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Combined Screening for Chromosomal Aneuploidies in the First Trimester: Results and Risk Assessment in an Indian Tertiary Care Population

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Abstract

Background: For the early detection of chromosomal aneuploidies, first trimester combination screening (FTCS), which combines nuchal translucency (NT) ultrasonography with maternal serum free beta-human chorionic gonadotropin (free beta-hCG) and pregnancy-associated plasma protein-A (PAPP-A), is recommended worldwide. Due to the lack of population-specific data on FTCS performance and risk distribution in India, clinical practice must be guided by institution-level outcome assessments.

Objectives: to examine the biochemical marker profiles, risk stratification patterns, and screening outcome distribution in a tertiary care cohort of 1941 pregnant women receiving FTCS.

Methods: 1941 singleton pregnancies at 11+0 to 13+6 weeks of gestation were the subject of a retrospective observational study. In addition to maternal age and clinical history, the combined test protocol included NT measurement, free beta-hCG, and PAPP-A levels represented as multiples of the median (MoM). The Fetal Medicine Foundation (FMF) methodology was used for risk categorization.

Results: 1841 (94.85%) of the 1941 pregnancies were categorized as low risk. There were 33 (1.70%), 7 (0.36%), and 2 (0.10%) instances with increased risk for Trisomy 21 (T21), T18, and T13, respectively. 124 (6.39%) women were identified as having advanced maternal age (AMA). Biochemical abnormalities included low PAPP-A MoM in 12 (0.62%) instances and excessive free beta-hCG MoM in 118 (6.08%) cases. Eight instances (0.41%) had ultrasonography abnormalities, and ten cases (0.52%) were classified as intermediate risk.

Conclusion: With a high percentage of low-risk outcomes, FTCS successfully stratified chromosomal risk in the research cohort. The significance of biochemical and clinical risk factors in Indian obstetric populations is highlighted by the high rates of AMA and elevated free beta-hCG. These results emphasize the necessity of integrated counseling protocols in tertiary care settings and encourage the regular application of FTCS.

Keywords: *first trimester screening, nuchal translucency, PAPP-A, free beta-hCG, chromosomal aneuploidy, trisomy 21*

1. INTRODUCTION

Worldwide, congenital anomalies, cognitive disabilities, and pregnancy loss are primarily caused by chromosomal aneuploidies, specifically Trisomy 21 (Down syndrome), Trisomy 18 (Edwards syndrome), and Trisomy 13 (Patau syndrome) [1]. By enabling accurate risk assessment as early as 11 to 13 weeks and 6 days of gestation, first trimester combined screening (FTCS) revolutionized prenatal care in the late 1990s. This allowed for prompt counseling and the possibility of an early, definitive diagnosis through chorionic villus sampling (CVS) [2, 3].

Maternal age, nuchal translucency (NT) thickness as determined by ultrasonography, and maternal serum concentrations of free beta-human chorionic gonadotropin (free beta-hCG) and pregnancy-associated plasma

protein-A (PAPP-A), expressed as multiples of the gestational age median (MoM), are all combined in the FTCS algorithm. This combination method produces a detection rate of about 90% for Trisomy 21 at a 5% false-positive rate, as confirmed by the Fetal Medicine Foundation (FMF) [4]. In specialist centers, additional markers such as nasal bone, tricuspid regurgitation, and ductus venosus Doppler waveform may help to further improve the risk assessment.

Historically, the main justification for invasive testing has been advanced maternal age (AMA), which is defined as a mother who is 35 years of age or older at the time of birth. However, the paradigm has evolved toward universal screening, with AMA acting as an auxiliary risk factor within the combined algorithm, due to the realization that a considerable percentage of chromosomally defective births occur in younger moms [5]. The therapeutic value of FTCS goes beyond chromosomal risk alone because biochemical markers including low PAPP-A MoM and high free beta-hCG MoM are also linked to unfavorable obstetric outcomes such preeclampsia, fetal growth restriction, and preterm birth [6,7].

The prenatal screening landscape in India is changing quickly. The epidemiology of chromosomal anomalies is shaped by a number of factors, including increased urbanization, delayed childbearing, rising consanguinity in some populations, and restricted access to genetic counseling. To describe regional risk trends, direct the calibration of laboratory reference ranges, and influence national prenatal screening policies, institution-level data from Indian tertiary institutions are crucial. There are still few published studies that provide thorough risk distribution data from the Indian subcontinent, despite the growing adoption of FTCS in urban hospitals.

