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First Trimester Anomaly Scan and the Available Biochemical Markers For Detection of Aneuploidies

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HIGHLIGHTS

1. First trimester scan crucialfor early anomaly detection.
2. Nuchal translucency measured to assess chromosomal risk.
3. Nasal bone absence suggests potential genetic abnormalities.
4. Ductus venosus flow patterns offer diagnostic clues.
5. Biochemical markers include free β-hCG, PAPP-A levels.
6. Combined screening improves aneuploidy detection accuracy significantly.
7. Early identification allows timely intervention and counseling.
8. Integration of imaging and biochemistry ensures optimal screening.

Key words:
First trimester
Anomaly scan
Nuchal translucency
Biochemical markers
β-hCG
PAPP-A
Aneuploidies
Structural abnormalities

ABSTRACT

Introduction: Early detection of chromosomal anomalies is crucial for managing pregnancy risks and enabling timely interventions. First-trimester screening, which combines NT measurement and biochemical markers, has proven effective in identifying pregnancies at risk for aneuploidies. These methods provide an opportunity for early intervention and informed decision-making in prenatal care. **Aim:** This study aims to evaluate the first-trimester anomaly scan and biochemical markers (□-hCG and PAPP-A) for risk assessment, correlating background risk with biochemical markers, and detecting aneuploidies and structural abnormalities in singleton pregnancies. **Materials and Methods:** A total of 50 singleton pregnancies were included in the study, with a mean gestational age of 13 weeks and 2 days and an average maternal age of 28.7 ± 3 years. NT measurements and maternal serum levels of □-hCG and PAPP-A were assessed during the first trimester. Follow-up scans were conducted for cases with abnormal NT measurements, and amniocentesis was offered for high-risk pregnancies to confirm the presence of chromosomal anomalies. **Results:** Most fetuses had NT measurements within the normal range (45 to 84 mm). Two cases showed NT measurements at the higher limit. Biochemical markers in these cases exhibited significant changes; however, follow-up scans did not reveal any significant abnormalities. Amniocentesis confirmed the absence of trisomies in these pregnancies. The aneuploidy detection rate ranged from 79% to 90%, with a 5% false positive rate, indicating the effectiveness of the combined first-trimester screening approach in detecting chromosomal abnormalities. **Conclusion:** The combination of NT measurement, maternal age, and biochemical markers (□-hCG and PAPP-A) is an effective first-trimester screening approach for detecting aneuploidies. This method demonstrated a high detection rate with a manageable false positive rate, supporting its clinical utility in prenatal care.

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INTRODUCTION

First-trimester screening plays a pivotal role in prenatal care by offering early identification of potential chromosomal anomalies and structural abnormalities in the fetus. With advancements in ultrasound technology and biochemical markers, first-trimester screening has become a standard approach in detecting conditions such as trisomy 21 (Down syndrome), trisomy 18, trisomy 13, and other aneuploidies. The integration of ultrasound findings, particularly the measurement of nuchal translucency (NT) thickness, with maternal serum biochemical markers such as pregnancy-associated plasma protein-A (PAPP-A) and free □-human chorionic gonadotropin (□-hCG) has demonstrated a high sensitivity for these conditions [1,2]. This screening approach not only aids in the early detection of chromosomal abnormalities but also provides valuable insights into the risk of adverse pregnancy outcomes, such as preterm birth and preeclampsia, which remain significant contributors to neonatal morbidity and mortality worldwide [3,4].

The first-trimester anomaly scan, typically performed between 11 weeks 6 days and 13 weeks 6 days, is a cornerstone of early prenatal screening. It serves multiple purposes, including confirming pregnancy viability, establishing accurate gestational dating, and identifying markers for chromosomal anomalies and structural defects. The measurement of NT, a fluid-filled space at the back of the fetal neck, is a critical component of this scan. When combined with maternal serum levels of PAPP-A and □-hCG, NT measurement forms the basis of a robust risk assessment algorithm for fetal aneuploidies. This integrated approach has been shown to achieve a detection rate of approximately 90% for trisomy 21, with a false-positive rate of 5% [5,6]. Furthermore, emerging evidence suggests that abnormal levels of these biochemical markers, particularly low PAPP-A, may also be indicative of adverse pregnancy outcomes, such as preterm birth and fetal growth restriction, highlighting their broader clinical utility [7,8].

