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REVIEW ARTICLE

Increased nuchal translucency with normal karyotype

Athena P. Souka, MD,[a,b] Constantin S. von Kaisenberg, MD,[a,b] Jonathan A. Hyett, MD,[a] Jiri D. Sonek, MD,[c] Kypros H. Nicolaides, MD[a,*]

Harris Birthright Research Centre for Fetal Medicine, King's College, London University, London, UK,[a] *Department of Obstetrics and Gynecology, Alexandra Maternity Hospital, Athens University, Athens, Greece,*[b] *and Department of Obstetrics and Gynecology, University of Schleswig-Holstein, Campus Kiel, Kiel, Germany*[c]

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Increased fetal nuchal translucency (NT) thickness between 11 and 14 weeks' gestation is a common phenotypic expression of chromosomal abnormalities, including trisomy 21. However, even in the absence of aneuploidy, nuchal thickening is clinically relevant because it is associated with an increase in adverse perinatal outcome caused by a variety of fetal malformations, dysplasias, deformations, dysruptions, and genetic syndromes. Once the presence of aneuploidy is ruled out, the risk of perinatal outcome dose not statistically increase until the nuchal translucency measurement reaches 3.5 mm or more (>99th percentile). This increase in risk occurs in an exponential fashion as the NT measurement increases. However, if the fetus survives until midgestation, and if a targeted ultrasound at 20 to 22 weeks fails to reveal any abnormalities, the risk of an adverse perinatal outcome and postnatal developmental delay is not statistically increased.

In the first trimester of pregnancy there is a subcutaneous collection of fluid in the fetal neck that is visualized by ultrasonography as nuchal translucency (NT).[1] In normal fetuses, NT thickness increases with fetal crown-rump length (CRL). In a study involving 96,127 pregnancies, the median and 95th centile at a CRL of 45 mm were 1.2, and 2.1 mm, and the respective values at CRL of 84 mm were 1.9 and 2.7 mm.[2] The 99th centile did not change significantly with CRL, and it was about 3.5 mm.

* Reprint requests: Professor KH Nicolaides, Harris Birthright Research Centre for Fetal Medicine, King's College, London University, Denmark Hill, London SE5 8RX.
E-mail: Kypros@fetalmedicine.com

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Increased NT refers to a measurement above the 95th centile, and the term is used irrespective of whether the collection of fluid is septated or not, and whether it is confined to the neck or envelopes the whole fetus.[1] After 14 weeks, increased NT usually resolves, but in some cases it evolves into nuchal edema or cystic hygromas.[3-6]

The technique for measurent of NT, the need for appropriate training of sonographers and external quality assurance, as well as the application of NT in effective screening for chromosomal abnormalities are well established.[7] In this article we review the association between increased fetal NT thickness in chromosomally normal fetuses and a wide range of fetal malformations, deformations, dysgeneses, and genetic syndromes.

Table I Relation between nuchal translucency thickness and prevalence of chromosomal defects, miscarriage, or fetal death and major fetal abnormalities

Nuchal translucency	Chromosomal defects[2]	Fetal death[8-10]	Major fetal abnormalities[8-10]	Alive and well
<95th centile	0.2%	1.3%	1.6%	97%
95th-99th centiles	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%

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

Outcome of fetuses with increased nuchal translucency

The relation between NT thickness and the prevalence of chromosomal defects, miscarriage, or fetal death and major fetal abnormalities is summarized in Table I.[2,8-10] On the basis of these data it is possible to estimate, for each NT group, the chances of intrauterine survival and delivery of a healthy fetus with no major defects.

Chromosomal defects

The prevalence of chromosomal defects increases exponentially with NT thickness. The relation between fetal NT and chromosomal defects was derived from a screening study involving 96,127 singleton pregnancies.[2] In the chromosomally abnormal group, about 50% had trisomy 21, 25% had trisomy 18 or 13, 10% had Turner syndrome, 5% had triploidy, and 10% had other chromosomal defects.

Fetal death

In chromosomally normal fetuses, the prevalence of fetal death increases exponentially with NT thickness. In the combined data from 2 studies on a total of 4540 chromosomally normal fetuses with increased NT but no obvious fetal defects, the prevalence of miscarriage or fetal death increased from 1.3% in those with NT between the 95th and 99th centiles to about 20% for NT of 6.5 mm or more.[8,9] The majority of fetuses that die do so by 20 weeks, and they usually show progression from increased NT to severe hydrops. Another study of 6650 pregnancies undergoing NT screening reported that in chromosomally normal fetuses the prevalence of miscarriage or fetal death was 1.3% in those with NT below the 95th centile, 1.2% for NT between the 95th and 99th centiles, and 12.3% for NT above the 99th centile.[10]

Fetal abnormalities

Major fetal abnormalities are defined as those requiring medical and/or surgical treatment or conditions associated with mental handicap.

Several studies have reported that increased fetal NT thickness is associated with a high prevalence of major fetal abnormalities (Table II).[8-35] In the combined data of 28 studies on a total of 6153 chromosomally normal fetuses with increased NT the prevalence of major defects was 7.3%. However, there were large differences between the studies in the prevalence of major abnormalities, ranging from 3% to 50%, because of differences in their definition of the minimum abnormal NT thickness, which ranged from 2 mm to 5 mm.

The prevalence of major fetal abnormalities in chromosomally normal fetuses increases with NT thickness, from 1.6% in those with NT below the 95th centile,[10] to 2.5% for NT between the 95th and 99th centiles, and exponentially thereafter to about 45% for NT of 6.5 mm or more.[8,9]

Developmental delay

Seven studies have reported on the long-term follow-up of chromosomally and anatomically normal fetuses with increased NT (Table III). In 3 studies based on questionnaires to the parents, the prevalence of developmental delay was 2% in the combined total of 101 infants.[15,27,33] In 4 studies on a combined total of 207 infants that had increased NT in fetal life, clinical examination demonstrated developmental delay in 3.9% of cases.[28,30,34,36] It is difficult to assess the true significance of these findings because only 1 of the studies had a control group for comparison.[31] Brady et al performed a clinical follow-up study of 89 children that in fetal life had NT of 3.5 mm or more and 302 children whose fetal NT was less than 3.5 mm.[31] Delay in achievement of developmental milestones was observed in 1 of the children in each group.

Types of abnormalities associated with increased nuchal translucency

A wide range of fetal abnormalities have been reported in fetuses with increased NT, and these are summarized in Table IV.[8-21,23-25,27-128] The observed prevalence for