



## Relationship Between Nuchal Fold Thickness and Fetal Heart Disease in Pregnant Women Referred to a Pediatric Hospital in Bandar Abbas During 2018-2019

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### Abstract

**Background:** Congenital heart disease (CHD) is of the most common congenital anomalies. Most of the major cardiac defects can be diagnosed by fetal echocardiography at 20 weeks of gestation. Evaluation of nuchal thickness can be the first stage of screening in the diagnosis of CHD. Therefore, this study aimed to investigate the relationship between nuchal translucency (NT) and CHD in pregnant women.

**Materials and Methods:** The current study is an analytical-descriptive study conducted on fetuses of 44 pregnant women. Abdominal sonography of the participants at 10-14 weeks of gestation was performed, and they referred to a pediatric hospital in Bandar Abbas in order to undergo fetal echocardiography at 17-18 weeks of gestation.

**Results:** The mean age of the participants was  $28 \pm 6$  years. Out of 44 pregnant women, fetal heart disease was diagnosed in 4 pregnancies (9%), one of whom was reported as  $2.5 \leq NT < 3.5$  and three cases were reported as  $3.5 \leq NT$ . Out of 40 women with no fetal heart disease, two cases had  $NT \geq 3.5$ , 12 cases had  $2.5 \leq NT < 3.5$  and 26 cases had  $NT > 2.5$ .

**Conclusion:** The results of this study showed that 6.8% of the cases of CHD had an increase in the thickness of NT ( $NT \geq 3.5$ ) at 10-14 weeks of gestation. The sensitivity of this screening method was 75% at 18-20 weeks of gestation which is low for general population. Therefore, NT cannot be regarded as the only or main screening tool for CHD.

**Keywords:** Echocardiography, Fetal heart disease, Nuchal translucency

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### Introduction

The researchers have investigated the relationship between the thickness of nuchal translucency (NT) and cardio-chromosomal abnormalities for nearly 20 years. Benseraf et al in 1987 observed the relationship between Down syndrome and an increase in the thickness of NT after 16 weeks of gestation on 5500 fetuses. In line with these studies, Nicolaides et al in 1992 explained the increased risk of chromosomal abnormalities in fetuses with higher NT during 10-14 weeks of gestation (1, 2). However, the NT is defined as the transient subcutaneous collection of clear fluid behind the fetal neck seen in ultrasound sonography at 10-14 weeks of gestation, and then the normal range of NT was also identified (1). Measuring NT at 11-14 weeks of gestation is of great importance in the first trimester (3). It was observed

in sonographies performed on mothers that NT value in 95th percentile increases along with the increase in gestational age from week 11 to 14, and it is 2.5 mm based on CRL. However, NT size of the 99th percentile is fixed (3.5 mm) (2, 4). The increase in NT is not only a sign of chromosomal abnormality but also is a non-specified sign indicating the presence of disruption in growth and development at early stages of fetal development. This issue was confirmed by showing the relationship between the increase in NT and congenital heart disease (CHD) in fetuses with normal karyotype (5-7).

CHS is the most common congenital anomaly, and approximately, 3-8 individuals are affected among every 1000 infants (1, 2, 4, 5, 7), 2-3 (8%) of these heart defects are too severe and are described as potential threats to life, needing surgical procedure within the first year of

life (8). In addition, the diagnosis of specific types of CHD before birth might decrease mortality in infants (9); therefore, the current screening standard of fetal heart diseases in most advanced countries is performing fetal echocardiography at 20 weeks of gestation (10, 11).

Considering the relationship between the increase in NT and the incidence of CHD in fetuses, the fetuses at risk of CHD can be identified, and this makes it possible to perform accurate echocardiography on these fetuses. It is confirmed that when NT is greater or equal to the 95th percentile, it is used as a cut-off point for echocardiography. It seems that one out of 33 referral of fetal echocardiography is related to major CHD. However, in case of using the cut-off point of 99th percentile, the ratio of 1:3 increases to 1:1 (6). In 2008, the International Society of Ultrasound in Obstetrics and Gynecology emphasized the importance of performing echocardiography for identifying the increase in NT (11-14 weeks of gestation) in case of NT >3.5 and performing second echocardiography during 20-22 weeks of gestation. When primary echocardiogram shows no sign of heart failure, the scan should be performed subsequently, since it is probable that negligible anomalies develop into major CHD at 11-14 weeks of pregnancy (12-14). When NT is between 2.5 and 3.5, echocardiography should be done at 18-20 weeks of gestation, and there is no need to perform echocardiography at the time of diagnosis of NT increase (15). In addition, the results showed that performing early fetal echocardiography (in the first trimester or the early second trimester) is accurate and with no risk (12, 14). When fetal echocardiography is performed immediately after measuring NT, CHD is diagnosed sooner, and the spouses have enough time to make informed decisions on continuing the pregnancy. If they want to terminate pregnancy, they would do this sooner and confidently due to the early diagnosis and face less physiological complications in the long term (14). If the pregnancy is continued, preparations can be done for scheduling, location (hospital equipped with neonatal intensive care unit, equipment related to cardiac diseases and facilities of neonatal cardiac surgery), the mode of delivery, and postnatal cares. Accordingly, the health status of these neonates can be improved after birth (8, 16). Therefore, due to the importance of this issue, this study aimed to investigate the relationship between NT and CHD in the fetus, which is performed to identify high-risk fetuses and make an early diagnosis to suggest legal abortion. It is hoped that this strategy increases the diagnosis rate of CHD before birth and reduces the mortality rate caused by it after birth.

