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Increased Nuchal Translucency in Fetuses with Normal Karyotype

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Abstract

BACKGROUND: Increased nuchal translucency (NT) is associated with a high risk of chromosomal abnormalities and genetic syndromes. In fetuses with normal karyotype, thickened NT increases the likelihood of congenital heart malformations, spontaneous abortions, and stillbirths, especially in thickness > 3.5 mm. It was found that in the absence of accompanying structural abnormalities and a normal result of amniocentesis, the postnatal neurological development of the newborns did not differ from the general population.

CASE PRESENTATION: The authors describe a case of sIUGR of monochorionic twins with second trimester selective umbilical cord ablation and livebirth of a healthy singleton.

CONCLUSION: Abnormal NT thickness on early fetal morphology scan in euploid fetuses, especially in twin pregnancies, increase the suspicion for late complications of the pregnancy.

Introduction

Nuchal translucency (NT) is a sonographic presentation of fluid accumulation under the skin in the cervical region of the fetus during the first trimester of pregnancy. NT as a term is used regardless of whether it is limited as a measurement in the neck area or covers the entire fetus. The optimal gestational age for measuring NT is between 11 + 0 and 13 + 6 gestational weeks. The optimal crown-rump length should be between 45 and 84 mm.

Increased nuchal translucency (NT) is associated with a high risk of aneuploidy. In about half of the cases, the karyotype is normal, but there is a higher risk of structural abnormalities and genetic syndromes. Some of the abnormalities are the result of submicroscopic deletions and duplications that can only be diagnosed by prenatal microarray analysis. A thickened occipital fold is also associated with an adverse pregnancy outcome, such as risk of miscarriage or stillbirth [1], [2], [3].

Increased fetal NT is associated with a heterogeneous group of diseases, suggesting the existence of more than one underlying pathophysiological mechanism [1], [4].

Possible pathophysiological mechanisms are:

- Heart defects/failure
- Venous stasis in the head-and-neck area
- Changed composition of the extracellular matrix
- Impaired lymphatic drainage
- Fetal anemia
- Fetal hypoproteinemia
- Fetal infection

Screening by NT measurement can detect about 80% of fetuses with trisomy 21, as well as other more common aneuploidies with a false-positive result of 5%. In the era of NIPT and the possibilities of microarray analysis and exome sequencing, increased NT remains an important prognostic marker for structural abnormalities and pregnancy complications in euploid pregnancies [5]. It should be kept in mind that the distinction between the concepts of thickened NT, enlarged jugular lymph sacs, cystic hygroma, and hydrops in the first trimester may be unclear, but the clinical behavior follows a similar approach regardless of variations in sonographic findings.

There is still no established consensus regarding the definition of increased NT in patients with a negative NIPT test result, with NT >3.5 mm being considered as a conditional limit. It has been established that the risk of complications during pregnancy with a normal result of invasive prenatal diagnosis (chorionic biopsy and amniocentesis) is proportional to the size of the NT (80% risk of complications for NT > 6.5 mm) [3], [5].

The International Society for Ultrasound in Obstetrics and Gynecology (ISUOG) does not define a specific definition of "increased HT", but the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) recommend a cutoff of 3.0 mm or the 99th percentile for gestational age [6].

Low-risk NIPT patients may be advised to schedule early first-trimester fetal morphology in the late first trimester, e.g., in the 12 + 4 to 13 + 6 weeks range, to increase the possibility of diagnosing structural defects. It is common practice to perform a "pre-NIPT" ultrasound at 10 weeks' gestation, which may result in the detection of nuchal edema in fetuses with a CRL < 45 mm, which would be incorrect.

In a retrospective study, 104 fetuses with CRL 28–45 mm and NT thickness > 2.2 mm (95th percentile for NT at 10 weeks) or hydrops were analyzed. The authors found that the risks of structural (4%) or chromosomal abnormalities (19%) increased with NT thickness. In 77 of the pregnancies (82%), resorption was detected in 11–13+6 weeks, and these cases had fewer complications during pregnancy (miscarriage, structural, or chromosomal abnormalities) compared to the group with NT ≥3.5 mm (10.9% vs. 76.5%, respectively, $p < 0.001$) [7], [8].

While the risk of presence of the most common aneuploidies is low with a negative NIPT result, their absence cannot be guaranteed. Most non-invasive prenatal tests do not exclude microdeletions/duplications and mosaicism for all aneuploidies. Increased NT in 11–13 gestational weeks should not be associated with intrauterine infections, since the latter more often lead to fetal hydrops in the second or third trimester.

Increased NT is associated with adverse pregnancy outcomes (miscarriage, intrauterine death, neonatal death, structural abnormalities), which is more likely in NT ≥6 mm and cystic hygromas. Few studies have analyzed the association between a thickened occipital fold and adverse pregnancy outcomes in euploid fetuses without structural abnormalities. Sheizaf *et al*. found a linear relationship between increased NT and the risk of gestational diabetes and perinatal mortality. Hourrier *et al*. reported an increased likelihood of pre-eclampsia, intrauterine retardation, and pre-term birth [9], [10], [11].

