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Increased nuchal translucency and congenital heart defects in euploid fetuses
The Szeged experience

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Abstract

Objective: To determine the utility of the first-trimester fetal nuchal translucency (NT) thickness in the prediction of fetal cardiac malformations. *Design*: Retrospective study. *Setting*: Department of Obstetrics and Gynecology and Medical Genetics, University of Szeged. *Methods*: The pre- and postnatal course and outcome, and the relationship between the first-trimester fetal NT thickness and fetal congenital heart defects (CHDs) in 4309 pregnancies ended up with birth or therapeutic abortion between January 1998 and June 2000 were registered. Prenatal care included first- and second-trimester fetal sonography at weeks 10–13 and 18–20, respectively. *Results*: 4251 births and 58 first- and second-trimester therapeutic abortions due to lethal congenital malformations or chromosomal abnormalities were recorded. Altogether 209 (4.9%) congenital malformations were detected, 39 (18.7%) of which were heart defects with normal karyotype. At birth, 151 congenital malformations were diagnosed, 34 of them were known prenatally. The prevalence of CHDs was 9 per 1000 pregnancies. The measurement of fetal NT thickness was available in 35 of the 39 fetuses with heart defects: it was $\geq$3 mm in 18 (51.4%) and <3 mm in 17 (48.6%). A sensitivity of 51.4% was found at a cutoff of 3 mm. *Conclusions*: An increased NT thickness in chromosomally normal fetuses was found to be highly associated with CHDs and identified in more than half of the affected cases. Furthermore, an increased NT of $\geq$3 mm can be regarded a selection criterion for early second-trimester targeted fetal echocardiography and for increased fetal and neonatal surveillance.

Keywords: Congenital heart defects; First-trimester screening; Nuchal translucency

1. Introduction

Congenital heart defects (CHDs) are the most common congenital abnormalities, with a birth prevalence of 8–10 per 1000 [1–3]. They account for 30% of all congenital malformations and are responsible for a significant proportion of fetal and neonatal mortality [3]. The high prevalence of CHDs in pre- and perinatal mortality underlines the need for prenatal screening.

Major abnormalities of the heart and the great vessels can be identified via a routine second-trimester ultrasound scan between weeks 16 and 22; examination of the four-chamber view of the heart allows a detection rate of 26% [4]. Combined examination of the four-chamber and outflow tract views of the heart in the second-trimester led to the identification of 61% of the fetuses with CHDs [5]. The detection rate was further increased to 81% when transvaginal ultrasound was used to predict fetal cardiac defects in a small series [6–9].

An increased fetal NT in the first-trimester was reported to be a highly efficient ultrasound marker for aneuploidies [10,11], and was also found to be highly suggestive of fetal cardiac [11–14] and other structural abnormalities [15–17].

At the regional perinatal center in Szeged, the mean birth prevalence of CHDs during the past 5 years has been 8.2 per 1000 live births. First-trimester screening for fetal abnormalities is rapidly spreading in this region in consequence of the regular theoretical and practical training of the obstetric health care personnel therefore we were interested in looking at the current prediction rate of fetal CHDs by means of an increased NT in chromosomally normal fetuses.

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2. Methods

The pre- and postnatal findings, the course and outcome of the pregnancies and the relationship between the first-trimester fetal NT thickness and fetal CHDs were retrospectively analyzed in 4309 pregnancies which ended either in birth or therapeutic abortion at the Department of Obstetrics and Gynecology, University of Szeged between January 1998 and June 2000.

The NT screening was performed by using a 6.5–7.5 MHz vaginal probe (Kretz Technik Combison 530, 3D). The NT thickness was measured at 10–13 weeks according to an international agreement suggested by the Fetal Medicine Foundation, London [15]. In summary, looking at and judging the nuchal contour and to distinguish between fetal skin and amnion in moving fetuses, the NT measurement was performed in quiet anteflexed embryos in saggittal section. The largest screen magnification was used and the maximum thickness of the subcutaneous translucency was measured using ''on to on'' position of the callipers. Second-trimester ultrasound evaluation was performed as routine prenatal surveillance at weeks [18–20]. Informed consent was obtained and all the women participated in the ultrasound study voluntarily.

The Prenatal Clinic of the University is a tertiary center where regular theoretical and practical training sessions are organized twice a year to teach first-trimester NT screening and fetal evaluation to obstetricians and sonographers. NT measurement is now being more routinely performed due to increased availability in the ultrasound labs of the hospital in the region of Szeged. However, not in all hospitals, so it is possible for women to deliver at our department without having had first-trimester NT measurement.

