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CLINICAL ARTICLE

Nuchal translucency as a predictor of adverse pregnancy outcome

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Abstract

Background: Thickened nuchal translucency (NT) has been related to fetal genetic syndromes, structural abnormalities, and other diseases. The aim of this research was to evaluate the association of NT with adverse pregnancy outcomes. *Study design:* In the period 2002–2004 in 2104 pregnant women between 10+6 and 13+5 weeks' gestation, NT was evaluated as a parameter for aneuploidy screening: out of these, 734 singleton pregnant women that underwent 2nd trimester amniocentesis and whose pregnancy outcome were known were selected. NT was statistically correlated to pregnancy and neonatal outcome. *Results:* Median gestational age (GA) at NT evaluation was 11+2 weeks' gestation. NT median was 1.1 mm (0.9–1.4 mm, 25th–75th centile, range 0.5–4.0 mm). After multiple logistic regressions, the variables significantly associated to NT values were: threatened preterm labor ($p<0.008$) and preterm labor ($p<0.02$). The best diagnostic accuracy point was NT>95th centile and >1.5 MoM for the prediction of threatened preterm labor. *Conclusion:* In this series, increased NT values were associated to threatened preterm labor and preterm labor in euploid fetuses: this finding may have clinical consequences in the management of such pregnancies.

1. Introduction

Increased fetal nuchal translucency (NT) thickness between 11 and 14 weeks' gestation is a common phenotypic expression of chromosomal abnormalities, including trisomy 21 [1–3].

Plasma levels of the pregnancy-associated plasma protein A (PAPP-A) in association with free human chorionic gonadotropin-beta (β-HCG) and with NT in the first trimester is commonly used as screening for the Down syndrome with a 90% of sensitivity and a 5% of false positive rate [4–8].

The aim of this study was to examine the potential association between NT thickness and adverse pregnancy

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outcome in fetuses with a normal karyotype and without apparent structural malformations.

2. Patients and methods

From the three parameters considered (PAPP-A, βhCG and NT), NT values were considered for the statistical analysis in a prospective fashion.

In a two years period (June 2002–June 2004), from a database of 2104 pregnant women between 10+6 and 13+5 weeks' gestation (weeks+days), multiple pregnancies, congenital malformations, structural abnormalities, smoke or drug users, insulin-dependent diabetes mellitus, chronic hypertension and pregnant women lost to follow-up and/or not delivering in our Institution were excluded. At the end, 734 singleton pregnant women with euploid fetuses as confirmed by amniocentesis were considered for analysis.

Briefly, the integrated test included assessment of NT within three hours from blood sampling for biochemical evaluation of PAPP-A. Nuchal translucency was evaluated with the fetus picture on at least 3/4 of the full Ultrasound (US) screen, in a mid-sagittal plane and in absence of fetal gross movements. Once reached the optimal scan, US pointer was placed in an *on-to-on* approach over the satisfactory NT segment to be measured, as described elsewhere [9,10]. Three measurements were performed, and the highest value was considered. The Aloka SSD-2000 equipment was used, with a convex 3.5 MHz probe. Ultrasound scans were performed by two physicians (*JP* and *AC*). The intra–inter observer differences means for values were 3.7% and 5.6%, respectively. Nuchal translucency data for statistical analysis was coded as follows: NT value in mm (crude data), NT multiple of median (MoM) and binary codes (for NT MoM ≥ 1, ≥ 1.5 and ≥ 2). Data were elaborated by LifeCycle Software (vers 2.2.4 PerkinElmer Life Sciences, Wallac Oy).

For each pregnant woman, data were fed in an electronic spreadsheet; the nominal variables (pregnancy complications and neonatal events) were encoded in a binary mode (presence=1, absence=0) and the gestational ages were corrected by fractions of week.

