Original article

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PREDICTIVE VALUE OF FETAL NUCHAL TRANSLUCENCY IN SCREENING OF CHROMOSOMAL ABERRATIONS

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In search for specific early ultrasound signs that could indicate an increased risk of hereditary or acquired disorders of the fetus, scientific researches confirm the value of exceptional ultrasound findings of nuchal translucencey (NT).

The aim of the study was to determine the predictive value of the diameter of fetal NT in the detection of chromosomopathy.

The investigation included 317 pregnant women with monofetal pregnancies, gestational age 11-14 weeks. The control group consisted of pregnant women in whom, after amniocentesis, a regular result of fetal karyotype was obtained. The limits of physiological and pathological findings of the NT value were not determined; instead, we used the diameters of NT that were obtained in pregnant women with pathological score of amniocentesis as potentially pathological values.

Mean value of NT in the control group was 1.92±0.39mm, and in the group with pathological findings of fetal karyotype it was 2.49±0.37mm, which is a statistically significant difference ($p<0.05$). Mean value of the rump-crown length in the control group was 64.83±8.23mm, and the group with pathological karyotype 60.12±8.48mm; gestational age in the control group was 7.10±87.40 days, and in the pathological one 85.69±3.98 days, which speaks of homogeneity of the investigated sample ($p>0.05$).The probability that a patient with negative NT findings be healthy is 0.97. NT sensitivity as a marker for chromosomopathy was 0.97. The rate of false positive findings was 0.027. Specificity of NT as a marker for chromosomopathy was 0.97. The probability that a patient with positive findings NT really be ill was 0.66.

Valid findings of NT can be considered safe ultrasonographic markers in the assessment of absence of chromosomopathy. Pathological finding, given the low positive predictive value of NT, must be amended by other prenatal tests before a pregnant woman is advised on prenatal invasive diagnostics. *Acta Medica Medianae 2011; 50(1):11-16.*

Key words: *nuchal translucency, ultrasonography, chromosomopathy, predictive statistics*

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Introduction

As part of antenatal care - monitoring growth and development of the unborn child, in most European countries three standard ultrasound examinations are recommended: between 9th and 12th week, then 19th and 22nd as well as 29th week and 32nd week (1). In any irregularity or the occurrence of complications in pregnancy, ultrasound examination provides additional security for pregnant woman as well as for a gynecologist who monitors the pregnancy. During searching for early specific ultrasound signs - markers that might indicate an increased risk of hereditary or acquired disorders - fetal chromosomopathy, scientific researches confirm the exceptional value of ultrasound finding of the nuchal translucency (nuchal translucency, NT) (2). Nuchal translucency indicates ultrasound finding of the fluid accumulation (lymph) between the skin and subcutaneous fascia in the neck area or neck and back of the embryo, which is detected by ultrasound examination between 11th and 14th week of pregnancy that is when the crown-rump length (CRL) is between 45-84 mm (3). Nuchal skin fold thickness that is usually tolerated is less than 99th percentile for CRL. Numerous studies show a connection of this ultrasound marker finding (nuchal translucency ≥ 3mm) with the specified chromosomal aberrations, especially with aneuploidy and Down syndrome.

The connection of this finding with Down syndrome is important to the extent that most authors, who study this phenomenon, classify ultrasound finding of nuchal fold in the screening procedures for Down syndrome. In the largest of all studies (King's group) in more than 96.000 pregnancies (22 perinatal centers, 306 gynecologists), this ultrasound finding was detected in 82% of fetuses with Down syndrome (incidence of false positives: 8.3%). Besides the association to chromosomal aberrations, the result from nuchal fold is also a marker for other genetic syndromes, in which process it is most frequently about cardiac anomalies. Fetal NT increases with CRL and therefore it is very important to take gestation age into account when determining whether the measured NT is increased or not (4). In a study involving 96.127 pregnancies, the mean value and 95th percentile of NT at a CRL of 45 mm were 1.2 and 2.1 mm, and with the CRL of 84 mm, 1.9 and 2.7 mm (5). With pregnancies with fetal NT below the 99th percentile (3.5 mm), the parents decision of whether the fetal karyotype is to be determined will depend on individual risk, which is derived from a combination of maternal age, ultrasound findings and free β-hCG and PAPP-A in maternal serum at 11-13 +6 weeks (6).

Study aim

The aim was to determine the predictive value of the diameter of fetal nuchal translucency in detecting chromosomopathy.

