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# Defects and syndromes in chromosomally normal fetuses with increased nuchal translucency thickness at 10–14 weeks of gestation

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## ABSTRACT

*Increased fetal nuchal translucency thickness at 10–14 weeks of gestation is a common phenotypic expression of fetal chromosomal defects, structural abnormalities and genetic syndromes. This study reports on the prevalence of structural abnormalities and genetic syndromes in 4116 chromosomally normal pregnancies with increased fetal nuchal translucency thickness and reviews the relevant literature. In fetuses with increased nuchal translucency thickness, the prevalence of major cardiac defects, diaphragmatic hernia, exomphalos, body stalk anomaly and fetal akinesia deformation sequence is substantially higher than expected in the general population. In addition, there may be an association between increased nuchal translucency thickness and a wide range of rare skeletal dysplasias and genetic syndromes that are usually found in less than one in 10 000 pregnancies; however, the number of affected cases, both in the present and in previous series of fetuses with increased nuchal translucency thickness, is too small for definite conclusions to be drawn. The rates of miscarriage and perinatal death increase, whereas the rate of survival and the prevalence of live births with no obvious abnormalities decrease with increasing nuchal translucency thickness.*

## INTRODUCTION

Subcutaneous edema in the neck region, visualized by ultrasonography as increased fetal nuchal translucency thickness at 10–14 weeks of gestation, is a common phenotypic expression of trisomy 21 and other chromosomal abnormalities. Extensive studies have now demonstrated that maternal age can be combined with fetal nuchal translucency thickness to provide an effective method of screening for trisomy 21 in the first trimester of pregnancy; for a screen-positive rate of 5%, the sensitivity is about 80%[1–3].

Several case reports and small series have also suggested that, in chromosomally normal fetuses, there may be an association between increased nuchal translucency thickness and a wide range of fetal abnormalities and genetic syndromes[4–19]. This study reports on the prevalence of such abnormalities in more than 4000 chromosomally normal pregnancies with increased fetal nuchal translucency thickness and reviews the relevant literature.

## METHODS

This is an ongoing multicenter project on assessment of risk for trisomy 21 by a combination of maternal age and fetal nuchal translucency thickness at 10–14 weeks of gestation[3]. The scans were carried out in 22 centers by 306 sonographers who had received the Fetal Medicine Foundation certificate of competence in the theory and practice of the 10–14-week scan.

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The fetal crown–rump length and nuchal translucency thickness were measured, as previously described, by transabdominal ultrasound examination, unless visualization was poor, in which case vaginal sonography was carried out[1]. To achieve uniformity of results from different operators, the following criteria were used:

(1) A good sagittal section of the fetus was obtained;

(2) The magnification was such that the fetus occupied at least 75% of the image;

(3) Care was taken to distinguish between fetal skin and amnion;

(4) The maximum thickness of the subcutaneous translucency between the skin and the soft tissue overlying the cervical spine was measured.

Demographic details and ultrasound findings, including number of fetuses, crown–rump length and nuchal translucency thickness, 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, the general practitioners or the patients themselves.

A computer search of the database was made to identify all singleton pregnancies with live fetuses at the 10–14-week scan, with fetal crown–rump length of 38–84 mm and nuchal translucency thickness above the 95th centile[2], normal karyotype (or birth of a child with no features suggestive of chromosomal abnormality), estimated date of delivery before June 1, 1997 and known pregnancy outcome. The prevalence of structural defects and genetic syndromes and their relation to fetal nuchal translucency thickness were calculated. In these calculations, we did not include minor defects, such as choroid plexus cysts, pyelectasia, digital abnormalities or cardiac defects that would not require therapy.

A review of the literature was carried out to determine the reported defects in chromosomally normal fetuses with increased nuchal translucency 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 nuchal translucency thickness.

## RESULTS

There were 4116 singleton, chromosomally normal pregnancies with fetal nuchal translucency thickness above the 95th centile for crown–rump length[2], at a median gestation of 12 weeks (range 10–14 weeks). The patients were subdivided according to nuchal translucency thickness into five groups: 95th centile to 3.4 mm, 3.5–4.4 mm, 4.5–5.4 mm, 5.5–6.4 mm and ≥ 6.5 mm. Nuchal translucency normally increases with crown–rump length[2], and the 95th centile is 2.2 mm for a crown–rump length of 38 mm and 2.8 mm for a crown–rump length of 84 mm; the 99th centile does not change significantly with crown–rump length and is about 3.5 mm.

