Original Article

The diagnostic performance of 4D ultrasound in nuchal translucency and anomalies association

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ABSTRACT

Purpose: To determine the association of increased NT with varies anomalies in the 1st trimester by 4D ultrasound.

Patient and methods: Two hundred selected women with viable pregnancies were recruited in this prospective study. All underwent 4D ultrasound at 11–14 completed weeks of gestation for NT measurement. They were classified into 3 groups according to NT thickness: Group I NT < 3.5 mm, group II NT between 3.5 and 4.4 mm and group III NT > 4.4 mm. Statistical analysis was done using Chi-square test for qualitative data between the three groups with significant correlation at p value ≤ 0.05.

Results: Out of 200 pregnant women, 30 was missed follow-up while 159 live birth and 11 pregnancies were terminated by abortion postnatal (n = 2), spontaneous (n = 3) or artificial (n = 6). The highest median maternal age and fetal gestational age were found in group I. The higher frequencies of congenital anomalies were found in fetuses with NT 3.5–4.4 mm and >4.5 mm. The most common heart defect anomalies were VSD (13 fetuses); retrognathia was found in 13 fetuses and hydronephrosis in 12 fetuses.

Conclusion: 4D ultrasound measurement of NT is of utmost importance in evaluation of increased NT and associated fetal anomalies.

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1. Introduction

Increased nuchal translucency (NT) is associated with a spectrum of fetal abnormalities. It can help us identify the high-risk fetuses for trisomy 21 and other chromosomal abnormalities. The commonest association is with chromosomal defects [1]. The association between increased nuchal translucency and different chromosomal aneuploidies was proved by several reports. It has been observed that, in normal fetuses NT thickness increased with fetal crown rump length (CRL) [2].

Recently, screening for chromosomal abnormalities is increasingly done in the first trimester. The perceived advantages of such first trimester diagnosis include a decrease in surgical and psychiatric morbidity by allowing option of an early versus late termination of pregnancy [3].

First-trimester ultrasound offers the advantages of identifying and measuring small subcutaneous collections of fluid behind the fetal back and neck. The size of the NT increases with gestational age and fetal crown rump length [3–5]. The translucent area disappears after 14 weeks gestational age, when the subcutaneous tissue becomes more echogenic. Advantages of first-trimester screening let us to learn the baby’s risk for chromosomal problems relatively
early in the pregnancy without slight risk of miscarriage from an invasive test like chorionic villous sampling (CVS) [3].

Like other screening tests, an NT scan will not give a diagnosis, but the scan can assess the baby’s risk for certain problems and help decide whether to have chorionic villus sampling (CVS) or amniocentesis to find out whether the baby is actually affected or not [6].

Several studies have also shown that in euploid fetuses with increased NT thickness, the risk of congenital heart defects, other structural anomalies and fetal death is increased [7,8].

The aim of this work was to determine the association of increased NT with varied anomalies on the 1st trimester of pregnancy by 4D ultrasound evaluation.

2. Patients and methods

Two hundred selected women with viable pregnancies were recruited in this prospective study, and all these pregnant women were attending the prenatal diagnosis at the radiology department in our institution between March 2015 and March 2016 at 11–14 completed weeks of gestation for NT measurement. They were included in our study after approval of the local ethics committee. An informed oral consent from each woman given before enrollment into the study was taken.

2.1. Inclusion criteria

The mean maternal age was 34 (range, 20–46) years.

2.2. Exclusion criteria

The exclusion criteria were the loss to follow-up, the chromosomal abnormalities or no information on karyotype in a fetal loss.

The cases were classified into 3 groups according to NT thickness

I- Group NT < 3.5 mm
II- Group NT between 3.5 and 4.4 mm
III- Group NT > 4.4 mm

2.3. Technique of examination

US examination was done using ESAOTE, My lab 40 X vision, Milan, Italy with 3.4 MHz on 2D probe and 5–9 MHz on 4D probe. 4D US examination was done by 2 consultant radiologists in consensus with 10 years of experience in performing 4D ultrasound examination.

2.4. Demographic details and ultrasound findings including

- We introduce the name of the patient, date and time of examination into specially developed software and store them.
- Then after telling the patient about the procedure details, we use the 2D ultrasound to evaluate the fetal viability, position and anatomy as well as measure the CRL and NT. We use also the 2D ultrasound high resolution colored view to accurately estimate the previously reported data.
- The NT is the maximum distance from the inner aspect of the skin to the soft tissue over the cervical spine. It should be measured in the sagittal view when the fetus is in a neutral position. We measure the NT many times (preferably three times) and the thickest one is recorded.
- Then we shifted to the 4D probe to evaluate the fetus for any congenital anomalies and accurately measure the NT.

