RESEARCH ARTICLE

Is nuchal translucency measurement feasible in early pregnancy?

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Abstract

Background: To investigate whether early nuchal translucency measurement at 7^{+0} to 9^{+0} weeks ($NT_{7\text{-}9w}$) is feasible, obtain normal values for different crown-rump lengths (CRL) in the above weeks and create percentile tables.

Methods: A prospective study was conducted in the Obstetrics and Gynecology Department of the University Hospital of Ioannina, including data from women with singleton pregnancies, examined in the early pregnancy unit between November 2010 and May 2015 at a CRL of 10-27 mm. The early pregnancy scan was performed vaginally, and the $NT_{7\text{-}9w}$, CRL, fetal heart rate, and mean yolk sac diameter were measured. Demographic data, including body mass index and smoking, were recorded.

Results: $NT_{7\text{-}9w}$ was measured successfully in 192 fetuses out of 210 (91.4 %), with a CRL ranging from 10-27 mm. The median maternal age was 31 (range 18-43) years, and the median CRL was 19.9 (range 10.0-27.0) mm. Considering the above measurements, we created normal values and percentiles tables of NT at 7^{+0} to 9^{+0} weeks in relation to the corresponding CRL measurement.

Conclusion: According to the literature, this is the first attempt to measure NT in such weeks of pregnancy. NT measurement as early as 7^{+0} to 9^{+0} is feasible and normal values can be created and correlated with CRL measurements. HIPPOKRATIA 2021, 25 (4):151-155.

Keywords: Nuchal translucency, early pregnancy, screening, normal values, aneuploidy

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Introduction

Ultrasound is a non-invasive method for early evaluation of the fetus and intrauterine environment. There is sufficient evidence that effective screening aiming at detecting chromosomal abnormalities and other major fetal malformations may be provided in the first trimester of pregnancy. A well-established screening method for genetic syndromes and malformations is the late first-trimester combined screening[1-4].

Nuchal translucency (NT) is the most acceptable aneuploidy screening marker to date. International guidelines recommend its measurement in fetuses with a crown-rump length (CRL) from 45 to 84 mm, corresponding to a gestational period of 11^{+0} to 13^{+6} weeks of pregnancy[5].

In most developed countries, health systems do not offer a routine scan between 7 to 11 weeks. In Greece, the Hellenic Society of Obstetricians and Gynecologists recommends a scan in early pregnancy to confirm intrauterine pregnancy, determine the number of fetuses and chorionicity, and accurately date the pregnancy. Evidently, many women miss this scan because of late booking. Furthermore, in most countries where this early scan is not offered, it is common for women to undergo an ultrasound scan early, in the first weeks of pregnancy, for various clinical indications. These women subsequently undergo a routine first-trimester combined screening test. It has been reported that NT measurement at embryos with a CRL ranging from 28-44 mm seems to be a useful marker for the early detection of fetal trisomies[6].

Early detection of aneuploidy, prior to the NT scan at 11^{+0} to 13^{+6} weeks, may be achieved with Non-Invasive Prenatal Testing (NIPT) as early as at ten weeks, with a substantial cost[7-11] and even earlier than ten weeks by the invasive approach of coelocentesis (coelomic fluid aspiration)[7,12-15]. Therefore, a non-invasive, nonexpensive, and easily performed screening method earlier than ten weeks would be ideal for identifying pregnant women at high risk for adverse pregnancy outcomes. If such a method was developed as early as 7-9 weeks, clinicians

could offer an individualized coelocentesis or NIPT later in the first trimester to allow earlier diagnosis of trisomies.

This study aimed primarily to determine whether the early measurement of NT in fetuses with CRL ranging from 10-27 mm is feasible and secondarily to creating normal values for different CRL in the above weeks and creating percentile tables.

Methods

Study population and inclusion criteria

This was a longitudinal case series study performed in the Obstetrics and Gynecology Department of the University Hospital of Ioannina, in Greece, where ultrasound scanning was routinely offered in early pregnancy to determine an intrauterine pregnancy, viability, number of fetuses and chorionicity. We prospectively collected and analyzed the data regarding women with intrauterine singleton pregnancies referred to the early pregnancy unit from November 2010 until May 2015. We only included women carrying fetuses with a CRL that ranged between 10-27 mm, corresponding to 7^{+0} to 9^{+0} weeks, according to the Robinson and Fleming charts[16]. We excluded pregnancies following Assisted Reproduction Treatment (ART) and those referred for vaginal bleeding from this study. The study was approved by the Scientific and Research Ethics Committee of the University Hospital of Ioannina (decision No: 432/10, date: 14/3/2011) and written informed consent was obtained from every pregnant woman included in the study.