Newborns were examined on the first and fourth postnatal days by a neonatologist. In the event of any clinical sign of CHDs (i.e. cyanosis, a murmur, an increased oxygen

Table 1
First-trimester nuchal translucency (NT) thickness and the crown-rump length in neonates with major defects of heart and great vessels[a]

No.	NT thickness (mm)	CRL	Cardiac defects	Gestational age (weeks)	Outcome
1	5	63	ASD, PS	39	NICU
2	4.8	43	ASD	38	CCC
3	4.3	42	Tetralogy of Fallot	32	Intrauterine death
4	4.2	39	VSD	40	CCC
5	4.1	55	VSD	40	CCC
6	4	62	Hypoplastic left heart syndrome	40	NICU, death
7	4	40	Hypoplastic left heart syndrome	37	NICU, death
8	3.5	37	ASD, club-foot	39	CCC
9	3.4	37	ASD	36	CCC
10	3.4	40	ASD, PDA	39	CCC
11	3.2	43	ASD	36	CCC
12	3.2	42	Tetralogy of Fallot	38	NICU
13	3.1	41	ASD	40	CCC
14	3.1	48	Tetralogy of Fallot	40	NICU
15	3	45	Aortic stenosis	39	NICU
16	2.4	39	ASD, PDA	40	CCC
17	2.3	45	ASD	36	CCC
18	2.1	55	VSD	37	CCC
19	2.1	43	PDA	40	CCC
20	2	50	Transposition of pulmonary vein	40	NICU
21	1.9	51	Tetralogy of Fallot	41	NICU
22	1.7	39	Transposition of pulmonary vein	38	NICU, death
23	1.6	42	VSD	39	CCC
24	1.6	34	ASD, VSD	39	CCC
25	1.5	49	Tetralogy of Fallot	39	NICU
26	1.5	38	VSD	40	CCC
27	1.4	43	Tetralogy of Fallot	40	CCC
28	1.3	34	Transposition of great arteries	39	NICU
29	1.3	39	Hypoplastic left heart syndrome	37	NICU, death
30	1.2	45	AS, MS	39	NICU, death
31	1.2	45	ASD	39	CCC
32	0.9	37	PS	39	NICU
33	–[b]	50	Tetralogy of Fallot, hypospadiasis	39	NICU, death
34	–	63	ASD	38	CCC
35	–	38	VSD	41	CCC
36	–	43	ASD	39	CCC

[a] ASD: atrial septal defect, VSD: ventricular septal defect, PDA: patent ductus arteriosus, PS: pulmonary stenosis, MS: mitral stenosis, AS: aortic stenosis, NICU: neonatal intensive care unit, CCC: continuous cardiac control.

[b] Not measured.

requirement or fatigue), a pediatric cardiologist was involved in exploring the diagnosis.

3. Results

Between January 1998 and June 2000, 4251 births and 58 therapeutic abortions (altogether 4309 pregnancies) were recorded at our Department of Obstetrics and Gynecology. At birth, 151 congenital malformations were diagnosed; 34 of them were known prenatally. In the 58 pregnancies ending with therapeutic abortion, there were 22 fetal chromosomal abnormalities, 19 neural tube defects and 17 severe multiple fetal malformations. Altogether, 209 (4.9%) congenital malformations were detected, 39 (18.7%) of which were CHDs. Eight of the 39 CHDs were diagnosed by fetal echocardiography, while the others were suspected on neonatal examination and were confirmed by ultrasonography. The prevalence of major CHDs was 9 per 1000 pregnancies (39/4309).

First-trimester fetal NT measurement was available in 35 of the 39 fetuses with CHDs: it was $\geq$3 mm in 18 (51.4%) and <3 mm in 17 (48.6%) (Tables 1 and 2). Table 1 shows the crown-rump length at which the NT thickness was measured in 36 pregnancies. The types of CHDs, the gestational age in weeks at term and the outcomes are also listed. The NT was not measured in four fetuses with CHDs. The NT thickness was $\geq$3 mm in 15 and $\geq$2 mm in 20 of 32 fetuses with CHDs. Table 2 presents data on three additional fetuses with prenatally detected severe CHDs combined with other structural abnormalities. The NT thickness was >3 mm in all three cases. With regard to the virtual certainty of extremely unfavorable outcomes of these three pregnancies, therapeutic abortion was offered (after careful and extensive non-directive counseling) by members of the University Fetal Board (obstetrician–sonographer, pediatric cardiologist, neonatologist, heart surgeon and geneticist). In all three cases, the couples opted for therapeutic abortion, which was performed in weeks 17, 22 and 23, respectively. Autopsy confirmed the prenatal findings.

