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Original Article

Increased Nuchal Translucency and Pregnancy Outcome

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Abstract

Background: To study the outcome of cases with nuchal translucency (NT) ≥ 95th centile in the first trimester of pregnancy.

Methods: This cross sectional study was performed at Iranian Fetal Medicine Foundation (FMF) between January 2009 and December 2011. Totally, 186 cases with NT≥ 95th centile who attended for the first trimester screening were studied. All cases with increased NT including those with normal karyotype were followed up with anomaly scan at 18-22 weeks and fetal echocardiography at 22-24 weeks. Pregnancy outcome was extracted from delivery records and pediatrics notes and telephone interviews.

Results: Of screened cases, 186 fetuses had an NT≥95th centile, of them 19.8% were abnormal karyotype, including 29 cases of trisomy 21, three of trisomy 18, two of trisomy 13, three of Turner syndrome. 77.8% did not show any abnormalities on follow-up examinations. 4.6% of cases were found to have malformation antenatally and 4% cases postnatally. 11.4% women elected termination of pregnancy without further follow up. There were 4.6% fetal loss and 1.3% hydrops fetalis.

Conclusion: In this unselected population, the study showed one out of four fetuses with enlarged NT had an adverse pregnancy outcome (miscarriage, fetal loss, and fetal abnormalities), however the chance of having a normal child after exclusion of chromosomal abnormalities and adverse pregnancy outcome was 95%.

Keywords: Nuchal translucency, Pregnancy outcome, Chromosomal abnormalities

Introduction

Nuchal translucency (NT) measurement is an excellent and sensitive screening test for fetal chromosomal abnormalities. It is the sonographic appearance of subcutaneous accumulation of fluid behind the fetal neck in the first trimester of pregnancy. Possible causes for the development of this increased fluid-filled space include cardiac failure secondary to structural malformation, abnormalities in the extracellular matrix, and ahnormal or delayed development of the lymphatic system. Increased NT which is defined a NT measurement above the 95th centile (1) is found in 5% of the screened fetuses (2), of which the majorities are chromosomally and anatomically normal. The association of increased NT with chromosomal and nonchromosomal abnormalities has been studied for the past two decades (2-7). In addition, the prevalence of chromosomal defects and adverse pregnancy outcome (APO) including miscarriage, fetal loss, and fetal abnormalities increases exponentially with NT thickness (8). Despite of many studies, there is still uncertainty and concern about the outcome of fetuses with increased NT; this may

cause severe anxiety in parents. In fact there is not a general agreement on how to counsel parents and diminish anxiety about fetal development.
In this study we aimed to evaluate the outcome of pregnancies with increased NT in our population in order to use in counseling.

Materials and Methods

This cross sectional study was performed at Iranian Fetal Medicine foundation (FMF) between January 2009 and December 2011 after approval by local Ethics Committee. Our study included 9746 pregnant women attending the clinic for routine first trimester screening. A computer search was carried out to identify all singleton pregnancies with crown–rump length of 45–84 mm and NT of ≥ 95th centile. The technique used to measure NT followed the guideline recommended by the UK Fetal Medicine Foundation (1). All cases were checked for nasal bone and examination of skull, brain, chest, abdominal wall, stomach, bladder and upper and lower extremities. Exclusion criteria were fetal aneuploidy, fetal major anomaly and multiple pregnancies. All examinations were performed transabdominal with a curvilinear 2-6MHz transducer,Aloka α-10 (Tokyo-Japan).The risk of fetal aneuploidy was calculated by astraia software. The screen positive cases were offered karyotyping. All cases with increased NT including those with normal karyotype were recommended follow-up scans at 18-20 weeks of gestation and fetal echocardiography at 20-24 weeks of gestations. All children were examined at birth by neonatologist or pediatrician. Karyotype was done by blood serum of neonates in suspected cases. Pregnancy outcome was obtained from delivery and nursery records and the patients themselves. The outcome was asked by telephone interviews with parents or the pediatrician whenever was necessary. The follow up period at the time of telephone interviews was ranged 2 months to more than 2 years. Normal karyotype was defined based on genetic testing or pediatric examination. The prevalence of adverse pregnancy outcome including miscarriage, hydrops, intrauterine death, fetal abnormalities diagnosed before or after delivery and termination of pregnancy including indicated and maternal request was recorded.

Results

In this study from 9746 screened pregnant women with mean maternal age of 29.8 years (range from 15 to 46), 186 cases had NT≥ 95th centile at 11-14 weeks of gestation (Fig. 1).
Nuchal translucency was between 2.4–14 mm with a median of 4.6 mm. There were 37(19.8%) cases of aneuploidy in the study population, including 29 cases of trisomy 21, three of trisomy 18, two of trisomy 13, three of Turner syndrome. The rate of abnormal chromosomal defects was increased with increasing NT thickness (Table 1).

