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The clinical impact of the first-trimester nuchal translucency between the 95th–99th percentiles

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Abstract

Objectives: To evaluate the clinical significance of nuchal translucency (NT) between the 95th–99th percentile in terms of typical and atypical chromosomal abnormalities (ACAs), associated fetal congenital defects and postnatal outcome.

Methods: A retrospective cohort study of fetuses with NT between the 95th–99th percentile. Data regarding the rate of associated fetal defects, genetic abnormalities and postnatal outcome were collected.

Results: A total of 306 cases of fetuses with an NT between the 95th–99th percentiles were included. The overall rate of genetic abnormalities was 12.1% (37/306). Chromosomal abnormalities were found in 10.1% (31/306) of cases and 2% were ACA (6/306). Within this group, two were pathogenic Copy Number Variants (CNVs) and four were single gene disorders. The overall rate of fetal congenital defects was 13.7% (42/306). All ACAs were found in fetuses with congenital defects. Postnatally, a new diagnosis of a single gene disorder was made in 0.85% of cases (2/236).

Conclusions: The presence of an NT between the 95th–99th percentiles carries a 10-fold increased risk of fetal defects, representing an indication for referral for a detailed fetal anatomy evaluation. The risk of ACA is mainly related to the presence of fetal defects, irrespective of the combined test risk.

Key points

What's already known about this topic?

- Increased nuchal translucency (NT) is a risk factor for aneuploidies, genetic syndromes and fetal malformations. However, management of NT between the 95th and 99th percentiles is still not clear.

What does this study add?

- Nuchal translucency between the 95th and 99th percentile increases the risk of fetal malformations 10-fold. The risk of genetic anomalies is mainly related to the presence of fetal malformations.

1 | INTRODUCTION

The assessment of nuchal translucency (NT) is an integral part of the first-trimester ultrasound scan, whether or not associated with the assessment of the risk of major fetal aneuploidies at 11^{+0}–13^{+6} weeks.[1,2] The larger the NT value, the higher the risk of adverse pregnancy outcomes, including chromosomal abnormalities, genetic syndromes, fetal congenital malformations and risk of miscarriage or intrauterine demise.[3–5] The presence of an NT ≥ 3.5 mm, which is above the 99th centile irrespective of the gestational age and fetal crown-rump length (CRL), is an established indication for invasive testing.[6,7] The recommended genetic analysis is the Chromosomal Microarray Analysis (CMA) which has a diagnostic yield of 6% for the detection of copy number variants (CNVs) in the presence of fetal malformations and increased NT.[8–10] Considering the increased risk of congenital defects, especially cardiac, a second-trimester detailed ultrasound and echocardiography are recommended when NT is > 99th percentile.[11,12]

However, there is a subgroup of fetuses with an NT between the 95th and the 99th percentiles that have a moderate risk of adverse outcome and whose clinical management is not standardized. Within this population, a risk of 7% of chromosomal abnormalities has been reported, of which 5% is represented by atypical chromosomal abnormalities.[4] The current practice is to recommend an invasive test only in case of high-risk result at the combined test and a fetal karyotype is usually performed. Noteworthy, this group carries an almost doubled risk of fetal congenital defects with a 2% prevalence of congenital heart anomalies, but the decision whether to perform a detailed scan with echocardiography depends on local protocols and facilities.[3,11,13]

The primary aim of this study was to assess the rates of typical and atypical chromosomal abnormalities (ACA) in the group of fetuses with an NT between the 95th and the 99th percentile at the first-trimester scan. The secondary aims were to evaluate the above-mentioned risk in relation to the subgroups of combined test risk (high, intermediate, low), the rate of major fetal congenital defects and the perinatal outcome until the age of 3 years in the presence of NT between 95th–99th percentiles.

