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**Identification of fetuses at increased risk of trisomies in the first trimester using axial planes**

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**Short title:** detecting fetuses at increased risk of trisomies by transverse planes.

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**Number of Figures:** 1

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**Keywords:** nuchal translucency, combined test, trisomy, first trimester.

## 22    **Mini - Summary**

- 23        •    What does this study add to current knowledge? Increased nuchal translucency can be  
24            accurately identified in the transverse plane, but the ability of axial measurements in the  
25            identification of fetuses with increased risk during the first trimester has not been assessed  
26            so far, especially in those with unfavorable position. The present study demonstrates that  
27            fetuses at increased risk of trisomies can be reliably identified by axial views during first  
28            trimester screening scan.
- 29        •    What are the main clinical implications? Assessment of nuchal translucency in the axial  
30            scan identified accurately fetuses at increased risk of trisomies during the first trimester  
31            aneuploidies screening. This approach may be technically advantageous in those fetuses  
32            with unfavorable position.

## 33 Abstract

34 **Introduction:** the measurement of nuchal translucency is crucial for the assessment risk of  
35 aneuploidies in the first trimester. We investigate the ability of nuchal translucency (NT) assessed  
36 by a transverse view of the fetal head to detect fetuses at increased risk of common aneuploidies at  
37 11-13 weeks of gestation.

38 **Methods:** we enrolled a nonconsecutive series of women who attended our outpatient clinic from  
39 January 2020 to April 2021 for aneuploidies screening by means of first trimester combined test.  
40 All women were examined by operators certified by the Fetal Medicine Foundation. In each patient  
41 NT measurements were obtained both from median sagittal view and transverse view. We  
42 calculated the risk of aneuploidy using NT measurements obtained both with sagittal and axial  
43 scans and then we compared the results.

44 **Results:** a total of 1023 women were enrolled. An excellent correlation was found between sagittal  
45 and transverse NT measurements. The sensitivity and specificity of the axial scan to identify fetuses  
46 that were deemed at risk of trisomy 21 using standard sagittal scans was  $40/40 = 100.0\%$  (95% CI  
47  $91.2\text{--}100.0$ ) and  $977/983 = 99.4\%$  (95% CI  $98.7\text{--}99.7$ ) respectively. The sensitivity and specificity  
48 of the axial scan to identify fetuses at risk of trisomy 13 or 18 was  $16/16 = 100.0\%$  (95% CI  $80.6\text{--}$   
49  $100.0$ ) and  $1005/1007 = 99.8\%$  (95% CI  $99.3\text{--}99.9$ ).

50 **Conclusions:** when the sonogram, a part of combined test screening, is performed by an expert  
51 sonologist, axial views can reliably identify fetuses at increased risk of trisomies without an  
52 increase of false negative results.

## 53 **Introduction**

54 The accurate measurement of nuchal translucency (NT) is a key part of the screening for  
55 chromosomal abnormalities in the first trimester of pregnancy[1-5]. In the so-called “combined  
56 test”, the assessment of the fluid space behind the fetal head in a sagittal scan is combined with  
57 demographic and anthropometric characteristics of the patient and with biochemical parameters  
58 (beta fraction of the chorionic gonadotropin and pregnancy-associated plasma protein A) to provide  
59 a risk assessment of fetal aneuploidies[4, 6]. An invasive procedure for the assessment of fetal  
60 karyotype is offered when the calculated risk of aneuploidies is increased as well as in case of a  
61 large NT measurements, most frequently when the measurement is in excess of the 99<sup>th</sup> percentile,  
62 i.e. greater than 3.5 mm[7-13].

63 At present the gold standard for NT sonographic measurement is the sagittal approach, that however  
64 is extremely dependent on the fetal position and is time consuming when the fetus is not lying on  
65 his back. We have recently demonstrated that NT measurement in the axial plane provides very  
66 similar results and can be accomplished more rapidly[14, 15].

67 The aim of the present study was to evaluate whether the axial measurement of NT was equally  
68 accurate in the calculation of the risk of common aneuploidies and in identifying fetuses at  
69 increased risk, compared with sagittal assessment.

