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Value of Nuchal Translucency in Detection of Chromosomal Aberration in Vietnam Population

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ABSTRACT

Objective: To examine the sensitivity and specificity of different thresholds of nuchal translucency in diagnosis of chromosomal defects.

Study Design: This is a longitudinal study of pregnant women have first trimester screening and ultrasound in center of diagnostic antenatal of national hospital of obstetrics and gynecology. A follow-up was made to identify, in all singleton pregnancies in both group of which fetal karyotyping was made and group of normal fetuses. The threshold for nuchal translucency was divided in to above the 95th percentile, the 99th percentile, the 3.0mm and 2.5 MoM of nuchal translucency. The sensitivity and specificity ware calculated in order to diagnosis the chromosomal abbreviation.

Results: The research identified 2645 fetuses, 743 amniocentesis (28%). There is 32.4% fetus has NT ≥ the 95th percentile, 28.6% ≥ 2.5mm percentile, 22.3% ≥ 3.0mm, 16.6% above 2.5 MoM. The fetal karyotype was abnormal in 157 (5.8%) pregnancies. The popular conditions were found including trisomy 21(52.2%). Then structural rearrangements occupied 31.2%. Other chromosomes like 13,18,21 occupied 12.7%. The abnormal of sex chromosome was smallest proportion with only 3.8%. At the 95th percentile of nuchal translucency has the highest sensitivity in detection of chromosomal defects (99.4%) but the threshold 2.5mm has a better detection rate (20.4%). The cut off 3.0mm has a better positive prediction rate (22.3%) but could detect less defects (only 132/157 abbreviation). The threshold 2.5xMoM had the highest specificity (86.4%) but lowest sensitivity (only 65%).

Conclusion: In fetuses with increased nuchal translucency, more than a half of the chromosomally abnormal group is affected by defects other than trisomy 21 (52.2%). Using threshold 2.5mm helps detect more 23 chromosomal defects in comparison with the threshold 3.0mm and it had the highest average of sensitivity and specificity (87.25%).

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Keywords: Chromosomal Defects, Amniocentesis, Thresholds, Sensitivity, Specificity.

Introduction

Fetal nuchal translucency refers to the sonographic finding of a subcutaneous collection of fluid behind the fetal neck in the first trimester of pregnancy, and the term is used irrespective of whether the fluid is septate and whether it is confined to the neck or envelopes the whole fetus [1]. Nuchal translucency is considered to be increased if the vertical thickness, measured in the midsagittal section of the fetus, is equal to or above the 2.5mm in a screening study involving 2570 pregnancies [2].

Amniocentesis is considered as an invasive procedure for prenatal diagnosis that began hundreds of years ago, which was initially prescribed to drain fluid in the treatment of polyhydramnios. Until 1966, the successful establishment of the fetal chromosome map by amniotic fluid culture has been reported and structural rearrangement of fetal chromosome was diagnosed a year later [1]. In 1968, Valenti and colleagues diagnosed aneuploidy of trisomy 21 in 1968 via amniotic fluid culture [3]. Since then, the method of obtaining fetal specimens by amniocentesis in prenatal diagnosis has been globally applied [4-6].

Increased nuchal translucency is associated with trisomy 21 and other chromosomal abnormalities as well as many fetal malformations and genetic syndromes [7,8,9]. Several studies have established that, first, increased nuchal translucency, both on its own and in combination with other sonographic or maternal serum biochemical markers, is effective in first trimester screening for trisomy 21, and second, the incidence of trisomy 21 increases with fetal nuchal translucency thickness [7]. The aim of this study was to identify the prevalence of all chromosomal defects and examine their distribution in fetuses with increased nuchal translucency

thickness and the sensitivity and specificity of different thresholds in diagnosis chromosomal defects in Vietnam population [10].

Materials and Methods

This is a clinic-based study. Participants were recruited 19 satellite hospitals in the North of Vietnam for increased nuchal translucency; amniocentesis was performed at Center for Prenatal Diagnosis, National hospital of Obstetrics and Gynecology, Hanoi, Vietnam.

We collect data from January 2019 to December 2020: we collect patient comes to the Center for diagnostic antenatal of the National hospital of Obstetrics and Gynecology based on their medical records which were composed: echography for 1st trimester, all maternal information and the pregnancy was followed until birth, infantile information was collected by telephone. Archived in center for prenatal diagnosis, period from 2019 to 2020: data collected directly from patients in center for prenatal diagnosis.

