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NIPT: RELEVANCE IN CURRENT INDIAN SCENARIO AND LITERATURE REVIEW

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Among the plethora of the health care issues for a developing country like India, genetic disorders may not be of top most priority, but still its existence could not be ignored. As reported by previous authors[1], the burden of the genetic diseases could be tabulated as:

Disorder	Incidence	Births/Year
Congenital malformations	1:50	678,000
Chromosomal diseases	1:166	160,000
Down syndrome	1:800	34,000
Trisomy 13	1:6,500	4,100
Trisomy 15	1:12,500	2,136
β-thalassemia + SCD	1:2,700	16,700

Here comes the role of the prenatal diagnosis, which is an important area of the obstetric care. Conventionally, this is done by certain biochemical markers (beta-HCG, alpha fetoprotein, PAPP) and sonographic features, done at stipulated gestational age. The high risk women screened out by this method are designated to undergo invasive procedures like chorionic villus sampling (10-13 weeks) and amniocentesis (15 weeks). This method has good diagnostic accuracy with regards to detect the chromosomal and non-chromosomal anomalies in the fetus.

Non invasive prenatal diagnosis (NIPT) is a relatively new test in this arena. It is a test detecting the presence of the fetal cell free DNA in the maternal serum and henceforth, giving the direct information of the fetal genetic composition. It is definitely a promising tool, as it combines the features of the two step conventional testing in one test. The accuracy to detect the fetal aneuploidies is more than the conventional testing, sans the fear of undergoing invasive procedure and henceforth, the avoiding the risk of pregnancy loss associated with them.

In spite of all these benefits, the matter of concern is that, is the present Indian healthcare system ready to accept a new test with a sky-rocketing cost and with credibility of just being a screening test? In this article, we would like to explore the likely issues with the implementation of this test in the present healthcare system.

❖Rationale of Nipt

Cell free DNA could be commonly found in the maternal serum which could have its origin from both mother and fetus. Maternal source of the cell free DNA is from the hematopoetic cells whereas the fetal sources of the cell free DNA is by the apoptosis of the placental cells (synctiotrophoblasts) and the fetal erthryoblasts. Since the fetus and placenta develop from the same fertilized egg so, they have same genetic composition therefore; the cells from the placenta mirror the genetic composition of the fetus. The cell free DNA is found to be highly segmented, and the length of the segments differentiates between the fetal or maternal origin.

The fetal cell free DNA is not only useful for the detection of aneuploidies but can also provide information regarding the status of the pregnancy. It is reported that increased levels of the fetal cell free DNA may be seen in conditions like pre-eclampsia which cause hypoxic stress resulting in the increased placental apoptosis and necrosis of the trophoblasts.[2-4] But its use in clinical situation is still under research. The fetal DNA can also be used to the fetal sex and rh factor which can be further useful in diagnosing several sex linked chromosomal anomalies and RH incompatibility in the earlier gestation.

Since, it is the actual fetal DNA which is dealt with, it has high sensitivity and specificity for fetal aneuploidy detection. At present, its use is limited for screening trisomy 21, trisomy 18, trisomy 13 and sex chromosome aneuploidies. The accuracy achieved in detecting the

anomalies is close to that of the invasive procedures done. As reported in the literature the screening accuracy can be summed up as.[2]

●Down syndrome – DR (detection rate) 99.4 percent, FPR (false positive rate) 0.1 percent, false-negative rate (FNR) 0.6 percent.
●Trisomy 18 – DR 97.7 percent, FPR 0.1percent, FNR 2.3 percent.
●Trisomy 13 – DR 90.6 percent, FPR 0.1 percent, FNR 9.4 percent.

Inspite of such good figures, it is still just a screening test and not a diagnostic test i.e. Even after a positive result, invasive diagnostic test is required to make the decision regarding continuation or termination of the pregnancy. This is because clinical sensitivity and specificity may be different from the results achieved. This could be seen in situations like: confined placental mosaicism, demised twins, maternal mosaicism, maternal cancer and maternal copy variants.[3–7]

❖**Probable Fallacies**

1. Issues with interpretation of the results

Although sensitivity and specificity are good enough markers of a screening test but for the use in clinical scenario PPV and NPV are of more importance. The positive predictive value (PPV) is the chance of a screen positive result being a true positive and the negative predictive value (NPV) is the chance of a screen negative result being a true negative. While sensitivity and specificity are unaffected by prevalence, PPV and NPV are significantly influenced by prevalence.[8] So, if, this test is applied to the population with low prevalence i.e. low risk population the values of the sensitivity would not be that good. Clinical implication of this would be that, a positive result would still require confirmation by the diagnostic tests.[4,7,9]

2. Low fetal cell free DNA fraction

There are three kinds of results being reported positive, negative and no call or the test failure. The test failure rates may be as high as 5-10%.[7] It may be due to many reasons like: early gestational age, suboptimal sample collection, obesity (more plasma volume causing dilution), anomalous fetal karyotyping (low fraction seen with triploidy, turner syndrome, trisomy 18 and trisomy 13). This results in undue stress on the women undergoing test. ACOG(2015) recommends invasive procedure in these cases as repeating the test, wastes time and money.

3. Cost

In India, there are only few labs offering this test, in collaboration with the foreign labs. This further increases the operational costs for this test which comes to be more than the invasive procedures. This further raises issue of mass availability to the general population. To be more acceptable to the population the cost issues need to be balanced, especially, in countries like India. For a country battling to provide basic ANC to its majority of the population, offering exuberantly expensive screening test for even high risk population seems economically unviable.

4. Lack of clear cut guidelines to deal with positive results

High sensitivity and specificity values provided in the literature provide impression for high performance of this test but the fact is that most of these values are achieved in high risk population with high prevalence of the fetal aneuplodies. It is important for the clinicians to know that for a low risk population the PPV may be lesser so, any kind of irreversible decisions should not be taken on the basis of the results of this test.

5. Lack of proper counseling and patient education

An updated clinician will provide appropriate counseling of the parents both before and after the test, which is very important for the success of this test. Labs will provide the results but its interpretation and bringing out its clinical significance has to be brought out by the care provider, which can't be done in isolation. It requires a wholesome view of the clinical aspect of the patient.

6. Lack of proper follow up

In line with the proper counseling, a proper follow up of the patients is required within the stipulated time.

7. Limited conditions detected

Even if above issues are dealt with, it would not be possible to eradicate the use of the conventional methods all together because the range of conditions detected by NIPT are lesser than the conventional screening. The advantage of the non- chromosomal conditions detected on the sonography can't be ignored.

8. Unfair discrimination

Introduction of such a costly test for an important cause is bound to create division among the patients who can afford and who can't afford the test. Possibility of skewed distribution of the anomalies among the people who can't afford these tests can't be ruled out.[3,6,9–11]

9. Probable misuse

The fact that this test can provide information regarding the fetal sex can be misused in the hands of unscrupulous elements. For, a country already dealing with the problem of genocide, this may further aggravate it.

❖ CONCLUSION

For implementation in Indian, it is important to review policy decisions and provide proper guidelines regarding.

1. Specific indications for its use.
2. Standardization of the laboratory procedures and interpretation of the results
3. Subsidization of the cost.

4. Provision of the proper counseling regarding the test procedures, results and its implementation in the clinical scenario.

If all these factors are taken care of properly, the benefits of the NIPT can't be ignored. It has potential to take the current prenatal diagnosis to a new level especially when its use in other areas is also been experimented rapidly.

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