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First Trimester Screening for Fetal Aneuploidy and its Outcome

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ABSTRACT
This prospective observational study aimed to evaluate the clinical utility of first trimester screening markers, including serum Beta human chorionic gonadotropin (ß-hCG), Pregnancy-associated plasma protein-A (PAPP-A) and Nuchal translucency (NT) measurements, in detecting fetal aneuploidies and assessing fetal outcomes. Primigravidae with singleton pregnancies underwent first-trimester screening between 11+0-13+6 weeks of gestation, comprising serum ß-hCG and PAPP-A measurements, along with NT ultrasonography. Pregnancy outcomes were monitored, including medical termination, miscarriages, stillbirths, low birth weight, intrauterine growth retardation, preterm birth and intrauterine death. Patients with positive screening results underwent confirmatory testing via amniocentesis. Among 115 patients, four screened positive, of whom three were diagnosed with Down syndrome and one tested negative for aneuploidy. Statistical analysis revealed a sensitivity and specificity of 75% and 63%, respectively, for the combined markers and NT in detecting chromosomal abnormalities. Maternal serum ß-hCG, PAPP-A and NT measurements in the first trimester serve as valuable screening tools for assessing the risk of fetal trisomies. Early identification enables informed decision-making regarding diagnostic testing and potential options for safe termination, thereby enhancing prenatal care and management strategies.

INTRODUCTION

Screening for fetal chromosomal abnormalities has evolved significantly since the mid-1960s when maternal age was initially used as the primary screening criterion. Advances in maternal serum screening and ultrasound techniques have enabled non-invasive screening tests for all pregnant individuals to assess their risk of fetal aneuploidies and determine the need for invasive prenatal diagnostic testing[1]. Screening involves surveying a population using specific markers with defined cutoff levels to identify individuals at higher risk for a particular disorder[2]. It is imperative that screening markers are sensitive with minimal false-positive rates and accurate diagnostic tests are available to confirm positive results, ensuring timely interventions for affected individuals[3].

Aneuploidies, such as Trisomy 18 (T18), Trisomy 13 (T13) and Trisomy 21 (T21), are major contributors to perinatal mortality and early psychophysical disorders. These conditions are associated with severe malformations and mental retardation, often leading to intrauterine death[4]. Thus, screening tests play a crucial role in identifying individuals at higher risk within the population. Screening programs encompass comprehensive provision of understandable information to patients and healthcare providers, facilitating timely assessment, informed decision-king, referral for follow-up testing and interventions to reduce fetal morbidity and mortality[5].

Nuchal translucency is the maximum thickness of the subcutaneous translucent space which is present between the skin and the soft tissues below the fetal spine at the back of the neck which is noticed in the late first trimester typically at (11-4 weeks of gestation)[6]. NT measures <2.5 mm: Risk is 5 times less >2.5 mm: Risk is 12 times more. 25. The phenotypic expression of trisomies, Turner syndrome and triploidies is increased NT at 11weeks-4 weeks, however this resolves after first trimester usually or it develops into hydrops[7]. At 11+0-4+0 weeks, the fetal lymphatic system will be developing and the peripheral resistance of the placenta will be high. After 14 weeks the lymphatic system would have developed sufficiently which drains away excess fluid if any and changes to placental circulation. So, after 14 weeks abnormalities causing accumulation of fluid may seem to get corrected and go missing undiagnosed[8].

Double Markers Include:

- Free beta human chorionic gonadotropin.
- Pregnancy associated plasma protein A.

Beta Human Chorionic Gonadotropin is a glycoprotein with biological activity similar to that of LH and is produced by placental syncytiotrophoblastic cells. It is structurally related to 3 other glycoprotein hormones-LH, FSH and TSH. All 4 glycoproteins share a common alpha subunit as it is made up of two subunits alpha and beta. The beta subunit is unique and distinguishes hCG from the other glycoprotein hormones[9]. Beta hCG peaks at 8-10 weeks in the maternal serum and then declines to reach a plateau at 18-20 weeks of gestation and remains constant till term. This change in hCG concentration in the pregnancy shows the importance of accurate gestational age estimation while interpreting aneuploidy screening strategies that include hCG[10]. Pregnancy Associated Plasma Protein-A PaPP-A is a glycoprotein encoded by the PaPP-A gene, which is located on human chromosome 9q33.159. PaPP-A is an established marker used in first trimester for screening of Down's syndrome and there has been emerging evidence that serum PaPP-A levels could predict adverse pregnancy outcomes in early pregnancy[11]. The performance of PaPP-A and free beta-hCG depends on gestational age in these screening programs. Studies have tested the hypothesis that low maternal serum levels of PaPP-A in the first trimester can predict adverse pregnancy outcomes associated with poor placental function[12-14].

