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ORIGINAL RESEARCH

Outcomes associated with fetal nuchal translucency between 3.0 and 3.4 mm in the first trimester

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Abstract

Introduction: Decisions concerning nuchal translucency (NT) between 3.0 and 3.4 mm remain controversial, particularly regarding whether to first calculate the combined first trimester screening test or to proceed directly with invasive testing. The literature suggests an increased risk of chromosomal aberration, as well as pathogenic copy number variations (CNVs) on chromosomal microarray, for fetuses with NT between 3.0 and 3.4 mm. The aim of this study was to describe genetic findings of fetuses with NT between 3.0 and 3.4 mm in the first trimester. The secondary objective was to describe ultrasound findings and adverse outcomes for these fetuses. The third objective was to compare genetic, ultrasound findings and adverse outcomes of fetuses with NT between 3.0 and 3.4 mm to those with NT ≥3.5 mm.

Material and Methods: We conducted an observational, retrospective study in a referral center between 2017 and 2022. Genetic and ultrasound findings were compared between fetuses with NT between 3.0 and 3.4 mm and those with NT≥3.5 mm. An adverse outcome was defined as one of the following: miscarriage, perinatal death (stillbirth or neonatal death) or termination of pregnancy at parental request, and all major abnormalities or genetic disorders diagnosed before or after delivery.

Results: We included 404 fetuses with NT≥3.0 mm who had invasive testing with available karyotype and chromosomal microarray, among whom 20.8% (84/404) had NT between 3.0 and 3.4 mm. The rate of adverse outcomes among fetuses with NT between 3.0 and 3.4 mm was 32.1% (27/84). The rates of chromosomal aberration, pathogenic CNVs, and major ultrasound abnormalities were 16.7% (14/84), 6.0%(5/84), and 9.2% (6/65), respectively, for fetuses with NT between 3.0 and 3.4 mm. In comparison, fetuses with NT greater than 3.5 mm had higher rates of chromosomal aberration and major ultrasound abnormalities, with rates of 47.5% (152/320) and 30.2% (49/162) respectively compared to 16.7% (14/84) and 9.2% (6/65) for fetuses with

Abbreviations: CMA, chromosomal microarray; CNV, copy number variations; NT, nuchal translucency; TOP, termination of pregnancy; VOUS, variants of unknown significance; WG, weeks of gestation.

NT between 3.0 and 3.4 mm ($p < 0.001$ for both comparisons). However, the rate of pathogenic CNVs was not significantly different between the two groups, with rates of 1.9% (6/320) for NT≥3.5 mm and 6.0% (5/84) for NT between 3.0 and 3.4 mm ($p = 0.06$).

Conclusions: The rate of chromosomal aberration and pathogenic CNVs on chromosomal microarray is high among fetuses with NT between 3.0 and 3.4 mm, although these rates remain lower than those observed among fetuses with NT≥3.5 mm.

KEYWORDS
chromosomal aberrations, chromosomal microarray, copy number variations, nuchal translucency, prenatal diagnosis

1 | INTRODUCTION

Increased nuchal translucency (NT) is an ultrasound sign of aneuploidies in the range of 20%–35%,[1,2] but also of other fetal disorders, including genetic syndromes and structural defects, mainly congenital heart defects. Increased NT is currently defined as a nuchal thickness greater than the 99th percentile or 3.5 mm regardless of gestational age in the first trimester.

The NT range between the 95th and 99th centiles varies according to gestational age.[3]

While the presence of NT ≥3.5 mm is a recognized indication for invasive testing, decisions concerning NT between 3.0 and 3.4 mm remain controversial depending on the country[4,5] and center.[6] In France, the French health authority recommends invasive testing only for NT ≥3.5 mm,[7] whereas 23.1% of centers perform invasive testing from an NT threshold of 3.0 mm.[6]

