Received: 1 June 2019 | Revised: 21 August 2019 | Accepted: 11 September 2019

DOI: 10.1111/chd.12852

ORIGINAL ARTICLE

Congenital Heart Disease WILEY

Screening performance of congenital heart defects in first trimester using simple cardiac scan, nuchal translucency, abnormal ductus venosus blood flow and tricuspid regurgitation

Natasa Karadzov Orlic MD, PhD[1] | Amira Egic MD, PhD[1] | Barbara Damnjanovic-Pazin MD[2] | Relja Lukic MD, PhD[1] | Ivana Joksic MD, PhD[3] | Zeljko Mikovic MD, PhD[1]

[1]High-risk Pregnancy Unit, Obsterics/Gynecolgy Clinic "Narodni font", School of Medicine, University of Belgrade, Belgrade, Serbia

[2]High-risk Pregnancy Unit, Obsterics/Gynecolgy Clinic "Narodni font", Belgrade, Serbia

[3]Genetic Laboratory, Obsterics/Gynecolgy Clinic "Narodni font", University of Belgrade, Belgrade, Serbia

Correspondence
Natasa Karadzov Orlic, Obsterics/Gynecolgy Clinic "Narodni font", High-risk Pregnancy Unit, School of Medicine, University of Belgrade, Str. Kraljice Natalije 62, Belgrade 11000, Serbia.
Email: orlicmail@yahoo.com

Abstract

Objective: The objective of this study was to analyze if the addition of simple cardiac scan in cases with increased nuchal translucency (NT) and/or abnormal ductus venosus (DV) blood flow, and/or tricuspid regurgitation (TCR) can improve detection of congenital heart defects (CHD) in chromosomally normal fetuses without non-cardiac defects at 11-13 + 6 gestational weeks in a population of singleton pregnancies.

Methods: During the 10 years period, all singleton pregnancies at 11-13 + 6 weeks were routinely scanned for NT, DV blood flow and TCR assessment and, if a single of these parameters was abnormal, simple cardiac scan with 2D gray scale and color and/or directional power Doppler in 4-chamber (4-CV) and 3 vessel and trachea views (3VTV) was performed.

Results: The sensitivity and specificity of NT ≥ 95th + DV R/A a-wave + TCR in detecting CHD were 77% and 97%, respectively, and of simple cardiac scan, 67% and 98%, respectively. Area under the curve of receiver operating characteristic curve of NT ≥ 95th + DV R/A a-wave + TCR was 0.838, and of NT ≥ 95th + DV R/A a-wave + TCR + simple cardiac scan was 0.915.

Conclusions: In chromosomally normal fetuses without non-cardiac anomalies, addition of simple cardiac scan to the combined first trimester screening parameters improves detection of major CHD during first trimester.

KEYWORDS

cardiac scan, congenital heart defect, ductus venosus, nuchal translucency thickness, tricuspid regurgitation

1 | INTRODUCTION

Congenital heart defects (CHD) represent the one third of all major congenital anomalies with a prevalence of 4-9 per 1000 live births.[1] First trimester screening recently started to play a pivotal role in the management of pregnancies. By the combination of maternal age, serum biochemistry, ultrasound anomaly scan, and additional ultrasonographic markers, this screening can identify most fetal aneuploidies and structural abnormalities in the fetus.[1,2] In addition, most CHD can be detected in the first trimester using increased

nuchal translucency (NT) and by color Doppler assessment, absent/reverse a-wave following atrial contraction in ductus venosus (DV) and tricuspid regurgitation (TCR).[2-7] Use of combination of these parameters increased a detection rate of CHD in the first trimester to 60%-80%.[8,9] Currently, detailed echocardiographic examination in the first trimester is recommended to be an integral part of the pregnancy management.[10,11] Major CHD that can be recognized from this type of screening might be adequately treated or pregnancy termination may be considered by the mother.

Of note, there is no evidence that extensive fetal echocardiography with longer fetal exposure and pulsed Doppler in the first trimester is safe for fetus. Therefore, simple cardiac scan, which is in accordance with ALARA principle (as low as reasonably achievable), giving a certain diagnostic accuracy in revealing CHD in first trimester, might become a part of routine clinical strategy.[12]

The objective of this study was to analyze whether addition of the simple cardiac scan in cases with increased NT and/or abnormal DV blood flow and/or TCR can improve diagnostics of CHD in chromosomally normal fetuses at 11-13 + 6 weeks of gestation in singleton pregnancies.

What's already known about this topic?

The implementation of first trimester ultrasound screening parameters (increased NT, abnormal DV, and TCR) and cardiac scan has changed prenatal care by moving the detection of major heart defects to early stages of gestation. However, safety of such detailed cardiac scan with greater fetal exposure has not been confirmed so far.

What does this study add?

Addition of simple cardiac scan (4-CV, 3VTV) to first trimester screening parameters can increase detection rate of major congenital heart defects while minimizing fetal exposure.

2 | METHODS

The study was performed between January 2006 and December 2015 analyzing prospectively collected data of routine first trimester screening in singleton pregnancies in the Clinic of Obstetrics and Gynecology «Narodni front», University of Belgrade, Serbia. The study protocol was approved by Ethics Committee of our Institution.

