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Ultrasound evaluation of fetal chromosome disorders

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ABSTRACT
Prenatal diagnosis of chromosomal disorders requires an invasive test in women regarded as being at high risk after screening. There is extensive evidence that effective screening for major chromosomal abnormalities can be provided in the first and second trimesters of pregnancy. With the association of some biochemical markers, it is possible to identify about 90% of chromosomal abnormalities. In this article, we aimed to review the important ultrasonographic markers of chromosomal abnormalities, including nuchal translucency, nasal bone, and nuchal skin-fold thickness, based on the data available in the literature.

Key words: • *ultrasonography* • *nuchal translucency measurement* • *nasal bone* • *nuchal skin-fold thickness*

During the last 30 years, extensive research has been aimed at developing a noninvasive method for prenatal diagnosis of chromosomal and other abnormalities. However, on the basis of currently available data, there is no realistic prospect that in the foreseeable future noninvasive diagnosis will replace the need for invasive testing. Consequently, invasive testing is conducted only in pregnancies that are considered to be at high risk for chromosomal abnormalities. In this article, we reviewed the important prenatal fetal sonographic markers, including nuchal translucency, nasal bone, and nuchal skin-fold thickness, which have the potential to be very powerful predictors of fetal chromosomal abnormalities.

Nuchal translucency (NT)

Nuchal translucency (NT) is the sonographic appearance of a subcutaneous collection of fluid behind the fetal neck. In the first trimester, the term translucency is used irrespective of whether the collection of fluid is septated, whether it is confined to the neck, or it envelopes the entire fetus (1). There are several hypotheses regarding the pathophysiology of increased NT, and it is unlikely that a single common etiology for this sonographic sign underlies all associated abnormalities. Possible etiologies include cardiac failure secondary to structural malformation, abnormalities in the extracellular matrix, abnormal or delayed development of the lymphatic system, failure of lymphatic drainage because of impaired fetal movements in various neuromuscular disorders, fetal anemia or hypoproteinemia, and congenital infection that manifests as anemia or cardiac dysfunction (1–3).

The ability to achieve a reliable measurement of NT is dependent upon appropriate training and adherence to a standard technique to achieve uniformity of results among different diagnosticians. The optimal gestational age for the measurement of fetal NT is between 11 weeks and 13 weeks 6 days. The minimum fetal crown-rump length (CRL) should be 45 mm, and the maximum should be 84 mm. Only the fetal head and upper thorax should be included in the image for measurement of NT. The magnification should be as large as possible. A good sagittal section of the fetus, as for the measurement of fetal CRL, should be obtained and the NT should be measured with the fetus in the neutral position. The maximum thickness of the subcutaneous translucency between the skin and the soft tissue overlying the cervical spine should be measured (Figs. 1–5). The calipers should be placed on the lines that define the NT thickness (4, 5).

Fetal NT thickness increases with CRL; therefore, it is essential to take gestation into account when a determination is made about whether a given NT thickness is increased. In a study that involved 96,127 pregnancies, the median and 95th percentile at a CRL of 45 mm were 1.2

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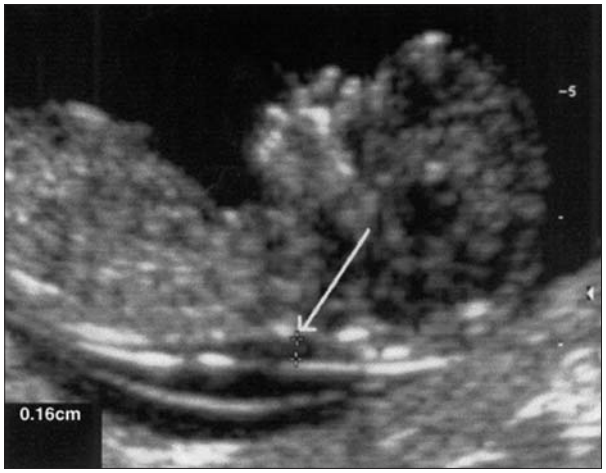

Figure 1. Ultrasound image showing measurement of nuchal translucency (NT) (1.6 mm) in a chromosomally normal fetus at 13 weeks. Various features of good NT ultrasound technique are evident in this image: adequate image magnification; midsagittal plane; neutral neck position; inner to inner caliper (+) placement perpendicular to the fetal body axis *(as indicated by white arrow)*.

