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Challenges in prenatal screening and diagnosis in the Netherlands

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Increased nuchal translucency with normal karyotype and anomaly scan: What next?

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Increased nuchal translucency with normal karyotype and anomaly scan: What next?

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Abstract:

Over the years, it has become clear that increased nuchal translucency is a marker for chromosomal abnormalities, and it is also associated with a wide spectrum of structural anomalies, genetic syndromes, a higher risk of miscarriage, and intrauterine fetal death. These risks are all proportionally related to the degree of nuchal translucency enlargement.

After the initial assessment of increased nuchal translucency, parents

should be counselled by the fetal medicine specialist about the possible outcomes and the value of additional karyotyping and array comparative genomic hybridisation. A detailed late first-trimester and subsequent 20-week scan should aim at identifying structural anomalies, with special focus on the fetal heart and subtle dysmorphic features. In the absence of structural anomalies or markers, the chance of a favourable outcome is high.

Introduction

In 1992, Nicolaides et al.¹ proposed nuchal translucency measurement as a marker for chromosomal abnormalities in the first trimester of pregnancy. Over the years, it has become clear that an increased nuchal translucency is also associated with a wide spectrum of structural anomalies, genetic syndromes, a higher risk of miscarriage, and intrauterine fetal death. These risks are all proportionally related to the degree of nuchal translucency enlargement.^{2,3}

At present, the most challenging part of managing pregnancies with increased nuchal translucency, after exclusion of chromosomal aberrations, is to establish an adequate diagnostic work up, and provide parents with realistic and correct information about outcome, especially long-term neurological outcome in the absence of structural anomalies.⁴⁻⁶

In this chapter, we provide an overview of issues relating to nuchal translucency. We subsequently suggest a protocol for managing these pregnancies to aid parental counselling once a normal karyotype or genotype has been confirmed.

At present, nuchal translucency measurement is offered in most countries as part of first-trimester screening for Down's syndrome. Participation rates vary considerably per country, as its uptake is influenced by local policies, socioeconomic factors, attitude towards Down's syndrome screening, and termination of pregnancy.⁷⁻¹² When women are informed about first-trimester screening, the focus of counselling is primarily on

the detection of Down's syndrome. They should, however, be informed that this type of screening may detect many other chromosomal anomalies, and an increased nuchal translucency is also a powerful marker for cardiac anomalies, other structural anomalies, and genetic syndromes.¹³⁻¹⁴ Furthermore, fetuses with an increased nuchal translucency have an increased risk of adverse pregnancy outcome, such as fetal loss and developmental delay.^{2,3,15-18}

Increased nuchal translucency

Nuchal translucency is a subcutaneous accumulation of fluid behind the neck of the fetus and generally visible by ultrasound up to 15 weeks of gestation. The size of the nuchal translucency is influenced by gestational age and is part of normal development.¹⁹ Nuchal translucency is considered abnormal only when it exceeds a certain cut-off.¹ Many different definitions and cut-offs for increased nuchal translucency have been used in the past.²⁰ Although debate continues about whether nuchal translucency should be regarded as an increase above the 95th or 99th centile, there is consensus that nuchal translucency above the 99th centile (3.5 mm) is definitely increased.

Nuchal translucency seems to be influenced by gender. Two studies have shown that male fetuses tend to have a slightly larger nuchal translucency than females, about 0.06-0.1 mm²¹⁻²⁴, but this finding could not be confirmed by another study.²³ Timmerman et al.²⁵ showed, that among fetuses with an increased nuchal translucency, significantly more male fetuses had a favourable outcome compared with females (adverse outcome male 20.1% compared with 35.9% in females). The favourable outcome was especially present in male fetuses, with a marginally increased nuchal translucency (between P95 and 99), suggesting that a different cut-off may be necessary in male fetuses.

Increased nuchal translucency and aetiology

The pathophysiology behind increased nuchal translucency is not yet fully understood, and many hypotheses about the cause of nuchal translucency and the pathophysiology behind an increased nuchal translucency have been forwarded.²⁷⁻³³ One of the possible causes for increased nuchal translucency is a congenital heart defect, but it is difficult to explain the exact mechanism behind this possible relationship, as different types of congenital heart defects with their own corresponding haemodynamics are encountered. An alternative explanation could be heart failure,³³⁻³⁶ although at present the relationship between impaired cardiac function as the main cause of increased nuchal translucency has not yet been established by all research groups.^{31,32} Bekker et al.³⁷ suggested that impaired endothelial development could be the link between increased nuchal translucency and congenital heart defects.

Another possibility is developmental delay of the lymphatic system. Lymphatic jugular sacs are part of the lymphatic system, and a delay in development of these sacs, could cause increased nuchal translucency owing to fluid accumulation.³⁸ A study by De Mooij et al.³⁹ showed that a disturbance in lymphatic endothelial differentiation is present in euploid fetuses, with increased nuchal translucency, and that this disturbance has a

similar phenotype as aneuploid fetuses with enlarged jugular lymphatic sacs. More research, however, is needed to ascertain that this is a plausible explanation for all cases of increased nuchal translucency.

Changes in the extra-cellular matrix, owing to a higher concentration of hyaluronan, and as a result excessive hydration of the extracellular matrix and a perturbed function or migration of the neural crest cells, have also been suggested as plausible causes of increased nuchal translucency.⁴⁰⁻⁴² The latter disturbance plays a key role in determining the craniofacial defects and cardiac abnormalities that are present in Noonan syndrome and other syndromes associated with increased nuchal translucency.⁴³

Increased nuchal translucency and chromosomal abnormalities

About 20% of fetuses with increased nuchal translucency will have a chromosomal abnormality.⁴⁴ The incidence increases with nuchal translucency thickness from about 7% for nuchal translucency between the 95th and 99th centile (3.5 mm), to 20% for nuchal translucency of 3.5-4.4 mm, 50% for nuchal translucency of 5.5-6.4 mm, and 75% for nuchal translucency of 8.5 mm or more.⁴⁴

Submicroscopic chromosomal abnormalities generally missed by conventional karyotyping may be responsible for, the sometimes subtle, structural anomalies or developmental delay later in the life of a fetus with increased nuchal translucency and apparently 'normal' karyotype. These submicroscopic chromosomal abnormalities may be identified using comparative genomic hybridisation (CGH) microarray. The main advantage of CGH-array is the ability to detect simultaneously aneuploidies, deletions, duplications, amplifications, or both, of any locus represented on an array. In addition, CGHarray has proven to be a powerful tool for the detection of submicroscopic chromosomal abnormalities in individuals with idiopathic mental retardation and various birth defects.

