

# Outcome of pregnancy in chromosomally normal fetuses with increased nuchal translucency in the first trimester

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**KEYWORDS:** 10–14-week scan, Cardiac defects, Fetal abnormalities, First trimester, Genetic syndromes, Nuchal translucency

## ABSTRACT

**Objectives** To study the outcome of chromosomally normal pregnancies with increased nuchal translucency at the 10–14-week scan.

**Design** Retrospective study of 1320 chromosomally normal singleton pregnancies with nuchal translucency of  $\geq 3.5$  mm. In addition to fetal karyotyping these patients were managed with follow-up scans at 14–16 and 20–22 weeks, specialist fetal echocardiography and in selected cases by infection screening and further genetic testing.

**Results** In the 1320 pregnancies there were 68 (5.15%) spontaneous abortions or intrauterine deaths, 18 (1.36%) neonatal and infant deaths and 154 (11.67%) terminations of pregnancy. In the 1080 (81.82%) survivors, 60 (5.56%) had abnormalities requiring medical or surgical treatment or leading to mental handicap. The chance of a livebirth with no defects in the group with nuchal translucency of 3.5–4.4 mm was 86%, for those with translucency of 4.5–5.4 mm it was 77%, for those with translucency of 5.5–6.4 mm it was 67%, and for those with translucency of  $\geq 6.5$  mm it was 31%.

**Conclusions** Increased fetal nuchal translucency is associated with chromosomal abnormalities, many fetal defects and genetic syndromes. In the majority of cases a series of antenatal investigations, including fetal karyotyping, detailed scans, fetal echocardiography, as well as genetic testing and infection screening, that can be completed by 20 weeks of gestation would distinguish between the pregnancies destined to result in adverse outcome and those leading to the delivery of infants without major defects.

## INTRODUCTION

The measurement of fetal nuchal translucency (NT) thickness at 10–14 weeks of gestation has been established as a sensitive, accurate and effective method of screening for chromosomal abnormalities<sup>1</sup>. In addition, several studies have reported on

the association of increased NT with major cardiac defects<sup>2</sup>, other structural defects and rare genetic syndromes<sup>3</sup>.

In a screening study involving 96 127 singleton pregnancies, the incidence of chromosomal defects increased with fetal NT thickness<sup>1</sup> (Table 1). A study of 693 chromosomally normal pregnancies with a fetal NT of at least 3.5 mm, which represents the 99th centile of the normal range, reported on the prevalence of adverse outcome, including major structural abnormalities and genetic syndromes<sup>3</sup>. This study is an expanded series of 1320 chromosomally normal fetuses with increased NT providing data on the prevalence of adverse outcome, which is examined in relation to both the measurement of fetal NT and the findings of the follow-up ultrasound scans.

## METHODS

The Harris Birthright Research Centre for Fetal Medicine is a tertiary referral center. Patients found to have increased NT at the routine first-trimester scan in their local hospitals are referred for a detailed first-trimester anomaly scan, counseling and invasive tests for fetal karyotyping. The first-trimester scan includes measurement of the crown–rump length and NT as previously described<sup>4</sup> and ultrasound examination of the following structures: skull, brain, chest, abdominal wall, stomach, bladder and upper and lower extremities. In pregnancies with increased NT and normal karyotype we recommend follow-up scans at 16 and 20 weeks of gestation and

**Table 1** Incidence of chromosomal defects according to fetal nuchal translucency in a screening study involving 96 127 singleton pregnancies (Snijders *et al.* 1998<sup>1</sup>)

Nuchal translucency (mm)	Total n	Chromosomal defects (n (%))
$\leq 3.4$	95 086	315 (0.33)
3.5–4.4	568	120 (21.12)
4.5–5.4	207	69 (33.33)
5.5–6.4	97	49 (50.51)
$\geq 6.5$	166	107 (64.45)

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**Table 2** Outcome of 1320 chromosomally normal pregnancies with increased nuchal translucency

NT (mm)	Total n	Termination of pregnancy (n (%))	Spontaneous fetal loss (n (%))	Postnatal death (n (%))	Live birth with abnormalities (n (%))	Live birth with no defects (n (%))
3.5–4.4	854	53 (6.2)	26 (3.0)	8 (0.9)	33 (3.9)	734 (85.9)
4.5–5.4	229	22 (9.6)	10 (4.4)	6 (2.6)	14 (6.1)	177 (77.3)
5.5–6.4	99	20 (20.2)	9 (9.1)	1 (1.0)	3 (3.0)	66 (66.7)
≥ 6.5	138	59 (42.8)	23 (16.7)	3 (2.2)	10 (7.3)	43 (31.2)
Total	1320	*154 (11.7)	68 (5.2)	18 (1.4)	60 (4.5)	1020 (77.3)

\*In 102 (66%) of the 154 cases the termination was carried out after the diagnosis of fetal defects. NT, nuchal translucency.

from 1998 these patients have also had specialist fetal echocardiography. The follow-up scans are performed at the Harris Birthright Centre in the majority of cases. However, some women opt to have follow up at their local hospitals.

