

DETECTION OF SEX CHROMOSOME ABNORMALITIES BY NUCHAL TRANSLUCENCY SCREENING AT 10–14 WEEKS

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SUMMARY

At 10–14 weeks of gestation more than 80 per cent of fetuses affected by trisomy 21 can be detected by a screening programme based on a combination of maternal age and fetal nuchal translucency thickness (NT). The screen positive group in such a programme also identifies fetuses with sex chromosome abnormalities. In this ongoing multicentre screening study, involving 61 972 singleton pregnancies, 53 cases of sex chromosome abnormalities were identified. The fetal NT was above the 95th centile in 87.9 per cent of the 33 cases with 45,XO, and in 40 per cent of the 20 cases with 47,XXY, 47,XYY or 47,XXX. However, it was estimated that at 12 weeks of gestation our population would contain 42 cases with 45,XO and 104 cases with 47,XXY, 47,XYY or 47,XXX. Since the rate of intra-uterine lethality, between 12 and 40 weeks of gestation, is about 65 per cent for 45,XO and four per cent for 47,XXY, 47,XYY or 47,XXX, the respective number of livebirths with these chromosomal abnormalities would have been 15 and 100, respectively, without prenatal diagnosis. Assuming that all intra-uterine deaths are from those with increased NT, screening for trisomy 21 by maternal age and fetal NT would have identified only 20 per cent of potential livebirths in the 45,XO group and nine per cent of those with 47,XXY, 47,XYY or 47,XXX. © 1998 John Wiley & Sons, Ltd.

KEY WORDS: nuchal translucency; first trimester; sex chromosome defects

INTRODUCTION

At 10–14 weeks of gestation 70 per cent of fetuses with trisomy 21 have increased nuchal translucency thickness (NT), and in more than 80 per cent of affected pregnancies, the estimated risk, based on a combination of maternal age and fetal NT, is more than one in 300, which corresponds to a false positive rate of five per cent (Pandya *et al.*, 1995; Snijders *et al.*, 1996). In the screen positive group fetal karyotyping has also identified fetuses with other trisomies and sex chromosome abnormalities. This study examines the potential detection rate of sex chromosome

abnormalities by a screening programme for trisomy 21 based on maternal age and fetal NT.

MATERIALS AND METHODS

This is an ongoing multicentre screening project for trisomy 21 by a combination of maternal age and fetal NT at 10–14 weeks. In all cases the crown–rump length (CRL) and fetal NT were measured as previously described (Nicolaides *et al.*, 1992), and in all centres demographic details and ultrasound findings were entered into a computer database at the time of scanning. Karyotype results and details on pregnancy outcome were recorded in the database as soon as they became available. Pregnancy outcome was obtained from the maternity units or the patients themselves.

A computer search was made to identify all singleton pregnancies with live fetuses at the 10–14

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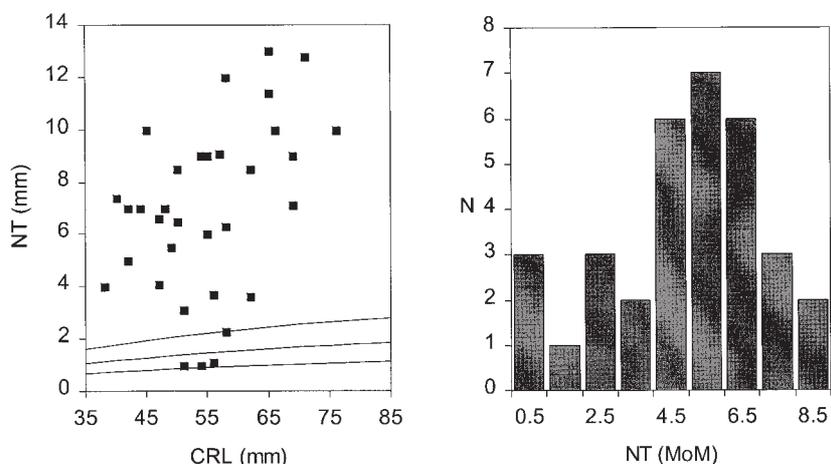


Fig. 1—Fetal nuchal translucency thickness (NT) in 45,XO pregnancies, plotted on the normal range for crown-rump length (median, 95th and fifth centiles). On the right is the frequency distribution of NT for crown-rump length in MoMs

week scan and CRL of 38–84 mm that had an estimated date of delivery before 1 June 1996. The population was subdivided into a sex chromosome abnormality group, where the diagnosis was made by fetal or postnatal karyotyping ($n=53$), and a normal group, where either the fetal karyotype was normal or the pregnancies resulted in livebirths with no obvious dysmorphic features suggestive of a chromosomal abnormality ($n=59\ 078$). Excluded were pregnancies with chromosomal defects other than sex chromosome abnormalities, pregnancies where no follow-up details were obtained or those with perinatal deaths that were not karyotyped ($n=2841$).

