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Prenatal diagnosis of trisomy 18 at the 10–14-week ultrasound scan

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ABSTRACT

A beneficial consequence of screening for trisomy 21 by a combination of maternal age and fetal nuchal translucency thickness (NT) at 10–14 weeks is the early diagnosis of trisomy 18. In a multicenter study of 91 091 singleton pregnancies there were 106 fetuses with trisomy 18 and 83% were identified by NT screening. Trisomy 18 was also associated with early onset intrauterine growth retardation, decreased fetal heart rate and the presence of exomphalos.

INTRODUCTION

At 10–14 weeks of gestation about 70% of fetuses with trisomy 21 have increased nuchal translucency thickness (NT) and in more than 80% of affected pregnancies the estimated risk based on a combination of maternal age and fetal NT is more than 1 in 300[1]. Other first-trimester sonographic markers for trisomy 21 that have been investigated are fetal heart rate (FHR), which is increased[2], and crown–rump length (CRL), which is not significantly different from normal[3].

Trisomy 18 is the second most common autosomal trisomy and in the second or third trimesters of pregnancy a wide range of associated ultrasonographic features have been described, including strawberry-shaped head, ventriculomegaly, posterior fossa cysts, choroid plexus cysts, facial cleft, micrognathia, nuchal edema, esophageal atresia, diaphragmatic hernia, cardiac defects, exomphalos, renal defects, short limbs, talipes, overlapping fingers, polyhydramnios and intrauterine growth retardation[4]. However, during the first trimester, the only consistent abnormality that has been reported is exomphalos[5,6].

This multicenter ultrasound study on fetal NT at 10–14 weeks examined the distribution of NT, CRL and FHR as well as the prevalence of exomphalos in fetuses with trisomy 18.

METHODS

Since September 1992, pregnant women living in London and the surrounding areas were invited to attend the Harris Birthright Research Centre for Fetal Medicine to participate in a screening study for trisomy 21 by a combination of maternal age and fetal NT at 10–14 weeks of gestation[1]. During the last 3 years a further 23 centers around London also introduced this method of screening. The scans were carried out by one of 275 sonographers who had received the Fetal Medicine Foundation certificate of competence in the theory and practice of the 10–14-week scan. The fetal NT was measured, as previously described, by transabdominal ultrasound examination, unless visualization was poor, in which case vaginal sonography was carried out[7].

Demographic details and ultrasound findings, including number of fetuses, CRL, NT, any obvious fetal abnormalities and, since 1994, the FHR, were entered into a computer database at the time of scanning. Karyotype results and details on pregnancy outcome were added as soon as these became available. Pregnancy outcome was obtained from the maternity units or the patients themselves.

A computer search was carried out to identify all singleton pregnancies with live fetuses at the 10–14-week scan and CRL of 38–84 mm with an estimated date of delivery before 1 April 1996. The database was then searched for all cases with trisomy 18.

In the fetuses with trisomy 18 the distribution of risks for trisomy 21, calculated by a combination of maternal age and the deviation from normal in fetal NT thickness, was determined and the sensitivity of a cut-off risk of 1 in 300 (corresponding to 5% of the population) was calculated[8]. In addition, the NT for CRL, the CRL for gestation (in those with regular 26–30-day menstrual cycles and a certain date of the last menstrual period) and FHR for CRL were expressed as delta values (for NT differences in millimeters and for FHR and CRL as the number of standard

