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Outcome of fetuses with enlarged nuchal translucency and normal karyotype

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ABSTRACT

The aim of this study was to examine the relationship between nuchal translucency measurements and outcome of pregnancy with special regard to fetuses with an enlarged nuchal translucency and a normal karyotype. Fetal nuchal translucency measurements were performed on consecutive mothers attending the prenatal diagnosis center of our hospital. A complete follow-up was obtained in 88.4% of the cases. Of the 74 fetuses (4.4%) with an enlarged nuchal translucency (≥ 3 mm), 25 (33.8%) had an abnormal karyotype. Two pregnancies ended in a spontaneous abortion before karyotyping was performed. In the remaining 47 eukaryotic fetuses with enlarged nuchal translucency, five (10.6%) had a structural anomaly, two were affected by genetic syndromes (4.2%) and an additional four fetuses (8.5%) were affected by a single-gene disorder. A spontaneous abortion or an intrauterine death occurred in 6.4% and in 2.1% of these fetuses, respectively. The total incidence of an unfavorable outcome in the group of chromosomally normal fetuses with enlarged nuchal translucency was 32%. In contrast, in the group with a normal nuchal translucency (< 3 mm), the incidence of an unfavorable outcome was 7.5%.

There is a strong association between enlarged nuchal translucency measurements and congenital (structural and genetic) abnormalities, as assessed by receiver operator characteristic analysis. This may represent, in fetuses with a normal karyotype, a non-specific sign of a disturbance in the developmental process. In these cases, detailed ultrasound surveillance is recommended.

INTRODUCTION

Fetal nuchal translucency measurement between 10 and 14 weeks' gestation has proven to be an effective screening method for chromosomal abnormalities[1]. Besides its association with aneuploidies, an enlarged nuchal translucency may represent a non-specific sign of a disturbance in the development of the fetus[2,3]. In fact, chromosomally normal fetuses with an enlarged nuchal translucency are reported to have an increased incidence of structural defects, mainly cardiac, diaphragmatic, renal, abdominal wall and of rare genetic syndromes[3–10]. Among the genetic syndromes, an association with enlarged nuchal translucency has been described for Noonan[7–9], Smith–Lemli–Opitz[11], multiple pterygium[3,8], Stickler[4], Jarcho–Levin[12] and for arthrogryposis[13]. Moreover, an enlarged nuchal translucency can occasionally be found in association with intrauterine infections[4,14].

Thus far, the published studies on fetal outcome in fetuses with neck abnormalities are based either on preselected populations[5–10], or report the incidence of abnormalities in the fetuses with enlarged nuchal translucency and not in the whole group screened by this method[4].

In this study, the discriminative capacity of nuchal translucency measurement with respect to fetal outcome was investigated in consecutive patients attending the prenatal diagnosis center of our hospital. A systematic ultrasound follow-up was performed on all fetuses with an enlarged nuchal translucency and normal karyotype. Outcome data on abnormalities detected before and after birth in the whole group of fetuses are reported.

METHODS

Consecutive women with viable singleton pregnancies at 10–14 completed weeks of gestation were prospectively included in this study. They attended the prenatal diagnostic unit of the Academic Medical Center in Amsterdam between February 1994 and June 1996. In all included patients, the expected date of delivery was before January 1st, 1997. All women were informed and consented to participate in the study which was approved by the Hospital Ethics Committee.

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In all cases, a transabdominal scan with a curvilinear 3.5- or 5-MHz transducer (Toshiba SSA 250A, Tokyo, Japan and Hitachi EUB 565, Tokyo, Japan) was performed for dating and for nuchal translucency measurement. The nuchal translucency was defined as the thin translucent area lying between the inner surface of the skin and the soft tissue interface overlying the cervical spine. The maximal nuchal translucency thickness was measured on a sagittal section of the fetus and the measurement was considered as enlarged when it was ≥ 3 mm. Whenever the nuchal translucency could not be satisfactorily imaged, the measurement was recorded as failed.

A nuchal anomaly was defined as a cystic hygroma when it consisted of two symmetrical cavities completely separated by a midline septum[15].

Gestational age was calculated by the crown–rump length[16] and biparietal diameter measurements[17].