All patients attending for the 11 weeks to 13 weeks 6 days scan, maternal characteristics and ultrasound findings, nuchal translucency thickness and CRL in millimeter, recorded in a computer database. We did an echography by expert to estimate all risk of the abnormality. Women have to follow the screening strategy of 1st trimester. In case of high risk for chromosomal abbreviation or increased fetal nuchal translucency, an amniocentesis would be offered to get the karyotype results. Karyotype results were added into the computer database right after its availableness. The decision of termination of pregnancy was made by council multi-disciplines in case of chromosomal defects or on demand of couples. For pregnancy with minor abbreviation or structural rearrangement we could provide a follow- up until birth. 6 months after birth, we made a call to all families to acquire the situation of the infant to reassure the stability, malformation post-natal or any trouble in neurodevelopment.

Variables, Data Analysis

Cytogenetic findings were analyzed and classified into following categories: (1) aneuploidy of autosomal chromosomes, (2) sex chromosome aneuploidy, (3) structural rearrangements. Patients were consulted about clinical consequences of these findings by both obstetricians and geneticists before giving final decision of pregnancies. After receiving amniotic fluid, standard G-banding technique was applied to analyzed the karyotypes. All data were collected, entered and analyzed using SPSS 20.0. Categorical statistics are summarized in frequency distribution tables.

The 50^{th}, 95^{th}, 99^{th} value were withdrawn from the same population in this center but another research, then the thresholds for the increased nuchal translucency were made [11]. Finally, the value of the sensitivity, specificity, and the average of sensitivity and specificity were calculated. We made also the comparison between those numbers to know which is the most valuable.

Ethical Approval

This study was approved by the Ethical Committee of National Hospital of Obstetrics and Gynecology with the number of IRB00003121. Participants were informed of the study purpose and were asked to give a written informed consent to confirm their participation. Participants could withdraw anytime and their information was kept confidentially.

Results

We recruited patients from center for antenatal diagnostic. After exclusion following the critics mentioned above, we have 2645 cases in final to analysis. Among them we found 157 abnormal karyotypes.

From the table 1 we saw that at the 95th value of NT thickness, the rate of chromosomal defects is 18.2% with 156 chromosomal defects but it raises 20.4% in 2.5mm and 22.3% in 3.0mm and reaches 23.2% at the value of 2.5xMoM. The average rate of chromosomal defects is 6% with 157 chromosomal defects involved in 2645 pregnancies.

Table 1: Chromosomal Defects Following Nuchal Translucency

Nuchal translucency thickness	Number of cases	Chromosomal defects
95^{th}	858 (32.4%)	156 (18.2%)
2.5mm	757 (28.6%)	155 (20.4%)
3.0mm	591 (22.3%)	132 (22.3%)
2.5xMoM	440 (16.6%)	102 (23.2%)
Total	2645 (100%)	157 (5.9%)

We can saw in the table 2, among 157 chromosomal abbreviations, we found 52.2% trisomy 21 became the highest abnormal. Then structural rearrangements occupied 31.2%. Other chromosomes like 13,18,21 occupied 12.7%. The abnormal of sex chromosome was smallest proportion with only 3.8%.

Table 2: Trisomy 21 and other Abnormalities Rate

Abnormalities	n	%
Trisomy 21	82	52.2
Sex chromosome	6	3.8
Other chromosomes	20	12.7
Structural arrangement	49	31.2
Total	157	100

In the table 3, the 95th percentile threshold had the highest sensitivity for diagnosing chromosomal abnormalities up to 99.4%, specificity is 71.8%. At the 2.5mm threshold, the sensitivity was 98.7% and the specificity was 75.8%, the Se-Sp average is 87.25% and becomes the highest value. The 3.0mm cutoff has a sensitivity of 84.1% and a specificity of 81.6%. The 2.5xMoM cutoff had

a sensitivity of 65% and a specificity of 86.4% so the Se-Sp average is 75.7%, the positive predict value is 23.2 and becomes the highest value.

