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Natural history of trisomy 21 fetuses with increased nuchal translucency thickness

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ABSTRACT

Increased fetal nuchal translucency thickness at 10–14 weeks of gestation can identify 80% of trisomy 21 pregnancies. However, a potential disadvantage of screening in the first trimester of pregnancy is that earlier screening preferentially identifies those chromosomally abnormal pregnancies that are destined to miscarry. In this study, we report on the outcome of six fetuses with increased nuchal translucency thickness and trisomy 21 whose parents chose to continue with the pregnancy. During the second trimester, the nuchal translucency resolved in five of the cases and in one it evolved into nuchal edema. Therefore, resolution of translucency with advancing gestation is not indicative of a normal karyotype. All pregnancies resulted in live births, suggesting that increased nuchal translucency does not necessarily identify those trisomic fetuses that are destined to die in utero.

INTRODUCTION

Increased nuchal translucency thickness at 10–14 weeks of gestation, as a screening method for trisomy 21, can identify approximately 80% of affected pregnancies for an invasive testing rate of 5%[1,2]. However, trisomy 21 is associated with a high rate of intrauterine lethality and the prevalence in the first trimester of pregnancy is twice as high as in live births[3]. Consequently, if screening by nuchal translucency preferentially identifies those fetuses destined to die *in utero*, the test would detect less than 60% of trisomy 21 in live births. This study examines the natural history of trisomy 21 fetuses identified in the first trimester of pregnancy because of increased nuchal translucency thickness.

PATIENTS AND METHODS

During a 5-year period (1990–94), we performed first-trimester fetal karyotyping, by chorion villus sampling or amniocentesis, in 1171 singleton pregnancies, because ultrasound examination at 10–14 weeks of gestation had demonstrated increased fetal nuchal translucency (at least 2.5 mm). Trisomy 21 was diagnosed in 108 cases and in five of these the parents chose to continue with the pregnancy, whereas in 103 they chose termination. During the same period, trisomy 21 was diagnosed in one of the fetuses in a twin pregnancy, and the parents elected to avoid invasive prenatal diagnosis or selective fetocide.

In all cases, transabdominal ultrasound examination (curvilinear 5-MHz transducer, Toshiba SSA 250A, Toshiba Medical Systems Limited, Tokyo, Japan or Aloka 650, Aloka Limited, Tokyo, Japan) was used to image a sagittal section of the fetus for measurement of crown–rump length and the maximum thickness of the subcutaneous translucency between the skin and the soft tissue overlying the cervical spine[1]. At 18–21 weeks of gestation, detailed ultrasound examination was carried out and the nuchal fold thickness was measured in the mid-sagittal plane of the neck[4].

RESULTS

The maternal age, ultrasound findings and outcome of the six trisomy 21 fetuses are shown in Table 1. In five of the six fetuses, the nuchal translucency resolved and at the second-trimester scan the nuchal fold thickness was normal (less than 7 mm)[4]. At the second-trimester scan, one fetus had nuchal edema that produced a characteristic tremor on ballottement of the fetal head, three had septal defects, two had echogenic bowel and one had mild hydronephrosis or pyelectasia.

All six trisomy 21 babies were born alive and five are healthy. One had a major atrioventricular septal defect and died at the age of 6 months. Another two of the babies had small ventricular septal defects and these are being managed conservatively, awaiting spontaneous closure.

In the chromosomally normal fetus from the twin pregnancy, the thickness of the nuchal translucency at 12 weeks was 1 mm and the thickness of the nuchal fold

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Table 1 Maternal age, gestational age, ultrasound findings (NT, nuchal translucency thickness; NF, nuchal fold thickness) and outcome including gestation at delivery, birth weight (BW) and abnormalities in six fetuses with trisomy 21 and increased nuchal translucency. In case 5, the baby had a major atrioventricular septal defect and died at the age of 6 months. Case 6 was a twin pregnancy and in the chromosomally normal co-twin the thickness of the nuchal translucency was 1 mm and the nuchal fold 4 mm

