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Intrauterine lethality of trisomy 21 fetuses with increased nuchal translucency thickness

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ABSTRACT

This study investigates whether first-trimester screening for trisomy 21 by fetal nuchal translucency thickness preferentially identifies those fetuses destined to die in utero *and examines the potential impact of such a method of screening on the live birth incidence of trisomy 21. In 70 pregnancies, trisomy 21 was diagnosed at 12 (range 11–14) weeks of gestation and the parents opted for elective termination which was carried out at 14 (12–20) weeks. In all cases, viability was established by ultrasound scan at the time of chorion villus sampling (CVS) and just before termination of pregnancy. Eight (11.4%) fetuses died in the interval between CVS and termination of pregnancy and this rate of lethality was higher than the 6.9% estimated rate for an unselected population of trisomy 21 fetuses. This 4.5% increase may, in part, be attributed to the effects of CVS and may also be due to patient selection on the basis of increased nuchal translucency. The rate of lethality increased with translucency thickness from 5.3% for those with translucency of 1–3 mm to 23.5% for translucency of > 7 mm. In trisomy 21, the rate of intrauterine lethality is associated with nuchal translucency thickness. Nevertheless, a policy of screening by maternal age and fetal nuchal translucency followed by selective termination of affected fetuses would still result in a more than 70% reduction in the live birth incidence of trisomy 21.*

INTRODUCTION

Screening for trisomy 21 by a combination of maternal age and fetal nuchal translucency thickness at 10–14 weeks of gestation can identify 80% of affected pregnancies for an invasive testing rate of 5%[1,2]. However, many fetuses with trisomy 21 die *in utero*; the estimated rate of intrauterine lethality between 12 weeks and term is 40%[3]. This study investigates whether screening by nuchal translucency thickness preferentially identifies those fetuses destined to die *in utero* and estimates the potential impact of first-trimester screening by maternal age and fetal nuchal translucency on the live birth incidence of trisomy 21.

METHODS

Between December 1993 and July 1995, we performed 70 terminations of pregnancy at the request of the parents because chorion villus sampling (CVS) had demonstrated trisomy 21. The patients had first-trimester screening for trisomies based on maternal age and fetal nuchal translucency thickness and chose fetal karyotyping because they were classified to be at increased risk. The indications for fetal karyotyping were advanced maternal age ($n = 6$) or increased fetal nuchal translucency thickness (> 3 mm) at routine ultrasound examination at 10–14 weeks of gestation ($n = 64$).

At the time of CVS, transabdominal ultrasound examination (curvilinear 5-MHz transducer, Toshiba SSA 250A, Toshiba Medical Systems 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]. In all cases, ultrasound examination for detection of fetal heart activity was also performed immediately before termination of pregnancy.

Statistical analysis

Snijders and colleagues reported a model which provides estimates for the relative prevalence of trisomy 21 at different gestations compared to the prevalence in live births[3]. The expected rate of lethality in the present study was derived from the relative prevalences at the time of CVS and at the time of termination for individual fetuses. The significance of differences between observed and expected rates of lethality, both in the total group and in subgroups according to nuchal translucency thickness, was examined using the Fisher exact test.

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RESULTS

The mean gestation at CVS was 12 (range 11–14) weeks and at termination was 14 (range 12–20) weeks. At the time of CVS, all fetuses were alive. An ultrasound scan immediately before termination demonstrated that eight (11.4%) fetuses were dead. The rate of lethality increased with translucency thickness from 5.3% for those with translucency of 0–3 mm (there was one death in the six fetuses with translucency of 0–2 mm and no deaths in the 13 with translucency of 3 mm) to 8.8% for those with translucency of 4–6 mm and 23.5% for translucency of ≥ 7 mm (Table 1).

In the study population, the distribution of nuchal translucency thickness was different from that of an unselected population of trisomy 21 fetuses (23% for 0–2 mm, 20% for 3 mm, 43% for 4–6 mm and 14% for > 7 mm)[2]. From the observed rates of intrauterine lethality in each nuchal translucency group (Table 1), it was estimated that, in 100 trisomy 21 fetuses with the nuchal translucency thickness distribution of an unselected population[2], the rate of lethality between 12 and 14 weeks of gestation would be 9.35% (Table 2). This estimated rate of intrauterine lethality (9.35%) is similar to that calculated from the difference in prevalence of trisomy 21 at 12 and 14 weeks of gestation (6.87%, $p = 0.76$) as reported by Snijders and colleagues[3]. Assuming that the relative rate of intrauterine lethality by nuchal translucency thickness from 12 to 14 weeks (1.22/9.35 or 13% for translucency of 0–2 mm, 12% for 3 mm, 40% for 4–6 mm and 35% for ≥ 7 mm) remains similar throughout pregnancy, then it is possible to calculate the contribution of each nuchal translucency group to the estimated 40% lethality between 12 weeks and birth. In an unselected population of 100 trisomy 21 fetuses at 12 weeks, the translucency thickness would be 0–2 mm in 23 cases and at least 3 mm in 77[2]; 18 of the former and 42 of the latter would be expected to be liveborn. Therefore, translucency of at least 3 mm identifies 77% of trisomic fetuses at 12 weeks and 70% of those that would potentially be liveborn.

