Long-term Outcome of Pregnancies with Increased Nuchal Translucency and Normal Karyotype

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Abstract

Objectives: The aim of this study was to examine the prevalence of major and minor anomalies according to the increase of NT thickness.

Methods: This is a long-term retrospective study in which singleton gestations of euploid fetuses with increased NT were analyzed. NT measurement was performed in the first trimester examination according to the criteria of fetal medicine foundation (FMF) when the fetal crown-rump length (CRL) was 45 to 84 mm. The cases were followed up from 1 to 5 years postpartum to assess the presence of CHD and to point out other anomalies that could be associated with increased NT.

Results: The outcome of 133 cases could be analysed out of 198 pregnancies of which in 55 cases some congenital anomalies (minor or major) were revealed up to the 5 years of life (prevalence of 41.4%). The prevalence of CHDs, including the defects of the great vessels, stood out among the others. In the group with NT between 95th and 99th centiles four cases with minor heart problems were identified (11.1%, 4/36). The rate of major cardiac defects proved to be 13.3% (6/45) in the group with NT between 3.5-4.4 mm, and 17.3% (9/52) in the group with NT $\geq$ 4.5 mm. Among the 35 healthy children with various minor health problems not related to the presence of increased nuchal translucency there were 7 cases with hydrocele. In 3 of them it was associated with unilateral inguinal hernia but in 3 it was isolated and one was part of a complex malformation (The rate of other organ-specific anomalies did not prove to be significant). In the whole study population only thirteen cases (9.8%) ended up in intrauterine death, or arteficial abortion.

Conclusion: The prevalence of major cardiac defects as well as other major anomalies increases with fetal nuchal thickness. Since the prevalence of CHD is 100 times higher in the population of fetuses with NT above 4.5 mm, specialist fetal echocardiography should be offered in the second trimester together with other follow-up investigations. Among the children without any major abnormalities, a high number of minor anomalies were revealed during the long-term follow-up. These anomalies do not have significant disadvantage to the quality of life, but some of them necessitates short or long-term medical treatment and this should also be leveled with the future parents. Despite the numerous investigations the exact etiology of increased NT remains unknown. The relatively high prevalence of hydrocele in the newborns in our material raises the question wheather it is related to the presence of NT in the fetal period because of abnormal lymphatic development or alterations in the extracellular matrix. Further long-term follow-up studies could probably contribute to find explanation on the etiology of increased NT in the first trimester. These data can be used when counseling parents of euploid fetuses with increased fetal NT.

Keywords: Congenital heart defects, fetal echocardiography, nuchal translucency, hydrocele, first trimester screening, long-term follow-up.

INTRODUCTION

Prenatal diagnostic methods become more and more sophisticated. In the past two decades most of the fetal anomalies and chromosomal aneuploidies were, detected during the second trimester of pregnancy. More recently, screening for chromosomal abnormalities is increasingly performed in the first trimester.

In the 1990s, Hungarian authors J Szabó, J Gellén, and G Szemere were among the first who drawed attention to the prognostic value of nuchal translucency (NT), a hypoechogenic fluid between the skin and the subcutaneous tissue that covers the cervical spine of the fetus and is present in all fetuses. They reported on 105 fetuses and found 8 of them with increased nuchal fluid more than (3 mm), 7 with trisomy 21 and in one with normal fetal karyotype.[1]

Since then the association between increased nuchal translucency and different chromosomal aneuploidies has been proven by several reports. It has also been observed that in normal fetuses NT thickness increases with fetal crown-rump length (CRL).[2]

Since the 1990's, extensive studies have established that euploid fetuses with increased nuchal translucency have

also higher risk for wide range of fetal structural defects[3] especially for congenital heart defects (CHDs) and also for specific genetic syndromes.[4]

Heart defects comprise an important part of congenital malformations, the prevalence of CHDs in the general population is around 3-8:1000 live births.[5] Half of these malformations are asymptomatic minor defects and the other half are classified as major because they are either lethal or require surgery soon after birth. Complex CHDs are responsible for the majority of perinatal death.[6] Almost 35% of infant and child deaths are related to CHDs.[7] In the second trimester well trained fetal echocardiologists can identify most of the major cardiac defects,[8] but for financial reasons specialist fetal echocardiography is unaccomplishable in every pregnancy. One of the main challenges in prenatal ultrasound screening is to identify those pregnancies at high risk that need referral to specialist centers.

