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A study of nuchal translucency and other first-trimester sonographic markers of chromosomal abnormalities

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Abstract

Background: Genetic sonography following first-trimester combined screening appears to increase substantially detection rates for Down syndrome, but it relies on the unproved assumption of independence between these tests. **Aim and Objective:** To detect nuchal translucency and other first-trimester sonographic markers of chromosomal abnormalities. **Method:** This study was performed on pregnant women with a gestational age of 11 weeks and 13 weeks (6 days) at the department of radiology, VIMS, Gajraula, UP, India. Pregnant women undergone screening are followed up till delivery and assessment of congenital anomalies done. The subjects are followed up till the pregnancy outcome. The clinical assessment of the newborn baby was done to look for any congenital anomalies. The statistical analysis was done by using the chi-square test. $p < 0.05$ is considered to be significant. **Results:** An increase in NT is associated with congenital abnormalities. Increased NT is more likely to have anomalies compared with normal NT. **Conclusion:** Nuchal translucency is a strong predictor of congenital and chromosomal anomalies.

Key Words: nuchal translucency, first trimester screening, Down's syndrome, pregnancy, prenatal diagnosis

Introduction

Chromosomal anomalies are associated with considerable morbidity and mortality. Trisomy 21, in particular with its attendant's intellectual and physical challenges and long lifespan, places considerable demands on the affected individual, family, society, and nation. One of the aims of antenatal care has, therefore, been to identify fetuses with these disorders in order to give parents the option of terminating such a pregnancy.

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The protocol for identifying these fetuses had for many years included a single clinical criterion of maternal age. All mothers beyond 35 years of age were offered amniocentesis for a fetal karyotype. The fetal loss rate of one in 200, consequent to amniocentesis, resulted in a significant loss of normal fetuses for every abnormal fetus identified. Even with the safety of amniocentesis increasing and the loss rate falling to one in 500 to 800, it still remains unjustified to subject all mothers above 35 years of age to the procedure. Additionally, although the incidence of trisomy 21 is higher in older mothers, since most pregnancies occur in the younger age group, the age criterion alone identifies only 30% of affected fetuses. As a consequence, there has been an endeavor to identify criteria to help identify those mothers most likely to benefit from amniocentesis. These criteria are referred to as “markers” and include ultrasound findings and biochemical parameters. These constitute “screening” tests. Definitive diagnosis is done by invasive testing, such as amniocentesis between 16 and 20 weeks of pregnancy or by chorion villus sampling between 10 and 14 weeks of pregnancy, and these are referred to as “diagnostic” tests. Material obtained by these invasive tests can be assessed by culture and karyotype, fluorescent in situ hybridization (FISH), or quantitative fraction polymerase chain reaction (QF-PCR) to identify or exclude the trisomy. Advances in biochemical screening, combined with the excellent display of fetal dysmorphology afforded by technological advances in ultrasound equipment, have resulted in a paradigm shift in the diagnosis of chromosomal abnormalities in the fetus from the second trimester to the late first trimester. The accuracy of diagnosis, as reported in multiple large series from various parts of the globe over the past decade and a half, has pushed both screening and diagnostic testing for chromosomal disorders to the window now referred to as the 11 to 13-week + 6-day scan. [1-2] This section discusses techniques and clinical implications of ultrasound screening for markers of trisomy in the first trimester.

Only over the past 20 years has identifying fetuses with Down syndrome with the help of ultrasound become a routine practice. Earlier, only women over the age of 35 years were offered amniocentesis; this led to very low detection of the Down syndrome in the infant population, and a large number of fetuses with Down syndrome were undetectable prenatally. [3] The majority of the fetuses that are affected tend to get missed easily; however, 25–33% of fetuses with Down syndrome have major malformations that are recognized in the second trimester ultrasonographically. [4] Ultrasound imaging has improved quality over the past two decades. Many features of infants with Down syndrome have been picked up, like a small nose, redundant skin at the neck, short stature, and flat faces. [5] Specific ultrasound features such as pyelectasis, hyperechoic bowel, and echogenic intracardiac focus are used as markers to identify fetuses as high-risk for Down syndrome. [6]

