ORIGINAL ARTICLE

A Prospective Cohort Study with Diagnostic Accuracy Assessment for Sensitivity of Nuchal Translucency and Nasal Bone in First-Trimester Screening for Trisomy 21 and Association with Pregnancy Outcomes

Shumaila Khawaja Khail*, Abeera Choudry, Viqar-U-Nisa Ashraf, Asifa Siraj, Rabia Qasim, Amna Fareed

ABSTRACT

Objective: To determine the sensitivity and specificity of nuchal translucency and nasal bone for detecting trisomy 21 and other poor fetal outcomes.

Study Design: A prospective cohort study with diagnostic accuracy assessment.

Place and Duration of Study: The study was conducted at the Department of Obstetrics and Gynecology, Pak Emirates Military Hospital (PEMH), Rawalpindi, Pakistan, from January 2023 to June 2023.

Methods: One hundred and fifty-four pregnant females were included. After recording medical and geographical history, a single professional performed their sonographic assessment. Fetuses having crown-rump length between 45-84mm were evaluated for nuchal translucency and nasal bone. In cases of suspected aneuploidies, chorionic villus sampling was performed, and, according to the results, patients with signs of trisomy 13, 18, or 21 were advised to terminate. For fetal outcomes, a follow-up was done throughout the pregnancy. This study included females between 11 and 13+6 weeks of singleton pregnancy having CRL of 45-84mm, excluding high-order pregnancies and fetuses above 14 weeks of gestational age.

Results: Karyotype analysis revealed that 2.6% of fetuses had Trisomy 21. Among these, 3 had higher nuchal translucency thickness, and 1 had an absent nasal bone. The detection rate for Trisomy 21 was higher with increased NT (75%) than with an absent nasal bone (25%). All 4 cases of Trisomy 21 were terminated. Additionally, 3 cases with pre-eclampsia history had pre-term delivery, and 3 cases with raised NT but without Trisomy 21 experienced miscarriage.

Conclusion: In the first trimester, Increased NT was a more prevalent marker for trisomy 21 in our cohort than an absent nasal bone. The role of nasal bone assessment in this setting requires further investigation in larger studies.

Keywords: *Aneuploidies, Nasal Bone, Nuchal Translucency, Trisomy.*

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Introduction

Chromosomal abnormalities in babies place an added burden on parents and on society as a whole. These chromosomal anomalies are one of the main causes of developmental delays in children. This highlights the need to include early detection along with the management of chromosomal abnormalities as an important component in antenatal care. The most common chromosomal abnormalities include Patau syndrome (trisomy 13), Edwards syndrome (trisomy 18), and Down syndrome (trisomy 21).[1] In several countries all across the globe, definitive prenatal screening has become a standard testing practice for chromosomal disorders.[2] For the detection of these abnormalities, biochemical markers and ultrasonography are two of

Department of Obstetrics & Gynecology
Pak Emirates Military Hospital (PEMH), Rawalpindi, Pakistan

Correspondence:
Dr. Shumaila Khawaja Khail
Assistant Professor, Obstetrics & Gynecology
Pak Emirates Military Hospital (PEMH), Rawalpindi, Pakistan
E-mail: dskhawaja@gmail.com

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the several modalities.[3] First-trimester screening mainly involves double markers, which measure pregnancy-associated plasma protein A (PAPP-A) and free beta hCG levels, as well as an ultrasound usually done between 11-13 weeks and 6 days for nasal bone and nuchal translucency (NT).[4,5] While the quadruple test (hCG, inhibin A levels, unconjugated estriol levels, and AFP) and an Anomaly scan are mainly used in prenatal screening during the second trimester.[6]

Aneuploidies such as trisomies 13, 18, and 21 are usually identified by indicators such as variations in normal anatomy, structural defects, and biometric discrepancies, which are mainly referred to as "markers". Nuchal thickness (NT) is thought to be one of the most distinctive and sensitive individual markers among them.[7] Nuchal translucency (NT) thickness, an anechoic area behind the fetal neck, is detectable and measurable in all fetuses between gestational age of 11 and 14 weeks. Measurements of increased nuchal translucency (NT) have been adopted as a prenatal screening protocol for aneuploidies and have been found to indicate fetuses at increased risk for aneuploidies.[8] In quality-controlled circumstances, detection rates using NT measurements for trisomy 21 and other aneuploidies reach 80 to 90% with a 5% false-positive rate.[9] Moreover, the absence or presence of the nasal bone, either alone or in conjunction with nuchal translucency, also serves as a promising soft ultrasound marker for aneuploidies in first-trimester ultrasound.[10] Various investigations also demonstrated that using markers in groups, as compared to using them individually, yields the best results in terms of sensitivity and specificity.