Respondents and study methods

The study was carried out at the Gynecology and Obstetrics Clinic (GOC), in the Clinical Center Kragujevac on singleton intrauterine pregnancies in the first trimester of pregnancy during the period 2007-2009. During the research, we used a clinical-experimental study model. To every pregnant woman, who was planned for inclusion into the study, we explained in detail the plan and purpose of examination, and all respondents included in the study gave their voluntary written consent for testing after reading the information. The study included 317 pregnant women with monofetal pregnancies that were observed by the Genetic Counseling Commission of GOC CC Kragujevac.

Requirements for inclusion of pregnant woman in the study were related to following pregnancy parameters:

1. Distance CRL (crown-rump length) has to be from 45 to 84 mm.

2. Gestational age of pregnancy must be of 11-13 +6 weeks.

During the measurement of fetal NT, we used high-resolution ultrasound machine Aloka Pro Sound 3500 with the option "cine loop" for restoring the image, with calipers that provide measurement of one decimal. The screen image on which the NT is measured enclosed only the head and the upper part of the thorax. Magnification was at maximum, so that each slight caliper movement changes the measure by only 0.1 mm. Nuchal translucency was measured with the fetus in the neutral position. We measured a maximum thickness of the subcutaneous illumination between the skin and soft tissue in the cervical part of the spine. Calipers were placed on the lines that define the fold, so they were hardly visible on the white border line of the fold behind the neck. During the examination, we made a couple of measurements, and took into account the greatest thickness. In case the umbilical cord was around the fetal neck (in about 8% of cases) we measured NT thickness above and below the cord and used the average value of the two measures. All pregnant women underwent early amniocentesis, after which fetal karyotype was determined. For statistical processing, parametric and nonparametric tests were used for the significance of difference - t test, $\chi 2$ test, Fisher's exact test and contingency tables in order to calculate the parameters of predictive statistics.

Study results

This chapter presents the results of the study.

Table 2. Outline of mean values and standard deviations of the ultrasonographic parameters in the total sample

Parameters	Pathological karyotype =16	Control group =311	P
Nuchal translucency (mm)	2.49±0.37	1.92±0.39	<0.05
Crown-rump length (mm)	60.12±8.48	64.83±8.23	p>0,05
Gestational age (days)	85.69±3.98	87.40±7.10	p>0.05

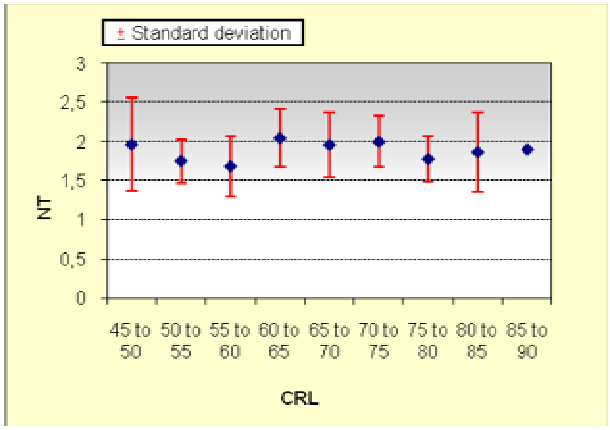
The nuchal translucency diameter was significantly different in statistics of pregnant women groups ($p < 0.05$). Crown-rump length and gestational age were not significantly different ($p > 0.05$).

After performed amniocentesis we divided the obtained karyotype results into two groups as follows: pregnant women with numerical aberrations (SP) and those with structural disorders on the chromosome level (LP).

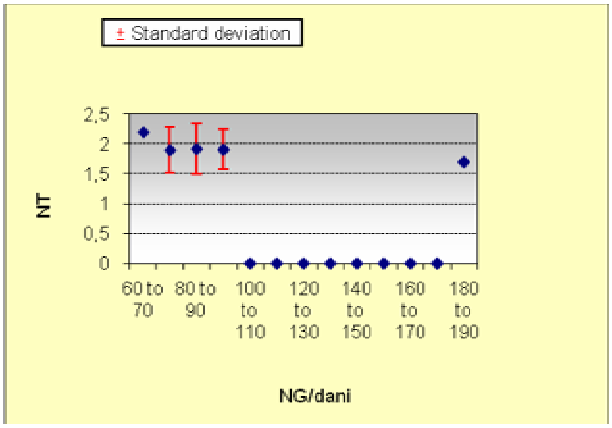
By using contingency tables we have been determining the predictive value of nuchal translucency (NT) as a possible marker of invasive prenatal screening of pregnant women in gestational age from 11 to 13 +6 weeks.

