CEOG Clinical and Experimental Obstetrics & Gynecology

Early fetal heart ultrasonography as additional indicator for chromosomopathies

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Summary

Objective: First trial of estimating values of scans of fetal heart structures (FHS) in first trimester of pregnancy, as more primary facts of possible chromosomopathies. *Materials and Methods:* The study included 2,643 fetuses that were examined in first trimester of pregnancy on Sono CT convex (C5-2MHz), endovaginal (ev 8-4MHz), and linear transducers (L12-5MHz) during a period of eight years. Fetal heart was evaluated using appropriate software with broad-band transducers and color Doppler, Sono CT, and HD ZOOM technologies. The scan was performed by three experienced physicians. FHS were based on: left and right ventricle morphology; AV valves (atrioventricular) position and existence of primal ostium; relationship of left ventricle outflow tract (LVOT) and right ventricle outflow tract (RVOT) and great vessels on three vessel view (3VV) and estimation of ductal and aortic arch. *Results:* Several developments, one being the ability to identify fetuses at risk for cardiac defects combining nuchal translucency (NT), ductus venosus (DV) Doppler, and evaluation of tricuspid regurgitation, have prompted reconsideration of the role of the first trimester prognostic factor of fetal evaluation. In low-risk pregnancies group, 36 (1.8%) fetuses were found to have congenital heart disease (CHD), and in high-risk pregnancies the number of fetuses with CHD was 75 (12%). Genetic amniocentesis or chorionic villus sampling (CVS) was performed in all fetuses with CHD. Forty-two (37.8%) fetuses with CHD were found to have chromosomal anomalies. Out of 111 fetuses with CHD 39 (35.1%) had an nuchal translucency (NT) above three mm. Out of 42 fetuses with chromosomal anomalies and CHD, 29 (69%) had an increased NT. *Conclusion:* Using first trimester fetal echosonography constitutes a further step in the earlier recognition of chromosomopathies, even in low risk groups. Still further steps are necessary as all facts of good clinical practice. In order to offer further benefits during pregnancies, improvements in diagnostics are still required.

Key words: Chromosomopathies; First trimester; Early diagnosis; Fetal echocardiography; Cardiac defects.

Introduction

A second-trimester fetal echocardiography is the gold standard for prenatal evaluation of fetal cardiac structure and function. Prenatal detection of congenital heart disease (CHD) is limited to the second trimester because screening programs among the unselected population are usually performed during the routine second-trimester scan. The segmental approach provides a consistent and detailed evaluation of cardiac anatomy and situs, and allows demonstration of the majority of fetal cardiac defects [1, 2]. First trimester fetal cardiac examination has largely been restricted to high-risk patients. The majority of CHDs, however, occur in low-risk patients [3].

Several developments, one being the ability to identify fetuses at risk for cardiac defects combining nuchal translucency (NT), ductus venosus (DV) Doppler, and evaluation of tricuspid regurgitation, and another - the role of the first trimester fetal cardiac examination, can predict chromosomopathies [3-5].

The association of CHDs with Trisomy 21 was reported many years ago and heart defects remain one of the most common and lethal abnormalities present postnatally in individuals affected by Down syndrome [4, 5]. However, even in specialized centers, expert cardiac study is performed only on fetuses with an NT increased above the 99th centile [6].

The present authors designed this study to assess the accuracy of fetal echocardiography at first trimester using a high-frequency, broad-band linear probe in pregnancies both with low and high risk for Trisomy 21. The examinations were performed by the physicians experienced in genetic sonography and fetal echocardiography [7-9].