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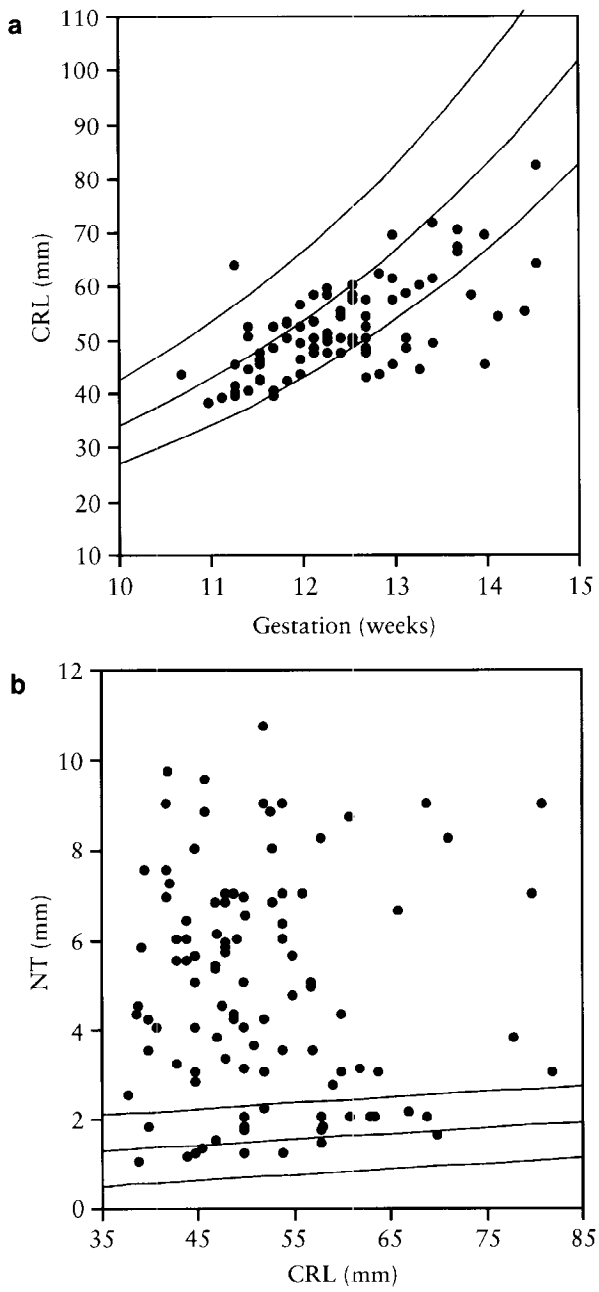

Figure 1 Fetal crown–rump length (CRL) with gestation (a) and fetal nuchal translucency thickness (NT) with CRL (b) and fetal heart rate (FHR) with CRL (c) in fetuses with trisomy 18 plotted on the appropriate normal ranges (mean, 95th and 5th centiles) for singletons. From references 2, 3 and 8

deviations by which the individual values differed from the appropriate normal mean)[2,3,8]. Student's *t* test was used to examine the significance of the delta values between the trisomy 18 and normal pregnancies. Regression analysis was used to examine the possible significance of associations between delta values for NT, CRL and FHR. In those trisomy 18 fetuses with a minimum CRL of 45 mm and an exomphalos, the delta values in NT, CRL and FHR were compared to those of trisomic fetuses with no exomphalos.

RESULTS

During the study period (September 1992 to September 1996), ultrasound examination was performed in 91 091 singleton pregnancies with a live fetus and a fetal CRL of 38–84 mm. The median CRL was 57 mm, which corresponds to a gestational age of 12 weeks. The median maternal age was 30 years (range 14–44 years).

The diagnosis of trisomy 18 was made prenatally in 102 cases and in the neonatal period in four cases. The fetal NT was above the 95th centile for CRL in 84 (79%) of the cases and above the 99th centile in 69 (65%) of the cases[8] (Figure 1); the median value was 2.1 mm from the normal median for CRL (mean difference 1.8 mm, 95% CI 1.6–2.0 mm, $t = 20.2$, $p < 0.0001$). The estimated risk for trisomy 21 based on maternal age and fetal NT was above 1 in 300 in 88 (83%) and above 1 in 100 in 81 (76%) of the cases.

Normal menstrual cycles were recorded in 98 of the 106 cases with trisomy 18 and the mean CRL for gestation was 1.1 SDs below the normal mean (mean difference 1.1 SDs, 95% CI 0.9–1.3 SDs, $t = 9.8$, $p < 0.0001$); in 21 (20%) cases the CRL was below the 5th centile[3] (Figure 1). There was no significant association between delta NT and delta CRL ($r = -0.12$, $p = 0.26$).