70

## 71 **Materials and methods**

72 This was a retrospective analysis of the obstetric population described in a previous study[14]. A  
73 non-consecutive series of women were enrolled from a larger project promoted by the Health  
74 Authorities of the Emilia-Romagna region, which aimed to compare the performance of the  
75 combined test and Non Invasive Prenatal Testing (NIPT) in identifying fetuses at increased risk of  
76 trisomies 21, 13 and 18. In accordance with the recommendations of the scientific literature and the  
77 Italian Ministry of Health, the risk of trisomy 21 is defined as increased when it is equal to or  
78 greater than 1 case in 300, while the risk of trisomy 13 and 18 is defined as increased when it is

79 equal to or greater than 1 case in 150. In these cases and in those with an NT equal or greater than  
80 3.5 mm[10, 16] the determination of fetal karyotype by means of chorionic villous sampling  
81 (usually between 11<sup>th</sup> and 14<sup>th</sup> weeks) or amniocentesis (between 16<sup>th</sup> and 18<sup>th</sup> weeks) is offered to  
82 the patient.

83 For each woman enrolled, an operator certified by Fetal Medicine Foundation (FMF) measured the  
84 NT by sagittal scan according to the FMF recommendations[4, 17]; this measurement was used as a  
85 part of the combined test to estimate the risk of trisomies using the software of the First Trimester  
86 Screening Program (version 2.8.1\_4). The same operator then acquired an axial image of the fetal  
87 head using a Voluson E8 or E10 machine (General Electric Kretz Ultrasound, Zipf, Austria) with a  
88 3-7 MHz probe. As previously described[14], a view of fetal head was obtained at the level of the  
89 suboccipitobregmatic plane that crosses the posterior cranial fossa, similarly to what is performed in  
90 the second trimester for the measurement of the nuchal fold. The frontal horns, the thalamus and the  
91 cerebellar peduncles are visualized. NT was then measured off-line by a second operator, blinded to  
92 the sagittal measurement, the combined test and NIPT results. The calipers, as previously  
93 described[14], were positioned from the external contour of the occipital bone to the external  
94 contour of the skin. This axial measurement was then used to calculate the risks of aneuploidies  
95 using the FMF software. In some cases, the skin is closely apposed to the occipital bone and no NT  
96 is visible in the axial plane. We have previously demonstrated that in these cases the NT in the  
97 sagittal plane is always within normal limits with a mean dimension of  $1.26 \pm 0.25$  mm (range 0.50  
98 to 2.10). In such cases, we used this value for the risk calculation.

99

## 100 *Statistics*

101 Mean and standard deviation were used as descriptive statistic for continuous variables, while  
102 frequencies and percentages were computed for discrete or categorical variables.

103 The degree of agreement between axial and sagittal NT measures in identifying fetuses at high risk  
104 of trisomies was measured by Cohen's kappa ( $\kappa$ ). To assess the validity of the novel approach (axial

scan) to discriminate between the two outcomes as compared with the gold standard (sagittal scan), two additional indices were evaluated: sensitivity (proportion of subjects with the condition who are correctly identified by the novel test) and specificity (proportion of subjects without the condition who are correctly identified by the novel test). The 95% confidence intervals (CIs) for Cohen's  $\kappa$  were calculated by Fleiss method, while the 95% CIs for sensitivity and specificity were calculated by Wilson score.

Moreover, the Bland–Altman plot was used to compare the two measurement techniques. More specifically, as suggested by the literature [Krouwer 2008], the differences between the two techniques were plotted against the reference method (i.e., the sagittal scan) instead of the averages of the two. Horizontal lines were drawn at the mean difference and at the 95% limits of agreement, which were defined as the mean difference  $\pm$  1.96 times the standard deviation of the differences. Ninety-five percent confidence intervals (CIs) for the mean difference and for both the upper and lower limits of agreement were also provided [Bland & Altman, 1999].

All analyses were performed by means of Stata 15 software (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP).

120

## 121 **Results**

1023 women were enrolled for the purpose of the study, whose demographic and ultrasound characteristics are shown in Table 1. Among those, 40 (3.9%) fetuses were found to be at high risk for trisomy 21, 16 (1.6%) for trisomy 13 or 18 by means of the sagittal views using the Fetal Medicine Foundation algorithm in the so-called combined test. Among these, 14 fetuses (1.4%) were at risk for all the three aneuploidies evaluated and in 2 fetuses the risk during the combined test was not computed due to an abnormally increased nuchal translucency both in the sagittal as well as in axial scan.