Table 3: Se, Sp, PPV, NPV of Nuchal Translucency in Diagnosis Chromosomal Defects

NT (mm)	Se	Sp	PPV	NPV	Se-Sp average	OR (95%CI)
95th	99.4	71.8	18.2	99.9	85.6	396.889 (55.450- 2840.768)
2.5	98.7	75.8	20.5	99.9	87.25	242.799 (60.004- 982.465)
3.0	84.1	81.6	22.3	98.8	82.85	23.340 (15.042- 36.217)
2.5 x MoM	65.0	86.4	23.2	97.5	75.7	11.797 (8.335- 16.696)

In the table 4, the sensitivity of NT thickness in the abnormal diagnosis of Down syndrome is 100 for both thresholds of the 95th percentile and 2.5mm. The negative predictive value was 100 which is also higher than the rest of the diagnostic thresholds. The sensitivity of the 3.0mm threshold is a bit lower around 84.1 % and the NPV is 99.4%, the Se-Sp average is only 81.85 and is a bit lower than 86.85 of 2.5mm. The sensitivity value of the 2.5MoM threshold is only 65.9 %, the lowest among thresholds but the specificity value is 84.9 is highest, and the PPV is 12.3 and is the highest value also.

Table 4: Se, Sp, PPV, NPV Values in Diagnosis of Down Syndrome

NT (mm)	Se	Sp	PPV	NPV	Se,Sp average	OR (95%CI)
95th	100	69.7	9.6	100	84.85	
2.5	100	73.7	10.8	100	86.85	
3.0	84.1	79.6	11.7	99.4	81.85	20.753 (11.386- 37.827)
2.5 x MoM	65.9	84.9	12.3	98.7	75.4	10.877 (6.804- 17.387)

In table 5 you can see the sensitivities of NT thickness in the diagnosis of sex chromosomal abnormalities were 100 for both the 95th percentile and 2.5mm made the highest values. The negative predictive values were 100 and were higher than the other thresholds. The sensitivity of 3.0mm was 83.3 only and the same with the 2.5MoM threshold which were the lowest value among those thresholds of NT thickness. The Se-Sp average was 85.75 in the threshold of 2.5mm.

Table 5: Se, Sp, PPV, NPV Values of NT Thickness in Diagnosis of Sex Chromosomal Defects

NT (mm)	Se	Sp	PPV	NPV	Se,Sp average	OR (95%CI)
95th	100	67.7	0.7	100	83.85	
2.5	100	71.5	0.8	100	85.75	
3.0	83.3	77.8	0.8	100	80.55	17.517 (2.043- 150.230)
2.5 x MoM	83.3	83.5	1.1	100	83.4	25.333 (2.952- 217.373)

In table 6 you can see the sensitivity of NT thickness in the diagnosis of other chromosomal abnormalities were 100 for the 95th percentile and 2.5mm, corresponding to negative predictive values were in equivalence to 100 which are also higher than the other thresholds. The specificity value is 71.9% in 2.5mm and is a bit higher than 58.1% of the 95th percentile. The sensitivity value of the 2.5MoM threshold was 80, lowest of among thresholds of NT thickness. The Se-Sp average is highest in the threshold of 2.5mm and was 85.95%.

Table 6: Se, Sp, PPV, NPV value of NT Thickness in Diagnosis of Other Chromosomal Aneuploidies

NT (mm)	Se	Sp	PPV	NPV	Se,Sp average	OR (95%CI)
95th	100	68.1	2.3	100	84.05	
2.5	100	71.9	2.6	100	85.95	
3.0	85.0	78.1	2.9	99.9	81.55	20.248 (5.913- 69.333)
2.5 x MoM	80.0	83.8	3.6	99.8	81.9	20.764 (6.908- 62.415)

In table 7 there's clear that the sensitivity of NT thickness in diagnosis of other chromosomal structural abnormalities was 98 and 95.9 for the 95th percentile and 2.5mm thresholds, respectively. The specificity of 2.5mm was 72.7% and was higher than the 95th percentile which was only 68.6 and was lower than the cutoff 3.0mm but the Se-Sp average value was 84.3 which was higher than the other thresholds. The specificity of the 2.5MoM threshold was 84.1 highest among those thresholds but the sensitivity was only 55.1 which formed the lowest Se-Sp average which was only 69.6%.

Table 7: Se, Sp, PPV, NPV Value of NT Thickness in Diagnosis of Structural Rearrangements of Chromosome

NT (mm)	Se	Sp	PPV	NPV	Se,Sp average	OR (95%CI)
95th	98	68.8	5.6	99.9	83.4	105.837 (14.583-768.096)
2.5	95.9	72.7	6.2	99.9	84.3	62.424 (15.123- 257.665)
3.0	83.7	78.8	6.9	99.6	81.25	19.065 (8.886- 40.904)
2.5 x MoM	55.1	84.1	6.1	99	69.6	6.487 (3.659- 11.501)

Comment

In Vietnam we have already used nuchal translucency as one method of first trimester screening for 20 years. In previous study, we used mostly the cutoff point for nuchal translucency is fixed cutoff of 3.0mm to identify the threshold for increased nuchal translucency. In 2006, Min-Hyoung Kim concluded that the threshold of 95th should be used in Korean population [12]. In 2010, Bestwick used the threshold of 2.5MoM to screen nuchal translucency in his study [13]. In 2018, first study which had used the threshold of 2.5mm was made in Vietnam In this research we try to describe the prevalence of chromosomal abbreviation and to verify the of sensitivity, specificity values of different thresholds to identify which is most valuable threshold to give a suggestion to hospitals in order to change the threshold with nuchal translucency thickness in order to screen more efficiently in first trimester [14].