A systematic review and meta-analysis by Hillman et al.⁴⁵ showed that, when conventional karyotyping was normal, array-CGH detected 3.6% additional genomic imbalances (regardless of referral indication). This increased to 5.2% when the referral indication was structural malformation on ultrasound. Leung et al.⁴⁶ showed that one out of 10 fetuses with increased nuchal translucency and an apparently normal karyotype had a submicroscopic chromosomal abnormality likely to be pathological.

A challenge of the application of CGH-array prenatally is determining whether a copy number variant (CNV) is *de novo* and likely to be causative, or inherited and likely to be benign. In case of doubt, the CGH-array of the fetus should be compared with the CNV's in parental blood.

A disadvantage of CGH-array is that balanced rearrangements, such as translocations and inversions, cannot be identified. Furthermore, information is gained on treatable and non-treatable diseases that may develop later in life, and parents need to decide whether they wish to receive this information.

Fetuses with increased nuchal translucency should undergo conventional karyotyping and also receive counselling about array-CGH.

Increased nuchal translucency and structural abnormalities

Convincing evidence shows that increased nuchal translucency in an euploid fetus is associated with an increased risk for structural anomalies, most commonly congenital heart defects.^{6,20,36,47} A review by Souka et al.²⁰ showed large differences between studies in the prevalence of major anomalies, ranging from 3% to 50%, mainly because of differences in population, differences in definition of increased nuchal translucency and varying distribution of the nuchal translucency.⁴⁸ A study by Westin et al.⁴⁹ showed that nuchal translucency 3 mm or more increased the likelihood of lethal or serious malformation about 15-fold, nuchal translucency 3.5 mm or more about 40-fold, and nuchal translucency 4.5 mm or more about 80-fold.

Major congenital heart defects are found in about 4-5% of chromosomally normal fetuses with increased nuchal translucency.^{27,47,50} The prevalence increases from 0.6 to 2.5% with nuchal translucency between 95th and 99th centile to 64% in nuchal translucency greater than 8.5 mm.^{35,51-53} No specific type of congenital heart defect predominates.⁵⁴

A meta-analysis by Makrydimas et al.⁵⁵ showed that the 99th centile threshold captures about 30% of congenital heart defects, instead of 56%, initially suggested by Hyett et al.⁵³ Michailidis et al.⁵² found that 27% and 36% of all major cardiac defects occurred within the group of chromosomally normal fetuses with nuchal translucency above the 95th and 99th centile, respectively. In contrast, Mavrides et al.⁵¹ found that only 11% and 15% of major congenital heart defects occurred in those similar groups. Muller et al.⁵⁶ found similar results, with a prevalence of major congenital heart defects in fetuses with nuchal translucency above the 99th centile of 9.5%.

A meta-analysis by Sotiriadis et al.⁵⁷ showed that when analysis was restricted to studies with operators certified by the Fetal Medicine Foundation, the sensitivity was 40.7% using the 95th centile cut-off and 14.5% using the 99th centile cut-off.

Wald et al.⁵⁸ found that an enlarged nuchal translucency is especially of value in identifying (duct dependent) congenital heart defects that benefit from prenatal detection. Thus far, the heterogeneity of studies prevents the assessment of the true predictive value of nuchal translucency measurement in the screening for congenital heart defects. At present, however, nuchal translucency measurement is the most effective early screening method for cardiac defects. Future research should focus on the role of the Doppler of the hepatic artery, ductus venosus and tricuspid valve as sonomarkers for congenital heart defects in fetuses with and without increased nuchal translucency.

Besides congenital heart defects, a clear association can also be found between orofacial clefts and increased nuchal translucency. Timmerman et al.⁵⁹ showed a 19-fold higher chance of having a facial cleft in fetuses with an increased nuchal translucency compared with fetuses with a normal nuchal translucency.

A study by Bilardo et al.⁶ and Souka et al.²⁰ showed that when no (subtle) structural anomalies or markers are present at the 20-week anomaly scan, the chance of a normal outcome is similar to that of the general population, around 4%, irrespective of the enlargement of the nuchal translucency. A limitation of these studies is the small number of fetuses with a large nuchal translucency.

Scott et al.⁶⁰ examined 120 cases of fetuses with a nuchal translucency over 6.5 mm; 74% had a chromosomal abnormality and 26% had a normal karyotype. In the group with a normal karyotype, only eight babies were liveborn, of whom seven showed no

abnormalities at the detailed ultrasound scan. Four of the seven babies had a structural abnormality or genetic syndrome at birth. It is difficult to draw a definite conclusion on outcome of fetuses with a large nuchal translucency, as few are alive due to a high chance of fetal demise or termination of pregnancy. Furthermore, follow up over a longer period of time is necessary as some conditions present later in childhood.

Increased nuchal translucency and genetic syndromes

In 3% of fetuses with an increased nuchal translucency, an increased nuchal fold (6 mm) will be present at the 20-week anomaly scan.⁶ The cause of this phenomenon is not yet clear, although many hypotheses exist.⁶¹ When an increased nuchal fold is present, a 10% risk on a genetic syndrome or fetal hydrops and possible perinatal death is present.²⁰

A long, and still growing, list of genetic syndromes present with increased nuchal translucency.^{5,20} For syndromes, such as Noonan syndrome and syndromes with mutations in the same pathway, Smith-Lemli-Opitz syndrome, spinal muscular atrophy and other muscle-skeletal disorders, the association with increased nuchal translucency is undisputed. In sporadic syndromes, the association with an enlarged nuchal translucency is more difficult to prove. Some syndromes are rare, and the available information is based on case reports, implying that the association could be coincidental. In case a genetic syndrome is suspected, a clinical geneticist should be consulted to discuss additional genetic testing.