In the 4116 pregnancies, there were 3885 live births of infants who survived the neonatal period, 38 neonatal deaths, 74 spontaneous abortions or intrauterine deaths and 77 terminations at the request of the parents because of fetal abnormalities detected by ultrasonography at 10–14 weeks or at follow-up scans; termination of pregnancy was also performed in 42 cases because of the uncertain prognosis, since a repeat scan 2 weeks after presentation demonstrated persistence of, or increase in, the large translucency (Table 1).

There was a wide range of structural defects and genetic syndromes and the prevalence of these increased with nuchal translucency thickness (Table 2). The diagnosis of abnormalities was made by ultrasound examination in mid-pregnancy, or by pathological examination in terminations of pregnancy and intrauterine or neonatal deaths, or by clinical examination and appropriate investigations in live births.

The literature search identified 16 studies providing data on fetal defects in chromosomally normal pregnancies with increased nuchal translucency thickness at 10–14 weeks of gestation and the data from 15 of these studies[4–19] are summarized in Table 3; the data on 565 fetuses previously reported by Pandya and colleagues[10] are not in the table, because they are included in the present study. In the combined data on a total of 416 fetuses, there were 68 (16%) with defects (Table 3), including anencephaly ($n$ = 1), spina bifida ($n$ = 2), holoprosencephaly ($n$ = 1), Dandy–Walker malformation ($n$ = 1), facial cleft ($n$ = 2), agnathia ($n$ = 1), cystic hygromas ($n$ = 1), cardiac defects ($n$ = 17), pentalogy of Cantrell ($n$ = 1), Ivemark syndrome ($n$ = 1), Toriello–Carey syndrome ($n$ = 1), diaphragmatic

**Table 1** Pregnancy outcome in 4116 chromosomally normal fetuses with increased nuchal translucency thickness at 10–14 weeks of gestation

| *Nuchal translucency* (mm) | *Total* ($n$) | *Terminations* | | *Intrauterine death* | *Postnatal death* | *Alive* |
|---|---|---|---|---|---|---|
| | | *Total* | *Abnormal* | | | |
| 95th centile–3.4 | 3423 | 49 | 36 | 47 | 29 | 3298 (96.3%) |
| 3.5–4.4 | 448 | 23 | 14 | 9 | 4 | 412 (92.0%) |
| 4.5–5.4 | 138 | 13 | 8 | 4 | 3 | 118 (85.5%) |
| 5.5–6.4 | 48 | 13 | 7 | 4 | 0 | 31 (64.6%) |
| ≥ 6.5 | 59 | 21 | 12 | 10 | 2 | 26 (44.4%) |
| Total | 4116 | 119 | 77 | 74 | 38 | 3885 (94.4%) |

**Table 2** Fetal abnormalities and genetic syndromes in chromosomally normal fetuses with increased nuchal translucency thickness at 10–14 weeks of gestation according to translucency thickness

| | *Fetal nuchal translucency thickness* (mm) | | | | | *Pregnancy outcome* | | | |
|---|---|---|---|---|---|---|---|---|---|
| *Fetal abnormality* | *< 3.5* | *3.5–4.4* | *4.5–5.4* | *5.5–6.4* | *≥ 6.5* | *TOP* | *IUD* | *NND* | *Alive* |
| Anencephaly | 4 | 1 | | | | 5 | | | |
| Encephalocele | 3[1] | | | | 1 | 4 | | | |
| Ventriculomegaly | 6 | | | | | 5 | | | 1 |
| Dandy–Walker cyst | 1 | | | | | 1 | | | |
| Holoprosencephaly | 1 | | | | | 1 | | | |
| Microcephaly | 1 | | | | | | | | 1 |
| Facial cleft | 2 | | | | | | | | 2 |
| Microphthalmia | 1[7] | | | | | | | | 1 |
| Laryngeal cyst | 1 | | | | | | | | 1 |
| Cystic hygroma | 1 | | | | | | | | 1 |
| Major cardiac defect | 12 | 12 | 6 | 3 | 10 | 19 | 6 | 3 | 15 |
| Diaphragmatic hernia | 4 | 1 | 3 | 1 | | 1 | | 5 | 2 |
| Exomphalos | 2[2] | 3[3,4] | 1[5] | 1[6] | | 5 | 1 | | 1 |
| Gastroschisis | | 1 | | | | | | 1 | |
| Bowel obstruction | 2 | | | | | | | | 2 |
| Duodenal atresia | | 1 | | | | | | | 1 |
| Hydronephrosis | 2 | 2 | 1 | | | 1 | | | 4 |
| Multicystic kidneys | 4 | | | | | 3 | | | 1[7] |
| Polycystic kidneys | | | | | 1 | 1 | | | |
| Renal agenesis | 1 | 1 | | | | 1 | | | 1[7] |
| Megacystis | 7 | 1 | | | | 2 | 2 | | 4 |
| Spina bifida | 3 | 1 | | | | 2 | 1 | | 1 |
| Kyphoscoliosis | | | | 1 | | 1 | | | |
| Body stalk anomaly | 1 | 3 | 1 | 1 | 4 | 10 | | | |
| Diastomatomelia | 1 | | | | | | | | 1 |
| Talipes | 10 | 4 | 1 | | | 1 | | | 14 |
| Akinesia deformation | 2 | | | 1 | 3 | 6 | | | |
| Jarcho–Levin syndrome | 1 | | 1 | | | 1 | | 1 | |
| Joubert syndrome | 1 | | | | | 1 | | | |
| Nance–Sweeney syndrome | | | 1 | | | | | | 1 |
| Noonan syndrome | | | | | 1 | | | | 1 |
| Smith–Lemli–Opitz syndrome | 1 | | 1 | 1 | | 2 | | 1 | |
| Spinal muscular atrophy | 1 | | | | | | | 1 | |
| Thanatophoric dysplasia | 1 | | | | | 1 | | | |
| Trigonocephaly 'C' | 1 | | | | | | | | 1 |
| VACTER association | 2 | | | | | 1 | | | 1 |
| Unspecified syndrome | 3 | 1 | 1 | | 1 | 2 | | | 4 |