To be able to compare the current data with the literature cohort tested with karyotyping, we took only microscopically visible aberrations into account. Strong association between chromosomal aberrations and fetal NT >3 mm was already suggested by. When karyotypically visible aberrations are taken into account, our pooled cohort showed 11% of abnormal cases, whereas the clinical data of showed chromosomal aberrations in 7.1% of fetuses (p95 -> 3.4 mm, 507/7109), in 9.6% (p95 -> 3.4 mm, 65/679), in 13% (NT = 3 mm 7/52) and in 14% (p95-p99, 124/894) [15-18].

This study is the first study to compare the sensitivities of nuchal translucency alone as a screening test for chromosomal aberration with different cut-offs in a Vietnam population. When using the 2.5mm cut-off of NT, we identified that the sensitivity was higher than that of 3.0mm for detecting chromosomal aberrations and detected more defects. So, we can suggest that this cut-off 2.5mm should be used for the nuchal translucency measurement screening method in Vietnam population.

Principal Findings

The threshold 2.5mm for increased fetal nuchal translucency had sensitivity- specificity average of 87.25 % and OR = 242.799(95%CI: 60.004-982.465) in diagnosis of chromosomal defects. It had sensitivity- specificity average of 86.85 % in diagnosis of Down syndrome. It had sensitivity- specificity average of 87.75 % in diagnosis of sex chromosomal defects. It had sensitivity- specificity average of 85.95% in diagnosis of other chromosomal aneuploidies. It had sensitivity- specificity average of 84.3% with OR= 62.424 (95% CI: 15.583-768.096) in diagnosis of structural rearrangement of chromosomes.

Results

The research identified 2645 fetuses, 743 amniocentesis (28%). There is 32.4% fetus has NT ≥ the 95th percentile, 28.6% ≥ 2.5mm percentile, 22.3% ≥ 3.0mm, 16.6% above 2.5 MoM. The fetal karyotype was abnormal in 157 (5.8%) pregnancies. The popular conditions were found including trisomy 21(52.2%). Then structural rearrangements occupied 31.2%. Other chromosomes like 13,18,21 occupied 12.7%. The abnormal of sex chromosome was smallest proportion with only 3.8%. At the 95th percentile of nuchal translucency has the highest sensitivity in detection of chromosomal defects (99.4%) but the threshold 2.5mm has a better detection rate (20.4%). The cut off 3.0mm has a better positive prediction rate (22.3%) but could detect less defects (only 132/157 abbreviation). The threshold 2.5xMoM had the highest specificity (86.4%) but lowest sensitivity (only 65%).

Clinical Implications

We all noticed about higher sensitivity- specificity average of 2.5mm threshold for nuchal translucency in diagnosis of chromosomal defects, Down syndrome, sex chromosomal defects, others aneuploidy and structural rearrangement.

Research Implications

In our country, NIPTs are not available in all hospitals and patients are confused of decision between invasive test and free cell DNA test when they have increased nuchal translucency. A combined between NT and NIPTs should be carry out in the future to estimate the potential of that combination in order to have a better screening strategy for high-risk pregnancy women.

Strengths and Limitations

We have large number of amniocenteses for increased fetal nuchal translucency. This study could bring us the comparison of different thresholds which led us know which is better in first trimester screening for chromosomal defects, Down syndrome, sex chromosomal defects, others aneuploidy and structural rearrangement in Vietnam. We need to do a longer study to reassure the situation of the infants were born with structural rearrangement and normal karyotype.

Conclusion

All achievements withdrawn from these data can bring us to the conclusion that in routine clinical activities, increased nuchal translucency should be considered from 2.5mm in fetus among 11 weeks and 13 weeks 6 days.

- ✓ Use of statistic: analysis by SPSS 20.0
- ✓ Acknowledgment: Special thanks to Prof Cuong Danh TRAN, director of national hospital of obstetrics and gynecology for ideas and supports to this study.

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