Recently, chromosomal microarray (CMA) analysis has been implemented for etiological assessment of fetuses with increased NT, as it improves diagnostic yield thanks to its higher resolution in comparison with conventional karyotyping.[5,8] In the meta-analysis of Grande et al., the authors showed that CMA allowed a 4.0% incremental yield of detecting copy number variations (CNVs) in fetuses with isolated increased NT and normal karyotype.[8] However, the majority of studies included in this meta-analysis were conducted on a population with NT greater than 3.5 mm,[8] as few countries have a policy of invasive testing for increased NT below 3.5 mm.[4]

A recent literature review suggested that the subgroup of NT between 3.0 and 3.4 mm is at increased risk of chromosomal abnormalities as well as of pathogenic CNVs on CMA, with a rate of 13.5% and 3.4%, respectively.[9] This review is limited by the selection biases of the population, as it included fetuses with NT between 3.0 and 3.4 mm undergoing invasive testing because of an increased risk after combined testing, and not only because of an apparently isolated NT of 3.0–3.4 mm. Moreover, data from different countries are heterogeneous.[9]

The aim of our study was to describe genetic findings of fetuses with NT between 3.0 and 3.4 mm in the first trimester. The secondary objective was to describe ultrasound findings and adverse outcomes for these fetuses. The third objective was to compare genetic findings, ultrasound findings and pregnancy outcomes of fetuses with NT between 3.0 and 3.4 mm to those with NT ≥3.5 mm.

Key message

Fetuses with nuchal translucency between 3.0 and 3.4 mm have high rates of chromosomal aberrations, highlighting the importance of prenatal screening. Our findings support proposing routine invasive testing for fetuses with nuchal translucency between 3.0 and 3.4 mm.

2 | MATERIAL AND METHODS

2.1 | Study design

We performed an observational, retrospective, single-center study at a university referral center (Pellegrin university hospital), located in Bordeaux, France, over a five-year period between June 1st, 2017, and July 1st, 2022.

2.2 | Inclusion/exclusion criteria

We included singleton pregnancies with isolated (i.e., no other ultrasound findings at the first trimester scan) increased NT diagnosed on first-trimester ultrasound. The measurements were obtained between 11 and 13^{+6} weeks of gestation (WG), ensuring the fetal crown-rump length was within the recommended range for NT assessment. To ensure high measurement accuracy, the NT assessment adhered to the quality criteria specified by the Herman score.

The increased NT was defined by a thickness greater than or equal to 3.0 mm. The exclusion criteria were multiple pregnancies, and the absence of invasive testing with both karyotyping and CMA.

Both increased NT and cystic hygroma were included without distinction, as both entities are associated with chromosomal anomalies and require the same diagnostic work-up.[10]

2.3 | Collection of data

Women were identified through the electronic database. Clinical characteristics, genetic findings and pregnancy outcomes were abstracted from the clinical records.

2.4 | Management and follow-up

The first trimester scan and screening test are offered to all pregnant women as part of routine prenatal care in France. The scans are performed by certified sonographers who are trained and accredited in fetal ultrasonography. The first trimester screening includes a combination of NT measurement, maternal serum biochemistry, and maternal age to assess the risk of chromosomal abnormalities. Invasive testing is offered to pregnancies identified as being at risk due to high-risk first-trimester screening results, an increased NT greater than 3.0 mm, or the presence of ultrasound anomalies.

In the study center, the management policy was to offer invasive testing to all women whose fetus had NT greater than 3.0 mm. Karyotyping and CMA were performed either by chorionic villus sampling or amniotic fluid sampling, depending on the gestational age at which patients were referred to our center.

CNVs were considered variants of unknown significance (VOUS) when: (a) the chromosomal region contained no gene or transcript at all; (b) there was no report of a clinically abnormal phenotype associated with them; (c) dosage sensitivity for genes mapping to the region was unlikely or not demonstrated; and (d) CNVs did not meet the criteria for classification as pathogenic or benign.

