Ultrasonographic assesement of fetal nuchal translucency (NT) at 11th and 14th week of gestation – Polish multicentre study

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Abstract

THE AIMS OF THE STUDY WERE: • to evaluate range and median values of NT in a large, unselected Polish population; • to determine the value of the 95th percentile and the median values for NT for given weeks of late 1st trimester pregnancy and to determine the level of chromosomal aberration risk corresponding to the values of the 95th percentile in the examined groups; • to examine the possible correlation between CRL, NT width as well as the mother's age with the risk of the most frequent chromosomal aberrations. **MATERIAL & METHODS**: We have retrospective analyzed 7 866 pregnant women. All fetuses of this women had NT measurement performed, as well as CRL and assessed of the most frequent chromosomal abnormalities. The group of pregnant women was divided into 2 subgroups: until and above 35 years old. All population group was divided into 3 subgroups depending on gestational age (11, 12 and above 13th weeks of gestation). **RESULTS**: The median of NT in all population group was 1.5 mm and 95th percentile was 2.4 mm, whilst in group with low risk median of NT and 95th percentile were the same and in group with high risk of chromosomal abnormalities respectively 1.5 mm and 2.5 mm. There were strong correlations between maternal age and the risk of most frequent chromosomal abnormalities from NT. **CONCLUSIONS:** The obtained results of median values and the 95th percentiles of NT in the examined group and the age groups under 35 and 35 plus are similar to these quoted by FMF. The risk levels of trisomy of 21st chromosome were similar to the reference values used by FMF. With gestational age, NT value increases in a non-linear way, therefore it is incorrect to use the term "a normal value" for NT, therefore, only the risk level calculated with the dedicated software using NT and CRL measurements with maternal age should be stated.

ORIGINAL ARTICLE

INTRODUCTION

Improved resolution of ultrasound transvaginal and transabdominal probes has made it possible to describe the normal anatomy of the fetus, to diagnose early a wide range of fetal abnormalities, and to measure fetal nuchal translucency (NT) thickness at the late 1st trimester scan. Nuchal translucency (NT) is a term used specifically to describe a collection of fluid in the fetal neck area between 11th and 14th week of gestation. There is an extensive evidence that these measurements provide effective screening for major chromosomal abnormalities. In addition, increased NT may be associated with various genetic syndromes, congenital heart defects and even with some skeletal dysplasias. NT thickness above the 95th percentile for a given gestational age as a recognised ultrasonographic marker of chromosomal aberration can indicate trisomy 21 with a detection ratio 80%, with 5% of false-positive results. According to various authors sensivity of this test approaches 82% with positive predictive value equal to 8.3% and negative predictive value approaching 99.9% [7,10]. NT increased above the 95th percentile enables the detection of a significant percentage of chromosomal aberration, congenital heart diseases and other developmental and genetic disorders. The algorithm proposed by the Fetal Medicine Foundation (FMF) suggests early screening based on ultrasonographic fetal NT measurements with biochemical analysis of free β hCG and PAPP-A (Pregnancy Associated Plasma Proteine A) in maternal serum by the end of the first trimester of pregnancy [4,12,14]. The examination must be conducted in a specified period, between 11 weeks 0 days and 13 weeks + 6 days. This gestational age corresponds with a fetal Crown-Rump Length (CRL) values between 45–84 mm. Repetability and good quality of the performed screening examination and their constant cross-validation are essential. For this reason FMF has created and introduced a comprehensive training and certification process as well as a very high quality examination check which can be accessed at the internet URL www.fetalmedicine.com.

AIMS OF THE WORK:

The aims of the work were as follows:

- to evaluate range and median values of NT in a large, unselected Polish population;
- to determine the value of the 95th percentile and the median values for NT for given weeks of late 1st trimester pregnancy and to determine the level of chromosomal aberration risk corresponding to the values of the 95th percentile in the examined groups;
- to examine the possible correlation between CRL, NT width as well as the mother's age with the risk of the most frequent chromosomal aberrations.