In all cases in which an enlarged nuchal translucency was found, a two-step detailed ultrasound scan was offered, the first, performed transvaginally, shortly after the enlarged nuchal translucency was detected (12–14 weeks' gestation) and the second, transabdominally, at 20 weeks' gestation. This second scan was only performed in fetuses with a normal karyotype. In contrast, all the remaining patients with chromosomally normal fetuses and a normal nuchal translucency returned to their prenatal care practitioners (midwives or gynecologists) and – according to the standard Dutch obstetric care – were not offered a routine ultrasound scan unless they were at increased risk of structural abnormalities or specific obstetric conditions had formed an indication for it.

After birth, all women were asked to return a form in which information on the mode of delivery, neonatal outcome and postnatal follow-up was requested.

The nuchal translucency results were compared with fetal karyotype and neonatal outcome. The association between nuchal translucency measurement and neonatal outcome was assessed by receiver operator characteristic (ROC) analysis. An abnormal neonatal outcome was defined by the presence, either isolated or in combination, of genetic inherited syndromes and structural abnormalities, after exclusion of the chromosomally abnormal cases. A ROC curve was constructed and the area under the ROC curve, which can be regarded as the measure of the performance of a diagnostic test, was calculated. A ROC curve was also constructed after 'delta' correction, i.e. correcting all nuchal translucency measurements for the effect of gestational age (actual measurements subtracted from the normal mean for that gestation)[18].

RESULTS

A total of 1911 women participated in the study. A complete follow-up was available in 1690 cases (88.4% of the deliveries) and the following results are based on these cases. The indications for prenatal counselling or diagnosis at the time nuchal translucency measurement was performed were maternal age (n = 1393), increased risk of a structural anomaly (n = 154), parental anxiety (n = 92), and increased risk of a detectable genetic disorder (n = 51).

The mean gestational age at which the measurement was performed was 11 weeks and 4 days; the mean maternal age was 37.1 years (range 20–46 years).

Table 1 reports the outcome measures for the whole group and for the four subgroups: failed measurements, normal nuchal translucency, enlarged nuchal translucency, and cystic hygromas, respectively. In 40 cases (2.4%), we were unable to obtain a satisfactory nuchal translucency measurement because of fetal position or maternal obesity. In this group, the perinatal outcome was normal in 37 cases. Of the remaining three cases, two ended in a spontaneous abortion and, in the third case, termination of pregnancy was performed because of an unbalanced translocation.

An enlarged nuchal translucency (mean 4.2 mm, range 3–8.4 mm) was detected in 74 fetuses (4.4%). In this group, an abnormal karyotype was diagnosed in 25 fetuses (33.8%) (trisomy 21, 18 cases; trisomy 18, 4 cases; trisomy 13, 1 case; triploidy, 1 case; mosaicism, 1 case). Two cases resulted in a spontaneous abortion before fetal karyotyping by amniocentesis could be performed. The remaining 47 fetuses had a normal karyotype. Details on the outcome of these fetuses are reported in Table 2. In five of these fetuses (10.6%), structural abnormalities were detected: in four cases by ultrasound examination – either transvaginally or transabdominally – and in one case (esophageal atresia with tracheoesophageal fistula) postnatally. Details on the type of malformation, time of diagnosis and outcome are

Table 1 General outcome in the total group and in the four subgroups: failed nuchal translucency (NT), normal nuchal translucency, enlarged nuchal translucency and cystic hygroma

	Total group (n = 1690)		*Failed NT* (n = 40)		*Normal NT* (n = 1568)		*Enlarged NT* (n = 74)		*Cystic hygroma* (n = 8)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Chromosomal defects	56	3.3	1	2.5	25	1.6	25	33.8	5	62.5
Structural anomalies	22	1.5			16	1.0	5	6.8	1	12.5
Genetic syndromes	5	0.1			3	0.2	2	2.7		
Single-gene disorders	19	1.1			15	1.0	4	5.4		
Spontaneous abortions	37	2.2	2	5.0	30	1.9	5	6.8		
Intrauterine death	21	1.2			18	1.1	1	1.4	2	25.0
Neonatal death	11	0.7			11	0.7				
Alive and well	1519	89.9	37	92.5	1450	92.5	32	43.2		