Symbols 1–6 refer to one case in each group that had additional abnormalities. [1], atrioventricular septal defect; [2], spina bifida and cloacal exstrophy; [3], Beckwith–Wiedemann syndrome; [4], extrocardia; [5], spina bifida and anencephaly; [6], spina bifida and coarctation; [7], in these three cases the defect was unilateral

TOP, termination of pregnancy; IUD, intrauterine death; NND, neonatal death

hernia ($n$ = 2), esophageal atresia ($n$ = 1), duodenal atresia ($n$ = 1), exomphalos ($n$ = 3), megacystis ($n$ = 3), multicystic kidneys ($n$ = 1), polycystic kidneys ($n$ = 3), amnion rupture sequence ($n$ = 1), achondrogenesis ($n$ = 1), achondroplasia ($n$ = 1), campomelic dwarfism ($n$ = 1), ectrodactyly-ectodermal dysplasia–clefting syndrome ($n$ = 1), fetal akinesia deformation sequence ($n$ = 3), $G_{M1}$ gangliosidosis ($n$ = 1), Joubert syndrome ($n$ = 1), Meckel–Gruber syndrome ($n$ = 1), myotonic dystrophy ($n$ = 1), Noonan syndrome ($n$ = 5), spinal muscular atrophy type 1 ($n$ = 2), Zellweger syndrome ($n$ = 1) and unspecified syndromes ($n$ = 5).

The search of the literature for studies reporting the diagnosis of fetal abnormalities at the 10–14-week scan identified the following conditions that were associated with increased nuchal translucency thickness: major cardiac defects, diaphragmatic hernia, exomphalos, megacystis, body stalk anomaly, achondrogenesis, asphyxiating thoracic dystrophy, Jarcho–Levin syndrome, akinesia deformation sequence, Roberts syndrome, Smith–Lemli–Opitz syndrome, Fryns' syndrome and hydrolethalus syndrome[20–39] (Table 4).

## DISCUSSION

The findings of this study and previous reports demonstrate that increased nuchal translucency thickness at 10–14 weeks of gestation is associated with a wide range of fetal abnormalities. The observed prevalence for some of the abnormalities, such as anencephaly, holoprosencephaly, microcephaly, facial cleft, gastroschisis, renal abnormalities, bowel obstruction and spina bifida, may not be different from that in the general population. However, the prevalence of major cardiac defects, diaphragmatic hernia, exomphalos, body stalk anomaly and fetal akinesia deformation sequence appears to be substantially higher than in

**Table 3** Studies reporting defects in chromosomally normal fetuses with increased nuchal translucency (NT) thickness at 10–14 weeks of gestation