Prenatally, Noonan syndrome is the most frequently reported genetic syndrome in association with increased nuchal translucency, with an incidence ranging from 2 - 5%.⁶²⁻⁶⁴ It is an autosomal dominant disorder, and is caused in about 50% of the cases by a missense mutation in the PTPN11 gene on chromosome 12.⁶⁵ Mutations in the SOS1-, RAF1-, KRAS-, BRAF-, MAP2K1/2-, NRAS- and SHOC2-genes account for a small percentage of Noonan syndrome cases.⁶⁶ In chromosomally normal fetuses with enlarged nuchal translucency, the prevalence of Noonan syndrome tested by PTPN11 seems to vary from 6 to 18%.^{63,64,67}

Houweling et al.⁶⁸ advocate that, given the high incidence of Noonan syndrome in fetuses with increased nuchal translucency and normal karyotype, genetic counselling and Noonan syndrome mutation detection should be offered in all cases, irrespective of additional abnormalities. It is debatable, however, if nuchal translucency measurement should be used as a screening tool for Noonan syndrome, mainly as this syndrome has a highly variable expression and most cases only have mild dysmorphic features and normal neurodevelopment.⁶⁹

Moreover, testing for Noonan is expensive, and the important clinical question is in which cases testing should be offered. Our group proposes a more cost-effective selection of cases. We showed that the diagnosis of Noonan syndrome can be suspected prenatally, especially in chromosomally normal fetuses with a large nuchal translucency and one or more of the following characteristics: persistent nuchal fold or cystic hygroma, hydrops fetalis, pleural effusion, cardiac anomalies, polyhydramnios, or specific facial features.⁷⁰ Croonen et al.⁶⁷ recommend that, in the presence of the above mentioned ultrasound features, testing should be extended to KRAS, RAF1, BRAF, and MAP2k1 genes for mutations, in case PTPN11 is negative.

Increased nuchal translucency and development (delay)

Fourteen original studies have reported on the long-term follow up of fetuses with increased nuchal translucency, normal ultrasound findings, and normal karyotype. The proportion of developmental delay in early childhood reported in these studies ranges from 0 to 8.7% (Table 1).^{6-17,18,62,71-80} Interpretation of the studies so far is hampered by lack of standardisation: the cutoff values used to define increased nuchal translucency range between 3 mm, 3.5 mm, 4 mm, 95th centile and the 99th centile; the age of the children at follow up ranges from 6 months to 75 months; there are different ascertainment methods for developmental delay; and only three studies use a control group.^{17,49,72}

The heterogeneity in prenatal and postnatal studies makes information on the prevalence of neurodevelopmental delay in euploid fetuses with increased nuchal translucency difficult to interpret to reach a final conclusion.^{21,48} In studies in which a control group was used, and having excluded for chromosomal abnormalities, structural defects and genetic syndromes, no statistically significant difference was found between fetuses with an increased nuchal translucency compared with the general population, where developmental delay is about 4-5%.^{17,49,72} In a systematic review by Sotiriadis et al.⁷¹ the same conclusion was reached; however, the reviewers concluded that the reassuring results should be interpreted with caution. In fact, no consensus has yet been reached on

■ Table 1 – Postnatal follow up in chromosomally normal fetuses with increased nuchal translucency thickness

Author	Study	Nuchal translucency	Control group	Follow up (months)	Follow up type	Development delay	
						Case	Control
Van Vugt et al., 1998 ⁸⁰	P	≥3 mm	No	7-75	Questionnaire	(1/34) 2.9%	
Brady et al., 1998 ⁷⁹	C-C	≥3.5 mm	Yes	6-42	Clinical examination	(1/89) 1.1%	(1/302) 0.33%
Adekunle et al., 1999 ⁷⁵	P	≥4 mm	No	12-38	Questionnaire	(2/23) 8.7%	
Maymon et al., 2000 ⁷⁷	P	≥95th centile	No	12-36	Questionnaire or by telephone	(0/36) 0	
Souka et al., 2001 ⁷⁴	R	≥3.5 mm	No	NA	Information from maternity units, the patient or GP	(4/980) 0.4%	
Hiippala et al., 2001 ⁶²	P	≥3 mm	No	24-84	Clinical examination	(1/50) 2%	
Senat et al., 2002 ¹⁸	R	≥4 mm	No	12-72	Clinical examination	(3/54) 5.6%	
Cheng et al., 2004 ⁷⁶	R	≥3 mm	No	8-30	Clinical examination	(1/14) 7.1%	
Senat et al., 2007 ⁷⁸	P/R	≥99th centile	Yes	0-24	Clinical examination and ASQ	(2/162) 1.2%	(?/370) ?
Bilardo et al., 2007 ⁶	R	≥95th centile	No	6-60	Questionnaires or by telephone	(7/425) 1.6%	
Saldanha et al., 2009 ¹⁷	P	≥95th centile	No	29 days to 72 months	Questionnaires and clinical examination	(0/128) 0	
Mula et al., 2012 ⁷³	P	≥99th centile	No	24	Four paediatric consultations or ASQ	(4/108) 3.7%	
Miltoft et al., 2012 ⁷²	C-C	≥4 mm	Yes	24	ASQ	(1/80) 1.3%	(6/137) 4.4%
Sotiriadis et al., 2012 ⁷¹	SR	Total ≥95th centile ≥99th centile >3 mm				(28/2458) 1.14% (7/669) 1.05% (15/1567) 0.96% (6/222) 2.70%	

ASQ = ages and stages questionnaire. C-C = case-control study. P = prospective study.

P/R = prospective and retrospective study. R = retrospective study. SR = systematic review.

the definition of developmental delay, and assessment is not standardised. Moreover, large and long-term follow-up studies are needed.