### Materials and Methods

This was a prospective analytical-descriptive study approved by the Ethics Committee of Bandar Abbas University of Medical Sciences (IR.HUMS.REC.1397.290), which was conducted from March 2018 to March 2019 at

Echocardiography Center of Pediatric Hospital of Bandar Abbas. The convenience sampling method was used and a total of 44 samples were determined. After obtaining informed consent, 44 pregnant women at gestational age of 10-14 weeks who had sonography to determine the thickness of NT and referred to Bandar Abbas Hospital for fetal echocardiography enrolled in the study. The inclusion criteria were the lack of history of diseases in pregnant women and normality of the fetus based on chromosomes. Echocardiography was done by a pediatric cardiologist using the VIVID system. Then, the required data were gathered including age of pregnant mother, fetal echocardiography information on the presence or absence of cardiac disease, pre-reported NT thickness, and diagnosis of prenatal cardiac diseases using a researcher-designed checklist. SPSS software version 21.0 was used to analyze the data. To investigate the objectives and hypotheses of the study, descriptive statistics including mean and standard deviation were used, and to determine the relationships between NT thickness and fetal cardiac disease, chi-square test was used. The exclusion criteria were the lack of cooperation of some patients.

### Results

A total of 44 pregnant patients who underwent echocardiography to be investigated for fetal cardiac disease by evaluating NT thickness were included in the study.

The mean (and the standard deviation) of participants' age was  $28 \pm 6$  years and their age ranged from 18 to 44 years. Fetal cardiac disease was diagnosed in 4 pregnancies (9%).

Detailed information is presented in Table 1. There was a significant statistical difference between the mean age of pregnant women with a healthy fetus and pregnant women with a fetus affected by CHD ( $P < 0.001$ ).

The data on the relationship between the thickness of NT and fetal cardiac disease are reported in Table 2. There was a significant difference between NT of healthy fetuses and fetuses with CHD ( $P < 0.001$ ).

There were 4 cases of fetal cardiac disease in this study which included atrioventricular septal defects, VSD, right heart anomaly, left heart anomaly, and their results are reported in Table 3.

The sensitivity, specificity, positive and negative predictive value of NT thickness for each fetal cardiac diseases are presented in Table 4, showing that sensitivity and specificity for  $NT \geq 3.5$  are 75 and 5%, respectively.

### Discussion

This study aimed to investigate the relationship between fetal NT thicknesses and fetal cardiac disease in pregnant women referred to Pediatric Hospital in Bandar Abbas in 2018-2019. The mean age of participants was  $28 \pm 6$  years. Among 44 pregnant women, fetal cardiac disease was identified in 4 cases (9%), one of whom had  $2.5 \leq NT < 3.5$ . Out of 40 pregnant women without fetal cardiac disease, 2

**Table 1.** Frequency of Fetal Cardiac Disease in Pregnant Women

Fetal cardiac disease	Frequency	Percent	P Value
Yes	4	9	<0.001
No	40	91	

**Table 2.** Relationship Between NT Thickness and Fetal Cardiac Disease

		NT<2.5	2.5≤NT<3.5	NT≥3.5	Total
Fetal cardiac disease	No	26	12	2	40
	Yes	0	1	3	4
Total number		26	13	5	44

cases had NT≥3.5, 12 cases had 2.5≤NT<3.5, and 26 cases had NT>2.5.

The results of this study showed that the thickness of NT below the 95th percentile was observed in 26 pregnancies (59%), between the 95 and 99th percentile in 13 pregnancies (29%), and higher than the 99th percentile in 5 pregnancies (12%). However, in the study by Makrydimas et al (6), NT sizes were 35.5 and 23 for 95 and more than 99th percentiles, respectively, in patients with congenital disease. In addition, in a study by Hyett et al (5), the thickness of NT in 95th percentile was reported in 1822 pregnancies (6.3%) and NT values higher than the 99th percentile were reported in 315 pregnancies (1.1%).