MATERIAL AND METHODS:

We retrospectively analyzed the data from 7 866 women with intrauterine singleton pregnancies who were examined in several ultrasound units between January 2004 and August 2006. The examinations were performed in the following perinatological centres: Department of Obstetrics and Gynecology in Ruda Slaska of the Silesian Medical University in Katowice, Ultrasound in Obstetrics and Gynecology Unit of the Polish Mother's Memory Institute Lodz, Institute of Mother and Child, Warsaw, Department of Gynecology Lublin, Medical University in Lublin, 1st Department of Obstetrics and Gynecology, Medical University of Warsaw, Prenatal Diagnostic and Infertility Unit Provita, Katowice, Ultrasound in Obstetrics and Gynecology Unit of the 1st Department of Obstetrics and Gynecology Medical University of Lodz, Obstetrics and Gynecology Clinic, Department of Obstetrics and Gynecology Medical University in Poznan.

Hospital records and regional cytogenetic registries were reviewed to determine the postnatal outcome for each subject. All fetuses with abnormal karyotype or major structural abnormalities were excluded from the study, as were the cases of pregnancy loss. NT measurements were performed in fetuses from singelton pregnancies, between 11–13 weeks + 6 days, which corresponded with CRL between 45 mm and 84 mm. The exclusion criteria were:

- presence of chromosomal aberrations and/or structural defects in previous pregnancies
- intrauterine fetal demisse diagnosed during examination
- multiple pregnancy.

All sonographers performing pregnancy examination were appropriately trained prior to the study and obtained the FMF certificates of proficiency in conducting examination between 11th and 14th week of gestation. The gestational age was determined on the basis of the date of the last menstruation, modified by CRL measurement if the difference was greater than 3 days. CRL measurement was conducted after obtaining mid -sagittal section of the fetus. NT measurement was performed according to the FMF guidelines. Specialized FMF computer software was used to calculate the risk of chromosomal aberrations based on the mother's age, CRL and NT thickness. The data obtained from the examinations was entered into MS Excel for Windows application. Medians and centiles were calculated as suggested by Royston et al. [9]. The statistical analysis of the data was performed with the use of Statistica for Windows PL v. 5.1 PL. The assumed value of statistical significance was $p<0.05$

RESULTS:

All pregnant women were divided into 3 groups of chromosomal aberration risk:

Group 1 – included all studied women – further referred to as "a population group"

Group 2 – included women under 35 years of age – referred to as "a group of low chromosomal aberration risk"

Group 3 – included women at and over 35 years of age – referred to as "a group of high chromosomal aberration risk"

Maternal age, centiles of CRL and NT values of he studied groups are presented in Tables 1–3.

The median age of pregnant women in the "population group" was 29 years (mean = 29.8 years). In women under 35 years old median age was 28 years (mean = 28.1 years) whereas in the group of women over 35 years median age was 37.5 years (mean = 37.3 years). The median CRL value and the range of gestational age in which the examination was performed was 64.2 mm (12 weeks + 5 days); mean CRL in this group was 64,6 mm. In all the examined groups the mean and median values were almost identical – 65.0 mm (mean = 65.3 mm) in the group over 35 years to 64.0 mm (mean = 64.21 mm) in the group of women under 35 years. The value of the 95th percentile of NT in all the examined groups was similar ranging from 2.4 mm for the entire group and a group of women under 35 the 95th percentile for NT – 2.4 mm; whilst in the group of women over 35 years old, the 95th percentile of NT was 2.5 mm. The median NT values in the "population group" and in the group of women with low risk were 1.5 mm, such as in the group of high risk (35 years and over) – the median NT value was 1.5 mm.

Table 4 presents the values of the 95th percentile of NT for all the examined groups and the corresponding calculated risk of the most frequently encountered fetal chromosomal aberrations.

In Group 2 the value of the 95th percentile of NT (2.4 mm) was slightly higher than its value in Group 3 (2.5 mm). The value of the 95th percentile of NT in all the examined foetuses (Group 1) equalled 2.4 mm. All the patients were divided further into 3 subgroups of gestational age:

- **A:** 11 weeks + 0 days (CRL = 45.0 mm) to 11 weeks + 6 days (CRL = 54.0 mm)
- **B:** 12 weeks + 0 days (CRL = 55.0 mm) to 12 weeks + 6 days (CRL = 67.6 mm)
- **C:** 13 weeks + 0 days (CRL = 67.8 mm) to 13 weeks + 6 days (CRL = 84.0 mm)

Table 1. Maternal age, centiles of CRL and NT values.

