Elevated nuchal translucency, is it time to discuss the cut off?. A retrospective study

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Abstract

Objectives To evaluate pregnancy and postnatal outcomes of fetuses with NT between 95th and 99th percentile and whether they could benefit from further investigations rather that routine scans. Design Retrospective multicenter observational study. Setting Two Italian Fetal Medicine centre Population All cases with NT between 95th and 99th percentile (667) among women undergoing NT measurement between January 2015 and December 2020. Methods Unfavourable outcome was considered as: miscarriage or intrauterine fetal death (IUFD), chromosomal abnormality/genetic syndrome, major malformation or neurodevelopmental delay. Study population outcomes were compared with general population. Main Outcome Measures Unfavourable pregnancy and postnatal outcomes. Results The rate of unfavourable outcome was 25.44%. We reported: 6 (0.90%) second trimester miscarriage or IUFD, 90 (13.49%) chromosomal abnormalities/genetic syndromes, 57 (8.55%) major malformations, 13 (1.95%) cases of neurodevelopmental delay. The incidence of chromosomal abnormalities/genetic syndromes and major malformations were significantly higher (OR 6.99 (IC 95% 4.33 - 11.28), p<0.001 and OR 17.77 (IC 95%7.22 - 43.75), p<0.001 respectively) compared to the general population. The incidence of neurodevelopmental delay was not increased (OR of 0.64 CI 95% 0.33 - 1.24 p=0.185). Conclusions Fetuses with NT between 95th and 99th percentile have an increased risk of pregnancy and postnatal adverse outcomes. According to our data it is reasonable to consider a lower NT cut off (NT>95th percentile) for offering further investigations such as detailed ultrasound scan, fetal echocardiography and counselling where the option of performing fetal karyotype and CGH array should be discussed. Funding The authors have no funding to declare.

Introduction

Nuchal translucency (NT) is a subcutaneous fluid collection behind fetal neck and it is physiologically present in the first trimester in all fetuses[1]. In the early '90, Nicolaides introduced NT measurement as part of first trimester screening for trisomies 21, 13 and 18[2] and over the years an increased NT has been associated with several pathological conditions such as adverse pregnancy outcome[3-4], chromosomal abnormalities other than common trisomies, genetic syndromes[5-9], and structural anomalies[3;8], in particular cardiac malformations[10-11]. Therefore, pregnancies with an increased NT are considered at high risk and detailed fetal ultrasound, fetal echocardiography, genetic counselling and chorionic villous sampling (CVS)/amniocentesis are usually offered to these patients.

Reference ranges and percentiles for NT based on gestational age have been established in a large study by Snijders et al.[12]. International guidelines, however, do not show complete agreement regarding the cut off of NT value or percentile that requires further investigations; the most commonly used are either 3.5 mm, 3

mm or the 99th percentile[13-17](Table 1). Usually, cases of NT between the 95th-99th percentile are managed as healthy pregnancies.

Recently, the accuracy of ultrasonographic technology has markedly increased and new genetic tests such as CGH-array (Comparative Genomic Hybridization) and exome sequencing, have been introduced in clinical practice, allowing to be more accurate in the diagnosis of fetal anomalies, chromosomal abnormalities and genetic syndromes.

The aim of our multicentric study was to evaluate all women with NT between 95th and 99th percentile and discuss a possible new cut off for fetal and genetic tools usually provided to higher cut offs.

Methods

A multicenter retrospective observational study promoted by the Fetal Medicine Unit of the Azienda Ospedaliero Universitaria Careggi (Florence) with the collaboration of Piero Palagi Hospital (Florence).

All patients who underwent NT measurement in the first trimester between January 2015 and December 2020 were included. Among them, all cases with NT between 95th and 99th percentile for gestational age were selected[12]. Exclusion criteria were: maternal age under 18 years, monochorionic placentation, multiple pregnancies, incomplete data or absent informed consent for the study.

NT was measured according to the Fetal Medicine Foundation guidelines[18]. All ultrasound examinations were performed by a certified FMF sonographer. Cases with positive combined test or NT[?]3mm were offered genetic counselling, CVS or amniocentesis, monthly detailed ultrasound and fetal echocardiography as per local protocol. Information regarding maternal demographic characteristics, genetic tests, ultrasound scans and other prenatal investigations (such as fetal magnetic resonance imaging in selected cases), pregnancy outcome and long-term postnatal outcome were obtained by reviewing hospital records and patients' interviews. Patients were asked to provide copy of medical records in case of postnatal diagnosis of neonatal disease.

We considered as unfavourable outcome: miscarriage or intrauterine fetal death (IUFD), the presence of chromosomal abnormality/genetic syndrome, major malformation or neurodevelopmental delay. Major malformations were defined as those requiring chronic medical treatment or major surgery and/or associated with mental or physical disability. Minor malformations were not included in the unfavourable outcome. In all cases of neurodevelopmental delay the diagnosis was made by an expert clinician.

