Nuchal translucency beyond Down syndrome screening
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Increased nuchal translucency in euploid fetuses - what should we be telling the parents

C.M. Bilardo, E. Timmerman, E. Pajkrt and M.C. van Maarle

Chapter 9

ABSTRACT

Nuchal translucency (NT) measurement between 11 and 14 weeks’ gestation is an undisputed marker for aneuploidies. When conventional karyotyping is normal, enlarged NT is a strong marker for adverse pregnancy outcome, associated with miscarriage, intrauterine death, congenital heart defects, and numerous other structural defects and genetic syndromes. The risk of adverse outcome is proportional to the degree of NT enlargement. Although the majority of structural anomalies are amenable to ultrasound detection, unspecified genetic syndromes involving developmental delay may only emerge after birth. Concern over these prenatally undetectable conditions is a heavy burden for parents. However, following detection of enlarged NT the majority of babies with normal detailed ultrasound examination and echocardiography will have an uneventful outcome with no increased risk for developmental delay when compared to the general population. Counselling should emphasize this to help parents restore hope in normal pregnancy outcome and infant development.
INTRODUCTION

Although NT screening was introduced over 15 years ago, there is not yet a general consensus on how to counsel parents of a euploid fetus with enlarged NT. In an editorial published in 2001 entitled ‘Nuchal translucency in the first trimester of pregnancy: ten years on and still a pain in the neck?’ Ville clearly depicts how challenging it can be to give parents realistic and correct information on the subject. The visual impact on the parents of the nuchal fluid collection seen at ultrasound examination can raise anxiety about future development and postnatal outcome. Even if this accumulation usually tends to disappear after 14 weeks, the uncertainty can persist and be exacerbated by excessively cautious or defensive counselling by the medical practitioner. This is also reflected by the fact that some couples in these circumstances request pregnancy termination even in the absence of clear fetal anomalies. In this overview of the most recent literature, the current knowledge on the association between an enlarged NT in karyotypically normal fetuses and fetal outcome will be discussed and guidelines for objective parental counselling suggested.

The test: NT measurement

There is much evidence that NT measurement alone or as part of the combined test is an excellent screening test for fetal aneuploidies. The measurement should be made between 11 and 14 weeks, with best performance obtained at 11–12 weeks when the measurement is performed by qualified ultrasonographers undergoing regular quality assessment. Of fetuses with NT above the 95th centile, about 20–30% have a chromosomal aberration. In the presence of a normal karyotype, there remains an increased risk of adverse pregnancy outcome because of spontaneous fetal loss, isolated anomalies, and genetic syndromes. The normal range of NT measurement changes with gestational age and enlarged NT is variably defined in the literature using a fixed cut off (2.5 or 3 mm, 95th or 99th percentile) or the multiple of the median (MoM) approach. Whether a distinction should be made between NT and cystic hygroma in the first trimester is questionable, and of limited clinical relevance since the management is identical.

Pathological associations with increased NT in euploid fetuses

In euploid fetuses, the prevalence of fetal death increases exponentially with increasing NT. In the combined data from three studies reporting on a total of 4991 euploid fetuses with increased NT, the prevalence of miscarriage or fetal death increased from 1.6% in those with NT between the 95th and 99th centiles to about 20% for NT of ≥6.5 mm. However, this is likely to be an underestimation of true mortality rate, as in cases of
deteriorating fetal hydrops up to 30% of couples decide to terminate pregnancy before intra uterine fetal death occurs.

Fetal death
A large variety of structural anomalies and developmental disorders have been described in the setting of an enlarged NT. Congenital heart defects (CHDs) are predominant, followed by cleft lip and palate, diaphragmatic hernia, skeletal dysplasias, and renal anomalies. The prevalence of major abnormalities in euploid fetuses increases exponentially with NT size, from 2.5% for NT between the 95th and 99th centiles, to about 45% for an NT ≥6.5 mm.

Congenital heart defects
The prevalence of CHD is in the order of six times higher in fetuses with a NT ≥99th percentile than in an unselected population. There does not seem to be an association between any specific CHD and enlarged NT. The chance of CHD increases exponentially with increasing NT from 0.6 to 5% when the NT is between 2.5 and 3.5 mm, to 64% when it is >8.5 mm.