Effective screening for fetal aneuploidies during the first trimester is feasible using a combination of tests including Nuchal translucency (NT) measurement, free beta-hCG, and Pregnancy-associated plasma protein-A (PAPP-A) levels between 11+0-13+6 weeks of gestation[15]. These tests offer a detection rate of 90% with a 5% false-positive rate. Importantly, they enable risk assessment for fetal chromosomal aberrations while potentially reducing the need for invasive procedures like chorionic villous sampling and amniocentesis, which carry a risk of miscarriage[1].

National guidelines, such as those issued by the National Board of Health in Denmark, recommend offering first-trimester combined risk assessment for T21 to all pregnant women[16].

MATERIALS AND METHODS

The study was conducted on patients in the outpatient department and the Inpatient department at SDM College of Medical Sciences and Hospital. All patients falling under inclusion criteria with the informed and written consent underwent blood investigations like serum Beta hCG, PaPP-A and an ultrasonography was performed to measure NT as a first trimester screening procedure and the impact of normal and abnormal values on the fetal outcome were assessed.

Type of Study: A prospective observational study.

Study Period: 1 year.

Sample Size: A total of 115 primigravidae with singleton pregnancies who underwent first-trimester screening were included in the study. Blood

investigations for serum beta-hCG, PAPP-A and NT measurements were performed and patient-specific risks for aneuploidies were calculated based on multiple factors including gestational age, maternal characteristics and assay methodologies.

Inclusion Criteria: All primigravidae with singleton pregnancies, irrespective of the age who are willing for the study.

Exclusion Study: Multigravida, Multiple pregnancies sampling population: All Primigravidae with singleton pregnancies, irrespective of the age who are willing for the study during the study period.

Data Collection: After obtaining permission from the institutional ethical committee and informed and written consent from the patient, prospective observational study was conducted. The participants underwent first trimester screening tests. Maternal serum free Beta HCG and PAPP-A were measured and an ultrasound examination was carried out to measure fetal NT to diagnose any major fetal abnormalities. All scans were carried out between 11+0-to-13+6 weeks of gestation. Data on pregnancy outcome were obtained by regular follow up at SDM hospital. The association between free ß-hCG, PaPP-A and NT measurements and the incidence of miscarriages, MTP, preterm deliveries, full term deliveries, low birth weight, intra uterine growth retardation, still births etc. were assessed.

RESULTS AND DISCUSSIONS

A total of 41.7% of participants belonged to the age group of (26-30 years), 25.5% of them belonged to (21 to 25 years), 20% belonged to (31-35), 7% and 6.1% belonged to the age group of ≤20 and >35 years respectively. (Table 1).

Table 1: Distribution of Participants According to the Age

Age groups (years)	Number	Percentage
≤20	8	7.0
21-25	29	25.2
26-30	48	41.7
31-35	23	20.0
>35	7	6.1
Total	115	100.0

Distribution of patients according to the age who tested screen positive shown in (Table 2).

Table 2: Distribution of Patients According to the Age who Tested Screen Positive

Age groups (years)	Number	Percentage
≤20	0	0
21-25	1	25
26-30	1	25
31-35	1	25
>35	1	25
Total	4	100.0

Out of 115 participants, second degree consanguineous marriage was represented in 6% of them and third-degree consanguineous marriage was represented in 2.7% of them and 113 participants had no h/o consanguinity. (Table 3).

Table 3: Distribution of Participants According to Consanguinity

Consanguinity	Number	Percentage
NCM	105	91.3
2nd degree	7	6
3rd degree	3	2.7
Total	115	100.0

Distribution of patients according to consanguinity who tested screening tests positive shown in (Table 4).

Table 4: Distribution of Participants According to Consanguinity who Tested Screen Positive

Consanguinity	Number	Percentage
NCM	3	75%
2nd degree	1	25%
3rd degree	0	0
Total	4	100.0

All the screening tests that are performed should be efficient enough to identify an anomaly at the right time and should be able to offer a solution. Most women prefer screening to be performed early in pregnancy and the fetus to be diagnosed with aneuploidies so that the women can opt for safer termination of pregnancy in the first trimester itself. Therefore, Prenatal screening between 11+0 weeks to 13+6 weeks of gestation using maternal serum beta hCG, PaPP-A and nuchal translucency measurements is becoming more and more available and efficient worldwide. Moreover, the introduction of these first trimester combined screening methods also resulted in a marked decrease in the number of diagnostic invasive testes. A study conducted by Malone FD *et al*., also concluded that the sensitivity of first trimester screening (87%) is much more than second trimester tests (81%)[17].