Postnatal outcomes were compared with general population's data from the EUROCAT (European Network of Population Based Registries for the Epidemiological Surveillance of Congenital Anomalies)[19] register regarding chromosomal abnormalities/genetic syndromes and major malformations. With regards to neurodevelopmental delay, a recent review by Sotiriadis et al.[20] was used for comparison.

The study was approved by the local Ethic Committee (CEAVC n=17892) and it was conducted in accordance with the standards of the Helsinki Declaration.

Statistical analysis was performed using "Statistical Package for Social Sciences" (SPSS Inc, version 21, Chicago, Il USA), and Microsoft Office Excel package (Microsoft Corp., Redmond, WA, USA). Chi-square or Fisher exact test were used to compare categorical variables and T Test for continuous variables. A p-value of 0.05 was considered as statistically significant. Odds ratio (OR) and 95% confidence intervals (IC 95%) were also calculated.

Results

During the study period 667 fetuses met the inclusion criteria (on a total of 12.250 NT tests). Mean maternal age was 35.64 ± 3.44 years, 617 (92.92%) were spontaneous pregnancies while 47 (7.08%) pregnancies were conceived by assisted reproductive technology. All fetuses were assessed by ultrasound follow up scans, while CVS or amniocentesis were performed in 288 (43.37%). For children with normal paediatric examination at birth, mean age at the time of follow up was 2.65 years (range 4 months-6 years). There was a live birth

of a healthy fetus in 500 (74.96%) cases. The outcome was unfavourable in 167 (25.44%) cases: there were 90 (13.49%) cases of chromosomal abnormalities/genetic syndromes, of which 45 (50%) were trisomy 21, 57 (8.55%) cases of major malformations of which 23 (3.45%) were cardiac, 13 (1.95%) cases of neurodevelopmental delay. In 6 cases a second trimester miscarriage or IUFD occurred in fetuses with no detected abnormalities (0.90%). There was 1 (0.15%) case of metabolic disease (severe growth hormone (GH) deficiency). Details regarding postnatal outcome including the time of diagnosis (prenatal or postnatal) are reported in Table 2.

Details regarding each case of chromosomal abnormalities and genetic syndromes are reported in Table S1. Major malformations and other unfavourable outcome are listed in Table S2, cases of neurodevelopmental delays are listed in Table S3.

The incidence of chromosomal abnormalities/genetic syndromes and major malformations were significantly higher in our cohort (OR 6.99 (IC 95% 4.33 - 11.28), p<0.001 and OR 17.77 (IC 95%7.22 - 43.75), p<0.001 respectively) compared to the general population. Conversely, the incidence of neurodevelopmental delay was not increased (OR of 0.64 CI 95% 0.33 - 1.24 p=0.185) (Table 3 - Figure 1).

Discussion

Main Findings

Our present study showed that a NT between the 95thand the 99th percentile is associated with unfavourable outcome in 25.44% of cases; in particular the risk of chromosomal abnormalities/genetic syndrome and major malformations were 6.99 and 17.77 times higher, respectively, than the background risk of the general population.

Interpretation

These data agree with previous studies reporting an increased risk of adverse pregnancy outcome for mildly increased NT (NT 95th-99thpercentile)[4;21-22]. Bardi et al. reported that 21.3% of fetuses with an NT between the 95th and the 99th percentile had congenital abnormalities, either genetic or structural.

The reported prevalence of healthy live-born children varied between 83%[4] and 78.2%[22], similar to our study (74.96% of fetuses were born alive and healthy). A long term follow up is crucial in terms of reporting adverse postnatal outcome, in fact, in our cohort a high number of unfavourable diagnoses such as genetic syndromes and neurodevelopmental delay were made between 6 months and 2 years of age.

The incidence of chromosomal abnormalities and genetic syndromes varied in previous studies. Kagan et al. in 2006[6] reported a prevalence of 7.1% for NT between 95th and 99th percentile, but the only genetic investigation performed was however standard karyotype. In a study by Tekesin et al.[22] the incidence of abnormal fetal karyotype was 18.2% in a selected high risk population with NT between 95th and 99th percentile. In our study group, which mainly included a low risk population, fetuses with these conditions accounted for 13.49% of cases.

Furthermore, according to recent studies[23-24], the use of CGH-arrays in fetuses with NT>3.5 mm can reveal approximately 5% copy number variants (CNVs) with pathogenetic or uncertain significance. Despite the level of anxiety that variants of unknown significance (VOUS) could bring, it is now mandatory that couples who are offered karyotyping are at least informed on the existence of this genetic test.