At present, it is not possible to draw a definitive conclusion on the role of NT measurement in screening for major CHD. The first large study on the subject reported a sensitivity of 56% for critical CHD, requiring surgical treatment. A subsequent meta-analysis including other seven studies reported a sensitivity of 30%. In a pooled analysis of data from four large centres the same author found that a NT ≥2.5 and ≥3.5 mm was found in 35.5 and 23%, respectively, of 397 euploid fetuses with major CHD. Low detection rates for CHD (around 15%) are reported in studies where NT is measured in unselected or low-risk populations and when fetuses with cystic hygromas are excluded. However, two recent studies, a meta-analysis of four studies and a 10-year overview of the association between nuchal fluid accumulation and CHD diagnosed at referral centres, re-evaluated the role of NT measurement in screening for CHD and showed enhanced detection and improved neonatal outcome in duct dependent CHD, such as transposition of the great arteries. Study of ductus venosus (DV) flow patterns in these fetuses may improve the selection of those requiring specialized echocardiography as absent or reversed flow during the a-wave is associated with a three-fold increase in the likelihood of a major CHD. Tricuspid regurgitation (TR) at 11–13 + 6 weeks’ gestation may also play a role in identifying fetuses with CHD as those with TR have an 8-fold increased risk.

Genetic syndromes
The list of genetic syndromes presenting with an increased NT is growing constantly (Table 1). Most of these syndromes are sporadic with prevalence in the order of 1 : 10,000 or lower, making it impossible to prove a definite association between specific syndromes and
Parental counselling after enlarged NT

**Table 1.** Genetic syndromes and chromosomal aberrations described in fetuses with increased NT and reported after publication of Souka’s overview (2005)

<table>
<thead>
<tr>
<th>Syndrome/Mutation</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pallister Killian syndrome 96, 97, 98</td>
<td></td>
</tr>
<tr>
<td>Apert syndrome 99, 100</td>
<td></td>
</tr>
<tr>
<td>Walker-Warburg syndrome 101</td>
<td></td>
</tr>
<tr>
<td>Coffin-Siris syndrome 6</td>
<td></td>
</tr>
<tr>
<td>Fryn’s syndrome 6</td>
<td></td>
</tr>
<tr>
<td>Ritscher-Schinzel syndrome 102</td>
<td></td>
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<tr>
<td>Split-hand/foot malformation 103</td>
<td></td>
</tr>
<tr>
<td>Diastrophic dysplasia 6</td>
<td></td>
</tr>
<tr>
<td>Spondyloepiphysed dysplasia congenita (SEDC) 25</td>
<td></td>
</tr>
<tr>
<td>Cerebro-fronto-facial syndrome (Dandy-Walker variant and frontofacial dysmorphisms)</td>
<td>104</td>
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<td>Chondroectodermal dysplasia (Ellis-Van Creveld syndrome) 105</td>
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<td>Thrombocytopenia-absent-radius (TAR) syndrome 106</td>
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<td>Cardiofaciocutaneous syndrome 107</td>
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<td>Multiple pterygium syndrome 108</td>
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<td>Orofaciodigital syndrome Type IV (Mohr-Majewski) 109</td>
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<tr>
<td>Arthrogryposis, renal dysfunction, cholestasis (ARC) 110</td>
<td></td>
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<tr>
<td>Thanatophoric dysplasia 111</td>
<td></td>
</tr>
<tr>
<td>Type I 112</td>
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<tr>
<td>Osteochondrodysplasia with severe osteopenia, preaxial polydactyly, clefting and dysmorphic features resembling filamin-related disorders 113</td>
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<td>Androgen insensitivity syndrome 114</td>
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<td>Unbalanced translocations: 115</td>
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<td>— mono 9p24.3-pter and tri17q24.3-qter 116</td>
<td></td>
</tr>
<tr>
<td>— 46,XY,invdup(9)[p22.1p24] [arrCGH 9p22.1p24 (RP11-130C19-&gt;RP11-87O1)x3] 117</td>
<td></td>
</tr>
<tr>
<td>— Trisomy 15q due to t(X;15) (q22.3;q11.2) translocation 118</td>
<td></td>
</tr>
<tr>
<td>Deletions:</td>
<td></td>
</tr>
<tr>
<td>— Chromosome 8 deletion 6</td>
<td></td>
</tr>
<tr>
<td>— De novo proximal interstitial 9q deletion 68</td>
<td></td>
</tr>
<tr>
<td>— Six-megabase deletion of chromosome 14q = 46,XX,der[14][t(13;14)]q34;q32.2] 119</td>
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<td>— 13q-syndrome 120</td>
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<tr>
<td>— Partial deletion of chromosome 6p21 (46,XX,del(6)[p21]) 121</td>
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<td>— De novo 16p13.11 microdeletion 70</td>
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<td>— Chromosome 5q subtelomeric deletion syndrome 122</td>
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<tr>
<td>Marker chromosome (16) (p13.1-&gt;q12.2) 123</td>
<td></td>
</tr>
<tr>
<td>Trisomy 1q 124</td>
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increased NT. For syndromes such as Noonan, Smith-Lemli-Opitz, spinal muscular atrophy and other muscle-skeletal disorders the association with increased NT is undisputed. However, an enlarged NT is a nonspecific indicator of abnormal development, common to several different pathologic pathways 15.
Neurodevelopmental delay

