Ultrasound Obstet. Gynecol. 5 (1995) 15–19

Chromosomal defects and outcome in 1015 fetuses with increased nuchal translucency

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Key words: NUCHAL TRANSLUCENCY, FETAL KARYOTYPING, ULTRASOUND, NUCHAL EDEMA, CYSTIC HYGROMATA

ABSTRACT

In 1015 fetuses undergoing first-trimester karyotyping because of increased nuchal translucency thickness, the incidence of chromosomal abnormalities increased with both maternal age and nuchal translucency thickness. The observed numbers of trisomies 21, 18 and 13 in fetuses with nuchal translucency thicknesses of 3 mm, 4 mm, 5 mm and ≥ 6 mm were approximately 3 times, 18 times, 28 times and 36 times higher than the respective numbers expected on the basis of maternal age. The incidences of Turner syndrome and triploidy were 9-fold and 8-fold higher but the incidence of other sex chromosome aneuploidies was similar to that of an unselected population of women undergoing first-trimester fetal karyotyping for maternal age. In the chromosomally normal group, the incidence of structural defects, mainly cardiac, diaphragmatic, renal and abdominal wall, was approximately 4%, which is higher than would be expected in an unselected population. The rates of fetal loss in the groups with nuchal translucency thickness of 3 mm and 4 mm were 2% and 4%, respectively, which is similar to the 2.3% rate of fetal loss observed in a group of fetuses with normal nuchal translucency thickness undergoing chorion villus sampling. For fetal nuchal translucency thickness of ≥ 5 mm, the rate of fetal loss was 13%.

INTRODUCTION

Abnormal collection of fluid behind the fetal neck (nuchal translucency) at 10–14 weeks' gestation is associated with increased risk for chromosomal defects. We have previously shown that the risk is related both to nuchal translucency thickness and maternal age[1–3]. In a series of 560 fetuses with nuchal translucency thickness of 3–9 mm, we wound that translucencies of 3 mm, 4 mm, 5 mm and ≥ 6 mm were associated with the respective 4-fold, 21-fold, 26-fold and 41-fold increase in maternal age-related risk for trisomies 21, 18 and 13[3]. In addition, nuchal translucency thickness ≥ 4 mm was associated with poor pregnancy outcome even when the fetal karyotype was normal. This study reports the findings of fetal karyotype and pregnancy outcome in an expanded series of 1015 fetuses with nuchal translucency thickness ≥ 3 mm.

PATIENTS AND METHODS

Between January 1990 and October 1994, chorion villus sampling or amniocentesis was performed for karyotyping of 1015 fetuses with nuchal translucency thickness ≥ 3 mm. In 307 cases, the patients were referred from other hospitals and in 708 cases the diagnosis was made in our center during routine scanning at 10–14 weeks' gestation. 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 (Figure 1). The chromosomally normal group was investigated further by detailed ultrasound examination and echocardiography at 20 weeks' gestation and by screening for maternal toxoplasmosis, cytomegalovirus, rubella virus, herpes virus, parvo B19 virus and coxsackie B virus. Details on pregnancy outcome were obtained from the referring doctors or the patients.

Estimates of the maternal age-related risks for fetal trisomies 21, 18 or 13 at 9–14 weeks' gestation were used to calculate the expected incidences in our various subgroups of increased nuchal translucency thickness[4]. The ratio of observed to expected number of cases was calculated. Regression analysis was applied to examine the association between the incidence of fetal trisomies and nuchal translucency thickness and maternal age, respectively.

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Received 15–10–94
Accepted 15–11–94