Fig. 1. Represents the technique of 4D ultrasound: Firstly we adjust the scanning plane to obtain the true mid-sagittal section of the fetus as on (A–C) - Show the transverse and frontal sections, respectively, of the fetus and allow control of the adjustment. (D) - A surface reconstruction of the fetus was done in abnormal cases. (E) - Represents the surface reconstruction of a fetus with increased NT thickness. The nuchal skin surface can be clearly seen as an echogenic line (arrow).
When we visualize the fetal nuchal region at the mid-sagittal section, the ultrasound probe should be kept and the volume mode switched on to display the 4D data. Here, we evaluate the NT by using the multiplanar mode on the three orthogonal planes. If there are fetal abnormalities detected, we do fetal surface reconstruction and accurately estimate the NT.

At the end of the examination, we enter CRL and NT thickness with the above stored data into an electronic database (PIA, Fetal Database version 3.23, View Point, Munich, Germany) and calculate the risk for trisomy 21.

All the recoded above data should be stored on a rewritable magneto-optical disc.

2.5. We measure the NT by 4D ultrasound as follows: (Fig. 1)

- Firstly, we adjust the exact mid-sagittal section of the fetus by fixing the three-axial center of rotation to the central part of the nuchal region.
- Then the transverse and frontal sections of the fetus showed and help for fine control of the adjustment.

2.6. Image interpretation

Images were evaluated by 2 radiologists in consensus with 10 years post fellowship experience in performing obstetric 4D US.

<table>
<thead>
<tr>
<th>NT thickness</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.5 mm</td>
<td>46</td>
</tr>
<tr>
<td>3.5–4.4 mm</td>
<td>57</td>
</tr>
<tr>
<td>≥ 4.5 mm</td>
<td>67</td>
</tr>
<tr>
<td>Total</td>
<td>170</td>
</tr>
<tr>
<td></td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 1
Outcome of 170 pregnancies in 3 NT groups.

<table>
<thead>
<tr>
<th>Age</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age</td>
<td>31.2</td>
<td>30.1</td>
<td>29.2</td>
</tr>
<tr>
<td>Newborn weight</td>
<td>3502</td>
<td>3325</td>
<td>3254</td>
</tr>
<tr>
<td>Gest. Age at birth</td>
<td>39.4 Ws</td>
<td>38.6 Ws</td>
<td>38.4 Ws</td>
</tr>
<tr>
<td>Sex</td>
<td>XX</td>
<td>XY</td>
<td>XX</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>24</td>
<td>33</td>
</tr>
</tbody>
</table>

Table 2
The median maternal age, newborn weight, gestational age at birth and sex distribution in different groups.