The pathophysiological mechanism of increased NT still remains unknown. Possible etiological factors include: 1. Cardiac dysfunction,[9] 2. Venous congestion in the head and neck,[10] 3. Abnormal or delayed development of the lymphatic system,[11] 4. Altered composition of the extracellular matrix,[12] 5. Failure of lymphatic drainage,[13] 6. Fetal anemia or hypoproteinemia,[14] 7. Congenital infection,[15] 8. Musculo-sceletal anomalies,[16] 9. Hormonal disorders.[17] The diversity of possible explanations coincides with the vary of defects in this population and also presages that many other new abnormalities could also have association with increased NT. The examination of these potential anomalies may help to throw light on the possible pathophysiology of NT.

The purpose of this study was to study the long-term outcome of pregnancies in chromosomally normal fetuses with increased nuchal translucency in the first trimester with respect to fetal loss, major and minor structural defects and possible genetic syndromes.

MATERIAL AND METHODS

A retrospective study was performed to examine the prevalence of major and minor cardiac defects and other possible anomalies in chromosomally euploid fetuses with increased nuchal translucency. The following inclusion criteria were used: 1. singleton gestations; 2. normal fetal karyotype 3. increased nuchal translucency. A computer program in the database of our Genetic Counseling Clinic from 1999 to 2008 identified 198 singleton pregnancies with live fetuses at 10-14 weeks of gestation (CRL of 45-84 mm) with a NT thickness above 95th centile adjusted for gestational age. The examinations were made by TAS, or by TVS or both depending on the visualization. The measurements were performed by sonographers according to the fetal medicine foundation (FMF) criteria. Karyotyping was performed from chorionic villi in most of the cases, in 12% of pregnancies with a relatively lower estimated risk for aneuploidies parents opted for amniocentesis. When they were informed about the normal result of fetal karyotype they were also informed about the higher risk of intrauterine death and other unfavorable pregnancy outcome or possible fetal malformations not revealed by ultrasound. Further follow-up scans were offered including specialist made fetal echocardiography.

Pregnancy outcome was obtained from maternity and newborn discharge slips, questionaries sent to parents and by telephone interviews. In case of terminations on parental request, miscarriages and intrauterine or postnatal death autopsy reports were collected and analized.

The cases were divided into three groups according to NT thickness. 1. group: NT between 95-99th centile. 2. group: NT between 3.5-4.4 mm. 3. group: NT above 4.5 mm. Cases were followed up from 1 to 5 years postnatally.

Statistical analysis: After data collection a descriptive univariate analysis of the variables of interest was performed. Fischer's exact test, 2 independent sample t-test were used to verify the reliability of the results.

RESULTS

The outcome of 133 cases could be followed up out of 198 pregnancies (Tables 1 and 2).

Table 1: The outcome of the 133 pregnancies in different NT groups respectively

NT thickness	n	Outcome			
		Live birth	Abortion		
			Postnatal exitus	Spontaneus	Artificial
< 3.5 mm	36	36	–	–	–
3.5-4.4 mm	45	41	–	1	3
> 4.5 mm	52	43	1	1	8
	100%	90.2%		1.5%	8.3%

Table 2: The outcome of anomalies in different NT groups respectively

NT thickness	N	Anomalies				Without anomalies
		Isolated		Multiplex		
		Minor	Major	Minor	Major	
< 3.5 mm	36	9	1	2	0	24
3.5-4.4 mm	45	14	3	1	3	24
> 4.5 mm	52	8	5	1	8	30
	100%	23.3%	6.8%	3.0%	8.3%	58.7%

In 12 cases increased first trimester NT evolved into enlarged nuchal fold or hydrops in the 2nd trimester. Seven of them underwent termination of pregnancy. One case ended up in postnatal death, Costello syndrome was diagnosed in the newborn in spite of the reassuring result of second trimester echocardiography. In this case esophageal atresia was associated with a fistula making the second trimester diagnosis of the atresia impossible and the facial and other dysmorphisms could not either be detected during the second trimester follow-up scan. Another case with various major and minor malformations was not detected during the second trimester scan, the infant had Sturge-Weber syndrome, ASD, PI, TI (see the list of abbreviations in Table 4) and mild hydrocephalus. Ventriculomegaly was not present at 22nd weeks. Among the 3 other newborns with enlarged nuchal fold or hydrops in the 2nd trimester there was one with complex CHD: ASD, PI, TI, and one with VSD. None of the patients attended the recommended echocardiography. In the third case only the persistent choroid plexus cysts were present in the neonatal period without any further consequence.