In the case of normal karyotype and CMA, a detailed structural ultrasound examination was systematically scheduled at 16–18 WG, and a second examination was scheduled at 22–24 WG, then monthly until delivery. Fetal echocardiography was performed by a fetal cardiologist at least once during pregnancy. All follow-up ultrasounds were conducted by specialized sonographers in fetal medicine within the same center.

2.5 | Outcomes

An adverse outcome was defined by one of the following: miscarriage, perinatal death (stillbirth or neonatal death) or termination of pregnancy (TOP) at parental request, and all major abnormalities or genetic disorders (defined by an alteration or mutation in DNA leading to a genetic syndrome) diagnosed before or after delivery.[10]

Major fetal abnormalities were defined as those requiring medical and/or surgical treatment or conditions associated with neurological impairment.[11] Minor abnormalities were defined as those that did not require any treatment within the first year of life.[11] Proportions of ultrasound abnormality were calculated among fetuses with normal karyotype and CMA.

Follow-up of neonates was available until discharge from hospital.

2.6 | Statistical analyses

Data for quantitative variables are expressed as mean with standard deviation (SD). Categorical data are expressed as percentages with one decimal point. Quantitative variables are compared using Student's *t*-test or the Wilcoxon–Mann–Whitney test when appropriate and categorical variables are compared using a the Chi2 test or Fisher exact test when appropriate.

The statistical analysis was performed using Stata 14 software (StataCorp LP, College Station, TX, USA).

3 | RESULTS

3.1 | Population

During the study period, among the 26 472 screened fetuses, 466 had NT greater than or equal to 3.0 mm, i.e., 1.8% of the whole population. We excluded 21 women with multiple pregnancies, 11 women without invasive diagnostic testing and 30 women without CMA analyzed on the diagnostic testing. Among the 11 women who declined invasive testing, none chose to terminate the pregnancy, as the test results would not have changed the course of their pregnancies. Thus, 404 fetuses with NT ≥3.0 mm were included (Figure 1). In the final sample, there were 20.8% ($n = 84/404$) of fetuses with NT between 3.0 and 3.4 mm and 79.2% ($n = 320/404$) with NT greater than or equal to 3.5 mm. Maternal demographic characteristics and ultrasound first-trimester findings are summarized for the whole population of fetuses in Table 1.

3.2 | Genetic findings for fetuses with NT between 3.0 and 3.4 mm

Among the fetuses with NT between 3.0 and 3.4 mm, the rate of chromosomal abnormalities diagnosed on karyotyping by conventional cytogenetic analysis was 16.7% ($n = 14/84$), including mainly trisomy 21, with a rate of 10.7%, (9/84) (Table 2). High-resolution CMA revealed additional pathogenic CNVs in 6.0% (5/84) of fetuses with normal karyotype on conventional cytogenetic analysis. Pathogenic CNVs detected on CMA are detailed in Table 2.

3.3 | Outcomes and ultrasound findings for fetuses with NT between 3.0 and 3.4 mm

Among the 84 fetuses with NT between 3.0 and 3.4 mm, there were no cases of miscarriage, stillbirth, or neonatal death. However, there was a 27.3% ($n = 23/84$) rate of TOP and a 4.8% ($n = 4/84$) rate of livebirth with genetic abnormality.

Thus, the rate of adverse outcome was 32.1% (27/84), with 14 cases of chromosomal aberration, 5 cases of pathogenic CNVs on CMA, 6 fetuses with major ultrasound abnormality, 1 TOP for