| | | | *Other defects* | |
|---|---|---|---|---|
| *Authors* | *NT thickness* (mm) | *n* | *n* | *Description* |
| Johnson *et al.* (1993)[4] Trauffer *et al.* (1994)[5] | > 2.0 | 32 | 5 | megacystis (1), amnion rupture sequence (1), Noonan syndrome (1), unspecified syndrome (2) |
| Shulman *et al.* (1994)[6] | ≥ 2.5 | 32 | 1 | cystic hygromas (1) |
| Hafner *et al.* (1998)[7] | ≥ 2.5 | 72 | 7 | camptomelic dwarfism (1), cardiac defect (2), exomphalos (1), pentalogy of Cantrell (1), Ivemark syndrome (1), Toriello–Carey syndrome (1) |
| van Zalen-Sprock *et al.* (1992)[8] | ≥ 3.0 | 13 | 3 | megacystis (1), polycystic kidneys (1), Noonan syndrome (1) |
| Ville *et al.* (1992)[9] | ≥ 3.0 | 61 | 10 | facial cleft (1), cardiac defects (3), multicystic kidneys (1), exomphalos (1), FADS (2), unspecified syndrome (2) |
| Hewitt (1993)[11] | ≥ 3.0 | 10 | 1 | achondrogenesis (1) |
| Salvesen and Goble (1995)[12] | ≥ 3.0 | 5 | 2 | holoprosencephaly (1), cardiac defects (1) |
| Reynders *et al.* (1997)[13] | ≥ 3.0 | 35 | 3 | polycystic kidneys (1), Noonan syndrome (1), Joubert syndrome (1) |
| Bilardo *et al.* (1998)[14] | ≥ 3.0 | 47 | 11 | Dandy–Walker malformation (1), agnathia (1), cardiac defects (2), EEC (1), esophageal atresia (1), Noonan syndrome (1), Zellweger syndrome (1), $G_{M1}$ gangliosidosis (1), myotonic dystrophy (1), spinal muscular atrophy type 1 (1) |
| Van Vugt *et al.* (1998)[15] | ≥ 3.0 | 63 | 7 | Meckel–Gruber (1), diaphragmatic hernia (1), cardiac defects (2), duodenal atresia (1), polycystic kidneys (1), megacystis (1), spinal muscular atrophy type 1 (1) |
| Nadel *et al.* (1993)[16] | ≥ 4.0 | 16 | 5 | facial cleft (1), cardiac defects (1), diaphragmatic hernia (1), exomphalos (1), FADS (1) |
| Moselhi and Thilaganathan (1996)[17] | ≥ 4.0 | 8 | 3 | cardiac defects (2), spina bifida (1) |
| Thilaganathan *et al.* (1997)[18] | ≥ 4.0 | 18 | 7 | anencephaly (1), spina bifida (1), cardiac defects (3), Noonan syndrome (1), unspecified syndrome (1) |
| Fukada *et al.* (1998)[19] | ≥ 5.0 | 4 | 2 | cardiac defect (1), achondroplasia (1) |

FADS, fetal akinesia deformation sequence; EEC, ectrodactyly-ectodermal dysplasia–clefting syndrome

**Table 4** Case reports and series of fetal abnormalities with increased nuchal translucency (NT) thickness at 10–14 weeks of gestation

| *Abnormality* | *Gestation* (weeks) | *Increased NT thickness* | *Authors* |
|---|---|---|---|
| Major cardiac defects | 10–14 | 17 of 21 | Gembruch *et al.* (1990)[20]; (1993)[21]; Bronshtein *et al.* (1990)[22]; Achiron *et al.* (1994)[23] |
| Diaphragmatic hernia | 10–14 | 7 of 19 | Sebire *et al.* (1998)[24] |
| Exomphalos | 11–14 | 8 of 14 | van Zalen-Sprock *et al.* (1997)[25] |
| Megacystis | 10–14 | 6 of 15 | Sebire *et al.* (1996)[26] |
| Body stalk anomaly | 10–14 | 10 of 14 | Daskalakis *et al.* (1997)[27] |
| Achondrogenesis type II | 11–12 | 2 of 2 | Fisk *et al.* (1991)[28], Soothill *et al.* (1993)[29] |
| Akinesia deformation sequence | 10–14 | 2 of 2 | Hyett *et al.* (1997)[30] |
| Asphyxiating thoracic dystrophy | 14 | 1 of 1 | Ben Ami *et al.* (1997)[31] |
| Fryns' syndrome | 12 | 2 of 2 | Bulas (1992)[32], Hosli *et al.* (1997)[33] |
| Hydrolethalus syndrome | 12 | 1 of 1 | Ammala and Salonen (1995)[34] |
| Jarcho–Levin syndrome | 12 | 1 of 3 | Eliyahu *et al.* (1997)[35] |
| Roberts syndrome | 11 | 1 of 1 | Petrikovsky *et al.* (1997)[36] |
| Smith–Lemli–Opitz syndrome | 10–11 | 3 of 3 | Hobbins *et al.* (1994)[37], Hyett *et al.* (1995)[38], Sharp *et al.* (1997)[39] |

the general population and it is therefore likely that there is an association between these abnormalities and increased nuchal translucency thickness. Similarly, there may be an association between increased nuchal translucency thickness and a wide range of rare skeletal dysplasias and genetic syndromes that are usually found in less than one in 10 000 pregnancies; however, the number of affected cases, both in the present and in previous series of fetuses with increased nuchal translucency thickness, is too small for definite conclusions to be drawn.