n = 7 866	Mean	Confidence interval –95%	Confidence interval +95%	Median	Min	Max	Lower Quartile	Upper Quartile	Percentile 95	Standard deviation
CRL (mm)	64.4	64.07	64.74	64.2	45.0	84.0	56.0	72.2		10.1884
NT (mm)	1.58	1.56	1.6	1.50	0.5	9.7	1.3	1.8	**2.4**	0.6626
mother's age (yrs)	29.8	29.6	29.93	29.0	14.0	47.0	27.0	33.00		4.9050

n – number of fetuses

Table 2. Maternal age, centiles of CRL and NT values for women <35 years of age.

n = 5 800	Mean	Confidence interval –95%	Confidence interval +95%	Median	Min	Max	Lower Quartile	Upper Quartile	Percentile 95	Standard deviation
CRL (mm)	64.21	63.84	64.59	64.0	45.0	84.0	56.0	72.0		10.2547
NT (mm)	1.59	1.57	1.62	1.5	0.5	9.7	1.3	1.80	**2.4**	0.6953
mother's age (yrs)	28.13	27.99	28.26	28.0	14.0	34.0	26.0	31.0		3.3628

n – number of fetuses

Table 3. Maternal age, centiles of CRL and NT values in women ≥ 35 years of age.

n =2 066	Mean	Confidence interval –95%	Confidence interval +95%	Median	Min	Max	Lower Quartile	Upper Quartile	Percentile 95	Standard deviation
CRL (mm)	65.3	64.53	66.08	65.0	45.0	84.0	58.0	73.6		9.8293
NT (mm)	1.53	1.49	1.53	1.5	0.5	4.8	1.2	1.8	**2.5**	0.4795
mother's age (yrs)	37.33	37.16	37.5	37.0	35.0	47.0	36.0	39.0		2.2550

n – number of fetuses

Table 4. The 95th percentile of NT values for all the examined groups and the corresponding risk levels of the most frequent chromosomal aberrations for the median values of the mothers' ages.

	n	NT95 percentile	T21 risk ensuing from the mother's age	T21 risk based on NT measurement	T18 and 13 risk ensuing from the mother's age	T18 and 13 risk based on NT measurement
Group 1	7866	2.4	1/110	1/265	1/291	1/1420
Group 2	5800	2.4	1/350	1/420	1/656	1/3659
Group 3	2066	2.5	1/76	1/190	1/150	1/905

n – number of singelton pregnancies

Table 5. Calculated 95th percentile of NT for all the examined groups and the corresponding risk levels of the most frequent chromosomal aberrations.

	n	NT95 percentile	T21 risk ensuing from the mother's age	T21 risk based on NT measurement	T18 and 13 risk ensuing from the mother's age	T18 and 13 risk based on NT measurement
Group A	1398	2.1	1/112	1/249	1/237	1/1210
Group B	3262	2.25	1/94	1/290	1/218	1/1289
Group C	3206	2.4	1/105	1/279	1/256	1/1492

n – number of singelton pregnancies
Group A: Hbd11 + 0d to 11+6d; Group B: Hbd2 + 0d to 12 + 6d; Group C: Hbd13 + 0d to 13 + 6d

Also for these subgroups the 95th percentile of NT and the given values of the most frequent chromosomal aberrations risk was determined, as presented in Table 5.

An increase of the 95th percentile of NT was observed with the length of pregnancy duration and CRL, with a similar level of risk of trisomy 21 and trisomy 18 and 13, both ensuing from the mother's age, and that obtained from NT measurement. The results of a correlation between: the mothers' ages, CRL, NT, the basic risk of trisomy of the 21st chromosome, and trisomy of the 18th and 13th chromosomes, risk of trisomy 21 determined on the basis of NT measurement and risk of trisomy 18 and 13 based on NT measurement are presented in Tables 6–8. Table 6 presents the calculated coefficients of correlation between the risk of trisomies and NT and CRL measurements in the studied group of women.