In Down syndrome, there is an extra chromosome, “21,” resulting in varying degrees of mental handicap. As the maternal age increases, the risk of having a child with Down syndrome also increases, especially over the age of 35 years. [7] However, 70% of Down syndrome babies are born to mothers below the age of 35 years, and hence there is a need for screening pregnant women of all ages to assess the risk of Down syndrome. [8] The risk for many of the chromosomal defects increases with maternal age. For a woman 35 years of age who has had a previous baby with trisomy 21, the risk at 12 weeks of gestation increases from 1 in 249 (0.40%) to 1 in 87 (1.15%); for a

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woman 25 years of age, it increases from 1 in 946 (0.106%) to 1 in 117 (0.856%). [9] Nuchal translucency (NT) is nothing but the normal subcutaneous fluid-filled space between the overlying skin and the back of the fetal neck. This area can be measured accurately on ultrasound between 11 weeks and 13^{+6} weeks of gestation. It is seen that the greater the NT measurement, the higher is its association with major structural malformations, adverse pregnancy outcome, Down syndrome, and other aneuploidy.

It is believed that the increase in NT is caused by fluid accumulation in the nuchal region because of delayed development of the lymphatic system, abnormal aortic isthmic narrowing, other fetal cardiovascular defects, or abnormalities in the extracellular matrix. [10] Nuchal translucency screening had a 77% sensitivity for Down syndrome and a 5% false-positive rate. [11-12]

Interpretation of NT

Naturally, there is an increase of NT measurement by 17% per week. This should be taken into account when calculating threshold levels for use with an increased NT. It is not appropriate to choose a single millimeter cutoff to define a specific NT measurement as abnormal or select a pregnancy that warrants invasive prenatal diagnostic testing.[13]

NT and aneuploidy

Nuchal translucency thickness and the prevalence of chromosomal defects, major fetal anomalies, miscarriage, and fetal death are directly proportional to each other. [14] An ultrasound evaluation of the fetus at $11–13^{+6}$ weeks of gestation, starting with the NT measurement, will help to accurately pick up chromosomal abnormalities and many nonchromosomal defects. [15]

Materials and Methods

Study Design: Prospective Study

The study was done at the Department of Radiology, VIMS, Gajraula, UP, India. The data were collected from women who were pregnant, in whom the fetal NT thickness was measured between 11 weeks and 13 weeks (6 days of gestation) during the period. The outcome of the pregnancy was obtained from the hospital records. The tool for examination of the fetus is a high-resolution real-time ultrasound machine (Logiq 500). The transabdominal ultrasound probe used for scanning was a curvilinear probe with a frequency band width of 3.5–5 MHz. The other facilities that are necessary to produce an atmosphere of security, comfort, and cooperation to complete the examination are also available, like variable-intensity lighting, individual linen, privacy screens, and lockable doors.

Study Population

All pregnant mothers presenting at VIMS, Gajraula, for routine antenatal scans from 11 weeks to 13 weeks (6 days of gestation) who had fetal NT done by radiologists.

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Our study population includes all patients from India who have had their antenatal scanning done at 11–13^{+6} weeks at the Department of Radiology, VIMS, Gajraula, UP.

Method

All pregnant women between 11 weeks and 13^{+6} weeks of gestation were offered counseling before the screening. In the counseling, the patients were made aware of the uses of ultrasound at 11–13^{+6} weeks of gestation (such as to date the pregnancy accurately, to diagnose multiple pregnancies, to diagnose the viability of the fetus, to assess the chance of Down syndrome and other fetal abnormalities/chromosomal abnormalities by measuring fetal NT). After counseling, pregnant women were offered. The scans were carried out by a trained radiologist. During the scan, uterine anomalies, cervix, internal os, adnexa, NT, and any structural abnormalities were looked for. After the scan, the estimated chance of having Down syndrome or other fetal abnormalities was discussed with the pregnant woman and her family. Our institution is registered under the PNDT Act and will follow the rules and regulations according to the act.