Based on the results of first-trimester screening, which includes markers such as nuchal translucency (NT) measurements and nasal bone (NB), this study aimed to determine the sensitivity and specificity of this marker cluster in predicting fetal aneuploidies and poor fetal outcomes.

Methods

The cohort study was carried out at the Department of Obstetrics and Gynecology, Pak Emirates Military Hospital (PEMH), Rawalpindi, Pakistan, from January 2023 to June 2023, after taking approval by the Institutional Review Board (IRB) of the hospital vide letter reference number: A28/EC/555/23, dated 23rd December 2022. The sample size was calculated using the WHO calculator with a 95% confidence level, a 5% margin of error, and a 10.7% prevalence of aneuploidies such as trisomy 13, 18, and 21. The sample size came out to be 154.[11] After providing a thorough explanation of the procedure, both verbal and written informed consent was obtained from every patient for their participation in the study. A non-probability consecutive sampling technique was used for data collection.

This study enrolled pregnant female patients aged 18-40 years. All these female patients presented with a singleton pregnancy, and the gestational age of the fetus population was between 11 weeks and 13 weeks and 06 days with a crown-rump length of 45-84 mm. All the pregnant patients with high-order pregnancies, and the fetal population having a gestational age of above 14 weeks were excluded from the current study. Moreover, all pregnant female patients who did not consent to be included in the study were excluded.

After informed consent was obtained, the history was taken from all participants, including their age, obstetrical history, prior history of a child with trisomy 13, 18, or 21, and any history of medical disorders. In addition, patients' addresses, contact numbers, and ethnicities were taken into account. After all the data had been recorded, the patient underwent a routine sonographic assessment by a single healthcare professional. After the dating scan, if the gestational age of the fetus was between 11-13+6 weeks and the CRL was between 45-84 mm, NT measurements were taken. The calculation of NT measurements was done using the Fetal Medicine Foundation (FMF) calculator. Nuchal translucency was considered enlarged if it exceeded or equaled the 95th percentile for the given crown-rump length (CRL) of the reference ranges, and the Nasal bone was classified as present or absent on the basis of the evaluation of the fetal facial profile. The risk evaluation was performed by calculating NT measurements and assessing the presence or absence of the nasal bone. In cases of suspected aneuploidies, patients were counseled and asked to undergo Chorionic Villus Sampling (CVS), which was guided by maternal factors, biochemical markers in maternal serum, and ultrasound findings. The CVS was done in patients who gave their consent. Their

samples were sent to the Armed Forces Institute of Pathology (AFIP), and the reports were received 2 weeks later. Based on the CVS results, subjects who showed positive results for trisomy 13, 18, or 21 were counseled and given the option of termination. All the other patients were followed throughout their pregnancies to assess fetal outcomes.

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the analysis of data. Descriptive statistics, including the median and range, were calculated for continuous variables such as age, maternal age, and gestational age. Frequencies and percentages were calculated for categorical variables such as pre-eclampsia, gestational diabetes mellitus, Trisomy, and nuchal translucency thickness. The diagnostic performance of Nuchal Translucency (NT) and nasal bone assessment for detection of Trisomy 21 was evaluated using a 2×2 contingency table to calculate sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV. Due to the small number of Trisomy 21 cases and low expected counts in some cells, Fisher's exact test was used to determine statistical significance. The *P*-values less than 0.05 were considered statistically significant. All cases were followed until delivery, and associations between maternal or fetal risk factors (such as history of pre-eclampsia or raised NT) and adverse outcomes (miscarriage, pre-term delivery, or termination) were descriptively analyzed.

Results

A total of 154 first and early-second-trimester singleton pregnancies that met the inclusion requirements were recruited in the study. The median maternal age was 29 years (range 18-40 years). Of these, 90 (58.4%) were aged 18-30, while 64 (41.6%) were aged 31-40. At the time of ultrasound, the median gestational age was 12 weeks (range, 11-14 weeks), with the number of women scanned in the 11th, 12th, 13th, and 14th weeks is shown in Table 1.

Among the study participants, 5 (3.2%) had a history of pre-eclampsia, and 3 (1.9%) had gestational diabetes mellitus (GDM). Nuchal translucency (NT) was raised in 7 (4.5%) of the total women, while the nasal bone was absent in 3 (1.9%).