Table 1: Incidence of chromosomal defects according To nuchal translucency

Nuchal Translucency (mm)	Total number	Abnormal karyotype n (%)
95th centile- 3.4	92	10(10)
3.5-4.4	50	6(12)
4.5-5.4	12	4(33)
5.5-6.4	15	7(46)
≥ 6.5	17	10(58)
Total	186	37(19.8)

There were 3 intra uterine fetal death (2 multiple anomaly, 1 unknown), 2 hydrops fetalis, 4 spontaneous fetal loss, 17 termination of pregnancy (TOP) for anxiety including 3 with normal karyotype. Fetal structural abnormalities were found in 13/149 (8.7%) on follow-up ultrasound examinations antenatally (7 cases) and postnatally (6 cases). The prevalence of fetal malformations was not proportional to the degree of NT thickness as shown in Table 2.

Table 2: Pregnancy outcome of 149 fetuses with increased NT in relation to degree of NT enlargement

		Adverse outcome [n (%)]					
NT(mm)	**n**	**Fetal loss**	**Hydrops**	**Structural abnormalities**	**Maternal request(TOP)**	**Total APO**	**Live birth, no defects**
95th centile- 3.4	82	1(1)	0	9(10)	1(1)	11(13)	71(86)
3.5-4.4	43	2(4)	1(2)	2(4)	3(7)	7(16)	35(81)
4.5-5.4	7	0	0	1(14)	4(57)	5(57)	2(28)
5.5-6.4	8	3(37)	0	0	4(50)	7(87)	1(12)
≥ 6.5	19	1(11)	1(11)	1(11)	5(55)	8(88)	1(11)
Total	149	7(4.6)	2(1.3)	13(8)	17(11)	39 (26)	110(74)

NT, nuchal translucency; APO, adverse pregnancy outcome; TOP, termination of pregnancy

The most common fetal malformation was heart defects. Therefore 110 (77.8%) children with NT≥95th centile, normal serial scans, and normal echocardiography were born alive and were reported normal at birth and postnatal follow up (Table 3).

Table 3: Detailed outcome of 149 fetuses with NT≥95th

	Malformations detected antenatally	**outcome**	**Malformations detected postnatally**	**NT(mm)**
Cardiac malformation	6			
	Tetralogy of Fallot& Ventriculomegaly& Renal agenesia	TOP		4.5
	Tetralogy of Fallot & Dady- walker Malformation& Polycystic kidney	Delivery		3.4
	ASD & Limbs Anomaly	TOP		3
			ASD	3.7
			ASD	3
			VSD	3.2
Unirary tract Abnormality	2			
	Infantile polycystic Kidney	Delivery		3
	Hydronephrosis	Delivery		3.9
Pulmonary defect	1			3
	Diaphragmatic hernia	Delivery		3
Gastrointestinal defects	2	Delivery	Hirschsprung disease	3
		Delivery	Esophageal atresia	7
Skeletal defects	2			
	Akinesia deformation	TOP		3.1
		Delivery	Digit deformity	3

TOP, termination of pregnancy; ASD, Atrial septal defect; VSD, ventricular septal defect