Demographic details and ultrasound findings were entered into a computer database at the time of scanning. Karyotype results and details of pregnancy outcome were entered as soon as they became available. Pregnancy outcome was obtained from the maternity units, the general practitioners or the patients themselves. Details on follow-up ultrasound scans were obtained from the Harris Birthright database or the obstetric ultrasound units if the follow-up scans were carried out locally.

A computer search was carried out to identify all singleton pregnancies with live fetuses and crown–rump length of 38–84 mm, NT of ≥ 3.5 mm, normal karyotype (or birth of a child with no features suggestive of chromosomal abnormality), estimated date of delivery before 1 July 2000 and known pregnancy outcome.

The prevalence of adverse pregnancy outcome (including miscarriage, intrauterine death, postnatal death or survival with mental handicap or defects requiring medical or surgical treatment) was calculated according to the NT measurement from the first-trimester scan. Minor structural defects, such as mild hydronephrosis, choroid plexus cysts, digital anomalies and cardiac defects not requiring treatment were not included in the calculations.

A review of the literature was carried out to determine the reported defects in chromosomally normal fetuses with increased NT thickness at 10–14-weeks of gestation. In addition, a search was made for studies reporting the diagnosis of fetal abnormalities at the 10–14-week scan and these studies were examined to identify the conditions that were associated with increased NT thickness.

**Table 3** Miscarriages and intrauterine deaths by gestation and nuchal translucency measurement

NT (mm)	Total n	Gestational age at fetal loss (weeks)			
		≤ 15	16–20	21–25	26–30
3.5–4.4	26	14 <sup>a,b</sup>	8 <sup>c</sup>	2 <sup>d,e</sup>	2
4.5–5.4	10	7 <sup>a,f,g</sup>	2 <sup>a,g</sup>	1	0
5.5–6.4	9	7 <sup>f,g</sup> (×2)	1 <sup>g</sup>	1 <sup>g</sup>	0
> 6.5	23	15 <sup>f</sup> (×3), <sup>g</sup> (×2), <sup>h</sup>	6 <sup>f,i,k</sup>	1 <sup>k</sup>	1
Total	68	43	17	5	3

NT, nuchal translucency; <sup>a</sup>obstructive uropathy; <sup>b</sup>parvovirus infection; <sup>c</sup>spina bifida; <sup>d</sup>fetal growth restriction; <sup>e</sup>diaphragmatic hernia; <sup>f</sup>cardiac defect; <sup>g</sup>hydrops; <sup>h</sup>exomphalos; <sup>i</sup>holoprosencephaly; <sup>k</sup>ventriculomegaly.

## RESULTS

The computer search identified 1320 chromosomally normal singleton pregnancies with NT ≥ 3.5 mm at a median gestation of 12 weeks (range, 10–14 weeks). The data of the first 693 fetuses that were previously reported by Souka *et al.*<sup>3</sup> are included in the present study.

The outcome of the 1320 pregnancies is summarized in Table 2. There were 68 (5.15%) spontaneous abortions or intrauterine deaths (Table 3), 18 (1.36%) neonatal and infant deaths (Table 4) and 154 (11.67%) terminations of pregnancy. The indications for termination of pregnancy were prenatal diagnosis of fetal abnormalities ( $n = 102$ ), progressive fetal hydrops ( $n = 15$ ) and parental request ( $n = 37$ ). Of the 1080 (81.82%) survivors, 60 (5.56%) had abnormalities requiring medical or surgical treatment or leading to mental handicap. In total there were 200 (15.15%) cases with abnormalities and the condition was diagnosed prenatally in 162 (80.50%) cases (Table 5).

From the study group of 1320 pregnancies, 1137 had follow-up scans at 15 and/or 20 weeks of gestation; in the remaining 183 cases there was pregnancy termination or miscarriage before 15 weeks in 128 cases and between 15 and 20 weeks in 55 cases. In the group of the 1137 cases that were available for follow up, ultrasound examination demonstrated fetal defects in 75 cases, persistent nuchal edema in 82

**Table 4** Individual cases of neonatal and infant death and nuchal translucency measurement at the 10–14-week scan

NT (mm)	Diagnosis
3.5	Fetal akinesia deformation sequence
3.5	Growth restriction
3.6	Unexplained infant death
3.7	Pulmonary hypoplasia due to amniorrhaxis
4.0	Left isomerism
4.0	Gastroschisis
4.1	Congenital mesangial nephrotic syndrome
4.2	Dyserythropoietic anemia
4.5	Transposition of the great arteries
4.5	Growth restriction
4.6	Exomphalos
4.7	Diaphragmatic hernia
5.1	Diaphragmatic hernia
5.1	Diaphragmatic hernia
5.6	Congenital Finnish nephrosis
6.7	Spinal muscular atrophy
7.1	Fetal akinesia deformation sequence
10.0	Unexplained infant death

cases (including six cases with generalized edema, ascites and/or pericardial effusion) and in 980 cases the sonographic examination was unremarkable (Table 6). In 16 of the 75 cases with structural defects, persistent nuchal edema was also present.