Increased nuchal translucency and overall pregnancy outcome

Most fetuses with nuchal translucency above the 95th centile will have a normal karyotype.¹⁵ The chance of a favourable outcome is related to the degree of increased nuchal translucency, ranging from 90% in case of nuchal translucency between the 95th and 99th centile to around 17% in case of nuchal translucency greater than 6.5 mm.⁶⁻²⁰

Conversely, the prevalence of miscarriage or fetal death increases with increasing nuchal translucency, from 1.4% with nuchal translucency between the 95th centile (3.4 mm), 2.0% between 3.5 (4.4 mm), 2.9% between 4.5 (5.4 mm), 8.3% (5.5-6.4 mm), to 16.9% in fetuses with nuchal translucency 6.5 mm or greater.³

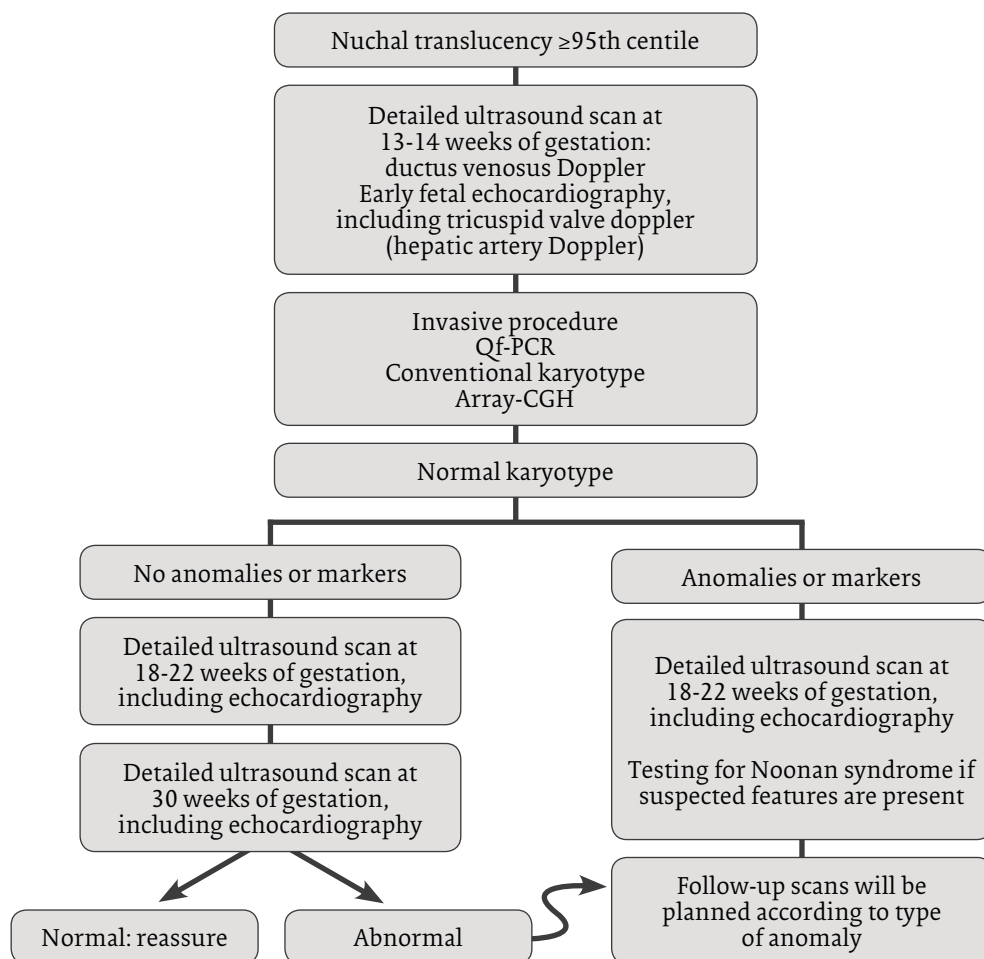
Where no anomalies or subtle variations from the norm are found, parents should be counselled that the chance of a normal outcome is high and no different from the normal population.

Nuchal translucency and macrosomia

Fetuses with an increased nuchal translucency tend to have higher birth weights. Poon et al.⁸¹ showed that prediction of macrosomia is related to maternal characteristics (e.g. ethnicity, maternal height and weight, previous delivery of a macrosomic baby, smoking and history of chronic hypertension and diabetes), and also to fetal characteristics. Their results show that an increased nuchal translucency is associated with an increased risk of delivering a macrosomic baby. These results were confirmed by Timmerman et al (unpublished data), who showed that normal fetuses with an increased nuchal translucency have a higher risk of being macrosomic at birth compared with fetuses with a normal nuchal translucency. Weissmann-Brenner et al.⁸² also showed the relation between nuchal translucency and birth weight in singletons from non-diabetic mothers. This correlation was independent of gender, and the predictive effect of nuchal translucency was limited to large for gestational age only.

Algorithm for the management of pregnancies with an enlarged nuchal translucency

After initial assessment of the fetus with an increased nuchal translucency, parents should be offered array-CGH in case no numerical anomalies are found with quantitative fluorescent polymerase chain reaction. A detailed late first-trimester scan should aim at identifying structural anomalies with special focus on the fetal heart. The current consensus is that detailed ultrasound examination, including fetal echocardiography, should be offered in all cases in which nuchal translucency is greater than 99th centile (3.5 mm). No consensus has been reached on the group with nuchal translucency between the 95th and 99th centile in view of the rather low positive predictive value of 2%.⁵⁶ When re-



■ Figure 1 – Flowchart for the clinical follow-up of a fetus with an increased nuchal translucency.

sources are available, we would suggest using the 95th centile cut off. A possible protocol for follow up of fetuses with a nuchal translucency greater than 95th and 99th centile is presented in Figure 1.

Results from several studies show that, with improved equipment and more extensive experience, it is possible to detect about 40-70% of all serious congenital anomalies in the first trimester of pregnancy.⁸³ This percentage is even higher in high-risk pregnancies, were 84% of severe anomalies and congenital heart defects can be detected by the end of the first trimester.⁸⁴

One of the benefits of a detailed scan early in pregnancy is that anomalies will be detected at an early stage. This allows more time for follow-up scans and more time for prenatal diagnostics if indicated. Another benefit is that parents may wish to opt for termination of pregnancy, which is clinically safer in the first trimester than in the second

trimester of gestation. Emotionally, termination of pregnancy in the first trimester may be less distressing for women than in the second trimester, as the relationship between the mother, embryo, or fetus deepens as pregnancy advances.^{85,86}

Some investigators have proposed that, in fetuses with enlarged nuchal translucency and severe structural anomalies, termination of pregnancy without first carrying out karyotyping, is a cost-saving option.⁸⁷ In our view, however, karyotyping is important to help parents make a decision, apart from determining the recurrence risk.

