

DOI: <https://dx.doi.org/10.18203/2320-1770.ijrcog20204832>

Case Series

## Increased nuchal translucency: it's not just aneuploidy

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**Received:** 09 August 2020

**Revised:** 17 September 2020

**Accepted:** 18 September 2020

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### ABSTRACT

Nuchal translucency (NT) measurement between 11- and 14-weeks' gestation is an established and consistently performing marker for chromosomal abnormalities, including trisomy 21. Even in the absence of aneuploidy in the event of normal conventional karyotyping or microarray analysis, increased NT is prognostic of adverse pregnancy outcome, because it is associated with miscarriages, congenital heart defects, several fetal malformations, many genetic syndromes, skeletal dysplasia's, intrauterine death; the majority of these structural anomalies are undetectable before birth. The parents should be reassured that in the absence of any abnormality detected the fetus will have a normal uneventful outcome and postnatal development when compared to the general population outcome.

**Keywords:** Nuchal translucency (NT), Chromosomal abnormalities, First trimester screening, Genetic syndromes, Euploid fetus

### INTRODUCTION

Fetal nuchal translucency (NT) has brought about a paradigm shift in predicting the health of fetus and inverting the pyramid of antenatal care where first trimester now offers an array of opportunity to evaluate the fetus. Approximately 20-50% fetuses with increased NT have a chromosomal abnormality/aneuploidy. Even euploid fetuses with increased NT may present with structural anomalies like cardiac defects, diaphragmatic hernias, rare genetic syndromes & rarely congenital infections.<sup>1</sup>

Although increased nuchal translucency (NT) is not commonly associated with fetal infection, parvovirus B19 infection is the only infection that has been reported in association with increased fetal NT. Therefore, increased NT in first trimester warrants extensive evaluation

comprising of karyotyping/microarray, fetal-echocardiography, detailed anomaly scan and molecular tests with next generation sequencing with clinical exome whenever indicated and a work up for congenital infection.<sup>2-4</sup>

We present here three cases of increased NT with diagnosis other than aneuploidy. There was association with parvovirus infection, Noonan syndrome and a euploid fetus with increased NT in all these cases.

### CASE SERIES

#### Case 1

The first case was 30 years old primigravida with O positive blood group, with dichorionic diamniotic (DCDA) IVF twin pregnancy. At 13 weeks' gestation

during her first antenatal visit, the NT scan report increased NT in both the twins (with CRL of 68 mm in Twin A with NT of 3.8 mm and 66 mm in Twin B having NT of 4.46 mm) which was more than 99 percentiles for the gestational age. Amniocentesis was offered to the parents at 16 weeks of gestation and karyotype reported normal for both the twins. However, at 19 weeks anomaly scan showed increased middle cerebral artery peak systolic velocity (MCA-PSV) in both twins suggestive of fetal anemia. On further evaluation to seek likely cause of fetal anemia, following tests were done- minor blood group testing, indirect coomb's test (ICT), Toxoplasmosis, other Agents, Rubella, Cytomegalovirus, and Herpes Simplex (TORCH) panel and parvovirus serology. Fetal echocardiography was normal for both fetuses. Parvovirus IgM & IgG positivity was detected in maternal serum. Parvovirus B19 DNA was detected in fetus by polymerase chain reaction (PCR) by a repeat amniocentesis at 21 weeks period of gestation (POG). Pregnancy was followed up with serial ultrasonograms where at 22 weeks features of MCA-PSV >1.5 MoM was detected in one fetus where increased NT persisted, whereas anemia was auto corrected for the other twin in the subsequent scan. Intrauterine transfusion (IUT) was offered at 22 weeks for the twin with persisting anemia. Pre-IUT hemoglobin (Hb) was 7.2 gm/dl and PCV was 21% whereas post transfusion Hb was 17 gm/dl with haematocrit of 51%. The fetus was monitored by serial MCA-PSV. There was no further need of intrauterine transfusion in subsequent antenatal period as there was no evidence of fetal anemia. Elective lower segment cesarian section (LSCS) was done at 35 weeks period of gestation for obstetric indication. Twin live female babies were delivered who had a brief period of newborn intensive care unit (NICU) stay in view of prematurity with no postnatal anemia and are currently thriving well.