Combined first trimester screening comprised a maternal age, fetal NT thickness, maternal serum free beta-hCG and PAPP-A in a one-stop clinic at 11 + 0 to 13 + 6 gestational weeks.[13,14]

The date of pregnancy beginning was assessed in accordance with the last menstrual period, but when the date was uncertain or the estimated gestation by crown-rump length (CRL) was more than 7 days away from the estimated gestation, then the CRL was used to determine the date of pregnancy.

Fetal NT thickness, DV blood flow velocity waveforms, and presence of TCR were evaluated by trans-abdominal ultrasound probe (3-7.5 MHz) or in difficult scanning conditions by trans-vaginal probe (5-9 MHz).[13-17] We applied ALARA (as low as reasonably achievable) principle with settings standardized to shorten anatomic scan duration of the heart.[12] These data were prospectively recorded in a database dedicated to a first trimester screening based on the software developed by the Fetal Medicine Foundation (Astraia, Munich, Germany). Only pregnancies with all three markers of first trimester screening available for analysis were included in this study.

Standard measurements for NT thickness were used as previously reported.[13-16] The increassed NT was defined as NT ≥ 95th percentile.[17]

The DV blood flow velocity waveforms were routinely obtained according to the standard criteria previously reported in detail.[5-7,18] The DV blood flow velocity waveforms were considered abnormal if the a-wave was reversed or absent.[18,19]

Presence of TCR was assessed by pulsed-wave Doppler during fetal quiescence.[20,21] In an apical four chamber view, a sample volume of 3.0 mm was placed at coaptation point of cusps of the tricuspid valve providing the angle between beam and flow of <30°. At least three attempts in TCR assessment were done due to potential variations in the regurgitation jet direction with each cardiac cycle. The diagnosis of clinically relevant TCR was established if it was present during a half of the systole or longer and if its velocity was >60 cm/s.[20,21]

Cardiac evaluation was done in the same visit by either trans-abdominal or transvaginal approach. An ideal angle between ultrasonographic beam and fetal heart interventricular septum of 45° allowed that 4-CV and 3VTV could be optimally obtained.[22-26]

In the 4-CV, by 2D gray scale, color and/or power Doppler, we assessed interventricular septum, atrial and ventricular size, apex,

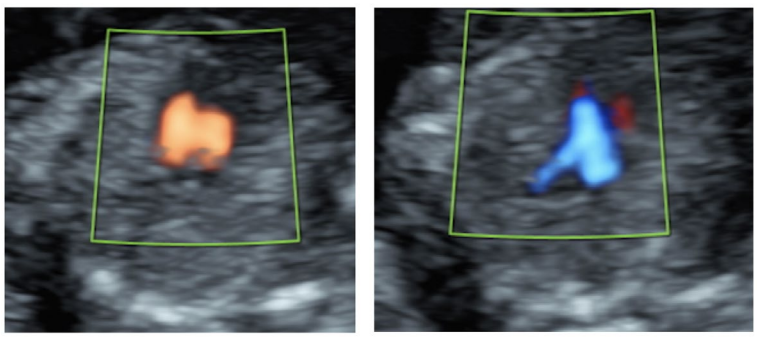

FIGURE 1 A case of normal heart at 12 weeks' gestation

crux, and atrioventricular valves.[22-24,26] In the 3VTV, by 2D gray scale, color and/or power Doppler, we evaluated number of arterial arms (pulmonary trunk, aorta and superior vena cava), their size ratio and flow direction (Figure 1).[23,24,26-29]

Highly suspected findings on cardiac scan in first trimester were re-evaluated by fetal echocardiography in the second trimester. A complete study interrogation was consisted of imaging of the 4-CV, left and right outflow tracts, and the ductal and aortic arches.[27,29] At least two independent sonographers, trained in first and second trimester screening for heart defects, examined each case suspected on having CHD. Every fetus suspected on CHD was evaluated by fetal cardiologist.

All CHD were classified as major if they required surgical or catheter-based intervention during the first year of the life. All major CHD were further classified into groups as follows: right heart defects (pulmonary stenosis or atresia; tricuspid valve atresia; Ebstein anomaly), left heart defects (aortic valve stenosis; hypoplastic left heart syndrome; coarctation of aorta), conotruncal anomalies (transposition of the great arteries; tetralogy of Fallot; double outlet right ventricule), atrioventricular septal defects, and others (double inlet left ventricle, tricuspid dysplasia, left atrial isomerism, complex atrioventricular septal defect).[30-32] The fetal heart defects that were not included in the study were ventricular septal defect, right aortic arch, persistent left superior vena cava, aberrant right subclavian artery, and heart tumors detected during the second or third trimester.[6]

Genetic consultation and fetal karyotyping were offered to all pregnancies who had adjusted risk of more than 1:250 based on data from combined first trimester screening.[14,15] Testing for chromosome abnormalities was performed by chorionic villus sampling (CVS) or early amniocentesis in all 92 pregnancies. Fluorescence in situ hybridization (FISH) test for deletions of 22q11.2 (DiGeorge syndrome) was performed when conotruncal anomaly was suspected.