Table 3: The median maternal age, newborns' weight, gestational age at birth, and sex distribution

Average	*Group I*		*Group II*		*Group III*	
Maternal age	30.3 years		29.1 years		27.6 years	
Newborns' weight	3501.2 gm		3324.4 gm		3250.3 gm	
Gest. age at birth	39.1. weeks		38.4. weeks		38.4. weeks	
Sex	XX	XY	XX	XY	XX	XY
	14	22	15	30	18	34

The mean age in Group I. was 30.3 years, 29.1 years in Group II, and 27.6 years in Group III. The median gestational age at delivery was 39.1 weeks in the first group, 38.4 in the second, and 38.4 weeks in the third group (Table 3). The median birth-weight was 3501 gm in the first, 3324 gm in the second and 3250 gm in the third group. 65 children had no malformation at the age of 1 to 5 years. In 41.4% of cases minor or major malformations were, detected prenatally, at birth or within 60 months after it. Two cases ended up in spontaneous abortion, in 11 cases termination of pregnancy was performed on parental request.

Nineteen cases of congenital heart defects (6 minor, 13 major) were diagnosed in the sample studied (Table 4). Of these, four (11.1%) with minor heart problems were in the first group, six (13.3%) in the second group, two out of them had only minor problems. The rate of cardiac defects proved to be 17.3% (nine cases) in the group with NT $\geq$ 4.5 mm. Most of them were major, and 57.9% was part of a multiplex malformation. The most common association was facial dimorphism (50%) and different types of hernia (37.5%). In the first two groups the cardiac malformation was isolated to the heart while in the third group the malformation of the great vessels were present in 44.4%. Prenatal fetal echocardiography was offered in every case but only 31.6% attended it. The prenatal detection rate of CHDs was poor due to the low number of cases attended specialist echocardiography (6 out of 19).

Table 4: Detailed descriptions of the heart defects

Nuchal translucency		
95-99th centile	3.5-4.4 mm	NT above 4.5 mm
Congenital heart defects		
ASD	ASD	AVSD
PFO, SH	AVSD	ASD, VD
PFO	VSD	3 VSD
HM, SH	HLHS	ASD, *AI*
	SH	HNOCM, ASD, *CTGA*
	VD	ASD, HCM, *AI*, PS
		ASD, *PI, TI*
Prevalence		
11.1%	*13.3%*	*17.3%*

PFO – Persisting forman ovale apertum, HLHS – Hypoplastic left heart syndrome, HCNOM – Hypertrophic nonobstructive cardiomyopathy, HCM – Hypertrophic cardiomyopathia, PI – Pulmonic valve insufficiency, TI – Tricuspidal valve insufficiency, AI – Aortic insufficiency, PS – Pulmonary stenosis, SH – Septal hypertrophy , CTGA – Complex transposition of the great arteries, HM – Heart murmur, VD – Ventricle deformation, Co-A – Coarctatio aortae

Figure 1 Shows in the second group most of the abnormalities were also minor, CHDs were responsible for 22% of all abnormalities. Urogenital malformations were the most common abnormalities (38%), prior to the abnormalities of central nervous system (11%), gastro-intestinal tract (7%) and the musculo-scleletal system (7%).

In Group I most of the anomalies were minor, 30% of the abnormalities were CHDs (Fig. 2).

In the third group in 59.1% of cases major malformations were present, most of them was complex (Fig. 3).

Altogether 7 cases of hydrocele occurred in the whole study population among the abnormalities of urogenital anomalies. This prevalence is 5.7% which is surprisingly high compared to the prevalence of hydrocele in general population of 0.04/1000 according to the Hungarian National Registry of Congenital Malformations.

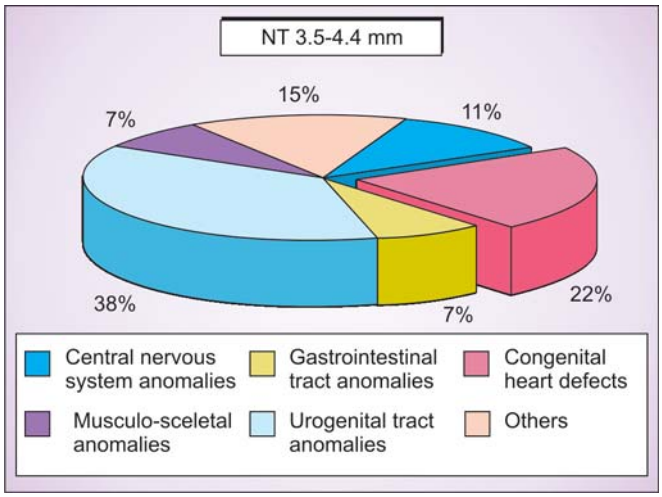

Fig. 1: The distribution of anomalies in Group II. CHD-ASD, AVSD, VSD, SH, HLHS; CNS–plexus cyst, stenosis of the auditory meatus; Others–hemangioma, umbilical hernia, inguinal hernia; GIT–hepatomegalia, hepatopathia, cholestasis, biliary tract malformation; Musculo-sceletal anomalies–limb deformity; Urogenital anomalies: Ectopic kidney, pyelectasis, renal pelvis duplication, hydrocele, adhesio cell. praeputii, testis retention