Biochemical screening in the first trimester relies on the analysis of maternal serum concentrations of □-hCG and PAPP-A. These markers exhibit distinct patterns in pregnancies affected by chromosomal abnormalities. For instance, in trisomy 21, □-hCG levels are typically elevated, while PAPP-A levels are reduced. Conversely, in trisomy 18 and trisomy 13, both markers tend to be significantly lower than in unaffected pregnancies [9,10]. The combination of these biochemical markers with NT measurement allows healthcare providers to calculate the risk of aneuploidies with high accuracy, enabling early interventions and informed decision-making regarding further diagnostic testing, such as chorionic villus sampling (CVS) or amniocentesis [11].

In addition to their role in aneuploidy screening, first-trimester biochemical markers have garnered attention for their potential in predicting adverse pregnancy outcomes. Preterm birth, defined as delivery before 37 weeks of gestation, remains a significant global health challenge, with rates ranging from 5% in developed countries to 25% in developing countries [12]. Preterm infants are at increased risk for a range of complications, including chronic lung disease, severe brain injury, neonatal sepsis, and long-term developmental impairments [13]. The economic burden of preterm birth is substantial, with healthcare costs escalating significantly for infants born at earlier gestational ages. Identifying pregnancies at risk for preterm delivery through first-trimester screening could facilitate targeted interventions, improve neonatal outcomes, and alleviate the economic burden on healthcare systems.

Chromosomal anomalies, significant genomic modifications, are a leading cause of miscarriage and congenital disorders, accounting for over 50% of spontaneous abortions and occurring in approximately 1% of newborns [14]. Early prenatal identification is crucial for counseling and management. Screening methods include biochemical tests (e.g., hCG, □-hCG, aFP, μE3, PAPP-A), ultrasonography (e.g., NT thickness), and genomic approaches like non-invasive prenatal testing (NIPT), which detects cell-free fetal DNA in maternal blood, improving aneuploidy detection accuracy [15].

Despite the advantages of non-invasive screening methods, abnormal results often necessitate confirmatory diagnostic testing through invasive procedures such as CVS or amniocentesis. These procedures, while highly accurate, carry a small risk of miscarriage and fetal damage, underscoring the importance of refining non-invasive screening strategies to minimize unnecessary invasive testing [16]. The integration of first-trimester biochemical and ultrasonographic markers into a comprehensive screening algorithm has significantly improved the detection of chromosomal anomalies and adverse pregnancy outcomes, paving the way for more personalized and effective prenatal care.

This study aims to provide a comprehensive overview of the first-trimester anomaly scan, highlighting its importance in the detection of aneuploidies and structural abnormalities, and to discuss the clinical value of available biochemical markers, including □-hCG and PAPP-A, in risk assessment. The integration of

these diagnostic tools is crucial for improving prenatal care and minimizing the risks associated with chromosomal abnormalities and preterm birth [8,9,10].

Materials and Methods

The study was conducted in the Department of Radiodiagnosis at Kempegowda Institute of Medical Sciences, Bangalore, as a prospective observational study over a period of 9 months. A total of 50 patients with singleton pregnancies undergoing routine first-trimester antenatal screening for chromosomal abnormalities were included. The gestational age of the participants ranged between 11 weeks 6 days and 13 weeks 6 days, with crown-rump lengths between 45 mm and 84 mm. Exclusion criteria included maternal age below 18 years, medicolegal cases, and gestational age outside the specified range. Ultrasound examinations were performed transabdominally using the Philips Affinity 70G ultrasound machine. Fetal anatomy and aneuploidy markers were evaluated, and biochemical markers such as Beta-hCG and Pregnancy-Associated Plasma Protein-A (PAPP-A) were considered. Gestational age was confirmed through crown-rump length measurements to ensure the accuracy of the study.

RESULT

A total of 50 singleton pregnancies were included in the study. The mean gestational age at the time of screening was 13 weeks and 2 days, and the average maternal age was 28.7 ± 3 years. The assessment focused on three key markers: nuchal translucency (NT), maternal serum pregnancy-associated plasma protein-A (PAPP-A), and beta-human chorionic gonadotropin (β-hCG). The results were analyzed to evaluate fetal well-being and the risk of chromosomal abnormalities.

The majority of participants (76%) were between 20 and 30 years old, while 24% were in the 30 to 40-year age group. This distribution aligns with the typical maternal age range for routine first-trimester screening.