Termination of pregnancy (TOP) was considered at the parents' request if major heart malformations were present. The fetal autopsy after TOP, with prior parental consent, confirmed or excluded the diagnosis of CHD. If the pregnancy with major CHD continued, those fetuses underwent a follow-up ultrasound examination by a fetal cardiologist. Postnatal echocardiography and neonatal evaluation were performed in all liveborn cases.

All cases with aneuploidies or non-cardiac defects detected prenatally or in the neonatal period were not included in this analysis. Also, pregnancies with no abnormal fetal findings at the 11-13 weeks scan and/or the 18-24 weeks scan which resulted in termination, miscarriage, or stillbirth and those lost to follow-up were not included in the study.

2.1 | Statistical analysis

The prevalence of NT ≥ 95th percentile, DV R/A a-wave, and TCR in fetuses with and without major CHD was expressed as percents. Comparisons between categorical variables for independent groups were performed by Chi-squared test or Fisher's exact test.[33] The screening performances of single and combined parameters were determined by receiver operating characteristic (ROC) curve and the areas under the ROC curves (AUC). The statistical program SPSS 21.0 (SPSS Inc., Chicago, IL) was used for data analyses.

3 | RESULTS

In 10 years period (2006-2015), we prospectively collected data on 22 900 singleton pregnancies with routine first trimester screening at 11-13 + 6 weeks of gestation. Out of this, 19 918 pregnancies ended in a live birth without fetal anomaly, while of the remaining 2982 pregnancies, 1091 had abnormal fetuses (401 with chromosomal anomalies and 690 with non-cardiac structural defects), 1351 were data loss cases, 239 had miscarriage and 301 fetuses had major CHD, out of which 209 had chromosomal anomalies. Major CHD with normal karyotype was found in 92 fetuses leading to a prevalence of 4.02 per 1000 pregnancies. TOP was done in 26 fetuses during the first trimester, and in 49 fetuses during the second trimester of pregnancy.

Age, BMI, smoking, and positive family history for non-cardiac congenital anomaly were similar between groups with and without CHD (Table 1). Diabetes mellitus and family history positive for CHD were more often in the group with CHD compared to the group without CHD (Table 1).

Sensitivity, specificity and negative predictive value of individual parameters increased when combined parameters were used:

TABLE 1 Maternal demographic characteristics in cases with and without CHD

Maternal demographic characteristics	CHD group *N* = 92	No CHD group *N* = 19 918	*P* value
Maternal age (yr)	32.25 ± 4.5	31.15 ± 5.5	.5
Body mass index (kg/m^2)	23.60 ± 3.2	25.0 ± 1.4	.7
Diabetes mellitus[a] (%)	20 (22%)	1 952 (9.8%)	.01
Family history of CHD (%)	14 (15%)	1 195 (6%)	.05
Family history of noncardiac congenital anomaly (%)	19 (21%)	3 525 (17.7%)	.4
Smoking (%)	23 (25%)	6 772 (34%)	.3

Abbreviation: CHD, congenital heart defect.
[a]Diabetes mellitus detected and treated before pregnancy.

NT ≥ 95th vs NT ≥ 95th+DV R/A a-wave (66% vs 70%; 78% vs 95%; 92% vs 97%, respectively) and NT ≥ 95th vs NT ≥ 95th+TCR (66% vs 74%; 78% vs 94%; 92% vs 95%, respectively). The highest sensitivity, specificity, and negative predictive value were found for the combined parameters: NT ≥ 95th + DV R/A a-wave + TCR (77%, 97%, and 98%, respectively; Table 2).

A case with normal findings in 4-CV and 3VTV in the first trimester is shown (Figure1). Abnormal 4-CV and 3VTV findings were disclosed in cases with aortic stenosis, coarctation of the aorta, hypoplastic left heart, pulmonary stenosis or atresia, and tricuspid atresia + VSD, solely 4-CV had abnormal findings in cases with Ebstein anomaly and AV septal defect, while only 3VTV had abnormal findings in cases with tetralogy of Fallot and transposition of the great arteries (Table 3).

During the first trimester, by simple cardiac scan, 62 (67%) of major CHD were detected. Of those, 29 fetuses had definite CHD and 33 had highly suspected CHD (25 cases in 12.0-12 + 6 weeks and 8 cases in 13.0-13 + 6 weeks). All 62 cases had confirmed diagnosis of CHD on autopsy or postnatal echocardiography.

The sensitivity, specificity, and negative predictive values of simple cardiac scan for the detection of CHD in the first trimester are depicted in Table 4.

The diagnostic accuracy of the first trimester screening parameters (NT ≥ 95th, DV R/A a-wave, TCR) and simple cardiac scan alone or in combination with them in the prediction of fetal CHD is shown in Figure 2.

The type and rate of detected CHD were shown in relation to the individual first trimester screening parameters and the time of diagnosis established either by cardiac scan and/or fetal echocardiography (Table 5). In the second trimester, 33% of cases that were not suspected in first trimester, were diagnosed for having CHD (Table 5). The majority of pregnant women (82%) decided to terminate pregnancy (Table 5).