There is still limited information on the real prevalence of neurodevelopmental delay in euploid fetuses with increased NT. Studies on large series and long term follow-up with standardized clinical evaluation of the infants are necessary to provide reliable data and prevent underestimation \(^5,49\). Nine long-term follow-up studies have thus far reported an incidence of developmental delay varying between 0 and 8.7% (Table 2) in chromosomally and anatomically normal fetuses with increased NT. The studies are heterogeneous in cohort size, cut off used for increased NT, follow-up length and methodology. Normality was reported by questionnaire completed by parents in four studies. In five studies, all infants were examined clinically, but only two used a control group. In Senat’s paper, follow-up at the age of 2 using the Ages and Stages questionnaire filled in by 162 couples, reassuring results were reported. The incidence of developmental delay in children with enlarged NT was 1.2%, which was not statistically different when compared to a control group of 370 unselected infants \(^50\). These results are in keeping with the incidence of developmental delay in our series: 1.6% (7/425), of which only 1/3 was not associated with ultrasound features that may have triggered suspicion (0.5%) \(^6\). In our experience, all seven cases with developmental delay occurred in fetuses with an NT >4 mm. In only three out of seven cases syndrome recognition was possible.

Table 2. Long-term follow-up of chromosomally and anatomically normal fetuses with increased NT

<table>
<thead>
<tr>
<th>Reference</th>
<th>NT cut off</th>
<th>Method</th>
<th>Control group</th>
<th>Age (month)</th>
<th>Lost (%)</th>
<th>Developmental delay [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brady (1998)</td>
<td>3.5 mm</td>
<td>Clinical examination</td>
<td>Yes</td>
<td>6–42</td>
<td>1</td>
<td>1/89 (1.1)</td>
</tr>
<tr>
<td>Van Vugt (1998)</td>
<td>3.0 mm</td>
<td>Questionnaire</td>
<td>No</td>
<td>7–75</td>
<td>32</td>
<td>1/34 (2.9)</td>
</tr>
<tr>
<td>Adekunle (1999)</td>
<td>4.0 mm</td>
<td>Questionnaire</td>
<td>No</td>
<td>13–38</td>
<td>26</td>
<td>2/23 (8.7)</td>
</tr>
<tr>
<td>Maymon (2000)</td>
<td>&gt;p95</td>
<td>Questionnaire/telephone</td>
<td>No</td>
<td>12–36</td>
<td>0</td>
<td>0/36 (0)</td>
</tr>
<tr>
<td>Hiippala (2001)</td>
<td>3.0 mm</td>
<td>Clinical examination</td>
<td>No</td>
<td>24–84</td>
<td>15</td>
<td>1/50 (2)</td>
</tr>
<tr>
<td>Souka (2001)</td>
<td>3.5 mm</td>
<td>NA</td>
<td>No</td>
<td>—</td>
<td>0</td>
<td>4/980 (0.4)</td>
</tr>
<tr>
<td>Senat (2002)</td>
<td>4.0 mm</td>
<td>Clinical examination</td>
<td>No</td>
<td>12–72</td>
<td>7</td>
<td>3/54 (5.6)</td>
</tr>
<tr>
<td>Cheng (2004)</td>
<td>3.0 mm</td>
<td>Clinical examination</td>
<td>No</td>
<td>8–30</td>
<td>0</td>
<td>1/14 (7.1)</td>
</tr>
<tr>
<td>Senat (2007)</td>
<td>&gt;p99</td>
<td>Clinical examination ASQ scores</td>
<td>Yes</td>
<td>0–24</td>
<td>0</td>
<td>2/162 (1.2)</td>
</tr>
<tr>
<td>Bilardo (2007)</td>
<td>&gt;p95</td>
<td>Questionnaire/telephone</td>
<td>No</td>
<td>6–60</td>
<td>3.3</td>
<td>7/425 (1.6)</td>
</tr>
</tbody>
</table>