## Cardiac defects

Studies involving pathological examination in both chromosomally abnormal and normal fetuses with increased nuchal translucency thickness at 10–14 weeks of gestation have demonstrated a high prevalence of abnormalities of the heart and great arteries[40–44]. Additionally, there are several case reports or small series on the sonographic diagnosis of cardiac defects at 10–14 weeks of gestation; in a total of 21 fetuses with major cardiac defects, 17 (81%) had increased nuchal translucency thickness[20–23]. Furthermore, a study of 1389 chromosomally normal fetuses with increased nuchal translucency thickness at 10–14 weeks reported that the prevalence of major cardiac defects increased with translucency thickness[45]. In this study, the prevalence of major abnormalities of the heart and great arteries was ten per 1000 and increased exponentially with translucency thickness from about four per 1000 for nuchal translucency thickness of the 95th centile to 3.4 mm, 27 per 1000 for nuchal translucency thickness of 3.5–4.4 mm, 43 per 1000 for nuchal translucency thickness of 4.5–5.4 mm, 63 per 1000 for nuchal translucency thickness of 5.5–6.4 mm and 169 per 1000 for nuchal translucency thickness of ≥ 6.5 mm. The clinical implication of these findings is that increased nuchal translucency thickness at 10–14 weeks constitutes an indication for specialist fetal echocardiography in later pregnancy.

## Diaphragmatic hernia

Diaphragmatic hernia is a sporadic defect with a birth prevalence of about one in 4000. In this study, the prevalence of diaphragmatic hernia (eight in 4116) was higher than expected in the general population, suggesting an association between this defect and increased nuchal translucency thickness. This was indeed found to be the case in a multicenter ultrasound screening study for chromosomal defects by a combination of maternal age and fetal nuchal translucency thickness at 10–14 weeks of gestation[24]. In a total of 78 639 pregnancies presumed to be chromosomally normal, there were 19 cases with diaphragmatic hernia, which was diagnosed at the initial or subsequent scans or at birth. At the 10–14-week scan, the nuchal translucency thickness was increased in 37% of cases of diaphragmatic hernia, including 83% of those resulting in neonatal death due to pulmonary hypoplasia and in 22% of the survivors[24]. It is possible that, in those cases with increased nuchal translucency thickness at 10–14 weeks, there is intrathoracic herniation of the abdominal viscera during this stage of gestation and the increased nuchal translucency thickness may be the consequence of venous congestion in the head and neck due to mediastinal compression and impedence of venous return. In the cases in which diaphragmatic hernia is associated with a good prognosis, intrathoracic herniation of viscera may be delayed until the second or third trimester of pregnancy.

## Exomphalos

Exomphalos is a sporadic abnormality with a birth prevalence of about one in 3000. At 8–10 weeks of gestation, all fetuses demonstrate herniation of the midgut, visualized as a hyperechogenic mass in the base of the umbilical cord; retraction into the abdominal cavity begins at 10 weeks and is completed by 11 weeks and 5 days[25,46,47]. In this study, the prevalence of exomphalos was increased (seven in 4116). Similarly, in the 15 previous studies on a total of 416 chromosomally normal fetuses with increased nuchal translucency thickness, there were three cases of exomphalos. Although van Zalen-Sprock and colleagues[25] reported that, in fetuses with exomphalos, increased nuchal translucency thickness signified an underlying chromosomal defect, it appears that, even in chromosomally normal fetuses with enlarged nuchal translucency thickness, the prevalence of exomphalos is about ten times higher than in the general population.

## Body stalk anomaly

This lethal, sporadic abnormality characterized by the presence of a major abdominal wall defect, severe kyphoscoliosis and a rudimentary umbilical cord, is reported in about one in 14 000 births[48]. In our study, the prevalence was increased (ten in 4116). In a previous screening study involving ultrasound examination at 11–14 weeks in 3991 patients, there were two cases of body stalk anomaly and in one of the cases there was increased nuchal translucency thickness[49]. In a multicenter study for chromosomal defects by nuchal translucency thickness and maternal age at 10–14 weeks, 106 727 fetuses were examined and 14 of these had body stalk anomaly[27]. The ultrasonographic features were a major abdominal wall defect, severe kyphoscoliosis and a short umbilical cord. In all cases, the upper half of the fetal body was in the amniotic cavity, whereas the lower part was in the celomic cavity, suggesting that early amnion rupture before obliteration of the celomic cavity is a possible cause of the syndrome. Although the nuchal translucency thickness was increased in 71% of the fetuses, the karyotype was normal in all cases[27].