In the sex chromosome abnormality group the distribution of risk for trisomy 21 by maternal age and fetal NT was determined (Pandya *et al.*, 1995). Fetal NT for CRL was expressed as multiples of the normal median (MoM) and the student t -test was used to examine the significance of the difference in NT between affected and normal pregnancies. The expected number of fetuses in the population affected by sex chromosome defects at 12 weeks and at birth were calculated using the maternal age and gestational age-specific prevalences (Snijders *et al.*, 1995).

RESULTS

In the study group ($n=59\ 131$) the median CRL was 57 mm, which corresponds to the gestational age of 12 weeks. First and second trimester fetal karyotyping was carried out in 4003 and 1736

cases, respectively. In addition, karyotyping was performed in 44 pregnancies that resulted in spontaneous abortion or perinatal death and in 15 infants with dysmorphic features suggestive of chromosomal abnormality.

Sex chromosome abnormalities were diagnosed in 53 cases, including 33 with 45,XO 10 with 47,XXY, five with 47,XYY and five with 47,XXX; in all cases the diagnosis was made by karyotyping in the first or second trimesters of pregnancy. In the 33 cases of 45,XO, the median NT was 5.3 (range 0.7 to 10.2) MoMs ($t=10.2$, $P<0.001$) and in 29 (87.9 per cent) cases the NT was above the 95th centile for CRL (Fig. 1). The estimated risk for trisomy 21 based on maternal age and fetal NT was above one in 300 in 30 (90.9 per cent) of the cases. In the 20 cases with 47,XXY, 47,XYY or 47,XXX, the median NT was 1.35 (range 0.6 to 4.8) MoMs ($t=3.05$, $P<0.01$) and in eight (40 per cent) cases the NT was above the 95th centile for CRL (Fig. 2). The estimated risk for trisomy 21 based on maternal age and fetal NT was above one in 300 in 13 (65 per cent) of the cases.

On the basis of the maternal age distribution of the population, at 12 weeks of gestation the expected number of cases with 45,XO was 42 and cases with 47,XXY, 47,XYY or 47,XXX was 104 (Snijders *et al.*, 1995) (Table I). On the assumption that the rate of intra-uterine lethality, between 12 and 40 weeks of gestation, is about 65 per cent for 45,XO and four per cent for 47,XXY, 47,XYY or 47,XXX (Snijders *et al.*, 1995), the respective number of livebirths with these chromosomal

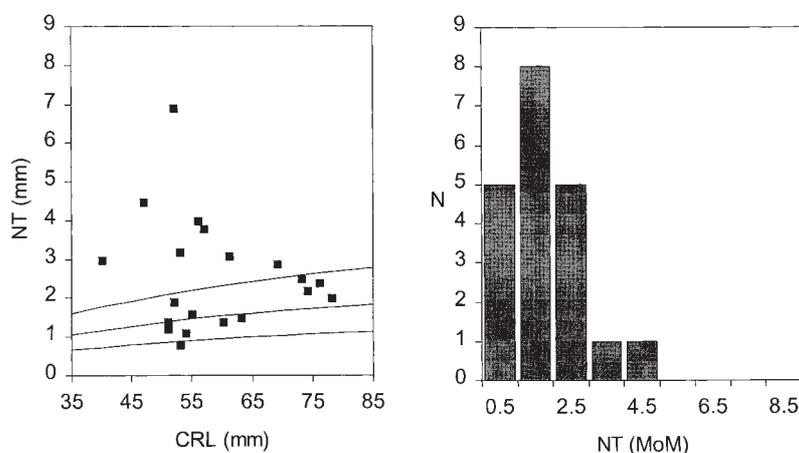


Fig. 2—Fetal nuchal translucency thickness (NT) in 47,XXX, 47,XXY and 47,XYY pregnancies, plotted on the normal range for crown-rump length (median 95th and fifth centiles). On the right is the frequency distribution of NT for crown-rump length in MoMs

Table I—Expected and observed prevalence of sex chromosome abnormalities at 12 and 40 weeks, and the sensitivity of screening by a combination of maternal age-related risk for trisomy 21 and fetal nuchal translucency (NT)