All fetuses that underwent NT scan and had normal NT or increased NT continued their pregnancy, and detailed examination for structural abnormalities, major and minor markers, was done. If a lethal anomaly is detected at the anomaly scan, pregnancy is terminated. If congenital anomalies were not picked up, fetal echocardiography was done to detect any congenital cardiac defect. If no lethal cardiac defect was detected, pregnancy was continued, followed by an interval growth scan. After delivery, the baby was evaluated by the pediatrician for anomalies.

Inclusion Criteria

- Gestational age: for NT 11 weeks to 13 weeks 6 days.
- Well-documented last menstrual period (known LMP with regular menstrual cycles or confirmed with early trimester pregnancy scans).
- Crown-rump length (CRL): measurement between 44 mm and 84 mm.

Exclusion Criteria

The patients who do not attend the scan within the specified period of gestational weeks will be excluded from the study.

Technique for Evaluation of NT with Images

A reliable measurement of NT can be obtained by appropriate training and following a standard technique in order to make sure that the results among different operatives are uniform. In our study, we used a transabdominal scan (TAS), as patient acceptability is less with a transvaginal scar (TVS).

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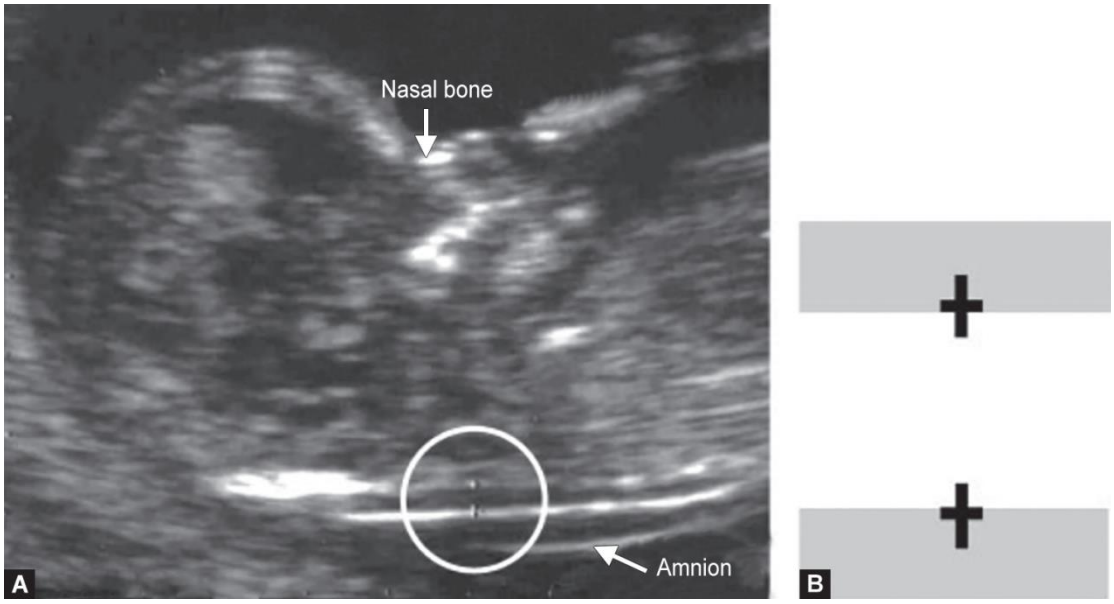
Image and Measurement

For the measurement of fetal NT, a high-resolution USG machine with a video loop function is needed. The calipers used will provide measurements to one decimal point. In almost 95% of the cases, fetal NT can be measured successfully by transabdominal ultrasound examination. However, in the others, a transvaginal sonography has to be done. The results from both are similar. [16]



Figs. 1A and B: Measurement of nuchal translucency

A: The fetus should be in neutral position for NT to be measured.

B: Calipers should be placed perpendicular to the fetal body axis and on the inner borders of the nuchal fluid—the transverse bar of the caliper should be such that it is hardly visible as it merges with the white line of the border and not in the nuchal fluid. Guidelines by the Fetal Medicine Foundation to Maximize Good Quality of NT Ultrasound: [17] The gestation should be 111/2–13+6 weeks, and the fetal crown-rump length should be 45–84 mm.

