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RESEARCH ARTICLE
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ADVANCING PRENATAL TESTING: NON-INVASIVE ANEUPLOIDY SCREENING IN HIGH-RISK PREGNANCIES

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Abstract

Introduction: Non-invasive prenatal testing (NIPT) has further advanced the idea of prenatal screening through the accurate identification of fetal aneuploidies. It is most effective for women who are considered to be at high-risk pregnancies to eliminate the use of invasive procedures.

Objectives: This study assesses the efficiency of the NIPT technology in the identification of trisomy 21, 18, and 13 in high-risk pregnancies concerning the sensitivity, specificity, and positive predictive value.

Materials and Methods: The current study was a hospital-based prospective study conducted at Department of Obstetrics and Gynaecology, Sir Ganga Ram Hospital / Fatima Jinnah Medical University Lahore, Pakistan from January 2024 to June 2024. Two hundred fifty high-risk pregnant women only got NIPT done and diagnostic tests among the positive ones. Sensitivity, specificity, and predictive values were analyzed.

Results: In terms of efficiency NIPT has high sensitivity since it disclosed 100% of trisomy 21, 88.9% of trisomy 18, and 50% of trisomy 13 while the specificity was 97.8%. Limitations of this research indicated that there were false positive cases that should undergo further testing.

Conclusion: NIPT can be helpful in high-risk pregnancies. It helps in the elimination of invasive procedures while improving the accuracy of detection of aneuploidies.

Keywords: Trisomy 21, high-risk pregnancy, fetal aneuploidy, non-invasive prenatal testing, and prenatal screening.

INTRODUCTION

Currently, prenatal screening has improved over the past decade, especially with the introduction of NIPT, which is a specialization in diagnosing fetal aneuploidies. Some of the high-risk mothers are those who are 35 years and above, fathers with a chromosome abnormality in their families, or

mothers who have a fetal anomaly on the ultrasound (1). Some routine procedures, such as amniocentesis, CVS, and maternal serum screening, were previously performed. These methods have certain disadvantages, including lower sensitivity and specificity, especially when screening in serum, and higher risks of pregnancy complications in case the invasive tests are utilized (2). To detect aneuploidies like trisomy 21, 18, or 13 in cffDNA in maternal plasma, NIPT has become safer and less erroneous than the previous method (3). Moreover, when pregnancies are considered to be involving a high risk of aneuploidies, NIPT has been very useful. As the findings indicate, NIPT improves the ability to detect diseases but reduces the risks of invasive diagnostic procedures such as miscarriage (4). These aspects place NIPT higher than other screening tests with high sensitivity and specificity above 99% to identify trisomy 21 (5). However, whole genome sequencing-based NIPT assay has expanded the detection spectrum with information on chromosomal aneuploidies other than the four targeted trisomies (6). This increasing use of NIPT establishes it as a first-line screening method, especially in cases where invasive testing bears several ethical and medical complications.

Another factor affecting NIPT's introduction in actual healthcare practices includes the technological development of sequencing technologies and analysis tools that allow for the high-accuracy identification of fetal DNA. Currently, NIPO is widely implemented into prenatal practice, especially in cases of high-risk pregnancies, owing to its non-invasive approach to gaining crucial genetic information on the fetus early in pregnancy (7). Volume research has supported it as being accurate, with massive groups supporting its applicability in lowering the false positives compared to routine biochemical and ultrasound screening methods (8). In addition, clinical utility has increased with the use of extended probes that encompass microdeletions, duplications, and other forms of chromosomal anomalies, providing a broader assessment of fetal health (9). However, some issues are bound to arise when implementing NIPT and interpreting results from the test. Nonetheless, false-positive and false-negative results are possible, and invasive follow-up testing should be pursued in certain situations (10). Also, the concern of incidental findings, detecting variants of unclear significance, and the psychological effects on both expectant parents continue to be debated (11). Some of the disadvantages of NIPT include its cost, which may be high given that access to advanced genomic technologies remains limited in many developing countries. Despite the evidence showing its affordability, its availability and accessibility may remain a significant issue affecting its use in multiple countries, especially in developing nations (12).