2 | METHODS

This is a retrospective study of a cohort of women undergoing first-trimester screening for major fetal aneuploidies at 11^{+0}–13^{+6} weeks of gestation performed in a single tertiary-care center. As we are a referral center, some women were referred for evaluation after the finding of an NT in the 95-99th centile. The study protocol was approved by the Internal Review Board, and patients provided their consent for access to electronically stored information (RC 34/23). The first-trimester combined test was offered to all patients according to our national health system recommendations. The Fetal Medicine Foundation (FMF) algorithm was used for the risk assessment for fetal major aneuploidies and included maternal characteristics and risk factors, maternal serum pregnancy associated plasma protein-A (PAPP-A) and free ß-human chorionic gonadotropin (hCG), and assessment of fetal NT thickness and nasal bone.[14] The gestational age was calculated based on the CRL measurement according to the reference nomograms.[15] All operators were certified by the FMF for the first-trimester scan or supervised by a certified operator. The assessment of NT was performed according to FMF standards. Women with a risk of ≥1:300 for trisomy 21 (T21) or ≥1:100 for trisomy 13 (T13) and trisomy 18 (T18) were considered to be at high risk; women with a risk between 1:300 and 1:999 for T21 and between 1:100 and 1:999 for trisomy 18 and 13 were considered to be at intermediate risk; women with a risk of <1:1000 were considered at low risk. As per local protocol, a basic fetal anatomy survey was performed, including the evaluation of fetal head and chorioid plexus, upper and lower limbs, stomach, abdominal insertion of the cord, and the bladder. In cases where a fetal congenital defect was suspected, a detailed scan with assessment of tricuspid and ductus venosus flow and color Doppler evaluation of the 4-chambers view and V-sign was performed.[1]

Data from 2013 to 2018 were included in the analysis. Inclusion criteria were the following: diagnosis of NT between the 95th–99th percentiles; detailed second-trimester anomaly scan performed by an experienced fetal medicine specialist as per local protocol; and postnatal follow-up of a minimum of three years. Exclusion criteria were first-trimester scan for pregnancy dating only, second-trimester routine scan, and absence of postnatal follow-up.

In line with local protocol, all patients with an NT between the 95th–99th percentile were counseled by a specialist in fetal medicine regarding possible implications taking account of the combined test result. Data from the study of Souka *et al*. were used for counseling.[3] Alternative methods for screening [that is, cell-free DNA test (cfDNA)] or diagnostic options [chorionic villous sampling (CVS) or amniocentesis] were discussed and a genetic counseling was offered. If the couple opted for an invasive test, information on the types of genetic evaluations were provided (QF-PCR, G-banding karyotype and CMA) with their associated implications, including the possibility of uncertain results known as *Variance of Unknown Significance* (VOUS). The samples were collected prenatally by CVS or amniocentesis by fetal tissue biopsy after termination of pregnancy, or

postnatally on neonatal blood, according to genetic indication and/or patient's choice. The karyotype was performed using the G-banding pattern, and CMA was performed using array comparative genomic hybridization (a-CGH) or high-density single-nucleotide polymorphism array (HD-SNP array) techniques. Since 2017, in line with the Italian Society of Human Genetics (SIGU) and the Italian Society of Ultrasound in Obstetrics and Gynecology (SIEOG), our local protocol included QF-PCR and CMA analysis only, while G-banding karyotype was performed only upon specific indications (i.e. one or both parents carrier of a balanced translocation). In case CMA was performed, a blood sample of both parents was taken in order to perform a trio analysis to assess the origin of any CNVs detected.

A detailed second-trimester scan with echocardiography at 20^{+0}–21^{+0} weeks was also offered in the presence of normal karyotype or low-risk combined test, performed by experienced physicians and according to ISUOG guidelines.[16,17] Follow-up scans were performed monthly if abnormal fetal karyotype and/or additional fetal congenital defects were detected. Otherwise, a routine ultrasound scan for growth evaluation was performed for 30–32 weeks.

All neonates were examined by an experienced neonatologist. Prenatal and neonatal findings were recorded in secured databases. Postnatal records stored in an electronic database were reviewed to look for long-term adverse outcomes, with a minimum follow-up of 3 years.

2.1 | Statistical analysis

Categorical variables were reported as absolute and percentage frequencies, while continuous variables were presented as median and interquartile range (IQR). Between-group differences were evaluated using a Chi-square test (or Fisher exact test, when appropriate). Multinomial logistic regression with "low risk" as the base outcome was used to assess if age was associated with an increased probability of being classified as intermediate or high risk. The significance level was set at 0.05. The statistical analyses were performed using the software StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX:182StataCorp LLC.

3 | RESULTS

In the period between 2013 and 2018, there were 6504 pregnant women who underwent the first-trimester combined test. Among these, there were 306 cases with an NT between the 95th–99th percentiles (4.7%). The demographic characteristics of the included population are shown in Table 1. The majority of patients with NT between the 95th–99th percentile (224/306, 73.2%) had the calculation of the first-trimester risk of major fetal aneuploidies through the combined test: 29.5% (66/224) had a low-risk, 21.4% (48/224) had an intermediate risk, and 49.1% (110/224) had a high-risk result, respectively. The remaining cases either chose not to perform further risk assessments (8.5%; 26/306) or underwent invasive testing (18.3%; 56/306).