	45,XO	47,XXY, 47,XYY, 47,XXX
Expected at 12 weeks	42	104
Observed at 12 weeks	33	20
Screen positive at 12 weeks	30 (91% or 71%)	13 (65% or 13%)
Increased NT at 12 weeks	29 (88% or 69%)	8 (40% or 8%)
Expected at 40 weeks	15	100
Screen positive at 12 weeks	3 (20%)	9 (9%)
Increased NT at 12 weeks	2 (13%)	4 (4%)

abnormalities would have been 15 and 100 if there was no prenatal diagnosis and selective termination in this population (Table I). In reality, termination of pregnancy was carried out at the request of the parents in 32 of the 33 cases with 45,XO and in 10 of the 20 with other chromosomal abnormalities; the remaining one and 10 cases, respectively, were liveborn.

The policy of screening for trisomy 21 by maternal age and fetal NT using a risk cut-off of one in 300 would detect 91 per cent (30 of 33) of the known cases of 45,XO but on the assumption that at 12 weeks there were another nine cases which were not detected, the actual sensitivity would be 71 per cent (30 of 42). Similarly, for 47,XXY, 47,XYY or 47,XXX the apparent sensitivity was 65 per cent (13 of 20) but the actual sensitivity

would have been only 13 per cent (13 of 104). On the assumption that all intra-uterine deaths are from the screen positive group with increased NT, screening for trisomy 21 by maternal age and fetal NT would have identified only 20 per cent (three of the 15) potential livebirths in the 45,XO group and nine per cent (nine of 100) in the 47,XXY, 47,XYY or 47,XXX group; in the latter group only four per cent of fetuses had an NT above the 95th centile of the normal range (Table I).

DISCUSSION

This study demonstrates that sex chromosome abnormalities can be detected by a policy of screening for trisomy 21 by a combination of maternal age and fetal NT. The data also illustrate

two important aspects of prenatal screening for fetal abnormalities in general; first, the need for ascertainment of all affected cases in the population examined, and secondly, definition of the potential impact of prenatal diagnosis on the prevalence of a given abnormality in livebirths.

Sex chromosome abnormalities are the most common chromosomal defects in livebirths. Thus, in a survey involving 68 159 livebirths there were 117 cases of 47,XXY, 47,XYY or 47,XXX, six cases of 45,XO, and 94 cases of trisomies 21, 18 or 13 (Hsu, 1992). However, unlike the situation with trisomies, neonates with sex chromosome abnormalities are often phenotypically normal. Consequently, studies that do not involve karyotyping of the whole population will inevitably underestimate the true prevalence of these abnormalities and overestimate the potential sensitivity of a screening test. As illustrated in our study, the erroneous conclusion could be reached that screening for trisomy 21 by maternal age and fetal NT could identify 65 per cent of fetuses with 47,XXY, 47,XYY or 47,XXX, when the true sensitivity is likely to be only about 10 per cent. Indeed if only NT is considered, four per cent of affected fetuses had values above the 95th centile of the normal range.

Fetuses with increased NT have a higher than normal risk of intra-uterine death (Hyett *et al.*, 1996). Consequently, a screening policy based on fetal NT may preferentially identify those chromosomally abnormal fetuses that are destined to die *in utero*. We have previously reported that, in the case of trisomy 21, although the observed sensitivity of screening by maternal age and fetal NT was 84 per cent, the estimated reduction in the livebirth prevalence of this condition would have been 78 per cent (Nicolaidis *et al.*, 1997). In the case of 45,XO the rate of intra-uterine lethality is much higher than in trisomy 21. It is thought that 1.5 per cent of all recognized pregnancies are 45,XO but less than one per cent of these survive beyond 28 weeks of gestation (Hook, 1981).

There are essentially three types of 45,XO; first, the vast majority, those that present as anembryonic pregnancies or first trimester abortions, secondly, those presenting during the second trimester with large nuchal cystic hygromas, hydrops fetalis and cardiac abnormalities (Azar *et al.*, 1991), and a third group that may be phenotypically normal both prenatally and at birth. As illustrated in Fig. 1, in the cases of 45,XO diagnosed at 10–14 weeks, the fetal NT is either within the normal range, which presumably represents

group three, or very much increased, and this may well be the group that develops the classical features of second trimester hydrops. Therefore, NT screening identifies the majority of affected fetuses at 10–14 weeks, but only about 20 per cent of those destined to be liveborn.

Screening for trisomy 21 by a combination of maternal age and fetal NT at 10–14 weeks identifies a high proportion of 45,XO fetuses but a minority of those destined to be liveborn. The prevalence of increased NT in fetuses with 47,XXY, 47,XYY or 47,XXX is not different from normal.

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