*p95 and p99: 95th and 99th percentiles; ASQ, Ages and Stages Questionnaires; —, information not provided.

Management of euploid fetuses with increased NT

A recent survey on which protocol should be used in fetuses with increased first trimester screening and normal karyotype \(^51\) points out that increased NT should always trigger detailed assessment of fetal cardiac anatomy (Figure 1).
The current consensus is that fetal echocardiography should be offered in all cases in which NT is >3.5 mm (99th percentile). The cost-effectiveness of using lower cut offs (2.5 mm, 95th centile) needs, in view of the rather low positive predictive value (PPV) (2–3%) further investigation. Our recommendation is that all cases of euploid fetuses with NT above 3.5 mm are referred to tertiary level centres for further investigations. However, if resources are available and parents are particularly anxious earlier, detailed investigations may be

**Figure 1.** Proposed management protocol for euploid fetuses with enlarged NT
offered at lesser degrees of enlargement (95th centile). Maymon et al. recommend use of NT MoM of 2 or a delta NT of 1.5 as cut off for further investigations. In experienced hands and with high-resolution ultrasound equipment the majority of severe malformations, as well as major CHD, may be detected by the end of the first trimester. This enables early reassurance for most women. Where anomalies are present it allows time for additional investigations, counselling and, if appropriate, for an ‘unrushed’ decision on termination of pregnancy (TOP) at an earlier stage where emotional impact may be less, although this is debated.

Some authors have proposed that, in fetuses with enlarged NT and obvious structural anomalies, TOP may be offered directly, saving the costs of karyotyping. However, karyotyping is important not only to define recurrence risk, but also to help parents in the decision making process.

Other first trimester screening markers can give an indication of the risk of detecting additional anomalies in euploid fetuses. For example, abnormal DV flow is associated with poor pregnancy outcome (cardiac and other anomalies, perinatal deaths) and should be regarded as an additional risk factor warranting close ultrasound surveillance.

Infection screening should not be routinely performed, but it may be appropriate when NT enlargement evolves in the second trimester into an increased nuchal fold, generalized edema, or unexplained hydrops or in women with young children who have been recently ill or have been ill themselves.

Additional genetic investigations in fetuses with enlarged NT and normal conventional karyotype, such as molecular testing (subtelomere MLPA and CGH microarrays) are promising techniques for identifying microscopic genomic aberrations (microdeletions, unbalanced translocations) responsible for syndromic associations including structural anomalies and mental retardation. However, as their value has not yet been investigated prospectively in large series, caution should be used in interpreting isolated findings in fetuses without structural anomalies. Screening for 22q11 deletions should only be performed in fetuses with confirmed cardiac defects.

When at subsequent scans even subtle anomalies and/or dysmorphic features are found, a genetic opinion should be sought to attempt identification of a classifiable syndrome. A thorough family history, including consanguinity, should be taken to distinguish inherited syndromes (autosomal recessive or dominant) with a high recurrence risk from sporadic syndromes (featuring a de novo mutation). In our experience the latter are predominant.

