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False Positive Results in High-Risk Pregnancy for Chromosomal Anomalies: Psychological Considerations

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: With a high sensitivity and specificity, non-invasive prenatal testing (NIPT) is an incomparable screening test for fetal aneuploidy. However, the method is rather newly introduced, and experiences with false positive results are few. Even rare cases of discordant results may cause psychological stress.
Aim of the Study: The aim of this study was to examine false positive cases of NIPT tests in high-risk pregnancies. The literature review was also performed to review psychological consequences of discordant results.
Materials and Methods: A retrospective study was conducted between 2015 and 2022. The Natera Panorama test was used to analyse the risk of trisomies 21 (Down syndrome), 18 (Edwars

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syndrome), 13 (Patau syndrome), X monosomy (Terner syndrome) and other sex chromosome abnormalities. High risk result of NIPT for aneuploidy was confirmed by the invasive testing.
Results: 2000 women with a singleton pregnancy participated in the study. Out of 2000 NIPT tests 22 cases with high risk results for chromosomal anomalies were detected. Only one false positive case with high risk result for trisomy 21 was detected. The overall positive predictive value (PPV) of NIPT for trisomies 21, 13, 18, X monosomy and XYY syndrome was 95%.
Conclusion: Our study has showed only one case with false positive result for trisomy 21. However these cases with discordant results are very sensitive from bioethical point of view. So such couples need further follow up and sometimes even psychological counselling. NIPT due to its high PPV significantly reduces the need for an invasive testing, thereby reducing the risk of miscarriage.

Keywords: Non-invasive prenatal testing; bioethics; false positive results; chromosomes.

1. INTRODUCTION

A high risk pregnancy for chromosomal anomalies is a pregnancy in which the possibility of the fetus having a chromosomal abnormality, such as trisomy 21 (Down Syndrome) or trisomy 18 (Edwards Syndrome), is increased [1]. The likelihood of such a pregnancy can be influenced by factors including maternal age, which is the most known risk (National Society of Genetic Counselors, 2016), as well as previous family history (American College of Obstetricians and Gynecologists, 2019). Testing such as chorionic villus sampling or amniocentesis are invasive prenatal diagnostic techniques used to determine whether a fetus has chromosomal abnormalities. In both techniques, it is required that an instrument is implemented close to the fetus itself which is why invasive techniques bear a higher risk and are less popular [2].

It is noted that even during the testing stage, psychological stress for the mother is already expected (Women's Ultrasound Specialists Melbourne). Due to the risk and associated stress, non-invasive prenatal testing (NIPT) techniques are more common [3,4]. A simple blood test is used to determine the chromosomal abnormalities which carries less risk for the fetus as well as less stress for the mother (Royal College of Pathologists of Australasia, 2017). Even though the NIPT causes less anxiety to the mother, the pure process of testing generally causes distress. After a positive result, the parents of the child should be educated on the consequences this result might bring, the future accommodations which might have to be taken into account, as well as psychological counselling to deal with the fear, stress, and worries the diagnosis might cause. The importance of previous testing is not only to rule out possible disabilities and risks, but to possibly treat or prepare for an abnormality. This preparation is through being educated but mainly mentally since a child with a disability can cause a multitude of emotional strains [5]. However, what happens in case of a false positive, meaning the case in which a diagnosis was mistakenly made according to test results which wrongly appeared to be positive and a mother is emotionally prepared as well as strained?

2. MATERIALS AND METHODS

2.1 Study Subjects

We collected the data retrospectively on pregnant women with a singleton pregnancy who underwent NIPT in InMedica clinic. Study included 2000 pregnant women with high risk (age >35 years; increased risk for chromosomal anomalies according to biovhemical screening results) and low risk pregnancies. The exclusion criteria were multiple gestation and gestational age ≥ 21 weeks. The Panorama Test (NIPT) was performed to all the subjects of our study. The medical personnel took two blood samples of 10 ml from each subject. The study was authorised by the Ethics Committee of the Lithuanian University of Health Sciences, and a written informed consent was obtained from all participants. Literature review about possible psychological consequences of false positive NIPT results was performed and delivered at discussion section.