The goal of the current study was to examine how screening results were distributed among 1941 pregnant patients who had FTCS at a tertiary care facility in Chennai, Tamil Nadu. Quantification of biochemical marker abnormalities, determination of the percentage of pregnancies flagged owing to AMA, and classification of risk categories (low, moderate, elevated, and ultrasound-based) were among the specific goals. The results are meant to add to the expanding body of evidence supporting context-specific FTCS program improvement in India.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

A retrospective observational study was conducted at the Department of Obstetrics and Gynaecology of a tertiary care teaching hospital affiliated with Dr. M.G.R. Educational and Research Institute, Chennai, India. The study period encompassed consecutive first trimester screenings performed over a defined interval. Ethical approval was obtained from the Institutional Ethics Committee (IEC Ref. No.: [XXXX]), and patient data were anonymized prior to analysis.

2.2 Study Population

Included were 1941 singleton pregnancies with gestational ages ranging from 11+0 to 13+6 weeks. Crown-rump length (CRL) measurements taken during the NT scan were used to establish gestational age. Multiple gestations, known chromosomal or structural fetal abnormalities identified before the index scan, incomplete biochemical data, and scan quality inappropriate for NT measurement according to FMF standards were among the exclusion criteria.

2.3 First Trimester Combined Screening Protocol

Sonographers with FMF certification conducted all ultrasound evaluations. The published FMF guidelines were followed when measuring nuchal translucency. Between 10+0 and 13+6 weeks, maternal venous blood was drawn for PAPP-A and free beta-hCG serum measurement. Gestational age-specific medians from the laboratory's reference population were used to convert analyte concentrations to MoM values. The FMF combination test algorithm was used to calculate risk, taking into account maternal age, NT MoM, free beta-hCG MoM, and PAPP-A MoM. Results were categorized as elevated risk (1 in 150), intermediate risk (1 in 151 to 1 in 1000), and low risk (less than 1 in 1000) using a prior risk cutoff of 1 in 150.

2.4 Variable Definitions

Advanced Maternal Age was defined as maternal age >= 35 years at estimated date of delivery. High free beta-hCG MoM was defined as a value > 2.0 MoM, and Low PAPP-A MoM as < 0.4 MoM, consistent with established biochemical risk thresholds. Ultrasound abnormality was recorded when structural findings beyond NT elevation were identified at the first trimester scan.

2.5 Statistical Analysis

Categorical variables were summarized as frequencies and percentages. Data were analyzed using Microsoft Excel and IBM SPSS Statistics v26. Figures were generated using Python 3 (Matplotlib library). All percentages were computed relative to the total cohort of 1941 cases.

3. RESULTS

3.1 Overall Screening Outcomes

During the study period, 1941 pregnant women had combination screening during the first trimester. Table 1 shows the distribution of all screening results, and Figure 1 provides a visual representation. 1841 women (94.85%) of the cohort as a whole were categorized as low risk, reflecting a comfortingly high percentage of normal test results. Ten instances (0.52%) were classified as intermediate risk, and forty-two pregnancies (2.16%) were found to be at higher risk for one of the three major aneuploidies.

3.2 Chromosomal Risk Stratification

Trisomy 21 was found in 33 pregnancies (1.70% of all cases with higher risk), followed by Trisomy 18 in 7 instances (0.36%) and Trisomy 13 in 2 cases (0.10%). The current cohort's prevalence of elevated T21 risk is in line with estimates from tertiary care populations around the world. For Trisomy 21, ten instances (0.52%) were classified as intermediate risk (1:151 to 1:1000), which calls for careful observation or more research. The comparative distribution of chromosomal risk categories and anomalies in biochemical markers is shown in Figure 3.

3.3 Ultrasound Abnormalities

Eight pregnancies (0.41%) were flagged on the basis of ultrasound abnormalities identified at the first trimester scan, including increased NT, absent nasal bone, and other structural findings. These cases were referred for detailed anomaly assessment and genetic counselling.

3.4 Advanced Maternal Age

Advanced maternal age (AMA, >= 35 years) was recorded in 124 women (6.39% of the cohort). AMA independently increases the background risk for autosomal trisomies and serves as a significant contributor to elevated combined test risk. The proportion of AMA in the present cohort reflects the pattern of deferred childbearing increasingly observed in urban Indian populations.

3.5 Biochemical Marker Abnormalities

High free beta-hCG MoM (> 2.0 MoM) was observed in 118 pregnancies (6.08%), representing the second most frequent finding in the cohort. Low PAPP-A MoM (< 0.4 MoM) was recorded in 12 cases (0.62%). Among low-risk cases, 9 (0.46%) showed concurrent high BHCG, and 5 (0.26%) showed abnormal PAPP-A MoM, indicating biochemical risk factors in the absence of an elevated combined test risk score. One case had a family history of genetic abnormalities; no case in the cohort had a previous history of chromosomal abnormalities.

