

Outcome of chromosomally normal livebirths with increased fetal nuchal translucency at 10-14 weeks' gestation

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Abstract

The aim of this study was to determine the outcome of chromosomally normal livebirths with increased fetal nuchal translucency at 10-14 weeks' gestation. Clinical follow up of 89 chromosomally normal livebirths that in fetal life had a minimum nuchal translucency thickness of 3.5 mm and a comparison group of 302 infants whose fetal nuchal translucency thickness at 10-14 weeks of gestation was less than 3.5 mm was performed. Major abnormalities, mainly structural defects of the cardiovascular or skeletal systems, were found in 10.1% (nine of 89) of the group with increased translucency, compared to 2% (five of 302) in those with translucency of less than 3.5 mm ($\chi^2=11.9$, $p<0.001$). Delay in achievement of developmental milestones was observed in one of the infants with increased translucency and in one of the comparison group. The findings of this study show that in chromosomally normal fetuses increased nuchal translucency thickness at 10-14 weeks of gestation is a marker for fetal abnormalities including structural defects and genetic syndromes.

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There is a strong association between an abnormal collection of fluid behind the fetal neck (nuchal translucency) at 10-14 weeks of gestation and chromosome abnormalities.¹⁻¹¹ Furthermore, in chromosomally normal pregnancies increased nuchal translucency in the first trimester or nuchal fold thickness in the second trimester is associated with a high risk of miscarriage and a wide variety of fetal abnormalities, including cardiovascular, pulmonary, skeletal, metabolic, and haematological defects, as well as congenital infections and single gene disorders, in particular Noonan syndrome.¹²⁻¹⁷

The aim of this study was to investigate the prevalence of congenital anomalies in chromosomally normal livebirths that had a nuchal translucency thickness at 10-14 weeks of gestation of ≥ 3.5 mm; this measurement corresponds to the 99th centile of the reference range of translucency thickness at this gestation.¹

Methods

Clinical follow up (age range 6 months to 3½ years) was carried out in a consecutive series of 90 chromosomally normal infants, born between January 1991 and October 1994, whose mothers had attended The Harris Birthright Research Centre for Fetal Medicine for ultrasound examination at 10-14 weeks of gestation. The scan had shown that the fetal nuchal translucency thickness was at least 3.5 mm and chorion villus sampling or amniocentesis showed a normal karyotype. Further antenatal investigations included detailed ultrasound examination and echocardiography at 20 weeks of gestation and maternal serum testing for toxoplasmosis, coxsackie B virus, cytomegalovirus, rubella virus, herpes virus, and parvo B19 virus. The findings in this group were compared to those in 302 chromosomally normal infants whose fetal nuchal translucency thickness at 10-14 weeks of gestation was less than 3.5 mm. This latter group of infants were a group of consecutive cases born during the same period as the study group and they lived near King's College Hospital.

The parents were contacted by telephone and asked whether they would be willing to bring their child to the hospital for clinical assessment. In those that were unable to attend ($n=67$), details concerning the pregnancy and delivery, early infancy, and the age at which developmental milestones were reached were obtained by telephone. All clinical examinations were carried out either by a clinical geneticist or a paediatrician and features associated with genetic syndromes were specifically looked for. When it was considered necessary ($n=17$), further information was sought from the patients' general practitioners or hospital consultants.

STATISTICAL ANALYSIS

Yates' corrected chi-squared test was used to determine the significance of differences in the prevalence of major abnormalities in the group with NT ≥ 3.5 mm compared to those with NT < 3.5 mm and within the group with NT ≥ 3.5 mm in those where the translucency resolved by 20 weeks of gestation compared to those in which it persisted.

Results

In the series of 90 chromosomally normal infants with fetal NT ≥ 3.5 mm only one was lost to follow up. Major abnormalities were diagnosed in 10.1% (nine of 89) infants with

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Table 1 Ultrasound findings and major abnormalities in the group with fetal nuchal translucency thickness ≥ 3.5 mm at 10-14 weeks of gestation

Nuchal translucency thickness at 10-14 weeks of gestation	Ultrasound findings at 20 weeks	Abnormalities
3.5 mm	No nuchal oedema	Right multicystic non-functioning kidney
3.6 mm	No nuchal oedema	Severe motor developmental delay. Right convergent squint
3.8 mm	No nuchal oedema	Tetralogy of Fallot
4.0 mm	No nuchal oedema	Vitamin D resistant rickets
4.2 mm	No nuchal oedema	Atrial septal defect. Feeding difficulties
5.0 mm	No nuchal oedema	Pyloric stenosis
5.0 mm	No nuchal oedema	Nance-Sweeney dwarfism (chondrodystrophy)
6.0 mm	Nuchal oedema that persisted until 30 wk	Mild pulmonary valve stenosis. Right renal pelvis mildly dilated. No dysmorphic features. Normal development
8.0 mm	Nuchal oedema that persisted until 31 wk	Noonan syndrome with dysmorphic facies, short stature, and pulmonary valve stenosis