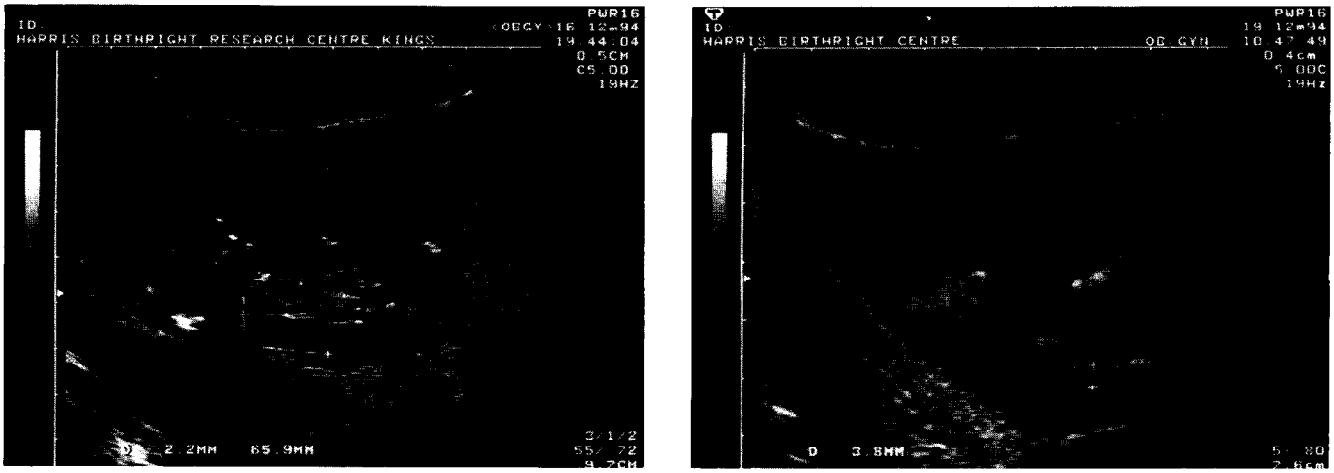

Figure 1 Ultrasound pictures showing measurement of the fetal nuchal translucency (2.2 mm on the left and 3.8 mm on the right). The amnion can be seen as a separate membrane from the fetal skin