Table 1: Distribution of First Trimester Screening Outcomes (n = 1941)

Screening Parameter / Risk Category	Number of Cases	Percentage (%)
Total Number of Cases	1941	100.00
Low Risk	1841	94.85
Increased Risk for T21 (Trisomy 21)	33	1.70
Increased Risk for T18 (Trisomy 18)	7	0.36
Increased Risk for T13 (Trisomy 13)	2	0.10

Screening Parameter / Risk Category	Number of Cases	Percentage (%)
Intermediate Risk	10	0.52
Ultrasound Abnormality	8	0.41
Advanced Maternal Age (AMA)	124	6.39
High Free Beta-HCG MoM	118	6.08
Low PAPP-A MoM	12	0.62
Low Risk with High BHCG	9	0.46
Low Risk with Abnormal PAPP-A MoM	5	0.26
Previous History of Chromosomal Abnormalities	0	0.00
Family History of Genetic Abnormalities	1	0.05

T21 = Trisomy 21 (Down syndrome); T18 = Trisomy 18 (Edwards syndrome); T13 = Trisomy 13 (Patau syndrome); MoM = Multiples of the Median; BHCG = Free Beta Human Chorionic Gonadotropin; PAPP-A = Pregnancy-Associated Plasma Protein-A.

Figure 1: Distribution of First Trimester Screening Outcomes

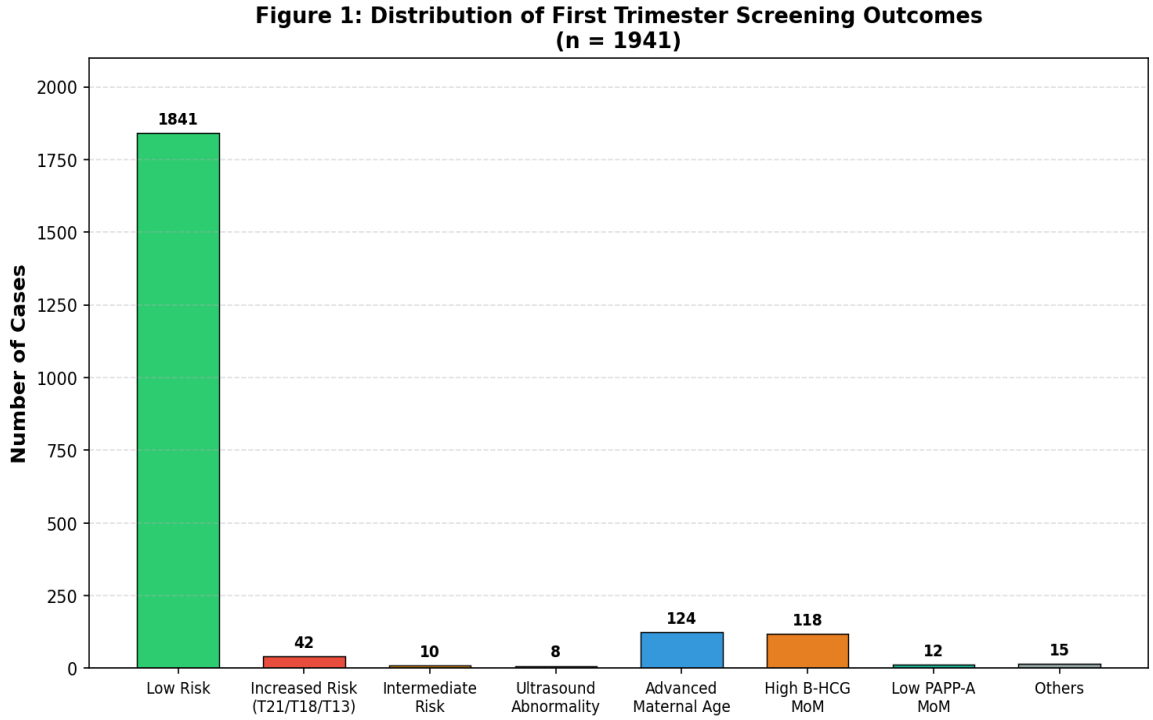

Figure 1. Bar chart showing the absolute number of cases across all first trimester screening outcome categories (n = 1941).