TABLE 1 Demographic characteristics of the study population.

	N (median, IQR)
Age, years	33 (29–37)
Height, cm	165 (161–170)
Weight, kg	61 (57–69)
BMI	22.6 (20.9–24.9)
	N (%)
Smoking, no	268 (87.6%)
Method of conception	
Natural	297 (97.1%)
Assisted by ovulation drugs/IUI	5 (1.6%)
IVF	4 (1.3%)
Nulliparous, yes	165 (53.9%)
Diabetes	
GDM (diet)	17 (5.6%)
GDM (insulin)	5 (1.6%)
Pregestational diabetes	1 (0.33%)
	N (median, IQR)
Gestational age, weeks	12.3 (12.0–12.6)
Crown rump length, mm	60.4 (55.3–65.6)
Nuchal translucency, mm	2.8 (2.6–3.1)

Note: Data are represented as median and interquartile range (IRE) or number (N) and percentage (%).
Abbreviation: GEM, gestational diabetes mellitus.

The median age of patients in the low-risk group was 30.5 years (IQR 27–33), 32 years (IQR 29–34) in the intermediate-risk group and 35 years (IQR 31–38) in the high-risk group. The distribution of combined test risk categories according to maternal age <35≥ years is shown in Figure 1. For NT between the 95^{th} –99^{th} percentiles, the risk of being classified as intermediate-risk was not significantly different in the two subgroups of women (RR 1.49; 95% CI 0.58–3.78; $p = 0.4$), while the risk of being classified as high-risk was five-fold higher in women ≥35 years compared to women <35 years (RR 5.19; 95% CI 2.46–10.95; $p < 0.001$).

Genetic analyses were performed in 58.8% of cases (180/306) of which 95 were CVS, 81 were amniocentesis and four were post-natal or post-abortion samples. Among these, 66% (119/180) performed a combined risk assessment for major aneuploidies (Table 2). QF-PCR was performed in 26.1% (47/180), G-banding karyotype was performed in 55.6% (100/180) and CMA in 45% (81/180) of cases, respectively. In 3.9% (7/180) of cases, a multi-gene panel sequencing for RASopathies was performed due to the presence of ultrasound findings such as lymphatic jugular sacs, increased nuchal fold or pleural effusion.

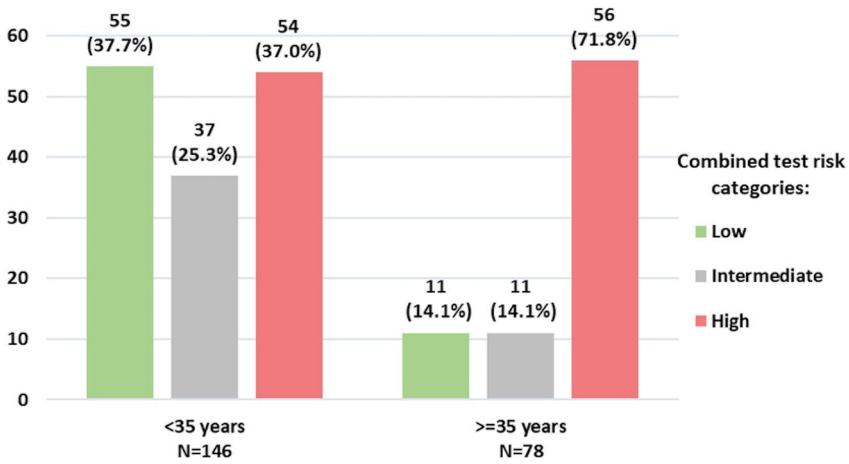

FIGURE 1 The distribution of the first-trimester combined screening test risk categories according to maternal age (<35≥ years). [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Prenatal and/or postnatal genetic testing according to the combined test risk categories and indications.