Materials and Methods

This was a prospective study conducted between June 2005 and August 2013, during which the authors examined 2,643 fetal hearts between 12th and 14th week of gestation. This was planned

Revised manuscript accepted for publication December 18, 2014

Table 1. — *Number of fetuses with CHD in high and low risk groups of pregnancies.*

			CHD		Total
			Yes	No	
Group	Low risk	Count	36	1974	2,010
		% within group	1.8%	98.2%	100%
	High risk	Count	75	558	633
		% within group	11.8%	88.2%	100%
Total		Count	111	2532	2,643
		% within group	4.2%	95.8%	100%

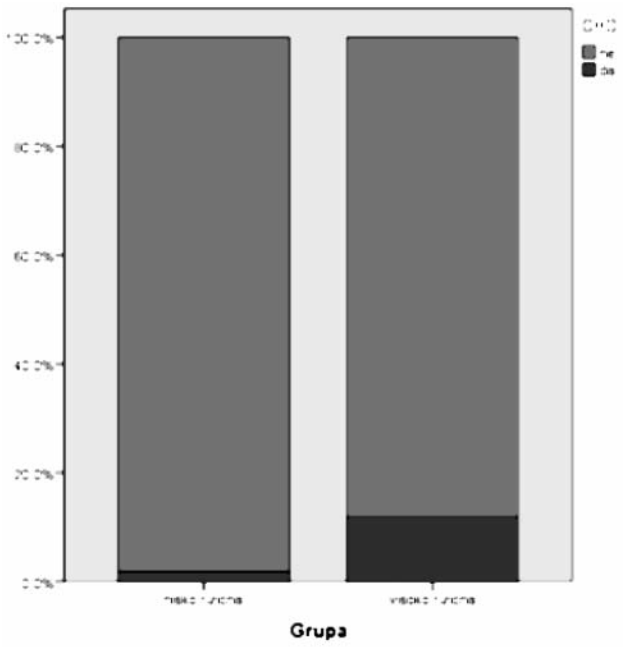

Figure 1. — Percentage of fetuses with CHD in high and low risk pregnancy groups.

Table 2. — *Coordination of NT and CHD (yes: NT > 3 mm; no: NT < 3 mm.*

	Frequency	Percentage
Yes	39	35.1
No	72	64.9
Total	111	100.0

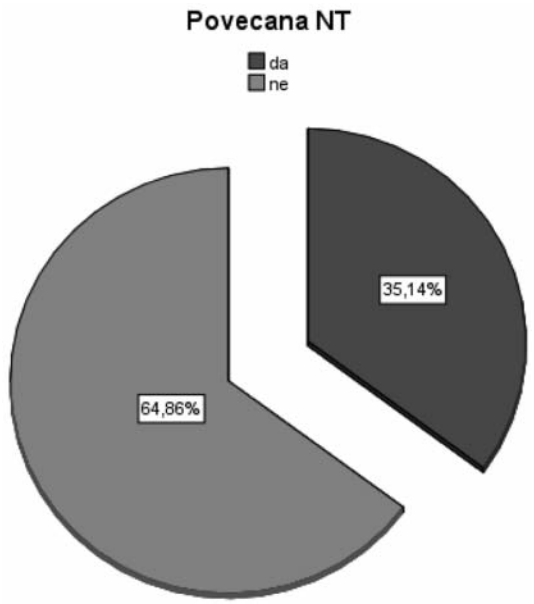

Figure 2. — NT distribution of pregnancy with NT and CHD (yes: increased NT > 3 mm; no: NT < 3 mm.

as a validation study in low-risk population and patients with risk factors for congenital heart disease (pre-gestational diabetes, epilepsy, family history of congenital heart defects, maternal exposure to teratogens and pregnancy upon an assisted reproductive technology). The authors obtained approval from the Institutional Ethics Committee for the study and a written consent from each participant. The exclusion criteria were: multifetal pregnancies, missed abortions, and high obese women.