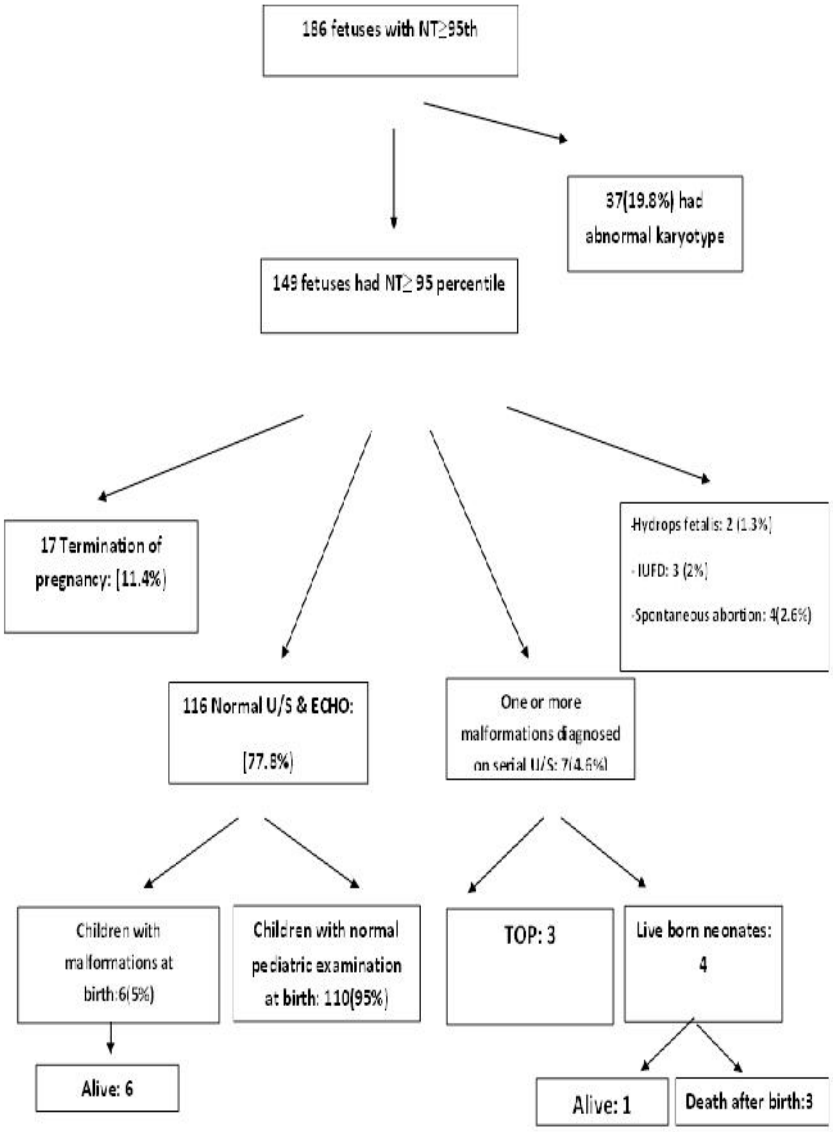

Fig.1: Outcome of 186 fetuses with NT≥ 95 percentile

Discussion

Approximately 20% of screened women in our study had abnormal karyotype that is in agreement with Kagan et al. (9) that used cut off 95th centile, but disagree with Bilardo et al. (10) who reported 33.8% abnormal karyotype with the same cut off. In a study the prevalence of abnormal karyotype was 44% (11) which was much higher than our study, this can be explained by considering different cut off for NT measurement by them. After exclusion of adverse pregnancy outcome, the chance of having a normal baby was 95%, this figure can be used in counseling of parents with increased NT in the future. Structural anomalies were detected in 8.7% of fetuses which is in agreement with another study (12) who reported 7.3% and Bilardo et al. (13) (6.3%) while in the study by senat et al. (11) the prevalence of fetal malformations was 26%, much higher than our rate, this maybe for including NT above 4 mm as cut off. The prevalence of fetal malformations was not proportional to the degree of NT thickness as shown in Table 3, this can be explained with

higher rate of TOP based on maternal request in group with NT≥3.5, but the overall rate of APO was proportional to the degree of NT enlargement. Termination of pregnancy was done by 11.4% parents after first trimester screening due to anxiety and uncertainty of future outcome. These parents had rushed decision on TOP despite of 3 with normal karyotype; it seems limitation of termination of pregnancy to the age of less than 18 weeks in our country helps this decision. Besides, our defensive and cautiously counseling has exacerbated parental anxiety as Ville (14) clearly described the challenging of counseling in cases with increased NT.

Fortunately a recent review of article reported the rate of neurodevelopmental delay as 1% that is not much different from general population (15). Our study was not designed for this issue but according to parent's declaration and follow 2-3 years by the pediatricians, neurodevelopmental delay was not reported. The most common fetal malformation was heart defects that are in keeping with the other studies (5, 16-19). The prevalence of cardiac defects was 6 times higher in fetuses with NT above 99th centile in some studies (19-21), but our small sample size does not let us to draw any conclusion about heart defects. The spontaneous fetal loss rate of 4.6% in the fetuses with increased NT was in correspondence to Bilardo et al. (13).

Conclusion

Our study showed that one out of four fetuses with enlarged NT had an adverse pregnancy outcome according to our definition for APO. Uncertainty and rushed decision on TOP falsely raised the rate of APO, as after exclusion of those with adverse outcome, the chance of having a normal outcome was found to be 95%, that is good information and new hope for counseling in the future. However, larger prospective studies with long-term follow -up and focus on neurodevelopmental delay with standard definition and standardized tools for delay are needed.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

Acknowledgement

The authors declare that there is no conflict of interests. We would like thank Nahal Bayani and Babak Farrokhi for assisting in data collection.