Table 1. Ultrasonographic markers outline in pregnant women group with pathological karyotype result after early amniocentesis

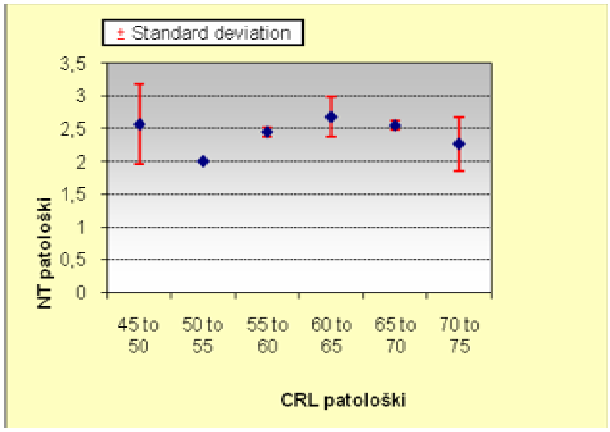
Register protocol number -year	Nuchal translucency in mm (NT)	Crown-rump length in mm (CRL)	Gestacional age in days (GA)	Karyotype result after early amniocentesis
3-2007	2.2	60	86	46,xy/47xyy
11-2007	3.0	62	88	46,xx/46,xx; del 7t(7;17)
47-2007	2.5	65	88	47,xy +21
151-2007	2.6	63	86	47xy+21
74-2008	1.8	73	90	47, xy+18
76-2008	2.4	72	89	Robertsonian translocation 45, xy,-14, -21 +t (14q;21q)
158-2008	2.5	56	82	47, xx+21
99-2008	2.6	65	87	Robertsonian translocation 45,xx,-14,-21+t (14q21q)
161-2008	2.7	48	81	47, xx+21
164-2008	2.0	50	81	46,xy/46, y del(x)t(7;x)q35;q22)
162-2008	1.9	48	78	46,xy/46,xy (-4q3)
167-2008	3.1	48	80	47,xy+21
231-2009	2.8	61	89	47,xx+21
267-2009	2.6	71	91	47,xx+21
237-2009	2.4	56	87	46,xx/47,xx t (9;6)(q31;q14)
271-2009	2.8	64	88	46, xy/47,xy+13



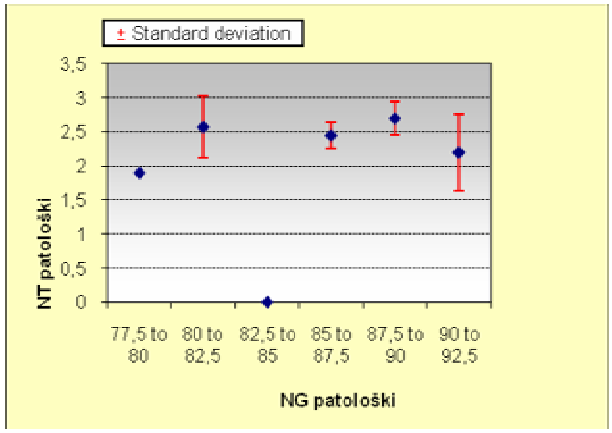
Graph 1. Value distribution of nuchal translucency (NT) in relation to the distance between crown-rump lengths (CRL) in the total sample



Graph 2. Value distribution of nuchal translucency (NT) in relation to gestational age of pregnancy (NG / days) in the total sample



Graph 3. Value distribution of nuchal translucency (NT pathological) with pathological karyotypes in relation to crown-rump length (CRL pathological)



Graph 4. Value distribution of nuchal translucency (NT pathological) in pathological karyotypes in relation to gestational age of pregnancy (NG pathological)

Table 3. Contingency table

Test result	Disease present	Disease absent	Total
Positive	SP -16	LP- 8	SP+LP -24
Negative	LN -8	SN-285	LN+SN- 293
Total	SP+LN- 24	LP+SN-293	N- 317

Legend:
SP-really positive;
LP-false positive;
LN-false negative;
SN- really negative
Positive predictive value SP/SP+LP = 0.66
Negative predictive value SN/SN+LN=0.97

Positive predictive value shows the number of people with positive test result that have the disease.

Negative predictive value shows the number of people with negative test result that do not have the disease.

The likelihood that a patient with positive NT result will really be sick, that is to have a numerical aberration is 0.66.

The likelihood that a patient with negative result of nuchal translucency (NT) will be healthy is 0.97.

We determined the sensitivity of measurement of nuchal translucency (NT) as a marker for chromosomopathy according to the formula: SPP SP / SP + LN = 0.66.

False-positive rate was determined by the following formula: SLP=LP/LP+SN=0.027

We were determining the specificity of measurement of nuchal translucency (NT) as a marker for chromosomopathy according to the formula:

SSN=SN/SN+LP=0.97.