Doppler of the ductus venosus and tricuspid valve should be measured in addition to carrying out an anomaly scan, as an abnormal ductus venosus flow or tricuspid regurgitation can be associated with poor pregnancy outcome (e.g. cardiac and other structural anomalies, miscarriage or intrauterine demise), although, in most cases the outcome will be normal.^{33,88-90} Furthermore, the use of these two markers in first-trimester screening reduces the false-positive rate.

In addition to tricuspid regurgitation and abnormal ductus venosus flow, measurement of lowresistance flow in the hepatic artery is an unfavourable prognostic factor, as it is associated with chromosomal abnormalities, genetic syndromes, and structural anomalies. Furthermore, lowresistance flow in the hepatic artery is associated with tricuspid regurgitation and abnormal ductus venosus flow.⁹¹ One of the mechanisms suggested as explanation for the increased hepatic artery flow is the hepatic arterial buffer response to hypoxaemia.⁹¹ Cardiac dysfunction, resulting in abnormal ductus venosus flow and secondary dilatation in the vascular tree supplied by the hepatic artery, is suggested as explanation for the association between increased hepatic artery flow, abnormal ductus venosus flow and tricuspid regurgitation.⁹⁰⁻⁹²

If an abnormal Doppler of the ductus venosus or tricuspid regurgitation is present, irrespective of the nuchal translucency, a detailed follow-up scan at 18-19 weeks of gestation should be carried out, including a fetal echocardiography.

Screening for Noonan syndrome should be discussed with the parents if nuchal oedema or hydrops persists in the second trimester or other subtle features are present as mentioned above.

During the whole diagnostic work up, parents may benefit from psycho-social guidance while facing the burden of coping with the uncertainty of fetal and neonatal outcome after an enlarged nuchal translucency.⁹⁰⁻⁹³

In the absence of anomalies or subtle variations from the norm, parents should be counselled that the chance of a normal outcome is high and not dissimilar from the normal population.

In case of doubt, such as in the presence of subtle anomalies, the infant may be seen by a geneticist after birth, and the achievement of developmental milestones should be checked (Figure 1).^{5,94}

Conclusion

Increased nuchal translucency is much more than just a marker for Down's syndrome. It is also associated with other chromosomal abnormalities, structural anomalies, genetic syndromes, a higher risk of miscarriage, and intrauterine death. When no structural anomalies or markers are found on the detailed scans, the chance of a favourable outcome is high.

Future perspectives

At present, non-invasive fetal karyotyping is becoming increasingly available, and will probably replace the initial purpose of nuchal translucency measurement: screening for Down's syndrome.^{26,95-98} Although non-invasive fetal karyotyping may replace the combined test we believe in the need of an early risk assessment in pregnancy and in the importance of a scan at 12-13 weeks of gestation, including the nuchal translucency measurement as marker of normal development. Furthermore, the first trimester scan has the potential for more than only risk calculation on chromosomal and structural anomalies. At present, research is under way on risk calculation for pre-eclampsia, preterm labour, intrauterine growth restriction, macrosomia, and gestational diabetes in the first trimester of pregnancy.

References

1. Nicolaides K. H., Azar G., Byrne D. et al. Fetal nuchal translucency: ultrasound screening for chromosomal defects in first trimester of pregnancy. *BMJ* 1992; 304: 867-9.
2. Bilardo C. M., Pajkrt E., De Graaf I. et al. Outcome of fetuses with enlarged nuchal translucency and normal karyotype. *Ultrasound Obstet Gynecol* 1998; 11:401-6.
3. Souka A. P., Snijders R. J., Novakov A. et al. Defects and syndromes in chromosomally normal fetuses with increased nuchal translucency thickness at 10-14 weeks of gestation. *Ultrasound Obstet Gynecol* 1998; 11: 391-400.
4. Ville Y. Nuchal translucency in the first trimester of pregnancy: ten years on and still a pain in the neck? *Ultrasound Obstet Gynecol* 2001; 18: 5-8.
5. Bilardo C. M., Timmerman E., Pajkrt E. et al. Increased nuchal translucency in euploid fetuses – what should we be telling the parents? *Prenat Diagn* 2010; 30: 93-102.
6. Bilardo CM, Muller MA, Pajkrt E et al. Increased nuchal translucency thickness and normal karyotype: time for parental reassurance. *Ultrasound Obstet Gynecol* 2007; 30: 11-8.
7. Seror V., Ville Y. Prenatal screening for Down syndrome: women's involvement in decision-making and their attitudes to screening. *Prenat Diagn* 2009; 29: 120-8.
8. Gidiri M., McFarlane J., Holding S. et al. Maternal serum screening for Down syndrome: are women's perceptions changing? *BJOG* 2007; 114: 458-61.
9. Ekelund C. K., Petersen O. B., Skibsted L. et al. First-trimester screening for trisomy 21 in Denmark: implications for detection and birth rates of trisomy 18 and trisomy 13. *Ultrasound Obstet Gynecol* 2011; 38: 140-4.
10. Maxwell S., Brameld K., Bower C. et al. Socio-demographic disparities in the uptake of prenatal screening and diagnosis in Western Australia. *Aust N Z J Obstet Gynaecol* 2011; 51: 9-16.
11. Bakker M., Birnie E., Pajkrt E. et al. Low uptake of the combined test in the Netherlands – which factors contribute? *Prenat Diagn* 2012; 32: 1305-12.
12. Shantha N., Granger K., Arora P. et al. Women's choice for Down's screening: a comparative experience in three district general hospitals. *Eur J Obstet Gynecol Reprod Biol* 2009; 146: 61-4.
13. Muller M. A., Bleker O. P., Bonsel G. J. et al. Women's opinions on the offer and use of nuchal translucency screening for Down syndrome. *Prenat Diagn* 2006; 26: 105-11.
14. Favre R., Moutel G., Duchange N. et al. What about informed consent in first-trimester