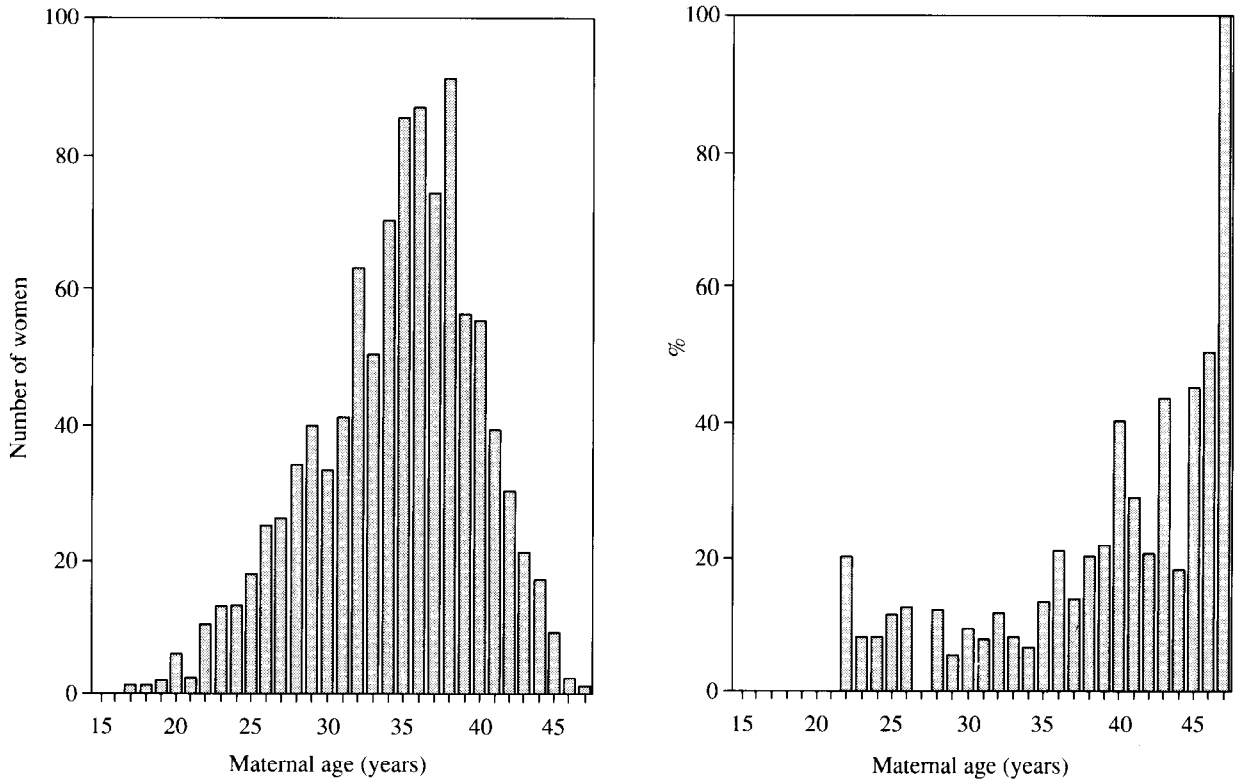

Figure 2 The maternal age distribution of 1015 women with increased fetal nuchal translucency (left) and the percentage of fetal trisomies 21, 18 and 13 (right)

RESULTS

The median maternal age was 35 years (range 17–47 years) and the median crown–rump length was 62 mm (range 38–84 mm), corresponding to 12 weeks (range 10–14 weeks). The fetal karyotype was normal in 821 and abnormal in 194 (19.1%) of the cases (Table 1). The incidence of chromosomal abnormalities was significantly associated with fetal nuchal translucency (Table 1, $r = 0.794$, $p < 0.05$) and maternal age (Figure 2, $r = 0.685$, $p < 0.0001$). The observed numbers of trisomies 21, 18 and 13 in fetuses with nuchal translucency thickness of 3 mm, 4 mm, 5 mm, and ≥ 6 mm were approximately 3 times, 18 times, 28 times and 36 times higher than the respective numbers expected on the basis of maternal age (Figure 3, Table 2).

In the chromosomally abnormal group, the pregnancies were terminated at the request of the parents in 186 of the 193 cases. The seven cases where the pregnancies continued included three with trisomy 21, two with 47,XYY, one with 45,X and one with 46,XY+mar16. In these cases, the nuchal translucency thickness at presentation was 3–9 mm but this resolved by 20 weeks in all cases; six pregnancies resulted in live births and one is continuing.

In 706 of the 1015 pregnancies, the estimated date of delivery was before 15th October 1994. In 141 of these,

Table 1 Fetal nuchal translucency thickness and incidence of chromosomal abnormalities

Nuchal translucency thickness (mm)	*Total*	*Abnormal karyotype*								
		Trisomies				*Sex chromosomes*				
		21	*18*	*13*	*21/18/13*	*45,X*	*47,XXY or 47,XYY*	*Polyploidy*	*Other*	
3	696	24	8	2	34 (5%)	1	3	3	4	47,XY+fr; 47,XX+22; 46,XX–4p; 46,XYm16
4	139	26	5	3	34 (24%)	—	—	2	2	47,XY+20; 47,XX+22
5	66	24	8	2	34 (51%)	—	—	1	—	
6	39	6	9	1	16 (41%)	3	—	—	—	
7	24	6	10	1	17 (71%)	3	—	—	—	
8	23	6	6	3	15 (65%)	1	—	—	—	
9	28	8	5	1	14 (50%)	6	—	—	—	
Total	1015	101	51	13	164 (16%)	14	3	6	6	

Table 2 Observed number of trisomies 21, 18 and 13 in relation to fetal nuchal translucency thickness and the expected number on the basis of maternal age

Nuchal translucency thickness (mm)	*n*	*Observed*			*Expected*			*Observed to expected ratio*		
		21	*18/13*	*21/18/13*	*21*	*18/13*	*21/18/13*	*21*	*18/13*	*21/18/13*
3	696	24	10	34	7.47	3.23	10.70	3.2	3.1	3.2
4	139	26	8	34	1.31	0.56	1.87	19.8	14.0	18.2
5	66	24	10	34	0.84	0.36	1.20	28.6	27.8	28.3
> 5	114	26	36	62	1.20	0.52	1.72	21.7	69.2	36.0
Total	1015	100	64	164	10.82	4.67	15.49	9.2	13.7	10.6