This shows that apart from the technical and financial barriers, perception and acceptance of NIPT are essential determinants in implementation. Research has indicated that pregnant women, especially those in the high-risk groups, have a preference for NIPT over conventional tests because it is non-invasive and highly accurate (13). However, there is still the need for counseling and decision-making to help patients consider various tests and their outcomes, whether they are false-positive or false-negative. Healthcare personnel can only guide clients through screening and appreciate such results in conjunction with the need for further diagnostic processes if the results warrant (14). Implementation of NIPT in antenatal care requires the collaboration of genetic counselors, obstetricians, and perinatal caregivers to enhance patient's experiences and make appropriate reproductive decisions (15). Published studies that improve NIPT's diagnostic effectiveness as well as technological advancements may progress NIPT further in time. Some of the upcoming technologies like single cell sequencing along with integrated approach of NIPT along with first trimester ultrasonography and biochemical markers can be helpful in increasing sensitivity and also expanding the range of workable pathologies.

Objective: The objective of this study was to assess the benefits, diagnostic performance, and evidence-based clinical application of NIPT for aneuploidy screening to decrease invasive prenatal diagnostic methods and enhance prenatal health outcomes in such cases.

MATERIALS AND METHODS

Study Design: Cross-sectional observational Study.

Study setting: The study was done at Department of Obstetrics and Gynaecology, Sir Ganga Ram Hospital / Fatima Jinnah Medical University Lahore, Pakistan

Duration of the study: The study was done from January 2024 to June 2024, a period of six months.

Inclusion Criteria:

High-risk pregnant women was included in the study according to specific criteria such as maternal age ≥ 35 years, first trimester screening results showing anomaly, history of chromosomal disorders, and anomalies on ultrasound imaging. The participants included only women who have singleton pregnancies and was willing to perform NIPT and follow-up diagnostic scans if required.

Exclusion Criteria

Ladies with multiple gestations, abnormal karyotypes in the parents, history of organ transplantation, or recent blood transfusion was excluded to eliminate interference on cffDNA testing.

Methods

These pregnant women was selected from the Department of Obstetrics and Gynaecology, Sir Ganga Ram Hospital / Fatima Jinnah Medical University Lahore, Pakistan, who satisfy the following inclusion criteria. Following the assessment, the mother's blood samples of 10-20 ml was drawn from the participants between 10 and 20 weeks of pregnancy to conduct the non-invasive prenatal testing. cffDNA is obtained from maternal plasma, and NGS was employed to detect common aneuploidies such as trisomy 21, 18, and 13. Pre and post-test counseling was provided for all participants to make them aware of their rights. NIPT was followed by confirmatory diagnostic procedures such amniocentesis or chorionic villus sampling in situations where high-risk results are indicated.Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) was calculated from the data. Data analysis was conducted by using Statistical Package for Social Sciences (SPSS) to test the clinical efficacy and relevance of NIPT in high-risk patients.

RESULTS

The participants included a total of 250 high-risk pregnant women with a mean maternal age of 37.2 ± 3.5 years. The time at which the samples were collected was from 10 to 20 weeks of gestation, with an average of 13.8 weeks. The main reason for undergoing NIPT was advanced maternal age 60% while the other reason was first trimester screening 25% and previous history of chromosomal abnormalities 15%.

Table 1: Baseline Characteristics of Study Participants

Characteristic	Value (n=250)
Mean Maternal Age (years)	37.2 ± 3.5
Mean Gestational Age (weeks)	13.8 ± 2.4
Indication for NIPT	
- Advanced Maternal Age	150 (60%)
- Abnormal First-Trimester Screening	62 (25%)
- History of Chromosomal Abnormalities	38 (15%)

The NIPT results revealed that 215 (86%) were low risk, and 35 (14%) were high risk for chromosomal aneuploidies. Of all the complications, the most abundant frequency exhibited trisomy 21 in 22 (63%), followed by trisomy 18 in 9 (26 %) and trisomy 13 in 4(11%) cases.

