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Original Research Article

Clinical utility of Pregascreen™ reflex genetic testing for pre-natal screening in Indian population: A new diagnostic approach

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ABSTRACT

Background: Prenatal screening with maternal biochemical dual and quadruple markers, along with reflex testing using karyotyping, and non-invasive prenatal testing via next-generation sequencing (NIPT-NGS) were evaluated to determine the clinical validity of Metropolis Pregascreen™ reflex testing approach among Indian women.

Materials and Methods: Retro-prospective data of 51574 Indian women undergoing maternal marker screening from January 2021 to March 2022 were analysed at Metropolis Healthcare Limited, India. First and second-trimester prenatal screening were performed using Roche and Siemens platforms. Risk calculated using SSDW and PRISCA software, USG findings and biochemical values were incorporated. NIPT reflex testing was carried out using Thermo Ion torrent S5 NGS systems, while karyotyping on chronic villus sampling or amniocentesis.

Results: Total 51574 women opted for the combined biochemical markers test (dual and quadruple), 1394 cases (2.70%) and 50180 cases (97.28%) were screened as high-risk and low-risk, respectively. Of the total high-risk cases, 483 women (34.65%) opted for NIPT, while 25 (1.79%) opted for karyotyping reflex testing. Dual marker 92% and quadruple marker 94% of high risk cases were reclassified as low risk post NIPT, while dual marker 91% and quadruple marker 93% of high risk cases were reclassified as low risk post karyotyping.

Conclusion: Possibility of ruling out false positive is almost equal with NIPT and karyotyping. Hence, invasive screening could be avoided as first line of investigation. Metropolis Pregascreen™ reflex testing with NIPT assisted in the delineation of actual high risk cases for accurate and safer diagnosis.

1. Introduction

Chromosomal anomalies in newborns causes a significant burden on the family and society at large.[1] A crucial component of prenatal care presently includes the early screening of foetal chromosomal abnormalities in pregnant women of any age. In early pregnancy, all women are offered biochemical marker screening tests i.e. first trimester risk assessment, quadruple marker and routine ultrasonography, to evaluate the foetal risk for genetic abnormalities and birth defects. Traditionally, first trimester maternal screening includes ultrasonography and biochemical dual marker test. Ultrasonography is commonly used in the first trimester to assess for soft markers including nasal bone and nuchal translucency measurements between 11–13 weeks of pregnancy. Biochemical dual marker test during first trimester includes the measurement of free beta human chorionic gonadotropin

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(hCG) levels and pregnancy-associated plasma protein A (PAPP-A) levels in the maternal serum, while quadruple test during second trimester, measures the levels of alpha-fetoprotein (AFP), unconjugated estriol, hCG and inhibin A levels in the maternal serum. These screening tests are non-invasive and inexpensive, but have their limitations on detection rate and true positivity.[2–4]

The advances in molecular technology gave the ability to isolate and test cell free foetal DNA (cfDNA) from maternal blood to test for chromosomal aneuploidies. This changed the paradigm and introduced an innovative approach of prenatal testing in clinical practice. The NextGen NIPS test is a screening test which evaluates genetic information of the cell free DNA (cfDNA), the extracellular DNA originating from the trophoblastic cells, derived from maternal blood specimen to assess the probability of common chromosomal abnormalities. This process involves the isolation of cell free foetal DNA from maternal blood, generation of genomic DNA library, high throughput sequencing of the extracted cell free foetal DNA followed by calculation of molecular mass of foetal DNA in the chromosomes. NIPT has the potential to detect aneuploidies of sex-chromosomes, aneuploidies of the common chromosomes 21, 18, and 13 and currently considered as the best adjunct to serum-based prenatal screening tests in first and second trimester like the double and quadruple marker.[5–9]

Women considered high risk during first or second trimester screening need to confirm the presence of the reported aneuploidy by invasive procedures such as chorionic villus sampling (CVS) or amniocentesis that would help them to take appropriate clinical decisions. The invasive procedures provide a final diagnosis using tests such as karyotype, FISH and microarray. Invasive methods are accurate with high detection rate, low false positive rate and they also carry risk (1/1000 for amniocentesis; 1/200 for chorionic villus) of miscarriage.[10,11] NIPT-NGS testing is a non-invasive reflex test and its efficacy was found to be almost similar to karyotyping.[12]