4 | DISCUSSION

The main result of this study is that the addition of simple cardiac scan in cases with NT ≥ 95th and/or abnormal DV R/A a-wave and/or TCR improves detection of CHD in chromosomally normal fetuses without non-cardiac defects at 11-13 + 6 gestational weeks in a population of singleton pregnancies. The second result of this study is that simple cardiac scan has high diagnostic accuracy in detection of major CHD in the first trimester. Abnormal 4-CV alone has moderate detection rate for CHD, which is substantially improved in combination with 3VTV. The third result of this study is that the combination of three ultrasonographic parameters (NT ≥ 95th, DV R/A a-wave and TCR) has greater sensitivity, specificity, and negative predictive value for the detection of major CHD during the first trimester, than any single of these parameters.

In high-risk pregnancies, a fetal heart should be initially evaluated by echocardiography in the first trimester to exclude major CHD and subsequently in the second trimester to exclude minor defects and malformations related to fetal heart development.[27] In this study, based on the findings of first trimester screening parameters of NT, DV, and TCR, we identified a high-risk pregnancy group for CHD and then applied simple cardiac scan protocol consisting of 4-CV and 3VTV with color and power Doppler for the diagnosis of major CHD.[22,31,34,35] Diagnostic accuracy of the fetal heart examination

TABLE 3 Findings of simple cardiac scan using 4-CV and 3VTV in the first trimester in relation to the type of CHD

		Simple cardiac scan	
Type of CHD	Cases	4-CV	3VTV
Coarctation of the aorta	2	Abnormal	Abnormal
Hypoplastic left heart	17	Abnormal	Abnormal
Aortic stenosis	1	Abnormal	Abnormal
Ebstein anomaly	2	Abnormal	Normal
Pulmonary stenosis or atresia	1	Abnormal	Abnormal
Tricuspid atresia+VSD	1	Abnormal	Abnormal
Tetralogy of Fallot	12	Normal	Abnormal
Transpositio of the great arteries	9	Normal	Abnormal
AV septal defect	17	Abnormal	Normal
Total	62		

Abbreviations: AV, atrioventricular; CHD, congenital heart defect; CV, chamber view; VSD, ventricular septum defect; VTV, vessel trachea view.

TABLE 2 Sensitivity, specificity, relative risk, and negative predictive value of first trimester screening parameters (NT ≥ 95th percentile, DV R/A a-wave, TCR) in the detection of major CHD

	Congenital heart defects					
Parameters	NT ≥ 95th	DV R/A a-wave	TCR	NT ≥ 95th + DV R/A a-wave	NT ≥ 95th + TCR	NT ≥ 95th + DV R/A a-wave+TCR
Sensitivity (%)	66%	58%	55%	70%	74%	77%
Specificity (%)	78%	91%	90%	95%	94%	97%
Relative risk (95% CI)	3.7 (2.8-7.2) $P < .001$	4.4 (3.7-6.9) $P = .001$	4.7 (3.3-7.1) $P = .001$	6.2 (4.8-9.5) $P = .0001$	6.3 (4.6-8.8) $P = .0001$	7.5 (5.6-8.2) $P = .0001$
Negative predictive value (%)	92%	96%	91%	97%	95%	98%

Abbreviations: DV R/A a-wave, ductus venosus revers or absent a-wave; NT, nuchal translucency; TCR, tricuspid regurgitation.

TABLE 4 Screening performance of simple cardiac scan for CHD

Parameters	4-CV	3VTV	4-CV + 3VTV
Sensitivity (%)	53.3 (44.3-60.5)	61.3 (58.3-65.5)	67.0 (60.1-71.2)
Specificity (%)	95.0 (93.2-98.0)	96.1 (94.5-98.0)	98.3 (96.0-100)
Negative predictive value (%)	99.0 (98.5-100)	99.0 (97.3-100)	99.0 (98.7-99.0)

Abbreviations: CV, chamber view; VTV, vessel trachea view.

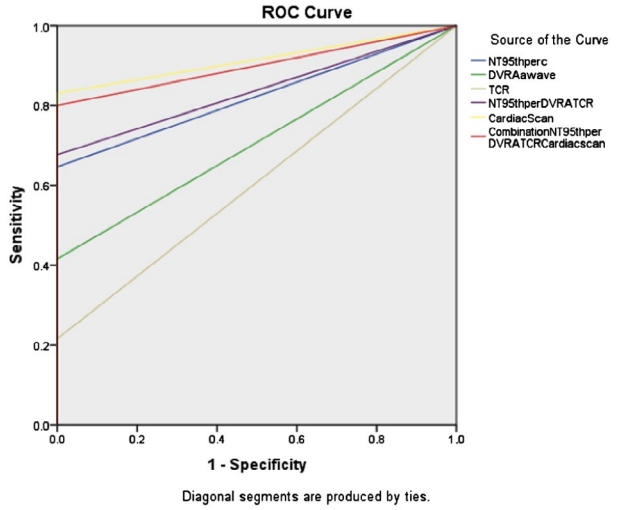

FIGURE 2 Receiver operating characteristic (ROC) curves of first trimester screening parameters (NT ≥ 95th percentile, DV R/A a-wave, TCR) and simple cardiac scan in the prediction of CHD

in the first trimester might be reduced mainly by the small size of the fetus and by the fact that some abnormalities slowly evolve and might become manifested later in pregnancy.[10]