Table 2: NIPT Results and Confirmatory Testing Outcomes

NIPT Result	Cases (n=250)	Confirmed by Diagnostic Testing
Low-Risk	215 (86%)	Not Required
High-Risk	35 (14%)	30 Confirmed, 5 False Positives
- Trisomy 21	22 (63%)	20 Confirmed, 2 False Positives
- Trisomy 18	9 (26%)	8 Confirmed, 1 False Positive
- Trisomy 13	4 (11%)	2 Confirmed, 2 False Positives

All women in the high-risk category underwent confirmatory tests such as amniocentesis or chorionic villus sampling. Among them, 30 cases were positive for chromosomal abnormality, and 5 cases were false positive, making the study's specificity 97.8%. The study concluded that no instances of false-negative results had been reported. The offered data reveal that the sensitivity of NIPT for trisomy 21, 18, and 13 is 100%, 88.9%, and 50%, respectively, and the PPV is 85.7%, 88.9, and 50%.

Table 3: Performance Metrics of NIPT for Aneuploidy Detection

Chromosomal Abnormality	Sensitivity (%)	Specificity (%)	Positive Predictive Value (PPV) (%)
Trisomy 21	100	99.0	90.9
Trisomy 18	88.9	99.5	88.9
Trisomy 13	50.0	99.0	50.0

Based on the results, the NIPT exhibits high sensitivity and specificity when screening aneuploidy in high-risk prenatal pregnancies. The results of the study support the clinical use of NIPT to eliminate invasive diagnostic procedures when the accuracy of diagnosing the chromosomal abnormalities in the fetus is not compromised.

DISCUSSION

As a screening method for fetal aneuploidies, NIPT has been established as an efficient, non-invasive solution, particularly in cases of high-risk pregnancies. This study evaluated the clinical efficacy of NIPT in diagnosing trisomy 21, 18, and 13, comparing sensitivity and specificity. These findings support other studies, highlighting NIPT as an effective in prenatal care that significantly reduces the need for invasive diagnostic options yet has a high detection rate. The trisomy 21 (100% sensitivity), trisomy 18 (88.9% sensitivity), and trisomy 13 (50% sensitivity) detection rates are consistent with previous research correlating cffDNA to precision and efficacy in clinical settings (2). However, the variation in the positive predictive values (PPVs) shows the need for confirmatory tests in order not to cause unnecessary panic and procedures.

The study's results support the results of other studies showing that NIPT is more accurate than any screening methods involving serum and ultrasound. Other methods, like combined first-trimester screening, have higher false positive results, subjecting pregnant women to invasive procedures, including amniocentesis or chorionic villus sampling (3). However, the specificity of NIPT, as noted in this study, was 97.8%, meaning there is less probability of having wrong results, making it a more favorable screening test for high-risk pregnant women (4). This high specificity is extraordinarily useful for conditions such as trisomy 21, where its sensitivity was 90.9%, which minimizes psychological stress and future health dangers connected with useless invasive diagnostic procedures (5).

However, like any diagnostic technique, NIPT has some disadvantages. Thus, the research detected five false-positive cases, emphasizing the need for additional diagnostic procedures. These may involve sequencing mistakes, maternal chromosomal defects, or restricted placental mosaicism (6). However, the sensitivity of specific aneuploidies, including trisomy 13(50%). Furthermore, the effectiveness of NIPT is questioned for some conditions similar to the concerns from prior studies (7). A few authors have pointed to fetal fraction, sequencing depth, and the choice of bioinformatics tools

that may influence the accuracy of NIPT (8). A significant limitation of NIPT includes low fetal fraction that may be due to obesity or early gestational age, leading to false negative results (9).

Another critical issue to consider is implementing or incorporating NIPT into clinical practice. In many centers, NIPT is used in high-risk pregnancies because of the high cost involved and the lack of advanced laboratory facilities (10). However, when the cost associated with the technology comes down and the technology for sequencing increases, then the NIPT may improve prenatal care among the obstetric population, even the general population. Several countries with national policies on implementing NIPT have cited a decrease in the number and frequency of invasive diagnostic procedures (12). The integration of whole-genome sequencing in NIPT can also strengthen NIPT's diagnostic capacity by detecting microdeletions, duplications, and other subtle subchromosomal disorders in addition to aneuploidies (13).

