementioned DR of 80% (retrospective study covering four-year countrywide screening) [12]. It is worth mentioning that even though other methods, including classic CST and noninvasive prenatal screening (NIPT), show better detection rates for T13 than the "NT+T13" algorithm, they are still not as effective in detecting T13 as they are in screening for T21 or T18 [6, 8, 12, 14, 15, 18, 19].

In conclusion, the effectiveness of the multiparameter ultrasound-only approach used for T13 screening showed promising results in patients older than 36 years and suboptimal results in patients between 26 and 36 years old, even using the 1/300 cutoff point in the targeted "NT+T13" protocol. A significant reduction in DR was found in younger patients. In our opinion, the main reason for this fact is the influence of the maternal age factor in the FMF algorithm in women aged below 35, which reduces the individual risk figures in some cases presenting positive ultrasound findings; and that more specific anomalies for trisomy 13 are not included in the FMF risk calculation algorithm.

To conclude, in ultrasound first trimester screening for T13 combinations of left heart defects, CNS anomalies, abdominal anomalies, increased NT, FHR above the 95th percentile, revDV and lack of NB should receive specific attention.

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