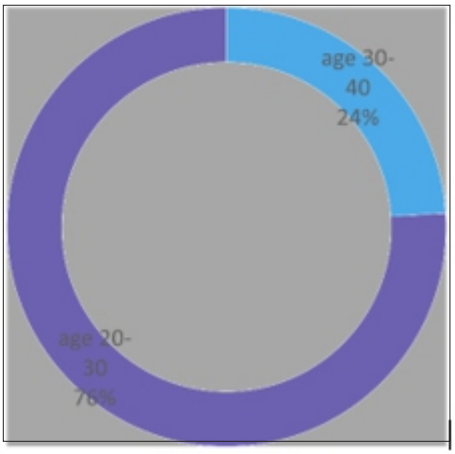

Figure 1: Donut Chart Representing the Maternal Age Distribution of Study Participants

The NT measurement was successfully obtained for all participants. Most fetuses had NT values within the normal range (<3.5 mm), with only two cases exhibiting values at the higher limit. These cases underwent additional monitoring and diagnostic testing, including amniocentesis, which revealed no chromosomal abnormalities.

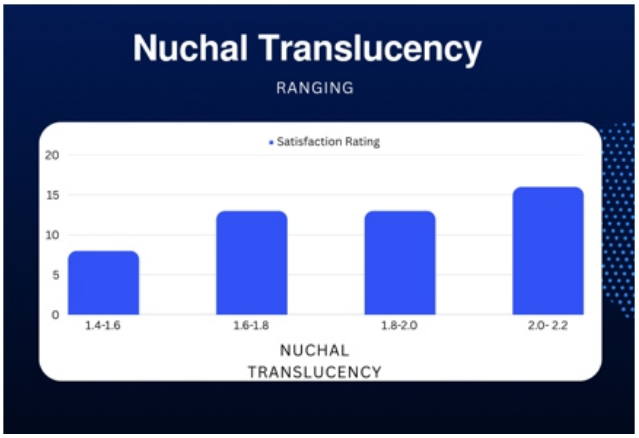

Figure 2: Bar Chart Representing the Distribution of Nuchal Translucency (NT) Values Among Study Participants.

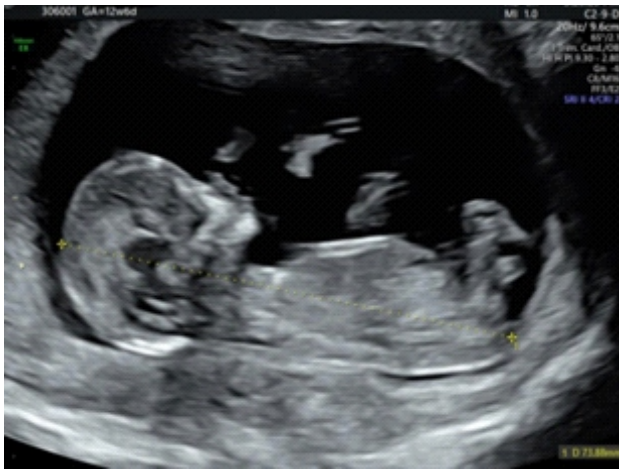

Figure 3: Ultrasound Image Showing the Measurement of Crown-Rump Length (CRL) At 12 Weeks And 6 Days of Gestation. the CRL is Approximately 73.88 MM, Which Falls Within the Normal Range for First-Trimester Screening

The CRL measurement was obtained for all cases, with values ranging between 45 mm and 84 mm, consistent with gestational age estimation criteria. The majority of cases had CRL measurements between 60 mm and 70 mm, indicating normal fetal growth.