First-trimester NT thicknesses of 3 or 2 mm or more were found in 18 (51.4%) and in 23 (72%), respectively, of the 35 fetuses with CHDs.

The CHDs were classified into five main groups: hypoplastic left heart; ventricular and atrial septal defects; tetralogy of Fallot; transposition of the great vessels; and others (Table 3). An increased first-trimester NT was found predominantly in fetuses with defects in the left heart tract (75%) or with atrial and ventricular septal defects (58.8%). All fetuses with transposition of the great vessels had a NT <3 mm. The numbers indicate only the tendency, and are insufficient for a statistical evaluation.

A sensitivity of 51.4%, a specificity of 97.6%, a positive predictive value of 17.8%, a negative predictive value of 99.5% and a false positive rate of 4.1% were found at cutoff of 3 mm (Table 4). The measurement of increased nuchal translucency (NT) for the detection of fetal cardiac abnormalities had a sensitivity of 51.4 and 71.9% at a cutoff of 3 and 2 mm, respectively.

The outcomes of pregnancies involving fetal CHDs are detailed in Table 5. The mean neonatal birth weight was 3141 $\pm$ 549.72 g and the mean neonatal gestational age was

Table 2
First-trimester nuchal translucency (NT) thickness and crown-rump length in fetuses who underwent therapeutic abortion because of severe cardiac and other structural abnormalities[a]

No.	NT thickness (mm)	CRL	Fetal abnormalities	Gestational age (weeks)	Outcome
1	4.8	42	VSD, hernia diaphragmatica, hypoplastic left lung	23	TOP
2	4.2	38	Hypoplastic left heart syndrome, dextrocardia	22	TOP
3	3.2	39	Congenital cardiomyopathy, bilateral renal agenesis, pulmonary hypoplasia, esophageal atresia, micropenis	17	TOP

[a] VSD: ventricular septal defect, CRL: crown-rump length, TOP: termination of pregnancy.

Table 3
Detection of specific cardiac defects using a nuchal translucency cutoff of 3 mm

Cardiac defect	No. of fetuses	Nuchal translucency thickness		Detection rate (%)
		<3 mm	$\geq$3 mm	
Hypoplastic left heart	4	1	3	75
Atrial and ventricular septal defects	20[a]	7	10	58.8
Tetralogy of Fallot	7[b]	3	3	50
Transposition of great vessels	3	3	0	0
Other defects	5	3	2	40
Total	39	17	18	51.4

[a] Three cases were not measured.
[b] One case was not measured.

Table 4
Sensitivity, specificity, positive and negative predictive values, and false positive rate of screening for major defects of heart and great vessels using 3 mm nuchal translucency cutoff

	Using 3 mm cutoff level (%)
Sensitivity	51.4
Specificity	97.7
Positive predictive value	17.8
Negative predictive value	99.5
False positive rate	4.05

Table 5
Outcome of 36 pregnancies with fetal cardiac defects[a]

	No.	%
Mode of delivery		
Spontaneous vaginal	24	66.6
Operative vaginal	1	2.8
Cesarean section	11	30.6
Premature labor	4	11.1
IUGR[b]	6	16.7
Apgar score at 5 min <7	1	2.8
Umbilical cord pH <7.20	10	27.8
Neonatal intensive care admission	15	41.7
Cardiac defects operated on in the first week	2	5.6
Cardiac defects operated on in the first year	2	5.6
Perinatal mortality	3	8.3
Neonatal mortality	4	11.1

[a] Birth weight (g) (mean ± S.D.) = 3141.71 ± 549.72; gestational age at birth (weeks) (mean ± S.D.) = 38.83 ± 1.34.
[b] IUGR: intrauterine growth retardation.

