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Contribution of Fetal Tricuspid Regurgitation in First Trimester Screening for Major Cardiac Defects in Ulaanbaatar

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Objective: To estimate the potential value of fetal assessment for tricuspid regurgitation, nuchal translucency and ductus venosus at 11-13 weeks of gestation in the prediction of major cardiac defects. **Methods:** Prospective cohort study data was derived from first-trimester screening of pregnant women at National Center for Maternal and Child Health between March 2014 to May 2017. A total of 318 patients at 110 to 136 weeks of gestation enrolled in the study. Trans abdominal ultrasonography (using 3 to 7.5 MHz curvilinear transducers) was performed to indirectly measure gestational age using the fetal crown-rump length, measure the fetal nuchal translucency thickness, and to assess blood flow across the tricuspid valve in 304 live fetuses in singleton pregnancies. **Results:** The median age of the mothers was 34 (range, 19-46 years). Crown-rump length of ranged from 45-84 mm. Eight (3.2%) of the 304 fetuses were diagnosed with major heart defects and increased nuchal translucency and tricuspid regurgitation were shown to be strongly associated with CHD. Increased nuchal translucency was present in 83% of fetuses with CHD (p=0.0001), while tricuspid regurgitation was present in 73% of those same fetuses (p=0.012). **Conclusion:** First trimester fetal ultrasound biomarkers can be sued to screen for major heart defects. Increased NT and TR are important indicators of the need for echocardiography, which is useful for early prenatal diagnosis of CHD.

Keywords: Nuchal Translucency, Tricuspid Valve Regurgitation, Congenital Heart Disease

Introduction

Congenital heart disease (CHD) is the most common congenital disorder in newborns and about 25% are complex heart diseases which need early intervention or open heart surgery during the neonatal period [1, 2]. The incidence of CHD varies from 8-10 in 1000 live births and half of them have major heart defects [3, 4]. Heart defects occur in fetuses with chromosomal abnormalities 6.5 times more frequently than in normal fetuses [2]. Spinal bifida occurs 4 times more frequently in fetuses with congenital heart

defects [5]. Worldwide, every year there are about 7.9 million infants born with congenital abnormalities and out of those 3.3 million die. Of the 3.2 million infants with developmental difficulties, only 1.4 million will survive [6].

According the statistical data from the Screening and Research department of Mongolian Maternal and Child Health Center, in 2017 355 congenital abnormalities were detected in their first 6 months of gestation and 64 of them were diagnosed with the congenital heart disease. Among all diagnosed congenital heart disease, 5 were detected prenatally and 21 fetuses did not grow in the uterus and heart defects were detected only by autopsy. Thirty neonates were diagnosed with at least one chromosomal abnormality and the combination of Down syndrome and heart defects were detected in 10 [7].

In the past 20 years, many research studies have been conducted to detect congenital heart disease and chromosomal anomaly in the first 11-13 weeks of gestation age by measuring the nuchal translucency. Hyett et al. reported in 1999 that in a cohort of 29154 pregnancies, 56% of the fetuses with major CHD had an increased NT measurement [10]. The 95th percentile for NT measurement increases with gestational age between 11-13 weeks and is 2.5 mm depending on crown rump length, where as the 99th percentile is fixed at 3.5 mm. After 14 weeks the normal NT regresses, coinciding with a reduction in placental resistance and beginning of fetal renal function.

In the last few years the clinicians are using the nuchal translucency, ductus venosus a-wave and tricuspid regurgitation in fetuses as a biomarker of congenital heart diseases.

Major congenital heart defects usually require immediate surgical intervention within neonatal period. It is important to diagnose heart defects in the fetal stage as it reduced the morbidity and mortality rates in affected neonates [8].

In Mongolia, congenital heart diseases are typically diagnosed late, sometimes after the birth. Congenital heart disease is the most frequent cause of mortality in early neonatal period. Therefore, our research team decided to identify fetal ultrasound biomarkers useful to detect congenital heart disease and to work to implement their use into the clinical practice.

Materials and methods

Study objectives

To estimate the potential value of fetal assessment for tricuspid regurgitation at 11^0-13^6 weeks of gestation for the prediction of major cardiac defects.

Prospective cohort study data was derived from first-trimester screening of pregnant women at the National Center for Maternal and Child Health between March 2014 to May 2017.

A total of 318 patients at 11^0 to 13^6 weeks of gestation enrolled in the study. The median age of pregnant women was 34 years of age, with range 19-44 years. An ultrasonography scan was performed trans abdominally (using SONOACE 8000 ultrasound machine 3 to 7.5 MHz curvilinear transducers), to determine gestational age from the measurement of the fetal crown-rump length; to measure fetal nuchal translucency thickness; and to assess blood flow across the tricuspid valve.

Needs a section describing here the calculations made?

Statistical analysis

Statistical analyses were performed using SPSS 20 software. Chi-Square tests with a p-value of <0.05 was considered statistically significant.