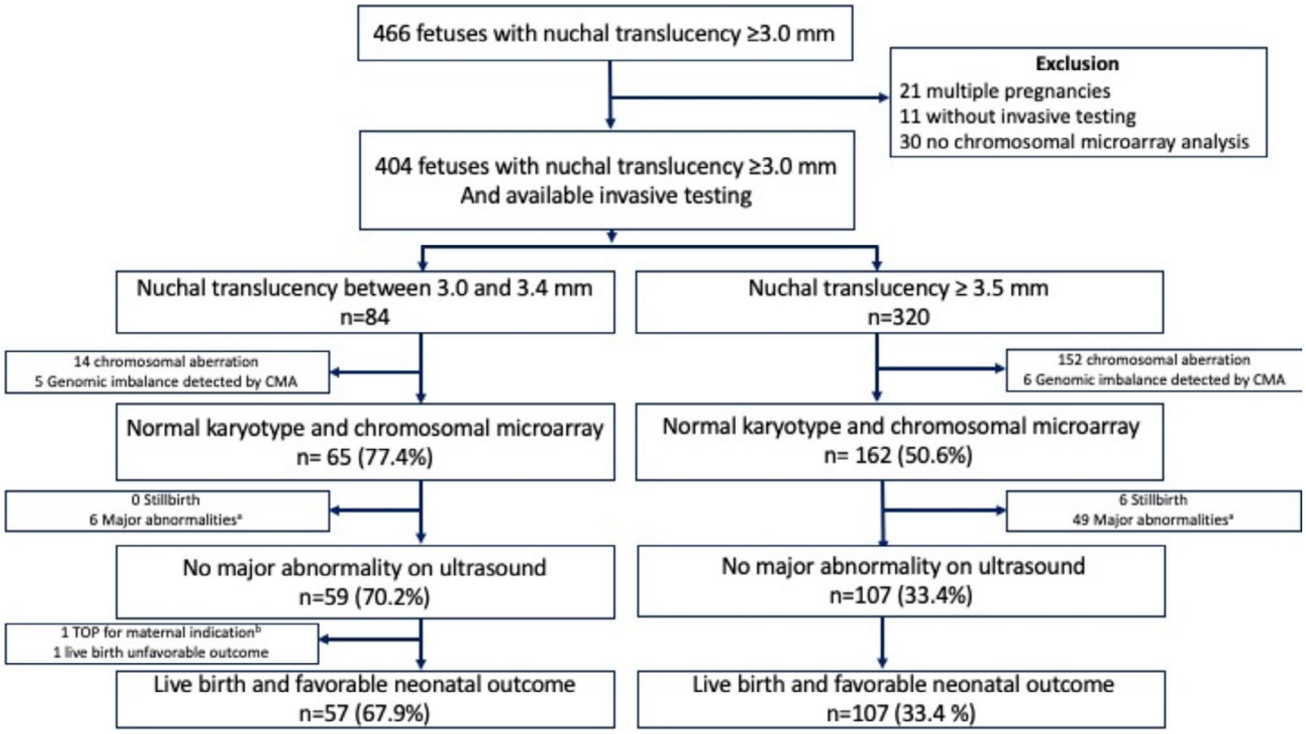

FIGURE 1 Flow chart. (a) Major fetal abnormalities were defined as those requiring medical and/or surgical treatment or conditions associated with neurological impairment. (b) Termination of pregnancy for severe preeclampsia at 20 weeks of gestation. CMA, Chromosomal microarray; TOP, Termination of pregnancy.

maternal indication and 1 fetus with at least two minor ultrasound abnormalities diagnosed with Noonan syndrome (Table 3). In one case with an NT of 3.2 mm, TOP was performed for maternal indication, as the woman presented severe and early preeclampsia at 20^{+0} WG. In this case, there was no structural abnormality or fetal growth restriction.

Among the 65 fetuses with normal karyotype and CMA, the ultrasound follow-up diagnosed a significant major abnormality in 9.2% of cases (6/65), which led to a TOP in all cases at parental request, and at least two minor ultrasound abnormalities in 2.0% of cases (2/65). A fetus with an NT of 3.3 mm had two minor ultrasound abnormalities: persistent increased NT and mild hydrothorax. This case was tested with a panel of RASopathies because of these associated signs, leading to a prenatal diagnosis of Noonan syndrome.

3.4 | Comparison of outcomes according to NT measurement

The two groups did not differ except for maternal age and invasive diagnostic testing. In the group of fetuses with NT between 3.0 and 3.4 mm, women were significantly younger than those in the group of NT greater than 3.5 mm: 31.4 ± 5.8 vs 32.9 ± 5.8 (Table 1) ($p = 0.03$).