Early fetal echocardiography according to the recommendations of ISUOG (2013) can be considered as a part of routine scan of fetal anatomy in the 11-13 + 6 weeks of gestation.[11] Detection rate is high (85%-100%), but varies depending on to the type of the heart abnormality: for hypoplastic left heart, it is up to 51%, but for tetralogy of Fallot and transposition of the great arteries, it is up to 18%.[13] Early fetal echocardiography requires a serious and prolonged examination that begins transabdominally and usually ends with transvaginal ultrasonography. Importantly, the proposed first trimester Doppler examinations are at the level of the ductus venosus and fetal heart, close to a spine, where a heating effect would be greatest.[11] Caution with Doppler use in the first trimester is needed, because its safety has not been established yet.[12] In meantime, by respecting ALARA principle (ie, Doppler use tailored to indications, exposure to Doppler <10 min), we are minimizing any possible risks.[12] A simplified examination (basic fetal echocardiographic examination or cardiac scan) was proposed to evaluate the fetal heart in low-risk populations at 11-13 + 6 weeks.[25] The sensitivity of this type of examination is high (80%-88.7%) for cardiac defects by combining the two proposed planes.[32,34-37]

In our study, based on the findings of the first trimester screening parameters of NT, DV, and TCR, we identified a high-risk pregnancy group for CHD and then applied simple cardiac scan. In the first trimester, 67% (62/92) of the CHD cases was detected. The sensitivity and specificity of simple cardiac scan in our study, ranging from 53% to 67% and from 95.9% to 98.0%, respectively, are similar to sensitivity and specificity in the another study of 1136 euploid and aneuploid cases (range from 45.7% to 87.5% and of 100%, respectively).[23,24] Eleftheriades studied 3774 fetuses analyzing only the 4-CV cross-section in the first trimester and obtained detection rate of 44.8% (13/29) for CHD.[38] Volpe studied 4445 low-risk fetuses with a 0.9% (42) prevalence of CHD and detected majority of CHD (29/39; 69%) during the first trimester scan. This author also reported that an abnormal 4-CV had a moderate detection rate of 50% for major CHD.[39] In addition, the authors from Bari in the largest study so far of 5343 cases pointed out the diagnostic value of the 3VTV in the detection of large blood vessel anomalies and reported detection rate of 75.8% for combination of 4-CV and 3VTV.[40] In a small study of 886 pregnant women, Persico used similar cardiac scan in the first trimester, and reported a sensitivity of 93.1% (54/58).[32]

In our study, AUC of ROC curve for combination of NT ≥ 95th + DV R/A a-wave +TCR + simple cardiac scan was in the range of excellent discrimination (0.92) and also for the simple cardiac scan alone (0.90). This high detection rate for CHD by the combination of first trimester ultrasound screening parameters with simple cardiac scan might favor this strategy as compared with the standard first trimester screening for routine use in clinical practice.

Of note, ease of performing these echocardiographic cross-sections (4-CV, 3VTV) and then color mapping in just a few minutes allows incorporation of the anatomical fetal heart analysis in the first trimester screening.[34,35,41] By combining the 4-CV and 3VTV with color and power Doppler mapping, various types of cardiac anomalies can be detected.[34,35,41,42]

Regarding the type of CHD, in the 4-CV, we detected heart situs, abnormal number and size of chamber which is in line with the findings in the other studies.[24,25] In the 3VTV section, we detected abnormal vessel number, abnormal vessel size, or abnormal spatial relationship similarly to the reported findings elswhere.[25-28,35,41,43]

In our study, the sensitivity of single parameters, NT ≥ 95th, DV R/A a-wave or TCR, was similar among each other ranging from 55% to 66%, but significantly increased when a combination of these parameters was used for the detection of major CHD, in a range of 70% to 77%. These results are concordant with the results of the study on 40 905 euploid fetuses, with low prevalence of CHD (2/1000), where the risk of major CHD increased exponentially with the increase in the thickness of the NT.[20] This risk was further increased if abnormal DV R/A a-wave or/and TCR were present in combination with NT ≥ 95th.[44] Also in our study, the sensitivity of DV for major CHD was 58%, which was slightly higher compared to a median of 40% (ranking: 24%-69%) in 10 studies with a total of 225 CHD.[16,17,23,25,26,29,44] In our study, sensitivity of TCR for CHD was higher (55%) compared to

TABLE 5 Type of CHD and its relation to the individual ultrasonic parameters, time of diagnosis and pregnancy outcome. Diagnosis of CHD in 11-13+6 wk was established by simple cardiac scan. Diagnosis of CHD in 18-24 wk was established by fetal echocardiography