Discussion

Implementation of NT screening in routine clinical practice was a theme of several prospective intervention studies (7). In some studies, the positive screening group was defined by the limit value of fetal NT or by combined risk derived from maternal age and NT deviation from the normal median for CRL. The important results of these studies were: (1) NT was successfully measured in more than 99% of cases, (2) there was the inevitable variation in false positive rates and detection rates between different studies, because of differences in age of examined women, the distribution of the examined population and used limit value of NT or risk and (3) in the combined data of more than 200.000 pregnancies, including more than 900 fetuses with trisomy 21; screening by NT identified more than 75% of fetuses with trisomy 21 and other major chromosomopathies with a false positive rate of 5%, and the detection rate was 60% for a false positive ratio of 1% (7). In the largest study, coordinated by the Fetal Medicine Foundation, 306 appropriately trained operators examined 100.311 singleton pregnancies at 22 centers in the United Kingdom (8). In all cases, CRL and NT were measured and the individual risks were calculated, based on maternal age, gestational age and fetal NT. Pregnancy outcomes were obtained in 96.127 cases, including 326 with trisomy 21 and 325 with other chromosomopathies. The mean gestation at the time of screening was 12 weeks and the mean maternal age was 31 years. The estimated risk for trisomy 21 was above 1 in 300 or more in 8% of normal pregnancies, in 82% of trisomy 21 pregnancies and 78% with other chromosomopathies. For positive screening rate of 5%, the detection rate was 77% (95% confidence interval 72-82%). The issue of fetal mortality has advantages over screening in the second trimester - earlier prenatal diagnosis and thus less traumatic termination of pregnancy for those couples who decide for this option. Potential lack of early screening is that it identifies those pregnancies with chromosomopathies that will be miscarried spontaneously. About 30% of all fetuses with trisomy 21 die between 12 weeks of gestation and delivery term. The issue of spontaneous intrauterine death with fetuses with chromosomopathies is, of course, a potential criticism of all antenatal screening methods, including biochemical screening in the second trimester because fetal mortality is about 20% between 16 weeks and delivery term. From prenatal screening studies it is not possible to find out how many pregnancies with fetuses with trisomy 21 that were terminated would actually result in liveborn children; however, it is still possible to assess the impact of prenatal screening on the prevalence of trisomy 21 with liveborn children. This can be done by comparing the number of liveborn children with trisomy 21 to the number estimated on the basis of prevalence of trisomy 21 of liveborn children according to the maternal age and maternal age distribution of the examined population. In the screening study of the Fetal Medicine Foundation, by combination of maternal age and fetal NT, the risk limit value of 1 in 300 had a false positive rate of 8% and a detection rate of 82% (8). It was estimated that prenatal screening would, after invasive diagnostics and selective termination of fetuses with trisomy 21, decrease the prevalence of potential liveborn children with trisomy 21 by 78-82%. The ability to obtain reliable measurement of NT thickness is dependent on adequate training, use of standard techniques and motivation of operators. The importance of all three components can be seen on the example of difference in results between intervention and observation studies, during which the operators measured the NT thickness, but did not act in case of increased thickness (7). In intervention studies, in over 99% of the cases, the NT measurement was successful, unlike observation studies, where NT was successfully measured in only 75% of cases. In addition, in

intervention studies, NT thickness was increased in 76% of trisomy 21 and 4.2% of chromosomally normal fetuses, compared with 38% and 5.0% cases in the observation studies. In observation studies, the ultrasound examinations were often performed in inadequate gestation, and operators were either not properly trained or they were not sufficiently motivated to measure NT. In one of the studies, for example, where the operators were told not to spend more time measuring NT that they need to measure CRL, NT thickness was successfully measured in only 66% (9). In another study, the CRL was less than 33 mm in 54% of cases and operators were told to measure the NT within three minutes; they could not do it in 42% of cases (10). These methodological problems are highlighted in a study performed in 47.053 singleton pregnancies examined between 6 and 16 weeks (11). In 23% of the pregnant women, it was not possible to obtain a valid NT measurement because it was performed in an inadequate gestation, the operators were unable to obtain appropriate measures or none of the images were of acceptable quality. An example of the difference between observation and intervention study is represented by the study carried out by Crossley et al (12). In this observation study, 17.229 cases were examined and fetal NT was successfully measured in 73% of cases. In the next study, for more than 2.000 pregnancies in which the examination results were given to women, fetal NT was successfully measured in 99.8% of cases. The results of our research show that in the total sample, 5.04% are pathological karyotypes, 50% of which are with numerical aberrations, which is consistent with the mentioned results from the available literature. Positive predictive value shows the number of people with positive finding that have the disease, in our sample 0.66. The negative predictive value shows the number of people with negative test finding that do not have the disease, 0.97 in our sample.