Cohen's  $\kappa$  for the classification of fetuses at risk of trisomy 21 was 0.927 (95% CI 0.869 to 0.985), suggesting an almost perfect agreement between axial and sagittal scans. In particular, as shown in



131 Table 2, the sensitivity of the axial compared with the sagittal scan was  $40/40 = 100.0\%$  (95% CI  
132 91.2 to 100.0), while the specificity was  $977/983 = 99.4\%$  (95% CI 98.7 to 99.7). Cohen's  $\kappa$  for the  
133 classification of fetuses at risk of trisomy 13 or 18 was 0.940 (95% CI 0.858 to 1.000), suggesting  
134 an almost perfect agreement between axial and sagittal scans. As shown in Table 3, the sensitivity  
135 of the axial scan to identify fetuses at risk of trisomy 13 or 18 compared with the sagittal scan was  
136  $16/16 = 100.0\%$  (95% CI 80.6 to 100.0), and the specificity to identify fetuses not at risk was  
137  $1005/1007 = 99.8\%$  (95% CI 99.3 to 99.9).  
138 As shown in Figure 2, mean difference between the risk measures for trisomy 21 obtained with the  
139 axial vs. sagittal scans was  $-25.97$  (95% CI  $-98.07$  to  $46.13$ ) and exhibited a 95% agreement  
140 ranging from  $-2327.05$  (95% CI  $-2450.25$  to  $-2203.85$ ) to  $2275.10$  (95% CI  $2151.90$  to  $2398.30$ ).  
141 Lastly, as shown in Figure 3, mean difference between the risk measures for trisomy 13 or 18  
142 obtained with the axial vs. sagittal scans was  $227.07$  (95% CI  $64.00$ ,  $390.14$ ) and exhibited a 95%  
143 agreement ranging from  $-4977.43$  (95% CI  $-5256.08$  to  $-4698.78$ ) to  $5431.57$  (95% CI  $5152.92$  to  
144  $5710.22$ ).

145

## 146 **Discussion**

### 147 *Principal findings of the study*

148 Our study indicates that as a part of the combined test axial NT measurements are as accurate as the  
149 sagittal measurements in the identification of fetuses at risk for common aneuploidies. As already  
150 demonstrated in a previous analysis of the same population, the axial measurement has excellent  
151 intra- and inter-operator reproducibility and, compared to the sagittal scan used as a gold standard,  
152 showed no systematic differences with an extremely low average difference in the  
153 measurements[14, 15]. Particularly in our population, axial scanning did not miss any fetus  
154 identified at increased risk for trisomy 21, 13, 18 on the basis of standard combined test.

155

### 156 *Results in the context of what is known, strengths and limitations*

157 This, to our knowledge, is the first study that compares the effectiveness of axial measurement of  
158 nuchal translucency in identifying high-risk fetuses for aneuploidy in the first trimester of gestation.  
159 Certainly, to confirm the usefulness of this method, a prospective validation is required. An  
160 important limitation was the finding of some false positives; in particular 6 fetuses not at increased  
161 risk for trisomy 21 with the standard sagittal scan were found to be at increased risk with the  
162 transverse approach, as well as 2 fetuses for trisomy 13/18. The routine use of this axial technique  
163 could lead to an increase, albeit slightly, in the use of invasive diagnosis, which is however been  
164 demonstrated to be safe in expert hands[18].

165

#### 166 *Clinical and research implications*

167 Additionally, all measurements and evaluations in our study were performed by experienced first  
168 trimester ultrasound operators, certified by the Fetal Medicine Foundation. The usefulness of axial  
169 scanning even in the hands of less experienced sonographers has yet to be demonstrated. Further  
170 prospective studies are needed to propose this scan particularly in patients who undergo a NIPT test.  
171 A sagittal view of fetal head in the first trimester of pregnancy is useful not only for the  
172 measurement of nuchal translucency, but also for the evaluation of fetal brain and profile[19, 20]. In  
173 particular, when an abnormal appearance of intracranial translucency or of brainstem-to-occipital  
174 bone diameter is detected, a suspect of open spina bifida or of posterior fossa malformation can be  
175 raised. However, these details can be evaluated by sagittal scans even when the fetus is not perfectly  
176 oriented, i.e. lying on his back, not separated from the amnion or in case of hyperextension -  
177 hyperflexion of the neck, all cases where the midsagittal scan specific for NT evaluation is not  
178 feasible according to the standards of the Fetal Medicine Foundation; this obstacle could be  
179 surmounted by an axial evaluation.

180

#### 181 *Conclusions*

182 Obviously, the goal of our study is not to replace in the clinical practice during first trimester  
183 screening the median sagittal scan, validated by a large variety of studies. However, we have shown  
184 that even using an axial approach, which is less time-consuming and less dependent on fetal  
185 position, the risk of fetal trisomies is not underestimated compared with a standard combined test.  
186 We suggest that in cases in which a sagittal view of the fetal head is difficult or impossible to  
187 obtain, an axial approach may be considered.

