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Research Article

EUPLOID FETUSES WITH INCREASED NUCHAL TRANSLUCENCY IN PRENATAL AND POSTNATAL FOLLOW UP

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ABSTRACT

The aim of this study was to evaluate the prenatal and postnatal outcomes of fetuses with increased nuchal translucency thickness (NT) and normal karyotype. This study from 2011 to 2013 included 8640 pregnant woman attending the outpatient clinic for the first trimester screening. 245 fetuses with increased NT were submitted to karyotyping analysis, serial anomaly scans, echocardiography and postnatal clinical evaluation. The karyotyping was abnormal in 14.2 % of the cases and normal in 85.8 %. In the present study, 86.6 % of cases with normal karyotype had a normal prenatal and postnatal evaluation. Adverse pregnancy outcome such as spontaneous fetal loss, hydrops, structural abnormality and termination of pregnancy due to multiple anomaly occurred in 13.3 % of cases with normal karyotype**.** Studying singleton fetuses with an increased NT above the 95th percentile and normal karyotype showed a percentage of 86.6 % intact survival.

Keywords: Nuchal translucency; Karyotype; Pregnancy outcome; Chromosomal abnormality

INTRODUCTION

Nuchal translucency (NT) refers to the normal subcutaneous space between the cervical spine and skin that observed on first trimester ultrasound evaluation. The pathophysiological mechanism of increased NT still remains unknown. Cardiac dysfunction[1], venous congestion in the head and neck[2], abnormal or delayed development of the lymphatic system[3], altered composition of the extra cellular matrix[4], impaired lymphatic drainage[5], fetal anemia or hypo proteinemia[6], congenital infection[7], musculoskeletal anomalies[8] and hormonal disorders[9] are the possible etiological factors. It should be considered that fetus with increased NT in 11-14 weeks of gestation are at increased risk of common chromosomal aneuploidies (trisomies 21, 18, 13 and monosomy X). Also it should be mentioned that in a normal karyotype fetus, the appearance of a thickened NT is also strongly associated with structural defects such as major cardiac malformation and rare genetic syndromes. It is proven that there is an association between increased NT and miscarriage and prenatal death and adverse pregnancy outcome[10]. Proposed pregnancy work up in fetuses with increased NT and normal karyotype includes anatomy scan, fetal echocardiography and in selected cases, infection screening and genetic testing. In this study prenatal and postnatal outcomes of fetus with increased nuchal translucency thickness and normal karyotype were investigated.

MATERIALS AND METHODS

This cross sectional study was performed between 2011 and 2013 to examine the outcome of chromosomally euploid Fetuses with increased nuchal translucency. The study protocol was approved by the local ethics committee. This study included 8640 pregnant woman attending the outpatient clinic for the first trimester screening. Identified 245 singleton pregnancies were with live fetuses at 11-14 weeks of gestation (CRL 45-84 mm) and NT of ≥ 95centile. The sonography technique for measuring NT has been standardized by the guideline recommended with London Fetal Medicine Foundation to minimize inter observer variability. The increased NT fetuses were recommended karyotyping by the cytogenetic analysis of the material obtained from chorionic villus sampling or amniocentesis. All euploid fetuses with increased NT were offered follow-up anomaly scan at 18-22 weeks of gestation and fetal echocardiography at 16-19 weeks of gestations. All children were examined at birth by neonatologist or pediatrician. Pregnancy outcome was obtained from maternity and newborn discharge slips and the parents themselves. The outcome was asked by telephone or face to face interview with parents or the pediatrician whenever was necessary. The follow-up period of the time of telephone interviews was ranged 3 days to 1 year. The prevalence of adverse pregnancy outcome including miscarriage, hydrops, intrauterine death, fetal abnormalities diagnosed before or after delivery.