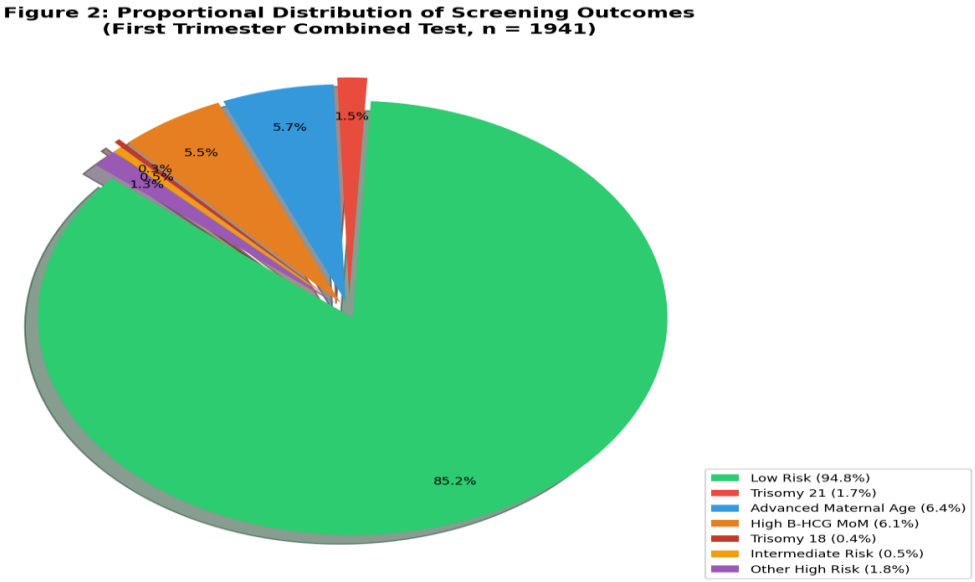

Figure 2. Pie chart illustrating the relative proportional distribution of screening outcome categories as a percentage of the total cohort.

Figure 3: Chromosomal Risk and Biochemical Marker Abnormalities

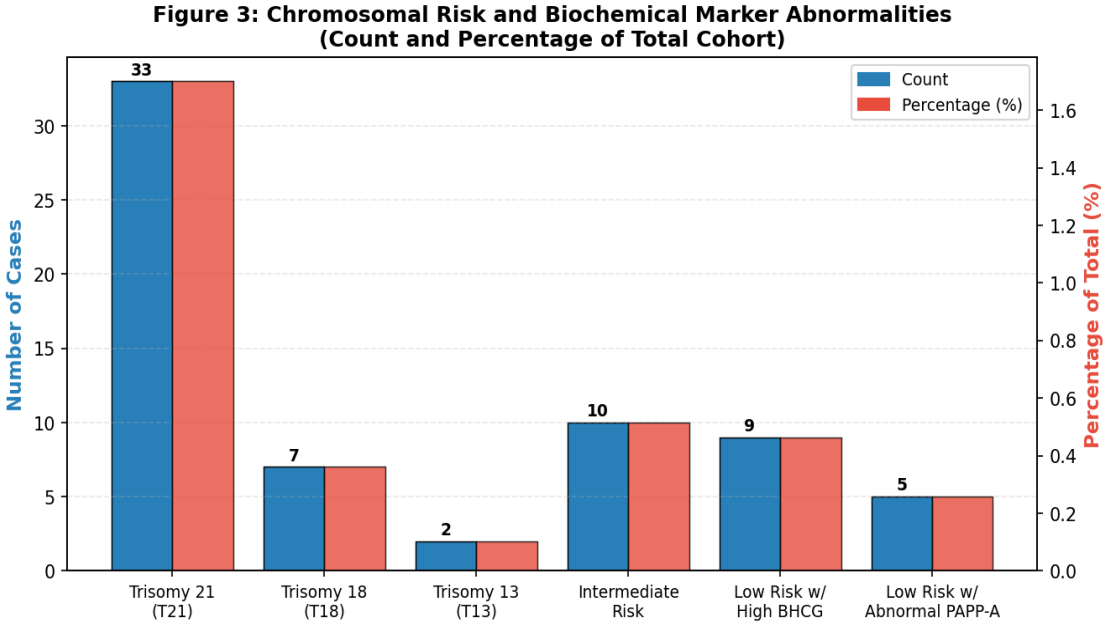

Figure 3. Grouped bar chart comparing the count (left axis) and percentage of total cohort (right axis) for each chromosomal risk category and biochemical marker abnormality subgroup.