- ultrasound screening for Down syndrome? *Fetal Diagn Ther* 2008; 23: 173-84.
15. Snijders R. J., Noble P., Sebire N. et al. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10-14 weeks of gestation. *Fetal Medicine Foundation First Trimester Screening Group. Lancet* 1998; 352: 343-6.
 16. Cha'ban F. K., Van Splunder P., Los F. J. et al. Fetal outcome in nuchal translucency with emphasis on normal fetal karyotype. *Prenat Diagn* 1996; 16: 537-41.
 17. Saldanha F. A., Brizot M. de L., Moraes E. A. et al. Increased fetal nuchal translucency thickness and normal karyotype: prenatal and postnatal follow-up. *Rev Assoc Med Bras* 2009; 55: 575-80.
 18. Senat M. V., De Keersmaecker B., Audibert F. et al. Pregnancy outcome in fetuses with increased nuchal translucency and normal karyotype. *Prenat Diagn* 2002; 22: 345-9.
 19. Pajkrt E., Bilardo C. M., Van Lith J. M. et al. Nuchal translucency measurement in normal fetuses. *Obstet Gynecol* 1995; 86: 994-7.
 20. Souka A. P., Von Kaisenberg C. S., Hyett J. A. et al. Increased nuchal translucency with normal karyotype. *Am J Obstet Gynecol* 2005; 192: 1005-21.
 21. Lam Y. H., Tang M. H., Lee C. P. et al. The effect of fetal gender on nuchal translucency at 10-14 weeks of gestation. *Prenat Diagn* 2001; 21: 627-9.
 22. Larsen S. O., Wojdemann K. R., Shalmi A. C. et al. Gender impact on first trimester markers in Down syndrome screening. *Prenat Diagn* 2002; 22: 1207-8.
 23. Yaron Y., Wolman I., Kupferminc M. J. et al. Effect of fetal gender on first trimester markers and on Down syndrome screening. *Prenat Diagn* 2001; 21: 1027-30.
 24. Spencer K., Ong C. Y., Liao A. W. et al. The influence of fetal sex in screening for trisomy 21 by fetal nuchal translucency, maternal serum free beta-hCG and PAPP-A at 10-14 weeks of gestation. *Prenat Diagn* 2000; 20: 673-5.
 25. Timmerman E., Pajkrt E., Bilardo C. M. Male gender as a favorable prognostic factor in pregnancies with enlarged nuchal translucency. *Ultrasound Obstet Gynecol* 2009; 34: 373-8.
 26. Verweij E. J., Jacobsson B., Van Scheltema P. A. et al. European Non-Invasive Trisomy Evaluation (EU-NITE) study: a multicenter prospective cohort study for non-invasive fetal trisomy 21 testing. *Prenat Diagn* 2013; 33: 996-1001.
 27. Haak M. C., Van Vugt J. M. Pathophysiology of increased nuchal translucency: a review of the literature. *Hum Reprod Update* 2003; 9: 175-84.
 28. Ghi T., Huggon I. C., Zosmer N. et al. Incidence of major structural cardiac defects associated with increased nuchal translucency but normal karyotype. *Ultrasound Obstet Gynecol* 2001; 18: 610-4.
 29. Galindo A., Comas C., Martinez J. M. et al. Cardiac defects in chromosomally normal fetuses with increased nuchal translucency at 10-14 weeks of gestation. *J Matern Fetal Neonatal Med* 2003; 13: 163-70.
 30. Hyett J. Does nuchal translucency have a role in fetal cardiac screening? *Prenat Diagn* 2004; 24: 1130-5.
 31. Haak M. C., Twisk J. W., Bartelings M. M. et al. First-trimester fetuses with increased nuchal translucency do not show altered intracardiac flow velocities. *Ultrasound Obstet Gynecol* 2005; 25: 246-52.
 32. Huggon I. C., Turan O., Allan L. D. Doppler assessment of cardiac function at 11-14 weeks' gestation in fetuses with normal and increased nuchal translucency. *Ultrasound Obstet Gynecol* 2004; 24: 390-8.
 33. Bilardo C. M., Muller M. A., Zikulinig L. et al. Ductus venosus studies in fetuses at high risk for chromosomal or heart abnormalities: relationship with nuchal translucency measurement and fetal outcome. *Ultrasound Obstet Gynecol* 2001; 17: 288-94.
 34. Clur S. A., Oude Rengerink K., Mol B. W. et

- al. Fetal cardiac function between 11 and 35 weeks' gestation and nuchal translucency thickness. *Ultrasound Obstet Gynecol* 2011; 37: 48-56.
35. Hyett J., Moscoso G., Papapanagiotou G. et al. Abnormalities of the heart and great arteries in chromosomally normal fetuses with increased nuchal translucency thickness at 11-13 weeks of gestation. *Ultrasound Obstet Gynecol* 1996; 7: 245-50.
 36. Hyett J. A., Perdu M., Sharland G. K. et al. Increased nuchal translucency at 10-14 weeks of gestation as a marker for major cardiac defects. *Ultrasound Obstet Gynecol* 1997; 10: 242-6.
 37. Bekker M. N., Haak M. C., Rekoert-Hollander M. et al. Increased nuchal translucency and distended jugular lymphatic sacs on first-trimester ultrasound. *Ultrasound Obstet Gynecol* 2005; 25: 239-45.
 38. Bekker M. N., Van den Akker N. M., Bartelings M. M. et al. Nuchal edema and venous-lymphatic phenotype disturbance in human fetuses and mouse embryos with aneuploidy. *J Soc Gynecol Investig* 2006; 13: 209-16.
 39. De Mooij Y. M., Van den Akker N. M., Bekker M. N. et al. Aberrant lymphatic development in euploid fetuses with increased nuchal translucency including Noonan syndrome. *Prenat Diagn* 2011; 31: 159-66.
 40. Brand-Saber B., Floel H., Christ B. et al. Alterations of the fetal extracellular matrix in the nuchal oedema of Down's syndrome. *Ann Anat* 1994; 176: 539-47.
 41. Von Kaisenberg C. S., Krenn V., Ludwig M. et al. Morphological classification of nuchal skin in human fetuses with trisomy 21, 18, and 13 at 12-18 weeks and in a trisomy 16 mouse. *Anat Embryol (Berl)* 1998; 197: 105-24.
 42. Bohlandt S., Von Kaisenberg C. S., Wewetzer K. et al. Hyaluronan in the nuchal skin of chromosomally abnormal fetuses. *Hum Reprod* 2000; 15: 1155-8.
 43. Nakamura T., Gulick J., Pratt R. et al. Noonan syndrome is associated with enhanced pERK activity, the repression of which can prevent craniofacial malformations. *Proc Natl Acad Sci U S A* 2009; 106: 15436-41.
 44. Kagan K. O., Avgidou K., Molina F. S. et al. Relation between increased fetal nuchal translucency thickness and chromosomal defects. *Obstet Gynecol* 2006; 107: 6-10.
 45. Hillman S. C., Pretlove S., Coomarasamy A. et al. Additional information from array comparative genomic hybridization technology over conventional karyotyping in prenatal diagnosis: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2011; 37: 6-14.
 46. Leung T. Y., Vogel I., Lau T. K. et al. Identification of submicroscopic chromosomal aberrations in fetuses with increased nuchal translucency and apparently normal karyotype. *Ultrasound Obstet Gynecol* 2011; 38: 314-9.
 47. Clur S. A., Mathijssen I. B., Pajkrt E. et al. Structural heart defects associated with an increased nuchal translucency: 9 years experience in a referral centre. *Prenat Diagn* 2008; 28: 347-54.
 48. Maymon R., Herman A. The clinical evaluation and pregnancy outcome of euploid fetuses with increased nuchal translucency. *Clin Genet* 2004; 66: 426-36.
 49. Westin M., Saltvedt S., Almstrom H. et al. By how much does increased nuchal translucency increase the risk of adverse pregnancy outcome in chromosomally normal fetuses? A study of 16,260 fetuses derived from an unselected pregnant population. *Ultrasound Obstet Gynecol* 2007; 29: 150-8.
 50. Lopes L. M., Brizot M. L., Lopes M. A. et al. Structural and functional cardiac abnormalities identified prior to 16 weeks' gestation in fetuses with increased nuchal translucency. *Ultrasound Obstet Gynecol* 2003; 22: 470-8.
 51. Mavrides E., Cobian-Sanchez F., Tekay A. et al. Limitations of using first-trimester nuchal translucency measurement in routine screening for major congenital heart