RESULTS

During the 3-year period, 245 singleton pregnancies with an NT above the 95th percentile were identified, resulting in a frequency of 245/8640. Mean maternal age was 30.4 (range, 16-45) years and mean gestational age at ultrasound was 12 weeks + 3 days (range 11 + 0 to 13 + 6). Nuchal translucency was between 2.4-9 mm. There were 210 (85.7 %) fetuses with increased NT and normal karyotype. There were 35 (14.2 %) cases of aneuploidy in the study population; including 34 cases of trisomy 21, one of trisomy 18. The rate of aneuploidy was increased with increasing NT thickness (Table 1). The outcome of the 210 pregnancies summarized in Table 2. There were 3 (1.4 %) spontaneous abortions and 1 (0.4 %) intrauterine death. In the prenatal study there were 19 fetuses with complication. 10 (4.7 %) hydrops fetalis, 1 (0.4 %) termination of pregnancy are due to multiple anomaly, and 8 fetuses with structural anomaly. Five

fetuses with abnormality were reported in the postnatal study. One of the cases with cardiac defect (PI + TR + Hypoplastic Lt Heart) had not done prenatal echocardiography while the others were diagnosed in postnatal evaluation; despite the prenatal investigation. Fetal structural defects were found in 13/210 (6.1 %) on antenatal (8 cases) and postnatal (5 cases) studies. There were 5 (2.3 %) cardiac defect, 2 (0.9 %) gastrointestinal defects, 2 (0.9 %) urinary tract and genitalia abnormality, 2 (0.9 %) pulmonary defect; 1 (0.4 %) skeletal defect, 1 (0.4 %) nuchal defect cases. The most common fetal malformation was cardiac defect (Table 3).

The prevalence of fetal malformation was not proportional to the degree of NT thickness as shown in Table 2. But the overall rate of adverse pregnancy outcome was proportional to the degree of NT increased. Mean NT as shown to vary according to the outcome of pregnancy: 4.1 mm in spontaneous fetal loss, 5 mm in hydrops fetalis, 5.4 mm in termination of pregnancy due to multiple anomaly, 4.1 mm in structural defect and 3 in survivors with no defect (Table 4). 182 (86.6 %) cases with normal karyotype and increased NT had a normal serial anomaly scan and echocardiography, and they born alive with normal postnatal follow-up.

Table 1: Incidence of chromosomal defect according to nuchal translucen

Nuchal Translucency (mm)	Total number	Abnormal Karyotype n (%)
95th centile-3	111	6 (5.4)
3.1-4	72	5 (6.9)
4.1-5	26	5 (19.2)
> 5	36	18 (50)
Total	245	35 (14.2)

Table 2: Pregnancy out of 210 euploid fetuses with increased NT in relation to degree of NT increased

NT (mm)	Total (n)	Spontaneous Fetal loss n (%)	Hydropsn (%)	Structural Abnormalities n (%)	Termination of pregnancy due to multiple anomaly n (%)	Total adverse outcome n (%)	Alive with no defect n (%)
95th percentile-3	105	0	1 (0.9)	1 (0.9)	0	2 (1.9)	103 (98)
3.1-4	67	2 (3.8)	1 (1.9)	5 (9.6)	0	8 (11.9)	59 (88)
4.1-5	21	1 (4.3)	2 (8.6)	4 (17.3)	0	7 (33.3)	14 (66.6)
> 5	17	1 (3.3)	6 (2.0)	3 (10)	1 (3.3)	11 (64.7)	6 (35.2)
Total	210	4 (1.9)	10 (4.7)	13 (6.1)	1 (0.4)	28 (13.3)	182 (86.6)

NT, nuchal translucency

Table 3: Fetal structural anomalies diagnosed at prenatal or postnatal examinations (n = 13)

	N (%)	Malformation detected antenatal	Malformation detected postnatal	NT (mm)
Cardiac defects	5 (2.3)	ASD + VSD		3.6
		ASD		4.2
		TOF		5.8
			PI + TR + Hypoplastic Lt Heart	2.9
			ASD	4.2
Gastrointestinal defects	2 (0.9)	Hyperechogenic bowel		4.1
			Esophageal atresia	6
Urinary tract and Genitalia abnormalities	2 (0.9)	Polycystic kidney	Hypospadias	5.3
				3.5
Pulmonary defects	2 (0.9)	Diaphragmatic hernia (2)		3.7
				3.2
Skeletal defect	1 (0.4)		Clubfoot + low set ear	
Nuchal defect	1 (0.4)	Cystic hygroma		5

ASD: Atrial septal defect, VSD: Ventricular septal defect, TOF: Tetralogy of fallot

Table 4: Mean nuchal translucency (NT) according to pregnancy outcome

Outcome	N	Mean (mm)
Spontaneous fetal loss	4	4/1
Hydrops	10	5
Termination of pregnancy due to multiple anomaly	1	5/4
Structural abnormality	13	4/1
Survivors without defect	182	3/2