Table 2 summarizes the diagnostic performance of Nuchal Translucency (NT) and nasal bone assessment for the detection of Trisomy 21. For NT, a measurement ≥95th percentile demonstrated a sensitivity of 75.0% and a specificity of 97.33% with a positive predictive value (PPV) of 42.86% and a

Table 1: Distribution of Women Scanned by Gestational Weeks

Gestational Age	Women Scanned (N %)
11th week	29 (18.8%)
12th week	71 (46.1%)
13th week	38 (24.7%)
14th week	16 (10.4%)

Table 2: Diagnostic performance of Nuchal Translucency and Nasal Bone for detection of Trisomy 21

NT Thickness Measurement	Trisomy		*P*-value
	Trisomy 21	No Trisomy detected	
< 95Percentile	1 (FN)	146 (TN)	<0.001
≥ 95 percentile	3 (TP)	4 (FP)	
Sensitivity= TP/(TP+FN)= 3/(3+1)*100=75.00 %			
Specificity= TN/(TN+FP)= 146/(146+4)*100=97.33%			
Positive Predictive Value= TP/(TP+FP)*100= 3/(3+4)= 42.86%			
Negative Predictive Value= TN/(TN+FN)*100=146/(146+1)= 99.32%			

Nasal Bone Assessment	Trisomy		*P*-value
	Trisomy 21	No Trisomy detected	
Present	3 (FN)	148 (TN)	0.076
Absent	1 (TP)	2 (FP)	
Sensitivity= TP/(TP+FN)= 1/(1+3)*100=25.00 %			
Specificity= TN/(TN+FP)= 148/(148+2)*100=98.67%			
Positive Predictive Value= TP/(TP+FP)*100= 1/(1+2)= 33.33%			
Negative Predictive Value= TN/(TN+FN)*100=148/(148+3)= 98.01%			

Table 3: Frequency of miscarriage, termination, pre-term, and full-term delivery

Parameters	N (%)
Full Term	144 (93.5%)
Pre-Term	3 (1.9%)
Miscarriage	3 (1.9%)
Termination	4 (2.6%)

negative predictive value (NPV) of 99.32% ($P < 0.001$). In comparison, the absence of the nasal bone showed lower sensitivity (25.0%) but slightly higher specificity (98.67%), with a PPV of 33.33% and an NPV of 98.01% ($P = 0.076$). These results indicate that NT thickness is a more sensitive marker for detecting Trisomy 21, whereas nasal bone absence is highly specific but less sensitive. Fisher's exact test was used to calculate *P*-values due to the small number of Trisomy 21 cases.

All the cases were followed till delivery, of which 144 had full-term delivery, 3 had pre-term, 3 had miscarriage, and 4 had termination, as given in Table 3.

All 4 cases with detected Trisomy 21 were terminated. Additionally, 3 cases with a history of pre-eclampsia had a pre-term delivery, and 3 cases with raised NT but without Trisomy 21 detection experienced miscarriage.

Discussion

The most frequent chromosomal anomaly found during first-trimester screening is Down syndrome, often referred to as trisomy 21, which is caused by the presence of an additional chromosome 21.[12] This extra chromosome results in developmental retardation, various medical conditions, intellectual disability, and changes in some physical features as well.[13] While other less frequent chromosomal abnormalities include Patau Syndrome (trisomy 13) and Edward Syndrome (trisomy 18).[14] They abnormalities have more severe impacts on the developing baby. Once occurred, all these anomalies cannot be reversed.[15] Therefore, the early detection of these chromosomal abnormalities is critical, which can be done using biochemical markers or ultrasonography.[16]

In the context of prenatal diagnosis, aneuploidies such as trisomies 13, 18, and 21 are typically identified by morphological anomalies, congenital malformations, and expected biometric discrepancies, collectively referred to as markers.[17] Primarily, Trisomy 13,18, and 21 can be identified using two markers: nuchal translucency and nasal bone.[18] The current study aimed to determine the sensitivity of the nuchal translucency and nasal bone for detecting different aneuploidies and poor fetal outcome. This study confirmed that an increase in nuchal translucency thickness is an effective marker in the detection of trisomy 21 during 11-13+6 weeks of pregnancy.