NT ≥ 3.5 mm (table 1), which was significantly higher than the 2% (five of 302, $\chi^2=11.9$, $p<0.001$) observed in those with fetal NT <3.5 mm. In the latter group there were two cases of ventricular septal defects associated with recurrent respiratory tract infections, and one case each of mild developmental delay, laryngomalacia associated with recurrent respiratory tract infections, and Pierre-Robin syndrome.

Minor abnormalities, including birth marks (for example, strawberry naevi and capillary haemangiomas), umbilical hernias, inguinal hernias, mild hypospadias, undescended testis, hydrocele, positional talipes equinovarus, clinodactyly, or one absent finger, were observed in 14 (16%) of those with fetal NT ≥ 3.5 mm and in 25 (8%) of those with NT <3.5 mm.

In the group with fetal NT ≥ 3.5 mm at the 10-14 week scan, the translucency resolved before 20 weeks in 75 cases and seven (9%) of these had major abnormalities, whereas in the 14 where the translucency evolved into oedema that persisted beyond 20 weeks there were two (14%) ($\chi^2=0.01$, $p=0.92$) with major abnormalities.

Discussion

The data in this study suggest that fetal nuchal translucency thickness ≥ 3.5 mm at 10-14 weeks of gestation in chromosomally normal pregnancies is associated with increased risk for major abnormalities, mainly structural defects of the cardiovascular or skeletal systems. These findings emphasise the need to counsel the parents that fetuses with increased nuchal translucency are not only at risk of chromosomal abnormalities but also of other anomalies including anatomical defects and genetic syndromes.

In a previous study on the outcome of 565 chromosomally normal fetuses with first trimester nuchal translucency 3-9 mm, we reported that about 4% had structural defects, mainly cardiac, diaphragmatic, renal, and abdominal wall, which is higher than would be expected in an unselected population.¹² However, the present study is the only one in which detailed genetic and paediatric follow up of infants with increased fetal translucency has been undertaken and the findings compared to those in a group with nuchal translucency <3.5 mm. Two previous studies examined a total of 26 chromosomally normal livebirths with increased fetal nuchal translucency (defined as >2 mm); 23 were reported as healthy, two had

non-specific dysmorphic features, and one had Noonan syndrome.^{4 16} In another study of 32 chromosomally normal fetuses with increased nuchal translucency (defined as >2.5 mm), there was one case with persistent hygromas that were successfully repaired at birth and in the other 31 cases the translucency resolved by 20 weeks and all babies were healthy at birth; follow up examination at 12 months showed normal growth and development in all infants.¹⁷ A recent study examining the outcome of 28 pregnancies associated with NT thickness >3 mm at 10-15 weeks and normal karyotype indicated that a more pronounced NT thickness is associated with a higher incidence of structural anomalies and a poorer fetal outcome.¹⁸

In our study there was no significant increase in the number of major abnormalities found in the group where the NT persisted beyond 20 weeks compared to those pregnancies where it resolved. However, it is acknowledged that the number of cases examined was too small to reach a conclusion that the outcome of pregnancies associated with nuchal translucency is not related to the time at which the thickening resolves.

It is well recognised that Noonan syndrome is associated with abnormal accumulation of nuchal fluid and hydrops fetalis.¹⁹ Witt *et al*²⁰ reported nine cases with lymphoedema and concluded that the major source was generalised dysplasia of the lymphatic vessels. Bennacer *et al*¹⁴ reported on the prenatal sonographic features in four infants with Noonan syndrome and all four fetuses had cystic hygromata. However, the diagnosis of Noonan syndrome cannot be predicted from the time of resolution of the abnormal nuchal fluid. Both in our case and two previously reported ones resolution did not occur until the third trimester.²¹ In contrast, Trauffer *et al*¹⁶ reported one case where resolution occurred before 20 weeks.

The findings of this study show that in chromosomally normal fetuses increased nuchal translucency thickness at 10-14 weeks of gestation is a marker for fetal abnormalities including structural defects and genetic syndromes. Consequently, parents should be counselled that in the presence of this sonographic marker the fetus is not only at risk of chromosomal abnormalities but also of other defects. Therefore, in addition to offering the parents the option for fetal karyotyping, the finding of

increased translucency should stimulate the search for other fetal defects by detailed ultrasonography and postnatal paediatric follow up should be arranged.

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