**Case 2**

Our second case was 30 years old G4A2L1 lady with consanguineous marriage, with previous history of LSCS, who conceived a singleton pregnancy spontaneously. Nuchal translucency scan demonstrated an increased NT at 11 weeks (with CRL of 44 mm and NT of 4.8 mm). After prenatal genetic counselling, patient opted for amniocentesis at 16 weeks where her amniotic fluid was subjected to chromosomal microarray analysis (350 k) which showed no pathogenic variant and conventional karyotype was also normal. Subsequently a detailed anomaly scan at 20 weeks revealed no gross congenital malformation. The NFT was normal in the anomaly scan. Fetal echocardiography revealed no abnormality. The parvovirus screen for mother was normal. At 26 weeks, patient developed polyhydramnios with no evidence of gestational diabetes. At 32 weeks, level III obstetric scan revealed a non-immune hydrops in fetus with bilateral pleural effusion (Figure 1) and reversal of blood flow in ductus venosus (Figure 2). Fetal echocardiography was repeated and there was no evidence of any structural defects. Patient was taken up for Emergency LSCS and a

male baby was delivered who had to be resuscitated and taken to NICU. Phenotype (Figure 3) showed suspicion of Noonan's syndrome and clinical whole exome sequencing (WES) confirmed the diagnosis. The new born baby expired after 3 days.



**Figure 1: Ultrasound of the fetus showing skin oedema and pleural effusion suggestive of non-immune hydrops.**



**Figure 2: Doppler ultrasound of the ductus venosus showing reversal of a wave in the waveform.**



**Figure 3: The phenotype of the baby born with Noonan's syndrome depicting.**

**Case 3**

This third case was 31 years old primigravida who had a spontaneous, triplet conception with dichorionic pregnancy with one monochorionic diamniotic pregnancy with spontaneous demise of one fetus and continuing twin monochorionic-diamniotic pregnancy. The couple reported at period of gestation 13 weeks 4 days. However, NT/NB scan during first antenatal visit (Figure 4) demonstrated an increased NT of 6.58 mm in one twin with crown rump length of 85 mm and also reversal of ductus venosus ‘A’ wave. Other twin had a normal NT value of 1.42 mm corresponding to 84.9 mm CRL with dilatation of B/L pelvicalyceal system (APD of 2 mm). In view of increased NT, amniocentesis was opted by the couple at 16 weeks and no significant chromosomal abnormality was revealed on microarray (Figure 5).



**Figure 4: First trimester ultrasound (NT/NB) showing an increased NT.**

Patient Information		
Name: AF of Mrs. Rachna Arora	Gender: Unknown	DOB/Age: 33 years
Sample Information		
Sample ID: G2M 4585	Sample Type: Amniotic Fluid	Hospital/Clinic: R. & R Hospital
Collection Date: 02.03.2019	Receiving Date: 02.03.2019	Report Date: 09.03.2019
Clinical Information		
Referred by: Dr. Keema Kumar Bhatt		
Disease Indication: USG shows increased NT in Twin A.		
Result Summary		
Test Performed -- CytoSure Microarray		
No clinically significant chromosomal abnormalities were found in the sample submitted for analysis.		
Karyoview		

**Figure 5: Microarray report revealed no karyotype abnormality in the fetus.**

Detailed anomaly scan done at 20 weeks that showed no gross congenital malformation except bilateral pyelectasis in both twins with auditory processing disorder (APD) of 4 mm (Twin I) and 7 mm (Twin II).