Case	*Maternal age* (years)	*Gestational age* (weeks)	*Ultrasound findings*	*Outcome*
1	22	13 20	NT 10 mm NF 6 mm	37 weeks, male, BW 2458 g, healthy
2	40	11 18	NT 7 mm NF 4 mm	37 weeks, male, BW 3260 g, healthy
3	26	11 21	NT 5 mm NF 5 mm, echogenic bowel, septal defect	39 weeks, female, BW 3934 g, small septal defect
4	27	12 20	NT 5 mm NF 5 mm, echogenic bowel, pyelectasia, septal defect	39 weeks, male, BW 3771 g, small septal defect
5	41	12 18	NT 4 mm NF 4 mm, septal defect	32 weeks, female, BW 1640 g, infant death, major septal defect
6	40	12 20	NT 8 mm NF 8 mm, nuchal edema	36 weeks, female, BW 1510 g, healthy

at 20 weeks was 4 mm; a healthy female baby was born with birth weight of 3240 g.

DISCUSSION

This study confirms the strong association between trisomy 21 and increased fetal nuchal translucency thickness at 10–14 weeks of gestation[1,2,5,6]. Screening for chromosomal defects in the first rather than the second trimester has the advantage of earlier prenatal diagnosis and consequently less traumatic termination of pregnancy for those couples that choose this option. A potential disadvantage is that earlier screening preferentially identifies those chromosomally abnormal pregnancies that are destined to miscarry. Snijders and colleagues compared the prevalence of trisomy 21 at 9–14 weeks with that in live births and estimated that approximately 53% of affected fetuses die *in utero*[3].

The findings of the present study, that all six trisomy 21 fetuses survived, suggest that increased nuchal translucency does not necessarily identify those trisomic fetuses that are destined to die *in utero*. However, the number of cases was too small to draw conclusions on the relationship between the thickness of nuchal translucency and the relative risk of intrauterine death in trisomy 21. Nevertheless, in a previous study of 821 chromosomally normal fetuses with nuchal translucency of 3–4 mm, the rate of fetal loss was about 3%, which is similar to that observed in fetuses with normal nuchal translucency undergoing chorion villus sampling; even in fetuses with translucency of ≥ 5 mm, the rate of fetal loss was only 13%[6].

During the second-trimester scan, increased nuchal fold thickness was found in one of our six trisomy 21 fetuses, hyperechogenic bowel was present in two, mild hydronephrosis in one and septal defects in three. These findings are in general agreement with the reported incidence of the various sonographic features in fetuses with trisomy 21. Although Benacerraf and co-workers reported increased nuchal fold thickness in 45% of trisomy 21 fetuses[7], a recent multicenter study found this sonographic sign to be present in only 8% of affected fetuses[8]. Bromley and associates reported that hyperechogenic bowel is found in 0.5% of normal fetuses and in approximately 13% of fetuses with trisomy 21[9]. Mild hydronephrosis or pyelectasia is present in 2% of normal fetuses and in 17% of those with trisomy 21[10].

Hyett and colleagues examined the fetal heart after termination of pregnancy in 21 fetuses with trisomy 21 and nuchal translucency of 4 mm or more; perimembranous ventricular and atrioventricular septal defects were detected in 17 (81%) of the cases[11]. In two cases, the perimembranous ventricular septal defect was partly obliterated by the overlying septal leaflet of the tricuspid valve. The incidence of septal defects was twice as high as in live births with trisomy 21[12,13], raising the possibility that in a high proportion of affected fetuses there is spontaneous intrauterine closure of septal defects; postnatally, spontaneous closure of septal defects during the first year of life has been reported in 45% of cases[14]. The findings of the present study provide indirect supportive evidence for the hypothesis of spontaneous intrauterine closure of septal defects; the nuchal translucency was 4 mm or more in all six trisomy 21 fetuses and yet only three of the babies had septal defects at birth, one major defect leading to infant death, and two minor defects.

The findings of this study emphasize the need to avoid using the term 'cystic hygroma' when referring to abnormal accumulation of nuchal fluid in the first trimester of pregnancy. Multi-septated nuchal cystic hygromata are an ultrasonographic finding in the second trimester and at least 70% of cases are associated with Turner syndrome[15]. In contrast, first-trimester nuchal translucency is usually associated with trisomies and, as shown in this study, in the second trimester the translucency either resolves or evolves into nuchal edema. In addition, the

resolution of nuchal translucency by the second trimester does not reduce the risk for fetal trisomy and should not falsely reassure the clinician or patient.

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