NIPT-NGS has surfaced as an efficient alternative to invasive procedures like amniocentesis and CVS.[13] In many countries, NIPT-NGS has led to a paradigm shift in prenatal screening, and found to be greatly reduce the usage of invasive testing and with almost no risk to procedure related miscarriage. The adoption and implementation of NIPT-NGS in India has been intermittent due to its relatively higher cost.

In this study, modified screening strategy was proposed using Metropolis Pregascreen^{TM} reflex testing. Pregascreen^{TM} reflex testing either NIPT-NGS or karyotyping-FISH as a confirmatory test was offered to patients at high risk (trisomy 21, 18 and 13) with no additional extra cost. This study attempted to evaluate the clinical validity of NIPT-NGS as a screening approach for prenatal testing by correlating the outcomes with maternal serum screening tests, the current trends in choice of prenatal screening and diagnostic tests among Indian women was also analysed.

2. Materials and Methods

A retrospective study was conducted in 51574 pregnant Indian women during the period of January 2021 to March 2022. The study was approved by the ethics committee and informed consent was obtained from all patients. Biochemical dual and quadruple marker tests were conducted using Metropolis Pregascreen^{TM} maternal reflex screening methodology.[14,15] The study was also conducted to monitor the choice pattern between the screening NIPT-NGS and confirmatory karyotyping-FISH test in the pregnant women. The cases with incomplete information and results were excluded.

Testing for all the pregnant women patients were performed at the same location for consistency. First trimester biochemical marker testing using free beta human gonadotrophin (free-ßHCG) and Pregnancy Associated Plasma Protein (PAPP-A) was performed on Roche platform by electrochemiluminescence method. Second trimester biochemical markers were performed on Siemens platforms by chemiluminescence method. The percentage of high-risk and low-risk women for prenatal abnormalities by dual and quadruple marker screening test was calculated by SSDW and PRISCA software respectively. The measured concentration of free β-hCG and PAPP-A was converted into Multiples of the Median (MoM) appropriate to the gestational age of pregnancy. The MoM value was obtained by dividing an individual's marker concentration by the median level of that marker for the entire population at the same gestational age in that laboratory.[14,16]

The high-risk population was further studied for choice pattern between women for NIPT-NGS and Karyotyping-FISH for the confirmation of results. The NIPT testing was carried out using Ion torrent S5 NGS systems as per ACMG guidelines while karyotyping was performed on chronic villus sampling or amniocentesis. NIPT utilises the chemistry of Whole Genome Sequencing method by NGS and is based on amplification by PCR of whole cell free fetal DNA (cfDNA) present in maternal plasma.[17] The process involves isolation of cell free fetal DNA from maternal blood, generation of genomic DNA library, clonal amplification by emulsion PCR, (Ion 540 kit – OT2, Ion Torrent, Thermofischer Scientific), high throughput sequencing using Ion S5 GeneStudio Semiconductor Sequencer. The sequenced data was statistically analysed using NIPT bioinformatics pipeline (Yourgene, Taiwan, Thermofisher) to get specificity and sensitivity of the assay.

3. Results

3.1. Distribution of Pregascreen™ dual and quadruple biochemical markers into low and high risk

Among the 51574 cases, 1394 (2.70%) cases were screened high-risk and the remaining 50180 (97.3%) cases were screened low risk for foetal chromosomal aneuploidies (Figure 1).