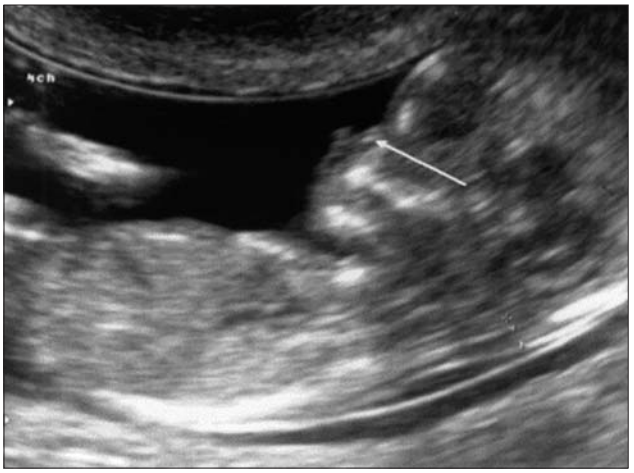

Figure 2. Ultrasound image of the nasal bone and nuchal translucency of a chromosomally normal fetus on the midsagittal plane. White arrow shows the fetal nasal bone and overlying skin as 2 echogenic lines.

and 2.1 mm, respectively, and respective values at a CRL of 84 mm were 1.9 and 2.7 mm. The 99th percentile did not change with CRL and was approximately 3.5 mm (4).

Recently, multiple studies have demonstrated that fetal NT has the potential of being a very powerful predictor of fetal aneuploidy. Prospective studies in 200,000 pregnancies, including 900 fetuses with trisomy 21, have demonstrated that NT screening can identify 75% of fetuses with trisomy 21 and other major chromosomal abnormalities (4). With the association of some biochemical markers, like maternal serum free β-human chorionic gonadotrophin (β-hCG) and pregnancy-associated plasma protein-A (PAPP-A), with ultrasonography at gestational weeks 11–14, it is possible to identify about 90% of chromosomal abnormalities (4, 5). Increased NT is also associated with major defects of the heart and great arteries, as well as a wide range of skeletal dysplasias and genetic syndromes. The prevalence of these abnormalities is related to the thickness of NT (6, 7) (Table 1).

Absence or hypoplasia of fetal nasal bone

In 1866 Down noted that a common characteristic of patients with trisomy 21 is a small nose. In an anthropometric study of 105 Down syndrome patients between the ages of 7 months and 36 years, it was reported that the nasal root depth was abnormally short in 49.5% of the cases (8).

The fetal nasal bone can be visualized by sonography throughout pregnancy. This examination requires that the image be magnified so that only the head and the upper thorax are included in the screen. A mid-sagittal view of the fetal profile is obtained with the ultrasound transducer held parallel to the longitudinal axis of the nasal bone. In the correct view, there are 3 distinct lines (Figs. 2, 3). The first 2 lines, which are proximal to the forehead, are horizontal and parallel to each other, resembling an equal sign (=). The top line represents the skin and the bottom line, which is thicker and more echogenic than the overlying skin, represents the nasal bone. A third line, which is almost in continuity with the skin, but at a higher level, represents the tip of the nose (4, 5, 9, 10).

Recent reports have suggested that an absent fetal nasal bone or nasal hypoplasia is a marker for aneuploidy, both in the first and second trimesters (Fig. 5), and that the absence of the nasal bone is not related to NT thickness; therefore, they could be combined relatively simply to provide a more effective method of early screening for trisomy 21 (5, 9, 10). Several studies have demonstrated a strong association between an absent nasal bone at 11–14 weeks of gestation and trisomy 21, and other chromosomal abnormalities (9, 11, 12). In the combined data from these studies, the fetal nasal bone was absent in 1.4% of chromosomally normal fetuses and in 69% of fetuses with trisomy 21 (4).

Table 1. The relationship between nuchal translucency and the prevalence of chromosomal defects, miscarriage, or fetal death and major fetal abnormalities

Nuchal translucency	Chromosomal defects	Fetal death	Major fetal abnormalities	Alive and well[a]
<95th percentile	0.2%	1.3%	1.6%	97%
95th–99th percentile	3.7%	1.3%	2.5%	93%
3.5–4.4 mm	21.1%	2.7%	10.0%	70%
4.5–5.4 mm	33.3%	3.4%	18.5%	50%
5.5–6.4 mm	50.5%	10.1%	24.2%	30%
>6.5 mm	64.5%	19.0%	46.2%	15%

[a]The last column is the estimated prevalence of delivery of a healthy baby with no major abnormalities.