Type of procedure for genetic analysis	*N* (%)
Overall	**180/306 (58.8)**
CVS	95 (52.8)
Amniocentesis	81 (45)
Postnatal or post-termination samples	4 (2.2)
Indication for an invasive procedure according to the combined test risk categories	**119/180 (66)**
Low-risk	**14/119 (11.8)**
NT 95th–99th percentile	8
First-trimester fetal congenital defect	1
Second-trimester fetal congenital defect	3
Advanced maternal age	2
Intermediate-risk	**19/119 (16)**
NT 95th–99th percentile	11
First-trimester fetal congenital defect	2
Second-trimester fetal congenital defect	2
Advanced maternal age	4
High-risk	**86/119 (72.3)**
NT 95th–99th percentile	85
First-trimester fetal congenital defect	1

Abbreviations: CVS, chorionic villous sampling; N, number; NT, nuchal translucency.

3.1 | Prenatal chromosomal abnormalities and uncommon genetic alterations

Overall, the rate of typical chromosomal abnormalities and ACA in fetuses with an NT between the 95th–99th percentile was 12.1% (37/306). Fetal chromosomal abnormalities were found in 10.1% (31/306), of which 64.5% T21 (20/31), 9.7% T18 (3/31), 6.4% T13 (2/31), 3.2% unbalanced translocation (1/31), 3.2% isochromosome 18q (1/31) and 13% were various types of fetal chromosomal mosaicisms (4/31). ACA was found prenatally in 2% of cases (6/306) (Figure 2). Of these, two were pathogenic CNVs found at CMA analysis and four were single gene disorders searched on the basis of specific ultrasound findings (Table 3).

When classified according to combined test risk categories:

- In the low-risk group, no fetal aneuploidies were found, while two cases had an ACA associated with fetal defects at ultrasound (22q11.23 microdeletion and chromosome 21 microduplication).
- In the intermediate-risk group, there was one case of fetal mosaicism and no ACA.
- In the high-risk group, there were 21 cases of chromosomal abnormalities (21/110: 19.1%) of which 17 cases were T21, one case T18, one case of fetal T21 mosaicism, one case of fetal trisomy 5 mosaicism, and one unbalanced translocation of the chromosomes 17,18. No case of UGA was detected in this group.

3.2 | Fetal congenital defects

Overall, the percentage of fetal congenital defects found in the group of fetuses with NT between the 95th–99th percentile was 13.7% (42/306), of which 2.9% was identified in the first trimester (9/306), 9.2% in the second trimester (28/306) and 1.6% in the third trimester (5/306) of pregnancy. Multiple abnormalities were the most represented group of fetal abnormalities, while congenital heart defects were those with the highest rate of CNVs (Table 4).

According to the combined test risk categories, there were 10.6% (7/66) fetal congenital defects in the low-risk group, 6.25% (3/48) in the intermediate-risk and 10.9% (12/110) in the high-risk ($p = 0.6$). A detailed list of the diagnosed fetal congenital defects is reported in Table S1.

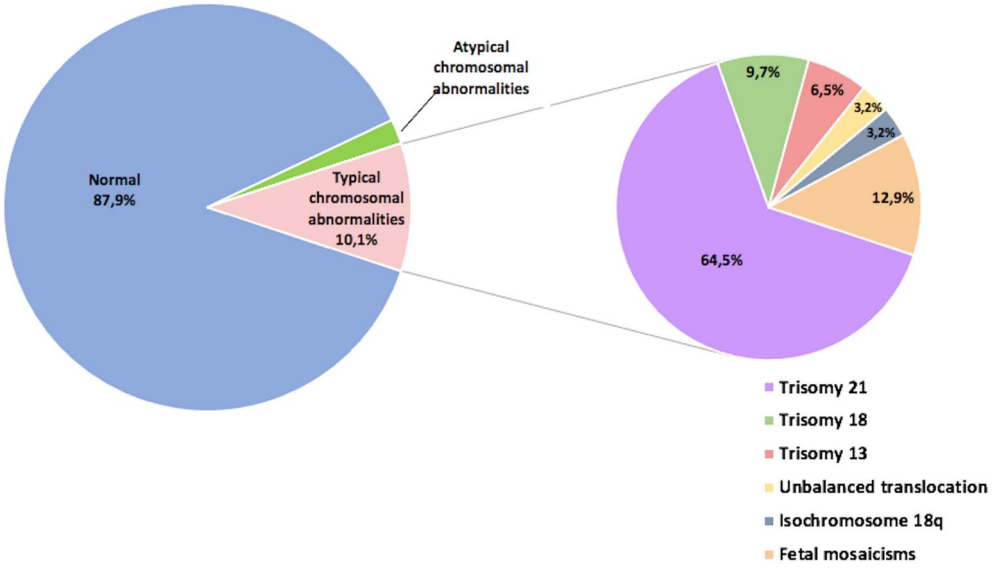

FIGURE 2 The rate of typical and atypical chromosomal/genetic abnormalities in the fetuses with NT between 95th and 99th percentiles. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Characteristics of the fetuses with a prenatal diagnosis of atypical chromosomal abnormalities.