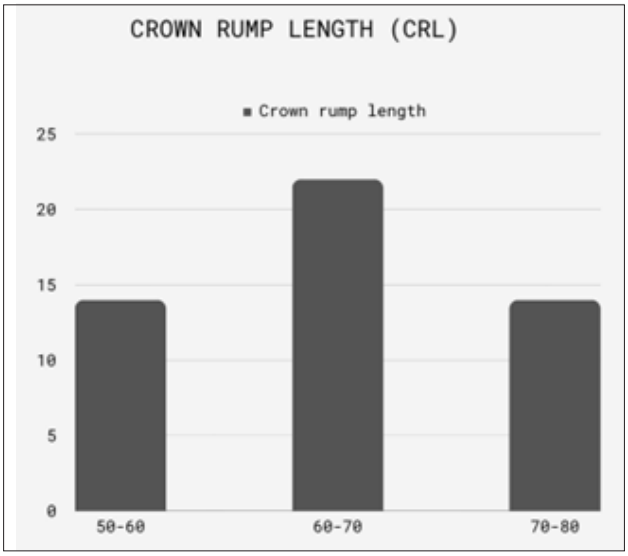

Figure 4: Distribution of Crown-Rump Length (CRL) Among Study Participants

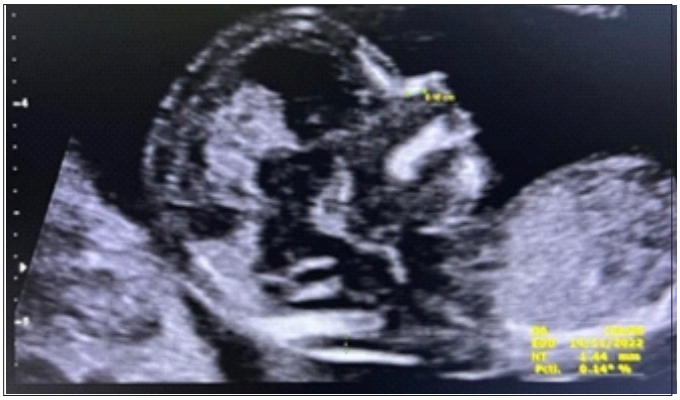

Figure 5: Ultrasound Image Demonstrating the Measurement of Nuchal Translucency (NT) at 13 Weeks and 3 Days of Gestation

The relationship between nuchal translucency and crown-rump length (CRL) in the study population. The data points demonstrate a dgenera-lly uniform istribution, with most NT values clustering within the normal range.

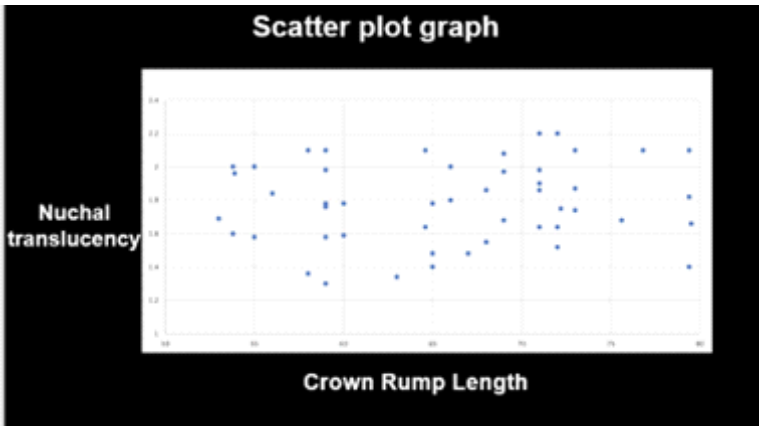

Figure 6: Scatter Plot Showing the Relationship Between Nuchal Translucency and Crown Rump Length (CRL)

· Pregnancy-associated plasma protein-A (PAPP-A): The measured PAPP-A levels were within the normal reference range of 0.3–4.2 IU/L for most cases. However, two cases showed significantly reduced PAPP-A levels.

· Beta-human chorionic gonadotropin (□-hCG): In the majority of cases, □-hCG levels followed the expected pattern for gestational age. Two cases demonstrated elevated □-hCG values, which initially suggested an increased risk of trisomy 21. However, further diagnostic evaluation was required.

The risk for aneuploidy was assessed using the Fetal Medicine Foundation (FMF) risk calculator, incorporating maternal age, NT measurement, and biochemical markers. The aneuploidy detection rate was estimated to range between 79–90%, with a false-positive rate of approximately 5%.

Two cases with abnormal marker levels underwent serial ultrasound assessments, which did not reveal any significant structural anomalies. Amniocentesis was performed in these cases, confirming the absence of trisomies.

DISCUSSION

Early risk assessment in prenatal screening is a critical component of modern obstetrics, aimed at identifying pregnancies at increased risk for chromosomal abnormalities, structural defects, and adverse pregnancy outcomes. The first-trimester screening combines ultrasound and biochemical markers, specifically nuchal translucency (NT) measurement, maternal serum pregnancy-associated plasma protein-A (PAPP-A), and maternal serum beta human chorionic gonadotropin (β-hCG). These markers, when used in combination, significantly improve the detection rate of fetal aneuploidies and other complications, such as preterm delivery and congenital abnormalities.