Congenital heart defects	NT ≥ 95th percentile (%)	DV R/A a –wave (%)	TCR (%)	Diagnosis 11-13 + 6 wk (%)	Diagnosis 18-24 wk (%)	Outcome	
						TOP (%)	Live birth (%)
Left heart defects							
Coartation of the aorta	4 (4.9)	5 (9.6)	1 (2.5)	2 (3.2)	3 (10.0)	2 (2.7)	3 (17.6)
Hypoplastic left heart	18 (21.9)	8 (15.4)	3 (7.5)	17 (27.4)	1 (3.3)	17 (22.7)	1 (5.9)
Aortic stenosis	5 (6.1)	4 (7.7)	3 (7.5)	1 (1.6)	4 (13.3)	3 (4.0)	2 (11.8)
Right heart defects							
Ebstein anomaly	7 (8.5)	8 (15.4)	2 (5.0)	2 (3.2)	6 (20.0)	7 (9.3)	1 (5.9)
Pulmonary stenosis or atresia	5 (6.1)	5 (9.6)	2 (5.0)	1 (1.6)	4 (13.3)	4 (5.3)	1 (5.9)
Tricuspid atresia	1 (1.2)	1 (1.9)	0 (0)	1 (1.6)	1 (3.3)	2 (2.6)	/
Conotruncal anomaly							
Tetralogy of Fallot	13 (15.9)	8 (15.4)	13 (32.5)	12 (19.4)	3 (10.0)	11 (14.6)	4 (23.5)
Transpositio of the great arteries	13 (15.9)	7 (13.5)	13 (32.5)	9 (14.5)	4 (13.3)	10 (13.3)	3 (17.6)
Atrioventricular septal defect							
AV septal defect	15 (18.3)	6 (11.5)	3 (7.5)	17 (27.4)	3 (10.0)	17 (22.7)	3 (17.6)
Others							
Left atrial isomerism	1 (1.2)	/	/	/	1 (3.3)	/	1 (5.9)
Total *N* = 92	82 (89.1%)	52 (53.7%)	40 (43.5%)	62 (67.4%)	30 (32.6%)	75 (81.5%)	17 (18.5%)

Abbreviations: CHD, congenital heart defect; DV R/A a-wave, ductus venosus revers or absent a-wave; NT, nuchal translucence; TCR, tricuspid regurgitation; TOP, termination of pregnancy.

19% in another recent study evaluating both euploid and aneuploid fetuses.[45] The authors concluded that TCR as a single parameter was poor screening tool for detection of CHD. However, they found that TCR in combination with other ultrasonographic parameters had higher sensitivity for aneuploidy, not specifically referring to CHD.[45]

Limitations of the study. The study was retrospective analysis. However, data were prospectively collected in the dedicated database keeping their high quality. Those cases in which obtaining 4-CV or 3VTV was not feasible or technically not possible were examined by fetal echocardiography in second trimester, but not included in this analysis. A certain number of falsely negative cases had a type of CHD that could be detected by simple cardiac scan. However, evolution and late appearance of some CHD should be taken into account. According to some authors, the pulsatile index of DV might be better predictor of CHD compared to the pathological characteristics of the "a" wave.[46] However, the pulsatile index was not evaluated in this study. This was a single center study conducted by certified sonographers which may limit generalizability of the data presented.

5 | CONCLUSION

In chromosomally normal fetuses without non-cardiac anomalies, simple cardiac scan increases the diagnostic accuracy of the combination of parameters of the first trimester screening for detection of major CHD. Safety, accuracy, and ease of performing of simple cardiac scan allow its incorporation in the first trimester screening for major CHD.

6 | AUTHOR CONTRIBUTIONS

Planned the study, carried out data analysis, and drafted the manuscript: Natasa Karadzov Orlic

Drafted the manuscript, critically reviewed manuscript: Amira Egic, Barbara Damnjanovic Pazin

Planned the study, critically reviewed manuscript: Ivana Joksic, Relja Lukic

Planned the study, analyzed data, drafted the manuscript, and critically reviewed manuscript: Zeljko Mikovic.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

ORCID

Natasa Karadzov Orlic https://orcid.org/0000-0003-1093-2760
Amira Egic https://orcid.org/0000-0003-0378-3285
Barbara Damnjanovic-Pazin https://orcid.org/0000-0002-6411-8468
Relja Lukic https://orcid.org/0000-0003-3650-828X
Ivana Joksic https://orcid.org/0000-0002-8890-0569
Zeljko Mikovic https://orcid.org/0000-0002-6770-9255