Table 1 Pregnancy outcomes of the study group* ($n=734$)

Complication	*n*	%	Complication	*n*	%
Threatened PRET	134	18.2	Intrahepatic cholestasis	26	3.5
Threatened spontaneous abortion	127	17.3	Placental abruption	20	2.7
PRET	84	11.4	Placenta previa	8	1.0
PROM	78	10.6	Fetal loss ≤24 weeks	8	1.0
PIH	73	9.9	Cytomegalovirus infection	6	0.8
Oligo-anhydramnios	39	5.3	Coagulation anomalies	4	0.5
IUGR	37	5.1	Spontaneous fetal loss >24 weeks	4	0.5
Not reassuring FHR trace	36	4.9	Uneventful pregnancies	391	53.2

*One pregnant woman could present more than one complication.
PRET: preterm labor, PROM: preterm rupture of membranes, PIH: pregnancy induced hypertension, IUGR: intrauterine growth retardation.

Table 2 NT MoM values significantly associated to pregnancy adverse outcomes

	Adjusted odds ratio	Wald statistics	5%*	95%*	*p*
Spontaneous abortion in previous pregnancies	2.20	4.53	1.06	4.57	0.03
Threatened PRET	1.94	7.02	1.18	3.17	0.008
PRET	2.41	5.24	1.08	6.82	0.02

*Confidence interval upper and lower ranges.
Odds ratio values represent the fact that an increased NT MoM may represent a risk for threatened PRET and PRET (preterm labor) in pregnancy, and are related to the presence of spontaneous abortions in precedent pregnancies.

Besides considering the mode of delivery, the following outcome measures in ongoing pregnancies were recorded: uneventful pregnancy (pregnancy not complicated), spontaneous loss ≤24 weeks' gestation, spontaneous loss >24 weeks' gestation, preterm labor (PRET, onset of labor at <37 weeks' gestation), threatened PRET, intrauterine growth retardation (IUGR, estimated fetal weight <10th centile concerning fetal growth curves), intrauterine death, hypertension in pregnancy (maternal blood pressure >140/90 mm Hg in two occasions 6 h apart after the 20th weeks' gestation), thyroid disease, coagulation changes, preterm rupture of membrane (PROM, rupture of membranes before the onset of labor <37 weeks' gestation), placenta previa, placental abruption, intrahepatic cholestasis, oligo-anhydramnios [11], non reassuring FHR patterns (bradytachycardia, repeated late/variable decelerations).

Data collected was managed under the supervision of an adviser statistician. All patients signed an informed consent for the study, previously approved by the Bioethical Council of this Department. Neonatal data and Apgar scores were evaluated by the neonatologist staff present in the delivery room, unaware of the study in progress.

3. Statistical analysis

For statistic analysis, the Sigma Stat 3.1 (Jandel Scientific, Ekrath, Germany) and the MedCalc statistical package (version 5.00.17, Mariekerke Belgium) were used.

For NT values, a >90th centile was considered oddly increased, as conventionally for the risk of trisomy 21 and other chromosomal anomalies. A Pearson correlation test was performed when suitable. Encoding all pregnancy outcomes in a binary way (presence=1, absence=0) and with the aim to find data confounders, a multivariable logistic modelling was completed including all data in worksheet. Data confounders found were: maternal age, maternal weight at integrated test (double test) performance and parity, excluded afterwards for subsequent analysis.

Then a multiple logistic regression was performed with a threshold probability for positive classification for NT crude data (NT in mm) and NT MoM for every pregnancy outcome studied in this research. This procedure permitted to find the

Table 3 Diagnostic accuracy for NT MoMs expressed in centiles values regarding complications significantly associated and precedent spontaneous abortions

Complication	≥90th				≥95th				>97th			
	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV
Previous Abortion	4.7	87.6	4.7	87.4	9.7	95.0	34.8	79.5	-	97.7	-	82.9
Threatened PRET	4.0	92.7	8.0	86.2	10.6	95.0	31.8	82.8	-	97.6	-	81.7
PRET	4.0	92.7	5.4	93.0	9.8	92.5	12.5	90.5	-	97.8	-	89.2

Values are percentages. Sens: Sensitivity, Spec: Specificity, PPV: Positive predictive value, NPV: Negative predictive value. Number of pregnancies related to NT centiles were as follows: <90°: 659, ≥90°: 55, ≥95°: 50, ≥97°: 16. True positive cases were present between 95° and 97° centiles.

adverse outcomes significantly related to NT values, with associated odds ratios (Wald statistic, 5%–95% CIs).