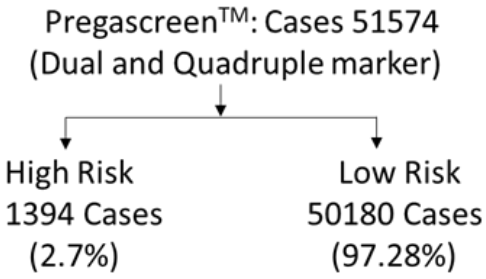

Fig. 1: Distribution of total study of population in high and low risk based on Pregascreen™ biochemical markers screening

3.2. Pregascreen™ segregation based dual and quadruple biochemical markers

From the 51574 cases, 32363 (62.75%) cases were first trimester screening tests (dual marker) and 19211 (37.25%) cases were of second trimester screening test (quadruple marker). Among the 32363 cases of dual marker, 675 cases (2.09%) were screened high-risk, and the rest 31688 cases (97.91%) were screened low risk. Out of 19211 cases of quadruple marker, 719 cases (3.74%) were screened high-risk, and the rest 18492 (96.26%) cases were screened low risk (Figure 2).

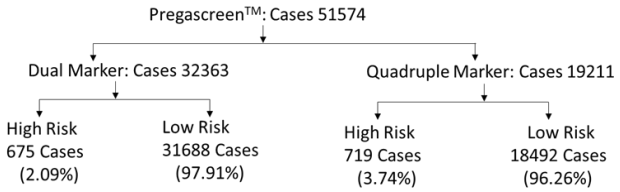

Fig. 2: Flow chart of maternal screening (Pregascreen™) cases: Dual and quadruple results

3.3. Distribution of high risk patients with NIPT-NGS and Karyotyping-FISH

Of the 1394 high-risk cases, 675 cases (48.42%) were of dual marker and 719 cases (51.58%) were of quadruple marker (Figure 3). From the 675 dual marker high-risk population only 321 patients (47.56%) opted for reflex testing, either NIPT-NGS or karyotyping-FISH test, and the rest 354 patients did not opt for further testing. From the 719 quadruple marker high-risk population 187 patients (26%) opted for reflex testing, and the remaining 532 patients did not opt for further testing.

Among the 321 high-risk patients from dual marker, 310 patients opted for NIPT-NGS and 11 patients opted for karyotyping-FISH respectively. From the 310 NIPT patients, 25 (8%) were screened high-risk and the rest 285 (92%) patients were screened low risk for chromosomal aneuploidies for 21, 18 & 13 chromosomes. From the 11 karyotyping patients, 1 (9%) was confirmed as abnormal and the rest 10 (91%) foetuses were classified as no chromosomal abnormalities.

Amongst the 187 high-risk patients from quadruple marker, 173 patients opted for NIPT and 14 patients for karyotyping-FISH. From the 173 NIPT patients, 10 (6%) were screened high-risk and the rest 163 (94%) patients were screened low risk for chromosomal aneuploidies. From the 14 karyotyping patients, only 1 (7.14%) was confirmed as abnormal and the rest 13 (92.86%) normal.

Thirty five high risk cases were followed up further for end to end correlation between the non-invasive NIPT results with invasive method (amniocentesis). Concordance was observed in 34 out of 35 cases, between the high risk NIPT cases [Dual (25 cases) and Quadruple (10) markers) with the amniocentesis for chromosomes 21 and 18; while only in one case, the sex chromosome result was discordant (Figure 3). Dual markerquadruple marker (Figure 4). From the 31low-risk population 10 women (0.03%) opted for NIPT. 31 From the 18492 quadruple marker low-risk population 7 women (0.04%) opted for NIPT. The remaining485 women (99.96%) did not opt for further testing secondaryternal screening population (51483 women (34.65%) (total 500 cases, 17 cases low risk) opted for NIPT as secondary screening test, and 25 women (1.79%) opted for karyotyping test as a confirmatory test from the high-risk Pregascreen maternal screening population (1394 cases) in the selected time duration.