On occasions a careful diagnostic workup, including examination of the parents, can reveal a specific syndrome or carrier status in one of them.

In couples known to be carriers of conditions with a high recurrence risk NT may be used as early reassurance or warning sign of likely recurrence.
How to counsel parents

**Before first trimester screening**

Not all women undergoing first trimester screening are aware of its possibilities and limitations. Women should also be properly informed that first trimester screening is not only for Down syndrome, but may reveal additional risk factors for the pregnancy requiring further investigations. The amount of anxiety that this uncertainty can cause should not be underestimated.

It is therefore mandatory that all pregnant women are properly counselled about prenatal screening and that Health systems provide guidelines to allow parents to make an informed choice regarding first trimester screening.

**After increased NT and normal karyotype**

After a normal karyotype has been established the first question parents usually ask is: ‘What is now the chance of a normal pregnancy outcome?’

Based on the literature, the overall chance of adverse outcome varies substantially according to the cohort characteristics. When fetuses with increased NT are part of a cohort of unselected fetuses undergoing first trimester screening, the incidence of adverse outcome (anomalies, miscarriages, TOP and fetal and neonatal death) varies between 3% and 6%. In contrast, in selected cohorts of fetuses with an enlarged NT the adverse outcome rate is about 3–6 times higher (~20%). The five largest studies published since 2000 comprise a total of 2271 fetuses and report a mean incidence of 10.6% (range 2.1–26%) for isolated structural anomalies and 4.4% (0.5–6.4%) for genetic disorders detected before birth with an additional 2.5% (2.2–6.6%) of anomalies detected after birth (Table 3). However, these studies are difficult to compare due to differences in populations, definitions of NT enlargement (3 mm, 95th centile, 99th centile).

| Table 3. Largest studies published after 2000 reporting on structural anomalies and genetic disorders detected in fetuses with enlarged nuchal translucency and percentage of anomalies only detected after birth. |
|---|---|---|---|---|
| Euploid fetuses (n) | NT (mm) | Structural anomalies | Genetic disorders | Anomalies detected after birth |
| Mangione (2001) 131 | 202 | ≥3.0 mm | 23/202 (11.4%) | 1/202 (0.5%) | — |
| Souka (2001) 18 | 1320 | ≥3.5 mm | 162/1320 (12.3%) | 44/1320 (3.3%) | 22/980 (2.2%) |
| Michailidis (2001) 27 | 235 | ≥P95 | 5/235 (2.1%) | — | — |
| Senat (2002) 19 | 89 | ≥4 mm | 23/89 (25.8%) | 4/62 (6.4%) | 4/62 (6.5%) |
| Bilardo (2007) 6 | 425 | ≥P95 | 27/425 (6.3%) | 23/425 (5.4%) | 10/375 (2.7%) |
| Total | 2271 | 240/2271 (10.6%) (range 2.1-25.8%) | 72/1629 (4.4%) (range 0.5-6.4%) | 36/1417 (2.5%) (range 2.2-6.5%) |

P95, 95th centile
—, not reported.
Genetic disorders include neurodevelopmental delay
centile or 4 mm) and NT distribution. Table 4 gives an overview of the frequency of various outcome variables according to degree of NT thickness. In Figure 2, the chance of favourable outcome reported by two studies is presented per degree of NT thickness. This information may be used for parental counselling, particularly for couples who can understand the concept of risk and statistics. In case of very large NT parents should be informed that there is a high chance of spontaneous lethality and that not all anomalies, and especially cardiac, are amenable to prenatal detection.

Recently, it has also been observed that an enlarged NT is more frequently observed in male fetuses. Boys with marginal degrees of NT enlargement (>95th–99th percentile) have a higher chance of uneventful outcome than females.