Molecular diagnosis	Classification	GA at diagnosis	NT	Indication for invasive test	Outcome
22q11.23 microdeletion, de novo	Pathogenic	12 + 3	2.3 mm	CHD (tricuspid regurgitation, single vessel at the V-sign)	Miscarriage
1q21.1q21.2 microduplication	Likely pathogenic	20 + 2	3.1 mm	Ventricular septal defect	Livebirth
Cystic fibrosis	Pathogenic variants	19 + 6	2.6 mm	Hyperechogenic bowel	TOP
Meckel-Gruber syndrome	Pathogenic variants	20 + 0	3 mm	Hyperechogenic kidneys, polydactyly, small bladder	TOP
L1CAM-related disease	Pathogenic variant	16 + 0	3.2 mm	Hydrocephaly, intra-familial recurrency	TOP
Noonan syndrome	Pathogenic variant	20 + 2	3.1 mm	Jugular lymphatic sacs, bilateral pyelectasis	TOP

Abbreviations: CHD, congenital heart disease; GA, gestational age; NT, nuchal translucency; TOP, termination of pregnancy.

3.3 | Perinatal outcome

In total, 77% of fetuses with NT between the 95th–99th percentile were born alive (236/306) and 13% (40/306) miscarried or pregnancies were terminated due to chromosomal/genetic abnormality and/or fetal congenital defect. In one case (0.3%; 1/306), neonatal death occurred in a newborn with prenatal diagnosis of polymicrogyria and single nucleotide variant in *PTEN* gene mutation diagnosed postnatally. Twenty-nine patients were lost to follow-up (9.5%; 29/306). Of the 236 cases that reached the term of pregnancy, excluding the neonatal death, 87.8% (208/236) had no short- or long-term adverse postnatal outcome, 8.9% (21/236) had a new diagnosis/confirmation of major congenital malformation, and 3.4% (8/236) had a diagnosis of abnormal neurological outcome with different degrees of severity, from language disorders to intellectual disability. A post-natal genetic evaluation was requested in 3.81% of cases (9/236), and the indications are summarized in Table S2. Further molecular evaluations, such as targeted or whole exome gene sequencing, were performed in 8 of 9 cases. A specific genetic condition was documented twice: a *PTEN*-related disease and an autosomal recessive sensorineural hearing loss related to the *MYO15* A gene (0.85%; 2/236). In one case, a specific molecular investigation identified two maternally inherited VOUS in disease genes, which may have partially contributed to the phenotype. For the other cases, further genetic testing was negative.

4 | DISCUSSION

As per current guidelines, the indication for invasive testing in fetuses with an NT between the 95th–99th percentiles is driven by the result of the combined test and offered only for high-risk result.[7,18] Although previous studies have shown that these fetuses have an increased risk of adverse outcomes, the indication for referral scan and/or echocardiography is universally accepted only for NT ≥ 99th percentile. The advent of the cfDNA test and its widespread use in clinical practice has prompted some authors to investigate whether performing CMA in this subgroup of fetuses may identify CNVs that

TABLE 4 Distribution of fetal congenital defects according to the system and genetic analysis result.

		Genetic analysis results				
Structural anomaly type (*n*)	***N* = 42 (%)**	**Normal (*n*, %)**	**Typical chromosomal abnormalities (*n*, %)**	**CNVs (n, %)**	**Monogenic abnormalities (*n*, %)**	**Total number of genetic diseases per system (*n*, %)**
Multiple defects (15)	15 (35.7)	8 (53.3)	5(33.3)	0 (0)	2 (13.3)	7 (**46.7**)
Central nervous system (8)	8 (19)	6 (75)	1 (12.5)	0 (0)	1 (12.5)	2 (**25**)
Genito-urinary (5)	5 (11.9)	5 (100)	0 (0)	0 (0)	0 (0)	0 (**0**)
Cardiac (5)	5 (11.9)	1 (20)	1 (20)	2 (40)	0 (0)	3 (**60**)
Gastro-enteric (3)	3 (7.1)	1 (33.3)	1 (33.3)	0 (0)	1 (33.3)	2 (**66.7**)
Skeletal (3)	3 (7.1)	2 (66.7)	1 (33.3)	0 (0)	0 (0)	1 (**33.3**)
Thorax (3)	3 (7.1)	3 (100)	0 (0)	0 (0)	0 (0)	0 (**0**)