Nuchal translucency is a key ultrasound marker measured between 11 weeks 6 days and 13 weeks 6 days of gestation. An increased NT, defined as a measurement greater than the 99th percentile for gestational age, is associated with a higher risk of aneuploidies, such as trisomy 21, 18, and 13, as well as structural abnormalities, including congenital heart defects. The detection rate of NT alone for trisomy 21 is approximately 70%, but its efficacy is significantly enhanced when combined with biochemical markers like PAPP-A and □-hCG. Increased NT thickness is also linked to adverse pregnancy outcomes, such as preterm delivery and fetal loss, necessitating further diagnostic testing and genetic counseling.

PAPP-A is a glycoprotein produced by the placenta, and its levels are significantly lower in pregnancies affected by trisomy 21. Low PAPP-A levels in the first trimester are also associated with other adverse outcomes, including fetal loss, preeclampsia, placental abruption, and fetal growth restriction. Studies have shown that PAPP-A levels below the 5th percentile multiple of the median (MoM) are predictive of preterm and early preterm delivery, with odds ratios (OR) ranging from 1.56 to 2.99 depending on gestational age at delivery [9, 17, 18]. This makes PAPP-A a valuable marker not only for aneuploidy screening but also for identifying pregnancies at risk for preterm birth.

β-hCG is another critical biochemical marker used in first-trimester screening. In pregnancies affected by trisomy 21, □-hCG levels are typically elevated, often doubling compared to normal pregnancies. Conversely, low levels of β-hCG are associated with trisomy 18 and 13. The combination of β-hCG and PAPP-A with NT measurement significantly improves the detection rate of aneuploidies, with a combined detection rate of up to 90% for trisomy 21 at a 5% false-positive rate [19]. Additionally, β-hCG levels are used to monitor the progression of pregnancy, with serial measurements providing insights into the viability of the pregnancy and the risk of miscarriage.

The integration of NT, PAPP-A, and β-hCG into a combined screening approach allows for a more accurate risk assessment. The measured concentrations of these markers are converted into multiples of the median (MoM), and the risk is calculated using algorithms such as the Fetal Medicine Foundation risk calculator. This combined approach not only improves the detection rate of aneuploidies but also identifies pregnancies at risk for other complications, such as preterm delivery and fetal growth restriction. For example, low PAPP-A levels (<0.3 MoM) are automatically flagged in prenatal screening reports, prompting further monitoring and intervention [17-19].

The data from various studies, including those by Ong et al. [9], Smith et al. [17], and Krantz et al. [18], confirm the predictive value of first-trimester biochemical markers for preterm delivery. Low PAPP-A and β-hCG levels are consistently associated with an increased risk of preterm birth, with detection rates ranging from 7.8% to 15.0% depending on the gestational age at delivery [20].These findings suggest that first-trimester screening markers can be used not only for aneuploidy detection but also for identifying pregnancies at risk for adverse outcomes, such as preterm delivery.

However, the clinical utility of these markers is often limited by the wide range of data presentation and the lack of standardized interventions for women identified as high-risk. For example, while tocolytic administration has been used to prevent preterm delivery, recent systematic reviews have shown limited efficacy [21]. Prophylactic administration of progesterone, particularly in women with a history of preterm birth, has shown promise in reducing the recurrence rate, but further research is needed to refine risk stratification and treatment protocols [22]. Incorporating cervical length measurement at 22–24 weeks' gestation into the risk assessment algorithm may improve the identification of women at risk for preterm delivery [23]. Additionally, further studies are needed to explore the role of PAPP-A and β-hCG in predicting other adverse outcomes, such as preeclampsia and fetal growth restriction, and to develop targeted interventions for these conditions.

CONCLUSION

First-trimester screening, combining ultrasound-based nuchal translucency (NT) measurement with maternal biochemical markers, such as free □-hCG and PAPP-A, significantly improves the detection of common trisomies. These markers show distinct patterns of up and down regulation in trisomies 21, 18, and 13. Screening between 11 weeks 6days and 13 weeks 6 days has proven to be an effective and reliable test for detecting aneuploidies. Elevated NT and abnormal biochemical markers prompt further assessment through chorionic villus sampling and follow-up scans. The earlier identification of pregnancies at risk for aneuploidy, cardiac anomalies, and the option of early diagnosis and management.

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