![Figure 2. Chance of favorable outcome after different degrees of NT enlargement (according to Bilardo et al., 2007 and Souka et al., 2005)](image)

Common questions from parents
When faced with the question by parents: ‘What is the cause for the extra fluid in the neck?’ it is easier to find a plausible explanation when increased NT is found in the setting of a definite spectrum of malformations: cardiac, skeletal, neuromuscular, diaphragmatic hernia, than in the absence of a clear cause. We still totally ignore the origin of ‘physiological’ nuchal fluid accumulation, as seen exclusively between 11 and 14 weeks. Variable degrees of nuchal edema may be present before full establishment of lymphatic development and prior to establishment of the intervillous circulation and renal function maturation.
This can ‘normalize’ before 14 weeks in one out of five fetuses. However, at present there is still insufficient data to equate a disappearing enlarged NT with true ‘normality’.

In about 3% of fetuses with increased NT nuchal edema, isolated or in combination with other forms of fluid accumulation, can persist at the time of the 20 weeks scan. It is not clear whether this finding represents failure of resolution or if it has a different etiology.

During embryogenesis tyrosine phosphatase (SHP2) deficiency affects neural crest cell function and triggers the events leading to the typical heart and skull anomalies seen, for instance, in Noonan syndrome (NS) fetuses.

When nuchal edema persists parents should be counselled that there is a 10% risk of evolution to hydrops and perinatal death or a live birth with a genetic syndrome, such as Noonan syndrome. Follow-up scans to monitor evolution of the condition are indicated.

When family history is taken a geneticist may advise on appropriateness of DNA testing for certain genetic conditions, such as spinal muscular atrophy.

Noonan syndrome is one of the most frequent genetic syndromes encountered in association with nuchal fluid or cystic hygroma in pregnancy. The exact incidence of NS in these fetuses is uncertain, but it may vary between 1 and 3%. Genetic testing for this condition is possible, but it takes a long time and it is not always clear-cut, due to the heterogeneity of the condition. In fact, half of the NT cases do not show a PTPN11 mutation. Parents should also be informed that, in the absence of severe cardiac anomalies, the prognosis of the condition is generally good, with a good chance of normal intellectual development in the vast majority of cases.

Residual risk of adverse outcome after ‘normal’ scans

After a normal mid-gestation scan the crucial question of parents is: ‘What is the residual chance that abnormal development will emerge after birth?’

Based on our series of 451 fetuses with increased NT, adverse outcome in fetuses with normal ultrasound examination occurred in 4% of cases and included an equal proportion of intrauterine deaths, undetected heart defects and genetic syndromes. In Senat’s report anomalies were detected after birth in 18/179 (11%) of fetuses with negative findings at ultrasound (US). Both Souka et al. and our studies found that, if at the 20 weeks scan no features of abnormal development were detected, including subtle anomalies (persistence of nuchal edema, pericardial effusion etc.), the chance of uneventful outcome was similar to the general population regardless of increase in NT (Figure 3). However, this observation needs to be substantiated by larger series as the numbers surviving with very large NT’s is small. Longer term follow-up is also required as some conditions may only present later in childhood. Thus, one case of NS syndrome with mild pulmonary stenosis was only diagnosed at 3 years of age after publication of our series. Moreover, ultrasound examination is not very specific. Critical examination of our data showed that 7 (14%) of the 50 fetuses with suspicious ultrasound findings had an uneventful outcome. This
means that obsessive searching for subtle ultrasound features of abnormal development may also lead to anxiety and unnecessary TOP in healthy fetuses.

CONCLUSION

Grossly, one out of five fetuses with enlarged NT and normal karyotype has an adverse outcome. The chance of an uneventful pregnancy outcome is inversely related to the initial degree of enlargement. Cases with suspicious ultrasound findings detected at the mid-trimester detailed scan should undergo extra investigations and counselling by a geneticist. Based on current knowledge, in pregnancies where the increased NT resolves and detailed ultrasound examinations reveal no additional anomalies, parents can be confidently reassured that the residual chance of structural anomalies and abnormal neurodevelopment may not be higher than in the general population. However, larger studies conducted with uniform protocols and with standardized long-term follow-up are necessary to definitively reinforce this conclusion.

**Figure 3.** Chance of favourable outcome after normal scan in euploid fetuses with different degrees of NT enlargement (according to Bilardo et al., 2007)
REFERENCES