<table>
<thead>
<tr>
<th>NT thickness</th>
<th>N</th>
<th>Minor</th>
<th>Major</th>
<th>Minor</th>
<th>Major</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3.5 mm</td>
<td>44</td>
<td>11</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>28</td>
</tr>
<tr>
<td>3.5–4.4 mm</td>
<td>56</td>
<td>12</td>
<td>3</td>
<td>2</td>
<td>7</td>
<td>32</td>
</tr>
<tr>
<td>≥ 4.5 mm</td>
<td>70</td>
<td>12</td>
<td>7</td>
<td>1</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>170</td>
<td>35</td>
<td>12</td>
<td>5</td>
<td>18</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 3
The outcome of anomalies in different NT groups respectively.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>n</th>
<th>NT range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart defect</td>
<td>25</td>
<td>2.9–4.2 mm</td>
</tr>
<tr>
<td>VSD</td>
<td>13</td>
<td>3.3–4.2</td>
</tr>
<tr>
<td>ASD and aortic coarctation</td>
<td>5</td>
<td>1.6–3.6</td>
</tr>
<tr>
<td>Hypoplastic left ventricle</td>
<td>4</td>
<td>1.9–3.7</td>
</tr>
<tr>
<td>Isolated valve anomaly</td>
<td>3</td>
<td>2.2–3.9</td>
</tr>
<tr>
<td>Other Anomalies</td>
<td>64</td>
<td>3.1–4.1</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>12</td>
<td>3.4–4.9</td>
</tr>
<tr>
<td>Cleft lip and/or cleft palate</td>
<td>3</td>
<td>2.6–4.6</td>
</tr>
<tr>
<td>Soft tissue edema</td>
<td>5</td>
<td>3.6–4.2</td>
</tr>
<tr>
<td>Nasal bone defect</td>
<td>4</td>
<td>1.6–3.8</td>
</tr>
<tr>
<td>Maxilla anomaly</td>
<td>3</td>
<td>2.9–4.4</td>
</tr>
<tr>
<td>Low set ear</td>
<td>8</td>
<td>1.6–3.9</td>
</tr>
<tr>
<td>Retro-gnathia</td>
<td>13</td>
<td>2.6–4.6</td>
</tr>
<tr>
<td>Hydropsfetalis</td>
<td>10</td>
<td>2.8–3.7</td>
</tr>
<tr>
<td>LL anomalies</td>
<td>12</td>
<td>1.6–3.9</td>
</tr>
</tbody>
</table>
Fig. 2. Female patient 40-year-old G 4 P3+1 with no history of consanguinity, was admitted for evaluation of the fetus in view of polyhydramnios. A- Shows increased NT by 2D ultrasound. B- The nose is seen broad and flat on high resolution focused 2D ultrasound. C and D- The fetal nose is seen flat and his ear seen low set by 4D image (arrow). E and F- Cardiac anomalies are seen in form of increased cardiothoracic ratio, enlarged Rt. atrium and presence of pericardial effusion (small arrows). G- Chromosomal analysis of the same fetus revealed translocation affecting chromosome number 21(arrow).
Fig. 3. Female patient 39 year-old G6 P4+1 with history of hypertension, was admitted for fetal evaluation. Patient’s obstetric history of TORSH infection is established A- Shows increased NT measured by high resolution focused 2D ultrasound (7 mm). B- Shows increased AC in comparison with BPD and HC by 4D ultrasound. C and D- Show retro-gnathia (white arrow). E- Shows echogenic bowels (thick short arrow). F- Shows ascites (long arrow). G- Shows pleural effusion (short arrow). H- Shows post labor image of the fetus.
2.7. Statistical analysis

– The associated congenital anomalies found by 4D assessment in association with increased NT will be calculated using Chi-square test for qualitative data between the three groups with the significant correlation was set at \( p \) value \(< 0.05\).

3. Results

Out of 200 pregnant women, 30 was missed to follow-up while the number of live birth was 159 and 11 pregnancies were terminated by abortion either spontaneous (\( n = 3 \)), artificial (\( n = 6 \)) or death after birth (\( n = 2 \)) (Table 1).

The fetuses had an average CRL of 64.3 mm, ranging from 45 to 84 mm.

The highest median maternal age and fetal gestational age were found in group I (Table 2).

The higher frequencies of congenital anomalies were found in fetuses with NT 3.5–4.4 mm and \( \geq 4.5 \) mm, 24 out of 56 and 30 out of 70 fetuses respectively with 42.8% for each. We found also, the most common multiplex major anomalies when the NT was more than 4.4 mm, as well as the isolated minor anomalies. On the other hand the least common anomalies were detected when the NT thickness was less than 3.5 mm (Table 3).

There was significant correlation between NT and incidence of congenital anomalies in group II (\( p \) value \(< 0.03\)) and group III (\( p \) value \(< 0.01\)) and overall (\( p \) value 0.02) (Table 3).

The most common heart defect anomalies was VSD (13 fetuses), while retro-gnathia was found in 13 fetuses and hydronephrosis in 12 fetuses (Table 4).

Many cases with variable encountered congenital anomalies associated with increased NT thickness are represented in Figs. 2–5.

4. Discussion

It was reported that an increase in NT is considered a useful marker of chromosomal abnormalities, fetal malformations and genetic syndromes. Consequently, the risk of adverse pregnancy outcome is proportional to the degree of NT enlargement, Bilardo et al. [9].

In this study, we evaluated the pregnancy outcome of a group of 170 fetuses with measurement of NT thickness. We found that the fetal loss rate reached 6.4% (11 fetuses were aborted either spontaneous in 3 fetuses, artificial
abortion found in 6 fetuses or death after birth in 2 fetuses). In a study done by Ksenija et al. [10] it was found that the overall fetal loss reached 7%. Also, in a study done by Westin et al. [11] it was concluded that fetal termination ranged from 2.3 to 16.9%.