- Nuchal translucency ultrasound should only be performed by a radiologist certified in the technique.
- A mid-sagittal section of the fetus for the measurement of fetal crown-rump length should be obtained, and the NT should be measured with the fetus in the neutral position. When the fetal neck is hyperextended, the measurement can be increased by 0.6 mm, and when the neck is flexed, the measurement can be decreased by 0.4 mm.
- Only the fetal head and upper thorax should be included for measurement of NT. The magnification should be as large as possible and always such that each slight movement of the calipers produces a 0.1 mm change in the measurement.

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- The subcutaneous translucency between the soft tissue overlying the cervical spine and the skin should be measured.
- It should be the maximum thickness.
- The calipers must be placed perpendicular to the fetal body axis and on the inner borders of the nuchal fluid—the transverse bar of the caliper should be on the white line of the border and not in the nuchal fluid. Generally, three measurements are taken during the scan, and the maximum one is recorded.
- We should take care to differentiate between fetal skin and amnion because both appear as thin membranes during this gestation. The best way to evaluate the amnion and skin is to watch the fetus during movement.
- Ethnic origin, diabetic control, fetal gender, cigarette smoking, conception by assisted reproductive techniques, bleeding in early pregnancy, or parity/gravidy do not show any relevant differences in the NT measurement.
- There is less than 0.5 mm difference in the intra- and interobserver differences in the fetal NT measurement in 95% of cases.

Statistical Analysis

In our study, descriptive statistical analysis has been done. Categorical measurement results are presented in number (%) and continuous measurement results are presented on mean ± SD. The 5% level of significance is assessed. The single-proportion Z test is used as the screening test to measure the detection rate of positive cases for significance. Significant figures and suggestive significance (p value: $0.05 < p < 0.10$)

*Moderately significant (p value: $0.01 < p \leq 0.05$)

**Strongly significant (p value: $p \leq 0.01$)

The statistical software SPSS 24.0 was used for data analysis. Excel and Microsoft Word have been used to prepare tables, graphs, etc.

Results

A total of 120 pregnant women who had an antenatal NT scan between 11 weeks and 13^{+6} weeks of gestation were selected into the study. A total of 120 fetuses were included. All 120 women were followed up till the end of their pregnancies.

Table 1: Age group distribution of study subjects (n **= 120)**

Age group (years)	**Number**	**Percentage**
<20	3	2.5
21-30	75	62.5
31-40	35	29.17
>42	7	5.83
Total	120	100

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Our study population involves a minimum age of 20 years and a maximum age of 42 years. Most of our patients are in the 21–30 years (62.5%) age group, and the mean maternal age was 28.31 years (SD: 4.67), as compared to Western data, where the peak age was 31 years. The percentage of patients aged 30 years and above was 29.17% (n = 35). Women aged <20 years are 3 (2.5%), 21–30 years are 75 (62.5%), 31–40 years are 35 (29.17%), and >40 years are 7 (5.83%), as shown in Table 1. In our study population, 65 women are primigravida and 55 women are multigravida.

Table 2: Frequency of congenital anomalies in a study group (n **= 120)**

Congenital anomalies	**Number**	**Percentage**
Congenital	7	5.33
No congenital	113	94.17

Among 120 study subjects, the number of fetuses born with congenital anomalies is 70 (5.33%) and those with no congenital anomaly are 113 (94.17%), as shown in Table 2.

Table 3: Distribution of normal and high nuchal translucency among study subjects

Age group (years)	**Normal NT (%)**	**High NT (%)**	**Total (%)**
<20	3	1	3.33
21-30	65	11	63.33
31-40			

The cutoff value for NT is taken as 3 mm. The NT value less than 3 mm is considered normal, and the NT value more than 3 mm is considered high NT. Mean NT is 2.204 mm, and standard deviation is 1.1028 mm. The total number of fetuses with normal NT values is 103 (85.83%), with 1 fetus having a congenital anomaly and 113 fetuses with no congenital anomaly. And fetuses with high NT values are 17 (14.17%), with 7 fetuses having congenital anomalies and 117 fetuses with no congenital anomaly. An increase in NT is 551.41 times more likely to have anomalies compared to normal NT. The number of fetuses having normal NT in the <20 years age group is 3, 21–30 years is 65, 31–40 years is 29, and >40 years is 6. The number of fetuses having high NT in the <20 years age group is 4, 21–30 years is 126, 31–40 years is 50, and >40 years is 0, as shown in Table 3.