In the group of 82 pregnancies with apparently isolated and persistent nuchal edema, 15 (18.29%) cases had an adverse outcome (Table 7). In the group of 980 pregnancies without abnormal findings at the follow-up scans, there were 22

**Table 5** Fetal abnormalities and genetic syndromes diagnosed prenatally, postnatally or by postmortem examination in chromosomally normal fetuses with increased nuchal translucency

Abnormality	Total n	Prenatal diagnosis (n)	Nuchal translucency (mm)				TOP (n)	IUD (n)	PND (n)	LB (n)
			3.5–4.4	4.5–5.4	5.5–6.4	> 6.4				
Anencephaly	3	3	2	1 <sup>p</sup>			3			
Encephalocele	2	2				2	2			
Ventriculomegaly	3	3	2 <sup>b</sup>			1 <sup>k</sup>	3			
Dandy–Walker malformation	4	4	2 <sup>a,g</sup>			2	4			
Holoprosencephaly	2	2		1		1	2			
Craniosynostosis	1			1						1
Facial cleft	1	1			1 <sup>i</sup>					1
Cystic hygroma	2	2			2			2		
Neck lipoma	1					1				1
Cardiac defect	58	44	22	12	6	18 <sup>m,q</sup>	29	6	2	21
Diaphragmatic hernia	6	6	1 <sup>n</sup>	3	2		2	1	3	
CAM of the lungs	1	1				1				1
Exomphalos	11	11	4 <sup>f,h</sup>	1	2 <sup>h,i</sup>	4 <sup>h,n</sup>	7	2	1	1
Gastroschisis	1		1						1	
Bowel obstruction	3	1	1	2						3
Duodenal atresia	1		1							1
Crohn's disease	1		1							1
Hydronephrosis	5	5	5							5
Multicystic dysplastic kidneys	2	2	2 <sup>c</sup>				1			1
Infantile polycystic kidneys	2	2	1 <sup>d</sup>			1	2			
Renal agenesis	6	6	4 <sup>c</sup>	2 <sup>c</sup>			1			5
Congenital nephrotic syndrome	2	1	1 <sup>*</sup>		1 <sup>*</sup>				2	
Obstructive uropathy	11	11	4	3	3	1	8	3		
Cloacal exstrophy	1	1		1			1			
Hypospadias	2		2							2
Ambiguous genitalia	1			1						1
Spina bifida	3	3	2			1	2	1		
Talipes	5	3	4			1	1			4
Kyphoscoliosis	2	1		1	1		1			1
Body stalk anomaly	15	15	3	5	1	6	15			
Congenital lymphedema	1		1 <sup>*</sup>							1
Limb reduction defect	2	2	1 <sup>e</sup>	1			2			
Sirenomelia	1	1	1				1			
Fetal akinesia deformation sequence	11	11	3		1	7	9		2	
Short rib polydactyly	1	1	1				1			
Thanatophoric dwarfism	1	1	1				1			
Osteogenesis imperfecta	2	2	2 <sup>*</sup>				2			
Jarcho–Levin syndrome	1	1		1			1			
Skeletal dysplasia	2	2	1			1	2			
Nance–Sweeney syndrome	1			1						1
Beckwith–Wiedemann syndrome	1	1	1							1
Meckel–Gruber syndrome	1	1	1				1			
Dyserythropoietic anemia	1	1	1						1	
Blackfan–Diamond anemia	1			1						1
Neonatal myoclonic encephalopathy	1			1						1
Smith–Lemli–Opitz syndrome	2	2	1		1		2			
Noonan syndrome	2	2				2				2
Treacher–Collins syndrome	1			1						1
Fryn syndrome	1	1				1	1			
Spinal muscular atrophy	1					1			1	
Deficiency of the immune system	1					1				1
Unspecified syndrome	2	2	1 <sup>o</sup>		1					2
Severe developmental delay	4	1	3 <sup>l</sup>			1 <sup>l</sup>				4
Total	200	162	83	41	22	54	107	15	13	65

TOP, termination of the pregnancy; IUD, intrauterine death (includes spontaneous miscarriages); PND, postnatal death (includes neonatal and infant death); LB, live birth; CAM, cystic adenomatoid malformation. Symbols a–q refer to one case in each group with additional abnormalities:

<sup>a</sup>exomphalos and hydronephrosis; <sup>b</sup>hypoplastic left kidney; <sup>c</sup>in these cases the defect was unilateral; <sup>d</sup>micrognathia, clinodactyly and hypospadias; <sup>e</sup>facial cleft; <sup>f</sup>kyphoscoliosis; <sup>g</sup>micrognathia and coarctation of the aorta; <sup>h</sup>Pentalogy of Cantrell; <sup>i</sup>ventricular septal defect, coarctation of the aorta and spina bifida; <sup>j</sup>horseshoe kidney; <sup>k</sup>hydrops; <sup>l</sup>microdeletion of chromosome 9; <sup>m</sup>Di George syndrome; <sup>n</sup>cardiac defect; <sup>o</sup>radial aplasia, micrognathia and arachnoid cyst; <sup>p</sup>exomphalos and spina bifida; <sup>q</sup>bilateral severe hydronephrosis. \*These cases have been presented as case reports.