The psychological implications of NIPT cannot be underestimated. Past research also revealed that pregnant women feel concerned while waiting for the results, especially when they are considered high-risk (14). Pre-test and post-test counseling of the patients minimize some of these concerns as much as they convey the implications of the results to the patients. All the participants in this study received genetic counseling, which can be expected to have improved the patients' ability to make further diagnostic tests decisions. An analysis of the literature suggests that patients are more likely to accept confirmatory testing when needed and may not base an informed decision to terminate pregnancy on screening (15).

The primary strength of the presented study was the precise definition of the inclusion criteria, which permitted the assessment of only high-risk pregnancies, increasing the significance of the results. The confirmation of its utility for all high-risk NIPT results also improves the accuracy of reported sensitivity and specificity levels. On another note, the study was carried out in the biggest tertiary care hospital, providing good diagnostic help excluding technical flaws that could exist in other centers.

There are a few limitations that have to be highlighted. The sample of 250 respondents might not accurately represent the general population since it's a relatively small sample size. Further, a significant, multicentred research investigation would be required to replicate these findings in various demographics and ethnicities. Also, this study was confined to the common trisomies (21, 18 and 13) while newer versions of NIPT include sex chromosome aneuploidies and subchromosomal anomaly which have not been incorporated in this study. Further studies should be conducted to extend NIPT to cover as many disorders as possible, mainly in the regions with high genetic predispositions.

Finally, the conclusion of this paper supports the use of NIPT as a valuable tool in the screening of fetal aneuploidies in high-risk pregnancies. The evidence from observed high sensitivity and specificity, particularly in trisomy 21, indicates that NIPT could drastically cut the number of invasive diagnostic procedures. However, with some false-positive cases and relatively lower sensitivity for trisomy 13, the confirmation testing of microarray should be done before making clinical decisions. With further development of NIPT, further dispersion of the technology into prenatal care settings, and better affordability, NIPT may well change the way prenatal screening is done in favor of the mother and the baby.

CONCLUSION

In this paper, NIPT is presented as a highly accurate and reliable screening method that can be used to identify aneuploidies in high-risk pregnancies. The studies provide clear evidence of NIPT's high sensitivity and specificity, especially in detecting trisomy 21, so that fewer invasive diagnostic tests are required. The experienced false positive cases further underline the need for the follow-up test to prevent people from undergoing unnecessary operations or increasing their stress levels. However, its limitations include lower sensitivity for trisomy 13 and the possibility of false positive results, which may warrant an appropriate interpretation of the outcomes. Proposed strategies to improve prenatal care utilizing NIPT include increasing its availability, incorporating it with genetic counseling, and improving the diagnostics of NIPT through WGS. It is expected that the expanded use of NIPT in

regular prenatal screening will alter prenatal diagnoses and enable safer and more effective management of high-risk pregnancies, resulting in fewer invasive procedures being required.

References

1- Merriel, A., Alberry, M. and Abdel-Fattah, S., 2021. Implications of non-invasive prenatal testing for identifying and managing high-risk pregnancies. European Journal of Obstetrics & Gynecology and Reproductive Biology, 256, pp.32-39.

2- Chen, Y., Yang, F., Shang, X., Liu, S., Li, M. and Zhong, M., 2022. A study on non-invasive prenatal screening for the detection of aneuploidy. Ginekologia Polska, 93(9), pp.716-720.

3- Zhu, H., Jin, X., Xu, Y., Zhang, W., Liu, X., Jin, J., Qian, Y. and Dong, M., 2021. Efficiency of non-invasive prenatal screening in pregnant women at advanced maternal age. BMC Pregnancy and Childbirth, 21, pp.1-6.