reported in Table 3. Two infants were shown to be affected by a genetic syndrome (4.2%). In one case, ectrodactyly-ectodermal dysplasia–clefting syndrome (EEC) was diagnosed prenatally by ultrasound and, in the second, Noonan syndrome was diagnosed postnatally at 6 months of age. In four cases (8.5%), a single-gene disorder was diagnosed. In one case, a pericardial effusion was observed at the 20-week scan; the infant was found postnatally to be affected by Zellweger syndrome. An enlarged nuchal translucency was also observed in three fetuses of women who underwent prenatal diagnosis because of an increased risk of single-gene disorders. The fetuses were subsequently found to be affected by glucomucopolysaccharidosis (G_{M1}) gangliosidosis, muscular dystrophy and spinal muscle atrophy 1, respectively. An enlarged nuchal translucency was present in four (23.5%) of the 19 fetuses that were shown to be affected by a single-gene disorder, in contrast to only one (2.9%) of the 34 non-affected fetuses.

In the fetuses with a normal nuchal translucency (1568), an abnormal karyotype was diagnosed in 25 cases (1.6%) (trisomy 21, 10 cases; trisomy 18, 2 cases; triploidy, 1 case; mosaicism, 3 cases; translocations, 4 cases; XXY, 4 cases; marker chromosome, 1 case). In the remaining 1543 fetuses, 13 anomalies (0.8%) were detected prenatally by ultrasound scan. Details on the type of malformation, nuchal translucency measurement, time of diagnosis, obstetric complication and neonatal outcome in this group are given in Table 4. In six of these fetuses (0.4%), a structural anomaly was detected after birth (Table 5).

A cystic hygroma (thickness, mean 15.6 mm; range, 10–24 mm) was detected in eight fetuses (0.5%). In five (62.5%) of these cases, a chromosomal abnormality was detected (Turner's syndrome, 4; trisomy 21, 1). Of the remaining three pregnancies, an intrauterine death occurred in two cases and the third pregnancy was terminated because of progressive hydrops fetalis (Table 1).

Figure 1 shows the ROC curve for the association between nuchal translucency measurement and fetal outcome. The area under the curve was 0.78 (SE 0.039). After 'delta' correction, it improved to 0.84 (SE 0.027).

Table 2 General details on the outcome of fetuses with an enlarged nuchal translucency and a normal karyotype

	n	%
Structural anomaly		
Ultrasound-detected	4	8.5
Detected after birth	1	2.1
Genetic syndromes		
Ultrasound-detected EEC syndrome	1	2.1
Detected after birth Noonan syndrome	1	2.1
Single-gene disorder		
Detected after birth Zellweger syndrome	1	2.1
Detected at chorionic villus biopsy G_{M1} gangliosidosis myotonic dystrophy spinal muscular atrophy type 1	3	6.4
Spontaneous abortion	3	6.4
Intrauterine death	1	2.1
Healthy babies	32	68.1
Total	47	100

EEC, ectrodactyly-ectodermal–clefting syndrome; G_{M1}, glucomucopolysaccharidosis 1

DISCUSSION

This study confirms the fact that an enlarged nuchal translucency, besides being a marker for chromosomal abnormalities, carries an increased risk of structural anomalies, of rare genetic syndromes and of fetal demise. The overall chance of a healthy baby in the total group of enlarged nuchal translucency was 43.2% and, after exclusion of the chromosomal abnormalities, 68.1%.

To date and to our knowledge, this is the only report providing the general fetal outcome of a pre-defined population of women in which fetal nuchal translucency has been measured. Structural anomalies were diagnosed in 10.6% of the fetuses with an enlarged nuchal translucency and normal karyotype, and genetic syndromes and single-gene disorders in 15%. The incidence of structural anomalies in these fetuses is about five-fold the 3% reported by the International Clearinghouse Monitoring System for birth defects in the general population[19]. The incidence of congenital anomalies in this study is similar to that reported by Johnson and colleagues[7] in a group of chromosomally normal fetuses with nuchal anomalies of more than 2 mm and by Trauffer and colleagues[9] for nuchal anomalies larger than 3 mm detected prior to prenatal diagnostic procedures. In a relatively non-selected population of younger women, Pandya and colleagues[4] observed,