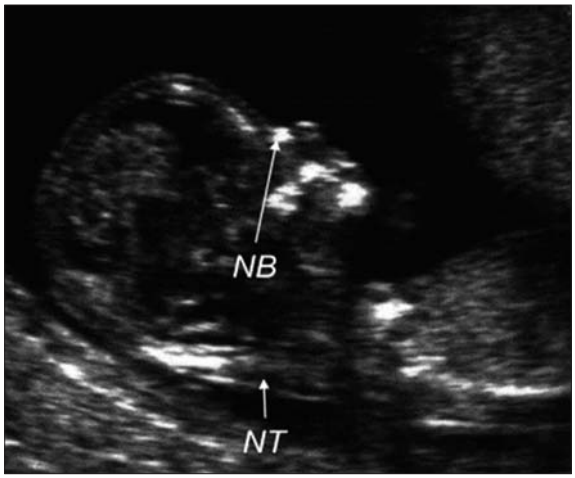

Figure 3. Ultrasound image of a chromosomally normal fetus at 12 weeks with normal nuchal translucency thickness *(short arrow)* and an observable nasal bone *(long arrow)*.

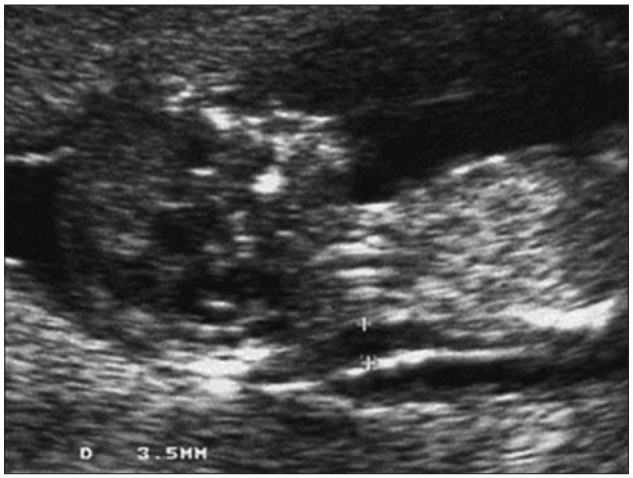

Figure 4. Increased nuchal translucency thickness in a trisomy 21 fetus at 12 weeks (3.5 mm represents the 99th percentile).

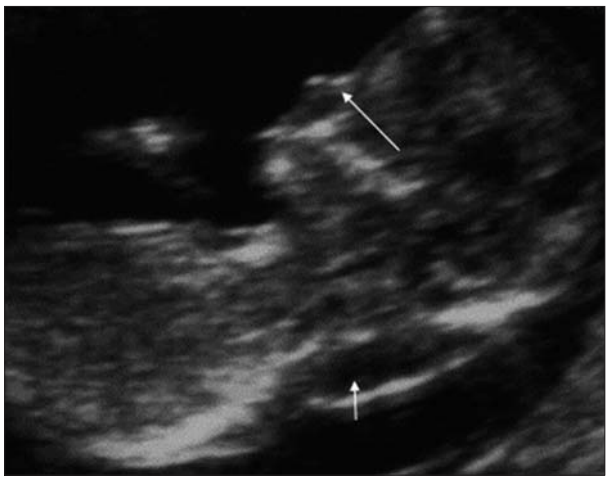

Figure 5. Ultrasound image of a 12-week trisomy 21 fetus with increased nuchal translucency thickness *(short arrow)* and an absent nasal bone *(long arrow)*.

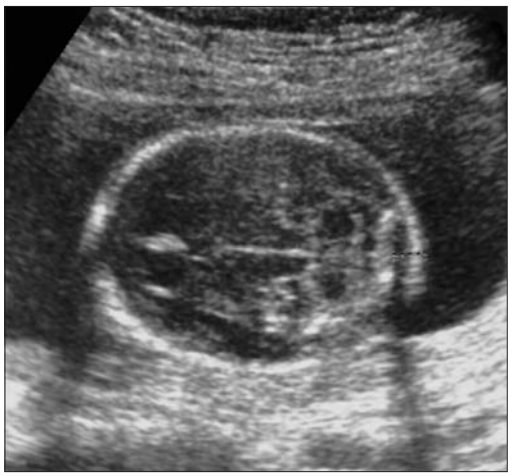

Figure 6. Correct plane for measuring nuchal skin-fold thickness. Critical landmarks include the cavum septi pellucidi, cerebral peduncles, and cerebellar hemispheres. Calipers (+) are placed from the outer skull table to the outer skin surface.