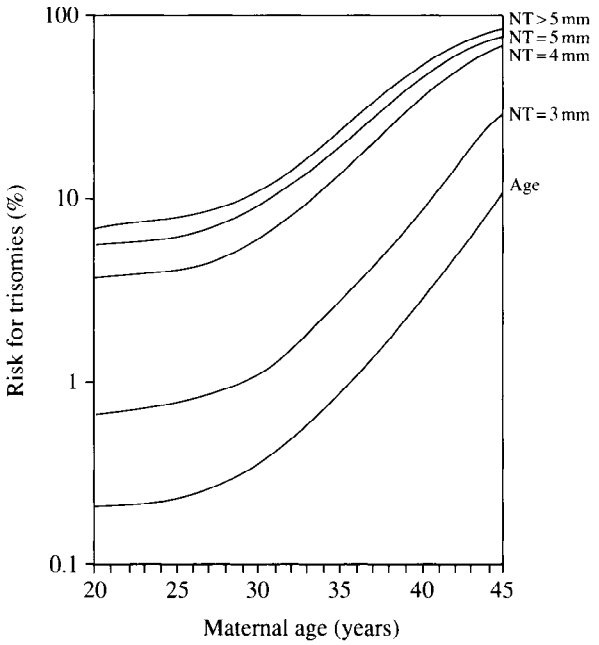

Figure 3 Semilogarithmic graph illustrating estimated risks for fetal trisomies 21, 18 or 13 at 10–14 weeks' gestation on the basis of maternal age alone and maternal age with fetal nuchal translucency thickness (NT) of 3 mm, 4 mm, 5 mm and > 5 mm

the fetal karyotype was abnormal and in 565 it was normal. The pregnancy outcome in the chromosomally normal group is shown in Table 3. Survival decreased from 97% for those with a nuchal translucency thickness of 3 mm to 91% for a nuchal translucency thickness of 4 mm and 53% for a nuchal translucency thickness of ≥ 5 mm. In all babies that survived, the translucency resolved by 20 weeks' gestation. One of the survivors has Stickler syndrome but all others are apparently healthy. In three cases, the maternal blood IgM was positive for parvo B19 virus, coxsackie B virus and toxoplasmosis, respectively. In all three cases, healthy infants were delivered at term; the mother with toxoplasmosis was treated with spiramycin.

In 21 of the 551 cases with a nuchal translucency thickness of 3–6 mm, the parents requested termination of pregnancy because fetal abnormalities were detected either at presentation (such as anencephaly or major exomphalos) or at follow-up scans (mainly cardiac defects). Termination of pregnancy was also performed at the request of the parents in nine of the 14 cases with a nuchal translucency thickness of 7–9 mm because of the uncertain prognosis; a repeat scan 2 weeks after presentation demonstrated persistence or increase in the large translucency and development of generalized edema.

DISCUSSION

This study confirms the strong association between chromosomal abnormalities and increased fetal nuchal translucency at 10–14 weeks' gestation. Furthermore, the findings emphasize the need to take into account maternal age in calculating the risk for chromosomal abnormalities when ultrasound examination demonstrates the presence of a fetal defect or 'marker'. For example, if the mother is 20 years old and the fetal nuchal translucency thickness is 3 mm, the risk for fetal trisomy 21 rises from 1 : 696 to 1 : 94, whereas for a 40-year-old the risk increases from 1 : 51 to 1 : 7.

In our group of fetuses with increased nuchal translucency thickness in addition to trisomies 21, 18 and 13,

Table 3 Outcome of chromosomally normal fetuses with nuchal translucency thickness at least 3 mm