References

1. Nicolaides KH (2004). Nuchal translucency and other first-trimester sonographic markers of chromosomal abnormalities. *Am J Obstet Gynecol*, 191(1):45-67.
2. Snijders R, Noble P, Sebire N, Souka A, Nicolaides K (1998). UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10-14 weeks of gestation. *The Lancet,* 352 (9125):343-6.
3. Grandjean H, Sarramon MF(1995). Sonographic measurement of nuchal skinfold thickness for detection of Down syndrome in the second-trimester fetus: a multicenter prospective study. *Obstetrics & Gynecology*, 85(1):103-6.
4. Watson WJ, Miller RC, Menard MK, Chescheir NC, Katz VL, Hansen WF, et al. (1994). Ultrasonographic measurement of fetal nuchal skin to screen for chromosomal abnormalities. *Am J Obstet Gynecol***,** 170(2):583.
5. Michailidis GD, Economides DL (2001). Nuchal translucency measurement and pregnancy outcome in karyotypically normal fetuses. *Ultrasound Obstet Gynecol,* 17(2):102-5.
6. Sepulveda W, Wong AE, Casasbuenas A, Solari A, Alcalde JL (2008). Congenital diaphragmatic hernia in a first-trimester ultrasound aneuploidy screening program. *Prenat Diagn,* 28(6):531-4.

7. Nicolaides KH, Azar G, Byrne D, Mansur C, Marks K (1992). Fetal nuchal translucency: ultrasound screening for chromosomal defects in first trimester of pregnancy. *BMJ*, 304(6831):867-9.
8. Bilardo C, Timmerman E, Pajkrt E, van Maarle M(2010). Increased nuchal translucency in euploid fetuses—what should we be telling the parents? *Prenat Diagn*, 30(2):93-102.
9. Kagan KO, Avgidou K, Molina FS, Gajewska K, Nicolaides KH(2006). Relation between increased fetal nuchal translucency thickness and chromosomal defects. *Obstetrics & Gynecology,*107(1):6.
10. Bilardo C, Pajkrt E, De Graaf I, Mol B, Bleker O (1998). Outcome of fetuses with enlarged nuchal translucency and normal karyotype. *Ultrasound Obstet Gynecol*, 11(6):401-6.
11. Senat M, De Keersmaecker B, Audibert F, Montcharmont G, Frydman R, Ville Y (2002). Pregnancy outcome in fetuses with increased nuchal translucency and normal karyotype. *Prenat Diagn*, 22(5):345-9.
12. Souka AP, Krampl E, Bakalis S, Heath V, Nicolaides KH (2001). Outcome of pregnancy in chromosomally normal fetuses with increased nuchal translucency in the first trimester. *Ultrasound Obstet Gynecol*, 18(1):9-17.
13. Bilardo C, Müller M, Pajkrt E, Clur S, Van Zalen M, Bijlsma E (2007). Increased nuchal translucency thickness and normal karyotype: time for parental reassurance. *Ultrasound Obstet Gynecol,* 30(1):11-8.
14. Ville Y(2001). Nuchal translucency in the first trimester of pregnancy: ten years on and still a pain in the neck? *Ultrasound Obstet Gynecol*, 18(1):5-8.
15. Sotiriadis A, Papatheodorou S, Makrydimas G(2012). Neurodevelopmental outcome of fetuses with increased nuchal translucency and apparently normal prenatal and/or postnatal assessment: a systematic review. *Ultrasound Obstet Gynecol,* 39:10-9.
16. Hyett J, Moscoso G, Papapanagiotou G, Perdu M, Nicolaides K (1996). Abnormalities of the heart and great arteries in chromosomally normal fetuses with increased nuchal translucency thickness at 1l–13 weeks of gestation. *Ultrasound Obstet Gynecol*, 7(4):245-50.
17. Westin M, Saltvedt S, Almström H, Grunewald C, Valentin L (2007). 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,* 29(2):150-8.
18. Souka A, Snijders R, Novakov A, Soares W, Nicolaides K(1998). Defects and syndromes in chromosomally normal fetuses with increased nuchal translucency thickness at 10–14 weeks of gestation. *Ultrasound Obstet Gynecol*, 11(6):391-400.
19. Mavrides E, Cobian, Sanchez F, Tekay A, Moscoso G, Campbell S, Thilaganathan B, et al(2001). Limitations of using first- trimester nuchal translucency measurement in routine screening for major congenital heart defects. *Ultrasound Obstet Gynecol*, 17(2):106-10.
20. Clur S, Mathijssen I, Pajkrt E, Cook A, Laurini R, Ottenkamp J, et al. (2008). Structural heart defects associated with an increased nuchal translucency: 9 years experience in a referral centre. *Prenat Diagn*, 28(4):347-54.
21. Vogel M, Sharland GK, McElhinney DB, Zidere V, Simpson JM, Miller OI, et al. (2009). Prevalence of increased nuchal translucency in fetuses with congenital cardiac disease and a normal karyotype. *Cardiol Young*, 19(5):441-5.