In the second trimester, more fetuses with Down syndrome can be detected by a sonographic screening approach based on nasal bone hypoplasia (10, 13, 14). The determination of nasal bone hypoplasia requires knowledge of the normative data for nasal bone length across gestation. Cusick et al. reported normative data for nasal bone length at 11–20 weeks of gestation in 814 fetuses (Table 2) (10).

Bromley et al. reported that nasal bone hypoplasia, defined as an increase in the biparietal diameter to nasal bone length ratio, might prove highly efficacious in identifying fetal Down syndrome in the second trimester (14). In their study, 81% of fetuses with Down syndrome and 11% of normal fetuses had a biparietal diameter to nasal bone length ratio of ≥10 (14).

Nuchal skin-fold thickness

Redundant nuchal skin folds are present in 80% of newborns with Down syndrome (15). Sonographic assessment of fetal nuchal skin-fold thickness was first proposed by Benacerraf et al. in 1985 (16).

Measurements are typically performed between gestational weeks 15 and 21 using a transverse axial image that is directed in the suboccipital-bregmatic plane. Critical internal landmarks include the cavum septi pellucidi, cerebral peduncles, cerebellar hemispheres, and cisterna magna (Fig. 6). Nuchal skin-fold thickness is measured with electronic calipers from the outer skull table to the outer skin surface, with values of ≥6 mm considered abnormal (Figs. 7, 8).

Table 2. Fetal nasal bone length between the 11th and 20th weeks of gestation

Gestational age (week)	Range (mm)	Mean (mm)
11–11.9	0.9–3.1	1.7
12–12.9	1–3.5	2
13–13.9	1.3–4	2.3
14–14.9	2.2–4.7	3.4
15–15.9	2.3–5.1	3.3
16–16.9	3.1–6.3	4.4
17–17.9	3.6–6.1	5
18–18.9	3.4–8.4	5.5
19–19.9	3.4–8.6	5.7
20–20.9	4.4–8.2	6.2

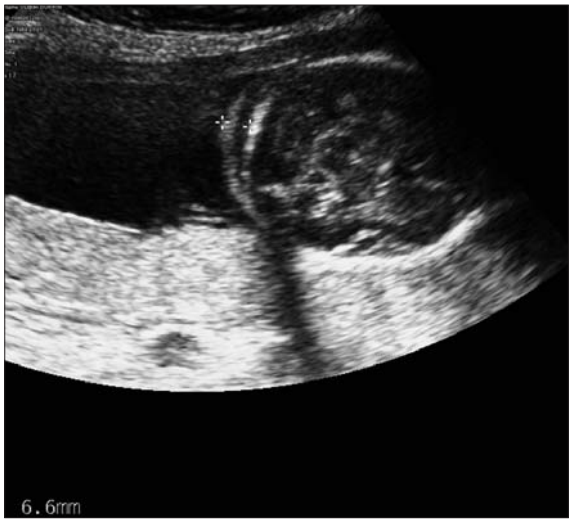

Figure 7. Increased nuchal skin-fold thickness measurement (6.6 mm) in a trisomy 21 fetus.

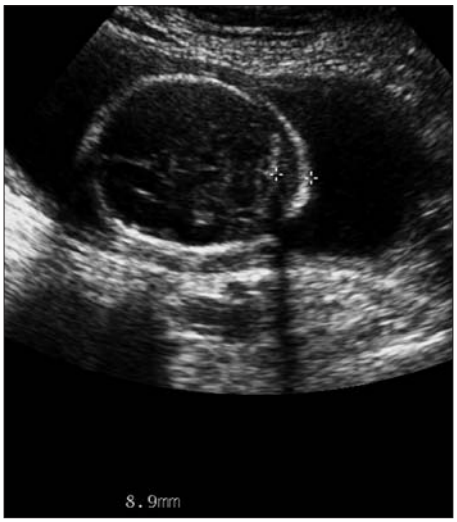

Figure 8. Abnormal nuchal skin-fold thickness measurement (8.9 mm) in a trisomy 15 fetus.

The effectiveness of nuchal skin-fold thickness as a screening tool for Down syndrome has been independently confirmed by 2 large prospective clinical trials (17, 18). The predictive value of nuchal skin-fold thickness for Down syndrome was also quite high (1/4 to 1/13), even after adjustment for the prevalence of Down syndrome in the general population (1/710 births). Given these findings, genetic amniocentesis should be offered when a nuchal skin-fold thickness of ≥6 mm is observed.

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