REFERENCES

1. van der Linde D, Konings EEM, Slager MA, et al. Birth prevalence of congenital heart disease worldwide: a systemic review and meta-analysis. *Am J Cardiol*. 2011;58:2241-2247.
2. Ghi T, Huggon IC, Zosmer N, Nicolaides KH. Incidence of major structural cardiac defects associated with increased nuchal translucency but normal karyotype. *Ultrasound Obstet Gynecol*. 2001;18:610-614.
3. Sotiriadis A, Papatheodorou S, Elefteriades M, Makrydimas G. Nuchal translucency and major congenital heart defects in fetuses with normal karyotype: a meta-analysis. *Ultrasound Obstet Gynecol*. 2013;42:383-389.
4. Makrydimas G, Sotiriadis A, Huggon IC, et al. Nuchal translucency and fetal cardiac defects: a pooled analysis of major fetal echocardiography centers. *Am J Obstet Gynecol*. 2005;192:89-95.
5. Matias A, Gomes C, Flack N, Montenegro N, Nicolaides KH. Screening for chromosomal abnormalities at 10-14 weeks: the role of ductus venosus blood flow. *Ultrasound Obstet Gyneco*. 1998;12:380-384.
6. Matias A, Huggon I, Areias JC, Montenegro N, Nicolaides KH. Cardiac defects in chromosomally normal fetuses with abnormal ductus venosus blood flow at 10-14 weeks. *Ultrasound Obstet Gynecol*. 1999;14:307-310.
7. Borrell A. The ductus venosus in early pregnancy and congenital anomalies. *Prenat Diagn*. 2004;24:688-692.
8. Smrcek JM, Berg C, Geipel A, et al. Detection rate of early fetal echocardiography and in utero development of congenital heart defects. *J Ultrasound Med*. 2006;25:187-196.
9. Becker R, Wagner RD. Detailed screening for fetal anomalies and cardiac defects at the 11-13-week scan. *Ultrasound Obstet Gynecol*. 2006;27:613-618.
10. Practice I. Guidelines (updated): sonographic screening examination of the fetal heart. *Ultrasound Obstet Gynecol*. 2013;41:348-359.
11. Carvalho JS. Fetal heart scanning in the first trimester. *Prenat Diagn*. 2004;24:1060-1067.
12. Selvesen K, Abramowicz C, Brezinka C, ter Haar G, Maršál K. Opinion. Safe use of Doppler ultrasound during the 11 to 13 + 6-week scan: is it possible? *Ultrasound Obstet Gynecol*. 2011;37:625-628.
13. Allan LD, Crawford DC, Chita SK, Tynan MJ. Prenatal screening for congenital heart disease. *Br Med J*. 1986;292:1717-1719.
14. Spencer K, Spencer CE, Power M. One stop clinic for assessmen Kt of risk for fetal anomalies: a report of the first year of prospective screening for chromosomal anomalies in the first trimester. *Br J Obstet Gynecol*. 2003;107:1271-1275.
15. Nicolaides KH, Azar G, Byrne D, Mansur C, Marks K. Fetal nuchal translucency: ultrasound screening for chromosomal defects in first trimester of pregnancy. *BMJ*. 1992;304(6831):867-869.
16. Karadzov-Orlic N, Egic A, Milovanovic Z, et al. Improved diagnostic accuracy by using secondary ultrasound markers in the first-trimester screening for trisomies 21, 18 and 13 and Turner syndrome. *Prenat Diagn*. 2012;32:638-643.
17. Nicolaides KH. Nuchal translucency and other first-trimester sonographic markers of chromosomal abnormalities. *Am J Obstet Gynecol*. 2004;191:45-67.
18. Maiz N, Valencia C, Emmanuel EE, Staboulidou I, Nicolaides KH. Screening for adverse pregnancy outcome by ductus venosus Doppler at 11-13+6 weeks of gestation. *Obstet Gynecol*. 2008;112:598-605.
19. Borrell A, Grande M, Bennasar M, et al. First-trimester detection of major cardiac defects with the use of ductus venosus blood flow. *Ultrasound Obstet Gynecol*. 2013;42:51-57.
20. Falcon O, Faiola S, Huggon I, Allan L, Nicolaides KH. Fetal tricuspid regurgitation at the 11.0 to 13.6-week scan: association with chromosomal defects and reproducibility of the method. *Ultrasound Obstet Gynecol*. 2006;27:609-612.
21. Kagan KO, Valencia C, Livanos P, et al. Tricuspid regurgitation in screening for trisomies 21, 18 and 13and Turner syndrome at 11.0-13.6 weeks of gestation. *Ultrasound Obstet Gynecol*. 2009;33:18-22.
22. Carvalho JS. Screening for heart defects in the first trimester of pregnancy: food for thought. *Ultrasound Obstet Gynecol*. 2010;36:658-660.
23. Batra M, Gopinathan KK, Balakrishman B, Gopinath P, Kariakose R, Gupta J. The detection rate of cardiac anomalies at 11-13+6 week scan using four chamber view and three vellel view. *J Fetal Med*. 2016;1:95-98.
24. Wiechec M, Knafel A, Nocun A. Prenatal detection of congenital heart defects at the 11- to 13-week scan using a simple Color Doppler protocol including the 4-chamber and 3-vesseland trachea views. *J Ultrasound Med*. 2015;34:585-594.
25. Quarello E, Lafouge A, Fries N, Salamon LJ, CFEF. Basic heart examination: feasibility study of first-trimester systematic simplified fetal echocardiography. *Ultrasound Obstet Gynecol*. 2017;49(2):224-230.
26. Sinkovskaya ES, Chaoui R, Karl K, Andreeva E, Zhuchenko L, Abuhamad AZ. Fetal cardiac axis and congenital heart defects in early gestation. *Obstet Gynecol*. 2015;125:453-460.
27. Allan L, Cook A, Huggon IC. *Fetal Echocardiography, A Practical Guide*. New York: Cambridge University Press; 2009.
28. Yoo S-J, Lee Y-H, Kim ES, et al. Three-vessel view of the fetal upper mediastinum: an easy means of detecting abnormalities of the ventricular outflow tracts and great arteries during obstetricscreening. *Ultrasound Obstet Gynecol*. 1997;9:173-182.
29. International Society of Ultrasound in Obstetrics & Gynecology. Cardiac screening examination of the fetus: guidelines for performing the 'basic' and 'extended basic' cardiac scan. *Ultrasound Obstet Gynecol*. 2006;27:107-113.
30. Clur S, VanBrussel PM, Mathijssen IB, et al. Audit of 10 years of referrals for fetal echocardiolography. *Prenat Diagn*. 2011;31:1134-1140.
31. Chelemen T, Syngelaki A, Maiz N, Allan L, Nicolaides KH. Contribution of ductus venosus Doppler in first trimester screening for major cardiac defects. *Fetal Diagn Ther*. 2011;29:127-134.
32. Persico N, Moratalla J, Lombardi CM, Zidere V, Allan L, Nicolaides KH. Fetal echocardiography at 11-13 weeks by transabdominal high-frequency ultrasound. *Ultrasound Obstet Gynecol*. 2011;37:296-301.
33. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. 2nd ed. Hoboken, NJ: JohnWiley & Sons Inc.; 2000:156-164. 20.
34. Hyett J, Perdu M, Sharland C, et al. Using fetal nuchal translucency to screen for majorcongenital cardiac defects at 10-14 weeks of gestation: population based cohort study. *BMJ*. 1999;318:81-85.
35. Pereira S, Ganapathy R, Syngelaki A, et al. Contribution of fetal tricuspid regurgitataion in first trimester screening for major cardiac defects. *Obstet Gynecol*. 2011;117:1384-1391.
36. Khalil A, Nicolaides KH. Fetal heart defect's: potential and pitfalls of first-trimester detection. *Semin Fetal Neonatal Med*. 2013;18:251-260.
37. Vimpelli T, Huhtala H, Acharya G. Fetal echocardiography during routine first-trimester screening: a feasibility study in an unselected population. *Prenatal Diagn*. 2006;26(5):475-482.
38. Eleftheriades M, Tsapakis E, Sotiriadis A, Manolakos E, Hassiakos D, Botsis D. Detection of congenital heart defects throughout pregnancy; impact of first trimester ultrasound screening for cardiac abnormalities. *Fetal and Neonatal Medicine*. 2012;25:2546-2550.
39. Volpe P, Ubaldo P, Volpe N, et al. Fetal cardiac evaluation at 11-14 weeks by experienced obstetricians in a low-risk population. *Prenat Diagn*. 2011;31:1054-1061.
40. DeRobertis V, Rembouskos G, Farelli T, et al. The three-vessel and trahea view(3VTV) in the first trimester of pregnancy: an additional tool in screening for congenital heart defects (CCHD) in an unselected population. *Prenat Diagn*. 2017;37:693-698.