Fetal echocardiography was normal for both twins. From 16 weeks onwards, the pregnancy was monitored for any development of twin-twin transfusion syndrome (TTTS) & selective growth restriction with doppler by ultrasound every two weeks. Ultrasound at 28 weeks and again at 31 weeks showed no growth lag and normal doppler studies. She had a full term normal vaginal delivery at 38 weeks bearing forth twin live male babies weighing 3.1 & 3.2 kilograms respectively with good Apgar scores. Postnatally, ultrasound of the kidneys and urinary system was done for both newborns which revealed persisting mild bilateral hydroureteronephrosis (right with APD 6.3 mm>left with APD 3.3 mm) in first baby while only mild right sided hydroureteronephrosis was seen in second baby (APD 8.6 mm). Presently babies are healthy and doing well. They are on continuous follow up at pediatric urology department at our hospital with no sequelae.

**DISCUSSION**

NT is defined as the maximal thickness of the sonolucent zone (fluid accumulation) between the inner aspect of the fetal skin and the outer aspect of the soft tissue overlying the cervical spine or the occipital bone. To avoid false negative or positive results, the fetus should be in a neutral position, with the head in line with the spine. During the scan, more than one measurement must be taken and the maximum one that meets the criteria should be considered. Fetuses with an increased NT ( $NT \geq 3$  mm) or more than 99th centile for that gestational age are considered for further investigation & detailed evaluation by an array of tests.<sup>5-7</sup> Increased nuchal translucency is thought to be related to dilated lymphatic channels and is considered a nonspecific sign of more generalized fetal abnormality. Thickening of the nuchal translucency can be associated with a number of anomalies, including: aneuploidy trisomies (down syndrome, turner syndrome), non-aneuploidy structural defects and syndromes (congenital diaphragmatic herniation, congenital heart disease, omphalocele, skeletal dysplasias, smith-lemlipitz syndrome, VACTERL association etc). Even in the presence of low risk on combined first trimester screening increased nuchal translucency warrants invasive testing. Our first case suggests an association of an increased NT measurement with fetal anemia due to an asymptomatic parvovirus B19 infection in the mother. The fetal anemia was successfully treated with fetal blood transfusion and subsequent prolongation of the pregnancy to term with no sequelae. Parvovirus B19 is a small single-stranded DNA virus and a potent inhibitor of erythropoiesis due to its cytotoxicity to erythroid progenitor cells. The fetus seems to be most susceptible to parvovirus B19 infection during the first and second trimesters of pregnancy, which coincides with the major development of the erythroid precursors.<sup>8</sup> Adult disease is generally mild, however fetal parvovirus B19 infection can cause spontaneous abortion in early pregnancy, aplastic anemia, nonimmune hydrops fetalis and in utero fetal demise. The prevalence of parvovirus B19 maternal infection during pregnancy is about 1–2%. The vertical

transmission occurs in 10–35%, being highest in the first and second trimesters. The risk of adverse fetal outcome is 10%.<sup>9-11</sup> The prevalence of first-trimester fetal loss associated with parvovirus B19 infection is low, ranging from 0.8% to 3%.<sup>12,13</sup> Whenever increased NT is found in the first trimester of pregnancy (11–14 weeks), the possibility of parvovirus infection must always be considered as in our case especially if increased NT persists despite normal karyotype and fetal echocardiography is normal and all cases of suspicious fetal anemia in a non-Rh isoimmunised pregnancy must undergo serological testing (IgG and IgM antibodies) for parvovirus B19 & MCA PSV monitoring. Fetal parvovirus infection can be confirmed with a positive PCR. An early diagnosis can enable intervention via intrauterine blood transfusions, which can potentially cure hydrops fetalis. Cordocentesis can be done to assess fetal haemoglobin, hematocrit and reticulocyte count. Furthermore, if the fetus is at or near term, delivery should be considered. A recent study suggested a fetal survival rate of 82% with transfusion compared to a fetal survival rate of 55% for those who were not transfused.<sup>14</sup>

Two to three transfusions may be required before resolution of the fetal hydrops or anemia, which usually takes place three to six weeks after the first transfusion. Hence, recommended monitoring includes weekly ultrasonography and doppler assessment to assess the MCA-PSV, which is a non-invasive method to measure a fetus at risk for anemia.<sup>15-17</sup> Our second case was a fetus with Noonan Syndrome (NS) which was diagnosed postnatally.