Early-NT technique

Both early and late first-trimester scannings were performed by two sonographers, who have extensive experience in the early first-trimester scans (Fetal Medicine Foundation accredited sonographers). Scans were performed transvaginally using a 5 MHz transducer (Philips HD9 Ultrasound Machine; Philips, Amsterdam, Netherlands). A midline profile was obtained with the embryo, ideally in a horizontal position and with sufficient magnification (Figure 1, Figure 2, and Figure 3). At the time of the ultrasonographic examination, we recorded NT, early biometry [CRL, fetal heart rate (FHR), yolk sac (YS) diameter], and demographic data (maternal age, parity, body mass index, smoking) in a database.

We measured the CRL as the embryo's greatest length and recorded the FHR using the M-mode. We calculated the mean YS diameter by dividing the two perpendicular diameters and the gestational age from the fetal CRL. We reviewed the pregnancy outcome from the hospital notes. In women who delivered in other units, we obtain the information from the patients themselves. All those data were recorded in our database.

Statistical analysis

All statistical procedures were carried out using the IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA) and statistical significance

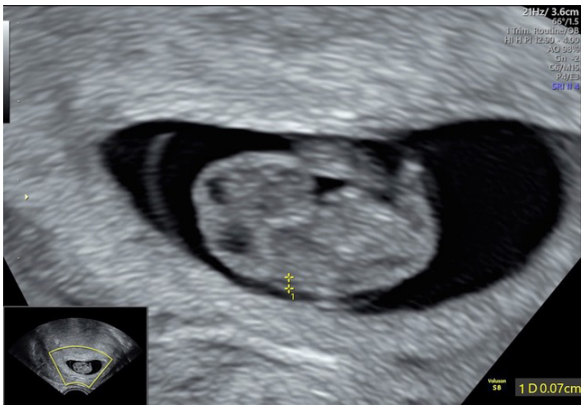

Figure 1: Fetal ultrasound image demonstrating nuchal translucency at $8w^{+0d}$ of gestation.

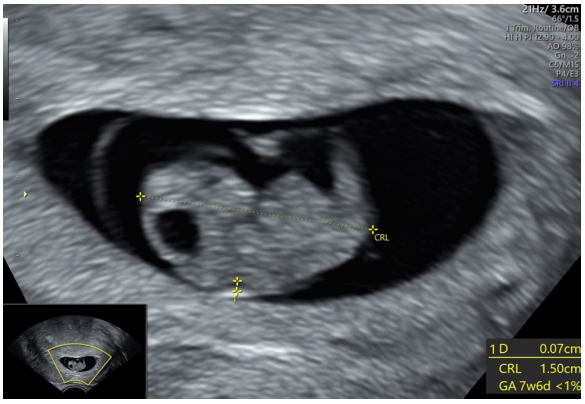

Figure 2: Fetal ultrasound image demonstrating nuchal translucency at $7w^{+6d}$ of gestation.

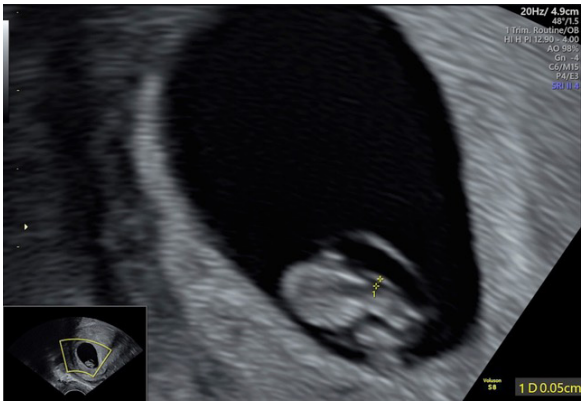

Figure 3: Fetal ultrasound image demonstrating nuchal translucency at $7w^{+1d}$ of gestation.

was set at 0.05 in all cases. The categorical data that were collected are described with the use of frequencies and percentages. Means and standard deviation are used for the scale measurements. To estimate the reference curves of Z-scores of the $NT_{7\text{-}9w,}$ we estimated the reference ranges for the 5^{th}, 50^{th}, and 95^{th} percentile using the CRL as an independent variable[17-19]. All valid measurements of the $NT_{7\text{-}9w}$ estimation were conducted with the Lambda-Mu-Sigma (LMS) method and the LMS chart maker software developed by Harlow Printing Limited[20].

Results

Demographics

Among 210 singleton pregnancies with a CRL between 10-27 mm (gestational age ranged from 7^{+0} to 9^{+0} weeks of pregnancy), successful NT measurement (NT_{7-9w}) was achieved in 192 cases (91.4 %). The mean maternal age was 31 ± 5 years, and the mean CRL was 19.9 ± 3.8 mm (Table 1).