4. DISCUSSION

In this study, a cohort of 1941 women who visited a tertiary care hospital in Chennai, India, had their first trimester combination screening results examined. The percentage of low-risk outcomes (94.85%) is consistent with existing global benchmarks, according to which, at a 5% false-positive rate threshold, FTCS algorithms employing the FMF methodology normally classify 85% to 95% of screened pregnancies as low risk [4,8]. This gives assurance about the screening program's specificity at the research facility.

The rate of increased risk for Trisomy 21 (1.70%) in the present cohort is notably higher than the expected population-based birth prevalence of approximately 1 in 800 to 1 in 1000 live births, which is expected given that FTCS screens all pregnancies including those that may subsequently undergo termination, miscarriage, or confirmed chromosomal diagnosis. Similarly, the detection of 7 cases at increased risk for Trisomy 18 and 2 for Trisomy 13 aligns with the lower relative prevalence of these conditions compared to Down syndrome, and their association with more severe ultrasound phenotypes that augment algorithm risk scores [9].

A particularly noteworthy finding in this cohort is the high proportion of cases flagged for Advanced Maternal Age (6.39%). This is substantially higher than the global AMA prevalence of 2-3% reported in population-based datasets, and likely reflects the demographic profile of women attending this urban tertiary institution, where delayed marriage and childbearing are increasingly common. AMA contributes an age-dependent prior risk to the combined test algorithm, and its high frequency in the study population is likely a contributing factor to the absolute number of increased-risk results observed [10].

The finding of elevated free beta-hCG MoM in 6.08% of the cohort warrants clinical attention beyond chromosomal risk. Isolated elevation of free beta-hCG in the first trimester, in the absence of an increased combined test risk score, has been associated with adverse placental outcomes, including preeclampsia, fetal growth restriction, and preterm labour [6]. Similarly, the 12 cases of low PAPP-A MoM (0.62%) represent a high-risk subgroup for placenta-mediated complications, even when the chromosomal risk score may be within the low range. The 9 low-risk cases with concurrent high BHCG and 5 with abnormal PAPP-A MoM identified in this study would benefit from additional surveillance including uterine artery Doppler assessment and aspirin prophylaxis protocols consistent with FMF guidelines.

The 8 cases flagged for ultrasound abnormalities (0.41%) highlight the indispensable role of high-resolution first trimester ultrasonography as a complement to biochemical markers. Structural findings such as absent nasal bone, tricuspid regurgitation, increased NT, ductus venosus abnormalities, and early structural defects of the cardiac outflow tract may markedly elevate the combined risk estimate and indicate the need for prompt further evaluation [3,11]. The integration of these sonographic markers into the routine FTCS protocol is increasingly feasible in tertiary centres with trained operators.

The absence of any prior chromosomal history in the cohort, and only one case with family history of genetic abnormality, suggests that the majority of detected risk cases arise de novo in the studied population. This underscores the importance of universal (rather than selective) screening strategies, as most high-risk cases would not have been identified through history-based referral alone.

Several limitations of the current study merit acknowledgment. As a single-centre retrospective analysis, the findings may not be fully representative of the broader Indian obstetric population, which is heterogeneous in terms of ethnicity, socioeconomic status, and access to prenatal care. The absence of follow-up data on pregnancy outcomes, amniocentesis or CVS results, and live birth records precludes computation of actual detection rates and false-positive rates for this cohort. Future prospective studies incorporating outcome tracking would significantly strengthen the evidence base. Additionally, the laboratory reference medians applied in this study were not independently validated for the local ethnic population, which may introduce systematic bias in MoM calculations.

Notwithstanding these limitations, the data presented here contribute meaningfully to the growing literature on FTCS utilization in India. The findings support the clinical value of the combined algorithm in routine tertiary care practice and highlight areas for further quality improvement, including systematic outcome tracking, local MoM calibration, and structured counselling pathways for women with biochemical marker abnormalities in the absence of increased chromosomal risk.

5. CONCLUSION

In this cohort of 1941 pregnancies, chromosomal aneuploidy risk was successfully stratified by first trimester combination screening, with a high proportion of low-risk classifications in line with international standards. The most common chromosomal risk found was trisomy 21, and a significant percentage of women had advanced maternal age, which reflects the demographic patterns of urban Indian tertiary care settings. The most common biochemical anomaly was elevated free beta-hCG MoM, which calls for targeted obstetric surveillance to prevent placenta-mediated unfavorable consequences. To maximize the effectiveness of the FTCS program, it is advised to include additional first trimester sonographic markers and implement thorough outcome tracking. These results offer a helpful institutional baseline for future prenatal screening quality improvement projects.

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