The NT in mm and NT MoM values were forced into a backward stepwise regression equation in order to assess if the dependent variables (adverse outcome significantly related by multiple logistic regression) can be predicted from a linear combination of the independent variables (NT values).

The *NT MoM-to-percentile* correlation was run in order to assess the diagnostic accuracy (sensitivity, specificity, positive predictive value and negative predictive value).

The conventional probability value $p<0.05$ was considered as significant. The total number of samples considered for statistical analysis always satisfied the statistical power (0.8 at alpha <0.05).

4. Results

Median gestational age (GA) at NT evaluation was 11 + 2 weeks' gestation. NT median was 1.1 mm (0.9–1.4 mm, 25th–75th centile, range 0.5–4.0 mm). Median maternal age was 32 years (25–39 years, 25th–75th centile). Median maternal weight at the time of NT evaluation was 60.1 kg (55–68 kg, 25th–75th centile). Nulliparous pregnant women were 319 (43.4%), pregnant women with spontaneous abortions in previous pregnancies were 302 (41.1%). Median GA at birth was 40 weeks' gestation (38–40 weeks, 25th–75th centile; range 29–42 weeks' gestation). Preterm deliveries ($n=84$) median GA was 33.1 weeks' gestation (29–34 weeks, 25th–75th centile).

Table 1 depicts the pregnancy complications in the study group. Uneventful pregnancies were 391 (53.2%), the most frequent adverse outcomes were: threatened PRET, PRET, threatened spontaneous abortion and PROM. Due to adverse pregnancy outcomes (4 intrauterine deaths and 8 spontaneous abortions) number of actual deliveries was 722. Cesarean sections in the study group were 295 (40.1%). Number of birth weights were the following: <2.5 kg: 39 (5.4%), 2.5–3.0 kg: 144 (19.9%), 3.0–4.0 kg: 502 (69.5%), >4.0 kg: 37 (5.1%).

Regarding NT values, number of pregnancies related to NT centiles were as follows: <90th: 659, ≥90th: 55, ≥95th: 50, ≥97th: 16. The number of pregnancies with an NT MoM >1 was 377 (51.3%).

After the performance of multiple logistic regressions, the variables presenting a significant adjusted odds ratio for NT MoM values were: threatened PRET ($p<0.008$) and PRET ($p<0.02$); interestingly also spontaneous abortion in previous pregnancies ($p<0.03$) (Table 2). All the other variables regarding adverse pregnancy outcomes were not statistically correlated.

With the former significant correlations between NT MoMs and adverse outcomes, it was detected if NT crude values (in mm) could help to predict adverse outcomes and to confirm that higher NT values are associated to adverse pregnancy outcomes. After a backward stepwise correlation, single MoMs values were statistically significant in the prediction of adverse pregnancy outcomes ($p<0.01$ both) and in the relationship with previous spontaneous abortions ($p<0.03$).

For significant associations between NT MoMs and pregnancy events (spontaneous abortion in precedent pregnancies, threatened PRET and PRET), and after calculating the relationship between NT MoMs and NT centiles as described in the Statistical analysis section, the diagnostic accuracy for NT centiles and NT MoM points higher than normal range was calculated. A true positive case is represented by a high centile or NT MoM associated to the presence of obstetric complication, conversely, a true negative case is represented by a low centile or NT MoM associated to the absence of an obstetric complication.

Table 4 Diagnostic accuracy for NT MoMs values regarding complications significantly associated and precedent spontaneous abortions

Complication	>1 MoM				>1.5 MoM				>2 MoM			
	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV
Precedent abortion	11.4	92.7	30.0	79.3	53.2	43.8	22.8	79.8	-	99.6	-	77.8
Threatened PRET	13.4	93.0	30.0	82.7	56.2	50.3	20.6	83.3	1.4	99.8	66.6	81.7
PRET	8.2	91.8	11.6	88.4	56.3	49.8	13.1	89.4	-	99.6	-	88.4

Values are percentages. NT MoMs limits regarding references curves. Sens: Sensitivity, Spec: Specificity, PPV: Positive predictive value, NPV: Negative predictive value.
The number of pregnancies with an NT MoM ≥1 was 377 (51.3%). True positive cases were present between 95th and 97th centiles.