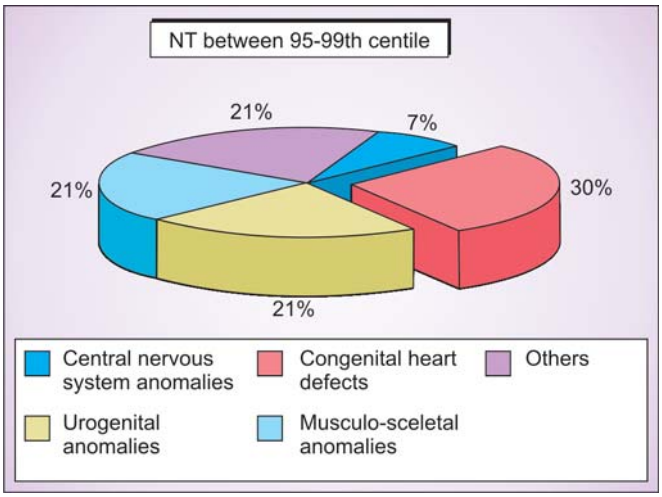

Fig. 2: The distribution of anomalies in Group I., and detailed list of different types of anomalies below. In multiplex anomalies each malformation was considered separately. CHD-ASD, PFO, HM, SH; CNS–choroid plexus cyst; Others-umbilical hernia, lymph node and lymphatic vessel malformation, hemangioma; Musculo-sceletal anomalies-hip dysplasia, minor abdominal wall deformation, synostosis; Urogenital anomalies: pyelectasis, hydrocele, synechia vulvae

DISCUSSION

The association between increased nuchal translucency (NT) and chromosomal aneuploidies is well known.[18] Several studies have also shown that in euploid fetuses with increased NT thickness the risk of congenital heart defects, other structural anomalies and fetal death is increased.[19,20]

In a recent study it was concluded that nuchal translucency thickness of ≥ 2 mm in euploid, anatomically

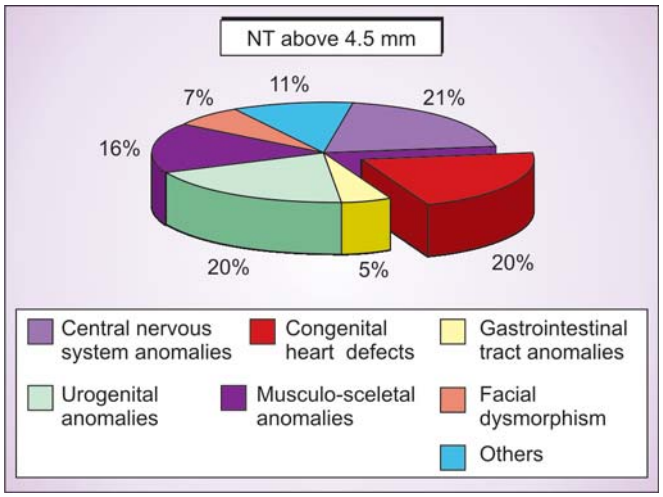

Fig. 3: The abnormalities in Group III. CHD - AVSD, ASD, VSD, AI, CTGA, HNOCM, PS, TI, PI; CNS–ventriculomegaly, hydrocephalus, stenosis of the auditory meatus, plexus cyst; Others–inguinal hernia, , umbilical hernia,; GIT–esophagus stenosis, biliary tract atresia; Musculo-sceletal anomalies–dyscrania, narrow chest, mitochondrial myopathy, hip dysplasia; Urogenital anomalies: pyelectasia, hydronephrosis, testis retention, adhesio cellularis praeputii. hydrocele Facial dysmorphism–hypertelorismus, epicanthus

normal fetuses posed a significant risk for adverse perinatal outcome.[21] A study conducted by Suoka et al. also reported higher risk of adverse outcome when the fetus had persistent second trimester nuchal fold. These fetuses are also likely to develop hydrops and die *in utero*,[22] and the risk increases exponentially according to the nuchal translucency thickness.[23] In several studies mean NT was higher in fetuses with an adverse prenatal outcome in comparison with those born alive.[24] In our material the spontaneous loss rate was very low but most of those cases that evolved into hydrops were termintated during the second trimester. IUGR and premature birth rate did not change significantly with NT thickness in our material.

