Identification of Fetuses at Increased Risk of Trisomies in the First Trimester Using Axial Planes

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Mini - Summary

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

Abstract

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

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

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

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

Introduction

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

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

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

Materials and methods

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

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

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

Statistics

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

The degree of agreement between axial and sagittal NT measures in identifying fetuses at high risk of trisomies was measured by Cohen's kappa (κ). 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 κ 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 ± 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).

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 κ 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

Table 2, the sensitivity of the axial compared with the sagittal scan was 40/40 = 100.0% (95% CI 91.2 to 100.0), while the specificity was 977/983 = 99.4% (95% CI 98.7 to 99.7). Cohen's κ for the classification of fetuses at risk of trisomy 13 or 18 was 0.940 (95% CI 0.858 to 1.000), suggesting an almost perfect agreement between axial and sagittal scans. As shown in Table 3, the sensitivity of the axial scan to identify fetuses at risk of trisomy 13 or 18 compared with the sagittal scan was 16/16 = 100.0% (95% CI 80.6 to 100.0), and the specificity to identify fetuses not at risk was 1005/1007 = 99.8% (95% CI 99.3 to 99.9).

As shown in Figure 2, mean difference between the risk measures for trisomy 21 obtained with the axial vs. sagittal scans was −25.97 (95% CI −98.07 to 46.13) and exhibited a 95% agreement ranging from −2327.05 (95% CI −2450.25 to −2203.85) to 2275.10 (95% CI 2151.90 to 2398.30). Lastly, as shown in Figure 3, mean difference between the risk measures for trisomy 13 or 18 obtained with the axial vs. sagittal scans was 227.07 (95% CI 64.00, 390.14) and exhibited a 95% agreement ranging from −4977.43 (95% CI −5256.08 to −4698.78) to 5431.57 (95% CI 5152.92 to 5710.22).

Discussion

Principal findings of the study

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

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

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

Clinical and research implications

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

Conclusions

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

Statements

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Statements of Ethics

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

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Authors contributions:

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

Data Availability statement:

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

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Figure legends

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

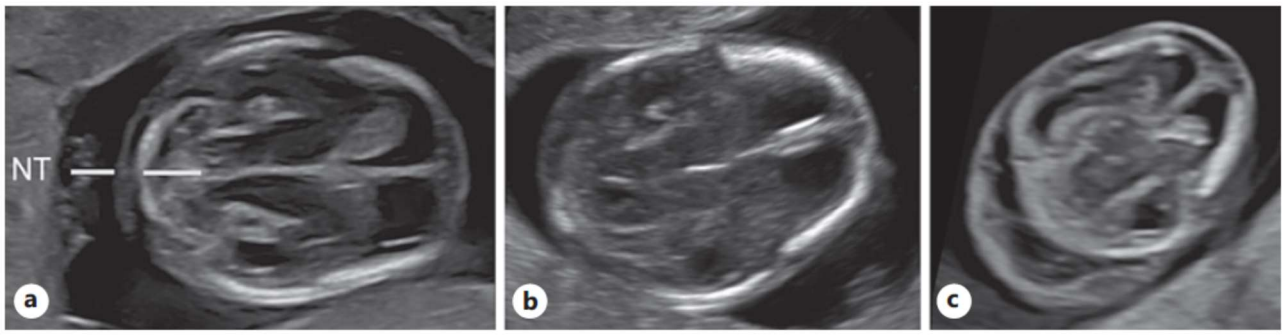

Fig. 2. Bland–Altman plot of risk measures for trisomy 21 obtained with axial vs. sagittal views. Dashed lines indicate the 95% limits of agreement of the differences between the two techniques.

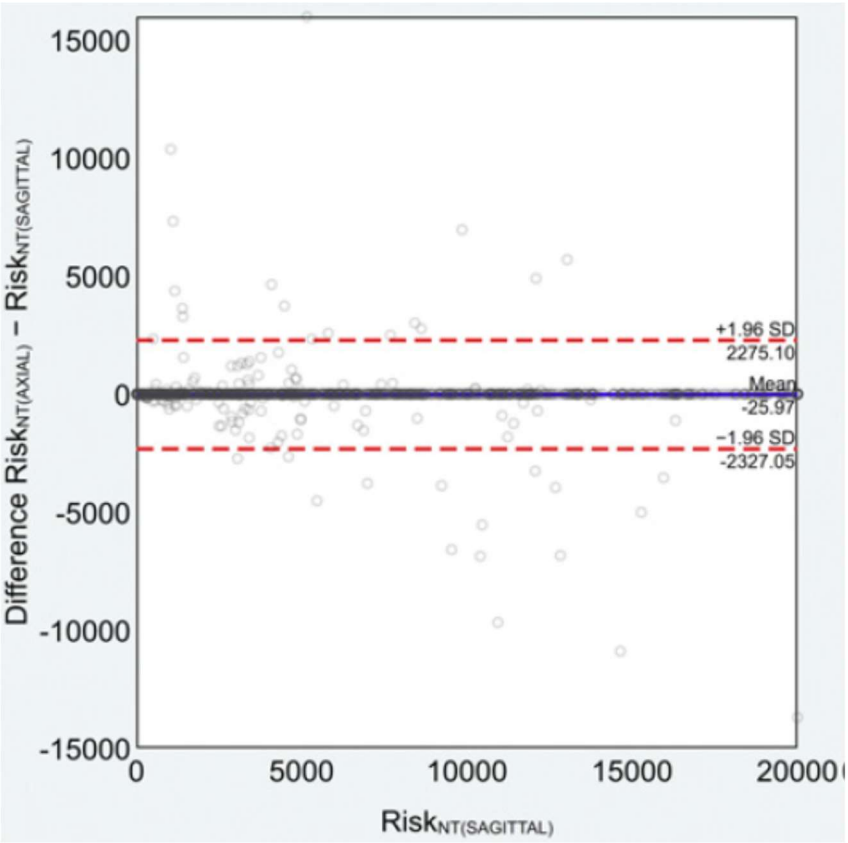

Fig. 3. Bland–Altman plot of risk measures for trisomy 13 or 18 obtained with axial vs. sagittal views. Dashed lines indicate the 95% limits of agreement of the differences between the two techniques.