

Increased nuchal translucency in normal karyotype fetuses

Roberta De Domenico¹,
Marianna Faraci¹,
Entela Hyseni³,
Fosca A. F. Di Prima⁴,
Oriana Valenti²,
Santo Monte²,
Elsa Giorgio¹,
Eliana Renda⁵

¹ Policlinico Universitario "G. Martino",
Department of Obstetrics and Gynecology,
University of Messina, Italy

² S. Bambino Hospital, Department of Obstetrics and
Gynecology and Microbiological Sciences,
University of Catania, Italy

³ Campus Biomedico, Operative Unit of Gynecology,
University of Rome, Italy

⁴ Policlinico Hospital, Department of Obstetrics and
Gynecology, University of Catania, Italy

⁵ Policlinico Universitario "P. Giaccone",
Department of Obstetrics and Gynecology,
University of Palermo, Italy

Corresponding author:

Roberta De Domenico
Policlinico Universitario "G. Martino",
Department of Obstetrics and Gynecology,
University of Messina, Italy
via Consolare Valeria Messina
dedom83@hotmail.com
Phone: +393496724072

Summary

Nuchal translucency (NT) measurement between 11 and 14 weeks' gestation is a reliable marker for chromosomal abnormalities, including trisomy 21. However, even if conventional karyotyping is normal, increased NT is a predictive value of adverse pregnancy outcome, because it is associated with several fetal malformations, congenital heart defects, genetic syndromes, intrauterine death and miscarriages; the majority of these structural anomalies are undetectable before birth. The risk is proportional to the nuchal translucency thickness, in fact it statistically increases after measurement reaching 3.5 mm or more. However, when these chromosomally normal fetuses with an enlarged NT survive, even if a detailed ultrasound examination and echocardiography fail to reveal any abnormalities, their uneventful outcome and postna-

tal developmental delay will be not statistically increased when compared to the general population. These parents should be confidently reassured that the residual chance of structural anomalies and abnormal neurodevelopment may not be higher than in the general population.

Key Words: Nuchal translucency (NT); Chromosomal abnormalities; First trimester screening.

Introduction

In the first trimester of pregnancy there is a subcutaneous collection of fluid in the fetal neck that is visualized by ultrasonography as a nuchal translucency (NT)(1). The measurement should be made between 11 and 14 weeks but the best performance is obtained at 11-12 weeks (2). Normally NT thickness increases with fetal crown-rump length (CRL), in fact at a CRL of 45 mm is between 1.2 and 2.1 mm and at a CRL of 84 mm is 1.9 and 2.7 mm (median and 95th centile values) (3). The 99th centile is about 3.5 mm. The measurement has to be performed by qualified ultrasonographers undergoing regular quality assessment (4). In this article we review the association between increased fetal NT thickness in chromosomally normal fetuses and several fetal malformations, deformations, dysplasias and genetic syndromes (5); moreover we analyze which is the right approach with the parents of the euploid fetuses with enlarged NT (6).

Pathological correlation between increased NT and euploid fetuses

On the basis of three studies reporting on a total of 4991 euploid fetuses with increased NT it is possible to estimate that the prevalence of miscarriage or fetal death increases from 1.6% in those with NT between the 95th and 99th centiles to about 20% for NT of ≥ 6.5 mm (5, 7).

The prevalence of fetal death increases exponentially with NT thickness and these values are underestimated because the mortality rate should include cases of deteriorating fetal hydrops in which the 30% of couples decide to terminate pregnancy before intrauterine fetal death occurs (6).

Several studies have reported that increased fetal NT is associated with fetal abnormalities which means fetuses requiring medical and/or surgical treatment or conditions associated with mental handicap: from 1.6% in those with NT below 95th centile (8), to 2.5% for NT between the 95th and 99th centiles, until about 45% for NT of 6.5 mm or more (9,10).

Abnormalities associated with increased NT

Several abnormalities have been reported in fetuses with enlarged NT, the major are cardiac defects, diaphragmatic hernia, exomphalos, body stalk anomaly, skeletal defects, and certain genetic syndromes, such as congenital adrenal hyperplasia, fetal akinesia, deformation sequence, Noonan syndrome, Smith-lemli-Opitz syndrome and spinal muscular atrophy and their incidence is higher than in the general population; instead anencephaly, holoprosencephaly, gastroschisis, renal abnormalities and spina bifida have the same prevalence that in the general population.

Cardiac defects

Regarding congenital cardiac defects, their prevalence is six times higher in fetuses with a NT $\geq 99^{\text{th}}$ percentile than in an unselected population (11-13). In chromosomally normal fetuses the most common abnormalities are narrowing of the aorta at the level of the isthmus and septal or valvular defects (14).

Eight studies have reported on the screening performance of NT thickness for the detection of cardiac defects (8, 15-18). In total, 67,256 pregnancies were examined, and the prevalence of major cardiac defects was 2.4 per 1,000. The detection rate of cardiac defects was 37.5% at a false positive rate of 4.9%. A meta-analysis of screening studies showed that specialist fetal echocardiography in all chromosomally normal fetuses with NT above the 99th centile would identify 1 major cardiac defect in every 16 patients examined; moreover the screening performance does not vary with the type of cardiac defect (19).