4- del Arco de la Paz, A., Giménez-Rodríguez, C., Selntigia, A., Meseguer, M. and Galliano, D., 2024. Advancements and Challenges in Preimplantation Genetic Testing for Aneuploidies: In the Pathway to Non-Invasive Techniques. Genes, 15(12), p.1613.

5- Giovannopoulou, E., Tsakiridis, I., Mamopoulos, A., Kalogiannidis, I., Papoulidis, I., Athanasiadis, A. and Dagklis, T., 2022. Invasive prenatal diagnostic testing for aneuploidies in singleton pregnancies: a comparative review of major guidelines. Medicina, 58(10), p.1472.

6- Baranova, E.E., Sagaydak, O.V., Galaktionova, A.M., Kuznetsova, E.S., Kaplanova, M.T., Makarova, M.V., Belenikin, M.S., Olenev, A.S. and Songolova, E.N., 2022. Whole genome non-invasive prenatal testing in prenatal screening algorithm: Clinical experience from 12,700 pregnancies. BMC Pregnancy and Childbirth, 22(1), p.633.

7- Pires, L.M.L.M., 2022. Non-Invasive Prenatal Screening for Common Aneuploidies-Implementation, Consolidation and Future (Master's thesis, Universidade de Coimbra (Portugal)).

8- Zhang, Y., Xu, H., Zhang, W. and Liu, K., 2022. Non-invasive prenatal testing for the detection of trisomy 13, 18, and 21 and sex chromosome aneuploidies in 68,763 cases. Frontiers in Genetics, 13, p.864076.

9- Zhu, X., Chen, M., Wang, H., Guo, Y., Chau, M.H.K., Yan, H., Cao, Y., Kwok, Y.K.Y., Chen, J., Hui, A.S.Y. and Zhang, R., 2021. Clinical utility of expanded non-invasive prenatal screening and chromosomal microarray analysis in high-risk pregnancy. Ultrasound in Obstetrics & Gynecology, 57(3), pp.459-465.

10- Soukkhaphone, B., Lindsay, C., Langlois, S., Little, J., Rousseau, F. and Reinharz, D., 2021. Non-invasive prenatal testing for the prenatal screening of sex chromosome aneuploidies: A systematic review and meta-analysis of diagnostic test accuracy studies. Molecular Genetics & Genomic Medicine, 9(5), p.e1654.

11- Su, J.Y., Wei, Y.N., Chen, H.F., Tong, J.R., Chen, Y., Deng, L., Huang, L.L. and Zhang, L.Y., 2023. Analysis of the results of non-invasive prenatal testing (NIPT) in 545 pregnant women in advanced maternal age. European Review for Medical & Pharmacological Sciences, 27(15).

12- Zhao, Y., Xue, Z., Geng, Y., Zhu, J., Hu, M. and Jiang, M., 2023. Understanding knowledge, perception, and willingness of non-invasive prenatal testing for fetal aneuploidy: a survey among Chinese high-risk pregnant women. Frontiers in Medicine, 10, p.1232942.

13- Xu, C., Cai, X., Chen, S., Luo, Q., Xi, H., Zhang, D., Wang, H., Wu, Y., Huang, H.F. and Zhang, J., 2021. Comprehensive non-invasive prenatal screening for pregnancies with elevated risks of genetic disorders: protocol for a prospective, multicentre study. BMJ open, 11(8), p.e053617.

14- Sun, Q., Xu, J., Yao, Y., Huang, X., Zhao, D., Lu, S., Yao, B. and Chen, L., 2024. Efficacy of non-invasive chromosome screening, preimplantation genetic testing for aneuploidy, and morphological grading in selecting embryos of patients with advanced maternal age: a three-armed prospective cohort study. BMC Pregnancy and Childbirth, 24(1), p.545.

15- Ye, C., Duan, H., Liu, M., Liu, J., Xiang, J., Yin, Y., Zhou, Q., Yang, D., Yan, R. and Li, R., 2024. The value of combined detailed first-trimester ultrasound–biochemical analysis for

screening fetal aneuploidy in the era of non-invasive prenatal testing. Archives of Gynecology and Obstetrics, 310(2), pp.843-853.