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EVALUATION OF FIRST TRIMESTER CONTINGENT TEST FOR DOWN'S SYNDROME SCREENING

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ABSTRACT: Down's syndrome is the most common chromosomal disorder among children. There are various screening strategies to detect Down's syndrome antenatally, each having its own advantages and disadvantages. Much research is being carried out to improve the detection rate, lower the false positive rate and to make it more cost effective. The emphasis is on first trimester screening as it allows us to reassure the majority of patient's early on in pregnancy and allows the patient to take an early decision regarding continuation of pregnancy. The gold standard of first trimester screening is the 'combined test'. Combined test involves measurement of Nuchal Translucency (NT) in all cases, and is difficult to implement in a developing country like India. Our study on first trimester 'contingent screening' showed that NT was required in 22% cases only, and the overall detection rate and the false positive rate were comparable to combined screening. Furthermore, this screening strategy is cost effective and will be easier to implement in our country. The study is being continued to include larger number of patients to evaluate the outcome analysis data more accurately.

KEYWORDS: Down's syndrome, contingent test, screening

INTRODUCTION: Down's syndrome, a classic chromosomal disorder resulting in mental retardation and severe congenital disorders, was the first medical condition known to be associated with a chromosomal abnormality. With increase maternal age, incidence of Down's syndrome is increasing considerably, now it is one in every 800-1000¹ live births. Prenatal diagnosis of chromosomal disorders using amniocentesis has been well established since the early 1970s. Amniocentesis is done at 16 weeks and termination of pregnancy if required is more difficult and traumatic at late stages of pregnancy². Early detection through screening in the first trimester is more helpful in prenatal diagnosis of Down's syndrome.

This will provide the option of early termination of pregnancy and better obstetric care to the women with Down's syndrome pregnancies. The recommended screening strategies are the first trimester combined ultrasound and biochemical (CUB) screening, integrated testing and serum integrated testing. There is ongoing research how to diagnose a Down's syndrome baby in poor set up without compromise the case detection rate and false positive rate. In this way the test which was used in the study is first trimester contingent test. These tests are expected to further improve the performance of Down's syndrome screening programmes³. Several studies have been done throughout the world to detect the syndrome in early weeks by free beta hCG and PAPP-A and Nuchal Translucency (NT) measurements. But it is not cost effective and also laborious. So, contingent test is appropriate for developing country like India as it cost effective. This study was planned to evaluate a model of Down's syndrome screening called "Contingent Screening" in our hospital setting.

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MATERIALS AND METHODS: CRL was measured with USG, and serum β hCG and PAPP-A were measured with appropriate methods in 100 consecutive women over 30 years of age at less than 13 weeks period of gestation. They were classified into three categories according to table 1.

Category	Criteria
High Risk	Cut off was defined as an estimated risk 1: 50 or higher.
Intermediate Risk	Cut-off was defined as an estimated risk <1: 50 to >1: 1000.
Low risk	Cut-off was defined as an estimated risk 1: 1000 or lower.

TABLE 1

The high risk group was counselled for invasive procedure for fetal karyotype. Low risk was counselled for continuing the pregnancy and intermediate group was counselled for NT. Intermediate group were recruited in 2nd step of contingent test after proper counselling for NT measurement. After measuring NT the women were recategorized into two groups according to the following table 2.

Category	Criteria
High Risk	The cut-off value $\geq$ 1: 100
Low risk	The cut-off value < 1: 100

TABLE 2

Low risk group were counselled for continuing pregnancies and high risk group were counselled for invasive procedure for fetal karyotype. Then they were followed up till delivery. After delivery if there was any clinical stigma for Down's syndrome we offered karyotype for confirmation for trisomy 21. If during follow up any miscarriage was occurred we offered karyotype to know the status of the product of conception. Data on pregnancy outcomes were obtained either from our local maternity delivery database for those who delivered in this institute or via telephone calls to the patients themselves. Then the outcome analysis of the first trimester contingent test was done regarding the sensitivity, specificity, false positive rate and false negative rate.

RESULT AND ANALYSIS: After measuring the CRL, free β hcg, and PAPP-A values, they were converted to MoM values by computer software package (Wallac Life Cycle with Ellipse Screening Engine). The posterior risk for Down's syndrome was then calculated by using the above software with CRL, PAPP-A MoM and free β -hCG.

Out of the 100 patients 77 were in low risk, 22 were in the intermediate risk and 1 was in high risk group. All 77 patients in the low risk category after 1st step of contingent screening continued their pregnancies and went on to have normal babies. The intermediate risk group patients (n=22) were counselled for the 2nd step of contingent screening (ie NT measurement). High risk patient (n=1) had fetal FISH study and was proved to be a Down's syndrome fetus. She underwent MTP.

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Categorized	Number of patients	Percent
Low risk	77	77
Intermediate risk	22	22
High risk	1	1

TABLE 3

Now, the intermediate group was re-categorised according to NT values. It was seen that out of 22 patients 21 were categorized as low risk and 1 was high risk. The high risk patient refused fetal karyotype. She was followed up till delivery. She delivered a normal baby. Thus this was a false positive case.