41. Maiz N, Nicolaides KH. Ductus venosus in the first trimester: contribution to screening of chromosomal, cardiac defects and monochorionic twin complications. *Fetal Diagn Ther*. 2010;28:65-71.
42. Timmerman ES, Clur AE, Pajkrt E, Bilardo CM. First-trimester measurement of the ductus venosus pulsatility index and the prediction of congenital heart defects. *Ultrasound Obstet Gynecol*. 2010;36:668-675.
43. Zidere V, Bellsham-Revell H, Persico N, Allan LD. Comparison of echocardiographic findings in fetuses at less than 15 weeks' gestation with later cardiac evaluation. *Ultrasound Obstet Gynecol*. 2013;42(6):679-686.
44. Yagel S, Weissman A, Rotstein Z, et al. Congenital heart defects: natural course and in utero development. *Circulation*. 1997;96:550-555.
45. Huggon IC, Ghi T, Cook AC, et al. Fetal cardiac abnormalities identified prior to 14 weeks' gestation. *Ultrasound Obstet Gynecol*. 2002;20:22-29.
46. Favre R, Cherif Y, Kohler M, et al. The role of fetal nuchal translucency and ductus venosus doppler at 11-14 weeks of gestation in the detection of major congenital heart defects. *Ultrasound Obstet Gynecol*. 2003;21:239-243.

How to cite this article: Karadzov Orlic N, Egic A, Damnjanovic-Pazin B, Lukic R, Joksic I, Mikovic Z. Screening performance of congenital heart defects in first trimester using simple cardiac scan, nuchal translucency, abnormal ductus venosus blood flow, and tricuspid regurgitation. *Congenital Heart Disease*. 2019;14:1094–1101. https://doi.org/10.1111/chd.12852