False-positive rate was determined by the following formula SLP=LP/LP+SN and amounts to 0.027.

Predictive value of NT as an ultrasonographic marker for chromosomopathies if used in isolated manner is questionable, which is also confirmed in the literature. Result of the significant difference of NT thickness in the group of pregnant women with pathological karyotype was expected ($p<0.05$), which is confirmed by numerous studies in this field. Crown-rump length and gestational age are not statistically different ($p>0.05$) in examined groups, which indicate the homogeneity of the sample that we examined. Sensitivity of screening for chromosomal aberrations by measuring the NT is 66% and specificity is 97%. Lower sensitivity of chromosomal aberrations screening by measuring the NT in the general population indicates that NT can not be the only screening tool. From the point of establishing the absence of chromosomal aberrations, it can be said that such screening by measuring NT turned out to be highly specific and is 97%.

Conclusion

The likelihood of chromosomal aberrations screening by measuring the NT is 66% and specificity is 97%. Very high negative predictive value of 97% gives the practical meaning that the test can be rather considered as "true negative" than "false positive". The likelihood that a patient with a positive finding of nuchal translucency will really be sick, that is to have a numerical aberration is 0.66. The likelihood that a patient with negative finding of nuchal translucency will be healthy is 0.97. The false positives rate is 0.026. The specificity of nuchal translucency measurement as a marker for chromosomopathies is 0.97. Very high negative predictive value of 97% gives a practical meaning that the test can be considered true negative rather than a "false positive".

Normal finding of nuchal translucency can be considered as a useful ultrasonographic marker in assessing the absence of chromosomopathies. Pathological finding of nuchal translucency diameter should be supplemented with other prenatal tests before we give a pregnant woman an advice to undergo invasive prenatal diagnosis.

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PREDIKATIVNA VREDNOST FETALNE NUHALNE TRANSLUCENCE U SKRININGU HROMOZOMSKIH ABERACIJA

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U traganju za specifičnim ranim ultrazvučnim znacima koji bi mogli ukazivati na povećani rizik od naslednih ili stečenih poremećaja fetusa, naučna istraživanja potvrđuju izuzetnu vrednost ultrazvučnog nalaza nuhalne translucence (NT).

Cilj rada bio je da se utvrdi prediktivna vrednost promera fetalne NT u otkrivanju hromozomopatija.

U ispitivanje je uključeno 317 trudnica sa monofetalnim trudnoćama gestacijske starosti 11-14 nedelja. Kontrolnu grupu činile su trudnice kod kojih je nakon amniocenteze konstatovan uredan rezultat kariotipa ploda. Nismo određivali granicu fiziološkog, odnosno patološkog nalaza vrednosti NT, već smo koristili promere NT koje smo dobili kod trudnica sa patološkim rezultatom amniocenteze kao potencijalno patološke vrednosti.

Srednja vrednost NT u kontrolnoj grupi iznosila je 1.92±0.39mm, a u grupi sa patološkim nalazom kariotipa ploda iznosila je 2.49±0.37mm, što je statistički značajna razlika ($p<0.05$). Srednja vrednost rastojanja teme trtica u kontrolnoj grupi bila je 64.83±8.23mm, a u grupi sa patološkim kariotipom 60.12±8.48mm, gestacijska starost u kontrolnoj gupi bila je 87.40±7.10 dana, a u patološkoj 85.69±3.98 dana, što govori o homogenosti ispitivanog uzorka ($p>0.05$). Verovatnoća da će bolesnik sa negativnim nalazom NT biti zdrav je 0.97. Senzitivnost NT kao markera za hromozomopatije iznosila je 0.66. Stopa lažno pozitivnih nalaza je 0.027. Specifičnost NT kao markera za hromozomopatije je 0.97. Verovatnoća da će bolesnik sa pozitivnim nalazom NT stvarno biti bolestan je 0.66.

Uredan nalaz NT može se smatrati pouzdanim ultrasonografskim markerom u proceni odsustva hromozomopatija. Patološki nalaz, s obzirom na nisku pozitivnu prediktivnu vrednost NT mora biti dopunjen i drugim prenatalnim testovima pre nego što trudnici damo savet o invazivnoj prenatalnoj dijagnostici. *Acta Medica Medianae 2011;50(1):11-16.*

***Ključne reči**: nuhalna translucenca, ultrasonografija, hromozomopatije, prediktivna statistika*