Increased NT in euploid fetuses can be due to heart defects, omphalocele, body stalk anomaly, skeletal defects; some genetic syndromes, such as congenital adrenal hyperplasia, fetal akinesia, or Noonan syndrome, have been suggested as possible causes. According to recent studies, a significant correlation has been found between increased NT and the presence of diaphragmatic hernia and a higher risk of cleft palate [12], [13], [14], [15].

The incidence of neurodevelopmental abnormalities in children with enlarged nuchal fold, normal karyotype, and normal anatomy does not appear to be higher than that reported for the general population [16], [17], [18].

In monochorionic twin pregnancies, the predictive value of prenatal screening at 11–13 gestational weeks by triad analysis – NT, umbilical cord insertion, and CRL variation between the two twins – was analyzed. Increased NT and differences in CRL between the two twins were found to be associated with an increased likelihood of TTTS (twin-to-twin transfusion syndrome) and sIUGR (selective-intrauterine growth restriction) [19]. The incidence of NT enlargement or discrepancy between the monochorionic twins ranges from 8 to 18%. This phenomenon was first described by Sebire *et al*. in a retrospective cohort study of 287 monochorionic twins and reported high predictive value for TTTS risk at HT >95th percentile [20].

Monochorionic diamniotic twins (MCDA) account for 70% of monozygotic pregnancies that result from embryo separation between days 4 and 8 after fertilization and are associated with increased perinatal morbidity and mortality as a result of placental vascular anastomoses. Twin-to-twin transfusion syndrome (TTTS) and selective intrauterine growth retardation (sIUGR) are the two main risks in MDCA, with a prevalence of 15–20% and 15%, respectively [2], [17].

Early prediction is needed to assess high-risk pregnancies. A number of studies have shown that differences in CRL, abnormal blood flow in the ductus venosus, and increased NT at 11–13+6 weeks of gestation can be used as predictors of complications in monochorionic pregnancies [20].

Clinical Case

A 26-year-old primigravida, after frozen single embryo transfer, was diagnosed at 6 weeks with monochorionic diamniotic pregnancy. On early fetal morphology scan at 11+2 weeks, enlarged NT at about 5.6 mm was measured for one of the twins, without accompanying structural abnormalities (Figures 1 and 2).

After a consultation with a certified specialist in the field of maternal-fetal medicine, combined first-trimester screening shown 1:72 risk for trisomy 21, and chorionic biopsy was conducted with negative result for chromosomal abnormalities. The patient was referred for early fetal morphology scan at 16 gestational weeks.

At 16 gestational weeks, an oligohydramnios in one of the fetuses and fetal growth discordance of

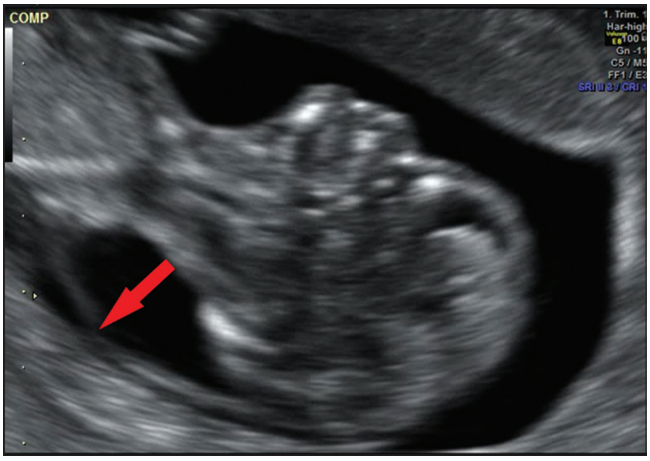

Figure 1: 2D visualization of the fetus in 11 + 2 gestational weeks with increased NT 5.6 mm in sagittal section (red arrow)

about 31% was detected, with suspected selective fetal growth retardation type 2 (sIUGR).

By definition, sIUGR means estimated fetal weight <10th percentile with persistent absent and/or reversed end-diastolic blood flow in the umbilical artery, in the absence of transfusion syndrome.