Table 3 Ultrasound-detected structural abnormalities in fetuses with an enlarged nuchal translucency (NT): type of malformation, gestational age in weeks (GA) at first scan and at diagnosis, NT measurement and fetal outcome

	First scan		*Gestational age at time of diagnosis* (weeks)	
Type of malformation	*Gestational age* (weeks)	*Nuchal translucency* (mm)		*Fetal outcome*
Agnathia and cleft palate	13	7.0	21	TOP at 23 weeks
Hypoplastic left ventricle	11	4.2	29	TOP at 32 weeks
Hypoplastic left ventricle	12	3.5	16	intrauterine death at 24 weeks
EEC syndrome	12	3.4	12	alive
Dandy–Walker	13	3.2	13	TOP at 13 weeks

TOP, termination of pregnancy; EEC, ectrodactyly-ectodermal–clefting syndrome

Table 4 Nuchal translucency < 3 mm and ultrasonographically detected anomalies (n = 13)

Type of anomaly	*n*	*Nuchal translucency* (mm)	*Gestational age at diagnosis* (weeks)	*Fetal outcome*
Genetic syndromes				
Spondylothoracic dysplasia	1	1.2	28	TOP at 30 weeks; Jarcho–Levin syndrome
Lateral cervical cysts	1	2.2	15	NND at 36 weeks; Noonan syndrome
Structural anomalies				
Anencephaly	2	0	10	TOP at 12 weeks
		1.2	12	TOP at 13 weeks
Omphalocele	2	0	12	IUD at 15 weeks
		0.8	13	IUD at 17 weeks
Renal agenesis (Potter syndrome)	2	2.0	17	TOP at 18 weeks
		1.4	27	TOP at 29 weeks
Dandy–Walker	1	2.3	11	TOP at 12 weeks
Intra-abdominal cyst	1	0.8	11	duodenal atresia and choledochal cyst; premature delivery at 31 weeks; alive and well after operation
Tetralogy of Fallot	1	2.0	22	term delivery at 39 weeks; alive and well after operation
Dilated left ventricle, lung hypoplasia	1	1.2	24	hypoplastic common pulmonary trunk; IUD at 25 weeks
Hydrops fetalis	1	2.0	16	TOP at 19 weeks

GA, gestational age in weeks; TOP, termination of pregnancy; NND, neonatal death; IUD, intrauterine death

Table 5 Anomalies detected after birth (n = 6)

Type of anomaly	*n*	*Nuchal translucency* (mm)	*Fetal outcome*
Genetic syndrome			
Coffin–Syris syndrome	1	1.2	premature delivery at 36 weeks; alive and well after operation
Structural anomalies			
Syndactyly	2	1.7	alive and well
		1.1	
Esophageal atresia	1	0	premature delivery at 32 weeks; alive and well after operation
Cleft palate	1	1.6	term delivery at 39 weeks; alive and well after operation
Rocker bottom foot	1	1.0	term delivery at 40 weeks; alive and well after operation

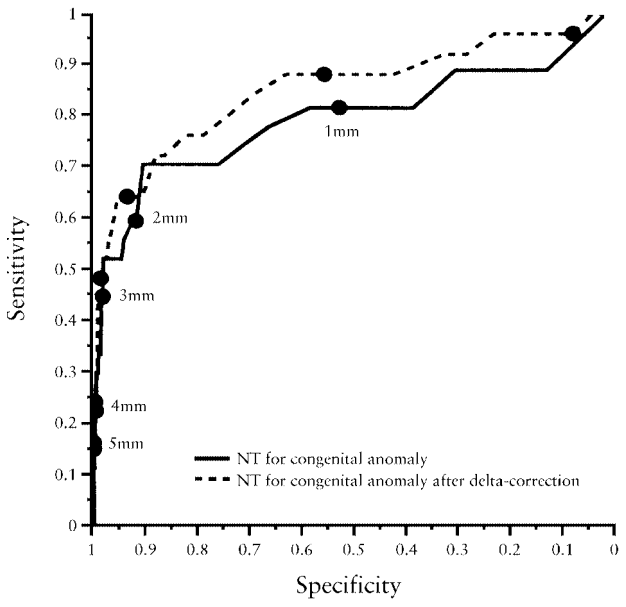

Figure 1 Receiver operator characteristic curve for nuchal translucency thickness (NT) (mm) and congenital (structural and genetic) anomalies detected in the fetuses screened by nuchal translucency measurement after exclusion of the chromosomal abnormalities