3.4. Distribution of Pregascreen™ low risk patients

3.5. Comparison of Pregascreen™ maternal biochemical marker screening and Genetic testing/Chromosomal analysis

Dual marker and quadruple marker test results were compared with the NIPT results. In the total of 500 women that opted for NIPT, 320 cases underwent dual marker test, and 180 cases underwent quadruple marker test as their primary screening test. The correlation is depicted in Table 1. When comparing dual marker results with NIPT results, it was observed that out of 310 (96.88%) high risk cases, 25 (8.06%) were screened high risk on NIPT (Table 1). Therefore, 285 (96.61%) of high-risk cases were false positives and 25 (8.06%) of high-risk cases were true

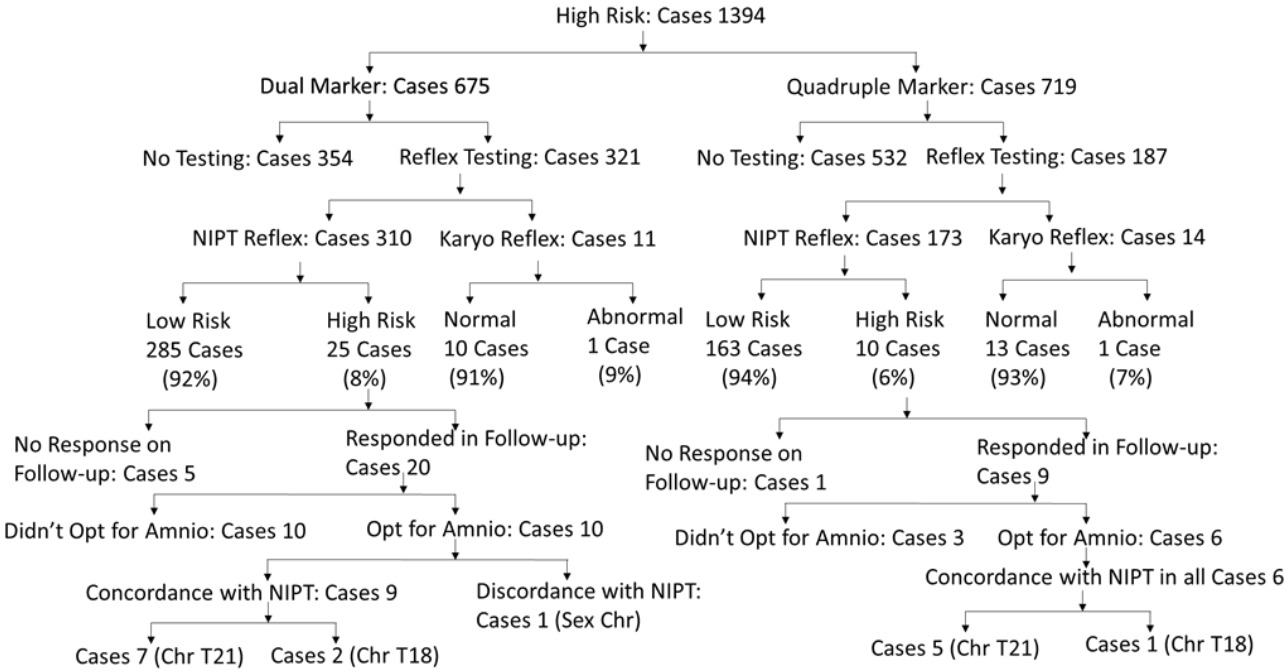

Fig. 3: Clinical distribution of maternal screening high-risk patients and Invasive/NIPT results