Significant positive correlations were found for the measurements of NT and CRL; NT and trisomy 21 and trisomy 18 and trisomy 13 risk determined according to NT measurement. As expected, with an increase of NT, the risk of the most frequent chromosomal aberrations in the examined group increased. Furthermore, with increased maternal age, the basic risk of the most frequent chromosomal aberrations in the examined group increased. As expected the maternal age and risk of trisomy 21 and trisomy 18/13 determined according to NT measurement increased the risk of these chromosomal aberrations. Additionally, an analysis of the similar cor-

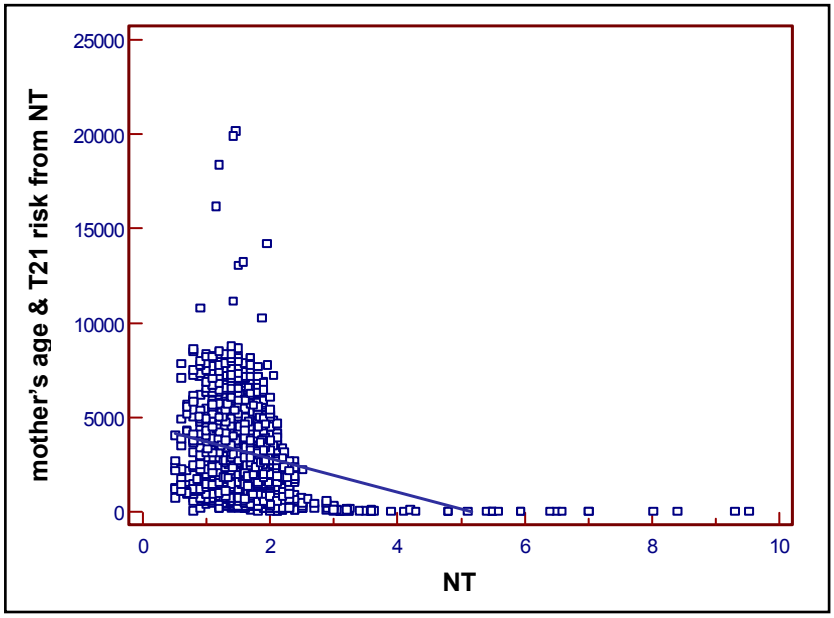

Figure 1. Correlation between NT values and risk of Trisomy 21 calculated on NT values in all examined cases.
p<0.001, R = –0.2392

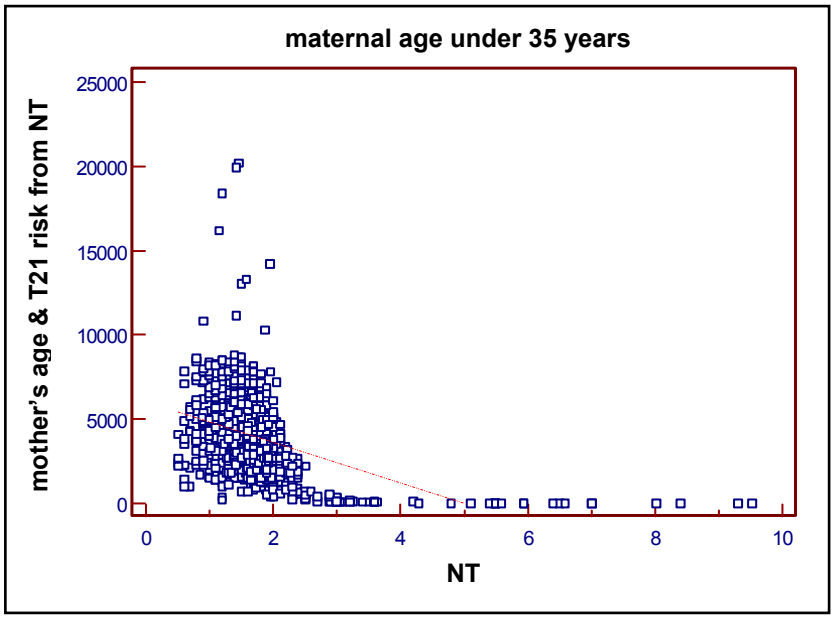

Figure 2. Correlation between NT values and the risk of trisomy 21 based on NT values in fetuses of mothers under 35 years old.
p<0.001, R = –0.4264