in fetuses with enlarged nuchal translucency and normal chromosomes, 4% of ultrasonographically detectable structural anomalies, mainly cardiac. One neonate (0.2%) was postnatally found to be affected by Stickler syndrome. The incidence of structural anomalies in chromosomally normal fetuses with nuchal anomalies increases four- to ten-fold when the study population consists of pre-selected cohorts of patients, irrespective of the cut-off used for the nuchal anomaly (20 and 40% for a cut-off of 3 mm and 35% for 4 mm)[10,11,13].

The most frequent structural defect encountered in this study was a cardiac defect. The spontaneous fetal loss rate in the group of fetuses with enlarged nuchal translucency and normal karyotype was 6.4%, which is much higher than the reported 3% for unselected pregnancies at 10–14 weeks' gestation[2]. It may be speculated that the high rate of intrauterine lethality observed in fetuses with an enlarged nuchal translucency and normal karyotype may have preferentially involved fetuses with critical cardiac defects. However, this hypothesis can only be tested by large studies also involving systematic pathological examinations. Pathological examination of the heart and/or great arteries in chromosomally normal fetuses with enlarged nuchal translucency has demonstrated a high incidence of

abnormalities (90%), such as septal or valvular defects (43%), narrowing of the aortic isthmus and narrowing immediately above the aortic valve (86%)[3]. With advancing gestation, severe septal and valvular defects may be detected at echocardiographic examination. In contrast, the detection of narrowing of the aortic isthmus and above the aortic valve may remain confined to pathological examination. It is also possible that this morphometric variation of the aortic isthmus observed in early gestation may only represent a developmental delay which tends to disappear with advancing gestation[3] or, alternatively, evolve into another potentially detectable cardiac defect such as coarctation of the aorta[21]. Routine ultrasound examination of the four-chamber view of the heart has a low sensitivity in the detection of critical cardiac defects[22]. To improve the cost effectiveness of third-level fetal echocardiography, this investigation may be confined to high-risk groups. However, the presence of an enlarged nuchal translucency may be a better selection criterion in identifying fetuses at risk for cardiac defects than the selection based on a generic increased *a priori* risk. Targeted fetal echocardiographic examination in this group of fetuses may considerably increase the efficacy of third-level fetal echocardiography and its yield[23].

Genetic syndromes are rare and, despite the increasing number of reports in the literature on their association with enlarged nuchal translucency, the numbers are still too small to depict a clear role for nuchal translucency screening in their detection. However, if this association is confirmed in larger series, this may be of great diagnostic help for a couple bearing a risk for inherited genetic syndromes in which prenatal diagnosis is not yet available. Moreover, in cases where mild dysmorphic features are detected by ultrasound in fetuses with an enlarged nuchal translucency and normal chromosomes, a genetic syndrome should be suspected.

Cystic hygromas were not included under the definition of nuchal translucency as they have a distinct aspect, a larger thickness, a known pathophysiology, and a clearly worse prognosis[15].

It is unlikely that the entity 'nuchal translucency' may be produced by a single pathophysiological mechanism. Both major hemodynamic rearrangements and the development of the lymphatic system take place between 10 and 14 weeks' gestation. A specific cause – infection or a structural heart defect – or a developmental delay may produce a temporary congestive heart failure responsible for the nuchal fluid accumulation[3] or, alternatively, interfere with the normal development of the lymphatic pathway[24].

In conclusion, this study demonstrates that screening by nuchal translucency measurements is effective in identifying, in addition to chromosomally abnormal fetuses, fetuses affected by structural and genetic disorders. Nuchal translucency measurement in the late first trimester may be an effective tool in selecting a high-risk population of fetuses requiring an intensive diagnostic surveillance. Targeted ultrasound and echocardiographic examinations on the basis of abnormal nuchal translucency measurements may result in a better, more cost-effective and earlier selection of a high-risk group than the selection based on a generic *a priori* risk.

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