- defects. *Ultrasound Obstet Gynecol* 2001; 17: 106-10.
52. Michailidis G. D., Economides D. L. Nuchal translucency measurement and pregnancy outcome in karyotypically normal fetuses. *Ultrasound Obstet Gynecol* 2001; 17: 102-5.
 53. Hyett J., Perdu M., Sharland G. et al. Using fetal nuchal translucency to screen for major congenital cardiac defects at 10-14 weeks of gestation: population based cohort study. *BMJ* 1999; 318: 81-5.
 54. Simpson J. M., Sharland G. K. Nuchal translucency and congenital heart defects: heart failure or not? *Ultrasound Obstet Gynecol* 2000; 16: 30-6.
 55. Makrydimas G., Sotiriadis A., Ioannidis J. P. Screening performance of first-trimester nuchal translucency for major cardiac defects: a meta-analysis. *Am J Obstet Gynecol* 2003; 189: 1330-5.
 56. Muller MA, Clur SA, Timmerman E et al. Nuchal translucency measurement and congenital heart defects: modest association in low-risk pregnancies. *Prenat Diagn* 2007; 27: 164-9.
 57. Sotiriadis A., Papatheodorou S., Eleftheriades M. et al. Nuchal translucency and major congenital heart defects in fetuses with normal karyotype: a meta-analysis. *Ultrasound Obstet Gynecol* 2013; 42: 383-9.
 58. Wald N. J., Morris J. K., Walker K. et al. Prenatal screening for serious congenital heart defects using nuchal translucency: a meta-analysis. *Prenat Diagn* 2008; 28: 1094-104.
 59. Timmerman E., Pajkrt E., Maas S. M. et al. Enlarged nuchal translucency in chromosomally normal fetuses: strong association with orofacial clefts. *Ultrasound Obstet Gynecol* 2010; 36: 427-32.
 60. Scott F., Evans J., McLennan A. Perinatal outcome in fetuses with extremely large nuchal translucency measurement. *Aust N Z J Obstet Gynaecol* 2009; 49: 254-7.
 61. Maymon R., Zimmerman A. L., Weinraub Z. et al. Correlation between nuchal translucency and nuchal skin-fold measurements in Down syndrome and unaffected fetuses. *Ultrasound Obstet Gynecol* 2008; 32: 501-5.
 62. Hiippala A., Eronen M., Taipale P. et al. Fetal nuchal translucency and normal chromosomes: a long-term follow-up study. *Ultrasound Obstet Gynecol* 2001; 18: 18-22.
 63. Lee K. A., Williams B., Roza K. et al. PTPN11 analysis for the prenatal diagnosis of Noonan syndrome in fetuses with abnormal ultrasound findings. *Clin Genet* 2009; 75: 190-4.
 64. Pergament E., Alamillo C., Sak K. et al. Genetic assessment following increased nuchal translucency and normal karyotype. *Prenat Diagn* 2011; 31: 307-10.
 65. Tartaglia M., Mehler E. L., Goldberg R. et al. Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. *Nat Genet* 2001; 29: 465-8.
 66. Jorge A. A., Malaquias A. C., Arnhold I. J. et al. Noonan syndrome and related disorders: a review of clinical features and mutations in genes of the RAS/MAPK pathway. *Horm Res* 2009; 71: 185-93.
 67. Croonen E. A., Nillesen W. M., Stuurman K. E. et al. Prenatal diagnostic testing of the Noonan syndrome genes in fetuses with abnormal ultrasound findings. *Eur J Hum Genet* 2013; 21: 936-42.
 68. Houweling A. C., De Mooij Y. M., Van der Burgt I. et al. Prenatal detection of Noonan syndrome by mutation analysis of the PTPN11 and the KRAS genes. *Prenat Diagn* 2010; 30: 284-6.
 69. Van der Burgt I., Thoonen G., Roosenboom N. et al. Patterns of cognitive functioning in school-aged children with Noonan syndrome associated with variability in phenotypic expression. *J Pediatr* 1999; 135: 707-13.
 70. Bakker M., Pajkrt E., Mathijssen I. B. et al. Targeted ultrasound examination and DNA testing for Noonan syndrome, in fetuses with increased nuchal translucency and normal karyotype. *Prenat Diagn* 2011; 31: 833-40.
 71. Sotiriadis A., Papatheodorou S., Makrydimas