NS is an autosomal dominant condition with an incidence of 1:1000–2500 live births. It is characterized by characteristic facies, short stature, congenital heart defects (CHD), skeletal abnormalities, cryptorchidism and variable development delay. NS is one of the 'RASopathies', a specific class of developmental disorders, caused by germline mutations in genes, encoding proteins of the RAS–mitogen-activated protein kinase (RAS–MAPK) pathway. This pathway has an essential role in the control of the cell cycle, differentiation, growth and cell senescence.<sup>18,19</sup> Several of these genes are also involved in Cardio-facio-cutaneous (CFC) syndrome and Costello syndrome.<sup>20-22</sup> Because of the high variability of clinical symptoms and the genetic heterogeneity establishing a diagnosis of one of these syndromes is often difficult. Patients are most frequently diagnosed postnatally. Prenatal features of NS are increased NT, distended jugular lymphatic sacs (JLS), cystic hygroma, hydrops fetalis, pleural effusion, polyhydramnios, CHD and renal abnormalities.<sup>23-26</sup> DNA of fetuses with a normal karyotype and one or more abnormal ultrasound findings is assessed for a mutation in one or more of the NS genes in a diagnostic setting. Whole exome sequencing (WES) using next generation sequencing (NGS) has emerged as a useful tool for definitive diagnosis and accurate genetic counselling of atypical cases. Next-generation sequencing (NGS) is a

rapid and economical technique that provides molecular-based diagnosis for clinically overlapping conditions. NGS facilitates early disease diagnosis, especially for patients with mild/moderate, atypical features, and can potentially direct clinicians towards more reliable genetic counselling and clinical treatment of the patients.<sup>27</sup> Eleven studies reporting on the pregnancy outcome of 2,128 euploid fetuses with increased NT ( $\geq 3$  mm or  $\geq 95$  centile) showed 2.2-10.6% of the fetuses has miscarried and 0.5-15.8% ended in perinatal death. There was an overall rate of 0.5-13% neurodevelopmental problems, and 2-8% of the malformations were undiagnosed before birth, the most common being cardiac anomalies. Nevertheless, 70-90% fetuses had normal outcomes.<sup>28</sup>

## CONCLUSION

Although measurement of the NT thickness combined with biochemical markers has a false positive rate of 5%, it is regarded as a basic screening test with high sensitivity for identifying fetuses at risk for aneuploidy. With the inversion of pyramid of antenatal care NT scan is the election test for determining the well-being of fetus in first trimester and gives a lot of information in terms of aneuploidy, genetic syndromes and infections as is evident by our first two cases. However, we also need to counsel the parents adequately that NT is increased in 4.4% of chromosomally normal fetuses, and these euploid fetuses are still at risk of a wide range of fetal malformations, dysplasias, disruptions, genetic syndromes and neurodevelopmental delay. The number of abnormalities known to be associated with enlarged NT is still increasing. However, there remains a large group of fetuses with increased NT that present as healthy neonates. Therefore, all couples with a euploid fetus with increased NT should be offered a detailed ultrasound scan at 18–20 weeks' gestation to exclude or diagnose structural anomalies or subtle ultrasound markers that are associated with genetic syndromes. Fetal echocardiography should be offered in addition if increased NT persists and work up for congenital infections should be offered too.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: Not required*

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**Cite this article as:** Bhatt R, Dwivedi P, Rana A. Increased nuchal translucency: it's not just aneuploidy. *Int J Reprod Contracept Obstet Gynecol* 2020;9:4677-81.