**Table 6** Adverse outcome in fetuses with no structural defects (with or without nuchal edema) at the 20-week scan classified according to nuchal translucency at the 10–14-week scan

NT (mm)	Total n	Alive at 20 weeks (n (%))	Adverse outcome	
			No nuchal edema (n (%))	Nuchal edema (n (%))
3.5–4.4	854	793 (92.9)	13 <sup>a</sup> /726 (1.8)	3 <sup>b</sup> /30 (10.0)
4.5–5.4	229	203 (88.6)	7/166 (4.2)	2 <sup>c</sup> /18 (11.1)
5.5–6.4	99	73 (73.7)	0/54	1/12 (8.3)
≥ 6.5	138	68 (49.3)	2/34 (5.9)	9 <sup>b</sup> /22 (40.9)
Total	1320	1137 (86.1)	22 <sup>a</sup> /980 (2.2)	15 <sup>d</sup> /82 (18.3)

Fetal cardiac defects that would have been detected by specialist echocardiography are included (<sup>a</sup>n = 5; <sup>b</sup>n = 1; <sup>c</sup>n = 2; <sup>d</sup>n = 4). NT, nuchal translucency.

(2.24%) cases of adverse outcome (Table 8). The prevalence of severe developmental delay was 1.22% (1/82) and 0.41% (4/980) in the groups of persistent nuchal edema and normal follow-up, respectively. Specialist fetal echocardiography was not offered to patients in the early part of the study and during this period nine detectable cardiac defects were not diagnosed prenatally. If these cardiac defects had been excluded from the analysis, the rate of unexpected adverse outcome would have been 14.10% and 1.74% in the groups with persistent nuchal edema and normal follow up, respectively.

The conditions that were identified by the literature search to be associated with increased NT are summarized in Table 9<sup>5–72</sup>.

**DISCUSSION**

This study provides further evidence that in chromosomally normal fetuses the risk of miscarriage, intrauterine death, diagnosis of major structural defects leading to termination of pregnancy, postnatal death or survival with defects, increases with increasing NT (Table 2). Consequently, in counseling parents with pregnancies with increased NT, the chance of an adverse outcome, including chromosomal defects (Table 1), in the group with a NT of 3.5–4.4 mm is 32%, for those with

**Table 7** Individual adverse outcomes in fetuses with persistent and apparently isolated nuchal edema according to nuchal translucency measurement at the 10–14-week scan

NT (mm)	Diagnosis
3.6	Coarctation of the aorta
4.0	Patent ductus arteriosus
4.2	Dyserythropoietic anemia
4.5	Transposition of the great arteries
4.7	Aortic stenosis, patent ductus arteriosus
5.6	Congenital Finnish nephrosis
7.8	Cleft palate
7.8	Noonan syndrome
7.9	Unexplained hydrops fetalis
7.9	Unexplained intrauterine death at 30 weeks
8.8	Neck lipoma
8.8	Unexplained intrauterine death at 22 weeks
9.0	Noonan syndrome
10.0	Pulmonary stenosis
10.0	Unexplained hydrops fetalis

NT, nuchal translucency.

a NT of 4.5–5.4 mm it is 49%, for those with a NT of 5.5–6.4 mm it is 67%, and for those with a NT of ≥ 6.5 mm it is 89% (Figure 1).

There is a wide range of conditions that have been reported in fetuses with increased NT (Tables 5 and 9). Although in some cases the defect may be purely coincidental, in other cases there may be a true association operating through one or more of the following mechanisms: cardiac dysfunction in association with abnormalities of the heart and great arteries; venous congestion in the head and neck in association with the constriction of the fetal body in amnion rupture sequence or superior mediastinal compression found in diaphragmatic hernia or the narrow chest in skeletal dysplasia; failure of lymphatic drainage due to abnormal or delayed development of the lymphatic system or impaired fetal movements in

**Table 8** Individual adverse outcomes in fetuses with no abnormal findings at antenatal follow-up ultrasound scans according to nuchal translucency measurement at the 10–14-week scan

NT (mm)	Diagnosis
3.5	Atrioventricular septal defect, asplenia
3.6	Severe developmental delay
3.5	Unexplained intrauterine death at 28 weeks
3.5	Neonatal death after delivery at 27 weeks
3.8	Severe developmental delay
3.8	Vesico-ureteric reflux
3.8	Ventricular septal defect, ventriculomegaly
4.0	Ventricular septal defect
4.2	Atrioventricular septal defect
*4.2	Severe developmental delay, microdeletion of chromosome 9
4.2	Unexplained intrauterine death at 28 weeks
4.2	Lymphedema
4.3	Tetralogy of Fallot
4.5	Treacher–Collins syndrome
4.6	Craniosynostosis
4.7	Neonatal myoclonic encephalopathy
4.8	Blackfan–Diamond anemia
5.0	Nance–Sweeney syndrome
5.1	Ambiguous genitalia
5.3	Scoliosis
6.7	Congenital immune deficiency
6.7	Neonatal death due to spinal muscular atrophy

In all cases there was no nuchal edema at the 20-week scan.