Increased nuchal translucency could constitute an indication for specialist fetal echocardiography, so it could be a substantially improved prenatal detection of congenital cardiac defects.

Study of ductus venosus (DV) flow patterns and tricuspid regurgitation (TR) may also improve the selection of those requiring specialized echocardiography (20, 21).

Sporadic abnormalities

Body stalk anomaly (BSA) is a sporadic polymalformative syndrome incompatible with extrauterine life. The fetus had a large anterior midline abdominal wall defect with evagination of the visceral organs into the amnio-peritoneal sac and a completely absent umbilical cord. We review that in an ultrasound screening study of 106,727 fetuses at 10 to 14 weeks, there were 14 cases of this anomaly and the fetal NT was increased in 84% of the fetuses, the karyotype was normal (22, 23).

Increased NT thickness is present in about 40% of fetuses with diaphragmatic hernia (24).

Increased NT is observed also in fetuses with exomphalos, in 85% chromosomally abnormal and in 40% chromosomally normal (5).

Megacystis is associated with increased NT, which is observed in about 75% of those with chromosomal abnormalities and in about 30% of those with normal karyotype (25).

Also rare genetic syndromes seem associated with increased NT but an indisputable association between their

presence and nuchal translucency thickness is difficult to prove (5).

Mechanism of increased NT

There are a lot of condition associated with increased NT, probably because there are many possible mechanisms for this condition. One mechanism could be the cardiac dysfunction in association with abnormalities of the heart and great arteries, probably the heart failure contributes to increase NT, in the first trimester fetus only a small impairment of cardiac diastolic function is necessary to result in an increase NT and abnormal ductal flow (5).

Another mechanism could be venous congestion in the head and neck resulted from constriction of the fetal body as, for example, in the superior mediastinal compression in diaphragmatic hernia or the narrow chest in skeletal dysplasias (5).

In the nuchal skin of trisomy 21 fetuses there is an increase in hyaluronic acid that can entrap large amounts of solvent in the extracellular matrix (26). Many genetic syndromes are associated with alterations in collagen metabolism, this could be responsible of increased fetal NT (5).

Moreover NT could be increased by a failure of lymphatic drainage for its abnormal development or for impaired lymphatic drainage resulting from reduced fetal movements in neuromuscular disorders. Other mechanisms are fetal anemia, fetal hypoproteinemia and parvovirus B19 fetal infection (5).

Management of euploid fetuses with increased NT

We reviewed the correlation between NT thickness and abnormalities, chromosomal defects, miscarriage and fetal death. On the basis of this data it is possible to plan the appropriate follow-up investigations and to counsel parents of these fetuses with increased NT.

With NT value below the 99th centile (3.5 mm) the decision in favor or against fetal karyotyping will be based on the patient-specific risk for chromosomal defects which depends on the first trimester screening, calculated on the basis of maternal age, sonographic findings and serum free β -hCG and PAPP-A at 11 to 14 weeks (27, 28). The chances of having a baby with no major abnormalities is about 97% for NT below the 95th centile and 93% for NT between the 95th and 99th centiles. However these fetuses will be undergone detailed fetal scan at 20 weeks to diagnose or exclude major malformations and abnormalities.

With fetal NT above 3.5 mm a fetal karyotyping by CVS should be offered, in addition a detailed scan at 11 to 13+6 weeks should be carried out; in those cases in which fetal karyotype is normal but NT is above 3.5 mm should be offered fetal echocardiography at 14 to 16 weeks. After this it will be necessary to make the detailed scan carried out by the general population at 20 to 22 weeks for the exclusion or diagnosis of major abnormalities and malformations. If these investigations demonstrate absence of major abnormalities the parents should be informed that they have the same probability of the general population to delivery a baby with serious abnormality or neurodevelopmental delay (5).

If increased NT persists at 14 to 16 weeks scan or it becomes nuchal edema at 20 to 22 weeks, it should be considered the possibility of congenital infection or a genetic

syndrome, parents should be also informed that there is a 10% risk of evolution to hydrops and perinatal death or the possibility of a genetic syndrome, such as Noonan syndrome (10). Moreover the risk of neurodevelopmental delay is 3% to 5%.

Conclusion

Increased NT is an expression, and so an useful marker, of chromosomal abnormalities, fetal malformations and genetic syndromes; the chance of an uneventful pregnancy outcome is inversely related to the initial degree of enlargement.

On the basis of the data reviewed the chances of delivering a baby with no major abnormalities are only about 70% for NT of 3.5-4.4 mm, 50% for NT of 4.5-5.4 mm, 30% for NT of 5.5-6.4 mm, and 15% for NT of 6.5 or more. The parents have to be informed on the need to undergo extra investigations and to take counsel with a geneticist. When investigations are normal and the increased NT resolves, parents should be confidently reassured that the possibility of adverse outcome may be not higher than in a general population. Finally the majority of fetal abnormalities associated with increased NT can be detected by investigations that can be satisfied at 14 weeks of gestation.

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