Values ≥95th centile and ≥1.5 MoM were related to best predictive diagnostic accuracy, especially for threatened PRET in comparison with other limits. Tables 3 and 4 depict these evaluations.

5. Discussion

Some researches have shown that altered values of PAPP-A and β-HCG assessed in a first trimester screening may be associated with obstetrical complications such as: antepartum hemorrhage, threatened preterm delivery, preterm delivery, intrauterine death and pre-eclampsia [12–15]. On the contrary, other studies have not found any negative prognostic values in patients with subsequent IUGR or preterm delivery [16]. In an interesting study, Cheng et al. described their experience in a 3rd level hospital in Taiwan, considering an unselected population, and using a cut-off value of 3 mm (prevalence of increased fetal NT was 0.7%). Of 17 chromosomally normal pregnancies, four resulted in fetal demise (spontaneous abortion, intrauterine death or termination of pregnancy due to fetal abnormalities). They recommended that a fetal NT measuring ≥3 mm may be associated with a poor pregnancy outcome with not only chromosomal abnormalities and congenital cardiac diseases, but also poor maternal and fetal health or adverse pregnancy outcomes [3]. The same group performed a study in pregnancy induced hypertension (PIH). However, the sensitivity of fetal NT measurement in first trimester was not sufficient as a single marker for predicting the pregnant women at risk for subsequent PIH [17].

Other studies considering exclusively babies with normal karyotype have been performed. In the most recent ones, it was concluded that once aneuploidy is ruled out, the risk of perinatal outcome (fetal malformations, dysplasias, deformations, disruptions, and genetic syndromes) does not statistically increase until the NT measurement reaches 3.5 mm or more (>99th percentile). This increase in risk occurs in an exponential fashion as the NT measurement increases [18]. The likelihood ratio for the occurrence of a spontaneous abortion was 3.1 for measurements between 3.0 and 3.9 mm, and 6.8 for measurements ≥4 mm in other researches [19]. A complete study performed in a multicenter approach, regards the association of extreme first-trimester free β-HCG, PAPP-A, and NT with IUGR and other adverse pregnancy outcomes. Regarding NT values, they concluded that PAPP-A <5th percentile (OR 2.3 95% CI 1.1–4.7) and NT >99th percentile (OR 3.5, 95% CI 1.1–11.3) were associated with increased risk of preterm delivery before 34 weeks [20], which is in agreement with one of the associations found in this study.

From this research data, the variables presenting a significant adjusted odds ratio for NT MoM, i.e., a statistical significant association are: spontaneous abortion in previous pregnancies, threatened PRET and PRET. The utility of NT MoM values was also demonstrated related to the former associations (*"crude" NT in mm may not be useful in the prediction of adverse outcome*).

The highest predictive value was found for threatened PRET (O.R.: 2.2 [1.06–4.57], $p<0.03$), confirmed by the better diagnostic accuracy considering NT values >95th (sensitivity: 10.6%, PPV: 31.8%) centile and MoM ≥1.5 (sensitivity: 56.2%, PPV: 20.6%), suggesting that patients within this group, with euploid fetuses, may benefit from increased surveillance for this condition.

In the context of a selected population (euploid fetuses), the aim was to basically observe: (1) if the association of the "crude" NT value (in mm) with any pregnancy outcome is of value; (2) if not, which numerical standard could be more significant regarding any association, and (3) the possible value of NT in the prediction of any adverse pregnancy outcome in a 3rd level midtown university obstetrical institution, with all pregnant women considered for the study being Caucasian (our study population did not include African, South-American, Chinese, etc.).

In the setting of routine antenatal screening, increased NT MoM values/MoM percentiles determine first of all cases which require antenatal investigation for fetal karyotyping. Once a euploid fetus is ascertained, we should keep in mind that an increased NT measurement is a marker of a high-risk pregnancy, especially of threatened PRET and PRET, even in karyotypically normal fetuses.

A closer follow-up of these pregnancies may therefore be implemented.

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