## Fetal akinesia deformation sequence

Fetal akinesia deformation sequence (FADS) is a heterogeneous group of conditions resulting in multiple joint contractures, including bilateral talipes and fixed flexion or extension deformities of the hips, knees, elbows and wrists. The sequence includes congenital lethal arthrogryposis, multiple pterygium and Pena–Shokeir syndromes. In this study, as well as the 15 previous studies on chromosomally normal fetuses with increased nuchal translucency thickness[4–19], the prevalence of FADS (six in 4116 and three in 416, respectively) was higher than expected in the general population. Furthermore, Hyett and colleagues[30], at 11–13 weeks, examined five pregnancies with a previous history

of FADS and, in the two cases with recurrence of FADS, the nuchal translucency thickness was increased, whereas, in the three normal fetuses, the translucency was normal. These findings, as well as the known association between FADS and nuchal edema or hydrops in the second and third trimesters, suggest that, at least in some of the cases of FADS, there is increased nuchal translucency thickness at 10–14 weeks of gestation[30].

## Achondrogenesis type II

This is a lethal, autosomal recessive, skeletal dysplasia with a birth prevalence of about one in 40 000. In the second trimester, the characteristic sonographic features are severe shortening of the limbs, narrow thorax, hypomineralization of the vertebral bodies and hydrops. In our study, there were no cases of achondrogenesis, but, in the previous studies on increased nuchal translucency thickness, there was one case with the condition[9]. Additionally, there are two case reports on the first-trimester sonographic diagnosis of achondrogenesis type II in high-risk pregnancies; both fetuses had increased nuchal translucency thickness and short limbs that were abnormally positioned, with lack of movement[28,29].

## Achondroplasia

This autosomal dominant syndrome has a birth prevalence of about one in 26 000, but the majority of cases represent new mutations. The characteristic features include short limbs, lumbar lordosis, short hands and fingers, macrocephaly and depressed nasal bridge. Intelligence and life expectancy are normal. Prenatally, limb shortening usually becomes apparent only after 22 weeks of gestation. There is one case report of achondroplasia presenting with increased nuchal translucency thickness in the first trimester of pregnancy[19].

## Beckwith–Wiedemann syndrome

This is a usually sporadic and occasionally familial syndrome with a birth prevalence of about one in 14 000. It is characterized by macrosomia and hyperplasia and/or hypertrophy of the tongue, kidneys, adrenals and pancreas, exomphalos and neonatal hypoglycemia and polycythemia. In some cases there is mental handicap, which is thought to be secondary to inadequately treated hypoglycemia. About 5% of affected individuals develop tumors during childhood, most commonly nephroblastoma and hepatoblastoma. In the present study, one of the fetuses with increased nuchal translucency thickness and exomphalos had Beckwith–Wiedemann syndrome.

## Campomelic dysplasia

This is a rare, lethal autosomal recessive syndrome characterized by shortening and bowing of the lower limbs, growth deficiency of prenatal onset, large calvarium with disproportionately small face and narrow chest. Some of the affected genetically male individuals show a female phenotype. Patients usually die in the neonatal period from pulmonary hypoplasia. There is one case report of this condition presenting with increased nuchal translucency thickness at 12 weeks of gestation[7].

## Ectrodactyly-ectodermal dysplasia–clefting syndrome

This is a rare autosomal dominant condition with a wide variability in phenotypic expression and none of the three cardinal signs of ectrodactyly (split hand and foot), facial cleft (lip and/or palate) and ectodermal dysplasia (anomalies of hair, teeth, nails, nasolacrimal ducts and sweat glands) are obligatory. There is one reported case of this syndrome presenting with a nuchal translucency thickness of 3.4 mm at 12 weeks[14].

## Fryns' syndrome

This is a usually lethal autosomal recessive disorder with a birth prevalence of about one in 15 000. It is characterized by the presence of diaphragmatic hernia, digital defects, coarse face and short webbed neck. In our study, there were no cases of Fryns' syndrome, but, in two case reports on the first-trimester presentation of this syndrome, both fetuses had increased nuchal translucency thickness[32,33].

## $G_{M1}$ gangliosidosis

This is a rare, lethal, autosomal recessive condition due to β-galactosidase deficiency. It is characterized by visceromegaly, generalized edema and progressive neurological deterioration, resulting in early and severe retardation of both motor and mental development. Death occurs within the first 10 years of life from chest infections. There is one reported case of this condition presenting with increased nuchal translucency thickness in the first trimester[14].