Women whose fetuses had NT between 3.0 and 3.4 mm were less likely to undergo chorionic villus sampling than amniotic fluid sampling, compared with women whose fetuses had NT greater than 3.5 mm: 80% (67/85) vs 93.4% (299/320), respectively ($p < 0.001$).

The rate of chromosomal aberration was significantly higher among fetuses with NT ≥3.5 mm in comparison with fetuses with NT between 3.0 and 3.4 mm: 47.5% (152/320) vs. 16.7% (14/84) ($p < 0.001$) (Table 3). However, the rate of pathogenic CNVs on CMA was not different between the two groups: 6.0% (5/84) in the group of fetuses with NT between 3.0 and 3.4 mm vs. 1.9% (6/320) in the group of fetuses with NT ≥3.5 mm ($p = 0.06$).

In the subsequent ultrasound follow-up of fetuses with normal karyotype and CMA, the rate of major abnormality was significantly higher among fetuses with NT ≥3.5 mm in comparison with fetuses with NT between 3.0 and 3.4 mm: 30.2% (49/227) vs. 9.2% (6/65) ($p < 0.001$). Specifically, among the 6 fetuses with NT between 3.0 and 3.4 mm, we identified 3 cases of congenital heart defects (one with left ventricular hypoplasia, one with Fallot's tetralogy, and one with right ventricular hypoplasia) and 3 cases of polymalformative syndromes, including one with VACTERL association, one with complete agenesis of the corpus callosum, posterior fossa anomaly, and congenital diaphragmatic hernia and one with hydrops fetalis characterized by bilateral pleural effusion, subcutaneous edema and polyhydramnios.

The rate of persistent increased NT was similar between the two groups: 4.6% (3/65) in the group of fetuses with NT between 3.0 and 3.4 mm vs. 6.2% (10/162) in the group of fetuses with NT ≥3.5 mm ($p = 0.65$).

TABLE 1 Women's demographic and obstetrical characteristics according to nuchal translucency measurement.

Women's characteristics	NT between 3.0 and 3.4 mm	NT ≥3.5 mm	
	n = 84	*n* = 320	*p*-value
Age m ± SD (years)	31.4 ± 5.8	32.9 ± 5.8	**0.03**
Geographic origin			0.65
• Caucasian *n* (%)	63 (75.0)	242 (75.6)	
• Maghreb *n* (%)	17 (20.2)	53 (16.6)	
• Black Africa *n* (%)	2 (2.4)	12 (3.8)	
• Asia *n* (%)	1 (1.2)	6 (1.9)	
• Others *n* (%)	3 (3.6)	5 (1.6)	
Consanguinity, *n* (%)	3 (3.6)	9 (2.8)	0.72
Smoking during pregnancy, *n* (%)	11 (13.0)	34 (11.0)	0.15
Pre-existing diabetes, *n* (%)	1 (1.2)	7 (2.2)	1.0
Obstetrical history			
Nulliparous, *n* (%)	36 (43.0)	117 (37.0)	0.29
Assisted reproductive technology, *n* (%)	1 (1.2)	12 (3.8)	0.32
Previous termination of pregnancy, *n* (%)	2 (2.4)	8 (2.5)	1.0
Previous stillbirth, *n* (%)	0 (0.0)	3 (0.7)	0.3
First-trimester ultrasound findings (between 11 + 0 WG and 13 + 6 WG)			
Gestational age m ± SD (WG)	13.0 ± 2.6	12.7 ± 2.4	**<0.01**
Craniocaudal length m ± SD (mm)	64.2 ± 9.4	60.7 ± 8.7	**<0.01**
Nuchal translucency m ± SD (mm)	3.2 ± 0.1	5.4 ± 2.1	**<0.001**
Invasive diagnostic testing			
Chorionic villus sampling, *n* (%) Amniotic fluid sampling, *n* (%)	67 (80.0) 17 (20.0)	299 (93.4) 21 (6.6)	**<0.001**

Note: Data are presented as number (percentage) or mean (± standard deviation).