All fetuses were examined by ultrasound–trained pediatric radiologists and obstetricians. Operators were using the same protocol as one used in the second and the third trimesters and applying color-Doppler (CD) flow mapping for morphological evaluation of the four chambers and great vessels [1, 10, 11]. The authors were usually able to visualize the following anatomic landmarks using a gray-scale, two dimensional (2D) and CD modalities: four-chamber view, position of ascending aorta (LVOT), descending aorta, heart size, cardiac axis, two equal-sized atria, position of right and left ventricles, position of two opening atrioventricular valves, two great arteries crossing, three-vessel view (3VV) and three-vessel and trachea view (3VT), two great arteries of equal diameter, V configurations and similar size of aortic and ductal arch, aortic and ductal arch in sagittal view, ductus venosus (DV) Doppler, diastolic filling of left ventricle, exclusion of tricuspid regurgitation, and forward flow in both arches.

In case of abnormal scan, non invasive genetics from maternal blood and chorionic villus sampling (CVS) was routinely offered for genetic analysis together with multidisciplinary counseling before decision on termination of pregnancy (TOP). Cases with inconclusive scans were rescheduled at 16 weeks of gestation.

When the pregnancy continued, the fetuses underwent a complete ultrasound scan and echocardiography examination at 26th and 32th week of gestation. The prenatally established diagnosis was confirmed, modified or changed according to postnatal echocardiography, surgery or autopsy findings.

All scans were carried out transabdominally using either a 12-5 MHz linear (L) broadband probe, C 8-4ev MHz transvaginal (ev) broadband probe, convex broad band probe 5-2MHz (C). The authors also used a Sono CT, high definition zoom (HD Zoom), software for fetal echocardiography at first trimester, broadband CD, color-power angio (CPA), and cineloop.

The SPSS statistical software package (release 18) was used to assess statistical significance if appropriate, with the level of significance set at 0.05.

Table 3. — *Correlation of CHD - NT chromosomal abnormalities (increased NT > 3 mm: yes; no: NT < 3 mm.*

	Frequency	Percentage
Yes	29	69.0
No	13	31.0
Total	42	100.0

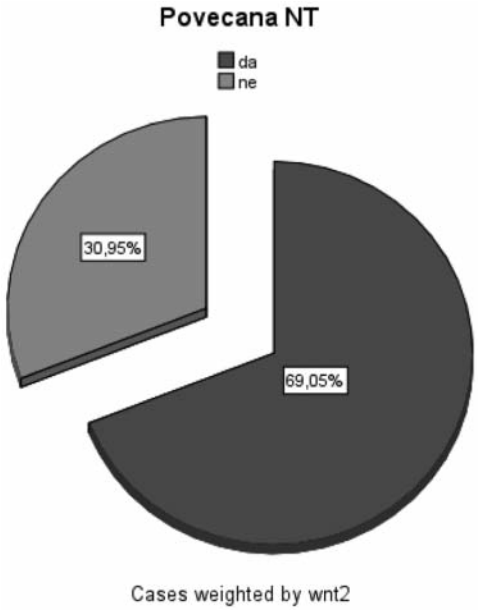

Figure 3. — Percentage of pregnancies with CHD and chromosomal abnormalities with elevated NT (yes: NT > 3 mm; no: NT < 3 mm.

Table 4. — *Correlations of chromosomopathies with CHD and NT measurements.*

			NT		Total
			Yes	No	
Grupa	CHD	Count	39	72	111
		% within group	35.1%	64.9%	100.0%
	Hromosom anomaly	Count	29	13	42
		% within group	69.0%	31.0%	100.0%
Total		Count	68	85	153
		% within group	44,4%	55,6%	100.0%

High statistical importance ($X^2 = 14.192$; $p < 0.001$).