38.83 ± 1.34 weeks. There were 24 (66.7%) spontaneous deliveries, one (2.8%) forceps delivery and 11 (30.6%) cesarean sections. The rates of premature delivery and IUGR were 11.1 and 16.7%, respectively. The 5 min Apgar score was <7 in only one (2.8%) case. The umbilical cord blood pH was less than 7.2 in 10 (27.8%) cases. Fifteen newborns (41.7%) were transferred to the Neonatal Intensive Care Unit (NICU). Two neonates underwent heart surgery in the first week and another two during the first year. Three babies (8.3%) died in the perinatal period, and four (11.1%) during the first year of life, resulting in perinatal and neonatal mortalities of 8.3% (3/36) and 11.1% (4/36), respectively.

4. Discussion

Screening for CHDs at the earliest possible stage of gestation is an important task, but a great challenge in prenatal diagnostics. Fetal echocardiography in the second or (more recently) the first-trimester of pregnancy has been found to be a promising screening method for CHDs. Evaluation of the four-chamber view of the heart and the outflow tracts in the second-trimester of pregnancy yielded a sensitivity as high as 61% [4,5].

An earlier and a higher rate of detection of fetal CHDs was found when ultrasound measurement of increased fetal NT thickness (≥3 mm) at weeks 10–13 of gestation was demonstrated to be associated with fetal cardiac malformations [9,12–15]. The findings in most of the publications are in accord from this respect, but Schwärzler et al. were not able to confirm such an association in an unselected population [18].

4.1. Cutoff

The prevalence of major CHDs increases in parallel with the NT thickness [12–14] and Zosmer et al. suggest the 95th centile of NT thickness as a cutoff at which the follow-up of such pregnancies by sonographers and specialists in fetal echocardiography is recommended. Our data indicate that screening on the basis of an increased NT thickness, with a cutoff of 3 mm, identifies 51.4% of the major abnormalities of the heart and great arteries at weeks 10–13 of gestation. The results compare favorably with the data reported by Hyett et al. [12,13]. An even higher detection rate of 71.9% (23/32) can be obtained at a cutoff value of ≥2 mm. Since the rate of a NT thickness >3 mm in the general population is between 2 and 3%, ultrasound follow-up of these selected pregnancies means an extra load for specialists in fetal echocardiography. If we use a lower cutoff, we can detect more fetal CHDs, but the workload will increase significantly. A practically acceptable cutoff value is therefore necessary to distinguish cases marked for follow-up. It is known that the NT thickness normally increases with crown-rump length and the 95th centile is 2.2 mm for a crown-rump length of 38 and 2.8 mm for a crown-rump length of 84 mm [13], and the use of a single cutoff may bias the sensitivity. We consider that 3 mm cutoff yielding 51% sensitivity is practically acceptable, especially if the NT screening concentrate on between weeks 11 and 12.

4.2. Types of fetal CHDs screenable via an increased NT

We found an association between the type of fetal CHDs and an increased NT. A hypoplastic left heart and septal defects displayed stronger associations with an increased NT. This observation is comparable with previous reports of the highest detection rate in cases involving a hypoplastic left heart syndrome [14,15].

4.3. Follow-up and clinical management of pregnancies with an increased NT and a normal karyotype

An increased fetal NT thickness at weeks 10–13 of gestation is associated with fetal aneuploidies [10,11], cardiac [11–14] and other structural abnormalities [15] and certain genetic syndromes [15,16]. Since an increased NT accompanies such a wide range of fetal abnormalities, careful clinical management should be observed. Our policy is first to determine the fetal karyotype; in chromosomally

normal fetuses, a thorough ultrasound follow-up is recommended, including targeted fetal echocardiography and scanning for structural abnormalities and genetic syndromes.

Spontaneous resolution of nuchal edema occurs in 90% of pregnancies with an increased NT and a normal karyotype. These pregnancies will result in normal neonates [19]. Only the remaining 10% of fetuses with an increased NT need further evaluation (with targeted fetal echocardiography), which does not mean too great an overload for the medical personnel.

Though the issue of whether the antenatal diagnosis of CHDs affects the postnatal outcome is still controversial, most authors favor an early prenatal diagnosis to avoid long-term cardiac and neurological consequences. Newborns with cardiac abnormalities should be born in hospitals where all appropriate cardiological facilities are available. Adequate care can then be provided in due time for the neonatal cardiac patient.

In conclusion, an increased fetal NT thickness at weeks 10–13 was found to be an important predictor and efficient method of screening not only for fetal aneuploidies [15,20], but also for fetal cardiac defects [14,15]. Furthermore, an increased NT of $\geq$3 mm can be regarded a selection criterion for early second-trimester targeted fetal echocardiography and for increased fetal and neonatal surveillance.

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