Success of early-NT measurement

The reasons for failing to obtain measurements were fetal position and small fetuses, especially before eight weeks. In 15 out of 52 (28.8 %) fetuses with gestational age less than eight weeks, we did not manage to measure NT, while we failed only in three out of 158 (1.9 %) fetuses when gestational age was above eight weeks (Table 2).

Construction of normal values tables

According to CRL measurements, we constructed reference ranges for NT between 7^{+0}- 9^{+0} weeks of pregnancy using the LMS method[20]. We finalized a table reporting NT reference ranges according to the abovementioned valid CRL measurements (Table 3).

The 5th percentile for NT increased from 0.38 to 0.59 mm when the CRL raised from 10 to 27 mm, the 50th percentile ranged from 0.63 to 0.88 mm, and the 95th percentile increased from 0.88 to 1.24 mm.

After completing the normal values of NT between 7-9 weeks of pregnancy, we attempted to correlate NT with the corresponding CRL (Figure 4).

Clinical Outcome

Of the 192 cases, eight reported first-trimester miscarriage (4.2 %). Forty-six out of 184 pregnancies (25 %) had further cytogenetic study via amniocentesis because of advanced maternal age or previous aneuploidy. No aneuploidies were detected in the present study population.

Table 1: Demographic data of study population consisting of 210 singleton pregnancies with a crown-rump lengths between 10-27 mm.

	Mean (SD)
Maternal age (years)	31.0 (5.0)
CRL (mm)	19.9 (3.8)
BMI	23.6

SD: standard deviation, CRL: crown-rump length, BMI: body mass index.

Table 2: Unsuccessful measurement of nuchal translucency between 7-9 weeks of pregnancy.

Study population (n =210)	Unsuccessful measurement (n=18)	p value
8^{+0}-9^{+0} weeks (n =158)	3/158 **(1.9 %)**	
7^{+0}-7^{+6} weeks (n =52)	15/52 **(28.8 %)**	<0.001

Table 3: Nuchal translucency (NT) reference ranges according to crown-rump length (CRL) in mm between 7 to 9 weeks of pregnancy

CRL (mm)	5th percentile	50th percentile	95th percentile
10	0.38	0.63	0.88
11	0.39	0.64	0.90
12	0.42	0.67	0.93
13	0.45	0.70	0.98
14	0.48	0.73	1.01
15	0.50	0.75	1.04
16	0.52	0.76	1.05
17	0.52	0.76	1.05
18	0.53	0.77	1.06
19	0.53	0.77	1.07
20	0.54	0.78	1.08
21	0.54	0.79	1.12
22	0.55	0.80	1.15
23	0.55	0.81	1.19
24	0.56	0.82	1.21
25	0.56	0.83	1.22
26	0.57	0.85	1.23
27	0.59	0.88	1.24

CRL: crown-rump length.

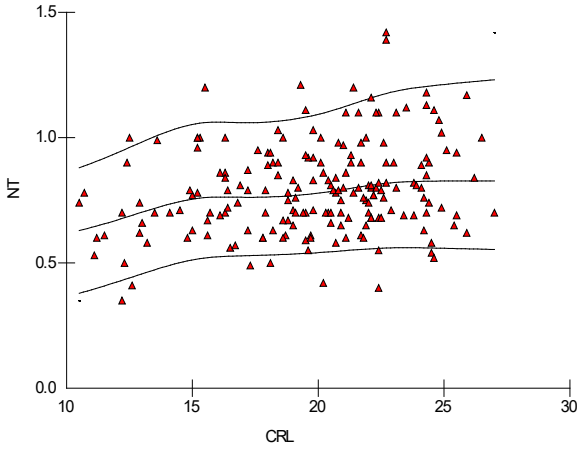

Figure 4: Nuchal translucency reference ranges (mm) according to crown-rump length (mm), with lines indicating the 5th, 50th, and 95th percentiles.

NT: nuchal translucency, CRL: crown-rump length.

Discussion

The current study primarily demonstrates that it is feasible to measure the NT at 7^{+0} to 9^{+0} gestational weeks (CRL ranging from 10 to 27 mm), especially between 8^{+0} and 9^{+0} weeks, and secondarily that there is a gradual increase in the NT between 7^{+0} and 9^{+0} weeks, where the minimum CRL was 10 mm, and the maximum was 27

mm. The miscarriage rate between this scan and the 11-13 weeks scan in our series was as low as 4 %.