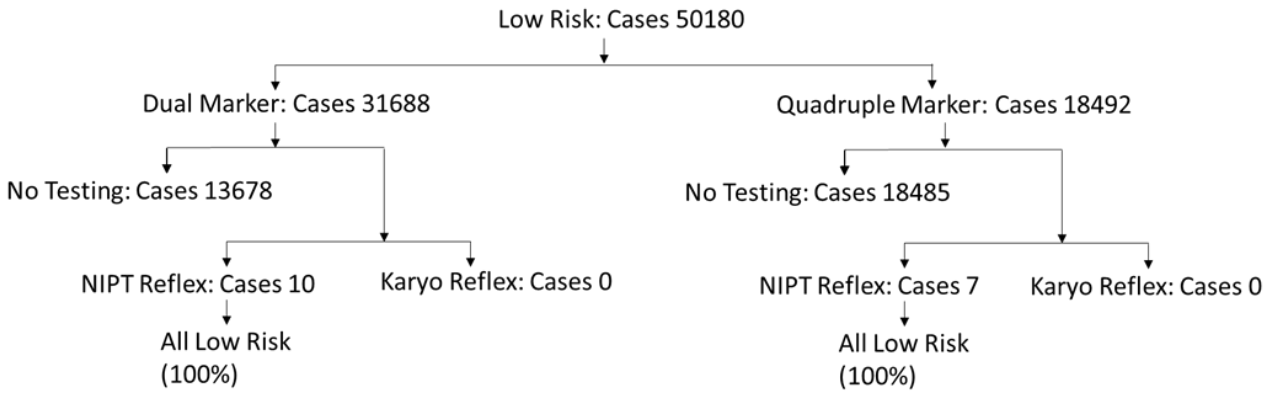

Fig. 4: Clinical distribution of maternal screening low-risk patients and their NIPT and karyotyping results

positives on the dual marker test. The invasive procedure was not required for 96.61% of cases. In addition, 10 (100%) of low-risk cases were also screened as low-risk on NIPT, thus they were true negatives, and no false negatives were observed on dual marker test (Table 1).

Quadruple marker with NIPT results showed that out of 173 (96.11%) high risk cases, 10 (5.78%) cases were screened high risk on NIPT. Therefore, 163 (95.88%) of high-risk cases were false positives and 10 (5.78%) high-risk cases were true positives on Quadruple marker test. The invasive procedure was not required for 95.88% of cases. In addition, 7 (100%) of low-risk cases were also screened as low-risk on NIPT, thus they were true negatives, and no false negatives were observed on Quadruple marker test (Table 2).

4. Discussion

In the present study, the prenatal testing pattern of 51574 Indian pregnant women from January 2021 to March 2022 was evaluated in the population of expectant mothers who opted for NIPT testing based on their clinical indications and their outcomes. The clinical significance of NIPT has been confirmed by several large and small-scale clinical studies.[18–21] It is apparent that 62.75% of the women preferred combined first trimester dual marker test done between 11th and 13th week of gestation than undergoing quadruple marker test done during 14th to 20th week of

Table 1: Comparison of high-risk and low-risk results of patients who underwent dual marker test (dual marker) screening followed by NIPT (n=320 cases)

Risk	Dual Marker (320)		NIPT (320)	
	No. of cases	Percentage (%)	No. of cases	Percentage (%)
High Risk	310	96.88	25 (25/310)	8.06
T21			15	60.00
T18			6	24.00
T13			2	8.00
Sex Chromosomal aneuploidies			2	8.00
Low Risk	10	3.23	10 (10/10)	100.00
Total	320	100.00		

Table 2: Comparison of high-risk and low-risk results of patients who underwent quadruple marker test (quadruple marker) screening followed by NIPT (n=180 cases)

Risk	Quadruple Marker (180)		NIPT (180)	
	No. of cases	Percentage (%)	No. of cases	Percentage (%)
High Risk	173	96.11	10 (10/173)	5.78
T21			5	50.00
T18			3	30.00
T13			0	0
Sex Chromosomal aneuploidies			2	20.00
Low Risk	7	4.05	7 (7/7)	100.00
Total	180	100.00		

gestation. NIPT test is advantageous in women who are in their first trimester in pregnancy, as it allows sufficient time for invasive testing in cases of high risk pregnancies. In contrast to women in their second trimester of pregnancy, who would then have very limited time for invasive testing and subsequent clinical decision, NIPT is not ideally suggested for women with 20 weeks gestation or more.