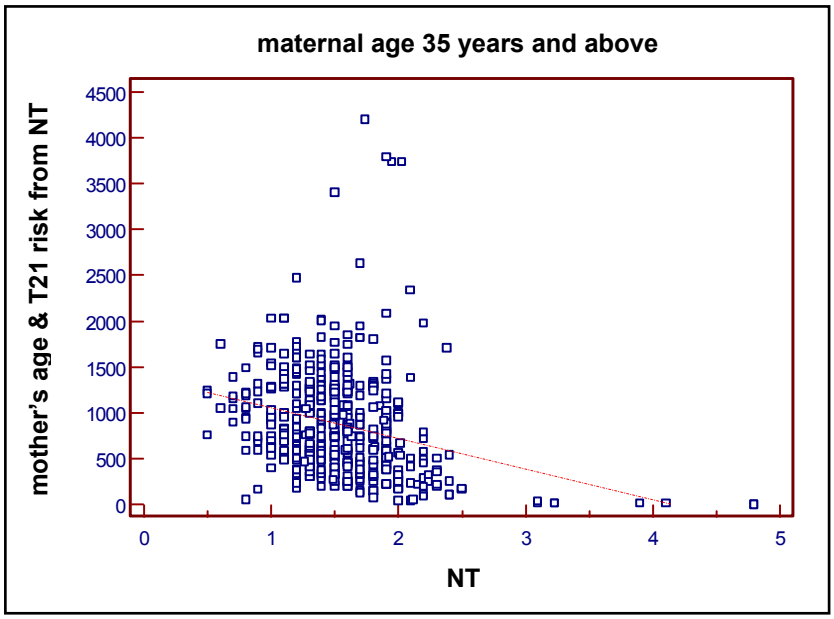

Figure3. Correlation between NT values and risk of Trisomy 21 based on NT values in fetuses of mothers ≥35 years old.
p<0.001, R = –0.3462

Table 6. Analysis of Spearman's rank correlation between maternal age, CRL, NT and calculated risk of trisomies.

		Group 1		
Examined parameters	*n*	*R**	*t(n-2)*	*p-value*
CRL & T21 basic risk	7866	0.0233	–0.964	0.3354
CRL & T18 andT13 basic risk	7866	0.0059	–0.245	0.8068
CRL & T21 risk from NT	7866	0.0473	–1.959	0.0502
CRL & T18 and T13 risk from NT	7866	0.0186	–0.769	0.4420
NT & T21 risk from NT	7866	0.2392	–10.186	0.0000
NT & T18 and T13 risk from NT	7866	0.1759	–7.388	0.0000
mother's age & T21 basic risk	7866	0.9577	–137.597	0.0000
mother's age & T18 and T13 basic risk	7866	0.7447	–46.136	0.0000
mother's age & T21 risk from NT	7866	0.8019	–55.504	0.0000
mother's age & T18 and T13 risk from NT	7866	0.6582	–36.154	0.0000
CRL & NT	7866	0.4053	23.221	0.0000

* Spearman's rank correlation coefficient
n – number of singleton pregnancies

Table 7. Correlations in the examined group (fetuses of patients under 35).

		Group 2		
Examined parameters	*n*	*R**	*t(n-2)*	*p-value*
CRL & T21 basic risk	5800	0.0057	0.203	0.8394
CRL & T18 andT13 basic risk	5800	0.0058	0.204	0.8381
CRL & T21 risk from NT	5800	0.0447	–1.581	0.1142
CRL & T18 and T13 risk from NT	5800	0.0155	–0.549	0.5834
NT & T21 risk from NT	5800	0.4264	–16.667	0.0000
NT & T18 and T13 risk from NT	5800	0.3013	–11.170	0.0000
mother's age & T21 basic risk	5800	0.9094	–77.322	0.0000
mother's age & T18 and T13 basic risk	5800	0.6494	–30.195	0.0000
mother's age & T21 risk from NT	5800	0.6719	–32.070	0.0000
mother's age & T18 and T13 risk from NT	5800	0.5228	–21.683	0.0000
CRL & NT	5800	0.4137	20.890	0.0000

* Spearman's rank correlation coefficient
n – number of fetuses

relations with the regard to age groups of the pregnant women (Group 2 and 3) was performed. The results are presented in Table 7 and Table 8, respectively.