\*In this case prenatal karyotyping showed no obvious defect and the diagnosis of microdeletion of chromosome 9 was made by postnatal karyotyping because of the developmental delay. NT, nuchal translucency.

**Table 9** Fetal abnormalities and genetic syndromes reported in association with increased nuchal translucency

Abnormality	Source
Central nervous system defect	
Anencephaly	Adekunle <i>et al.</i> 1999 <sup>5</sup> ; this study
Craniosynostosis	This study
Dandy–Walker malformation	Bilardo <i>et al.</i> 1998 <sup>6</sup> ; this study
Diastematomyelia	Souka <i>et al.</i> 1998 <sup>3</sup>
Encephalocele	This study
Holoprosencephaly	Pandya <i>et al.</i> 1995 <sup>7</sup> ; Salvesen and Goble 1995 <sup>8</sup> ; this study
Hydrolethalus syndrome	Ammala and Salonen 1995 <sup>9</sup>
Joubert syndrome	Reynders <i>et al.</i> 1997 <sup>10</sup>
Microcephaly	Souka <i>et al.</i> 1998 <sup>3</sup>
Macrocephaly	Adekunle <i>et al.</i> 1999 <sup>5</sup>
Spina bifida	Adekunle <i>et al.</i> 1999 <sup>5</sup> ; this study
Iniencephaly	Cha'ban <i>et al.</i> 1996 <sup>11</sup>
Trigonocephaly C	Souka <i>et al.</i> 1998 <sup>3</sup>
Ventriculomegaly	Pandya <i>et al.</i> 1995 <sup>7</sup> ; this study
Facial defect	
Agnathia/micrognathia	Bilardo <i>et al.</i> 1998 <sup>6</sup> ; this study
Facial cleft	Ville <i>et al.</i> 1992 <sup>12</sup> ; Nadel <i>et al.</i> 1993 <sup>13</sup> ; this study
Microphthalmia	Souka <i>et al.</i> 1998 <sup>3</sup>
Treacher–Collins syndrome	This study
Nuchal defect	
Cystic hygroma	Shulman <i>et al.</i> 1994 <sup>14</sup> ; this study
Neck lipoma	This study
Cardiac defect	Bronshstein <i>et al.</i> 1990 <sup>15</sup> ; Gembruch <i>et al.</i> 1990 <sup>16</sup> ; Ville <i>et al.</i> 1992 <sup>12</sup> ; Gembruch <i>et al.</i> 1993 <sup>17</sup> ; Nadel <i>et al.</i> 1993 <sup>13</sup> ; Achiron <i>et al.</i> 1994 <sup>18</sup> ; Pandya <i>et al.</i> 1995 <sup>7</sup> ; Salvesen and Goble 1995 <sup>8</sup> ; Cha'ban <i>et al.</i> 1996 <sup>11</sup> ; Bilardo <i>et al.</i> 1998 <sup>6</sup> ; Fukada <i>et al.</i> 1998 <sup>21</sup> ; Hafner <i>et al.</i> 1998 <sup>19</sup> ; van Vugt <i>et al.</i> 1998 <sup>20</sup> ; Adekunle <i>et al.</i> 1999 <sup>5</sup> ; Hyett <i>et al.</i> 1999 <sup>2</sup> ; Schwarzler <i>et al.</i> 1999 <sup>23</sup> ; Zosmer <i>et al.</i> 1999 <sup>22</sup> ; Chaoui <i>et al.</i> 2000 <sup>24</sup> ; Maymon <i>et al.</i> 2000 <sup>25</sup> ; Mavrides <i>et al.</i> 2001 <sup>27</sup> ; Michailidis and Economides 2001 <sup>26</sup> ; this study
*Di George syndrome	Lazanakis <i>et al.</i> 1998 <sup>28</sup>
Pulmonary defect	
Cystic adenomatoid malformation	This study