In our study sex distribution of fetuses seemed to depend on NT thickness. Among fetuses with NT above the 95th percentile male karyotype was 1.4 X times higher, while among fetuses with NT above 4.5 mm this rate was 2.3 X. The difference proved to be significant. We could not find data in the literature investigating this question. Our results could be due to the relatively low number of cases, but we think that by reviewing the data of the previous studies, it would be easy to answer the question whether this was a casual association or just an accidental finding.

In our study maternal age was significantly lower in the third group. The explanation must be that in the first two groups maternal age played more important role in the aneuploidy risk calculation and consequently in the parents'

decision-making regarding the acceptance of the offerred prenatal invasive test.

There was a wide spectrum of defects diagnosed pre- and postnatally altogether in 41.3% (55/133) of the cases. This figure is almost 2 times higher than found in other previous studies.[25] The reason could be that we took into account not only the major but also the minor abnormalities. If only the major anomalies are considered their prevalence (15%), corresponds to the literature data.[26,27]

The most common structural defects were cardiac anomalies (14.3%), accounted for 22.4% of all abnormalities in our population. The definition of CHD is not properly well-defined in the majority of the studies. Whereas some authors take into account only those CHDs wich require surgical intervention right after birth, others consider even the persistent ductus arteriosus as a CHD.[28,33] In our tables both the minor and major defects were listed. The prevalence of CHDs in the different groups respectively corresponds to those in the literature.[29,30] CHD frequency increased from 11%, with NT between 95 and 99 percentiles to 17.3% when NT was $\geq$ 4.5 mm.

The distribution of different types of cardiac defects in our study is similar to that of described in previous prenatal and postnatal series.[31] In the group with NT above 4.5 mm the malformation of the great vessels and valves appeared among CHDs. This statement is concordant with a study, where, conotruncal defects, branchial arch derivative defects, left and right obstructive lesions (inflow and outflow) and shunts were seen in cases with NT above 4.5 mm.[32] According to this statement if NT is higher than 4.5 mm sonographers should consciously look after malformations of the great vessels and valves as well.

The detection rate of CHDs is far from being optimal. CHD detection rate is based on the sonographers' experience.[33] The effectiveness of increased nuchal translucency as a screening tool for major cardiac defects in chromosomally normal fetuses ranges from 12 to 56%.[34-37] Above the fact that the analysis of the heart depends a great deal on the examiner's experience in our study the relatively poor rate of prenatal detection of CHDs could be explained by the remissness of patients and by the high rate of minor CHDs, which are hard or impossible to detect prenatally.[38] Although each patient was referred to specialist echocardiography, only every third of them attended.

An interesting result in our study was the relatively high prevalence of hydrocele in the newborns. Despite the numerous investigations the exact etiology of increased NT remains unknown. The heterogeneity of anomalies and syndromes associated with increased NT postulates that there may not be a single underlying mechanism for the collection of fluid in the skin of the fetal neck. Our finding raises the question wheather the high rate of hydrocele is related to the presence of NT in the fetal period because of abnormal lymphatic development or alterations in the extracellular matrix. Further long-term follow-up studies could probably contribute to find explanation on the etiology of increased NT in the first trimester.

The data of long-term outcome studies can be used when counseling parents with pregnancies with increased fetal NT in the first trimester. Specialist fetal echocardiography should be offered together with follow-up anatomy scans in the second trimester if aneuploidy could be excluded. In a recent study it was found that if the fetus looks to be normal by ultrasound at 22-24 weeks of gestation the risk of adverse neonatal outcome or developmental delay in early childhood is not increased.[39] Our results could not confirm their finding. Apart from the major CHDs in our study, 4 newborns were born with major anomalies which lead to severe handicap. The stenosis of the auditory meatus in one case caused severe hypacusis and there were further 3 cases with multiple anamalies (West syndrome, Mitochondrial myopathy with facial dysmorphism, and in the 3rd case biliary duct malfomation, severe gastro-esophageal reflux and duplex renal pelvis) that could not be detected during the second trimester follow-up scans.

Furthermore, a high number of minor anomalies were revealed during the long-term follow-up. These anomalies do not have significant disadvantage to the quality of life, but some of them necessitates short or long-term medical treatment and to our opinion this information should also be leveled with the future parents.

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