These correlations were found in the "population group" as well as in the respective age subgroups. Figures 1 to 3 depict correlations between NT values and risk of Trisomy 21 calculated on NT values in all examined groups (Spearman's rank correlation test)

DISCUSSION

In the above presented study we attempted to correlate late Ist trimester pregnancy fetal biometry with NT measured at 11–14 weeks of pregnancy in pregnancies with normal and abnormal outcome. To our knowledge this is the first study examining this relationship in a large group of low-risk Polish singleton pregnancies population. We demonstrated, as others [10,11] that there is a non-linear correlation between the increase of NT and the increase of CRL in normal pregnancies. The median value and the 95th percentile value for CRL equal 45 mm (11 weeks + 0 days) were 1.2 and 2.1 mm, respectively. For CRL length of 84 mm (13 weeks + 6 days) these values were 1.9mm and 2.7 mm, respectively. In the examined population a statistically significant correlation between CRL increase (gestational age) and NT thickness was observed, similarly to the published data [7,10]. The median values and that of the 95th percentile for CRL 45 mm–54 mm (11 weeks + 0 days) were 1.2 and 2.1 mm respectively, whilst for CRL 67.8–84 mm (13 weeks + 0 days–13 weeks + 6 days) the median was 1.7 and 2.4 mm (the value of 95th percentile). The difference between the values of the median and the 95th percentile is probably caused by non-normal distribution of measurement results (75% of fetuses from this group – above 13 weeks + 0 days–had NT value up to 1.9 mm, with CRL value up to 77.9 mm). The median NT value for the entire examined group was 1.5 mm, and the 95th percentile was 2.4 mm, with CRL median value of 64.2 mm (12 weeks + 5 days). These values differed non-significantly in the group of women under 35 and over 35 years of age. Also in this situation the difference was caused by differences in the values of the upper quartiles for CRL as well as non-normal distribution of NT measurements. The risk level of trisomy 21 was close to 1 in 300 in all the examined groups and corresponded with the cut-off threshold for this risk stated by the FMF [4,7,11,12] and others [5,6]. Several other sonographic markers of fetal trisomies have been identified and extensively studied in recent years. Among these the most important are nasal bone (NB) presence or absence and/or the presence of fetal heart tricuspid valve regurgitation (TR) [2,8,11]. According to the FMF guidelines these methods should be used if the risk of of trisomy 21 (T21) calculated on

Table 8. Correlations in the examined group of fetuses of women ≥35 years of age.

			Group 3	
Examined parameters	*n*	*R**	*t(n-2)*	*p-value*
CRL & T21 basic risk	2066	0.0213	0.455	0.6493
CRL & T18 andT13 basic risk	2066	0.0865	1.858	0.0639
CRL & T21 risk from NT	2066	0.0023	–0.050	0.9600
CRL & T18 and T13 risk from NT	2066	0.0794	1.704	0.0890
NT & T21 risk from NT	2066	0.3462	–7.898	0.0000
NT & T18 and T13 risk from NT	2066	0.1658	–3.597	0.0004
mother's age & T21 basic risk	2066	0.8784	–39.341	0.0000
mother's age & T18 and T13 basic risk	2066	0.5078	–12.615	0.0000
mother's age & T21 risk from NT	2066	0.7174	–22.039	0.0000
mother's age & T18 and T13 risk from NT	2066	0.4672	–11.307	0.0000
CRL & NT	2066	0.3857	10.475	0.0000

* Spearman's rank correlation coefficient
n – number of fetuses

he NT measurement basis is between 1/100 and 1/1 000. Further experience is needed to include this markers to the risk analysis in our country. Another proposed way to assess the risk of fetal heart malformations related to some trisomies is the examination of ductus venosus (DV) Doppler velocity waveforms. The latter method has not been standardized yet and it's use for screening purposes is controversial. This is mainly due to the interpretation problems related to the characteristic of flow autoregulation in this vessel. Threfore, at this time it is not a routine diagnostic procedure, such as NT assessement [1,11,13]. An important issue, and yet the most significant factor influencing the reliability of the results and their repeatability is the appropriate training of sonographers performing the examination and the annual audit of the screening results and ultrasonographic scans. Comparison of NT assessment performed by FMF qualified sonographers and with the measurements taken by sonographers who had not completed the FMF-approved training revealed that the results of their measurements were subject to significant variation between the same fetuses, therefore causing considerable decrease in screening potential of this method of prenatal diagnosis [3,8,13,14]. Our daily clinical observations seem to confirm these reports.

CONCLUSIONS:

1. The obtained results of median values and the 95th percentiles of NT in the examined group and the age groups under 35 and 35 plus are similar to these quoted by FMF.
2. The risk levels of trisomy of 21st chromosome were similar to the reference values used by FMF.
3. With gestational age, NT value increases in a non-linear way, therefore it is incorrect to use the term "a normal value" for NT, therefore, only the risk level calculated with the dedicated software using NT and CRL measurements with maternal age should be stated.

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