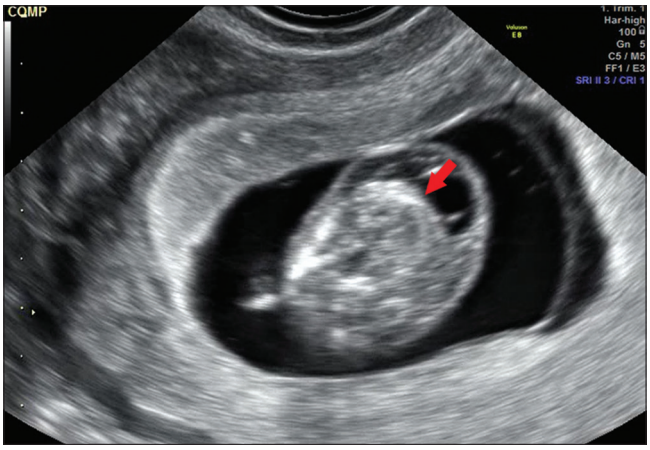

Figure 2: 2D visualization of the fetus in 11 + 2 gestational weeks with increased NT 5.6 mm in axial section (red arrow)

The possibility of intrauterine death of the retarded twin (20–25%) and the associated risks for the second twin (25% risk of CNS damage due to severe sudden blood loss) were discussed with the mother.

1. Two options for behavior were proposed:
2. Tracing the development of the pregnancy until evidence of fetal distress and the need for early delivery with a possible subsequent stay in the intensive care neonatology unit (level 3 competence)
3. Fetoscopic ablation with the aim of interrupting blood circulation of the retarded fetus and monitoring the development of the second twin if possible until term.

The pregnancy was actively followed until 22 gestational weeks when the following complications were detected:

1. First twin: with evidence of normal growth and Doppler velocimetry
2. Second twin: with zero end-diastolic blood flow at umbilical artery, high diastolic blood flow in middle cerebral artery (MCA), significant fetal anemia with high systolic velocity in MCA, and still positive blood flow in ductus venosus.

A decision was made for fetoscopic ablation of the umbilical cord of the affected twin at 23 gestational weeks.

Ultrasound finding 2 weeks after the procedure (Figure 3):

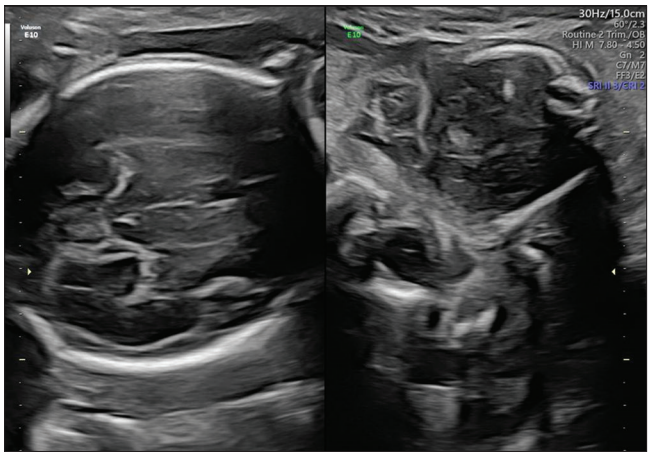

Figure 3: Transthalamic section of the head of the developing twin (left) and abdominal circumference of the fetus compressus (right)

The pregnancy proceeded without complications until 36 gestational weeks, with planned operative delivery by cesarean section due to evidence of oligohydramnios and an increased risk of accidents from the side of the umbilical cord

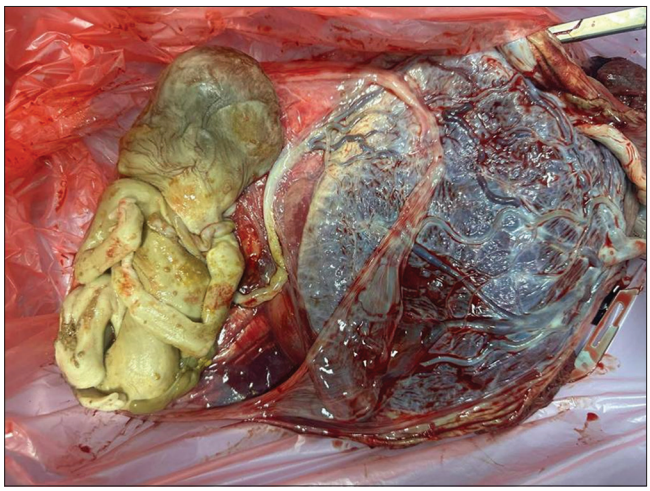

Figure 4: Visualization of fetus compressus (left) and the placenta (right)

compression. A live fetus was born, 3100 gs, 50 cm, with APGAR 8-9. During extraction of the placenta, a fetus compressus is visualized, separated from the amniotic sac.

Conclusion

Measurement of NT has a high predictive value in screening during the first trimester (11-13+6 gestational weeks). A thickened occipital fold greater than 3.0 mm is associated with a high risk of chromosomal abnormalities, structural defects, and pregnancy complications. In monochorionic pregnancies, it can be a predictive factor for the risk of twin-to-twin transfusion syndrome or selective fetal growth retardation. A detailed follow-up of pregnancies with an isolated enlarged occipital fold is necessary for early detection of adverse pregnancy outcomes.

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