Table 4: Distribution of CRL among a study group (n **= 120)**

CRL	**Number**	**Percentage**
41–50 mm	30	25
51–60 mm	35	29.17
61–70 mm	40	33.33
71–80	15	12.5

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Among the study group, 40 women got NT scanning done between 11 week 0 day and 11 week 6 days, 50 women between 12 week 0 day and 12 week 6 days, and 30 women between 13 week 0 day and 13 week 6 days. Table no. 4 shows that among the study group, 30 women fall in the CRL value of 41–50 mm, 35 women in 51–60 mm, 40 women in 61–70 mm, and 15 women in 71–80 mm.

Discussion

Chromosomal anomalies are associated with considerable morbidity and mortality. The protocol for identifying these fetuses had for many years included a single clinical criterion of maternal age. Advances in biochemical screening combined with the excellent display of fetal dysmorphology afforded by technological advances in ultrasound equipment have resulted in a paradigm shift in the diagnosis of chromosomal abnormalities in the fetus, from the second trimester to the late first trimester.

All mothers presenting at the Department of Radiology, VIMS, Gajraula, UP, India, who underwent routine antenatal scans from 11 weeks to 13 weeks (6 days of gestation for NT) were enrolled in the study and followed up till birth. Our study subjects underwent NT scanning between 11 weeks and 13^{+6} weeks of gestation, according to LMP. Among the study group, 40 women got NT scanning done between 11 week 0 day and 11 week 6 days, 50 women between 12 week 0 day and 12 week 6 days, and 30 women between 13 week 0 day and 13 week 6 days. Among the study group, 30 women fall in the CRL value of 41–50 mm, 35 women in 51–60 mm, 40 women in 61–70 mm, and 15 women in 71–80 mm.

Screen-positive groups were defined by a cutoff in fetal NT as taking 95th (Comas et al. 2012), 99th centile (Economides et al. 1918), and NT measurements as 2.5 mm (Pandya et al. 2015) or 3 mm (Taipale et al. 2017) as the cutoff value for the fetal CRL. [18] Out of 7 congenital anomaly fetuses, multiple organ involvement is noted in 8 fetuses and single organ involvement in 6 fetuses. In our study population, 65 women are primigravida and 55 women are multigravida. Out of 120 study subjects, 15 women had a previous history of miscarriages, and 105 women had no previous miscarriage history. 17–35 The number of pregnancies with NT thickness > 95th centile and an estimated risk for trisomy 21 that was based on fetal NT and crown-rump length is 90.9%. The trisomy 18 estimated risk was 9.1% with NT thickness > 95th centile. Other trisomies were not documented in our study. This establishes the role of first-trimester screening for the NT value at 11 weeks to 13 weeks (6 days) in anticipating aneuploidies and structural abnormalities. Our study was also supported by M. Raksha et al. and Ashok Khurana [38-39].

Conclusion

Ultrasound is an excellent tool for the detection of aneuploidy. It also helps in the detection of structural abnormalities. In our study, we used TAS for antenatal mothers, as patient acceptability is less with TVS. The NT value less than 3 mm is considered normal, and the NT value greater than 3 mm is considered the high NT value. Our study shows that as the NT value increases, the period of gestation of fetuses

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decreases proportionately (p value < 0.0001). This establishes a significant role of the NT value in pregnancy outcome and an important predictor of congenital anomalies. As there is a strong association with high NT values and congenital anomalies, routine NT scanning should be done between 11 weeks and 13 weeks and 6 days. This will guide the obstetrician to counsel the pregnant women and follow-up till termination of pregnancy.

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