In a study by Ghaffari SR et al., the 51 subjects showed chromosomal abnormalities, including 1 triploidy case, 6 sex chromosomal abnormality cases, 8 trisomy 18 cases, 33 trisomy 21 cases, and 3 other unbalanced abnormalities. According to this study, the false positive rate (FPR) and detection rate for trisomy 21 were 4.84% and 93.8% using nuchal translucency and biochemical markers, respectively, and the FPR and detection rate of trisomy 21 using tricuspid regurgitation, nuchal translucency, duct venosus flow, nasal bone, and biochemical markers were 3.4% and 100%, respectively.[19] This study showed somewhat similar results to the current study, as for the detection of trisomy 13,18, and 21, parameters such as nasal bone and nuchal translucency were used, while in the above-mentioned study, multiple parameters such as NB, NT, DV, TR, and biochemical markers were used.

A similar study by Sepulveda W et al. included 1,287 pregnancies screened over a 3-year period.[20] The median maternal age in this study was 33 years (range 14-47 years), while the median age in the current study was 29 years (range 18-40 years). In his study, NT was raised in 110 (8.5%) fetuses, and 25 (1.9%) fetuses had absent nasal bone, and in the current study, NT was raised in 7 (4.5%) fetuses, and nasal bone was absent in 3 (1.9%). Also, in his study, trisomy 21 was detected in 31 subjects, and out of these, 13 had absent nasal bone, and 28 had increased nuchal translucency (detection rate 41.9% and 90.3% respectively).[20] While in the present research, trisomy 21 was detected in 4 subjects.

Another study by Sepulveda W et al. assessed the effectiveness of nuchal translucency and nasal bone measurements in 1st-trimester twin or multiple pregnancies.[21] In the current study, only singleton pregnancies were included. This investigation included 440 subjects, including 1 case of quadruplets, 8 cases of triplets, and 206 twin pregnancies. NT measurements were taken in all the subjects. 6 (8.6%) of monochorionic fetuses and 10 (2.7%) of dichorionic fetuses showed signs of increased NT thickness greater than the 95th percentile ($P < 0.05$). Out of the total study population, only 4 subjects had an absent nasal bone, and 3 of them showed signs of aneuploidy.[21]

An investigation by Geipel A et al. showed somewhat contrasting results to the present study.[22] This study included a total of 49 subjects, out of which 4 had trisomy 13, 8 had trisomy 18, and 37 had trisomy 21. Similar to the current study, screening in this research was performed in the early 2nd trimester. As per this investigation, the most sensitive criterion for identifying fetuses with trisomy 21 was nasal bone hypoplasia. While in the current study, nasal bone absence showed low sensitivity (25%) and did not show any significance in the detection of any kind of trisomy.

Furthermore, Nuchal fold and nasal bone assessments in Geipel A et al. study, screening methods independent of mother age, detected 66.7% of subjects with trisomy 13/18 (false-positive rate (FPR), 5.8%) and 64.9% of cases with trisomy 21.[22] In contrast, the current study demonstrated that nuchal translucency alone achieved a higher sensitivity of 75% for trisomy 21, suggesting that NT was a more reliable screening parameter in our population. Moreover, the inclusion of tricuspid flow and ductus venosus assessment increased the detection rate to 75.7% for trisomy 21 (FPR, 10.8%) and to 83.3% for trisomy 13 and 18. These Doppler parameters were not discussed in the current investigation.

In addition to the existing literature, the present study strongly suggests that nuchal translucency is an effective ultrasonographic marker for detecting Down's syndrome. The outcomes of this study will contribute to the existing body of knowledge in prenatal diagnostics and potentially guide healthcare providers in making more informed decisions regarding patient management and counseling.

Conclusion

In this single-center cohort, increased nuchal translucency was the most prevalent and effective first-trimester ultrasonographic marker for Trisomy 21. The assessment of the nasal bone, in isolation, had a low detection rate. The evaluation of these markers for predicting other adverse outcomes, like miscarriage, was inconclusive and warrants larger prospective studies.

This was a single-center study that only included 154 pregnant females with singleton pregnancies. Furthermore, only a limited set of parameters, such as NB and NT, was used in this investigation to detect trisomies 13, 18, and 21. It is recommended that future studies include multicenter investigations that encompass patients with multiple pregnancies and cover a wide range of parameters, such as biochemical markers, ductus venosus flow (DV), and tricuspid regurgitation (TR).

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Author Contributions

SKK: Conception, design of the work, and approval for final submission
AC: Manuscript writing for methodology design, investigation, and approval for final submission
VNA: Writing the original draft, proofreading, and approval for final submission
AS: Data acquisition, curation, statistical analysis, and approval for final submission
RQ: Validation of data, interpretation, write-up of results, and approval for final submission
AF: Revising, editing, supervising for intellectual content, and approving for final submission
SKK is the nominated guarantor and takes full responsibility for the overall content and integrity of the work