Table 1. The Sensitivity of biomarkers to CHD

Biomarkers	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
NT	.839	.057	.000	.726	.951
HR	.419	.105	.394	.213	.626
TR	.739	.102	.012	.539	.940
DV.PI	.805	.067	.001	.673	.937
DV a-wave	.754	.095	.007	.567	.941

Table 2. The Specificity of biomarkers to CHD

Biomarkers	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
NT	.161	.057	.000	.049	.274
HR	.581	.105	.394	.374	.787
Tricuspid regurgitation	.261	.102	.012	.060	.461
DV.PI	.195	.067	.001	.063	.327
DV.a-wave	.246	.095	.007	.059	.433

Table 3. The statistical significance of biomarkers to major heart defects

	Normal		Major cardiac defect		p-value
	Count	%	Count	%	
DV.a-wave					0.001
no	144	97.3%	4	2.7%	
yes	13	68.4%	6	31.6%	
Tricusped regurgitation					0.001
no	155	96.9%	5	3.1%	
yes	3	37.5%	5	62.5%	
NT increased					0.001
no	157	95.2%	8	4.8%	
yes	2	50.0%	2	50.0%	

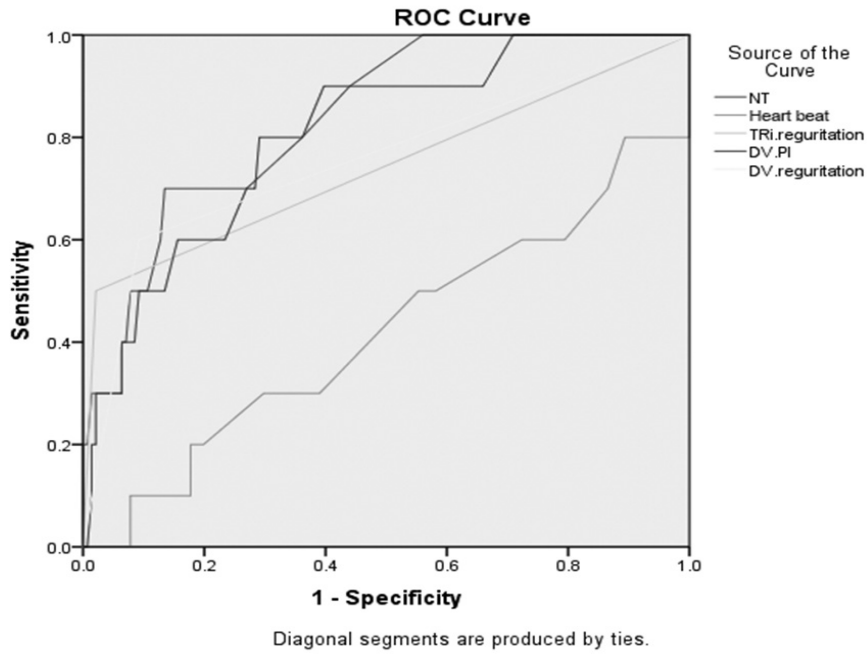

Figure 1. Receiver-operating characteristics curve for the diagnostic performance sensitivity and specificity of nuchal translucency, tricuspid regurgitation, ductus venosus a-wave to detect major cardiac defects.

Table 4. The association of chromosomal abnormality and major heart defects

	Chromosomal abnormality				p-value
	no		yes		
	count	%	count	%	
Cardiac Defect					0.001
normal	158	95.2%	1	33.3%	
CHD	8	4.8%	2	66.7%	

Results

The sensitivity of NT (p=0.0001), tricuspid regurgitation (p=0.01), ductus-venosus a-wave (p=0.007) CHD are found in Table 1.

The specificity of NT (p=0.0001), tricuspid regurgitation (p=0.01), ductus venosus a-wave (p-0.007), ductus venosus PI (p=0.001) in detecting CHD are included in Table 2.

The ductus venosus a-wave was detected in 6 (31.6%) cases with major heart defects (p=0.001). Tricuspid regurgitation was detected in 5 (62.5%) fetuses CHD and NT was also detected in 50% cases. Therefore, all 3 biomarkers had a statistical significance to detect major heart defects in the first trimester of pregnancy (Table 3).

Of the 8 fetuses with a major cardiac defect, 3 (38%) an associated chromosomal abnormality.

Discussion

During the meta-analysis conducted by Rachel and Rachael (2014), 7 completed studies were included regardless of NT status, 9 studies with increased NT were included and 7 studies with normal NT were included, and the summary revealed that sensitivity of abnormalities for TR and DV flow in the detection of CHDs were 50%, 93%, 83% while the specificity was 19%, 80% and 96% respectively [9].

Eight fetuses (3.2%) were diagnosed with a major heart defect and an increased NT, tricuspid regurgitation and ductus-venosus a-wave were strongly associated with CHD. First trimester screening sensitivity of nuchal translucency to CHD was 83%, ductus-venosus a-wave was 75% and ductus-venosus PI was 80%, and these results are comparable with the other studies. Hyett et al. reported in 1999 that in a cohort of 29154 pregnancies, 56% of the fetuses with major CHD had an increased NT measurement [10]. We found a prevalence of chromosomal anomalies in 66.7% of children with CHD, which is similar to other studies.

Although the NT measurement itself appears to be a moderately effective screening tool for the detection of CHD, its role in detection of specific CHD is likely to be enhanced by other prenatal testing. However, NT is an important of the need for specialized echocardiography. When TR and an abnormal DV Doppler flow profile are found in association with increased NT, the risk of CHD increases, and early detection of major cardiac defect is warranted. Hopefully, this strategy will improve the prenatal CHD detection rate and will have a great impact on reducing perinatal mortality in Mongolia.

Our study has some limitations. Based on the data for NT measurement, TR and DV regurgitation, we cannot predict fetal cardiac anatomy at 11^0-13^6 weeks of gestation. In cases of increased NT, TR, and DV abnormal Doppler flow we recommend a follow-up study at 20-21 weeks of gestation to detect major heart defects. According the study results there were diagnosed congenital heart disease only in 8 fetuses, future studies should involve larger numbers of pregnant woman.

Conclusion

First trimester fetal ultrasound biomarkers can be sued to screen for major heart defects. Increased NT and TR are important indicators of the need for echocardiography, which is useful for early prenatal diagnosis of CHD.

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