Regarding the 159 live birth fetuses, 44 fetuses have NT less than 3.5 mm, while 54 have NT from 3.5 to 4.4 mm and 61 fetuses have NT more than 4.4 mm. Among the lost pregnancies (11 fetuses), 2 of them (4.5%) had NT less than 3.5 mm (1 spontaneous abortion and the other artificial abortion), 3 of them had NT from 3.5 to 4.4 mm (5.5%) (1 spontaneous and the other 2 artificial abortion), and 6 fetuses had NT more than 4.4 mm (9.5%) (1 spontaneous abortion, 2 artificial abortions and 2 fetuses died after birth). So, we conclude that the incidence of fetal loss (abortion) increased when the NT thickness increased. These data were also proposed on a study done by Said et al., Axt-Fliedner et al. and Markov et al. [12,7,8].

In our research, maternal age was found lower in the 3rd group and proved by study done by Szabo et al. [4], this can be explained by the fact that in the 1st two groups, maternal age played an important role in the calculation of anomaly risk and so the parents can accept the prenatal invasive test.

Regarding our studied 170 pregnancies; 100 pregnancies have no anomaly while 70 pregnancies have different anomalies with an incidence of 41%. The higher incidence of fetal anomaly was detected among NT 3.5–4.4 mm (significant $P$ value 0.03) and on more than 4.4 mm representing 42.8% of the encountered anomalies (significant $P$ value 0.01). Also, there was significant correlation between NT and incidence of congenital anomalies in groups II and III and overall. This was also proved by Graesslin et al. [13], who stated that the frequency of congenital fetal anomalies increased when the NT thickness increased.

In this study, the congenital cardiac defects are the most common anomalies representing 35.7% of all anomalies and detected in 25/70 pregnancies. This percentage is higher than the outcome in other studies like those done by Evans et al. and Orosz et al. [14,15] who stated that the incidence of cardiac anomalies reached 14.3–22.4%, and this may be explained by difference in sample size and NT method of measurement.

We have 25 cardiac anomalies detected in this study, including ventricular septal defect in 13/25, complex heart anomaly (VSD, ASD and aortic knuckle) present in 4/25 and isolated valve anomaly detected on 3/25. Souka et al. and Burns et al. [16,17] proved that, the frequency of congenital heart defects increased from 11% when the NT 3.5–4.4 mm and reached to 17.3% when the NT was more than 4.4 mm. Most of CHD in our study occurred with NT less than 4.4 mm and this is in contrary to Clur et al. [18] who found that the frequency of congenital heart defects increased when the NT thickness was more than 4.5 mm.

**Fig. 5.** Female patient 29 year-old G4 P3+1 with no history of consanguinity or Down syndrome was admitted for fetal evaluation. A and B- Show increased NT measured by 2D ultrasound in (A) and 4D ultrasound on (B). C- Shows absent nasal bone (small arrows). D- No blood flow detected within the thickened cord.
As regards other encountered congenital fetal anomalies, hydrenephrosis was found in 12 out of 64 anomalies, cleft lip and palate detected in 3/64 fetuses, soft tissue edema in 5/64, nasal bone defect in 4/64, maxillary anomaly in 3/64, hydrops-fetalis in 10/64 and lower limb anomalies in 12/64 anomaly. In a study done by Ksenija et al. [10] it was found that the 2nd most common isolated anomaly was the hydrenephrosis followed by cleft lip and/or palate. A study done by Cicero et al. [19], reported that out of 701 fetuses with increased NT a nasal bone could not be visualized in 73% of Down syndrome (43/59) and could not be visualized in 0.5% of unaffected fetuses 3/603, while Hutchon et al. [20] described a series of 5 cases of Down syndrome with clearly visible nasal bones.

Markov et al. [21] considered a direct relationship between increased NT and the occurrence of facial cleft. Geipel et al. [22] stated an increased relationship between the increased NT measurements and the development of hydrops-fetalis and all those are corresponding to our research results.

5. Conclusion

4D ultrasound measurement of NT is of utmost importance as NT more than 3.5 mm should be considered a cutoff value and needs further investigations by serum markers. Increased NT is associated with a spectrum of fetal anomalies; the commonest of them is chromosomal cardiac defects. A study on a large number of pregnancies with long duration of follow-up is recommended to establish guidelines for objective parental counseling.

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All authors have apprised the article and actively contributed in the work

Moustafa Abdel Kader: Idea, ultrasound evaluation and image revision.

Mohamed F. Amin: Data collection, ultrasound evaluation and final editing.

Ahmed Gotb: Clinical evaluation and management.

Conflict of interest

- All authors have materially participated in the research preparation and agree for the submission.
- We have no conflict of interest to declare.

References