188

189 **Statements**

190 **Acknowledgements**

191 The authors report no acknowledgements.

192

193 **Statements of Ethics**

194 The study protocol was approved by the local Ethics Committee of Sant’Orsola-Malpighi Hospital  
195 and a consent form signed at recruitment was obtained from each eligible patient  
196 (203/2020/Oss/AOUBo). The study protocol conforms to the ethical guidelines of the “World  
197 Medical Association (WMA) Declaration of Helsinki-Ethical Principles for Medical Research  
198 Involving Human Subjects” adopted by the 18th WMA General Assembly, Helsinki, Finland, June  
199 1964 and amended by the 59th WMA General Assembly, Seoul, South Korea, October 2008.

200

201 **Conflict of interest:** the Authors report no conflict of interest.

202

203 **Funding sources:** no funding was received for the purpose of this study.

204

205 **Authors contributions:**

206 EM contributed to the conception of the study, collected data and drafted the manuscript; JD, BP,  
207 VA, MF, MC, AP and SA contributed to the conception of the study and collected data, JL  
208 performed statistical analysis, GP contributed to the conception of the study and to data collection.  
209 All Authors revised and approved the final version of the paper.

210

211 **Data Availability statement:**

212 The data that support the findings of this study are not publicly available due to privacy reason but  
213 are available from the corresponding author upon reasonable request.

214

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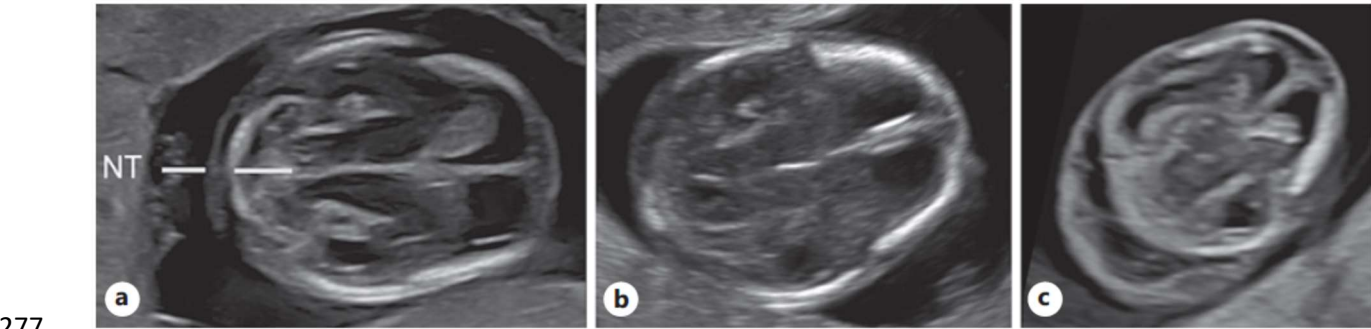
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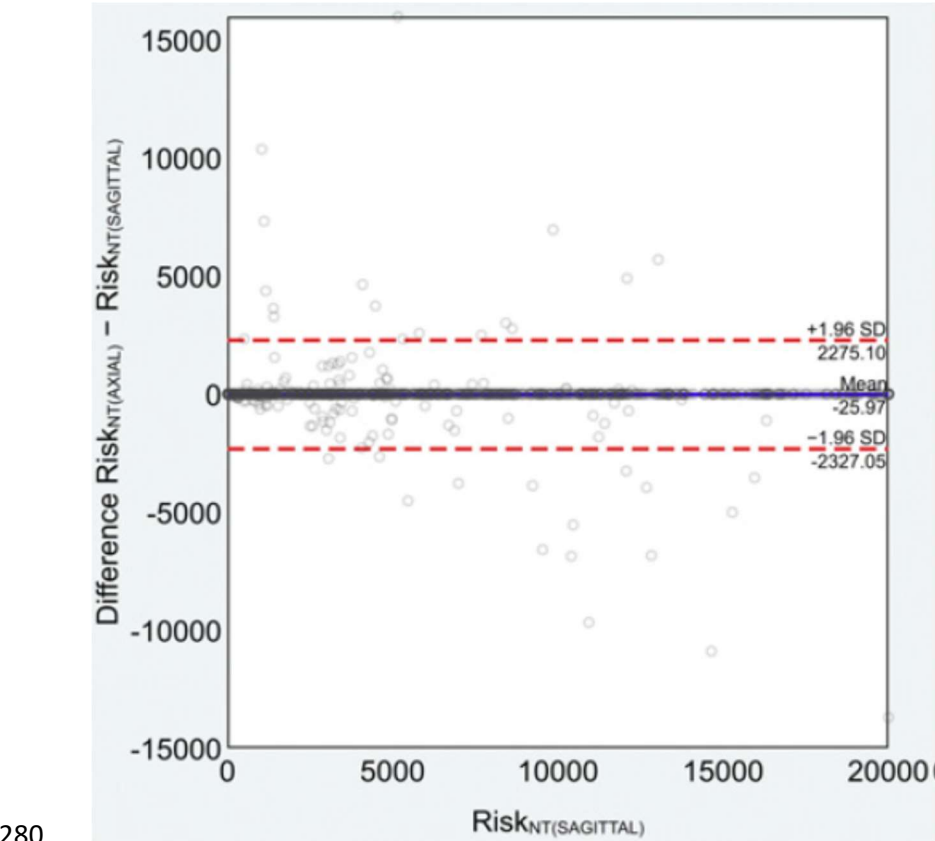
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271 **Figure legends**