Diaphragmatic hernia	Nadel <i>et al.</i> 1993 <sup>13</sup> ; Sebire <i>et al.</i> 1997 <sup>29</sup> ; Pandya <i>et al.</i> 1995 <sup>7</sup> ; van Vugt <i>et al.</i> 1998 <sup>20</sup> ; this study
Fryn syndrome	Bulas <i>et al.</i> 1992 <sup>30</sup> ; Hosli <i>et al.</i> 1997 <sup>31</sup> ; this study
Abdominal wall defect	
Cloacal exstrophy	This study
Exomphalos	Ville <i>et al.</i> 1992 <sup>12</sup> ; Nadel <i>et al.</i> 1993 <sup>13</sup> ; Pandya <i>et al.</i> 1995 <sup>7</sup> ; Snijders <i>et al.</i> 1995 <sup>32</sup> ; Cha'ban <i>et al.</i> 1996 <sup>11</sup> ; van Zalen-Sprock <i>et al.</i> 1997 <sup>33</sup> ; Adekunle <i>et al.</i> 1999 <sup>5</sup> ; this study
Gastroschisis	This study
Gastrointestinal defect	
Crohn's disease	This study
Duodenal atresia	van Vugt <i>et al.</i> 1998 <sup>20</sup> ; this study
Esophageal atresia	Bilardo <i>et al.</i> 1998 <sup>6</sup> ; Brown and Nicolaides 2000 <sup>34</sup>
Small bowel obstruction	This study
Genitourinary defect	
Ambiguous genitalia	This study
*Congenital nephrotic syndrome	This study
Hydronephrosis	This study
Hypospadias	This study
Infantile polycystic kidneys	This study
Meckel–Gruber syndrome	van Vugt <i>et al.</i> 1998 <sup>20</sup> ; this study
Megacystis	van Zalen-Sprock <i>et al.</i> 1992 <sup>35</sup> ; Johnson <i>et al.</i> 1993 <sup>36</sup> ; Trauffer <i>et al.</i> 1994 <sup>37</sup> ; Pandya <i>et al.</i> 1995 <sup>7</sup> ; Sebire <i>et al.</i> 1996 <sup>38</sup> ; van Vugt <i>et al.</i> 1998 <sup>20</sup> ; Favre <i>et al.</i> 1999 <sup>39</sup> ; Maymon <i>et al.</i> 2000 <sup>25</sup> ; this study
Multicystic dysplastic kidneys	van Zalen-Sprock <i>et al.</i> 1992 <sup>35</sup> ; Ville <i>et al.</i> 1992 <sup>12</sup> ; Pandya <i>et al.</i> 1995 <sup>7</sup> ; Cha'ban <i>et al.</i> 1996 <sup>11</sup> ; Reynders <i>et al.</i> 1997 <sup>10</sup> ; van Vugt <i>et al.</i> 1998 <sup>20</sup> ; this study
Renal agenesis	Pandya <i>et al.</i> 1995 <sup>7</sup> ; this study
Skeletal defect	
Achondrogenesis	Fisk <i>et al.</i> 1991 <sup>40</sup> ; Hewitt 1993 <sup>41</sup> ; Soothill <i>et al.</i> 1993 <sup>42</sup> ; Meizner and Barnhard 1995 <sup>43</sup>
*Achondroplasia	Fukada <i>et al.</i> 1998 <sup>21</sup>
Asphyxiating thoracic dystrophy	Ben Ami <i>et al.</i> 1997 <sup>44</sup>
Blomstrand osteochondrodysplasia	den Hollander <i>et al.</i> 1997 <sup>45</sup>
Campomelic dwarfism	Hafner <i>et al.</i> 1995 <sup>46</sup>
Jarcho–Levin syndrome	Eliyahu <i>et al.</i> 1997 <sup>47</sup> ; this study
Kyphoscoliosis	This study
Limb reduction defect	Trauffer <i>et al.</i> 1994 <sup>37</sup> ; this study