Bold value indicates statistically significant results with a *p*-value < 0.05

TABLE 2 Details of CNVs identified by CMA according to nuchal translucency measurement.

Anomalies detected on the CMA	Outcome
Nuchal translucency between 3.0 and 3.4 mm	
22q11.21 duplication; 2.5 Mb inherited from mother	Live birth
22q11.21 duplication; 2.5 Mb De novo	Live birth
15q11.2q13.1 deletion; 5.7 Mb De novo	Termination of pregnancy 12^{+4}WG
9q34.3 deletion (13 genes included *NOTCH1*); 490 kb De novo	Termination of pregnancy 15^{+0}WG
1q43 deletion (included gene *CGRM3*); 917 kb inherited from mother	Live birth
Nuchal translucency ≥3.5 mm	
22q11.21 duplication; 2.5 Mb inherited from mother	Live birth
6q24.3.q25.3 deletion; 50 Mb De novo	Termination of pregnancy 20^{+0}WG
8q11.1q11.21 duplication; 4.3 Mb De novo	Live birth
4q35.2 deletion + 22q12.3q13.33 duplication; 3.3 Mb/18.7 Mb De novo	Termination of pregnancy 19^{+3}WG
20p12.3p12.2 deletion; 2.9 Mb De novo	Termination of pregnancy 14^{+1}WG
Xp22.33 deletion; 300 kb De novo	Termination of pregnancy 20^{+0}WG

The fetuses with NT between 3.0 and 3.4 mm had a rate of adverse outcomes of 32.1% (27/84) compared to 66.5% (213/320) for fetuses with NT ≥3.5 mm (Table 3).

4 | DISCUSSION

In the group of fetuses with NT between 3.0 and 3.4 mm, the rates of chromosomal aberration and pathogenic CNVs detected by CMA were 16.7% and 6.0%, respectively. The rate of adverse outcomes in this group was 32.1%, compared to 66.5% for fetuses with NT ≥3.5 mm.

In our series, the rate of chromosomal abnormalities among fetuses with NT between 3.0 and 3.5 mm was high (16.7%). Very few studies have assessed the rate of chromosomal aberrations in this population, as international recommendations stipulate invasive testing for NT greater than 3.5 mm. In the case of NT between 3.0 and 3.4 mm, the strategy is two-stage screening with risk calculation followed by noninvasive prenatal testing or invasive testing in high-risk cases.[9] This finding underscores the importance of performing invasive testing in fetuses with NT measurements between 3.0 and 3.5 mm.

In cases of normal karyotype and CMA, increased NT is associated with a wide range of structural defects. In our study, the rate of major abnormalities on ultrasound in fetuses with NT between 3.0 and 3.4 mm and normal karyotype was 9.4%. In a cohort of 451 chromosomally normal fetuses and NT above the 95th centile, Bilardo et al. studied adverse outcome according to NT thickness.[10] The rate of adverse outcomes (same definition as ours) was 8.5% among the 223 fetuses with NT between the 95th centile and 3.4 mm and a normal karyotype, suggesting a possible increased risk in this subgroup compared to the general population.[10] However, in this study, there was no control group of fetuses with a normal NT measurement for comparison.[10] In another large cohort of 1901 pregnancies

TABLE 3 Genetic and ultrasound findings according to nuchal translucency measurement.