272 **Fig. 1.** Axial scan of the fetal head, passing through the frontal horns, the thalamus and the  
273 cerebellar peduncles. Axial nuchal translucency is measured from the external contour of the  
274 occipital bone and that of the skin (a). Example of a scan in which the translucency is not  
275 measurable because there is no accumulation of fluid between the occipital bone and the skin (b). A  
276 fetus with increased axial nuchal translucency (c).

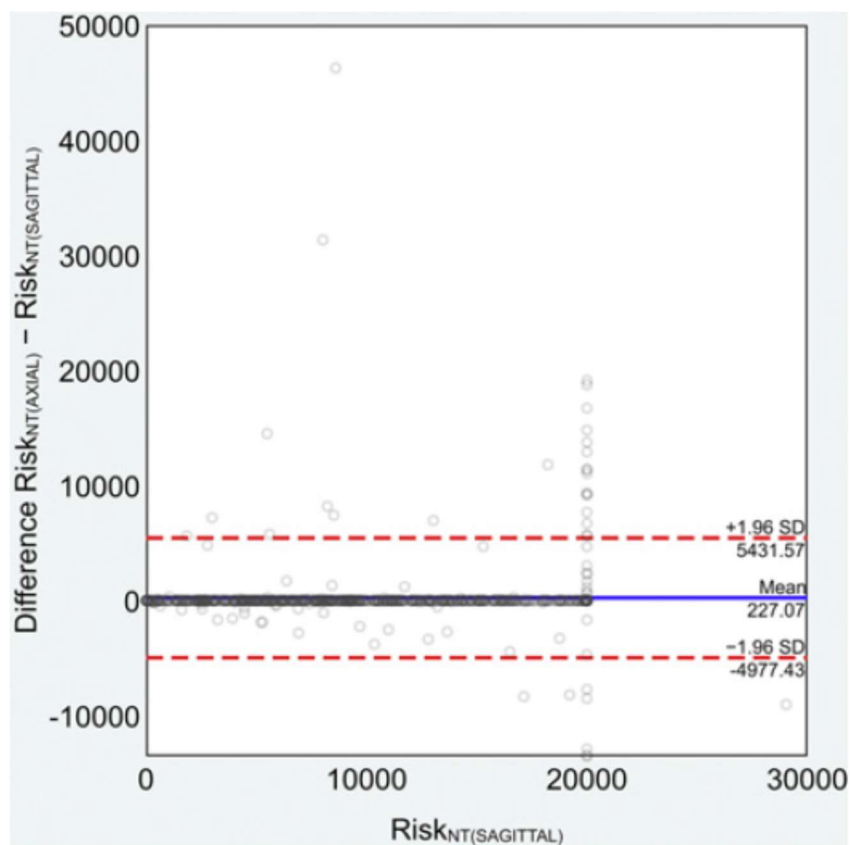


278 **Fig. 2.** Bland–Altman plot of risk measures for trisomy 21 obtained with axial vs. sagittal views.  
279 Dashed lines indicate the 95% limits of agreement of the differences between the two techniques.





281 **Fig. 3.** Bland–Altman plot of risk measures for trisomy 13 or 18 obtained with axial vs. sagittal  
 282 views. Dashed lines indicate the 95% limits of agreement of the differences between the two  
 283 techniques.



284