From the 32363 cases of dual marker screening test, 675 cases (2.09%) were screened high-risk, and 31688 cases were screened low risk. Out of the 19211 cases of quadruple marker screening test, 719 cases (3.74%) were screened high-risk, and 18497 cases were screened low risk. From the 675 dual marker high-risk population only 321 patients (47.56%) opted for a reflex testing, 310 for NIPT and 11 for karyotyping test, and 354 patients did not opt for further testing. Similarly, from 719 cases of quadruple marker high-risk population 187 patients (26%) opted for a reflex test. Patients 173 opted for NIPT and 14 for karyotyping reflex testing, and 532 patients did not opt for further testing. Overall, 483 women (34.65%) (total 500 cases, 17 cases low risk) opted for NIPT as secondary screening test, and 25 women (1.79%) opted for karyotyping test as a confirmatory test from the high-risk Pregascreen^{TM} maternal screening population (1394 cases) in the selected time duration. It can be observed from this data that more women opted for NIPT screening test compared to karyotyping test. There are several investigations which attempt to study the impact of NIPT on women's choice of further prenatal testing following a positive maternal marker screening result. The incorporation of NIPT resulted in a significant decrease in invasive diagnostic testing with fewer women, which also declined further testing when NIPT was available after they have been screened as high risk on maternal biochemical screening tests.[22,23] With the availability of NIPT testing, an increasing number of patients tend to prefer NIPT as an intermediate test or as a secondary screening test before directly opting for invasive prenatal testing. One study also highlighted that this may lead to missed diagnosis of chromosomal aberrations during prenatal screening which can be detected on invasive diagnostic testing.[24] Since NIPT generally detects common aneuploidies such as trisomy 21, trisomy 18, trisomy 13 and sex chromosomal aneuploidies; other chromosomal defects and aberrations can only be confirmed using cytogenetic testing where the sample is obtained through an invasive procedure. A preliminary study, which concluded the first Indian systemic study on NIPT stated that in situations where NIPT has been implemented, a significant reduction of invasive procedures has been observed.[25]

While comparing dual marker test results with NIPT, risk of aneuploidies were ruled out in 91.94% of cases while 8.06% was a true positive screen. Hence, invasive confirmatory procedure was not required for the majority of the cases. In addition, low-risk cases (n=10 cases) on dual marker test were also screened as low-risk on NIPT, thus they were true negatives, and no false negatives were observed. When correlating quadruple marker test results with NIPT results, we could rule out need for invasive

confirmatory testing in 94.22% of cases. In addition, low-risk cases (n=7 cases) on quadruple marker test were also screened as low-risk on NIPT, thus they were true negatives, and no false negatives were observed. In this study, it can be observed that NIPT helped to negate the need for invasive confirmatory testing. In a three- year retrospective study conducted in Punjab, India, it was observed that the sensitivity and specificity of dual marker test for detection of chromosomal abnormality is 50% and 85.94% respectively and that of quadruple test sensitivity is 50%, specificity is 95.3% when the results were confirmed with invasive test.[26] Another study stated that the false positive rate for the biochemical screening tests is 5%, while the positive predictive value is 2–5%.[25]

To determine the true false positives and the positive predictive values of the maternal screening marker tests and NIPT in our study, the high-risk patients would need to be followed up with an invasive diagnostic test such as karyotyping test, which is one of the limitations of this study. Around 879 high-risk women screened from dual and quadruple marker did not further opt for free of cost reflex NIPT or karyotyping test available at the given location. Follow ups of these high-risk women was necessary.

5. Conclusion

Prenatal screening with dual and quadruple marker testing is great strategy due to its inexpensive nature, however it comes with its limitation. Positivity and negativity based on cut off can over or under screen true aneuploidy cases at times. Dual and quadruple marker testing along with Pregascreen^{TM} reflex testing was found to be successful strategy. NIPT on the other hand, has proven to give >99% detection rate. Our study demonstrated that direct usage of NIPT can save >90% of women from the anxiety of positive dual or quadruple marker results. It also helps to take right decision for the need of invasive testing. Possibility of ruling out false positive is almost equal with both reflex offering i.e. NIPT and karyotyping. Hence, invasive screening could be avoided, we observed a 20 fold increase in women who opted for NIPT compared to karyotyping test. NGS based NIPT has a remarkably high sensitivity, the specificity and the positive predictive value for the tested trisomies and hence is an excellent option to the conventional first line maternal serum screening tests.

6. Source of Funding

None.

7. Conflict of Interest

None.

8. Ethical Approval

The study was approved by ethical review board and procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

9. Informed Consent

Informed consent was obtained from all individual participants included in the study.

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