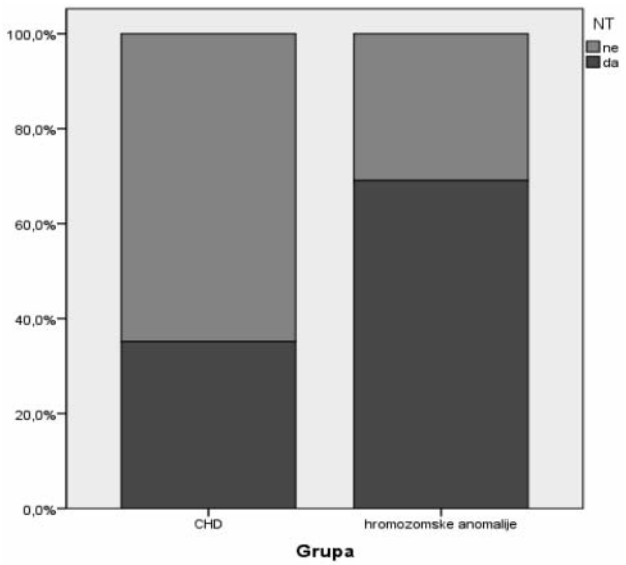

Figure 4. — Percentages of evlevated NT (above 3 mm) measurements in fetuses with CHD and with fetuses with chromosomal anomalies.

Results

Within an eight-year period the authors examined 2,811 pregnancies in the first trimester, and the fetal heart was examined in 2,643 pregnancies; 2,010 patients had low-risk pregnancies, while there were 633 high-risk pregnancies. The median maternal age was 37 (range, 19-45) years. The median crown-rump length was 68 (range, 46-84) mm. The total number of fetuses with CHD was 111 (4.2%), while there were 2,532 fetuses without CHD (Table 1).

In low-risk pregnancies 2,010 cases group, 36 (1.8%) fetuses were found to have CHD, and in high-risk pregnancies 633 cases the number of fetuses with CHD was 75 (11.8%). Genetic amniocentesis or CVS was performed in all fetuses with CHD (Table 1, Figure 1). In all cases in which the authors detected possible CHD, the chromosomal abnormalities were found in 42 cases (37.8%).

Statistically analyzing the coordination of NT and CHD, the authors found a large statistical importance ($p > 0.01$). Out of 111 fetuses with CHD, 39 (35.1%) had an NT above three mm (Table 2, Figure 2). In correlation with CHD-NT-chromosomal anomalies, 42 fetuses with chromosomal anomalies and CHD, 29 (69%) had an increased NT. It is statistically significant ($p > 0.01$) (Table 3, Figure 3).

The present results confirm the importance of NT nuchal translucency as an important parameter of chomosomopaties, and the correlation of NT with congenital heart defect CHD as additional parameter of precise diagnosis (Table 4, Figure 4).

Discussion

Analyzing the second trimester scan, the authors identified two major cardiac defects (both VSD) that had been missed in the first trimester scan. In review of the first trimester DVD clips, the heart appeared normal. The authors will have to perform even large studies, because they missed statistical importance in this number.

In cases with inadequate views at the first trimester scan, a normal heart was documented by a later scan or

after birth. Among different cardiac abnormalities, the present authors considered the predominant minor abnormality as disproportion of the ventricles and/or the great arteries. This minor cardiac defect was diagnosed between 11th-14th week and the follow-up data were available for eight patients. In this number of eight continuing pregnancies with diagnosis of disproportion ventricles and the great arteries, coarctation of the aorta was diagnosed at the mid-trimester scan.

Although the authors used three different probes, they failed to appropriately examine the fetal heart with any of these probes in 168 (6%) fetuses, hence they were not included in efficiency tests of ultrasound fetal heart diagnostics. To obtain the scan the authors used two L probes (L 12-5MHz), ev probe (ev 8-4MHz) and C probe (C 5-2 MHz). The basic reason for this was due to the fact that the pregnant woman habitus and the fetal position, i.e. its spine was in a parallel position to ultrasound waves.