Re-categorization after NT test	Number of patients	Percent
Low risk	21	95.45
High risk	1	4.55
Total	22	100

TABLE. 4

If we give a look on the pregnancy outcome of these patients then we see that 93 women went on to have delivery either vaginally or by LSCS. All the babies were assessed clinically by paediatrician at birth. There were no stigmata of Down's syndrome in any of them and hence they were classified as normal (Non- Down's babies). One patient had MTP following diagnosed Down's syndrome after fetal FISH study for trisomy 21. One patient had spontaneous miscarriage in the hospital. FISH study was done from the product of conception. The report was normal. Thus outcome analysis, as far as Down's syndrome was concerned, was possible in 95 patients. Out of 100 patients, the remaining 5 patients had spontaneous miscarriages at home and products of conception were not available for FISH/Karyotype study. They were thus excluded from the outcome analysis of the screening protocol.

Outcome	No. of patient	Down's syndrome	
		Yes	No
Vaginal delivery	25	0	25
LSCS	68	0	68
MTP	1	1 (fetal FISH study)	0
Spontaneous abortion	1	0	1 (FISH study of POC)
Total	95	1	94

TABLE 5

At this time, we calculated the overall outcome of Contingent screening in the study population. Results of 95 patients were; 1 was true positive, 1 was false positive and 93 were true negatives. False negative was 0 (which meant no Down's syndrome was missed).

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Contingent test result	Down's syndrome	Normal babies	Total
Screen Positive	1 (TP)	1 (FP)	2
Screen Negative	0 (FN)	93 (TN)	93
Total	1	94	95

TABLE 6

[TP = True Positive, FP = False Positive, TN = True Negative, FN = False Negative]

From the above table following inference was drawn.

Sensitivity:	TP/(TP+FN)	=1/(1+0)	=100%.
Specificity:	TN/(TN+FP)	=93/(93+1)	=98.9%
False positive:	FP/(FP+TN)	=1/(1+93)	=1.1%.
False negative:	FN/(TP+FN)	=0/(1+0)	=0%.

DISCUSSION: In the final analysis of the contingent screening followed in the current study it was observed that the test had sensitivity: 100%, specificity: 98.9%, false positive rate: 1.1% and false negative rate: 0%. So the case detection rate of the contingent test was 98.9% with a false positive rate was 1.1% in this study. Sahota et al 2009² found case detection rate was 87.5% with a false positive rate of 5%. In another study of contingent screening by Vadiveloo et al³ it was observed that the case detection rate was 90% and false positive rate was 5%. The high sensitivity and low false positive rate in our study could be due to small sample size, and there is a need to carry larger studies for revalidation.

SUMMARY: In this study, gestational age determination in first trimester was done by CRL measurement (by Trans abdominal USG). In the same sitting, maternal blood was taken for estimation of serum PAPP-A, and free β -hCG levels. MoM (multiple of the median) values were used to calculate the Down's syndrome risk.

The posterior risk calculation of the 1st step of contingent screening was done from the measurements of CRL, PAPP-A MoM and free β -hCG MoM. Using the Delfia Xpres hAFP system (Time-resolved Fluoroimmunoassay).

CUT-OFF VALUE: 1: 1000 was used to define low risk, $\geq 1: 50$ for high risk and, in between, as the intermediate risk group. In the study population, 77% were in the low risk group, 22% in the intermediate risk and 1% in the high risk group. Thus, after the 1st step of contingent screening 22% were offered NT and recruited in the 2nd step of contingent screening

In this model of first trimester contingent screening, women who were found to have high risk based on the initial biochemical test and maternal age were not offered NT measurement because these women would have ended up with a final risk $\geq 1: 50$ irrespective of the NT measurement. They were advised to undergo invasive test. Women with low risk (77%) were also not offered NT measurement as their cut off value was $\leq 1:1000$, and they were unlikely to reach the final cut-off value. The low risk patients were allowed to continue their pregnancy.

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All low risk patients in this study had non-Down's babies. FISH study of the high risk patient (n=1) showed she was carrying a Down's syndrome fetus and she underwent MTP.

All 22 patients in the intermediate risk group had NT measurement. This was the 2nd step of the screening protocol. Posterior risk of the 1st step was used as the prior risk of the 2nd step. Re-categorisation of 22 patients was done after doing NT scan and 95.5% (n=21) were re-categorised as low risk and 4.5% (n=1) came as high risk, taking the cut off value for high risk as $\geq 1:100$ and for low risk as $<1:100$. The posterior risk was calculated with the NT and CRL only. The high risk patient refused to do fetal karyotype. She was followed up till delivery. She delivered a normal baby. Thus she was considered as a false positive case.

Outcome of contingent screening in the study population with known results of 95 patients were; 1 was true positive, 1 was false positive and 93 were true negatives. False negative was 0 (which meant no Down's syndrome was missed).

From analysis of the above results, contingent screening test in this study had sensitivity: 100%, specificity: 98.9%, false positive rate: 1.1% and false negative rate: 0%. In other words, the case detection rate of the contingent test was 98.9% with a false positive rate of 1.1%. The false negative rate was 0%, ie, no Down's syndrome case was missed. This could be due to small number of patients (n=100) in the study population.

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