Nuchal translucency thickness (mm)	*Total*	*Alive*	*Perinatal death*		*Termination of pregnancy*	
			n	*Death*	*n*	*Abnormalities*
3	459	443 (97%)	9	IUD at 13 weeks IUD at 15 weeks IUD at 16 weeks IUD at 17 weeks IUD at 27 weeks IUD at 30 weeks IUD at 35 weeks NND at 28 weeks NND at 40 weeks	7	diaphragmatic hernia at 16 weeks hydrops at 18 weeks tricuspid atresia at 20 weeks obstructive uropathy at 14 weeks renal agenesis at 20 weeks multicystic kidneys at 20 weeks ventriculomegaly 22 at weeks
4	55	50 (91%)	2	IUD at 16 weeks IUD at 20 weeks	3	exomphalos at 12 weeks exomphalos at 13 weeks hypoplastic left heart at 19 weeks
5	24	15 (63%)*	3	IUD at 15 weeks IUD at 16 weeks NND at 38 weeks†	6	hypoplastic left heart at 16 weeks tricuspid atresia at 24 weeks holoprosencephaly at 20 weeks exomphalos at 13 weeks gonadal dysgenesis at 23 weeks hydrops at 13 weeks
6	13	8 (62%)	—		5	exomphalos at 13 weeks anencephaly, exomphalos at 12 weeks amnion disruption sequence at 16 weeks arthrogryposis at 16 weeks hydrops at 20 weeks
7	3	1 (33%)	1	NND at 35 weeks‡	1	hydrops at 12 weeks
8	5	3 (60%)	—		2	hydrops and talipes at 15 weeks hydrops at 17 weeks
9	6	—	—		6	hydrops at 13 weeks hydrops at 14 weeks hydrops at 14 weeks hydrops at 15 weeks hydrops and septal defect at 16 weeks hydrops at 20 weeks
Total	565	520 (92%)	15		30	

IUD, intrauterine death; NND, neonatal death; *, Stickler syndrome diagnosed postnatally; †, diaphragmatic hernia diagnosed at 20 weeks; ‡, CHARGE syndrome diagnosed postnatally

there were other chromosomal defects including sex chromosome aneuploidies and polyploidy. For trisomies 21, 18 and 13, the maternal age-related risks at 10–14 weeks have been established[4] and this made it possible to investigate the extent to which this risk was altered by a given fetal nuchal translucency thickness. For the other chromosomal abnormalities, there are insufficient data at present to calculate specific maternal age-related risks. Nevertheless, in our study the incidences of Turner syndrome (1.38%) and triploidy (0.59%) were 9 times and 8 times higher than in a study of an unselected population of 5814 women undergoing first-trimester fetal karyotyping for maternal age (triploidy 0.07%, Turner syndrome 0.15%)[4]. In contrast, the incidence of other sex chromosome aneuploidies was similar (0.30% in the present study compared to 0.28% in an unselected population).

In the chromosomally normal group, the incidence of structural defects, mainly cardiac, diaphragmatic, renal and abdominal wall, was approximately 4%, which is higher than would be expected in an unselected population. It is therefore necessary that detailed ultrasound scans are performed to diagnose such defects. Although congenital infection is a recognized cause of fetal hydrops and may certainly account for the transient nature of translucency, evidence of infection was found in only three of our cases and therefore the value of this investigation is questionable.

The incidences of spontaneous miscarriage or perinatal death for nuchal translucency thicknesses of 3 mm and 4 mm were 2% and 4%, respectively. These rates are similar to the 2.3% rate of fetal loss observed in a group of fetuses with normal nuchal translucency thickness undergoing chorion villus sampling[5]. In contrast, for a fetal nuchal translucency thickness of ≥ 5 mm, the rate of fetal loss was increased (13%) and presumably this would have been even higher had termination not been performed for those cases that developed hydrops.

In our studies nuchal translucency is measured transabdominally in the longitudinal section of the fetus and no attempt is made to distinguish between septated or non-septated edema and cystic hygromata; these are terms describing two different sonographic appearances

in the second trimester with distinct pathogenesis and patterns of associated chromosomal abnormalities[6,7]. In the first trimester, translucency observed in chromosomally normal fetuses does not evolve into either second-trimester edema or cystic hygromata but usually it resolves. In the chromosomally abnormal fetuses, the pregnancies are often terminated during the first trimester and it is therefore impossible to predict how they would have evolved during the second trimester. It is interesting that Turner syndrome is associated with a nuchal translucency thickness ≥ 6 mm and in these cases presumably the translucency will evolve into cystic hygromata. However, in 83% (62 of 75) of our chromosomally abnormal fetuses with a nuchal translucency thickness ≥ 6 mm, the abnormalities were trisomies that are not characterized by cystic hygromata in the second trimester. Increased nuchal translucency observed during the first trimester of pregnancy should be an indication for offering fetal karyotyping and detailed follow-up scans. Attempts at classifying the translucency into edema or hygromata are not useful.

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