The four-chamber heart view was obtained in all patients, and all parameters were demonstrated in 2,331 (92.1%) patients without CHD. Demonstration of individual parameters was somewhat variable. With CD, chamber situs was accessible in 97%, whereas without CD application it was possible to determine chamber situs in not more than 67%. DV assessment was possible in 91% of cases within the predicted time frame, while the assessment of the left chamber end-diastolic filling was possible in 99% of cases. At 3VV and 3VT, the authors were able to visualize the great arteries in 98%, while the "b" sign (the straight line of the pulmonary artery surrounded by aortic arch), "V" sign (the connection of the aorta and ductus arteriosus), and "X" sign (the crossing of the main pulmonary artery with the aorta) were seen in 96%. Ductal and aortic arches were seen in 91% and 93%, respectively, and forward flow with CD in both arches was determined in 97%. All parameters necessary for fetal heart analysis required the use of CD. Doppler was used in end-diastolic chamber flow and in DV. The use of CD was mandatory in estimation of the chambers situs, position of the aorta, estimation of AV valves, interventricular septum, foramen ovale, and aortic and ductal arches. DV with PI > 2.0 and more was found in 51 (45.9%) fetuses with CHD. Tricuspid regurgitation was found in 150 (7.5%) euploid fetuses, 22 (55%) of the 42 fetuses with chromosomal anomaly, and 42 (37,8%) with CHD. Separation of the "e" and "a" waves was found in 37 (33.3%) of the 111 fetuses with CHD. In 11 cases, the authors performed an additional examination in the 16th week, before the decision on possible pregnancy continuation or TOP.

CHD is the most common defect in human fetuses and affect approximately 0.3% to 0.8% of live births [12]. Prenatal detections of CHD are important because they allow searches for chromosomal, additional structural, and genetic abnormalities, with a potential for reduction of neonatal morbidity and mortality [13].

Technology progress in ultrasound hardware and software is likely to have contributed to the high success rate in the early assessment of fetal heart. Persico *et al.* [14], while using 4-8 MHz frequency probe were not able to scan 15% of fetuses. Different authors have reported different degrees of success of examination in the first and early second trimester scan, while using the same frequency probes - L 15-8MHz and L 15MHz, namely 99% [6, 7] and 75% [15], respectively. Rizzo *et al.* [16] achieved performance in fetal heart scan (92.4%) using a 4-8MHz probe from 18th – 24th week of gestation. Turan *et al.* [17], using the same probe and the ultrasonic equipment, achieved performance of 85% but much earlier, suggesting that pregnancy period in which the scan was performed did not significantly limit the level of their performance in fetal heart scan.

Overall, the median (range) accuracy, sensitivity, and specificity, as well as the positive and negative likelihood ratios, for the identification of fetuses with congenital heart defects were 79% (77%-83%), 90% (70%-96%), 59% (58%-93%), 2,35 (2.05-9.80), and 0,18 (0.08-0.32), respectively [18]. 2D ultrasound remains superior to spatiotemporal image correlation 4D-STIC at 11-14 weeks, unless volumes of good to high quality can be obtained [19].

Conclusion

The importance of fetal heart scan in the first trimester of gestation can be substantiated by the following facts: the significance of a mandatory fetal heart scan, lies also in the fact that one-third of fetuses with CHD (37.8%) also had chromosomal anomalies, which corresponds to the data from nine studies reported between 1961 and 2008 [21]. This signifies that the test on ultrasonic markers for chromosomal anomalies would not reveal two-thirds of fetuses with a heart defect not accompanied by a chromosomal anomaly. Moreover, for the sake of confirming this assertion, only 35.1% of fetuses with CHD had an increased NT, which is increased only in 69% in fetuses with both chromosomal anomaly and CHD.

The 1.8% of fetuses with CHD in low risk patients is few times higher than referenced to in literature, which can be explained with a higher average age of pregnant women which is in the present series around 37 years. The CHD percentage is considerably higher in high-risk pregnant women, being 12%. Such a high CHD incidence imposes the obligation of performing a mandatory fetal heart scan, both in low and high risk pregnancies.

In conclusion, this study can be used as additional parameter by standard protocol tests with NT, nasal bone, Dopler of DV, and echogenic intestines, to become one of helping markers in earlier detection of chromosomopathies in even low risk group patients.

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