The FHR was recorded in the last 58 cases and the median value was 0.40 SDs below the expected normal mean (mean difference –0.34 SDs, 95% CI 0.01–0.65 SDs, $t = -2.2$, $p < 0.05$); in six (11%) cases the FHR was below the 5th centile (Figure 1). There was no significant association between delta NT and delta FHR ($r = 0.18$, $p = 0.17$).

The CRL was more than 45 mm in 84 of the cases and in 22 (26%) of these there was exomphalos; there was no significant difference in the deviation in NT between those with and those without exomphalos ($z = 0.67$).

In the subgroup of 78 pregnancies with a reliable last menstrual period date and a CRL of more than 45 mm, there were 69 (89%) cases in which the estimated risk for trisomy 21 was 1 in 300 or more ($n = 64$), or there was exomphalos ($n = 4$) or the CRL was below the 5th centile ($n = 1$).

DISCUSSION

This study has demonstrated that at 10–14 weeks of gestation more than 70% of fetuses with trisomy 18 had increased NT and more than 80% of affected pregnancies were identified in a screening program for trisomy 21 based on a combination of maternal age and NT[1]. In addition, trisomy 18 fetuses demonstrated early-onset intrauterine growth retardation and relative bradycardia, and in about 30% of the cases there was an associated exomphalos.

In contrast to trisomy 21 and other chromosomal abnormalities, trisomy 18 is associated with severe growth retardation at birth. The findings of this study indicate that this growth retardation is manifested from the first trimester of pregnancy. This finding confirms the previous observation of two studies on a total of 37 fetuses with trisomy 18 and with a CRL that was significantly lower than in chromosomally normal fetuses or those with trisomy 21[3,9]. In the policy of screening for trisomy 21 by NT measurement, the pregnancies are dated by fetal CRL. Such a policy would improve the detection of trisomy 18, since NT normally increases with CRL and therefore in trisomy 18 a given NT for gestation would be exaggerated if the values were corrected for CRL.

In normal pregnancy the FHR increases from about 110 beats/min at 5 weeks of gestation to 170 beats/min at 9 weeks and then gradually decreases to 150 beats/min by 13 weeks[10–12]. The early increase in FHR coincides with the morphological development of the heart and the subsequent decrease may be the result of functional maturation of the parasympathetic system[10,12,13]. In trisomy 21 there is a tendency for increased FHR which was postulated to be due to a delay in the functional maturation of the parasympathetic system and consequent delay in the physiological decrease in FHR with gestation after 9 weeks[2]. The relative bradycardia of trisomy 18 fetuses may be related to the fact that in this chromosomal abnormality there is early-onset growth retardation and the developmental delay is more severe than in trisomy 21; in such fetuses the maturation in FHR would be consistent with about 8 weeks of gestation. An alternative hypothesis would be that bradycardia represents a preterminal decompensation in the cardiovascular system which could also explain the increased NT in such fetuses. However, there was no significant association between delta NT and delta FHR.

The prevalence of exomphalos at 11–14 weeks of gestation is about 1 in 1000 and 60% of affected fetuses are chromosomally abnormal, the commonest defect being trisomy 18[6]. Consequently, the finding of exomphalos constitutes a strong indication for offering invasive testing. Our study has demonstrated that exomphalos and fetal NT are independent markers of trisomy 18; thus inclusion of exomphalos in the screening test by the combination of maternal age and fetal NT would improve the detection rate of trisomy 18 by about 5% with a negligible increase in the rate of invasive testing.

Many trisomy 18 fetuses are identified during the second trimester by the presence of multiple sonographic features and the mothers undergo late terminations. Alternatively, the pregnancies are complicated by severe intrauterine growth retardation and about 70% are delivered by Cesarean section[14]. First-trimester diagnosis with the option of early termination of affected pregnancies would therefore be beneficial, even if the natural history of this condition led to death, either *in utero*[15] or during the first year of life[16].

This study demonstrates that screening for trisomy 21 by a combination of maternal age and fetal NT also provides sensitive prediction of trisomy 18.

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