DISCUSSION

Estimates of the prevalence of trisomy 21 at different gestations have been derived by combining data from studies reporting the frequency in live births, and in women having prenatal diagnosis at 16–20 weeks or at 9–14 weeks of gestation[3]. The rate of intrauterine lethality has been calculated from the differences between the estimated frequencies at a given gestation and frequencies in live births. For trisomy 21, the estimated rate of lethality between 18 weeks and birth was 30%, which was identical to the rate observed by Hook in a study where trisomy 21 was diagnosed at second-trimester amniocentesis and the parents decided to continue with the pregnancy[4]. Further support for the accuracy of the model is provided by the finding of the present study that the observed loss rate, after correction for the distribution of nuchal translucency thickness in an unselected population, was not significantly different from the rate expected on the basis of the difference in gestation between CVS and termination of pregnancy.

The findings of this study suggest that the rate of intrauterine lethality in trisomy 21 fetuses is related to the thickness of nuchal translucency. Although the pathophysiology of both increased nuchal translucency and intrauterine death remains uncertain, a common cause may be heart failure due to a cardiac defect. In a pathological study of 36 first-trimester trisomy 21 fetuses with increased nuchal translucency, the prevalence of cardiac septal defects was 56% and the frequency increased with translucency thickness[5]; in contrast, echocardiographic studies in trisomy 21 neonates found septal defects in only 30% of the cases[6,7]. However, increased translucency thickness does not invariably lead to intrauterine death. The majority of trisomy 21 neonates have abundant nuchal skin[8] which is presumably manifested as increased translucency during early fetal life. Additionally, in a study of six trisomy 21 fetuses with increased nuchal translucency thickness where the parents chose to continue with the pregnancy, the translucency resolved and all six infants were liveborn[9].

A policy of screening for trisomy 21 by fetal nuchal translucency thickness at 12 weeks of gestation can identify 77% of affected fetuses for an invasive testing rate of 5%; when the data from translucency thickness are combined with maternal age, the sensitivity of the test is 80%[2]. In

Table 1 Relation of fetal nuchal translucency thickness and rate of death in 70 trisomy 21 fetuses in the interval between chorion villus sampling and termination of pregnancy

Nuchal translucency thickness (mm)	*Trisomy 21 fetuses*	
	Total	*Dead*
0–3	19	1 (5.3%)
4–6	34	3 (8.8%)
7	17	4 (23.5%)
Total	70	8 (11.4%)

Table 2 Calculation of intrauterine lethality in 100 trisomy 21 fetuses with the nuchal translucency thickness (NT) distribution of an unselected population of trisomic fetuses[2] (column 2). The number of deaths between 12 and 14 weeks of gestation was calculated from the observed lethality rate by nuchal translucency thickness (Table 1) between chorion villus sampling at 12 weeks and termination of pregnancy at 14 weeks (column 3). The estimated number of 40 deaths between 12 weeks and term was calculated from the relative prevalence of trisomy 21 at 12 weeks of gestation and term[3] (column 5). The contribution of each translucency group to these 40 deaths was calculated from the relative contribution to the 9.35 deaths between 12 and 14 weeks (column 4)

Nuchal translucency thickness (mm)	*Trisomy 21 at 12 weeks*[2]	*Observed lethality at 12–14 weeks*[3]	*Deaths between 12 and 14 weeks*	*Deaths between 12 weeks and term*
0–3	43	5.3%	2.28	10
4–6	43	8.8%	3.78	16
≥ 7	14	23.5%	3.29	14
Total	100		9.35	40

addition to this high sensitivity, 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 of screening for trisomy 21 by fetal nuchal translucency is that earlier screening preferentially identifies those chromosomally abnormal pregnancies that are destined to miscarry. In this study, we made the extreme assumption that the relative rate of intrauterine lethality of trisomy 21 fetuses according to nuchal translucency thickness stays the same throughout pregnancy; for example, we assumed that all fetuses with translucency ≥ 7 mm died *in utero* (Table 2). Consequently, the methodology would underestimate the detection rate of viable fetuses. Nevertheless, the results demonstrate that, even in this extreme case, a policy of screening by maternal age and fetal nuchal translucency followed by selective termination of affected fetuses would be associated with a more than 70% reduction in the live birth incidence of trisomy 21.

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