Genetic findings	NT between 3.0 and 3.4 mm *n* = 84	NT ≥3.5 mm *n* = 320	*p*-value
Normal karyotype and chromosomal microarray analysis	65 (77.4)[a]	162 (50.6)[a]	**<0.001**
Chromosomal aberration (aneuploidies or unbalanced rearrangements)	14 (16.7)	152 (47.5)	**<0.001**
Trisomy 21	9 (10.7)	69 (21.6)	0.18
Trisomy 18	3 (3.6)	40 (12.5)	1.00
Monosomy X	1 (1.2)	21 (6.6)	0.70
Trisomy 13	1 (1.2)	15 (4.7)	1.00
Triploidy	0 (0.0)	4 (1.25)	1.00
Unbalanced rearrangement	0 (0.0)	3 (0.9)	1.00
Pathogenic copy number variation detected by chromosomal microarray (excluding VOUS)	5 (6.0)	6 (1.9)	0.06
Ultrasound findings[b]		***n* = 162**	
No abnormality	48 (73.8)	80 (49.4)	<0.001
Stillbirth	0 (0.0)	6 (3.7)	0.19
Major abnormalities[c]	6 (9.2)	49 (30.2)	<0.001
Isolated minor abnormalities[d]	9 (13.8)	26 (16.0)	0.68
Persistent increased nuchal translucency	3 (4.6%)	10 (6.2)	0.65
≥ 2 minor abnormalities	2 (3.1)	1 (0.6)	0.20
Adverse outcome[e]	27/84 (32.1)	213/320 (66.5)	<0.001

Note: Data are presented as number (percentage).

[a]1 VOUS was detected by chromosomal microarray among fetuses with NT between 3.0 and 3.4 mm and 2 VOUS among fetuses with NT greater than 3.5 mm.

[b]Among fetuses with normal karyotype and chromosomal microarray.

[c]Major fetal abnormalities were defined as those requiring medical and/or surgical treatment or conditions associated with neurological impairment.[11]

[d]Minor abnormalities were those that did not require any treatment within the first year of life.[11]

[e]An adverse outcome was defined by miscarriage, perinatal death (stillbirth or neonatal death), termination of pregnancy at parental request, or all major abnormalities or genetic disorders diagnosed before or after delivery.[10]

with NT above the 95th percentile, the rate of abnormalities, including both genetic and structural abnormalities, was 21% for fetuses with NT between the 95th and 99th percentile.[12] In this population, the prevalence of single-gene disorders, submicroscopic, chromosomal and structural abnormalities was 0.6%, 0.9%, 13.8%, 5.9%, respectively.[12]

Thus, our findings show that fetuses with NT between 3.0 and 3.4 mm are at high risk of genetic and structural abnormalities. The higher numbers of chromosomal aberrations observed in our study compared to other studies may be due to differences in population characteristics or study methodologies.

The policy management of increased NT in the first trimester differs according to countries: in Denmark and the Netherlands, invasive testing is considered for fetuses with NT between 3.0 and 3.4 mm with an increased combined risk (>1/200 or 1/300),[9] whereas in Israel, all fetuses with NT greater than 3.0 mm have been considered.[4] Different cutoffs have been investigated and reported in previous studies, such as 3.0 mm or the 95th centile.[12,13] There is a lack of consensus about the cutoff that should be used for invasive testing, although many recent data suggest reducing this threshold for invasive testing. The American College of Obstetricians and Gynecologists and the Society for Maternal Fetal Medicine now recommend a threshold of 3.0 mm to consider invasive testing,[14] whereas the International Society of Ultrasound in Obstetrics and Gynecology did not define a value for increased NT.[15]

The yield of CMA in fetuses with increased NT and normal karyotype has now been well demonstrated in the meta-analysis published by Grande et al.[8] However, in most of the studies included in this meta-analysis, increased NT was defined by a measurement greater than 3.5 mm.[8] Recent retrospective data suggest

that the yield of CMA after normal karyotype was also increased in fetuses with increased NT between the 95th percentile and 3.5 mm.[16,17] In a multicenter retrospective study conducted in Israel, pathogenic CNVs were found in 1.7% (8/462), 6.5% (11/170) and 13.8% (19/138) of fetuses with no abnormal findings on ultrasound but with NT ≤2.9 mm, NT of 3.0–3.4 mm and NT ≥3.5 mm, respectively.[16] In another study of 192 fetuses with NT above 2.5 mm, there was no significant difference in the incidence of clinically significant CNVs between fetuses with NT of 2.5–3.4 mm and those with NT ≥3.5 mm: 1.6% (2/119) vs 5.5% (3/55) ($p > 0.05$).[17] These studies as well as our findings suggest that CMA tends to provide more information for fetuses with isolated, mildly increased NT between 3.0 and 3.4 mm.