The most common malformations reported in our population were cardiac defects (40.35% of all malformations detected). This result is consistent with the incidence reported in a meta-analysis by Sotiriadis et al.[10] where 45% of fetuses with cardiac malformation showed an NT >95thpercentile, but only in 20% of them NT was above 99thpercentile. Therefore, the majority of fetuses with cardiac defects showed an NT between 95th and 99thpercentile. Similar percentages (34.1%-41.57%) can be observed in more recent studies[21-22]. These data suggest that an NT>95th percentile could be the proper cut off to offer fetal echocardiography.

With regards to neurodevelopmental delay , Hellmuth et al. in 2017[25] found no increased risk in a cohort

of children with NT between 95th and 99th percentile at first trimester scan, with a mean follow up of 4.4 years. The present study confirms the reported results, showing that the incidence of those disorders is 1.95% in our population, not significantly different from the general population.

A critical point in the management of pregnancies with NT between 95^{th} and 99^{th} percentile is the level of investigations that should be offered to couples. At the moment, international guidelines do not include NT>95^{th} percentile among the cases that should benefit from further examinations than the routine ones. Souka et al. in 2005[3] proposed a specific management for fetuses with NT between 95^{th} and 99^{th} percentile which included a detailed ultrasound at 20 weeks with examination of fetal heart, preferably performed by a fetal echocardiography specialist. This protocol was also recommended by De Domenico et al.[9]. Moreover, both authors stated that fetal karyotype should be performed based on patients-specific risk for chromosomal anomalies. Based on the high prevalence of chromosomal anomalies and genetic syndromes in our cohort, we suggest that fetal karyotyping should be offered also in case of NT between 95^{th} and 99^{th} percentile.

Strengths and Limitations

Strength of our study is the inclusion of a low risk population; this could have reduced population selection bias. Even though the study involved more than one Centre, a single protocol was shared and the management of all the patients was homogeneous. In addition, the long term follow-up of children was crucial because several postnatal diagnosis were made after 6 months of age.

A possible limitation of the study is that not all patients underwent fetal karyotyping and CGH-array. In particular, postnatal genetic examination of liveborns who showed normal long term follow up was not performed and this could lead to the underestimation of genetic disorders.

Conclusion

In conclusion, fetus with NT between 95^{th} and 99^{th} percentile are at increased risk of pregnancy and postnatal adverse outcomes; these data should guide clinicians in the management of pregnancies wit this condition. Our data support the new lower cut off of NT (NT>95th percentile) for offering further investigations to couples. These should include detailed ultrasound scan, fetal echocardiography and counselling where the option of performing fetal karyotype and CGH array should be discussed.

Conflict of Interest

The authors report no relevant financial, personal, political, intellectual or religious interest that could have influenced the outcome of this work.

Contribution to Authorship

The study was designed by IP, ES, FP and LP. The data were acquired by IP, EB and AC, and interpreted and analyzed by IP, ES and GM. Manuscript was drafted by IP, ES and EB, and revised for important intellectual content by GM, AC, FP and LP. All authors read and approved the final version of the manuscript.

Details of Ethical Approval

The study was approved by the local Ethic Committee (CEAVC - Comitato Etico Area Vasta Centro n=17892). All the procedures were conducted in accordance with the standards of the Helsinki Declaration.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Reference List

1. Nicolaides KH, Azar G, Byrne D, Mansur C, Marks K. Fetal nuchal translucency: ultrasound screening for chromosomal defects in first trimester of pregnancy. BMJ 1992 Apr 4;304(6831):867-9.