## Hydrolethalus syndrome

This is a rare, lethal, autosomal recessive condition characterized by hydrocephalus, absent corpus callosum, facial cleft, micrognathia, polydactyly, talipes and cardiac septal defects. The brain hemispheres lie separated from each other at the bottom of the skull and the lateral ventricles open medially into the fluid-filled space between and on the top of the hemispheres. Ammala and Salonen[34] reported the ultrasound diagnosis at 12 weeks in a high-risk pregnancy from Finland, where the condition may be more common. There were abnormal brain structures with midline echoes only at the bottom of the skull and a large cyst in the upper posterior part of the brain; in addition, there was increased nuchal translucency thickness.

## Jarcho–Levin syndrome

This is a heterogeneous disorder that is characterized by vertebral and rib abnormalities. An autosomal recessive

type is characterized by a constricted short thorax and respiratory death in infancy. Another autosomal recessive and an autosomal dominant type are associated with short stature and are compatible with survival to adult life, but with some degree of physical disability. In our study, there were two cases of this syndrome; in one the diagnosis was made postnatally and in the other by pathological examination after termination of the pregnancy for severe scoliosis at 12 weeks. In one previous report on the sonographic features of the syndrome, in three affected fetuses at 12 weeks of gestation there was misalignment of the cervical spine and ribs; additionally, one of the fetuses had increased nuchal translucency thickness at 12 weeks, but this had resolved spontaneously by 15 weeks[35].

## Jeune syndrome (asphyxiating thoracic dystrophy)

This is an autosomal recessive condition with a birth prevalence of about one in 70 000. The characteristic features are narrow chest and rhizomelic limb shortening. There is a variable phenotypic expression and consequently the prognosis varies from neonatal death due to pulmonary hypoplasia, to normal survival. Limb shortening is mild to moderate and this may not become apparent until after 24 weeks of gestation. In a case reported by Ben Ami and colleagues[31], routine ultrasound examination at 14 weeks demonstrated increased nuchal translucency thickness and the femur length was on the 5th centile for gestation. Repeat ultrasonography at 22 weeks showed a narrow thorax and short limbs.

## Joubert syndrome

This is a rare, lethal, autosomal recessive condition characterized by partial or complete absence of the cerebellar vermis. It is associated with profound mental retardation and developmental delay. Death usually occurs in the first 5 years of life. In our study, there was one case of the syndrome presenting with increased nuchal translucency thickness at 11 weeks, but the diagnosis was made at 20 weeks after the detection of agenesis of the vermis.

## Meckel–Gruber syndrome

This lethal, autosomal recessive condition with a birth prevalence of about one in 10 000 is characterized by the triad of encephalocele, bilateral polycystic kidneys and polydactyly. Although in one study, one affected fetus had increased nuchal translucency thickness[15], in another study reporting five affected fetuses, none had increased nuchal translucency thickness[50].

## Nance–Sweeney syndrome

This is a very rare autosomal recessive syndrome characterized by short limbs, vertebral abnormalities, deafness and flat face with depressed nasal bridge. Intelligence and life expectancy are normal. In our series, there was one case of the syndrome that was diagnosed postnatally.

## Noonan syndrome

This is an autosomal dominant condition with wide variability in expression, but about 50% of cases represent new mutations. The birth prevalence is about one in 2000. It is characterized by lymphedema, thought to be due to dysplasia of the lymphatic system, short and webbed neck, short stature, heart defects (most commonly pulmonary valve stenosis), shield chest, hypertelorism and low-set ears. Life expectancy is probably normal in those individuals without severe heart disease. Mild mental retardation is present in about one-third of cases. In our study, there was only one case of Noonan syndrome, but, in the previous 15 studies on a total of 416 chromosomally normal fetuses with increased nuchal translucency thickness, there were five cases of the syndrome[4–19].

## Roberts syndrome

This is a rare autosomal recessive condition characterized by symmetrical limb defects of variable severity (tetraphocomelia), facial cleft, hypertelorism, microcephaly and growth retardation. The condition is associated with the cytogenetic finding of premature centromere separation and puffing. Petrikovsky and colleagues[36] reported tetraphocomelia and increased translucency in an 11-week affected fetus from a high-risk pregnancy.