The current recommendation for the NT measurement is at 11^{+0} to 13^{+6} weeks of gestation, where the minimum CRL should be 45 mm and the maximum should be 84 mm. The reason was that, although some of the original studies measured NT from 10 gestational weeks onwards, the lower limit of CRL was later set at 45 mm because, in smaller fetuses, it is challenging to examine fetal anatomy and detect major malformations. For example, diagnosing anencephaly (acrania) is very difficult before 11 weeks of gestation[2]. Furthermore, at 8-10 weeks of gestation, all embryos demonstrate a herniation of the midgut, making the exclusion of exomphalos hard[21]. In addition, the views of the heart and great arteries are possible only after the 10^{th} week of gestation[22], while the bladder can be visualized in only 50 % of the embryos at ten weeks [23,24].

On the other hand, if anomalies are detected around 13 weeks, pregnancy termination in the late first trimester is more complicated and traumatic for the pregnant woman. Additionally, there are even legislative restrictions in many countries.

In the current study, we attempted to measure NT very early in pregnancy (7-9 weeks) and create normal values according to the CRL measured in these weeks. Should this approach be confirmed and further supported, an early nonexpensive screening method could be utilized to identify which patient would benefit more from a coelocentesis or NIPT as early as approximately ten weeks of gestation.

Previous studies, even since 1996, have tried to assess the feasibility of early NT measurement in a routine setting. Cornman et al reported successful measurement in almost 58 % of the examined fetuses at <13 weeks of gestation. They also found a reduction of success in the measurement when the gestational age was less than ten weeks. That finding drove authors to believe that the effectiveness of NT in everyday usage is "much less impressive"[25]. Nowadays, the advanced technology of ultrasound machines and the continuous training of gynecologists in fetal sonography have set NT measurement's success to almost 99 % between 11 and 14 weeks of pregnancy. Therefore, this study primarily aimed to prove that measurement as early as 7-9 weeks might be possible. Indeed, we demonstrated that in 91 % of the cases, we were able to obtain a reliable measurement of both CRL and $NT_{7\text{-}9w}$. With the improvement of ultrasound equipment, more undersized fluid accumulations in the nuchal region could be identified in even smaller fetuses, especially transvaginally.

Recent studies suggest that increased nuchal translucency measurement before ten weeks of gestation should alert sonographers, as it is related to possible adverse pregnancy outcomes[26].

To our knowledge, this is the first study attempting NT measurements as early as 7-9 weeks and constructing reference ranges at these gestational weeks related to CRL. According to our results, NT measurement at a CRL of 10-27 mm is feasible, and the success rate can be as high as 98 % after eight weeks. This indicates that probably eight weeks plus, might be the optimal time for designing studies for early nuchal translucency screening.

Early screening at pregnancy with NT measurements might be promising, as if it is correlated with the classical NT measurements at 11-14 weeks; thus, high values could predict pregnancy complications much earlier. It is known that increased classical $NT^{11\text{-}14}$ is associated with adverse pregnancy outcomes. Indeed, some authors attempted to perform NT earlier than the conventional 11-14 weeks, but still later than the current study and not in the general population. Grande et al measured NT at a CRL from 28 to 44 mm (9-11weeks) and concluded that NT in these weeks might be used as an early detection marker for fetal trisomies, with the limitation that fetuses used in the reference range construction were picked out of a high-risk population (advanced maternal age or previous chromosomal anomaly)[6]. Another study from Ramkrishna et al showed a high association between nuchal edema and chromosomal/structural abnormalities in fetuses with a CRL ranging from 28 to 44 mm, concluding that fetal edema may be an important early marker for adverse pregnancy outcomes[27].

We attempted for the first time in the literature to obtain reliable NT measurement even earlier than previous authors, as nowadays we have methods such as coelocentesis or NIPT able to detect chromosomal anomalies as early as ten weeks. Furthermore, we hypothesized that a common pathophysiological mechanism could underlie the association of all these pregnancy parameters. Whether early measured NT is related to the classic NT measured between 11^{+0} and 13^{+6} weeks is yet to be seen. However, we accept that certain limitations exist in the current study, i.e., the number of cases is low, and we had no trisomic cases detected. Therefore, we believe that further prospective studies should investigate the relation of these measurements with possible poor pregnancy outcomes (chromosomal abnormalities or miscarriages).

We conclude that NT measured in early pregnancy ($NT_{7\text{-}9weeks}$) could be a promising screening method for fetal anomalies. As Brown et al mentioned in a recent study, in the era of cfDNA, a detailed ultrasound prior to the NIPT (pre-NIPT ultrasound), that is, before ten weeks, has the potential to change management in almost one in ten pregnancies[28]. Therefore, values above the 90^{th} percentile as early as eight weeks could possibly help clinicians be more careful in the management of such pregnancies and either ask for karyotyping with coelomic fluid aspiration (coelocentesis) before ten weeks or suggest NIPT prior to the classic NT measurement. Hence, the table of normal values we have created could be beneficial for future researchers as a reference tool.

Conflict of interest

The authors have no conflicts of interest to report with respect to this paper.

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