DISCUSSION

In the present study, out of 245 fetuses with increased NT (above the 95th percentile) 210 (86 %) cases had normal karyotype. Tahmasebpour *et al*., (2012) reported 80 % fetuses with increased NT and normal karyotype that was similar to the present study[11]. Bilardo *et al*., (2007) and Miltoft *et al*., (2012) have also reported 67 % and 65 % normal karyotype fetuses with increased NT[12,13]. The present investigation confirms the association between increased NT and abnormal chromosomal defects. Based on the results 14 % of increased NT cases had abnormal karyotype and was in accordance with Fatima *et al*., (2009) study[22]. In Fatima *et al*., (2009) evaluation 14.2 % of abnormal chromosomal fetuses was reported. Tahmasebpour *et al*., (2012) informed 20 % and Bilardo *et al* (2007) reported 33 % aneuploid cases with the same cut off [11,12]. The results are different with Senat *et al*., (2007) study who reported 44 % and Miltoft *et al*., (2012) evaluation that reported 34.7 %. The difference may be due to the different cut off for NT measurement by them. NT cut off in their articles were NT > 4 and NT > 99 %, respectively[13,14]. The present article shows that an adverse pregnancy outcome, including spontaneous abortion, intrauterine death, hydrops fetalis, termination of pregnancy due to multiple anomaly; structural abnormalities occurred in 13 % (28/210) of euploid fetuses with NT above the 95th percentile. Lindsey *et al*., (2006) concluded 20 % of adverse pregnancy outcome in increased nuchal translucency euploid fetuses[15]. The overall rate of adverse pregnancy outcome was proportional to the degree of NT enlargement, ranging from 1.9 % to 64.7 % such as Bilardo *et al*., (2007) reported that the prevalence of adverse pregnancy outcome increased with NT thickness enlargement, ranging from 8 % to 80 %[12]. Similarly, Tahmasebpour *et al*., (2012) reported ranging from 13 % to 88 % and confirmed the results of Souka *et al*., (2005) study[16]. Structural defects specially cardiac abnormalities were detected in 6 % (13/210) of fetuses in prenatal and postnatal evaluation, which is in agreement with Mula *et al*., (2012) (7 %) and Tahmasebpour *et al*., (2012) (8 %), Bilardo *et al*., (2007) (6 %) and Hiippala *et al*., (2001) (10 %) studies[18,12,19]. Orsoz *et al*., (2009) reported 27 % fetuses with structural anomaly[20]. This difference can be due to 5 year postnatal follow up of cases. In the present survey the most common fetal malformation was cardiac defect such as results obtained from Zosmer *et al*., (1999) study, therefore they recommended doing echocardiography in all cases with increased NT[21]. Five fetuses (2.3 %) with malformation were reported in postnatal evaluation. One of them had not done prenatal echocardiography while 1.9 % (4/13) was diagnosed in postnatal study despite the prenatal investigation. In conclusion, there were 1.9 % risk for adverse postnatal anatomically outcome in euploid fetuses with increasing NT above the 95th percentile and normal prenatal evaluation. Tahmasebpour *et al*., (2012) reported 4 %, Fatima *et al*., (2009) reported 14.8 % which was much higher than our study[11,22]. This can be explained by considering that we did not observe delayed brain development in our study. Interestingly that Marie *et al*., (2007) reported that the prevalence of abnormal clinical pediatric examination and Age and Stage Questionnaires (ASQ) results at 2 years were not associated with NT thickness (> 99 %)[17]. Comparison with an external control group did not show an increased incidence of developmental delay. In our disquisition, postnatal follow up of euploid increased NT fetuses was normal in 86.6 %. This finding was similar to Tahmasebpour *et al*., (2012) study who was reported that 74 % normal postnatal follow up in euploid increased NT cases[11] and approximately like to Mula *et al*., (2012) (63 %), and Hiippala *et al*., (2001) (73 %), investigations[18,19]. So we can inform parents that the majority of euploid increased NT fetuses (86.6 %) will have a normal outcome. This information, together with an explanation of subsequent management, will help the parents to have more comforting pregnancy and will decrease probable termination gestation on the basis of an increased NT. Accordingly, our study emphasize on the necessity of follow up of normal chromosomal fetuses with increased NT during prenatal care and postnatal follow up, especially in fetuses with much high degree of NT enlargement. However, we reported 86.6 % normal outcome in this pregnancies. That is hopeful information for parents. Although, further studies are necessary to perform for long term follow up and considerations of neurodevelopmental delay.

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