In the current study, among 44 pregnant women who underwent fetal echocardiography, fetal cardiac diseases were diagnosed in 4 pregnancies and its prevalence was 90 in 1000 pregnancies. In the study by Hyett et al (5), among 29154 fetuses underwent only echocardiography, 50 cases of cardiac patients were diagnosed and the prevalence of fetal cardiac disease was reported as 1.7 in 1000 pregnancies. In addition, in a study by Mavrides et al (17), the fetal cardiac defect was observed only in 26 fetuses among 7339 fetuses and the prevalence of the fetal cardiac disease in this study was reported as 3.5 in 1000 pregnancies according to the results. In our study, the prevalence of fetal cardiac disease was higher than the total population. Based on the studies performed, the most important reasons for congenital defects are maternal diseases such as diabetes and medications used in treatment during pregnancy which can cause problems in the development of fetal heart. In general, congenital cardiac diseases are affected by environmental and genetic factors; however, the leading causes are not known, some of these defects occurred due to genetic and chromosomal changes (18, 19). In addition, 15% of CHDs are related to the genetic status of the individuals (20, 21). According to the risks caused by this disease and rate of prevalence in Bandar Abbas, screening pregnant mothers seems necessary for the identification of risk factors of cardiac diseases.

In this study, 44 pregnant women were studied. The results showed that out of 4 pregnancies (9%) in which

fetuses had cardiac disease, 3 pregnancies (75%) had an increase in NT thickness more than the 99th percentile and 1 case was between 95 and 99th percentiles. However, in a study by Hyett et al (5), out of 50 fetal cases with cardiac disease, 28 (56%) cases had an increase in NT thickness, out of whom, 0.08% were below the 95th percentile and 6.35% were higher than the 99th percentile. Considering the high percentage of diagnosis of fetal cardiac disease using NT in this study, the evaluation of NT in pregnant mothers can be presented as a screening way by neglecting the costs.

In this study, sensitivity for the thickness of NT higher than 95 and 99th percentiles were 25 and 75% and specificity for NT thickness higher than the 95 and 99th percentiles were 30 and 5%, respectively. In addition, positive predictive values for thickness of NT≥2.5 and NT ≥3.5 were respectively 7.6 and 60% and negative predictive values for NT thickness ≥2.5 and NT ≥3.5 were 92.3 and 40%, respectively.

However, in a study by Makrydimas et al (6), sensitivity and specificity for NT thickness greater than the 99th percentile were 31 and 98.7%. The values of sensitivity and specificity for thickness of NT for the 95th percentile were 37% and 96.6%. In a study by Mavrides et al (17), the sensitivity values for diagnosis of CHD for NT≥2.5 and NT≤3.5 were 15.4 and 3.5, respectively, and specificity values for diagnosis of CHD for NT≥2.5 and NT≥3.5 were 96.5 and 99.2%, respectively. Positive and negative predictive values for NT≥2.5 were 1.6 and 99.7% and for NT≥3.5 they were 5 and 99.7%.

In addition, in a study by Hyett et al (5), the normal range for positive and negative predictive values for NT≥2.5 were 1.5 and 99.9 and for NT thickness higher than the 99th percentile were respectively 1.5 and 99.9%. The sensitivity and specificity for NT≥2.5 were 56 and 93.8% and for NT≥3.5, they were 40 and 99%, respectively. These results showed that sensitivity was higher and

**Table 3.** The Diagnosis of Prenatal Cardiac Disease

Case	Age of Mother	NT Thickness	Cardiac Disease
1	33	4	Atrioventricular septal defects
2	20	1.4	Ventricular Septal Defect
3	24	3.3	Right heart anomaly
4	21	3.8	Left heart anomaly

**Table 4.** The Sensitivity and Specificity of Relationship Between NT Thickness and Fetal Cardiac Disease

NT Thickness	NT<2.5	2.5≤NT<3.5	NT≥3.5
Sensitivity (%)	0	25	75
Specificity (%)	65	30	5
Positive predictive value (%)	0	7.6	60
Negative predictive value (%)	100	92.3	40

specificity was lower compared to other studies. This study has several limitations including a small sample size in comparison to other studies, which can be due to the referral of participants by gynecologists. It might be possible that pregnant women with a sonography indicating an increase in NT thickness do not refer for echocardiography. Another limitation is that due to performing NT sonography by various urologists, NT is reported in different values, which can lead to distortion in decision making and final conclusion. Further studies with larger sample sizes should be selected, and in fetuses with NT greater than the 99th percentile, echocardiography should be performed earlier. In addition, it is recommended that when NT thickness is between 2.5 and 3.5 mm, fetal echocardiography should be repeated during the following weeks.

### Conclusion

Our findings showed that 6.8% of fetal cardiac anomalies are accompanied by an increase in NT (NT  $\geq$ 3.5) at 10-14 weeks of pregnancy. In addition, this screening method at 18-20 weeks of pregnancy has a sensitivity of 75%. Clinical outcome is that the increase in NT thickness is an alarm for more attention and early fetal echocardiography. However, since the sensitivity of NT for diagnosis of CHD in the general population is low, we found that NT cannot be regarded as the only or main screening tool for the diagnosis of fetal cardiac diseases.

### Conflict of Interest Disclosures

Authors declare no conflict of interests.

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### Ethical Statement

This project was approved by the Ethics Committee of Hormozgan University of Medical Sciences (IR.HUMS.REC.1397.290).

### Authors' Contribution

Both authors (SF and MR) performed all works related to this research such as design of the study, implementation of the research, data analyses and preparation of the manuscript.

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### Informed Consent

The nature of research and consent was explained to all pregnant women and informed consent was obtained.

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