Table 9 Continued

Abnormality	Source
Nance–Sweeney syndrome	This study
*Osteogenesis imperfecta	Makrydimas <i>et al.</i> 2001 <sup>48</sup> ; this study
Roberts syndrome	Petrikovsky <i>et al.</i> 1997 <sup>49</sup>
Short rib polydactyly	Hill and Leary 1998 <sup>50</sup>
Sirenomelia	Fukada <i>et al.</i> 1999 <sup>51</sup> ; this study
Talipes equinovarus	Adekunle <i>et al.</i> 1999 <sup>5</sup> ; this study
*Thanatophoric dwarfism	This study
VACTER association	Souka <i>et al.</i> 1998 <sup>3</sup>
Fetal anemia	
Blackfan–Diamond anemia	This study
Dyserythropoietic anemia	This study
Fanconi anemia	Tercanli <i>et al.</i> 2001 <sup>52</sup> ; Petrikovsky <i>et al.</i> 1996 <sup>53</sup> ; Smulian <i>et al.</i> 1998 <sup>54</sup> ; Markenson <i>et al.</i> 2000 <sup>55</sup>
Parvovirus B19 infection	
* $\alpha$ -thalassemia	Lam <i>et al.</i> 1999 <sup>56</sup>
Neuromuscular defect	
Fetal akinesia deformation sequence	Ville <i>et al.</i> 1992 <sup>12</sup> ; Nadel <i>et al.</i> 1993 <sup>13</sup> ; Pandya <i>et al.</i> 1995 <sup>7</sup> ; Hyett <i>et al.</i> 1997 <sup>57</sup> ; this study
*Myotonic dystrophy	Bilardo <i>et al.</i> 1998 <sup>6</sup>
*Spinal muscular atrophy	Rijhsinghani <i>et al.</i> 1997 <sup>58</sup> ; Bilardo <i>et al.</i> 1998 <sup>6</sup> ; van Vugt <i>et al.</i> 1998 <sup>20</sup> ; Stiller <i>et al.</i> 1999 <sup>59</sup> ; this study
Metabolic defect	
Beckwith–Wiedemann syndrome	This study
*GM1 gangliosidosis	Bilardo <i>et al.</i> 1998 <sup>6</sup>
*Long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency	Tercanli <i>et al.</i> 2000 <sup>60</sup>
*Mucopolysaccharidosis type VII	van Eyndhoven <i>et al.</i> 1998 <sup>61</sup>
*Smith–Lemli–Opitz syndrome	Hobbins <i>et al.</i> 1994 <sup>62</sup> ; Pandya <i>et al.</i> 1995 <sup>7</sup> ; Hyett <i>et al.</i> 1995 <sup>63</sup> ; Sharp <i>et al.</i> 1997 <sup>64</sup> ; Maymon <i>et al.</i> 1999 <sup>65</sup> ; this study
Vitamin D resistant rickets	Brady <i>et al.</i> 1998 <sup>66</sup>
*Zellweger syndrome	Bilardo <i>et al.</i> 1998 <sup>6</sup> ; de Graaf <i>et al.</i> 1999 <sup>67</sup> ; Christiaens <i>et al.</i> 2000 <sup>68</sup>
Other defect	
Body stalk anomaly	Pandya <i>et al.</i> 1995 <sup>7</sup> ; Daskalakis <i>et al.</i> 1997 <sup>69</sup> ; this study
Brachmann–de Lange syndrome	Sekimoto <i>et al.</i> 2000 <sup>70</sup>
Charge association	Pandya <i>et al.</i> 1995 <sup>7</sup>
Deficiency of the immune system	This study
Congenital lymphedema	This study
EEC syndrome	Bilardo <i>et al.</i> 1998 <sup>6</sup>
Neonatal myoclonic encephalopathy	This study
Noonan syndrome	van Zalen-Sprock <i>et al.</i> 1992 <sup>35</sup> ; Johnson <i>et al.</i> 1993 <sup>36</sup> ; Trauffer <i>et al.</i> 1994 <sup>37</sup> ; Reynders <i>et al.</i> 1997 <sup>10</sup> ; Bilardo <i>et al.</i> 1998 <sup>6</sup> ; Adekunle <i>et al.</i> 1999 <sup>5</sup> ; Achiron <i>et al.</i> 2000 <sup>71</sup> ; this study
Perlman syndrome	van der Stege <i>et al.</i> 1998 <sup>72</sup>
Stickler syndrome	Pandya <i>et al.</i> 1995 <sup>7</sup>
Unspecified syndrome	Ville <i>et al.</i> 1992 <sup>12</sup> ; this study
Severe developmental delay	van Vugt 1998 <sup>20</sup> ; Adekunle <i>et al.</i> 1999 <sup>5</sup> ; this study

\*Conditions that are amenable to early prenatal diagnosis by chorionic villus sampling.

various neuromuscular disorders; altered composition of the subcutaneous connective tissue and fetal anemia or hypoproteinemia.

There is strong evidence on the association between increased NT and trisomy 21 as well as all other major chromosomal abnormalities (Table 1). Consequently, the first line of management of such pregnancies should be the offer of fetal karyotyping. In the chromosomally normal group the parents should be counseled that even if the NT is more than 6.5 mm there is a one in three chance that the pregnancy would result in a live birth with no major defects (Table 2). Nevertheless, the association between increased NT and a wide range of structural abnormalities and genetic syndromes (Table 9) constitutes an indication for detailed follow-up scans, including fetal echocardiography, and possibly further genetic testing (Figure 2). Specialist echocardiography and anomaly scanning can lead to the diagnosis of many fetal

abnormalities from as early as 12 weeks<sup>73</sup>. Following chorionic villus sampling and exclusion of a chromosomal abnormality, a follow-up scan at 14–16 weeks would determine the evolution of the NT and diagnose or exclude many fetal defects.