2. Nicolaides KH, Brizot ML, Snijders RJ. Fetal nuchal translucency: ultrasound screening for fetal trisomy in the first trimester of pregnancy. Br J Obstet Gynaecol 1994 Sep;101(9):782-6.
3. Souka AP, Von Kaisenberg CS, Hyett JA, Sonek JD, Nicolaides KH. Increased nuchal translucency with normal karyotype. Am J Obstet Gynecol. 2005 Apr;192(4):1005-21.
4. Ayräs O, Tikkanen M, Eronen M, Paavonen J, Stefanovic V. Increased nuchal translucency and pregnancy outcome: a retrospective study of 1063 consecutive singleton pregnancies in a single referral institution. Prenat Diagn. 2013 Sep;33(9):856-62. Epub 2013 May 16.
5. Nicolaides KH. Nuchal translucency and other first-trimester sonographic markers of chromosomal abnormalities. Am J Obstet Gynecol. 2004 Jul;191(1):45-67.
6. Kagan KO, Avgidou K, Molina FS, Gajewska K, Nicolaides KH. Relation between increased fetal nuchal translucency thickness and chromosomal defects. Obstet Gynecol. 2006 Jan;107(1):6-10.
7. Souka AP, Krampl E, Bakalis S, Heath V, Nicolaides KH. Outcome of pregnancy in chromosomally normal fetuses with increased nuchal translucency in the first trimester. Ultrasound Obstet Gynecol. 2001 Jul;18(1):9-17.
8. Souka AP, Snijders RJ, Novakov A, Soares W, Nicolaides KH. Defects and syndromes in chromosomally normal fetuses with increased nuchal translucency thickness at 10-14 weeks of gestation. Ultrasound Obstet Gynecol. 1998 Jun;11(6):391-400.
9. De Domenico R, Faraci M, Hyseni E, Di Prima FAF, Valenti O, Monte S, et al. Increased nuchal traslucency in normal karyotype fetuses. J Prenat Med. 2011 Apr;5(2):23-6.
10. Sotiriadis A, Papatheodorou S, Eleftheriades M, Makrydimas G. Nuchal translucency and major congenital heart defects in fetuses with normal karyotype: a meta-analysis. Ultrasound Obstet Gynecol. 2013 Oct;42(4):383-9.
11. Atzei A, Gajewska K, Huggon IC, Allan L, Nicolaides KH. Relationship between nuchal translucency thickness and prevalence of major cardiac defects in fetuses with normal karyotype. Ultrasound Obstet Gynecol. 2005 Aug;26(2):154-7.
12. Snijders RJ, Noble P, Sebire N, Souka A, Nicolaides KH. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10-14 weeks of gestation. Fetal Medicine Foundation First Trimester Screening Group. Lancet. 1998 Aug 1;352(9125):343-6.
13. SIEOG: Società Italiana di Ecografia Ostetrica e Ginecologica e Metodologie Biofisiche [Internet]. Available from: https://www.sieog.it/.
14. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics; Committee on Genetics; Society for Maternal-Fetal Medicine. Screening for Fetal Chromosomal Abnormalities: ACOG Practice Bulletin, Number 226. Obstet Gynecol 2020 Oct;136(4):e48-e69.
15. Minakami H, Maeda T, Fujii T, Hamada H, Iitsuka Y, Itakura A, et al. Guidelines for obstetrical practice in Japan: Japan Society of Obstetrics and Gynecology (JSOG) and Japan Association of Obstetricians and Gynecologists (JAOG) 2014 edition. J Obstet Gynaecol Res. 2014 Jun;40(6):1469-99.
16. Audibert F, De Bie I, Johnson JA, Okun N, Douglas Wilson R, Armour C, et al. No. 348-Joint SOGC-CCMG Guideline: Update on Prenatal Screening for Fetal Aneuploidy, Fetal Anomalies, and Adverse Pregnancy Outcomes. J Obstet Gynaecol Can. 2017 Sep;39(9):805-817.
17. RANZCOG (The Royal Australian and New Zealand College of Obstetricians and Gynecologists) [Internet]. Available from: https://ranzcog.edu.au/.
18. The Fetal Medicine Foundation [Internet]. Available from: www.fetalmedicinefoundation.org,
19. EUROCAT (European Network of Population Based Registries for the Epidemiological Surveillance of Congenital Anomalies) [Internet]. Available from: www.eu-rd-platform.jrc.ec.europa.eu,
20. Sotiriadis A, Papatheodorou S, Makrydimas G. Neurodevelopmental outcome of fetuses with increased nuchal translucency and apparently normal prenatal and/or postnatal assessment: a systematic review. Ultrasound Obstet Gynecol. 2012 Jan;39(1):10-9.
21. Bardi F, Bosschieter P, Verheij J, Attie G, Haak M, Bekker M, et al. Is there still a role for nuchal translucency measurement in the changing paradigm of first trimester screening?. Prenat Diagn. 2020 Jan;40(2):197-205.

22. Tekesin I. Pregnancy outcome in foetuses with increased nuchal translucency - 10-years' experience in a prenatal medical practice. J Obstet Gynaecol. 2020 May;40(4):455-460.
23. Grande M, Jansen FAR, Blumenfeld YJ, Fisher A, Odibo AO, Haak MC, et al. Genomic microarray in fetuses with increased nuchal translucency and normal karyotype: a systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2015 Dec;46(6):650-8.
24. Egloff M, Hervé B, Quibel T, Jaillard S, Le Bouar G, Uguen K, et al. Diagnostic yield of chromosomal microarray analysis in fetuses with isolated increased nuchal translucency: a French multicenter study. Ultrasound Obstet Gynecol. 2018 Dec;52(6):715-721.
25. Hellmuth SG, Pedersen LH, Miltoft CB, Petersen OB, Kjaergaard S, Ekelund C, et al. Increased nuchal translucency thickness and risk of neurodevelopmental disorders. Ultrasound Obstet Gynecol. 2017 May;49(5):592-598.

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