The first trimester methods have higher sensitivity in comparison to other tests and cost-effective since the indication of number of invasive procedures will be clearly defined. One of the biggest advantages of the first trimester screening test is that counselling and invasive diagnosis of chromosomal defects can be accomplished early in pregnancy thus significantly reducing the anxiety in the patient by providing the option of early termination of pregnancy so that the situation becomes less complicated for both the patient and the obstetrician.

According to Carlson LM and Vora NL, the double marker test is only a screening test which provides a risk for the genetic disorder, but not the diagnosis[18].

The outcome of prenatal screening is in the form of screen positive or screen negative for Trisomy 21 and these results are based on the laboratory specific cut-offs.

The sensitivity of the estimated risk significantly depends on the accuracy of the information provided. The necessary adjustments are made in the measured maternal serum concentration of free ß-hCG and PaPP-A in accordance with the gestational age, maternal age, weight, ethnicity, smoking status, history of insulin dependent diabetes mellitus, method of conception, parity.

Hence, it is essential to submit accurate information along with maternal sample to laboratory for risk assessment failing which may lead to significant alterations.

A study conducted by Spencer K, Souter V estimated that, using the combination of age of the mother, Nuchal translucency levels and maternal serum markers (free beta hCG and PaPP-A, the detection of trisomy 21 pregnancies would be 89% at a fixed false-positive rate of 5%. Alternatively, at a fixed detection rate of 70%, the false- positive rate would be 1%[19].

A study conducted by Wright D showed that first-trimester prenatal screening encompassing a combination of maternal serum biochemistry assays (free ß-hCG and PaPP-A) and ultrasound-assessed nuchal translucency (NT) enables accurate identification of approximately 90% of chromosomal abnormalities with 5% false positive results[20,21].

Limitations of the study include a relatively small sample size compared to studies with larger cohorts, which may affect the generalizability of the results to the broader Indian population. Conducting the study at a single centre may limit the representativeness of the findings. Furthermore, the timing of tests could impact screening performance, as serum markers and NT measurements are influenced by gestational age. Variability in NT measurements due to multiple observers introduces potential error through inter-observer variation.

Screening tests are not confirmatory, leading to the possibility of false-negative results, particularly for cases with aneuploidies. Additionally, uncertainty in pregnancy outcomes for trisomies 21, 18 and 13 due to the absence of diagnostic tests like amniocentesis and chorionic villous sampling may result in underestimation of screening performance.

Notably, neonates with sex chromosome aneuploidy and other chromosomal abnormalities may present as phenotypically normal, unlike trisomies 21, 18 and 13. The absence of karyotyping for the entire population could lead to underestimation of the true prevalence of these abnormalities and overestimation of screening test sensitivity.

For instance, while screening for trisomies 21, 18 and 13 may identify a substantial proportion of foetuses with sex chromosome aneuploidies, the true sensitivity of prenatal screening tests may be lower than estimated, highlighting the need for cautious interpretation of results and further investigation into the efficacy of screening methods.

The combined test provides effective screening for trisomies 21, 18 and 13 and helps identify a high proportion of other chromosomal abnormalities, at a FPR of 4%.

In the last 5 years, a major improvement in screening for trisomies has been achieved through analysis of cell free fetal DNA in maternal blood.

A meta-analysis of clinical validation and implementation studies reported that, with cfDNA testing, the DR for trisomies 21, 18 and 13 were 99%, 96% and 91%, respectively, at an overall FPR of 0.35%74.

Universal screening by cfDNA testing as an alternative to the combined test would improve the DR of trisomy 21 and reduce the rate of invasive testing. However, such policy would be expensive and ignores the other benefits of the combined test, including early detection of many major fetal defects, diagnosis of multiple pregnancy and its chorionicity, detection of chromosomal defects other than trisomies 21, 18 and 13 and early prediction of pregnancy complications, such as pre-eclampsia, with the potential of prevention through prophylactic pharmacological interventions.

CONCLUSION

Using maternal serum free beta hCG, Pregnancy associated plasma protein-A along with Nuchal translucency measurements as a first trimester screening methods are helpful in assessing the risk of trisomies during the first-trimester which will help in selecting the patients with screen positive results to offer the option of diagnostic tests so that the mother will have an option to opt for safe termination methods during the first trimester itself.

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