would be missed if only cfDNA is performed. Some studies reported on the rate of CNVs identified by invasive testing for NT values between 3.0 and 3.4 mm,[19–22] while others included the whole population of NT ≥ 95th percentile.[23–26] Overall, the reported rate of pathogenic CNVs potentially diagnosable by CMA varied between 1.4% and 2.6%. Some studies did not find any difference in the rate of CNVs between the 95th–99th percentile group and for NT > 3.0 mm,[24] while others found a significant increase only for NT > 3.0 mm.[19]

In our cohort of fetuses with NT between the 95th–99th percentiles, we found a rate of ACA of 2% of which pathogenic CNVs were 1%, similar to the general population.[9] The differences from previous studies may be explained by the fact that we included all cases, not just those undergoing invasive testing. Moreover, none of these articles reported the impact of NT between the 95th–99th percentile in relation to the results of the combined test. Our data show that the combination of a high-risk result and NT between the 95th–99th percentiles would drive the women's decision toward an invasive test in 72% of cases even in the absence of fetal congenital defects. Conversely, invasive testing has been chosen in 12% and 16% of cases of low and intermediate risk, indicating that the result of the combined test may reassure the women notwithstanding the borderline value of the NT, after a proper counseling. In this particular subgroup of women, the rate of ACA is comparable to that of the general population, and cfDNA may be considered as an option if the couple wants to be reassured further, albeit informing the couple that cfDNA is not a substitute for invasive testing.

The role of a detailed ultrasound examination seems to be particularly important in cases of NT between the 95th–99th percentile. Major CHD is present in 36.5% of fetuses with NT values between the 95th–99th percentile and 21.3% of fetuses with an NT ≥ 99th percentile.[11–14,26,27] Despite this, fetal echocardiography is recommended by some guidelines for NT values > 3.0 mm or >99th percentile.[1,28–30] Our study showed that fetuses with an NT between the 95th–99th percentile have a 10-fold increased risk of fetal malformation, which may constitute an indication for referral for a detailed anatomy evaluation, as found by the study by Bardi *et al.*, which even report an association rate of 20%.[31] Moreover, ACA was found only in fetuses carrying a fetal congenital malformation. This highlights two aspects: the importance of the diagnosis of a congenital defect and that the second-level genetic analysis may be restricted to this group of fetuses, especially if the combined test is low or intermediate. These findings are consistent with recently published studies on the additional values of exome sequencing (ES) in fetuses with an isolated NT ≥ 3.5 mm throughout pregnancy, where a relatively low rate of diagnostic variants was found (1.8%). On the contrary, in the presence of congenital fetal defects, the diagnostic yield by ES increased up to 30%. [34] In this view, the role of a detailed ultrasound, already in the first trimester, becomes even more important and it should not be replaced by cfDNA test. A detailed anomaly scan with fetal echocardiography should be performed in all fetuses with an NT between the 95th–99th centile at a gestational age of 16 and/or for 20 weeks, according to local facilities.

The strength of this study is that we included all cases of fetuses with an NT between the 95th–99th percentile irrespective of the combined test risk and regardless of whether a genetic analysis was performed. Moreover, having a sufficiently long postnatal follow-up, our data better reflect the real frequency of genetic conditions and fetal congenital malformations in these fetuses. The main limitations are the small sample size with a rather small number of pathogenic results and the percentage of patients lost to follow-up that may have reduced the robustness of the statistical analysis. Furthermore, we do not have data regarding the group of fetuses with NT < 95th centile and the fact that we are a referral center could have led to an overestimation of affected fetuses. Finally, our information regarding cfDNA was incomplete as it was only provided privately.

5 | CONCLUSIONS

The presence of an NT between the 95th–99th percentile carries a 10-fold risk of fetal congenital malformations and should be an indication for referral for a detailed evaluation of fetal anatomy. The

diagnosis of ACA is linked to the presence of fetal congenital malformations, regardless of the combined test risk. In women with a high-risk result at the combined test, the greatest risk is represented by fetal aneuploidies, and thus, invasive testing is indicated. In low- and intermediate-risk women, after normal fetal anatomy has been established, cfDNA may be an option for couples who want further reassurance.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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