## Smith–Lemli–Opitz syndrome

This is an autosomal recessive condition with a birth prevalence of about one in 20 000. It is associated with a high perinatal and infant mortality. The features include severe mental retardation, characteristic minor facial anomalies, cleft palate, polydactyly and syndactyly, cardiac defects and, in the male, ambiguous or female external genitalia, and deficiency of the enzyme 7-dehydrocholesterol reductase. In our study, there were three cases of Smith–Lemli–Opitz syndrome. In one case, the diagnosis was made postnatally, and in the second a chromosomally normal male fetus was found by ultrasonography at 20 weeks to have female external genitalia; examination of cultured skin fibroblasts demonstrated increased levels of 7-dehydrocholesterol[38]. In the third case, the mother had a previous pregnancy resulting in unexplained neonatal death and the diagnosis of Smith–Lemli–Opitz syndrome in the current pregnancy was made by DNA analysis after chorionic villus sampling for increased (6 mm) nuchal translucency thickness. There are also two case reports on the first-trimester sonographic diagnosis of the condition in high-risk pregnancies, and in both cases there was increased nuchal translucency thickness[37,39].

## Spinal muscular atrophy type 1

This is a lethal autosomal recessive condition with a birth prevalence of about one in 25 000. It is characterized by degeneration of anterior horn cells of the spinal cord and brain stem with subsequent muscular hypotonia and

atrophy. The onset of symptoms may be intrauterine with decrease in fetal movements. Death, which occurs in the first 2 years of life, is usually due to respiratory failure. In our study, there was one affected case resulting in neonatal death. There are also two other reports of the syndrome presenting with increased nuchal translucency thickness; in one case the condition was diagnosed by chorionic villus sampling and the pregnancy was terminated, but in the other the fetus had transient mild hydrothorax during the pregnancy and died a few days after birth[14,15].

### Thanatophoric dysplasia

This is a sporadic condition with a birth prevalence of about one in 40 000. It is characterized by severe short limb dwarfism, narrow thorax with short ribs and enlarged head with prominent forehead; in some cases there is a cloverleaf skull. The condition is lethal, usually in the neonatal period. In our study, there was one case of thanatophoric dysplasia presenting with increased nuchal translucency thickness at 11 weeks; severe limb shortening and narrow thorax were detected at 17 weeks.

### Trigonocephaly 'C' syndrome

This is an extremely rare autosomal recessive condition characterized by trigonocephaly, short nose, prominent maxilla, joint deformities and loose skin due to hyperelasticity. About half of the affected individuals die in infancy, and survivors are severely mentally handicapped with progressive microcephaly. In our study, there was one case of the syndrome presenting at 13 weeks with a nuchal translucency thickness of 3.3 mm; the diagnosis of the condition was made postnatally.

### VACTER association

This is an acronym used to describe a rare, sporadic association of defects including vertebral abnormalities, anal atresia, cardiac defects, tracheoesophageal fistula with esophageal atresia and radial and renal defects. The prognosis of each patient depends on the particular combination and severity of the abnormalities present. Mental function is usually normal. In our study, there were two cases of the syndrome presenting at 12 weeks with increased nuchal translucency thickness (2.8 mm and 3.0 mm, respectively); the diagnosis of VACTER association was made prenatally in one case and postnatally in the other case.

### Zellweger syndrome

This lethal, autosomal recessive syndrome has a birth prevalence of about one in 25 000. It is characterized by absence or marked decrease in peroxisomes resulting in profound muscular hypotonia. Other features include dolichoturricephaly, hypertelorism, cataracts, brain abnormalities, cardiac defects, hepatomegaly and growth restriction. Death occurs in the first 2 years of life, most commonly due to chest infections and liver failure. Bilardo and colleagues[14] reported one case of the syndrome presenting with increased nuchal translucency thickness at 12 weeks and pericardial effusion at 20 weeks; the diagnosis of the condition was made postnatally.

## CONCLUSIONS

In addition to the association between increased nuchal translucency thickness and a wide range of fetal abnormalities, the data of this study demonstrate that the rates of miscarriage and perinatal death increase with fetal nuchal translucency thickness (Table 1). These data would be useful in counselling parents of affected pregnancies and in alerting sonographers to plan the appropriate follow-up investigations for such pregnancies. However, it should be emphasized to the parents that increased nuchal translucency thickness *per se* does not constitute a fetal abnormality and, once chromosomal defects have been excluded, about 90% of pregnancies with fetal nuchal translucency thickness below 4.5 mm result in healthy live births; the rates for nuchal translucency thickness of 4.5–6.4 mm and 6.5 mm or more are about 80% and 45%, respectively.

The heterogeneity in conditions associated with increased nuchal translucency thickness suggests that there may not be a single underlying mechanism for the subcutaneous edema in the fetal neck. Possible mechanisms include:

(1) Cardiac failure in association with abnormalities of the heart and great arteries;

(2) 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;

(3) Failure of lymphatic drainage due to impaired fetal movements in various neuromuscular disorders;

(4) Abnormal or delayed development of the lymphatic system;

(5) Altered composition of the subcutaneous connective tissue.

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