One of the strengths of our study is that it involves a large sample of 404 consecutive patients in an unselected population from a single referral center, with exhaustive data until discharge from hospital. In our study, 1.8% of fetuses had an NT >3.0 mm, which falls within the range reported in other populations,[18] underscoring the consistency of our findings with established data. The difference in the likelihood of undergoing chorionic villus sampling vs amniotic fluid sampling may be due to the timing of referral for invasive testing, with women whose fetuses had NT measurements between 3.0 and 3.4 mm potentially perceiving a lower risk and opting for amniocentesis later in pregnancy, whereas those with NT measurements greater than 3.5 mm, associated with a higher perceived risk, are more likely to undergo chorionic villus sampling earlier. However, this does not appear to have changed our results regarding genetic findings, ultrasound findings, and outcomes.

We acknowledge some limitations of our study. The retrospective nature of our study did not allow assessment of children's outcomes at 6 months and 1 year according to the standardized clinical examination and questionnaire to the parents that have been used in previous studies.[19] We did not include a comparison with fetuses having NT <3.0 mm due to the absence of systematic invasive diagnostic testing in this group, which represents a limitation difficult to overcome. Additionally, it should be noted that serum markers were not collected for fetuses with NT greater than 3.0 mm, as we considered that an increased NT is strongly associated with chromosomal abnormalities and may constitute an indication for invasive diagnostic testing. Including such data would have provided additional insight into whether these pregnancies would have been classified as high-risk based on combined first-trimester screening and how elevated their risk would have been. This information could also enhance counseling for pregnant couples when they are deciding whether to proceed with invasive testing. Finally, inter- and intra-observer variability in NT measurements could influence our results. To minimize this variability, we used a standardized follow-up protocol and applied strict quality criteria for NT measurements, all performed by sonographers specialized in fetal medicine.

Our data provide additional arguments to propose routine invasive testing to all women with a fetus with NT greater than 3.0 mm at the first trimester. Although invasive testing is specifically recommended for NT values greater than 3.5 mm, some centers choose to offer invasive testing for NT values between 3.0 and 3.4 mm based on current literature and the elevated risk associated with this NT range, reflecting a tailored approach to managing risk.[6]

It would also be interesting to conduct a large cohort study including prospectively all fetuses with NT between 3.0–3.4 mm, and to follow up the children until 5 years of life.

5 | CONCLUSION

The rate of chromosomal aberration and pathogenic CNVs on CMA is high in the population of fetuses with NT between 3.0 and 3.4 mm, even if these rates remain lower than those observed in the population of fetuses with NT ≥3.5 mm. Our findings support proposing routine invasive testing for fetuses with NT between 3.0 and 3.4 mm.

AUTHOR CONTRIBUTIONS

All the authors were involved in the conceptualization of the paper. Manon de Vriendt and Hanane Bouchghoul wrote the main paper and Loïc Sentilhes and Caroline Rooryck critically reviewed and revised it. Hanane Bouchghoul, Manon de Vriendt and Hugo Madar developed the methodology and carried out the statistical analysis. Frédéric Coatleven, Marie Vincienne, Perrine Prier and Sophie Naudion contributed to the original data collection and were involved in the revision of the article and the analysis and interpretation of data. All authors read and approved the final article.

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CONFLICT OF INTEREST STATEMENT

Loïc Sentilhes has carried out consultancy work and been a lecturer for Ferring Laboratories in the last 3 years. The other authors do not report any potential conflicts of interest.

ETHICS STATEMENT

The original identification of each patient in the database has been encrypted and replaced with surrogate identification. The study was approved by the Research Ethics Board for Obstetrics and Gynecology (CEROG 2022-OBS-0801) on August 21, 2022.[20]

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