Persistence of unexplained NT or evolution to hydrops fetalis raises the possibility of congenital infection or a genetic syndrome<sup>74</sup>. In this study nuchal edema was considered to be present if in the midsagittal plane of the neck there was subcutaneous edema that produced a characteristic tremor on ballotment of the fetal head<sup>74</sup>. As shown in Table 5, a significant number of genetic conditions, such as spinal muscular atrophy, are now amenable to prenatal diagnosis by DNA testing and it would therefore be possible to undertake such testing in the chorionic villus sample that has already been obtained for fetal karyotyping. The diagnosis of congenital infection can be investigated by maternal serum infection screening. Sebire *et al.* investigated the possibility of infection in 426

chromosomally normal pregnancies with increased fetal NT thickness at 10–14 weeks of gestation and 63 with ‘unexplained’ second- or third-trimester fetal nuchal edema or hydrops<sup>75</sup>. Evidence of recent maternal infection was present in six (1.4%) of the 426 pregnancies with increased fetal NT but in all cases a healthy infant was born with no evidence of infection. In contrast, ‘unexplained’ second- or third-trimester fetal hydrops was associated with maternal infection in six (9.5%) of the pregnancies and in all cases there was evidence of fetal infection.

The series of investigations suggested above would have identified the majority of conditions associated with adverse outcome in fetuses with increased NT. In those cases with no

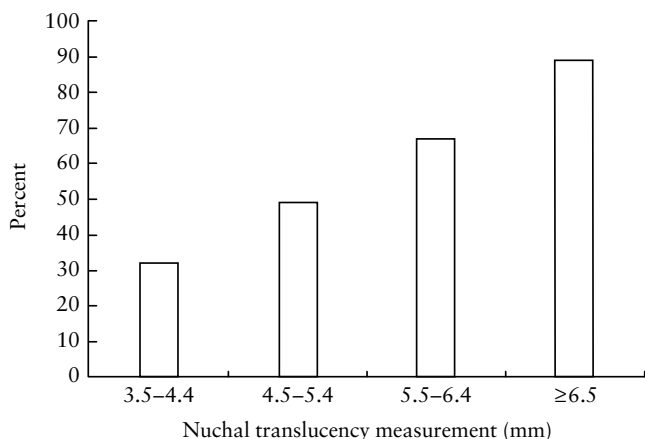


Figure 1 Incidence of adverse outcome in fetuses with increased nuchal translucency.

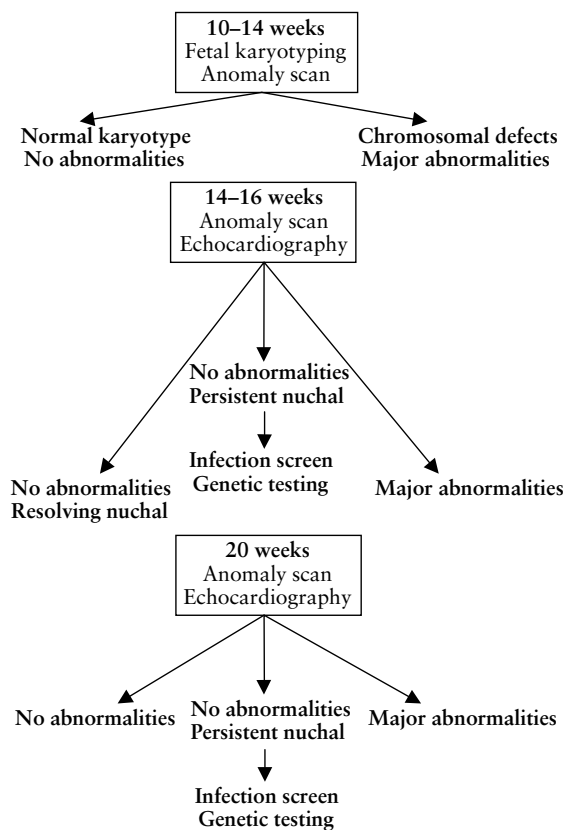


Figure 2 Management of pregnancies with increased fetal nuchal translucency

obvious abnormalities identified by 20 weeks of gestation, the parents can be counseled that the risk of an adverse outcome is very small. In the group of 980 pregnancies without abnormal findings at the follow-up scans, there were 22 (2.24%) cases of adverse outcome, including five with cardiac defects that are amenable to prenatal diagnosis by specialist fetal echocardiography (Tables 6 and 8). Although in patients with apparently unexplained nuchal edema at the 20-week scan, 18% had an adverse outcome, one third of these had potentially detectable cardiac defects, one third progressed to hydrops or resulted in unexplained intrauterine death and only one third resulted in live births with genetic syndromes, such as Noonan syndrome or Finnish nephrosis (Tables 6 and 7). In our study the prevalence of neurodevelopmental delay in the group with normal follow-up scans was 0.4% and in those with persistent nuchal edema it was 1.2%. In two previous studies of 63 and 38 pregnancies with increased NT, the prevalence of neurodevelopmental delay was 3.2% and 5.6%, respectively,<sup>5,20</sup>. However, we acknowledge that the true prevalence of neurodevelopmental delay is likely to be underestimated because many such cases may not become apparent until several years after birth.

Increased fetal NT is associated with chromosomal abnormalities, many fetal defects and genetic syndromes. In the majority of cases the proposed series of antenatal investigations can help distinguish between the pregnancies destined to result in adverse outcome and those leading to the delivery of infants with no major defects.

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