- G. Neurodevelopmental outcome of fetuses with increased nuchal translucency and apparently normal prenatal and/or postnatal assessment: a systematic review. *Ultrasound Obstet Gynecol* 2012; 39: 10-9.
72. Miltoft C. B., Ekelund C. K., Hansen B. M. et al. Increased nuchal translucency, normal karyotype and infant development. *Ultrasound Obstet Gynecol* 2012; 39: 28-33.
 73. Mula R., Gonc A., Bennasar M. et al. Increased nuchal translucency and normal karyotype: perinatal and pediatric outcomes at 2 years of age. *Ultrasound Obstet Gynecol* 2012; 39: 34-41.
 74. Souka A. P., Krampl E., Bakalis S. et al. Outcome of pregnancy in chromosomally normal fetuses with increased nuchal translucency in the first trimester. *Ultrasound Obstet Gynecol* 2001; 18: 9-17.
 75. Adekunle O., Gopee A., el-Sayed M. et al. Increased first trimester nuchal translucency: pregnancy and infant outcomes after routine screening for Down's syndrome in an unselected antenatal population. *Br J Radiol* 1999; 72: 457-60.
 76. Cheng C. C., Bahado-Singh R. O., Chen S. C. et al. Pregnancy outcomes with increased nuchal translucency after routine Down syndrome screening. *Int J Gynaecol Obstet* 2004; 84: 5-9.
 77. Maymon R., Jauniaux E., Cohen O. et al. Pregnancy outcome and infant follow-up of fetuses with abnormally increased first trimester nuchal translucency. *Hum Reprod* 2000; 15: 2023-7.
 78. Senat M. V., Bussieres L., Couderc S. et al. Long-term outcome of children born after a first-trimester measurement of nuchal translucency at the 99th centile or greater with normal karyotype: a prospective study. *Am J Obstet Gynecol* 2007; 96: 53.
 79. Brady A. F., Pandya P. P., Yuksel B. et al. Outcome of chromosomally normal livebirths with increased fetal nuchal translucency at 10-14 weeks' gestation. *J Med Genet* 1998; 35: 222-4.
 80. Van Vugt J. M., Tinnemans B. W., Van Zalen-Sprock R. M. Outcome and early childhood follow-up of chromosomally normal fetuses with increased nuchal translucency at 10-14 weeks' gestation. *Ultrasound Obstet Gynecol* 1998; 11: 407-9.
 81. Poon L. C., Karagiannis G., Stratieva V. et al. First-trimester prediction of macrosomia. *Fetal Diagn Ther* 2011; 29: 139-47.
 82. Weissmann-Brenner A., Weisz B., Lerner-Geva L. et al. Increased nuchal translucency is associated with large for gestational age neonates in singleton pregnancies. *J Perinat Med* 2011; 39: 305-9.
 83. Syngelaki A., Chelemen T., Dagklis T. et al. Challenges in the diagnosis of fetal non-chromosomal abnormalities at 11-13 weeks. *Prenat Diagn* 2011; 31: 90-102.
 84. Becker R., Wegner R. D. Detailed screening for fetal anomalies and cardiac defects at the 11-13-week scan. *Ultrasound Obstet Gynecol* 2006; 27(6): 613-8.
 85. Becker R., Schmitz L., Kilavuz S. et al. 'Normal' nuchal translucency: a justification to refrain from detailed scan? Analysis of 6858 cases with special reference to ethical aspects. *Prenat Diagn* 2012; 32: 550-6.
 86. De Graaf I. M., Tijnstra T., Bleker O. P. et al. Womens' preference in Down syndrome screening. *Prenat Diagn* 2002; 22: 624-9.
 87. Bronshtein M., Zimmer E. Z., Blazer S. The utility of detailed first trimester ultrasound examination in abnormal fetal nuchal translucency. *Prenat Diagn* 2008; 28: 1037-41.
 88. Matias A., Huggon I., Areias J. C. et al. Cardiac defects in chromosomally normal fetuses with abnormal ductus venosus blood flow at 10-14 weeks. *Ultrasound Obstet Gynecol* 1999; 14: 307-10.
 89. Oh C., Harman C., Baschat A. A. Abnormal first-trimester ductus venosus blood flow: a risk factor for adverse outcome in fetuses with normal nuchal translucency. *Ultrasound Obstet Gynecol* 2007; 30: 192-6.
 90. Maiz N., Plasencia W., Dagklis T. et al. Ductus venosus Doppler in fetuses with cardiac

- defects and increased nuchal translucency thickness. *Ultrasound Obstet Gynecol* 2008; 31: 256-60.
91. Bilardo C. M., Timmerman E., De Medina P. G. et al. Low-resistance hepatic artery flow in first-trimester fetuses: an ominous sign. *Ultrasound Obstet Gynecol* 2011; 37: 438-43.
 92. Zvanca M., Gielchinsky Y., Abdeljawad F. et al. Hepatic artery Doppler in trisomy 21 and euploid fetuses at 11-13 weeks. *Prenat Diagn* 2011;31:22-7.
 93. Schuth W., Karck U., Wilhelm C. et al. Parents' needs after ultrasound diagnosis of a fetal malformation: an empirical deficit analysis. *Ultrasound Obstet Gynecol* 1994; 4: 124-9.
 94. Bilardo C. M. Increased nuchal translucency and normal karyotype: coping with uncertainty. *Ultrasound Obstet Gynecol* 2001; 17: 99-101.
 95. Palomaki G. E., Kloza E. M., Lambert-Messerlian G. M. et al. DNA sequencing of maternal plasma to detect Down syndrome: an international clinical validation study. *Genet Med* 2011; 13: 913-20.
 96. Bianchi D. W., Platt L. D., Goldberg J. D. et al. Genome-wide fetal aneuploidy detection by maternal plasma DNA sequencing. *Obstet Gynecol* 2012; 119: 890-901.
 97. Chiu R. W., Akolekar R., Zheng Y. W. et al. Non-invasive prenatal assessment of trisomy 21 by multiplexed maternal plasma DNA sequencing: large scale validity study. *BMJ* 2011; 342: c7401.
 98. Nicolaides K. H., Syngelaki A., Ashoor G. et al. Noninvasive prenatal testing for fetal trisomies in a routinely screened first-trimester population. *Am J Obstet Gynecol* 2012; 207: 374.