2.2 Laboratory Analysis

All the blood samples were transported within 48 hours by plane to Natera laboratory in San Carlos, California (United States). The samples were analysed as previously described using validated methodologies for cfDNA isolation, polymerase chain reaction amplification targeting 19,488 SNPs, high-throughput sequencing, and

the analysis with the next-generation aneuploidy test using SNPs (NATUS) algorithm (15,19,20).

The Natera Panorama test was used to analyse a cffDNA from maternal blood for the detection of the following chromosomal abnormalities: 1) trisomies of 21, 18, 13; 2) X monosomy; 3) triploidy; 4) other sex chromosome abnormalities and fetal gender. All the samples with a risk score ≥ 9:10 were reported as a high risk for fetal aneuploidy and the samples with the risk scores < 1:10 000 were considered of low risk. The samples were processed and the results were obtained within 5–7 business days. The high risk results were confirmed by the invasive diagnostic procedures (amniocentesis or chorionic villus sampling). A follow-up was performed by a telephone call for a low-risk group in order to ascertain that the infants would be born without chromosomal abnormalities.

2.3 Statistical Analysis

The descriptive data of demographic information are presented as median and minimum/maximum values. Continuous variables for normal distribution were inspected using the Kolmogorov–Smirnov test. We used the Spearman and partial correlation tests to evaluate the correlation of various factors associated with the fetal fraction. The Mann–Whitney U test was used for comparing the continuous variables between the groups. PPV was calculated by the formula PPV= true positive (TP)/ (true positive (TP) + false positive (FP)). A p value < 0.05 was considered statistically significant. A statistical analysis was performed using the SPSS 23.0 program.

3. RESULTS

The flow chart for the study is presented as Fig. 1. We collected the data of 2000 women who received NIPT, the sample collection dates ranged between November 2015 and June 2022.

The prevalence of high risk cases among the study participants was 1.1% (22/2000). Table 1 represents all high risk results of NIPT test for different chromosomal abnormalities as well weather the result was confirmed with invasive testing. Only one false positive case with high risk result for trisomy 21 was detected. So positive predictive value (PPV) for Down syndrome is 91.7 %. The overall PPV of NIPT for all abnormalities - trisomies 21, 13, 18, X monosomy and XYY syndrome was 95%.

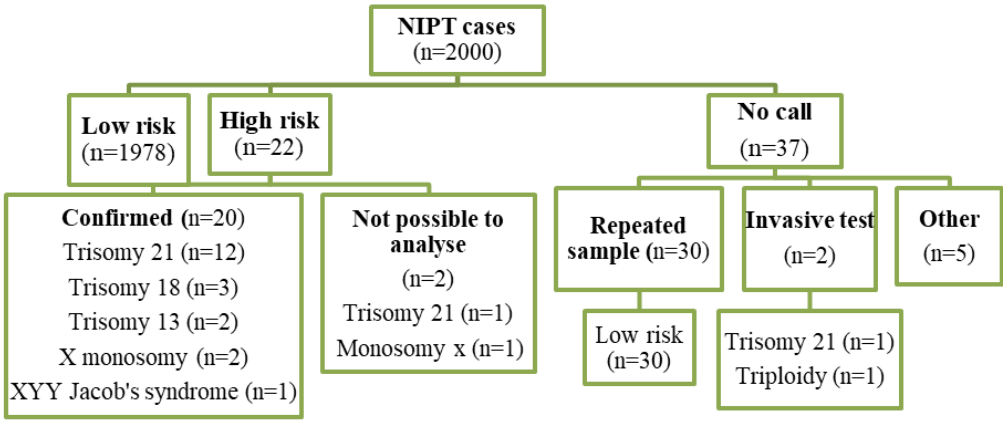

Fig. 1. Flow chart of the study

Table 1. Positive predictive values of non-invasive prenatal screening

	n	Confirmatory test	FP	FF (%)	PPV
High risk	22	21	0	6.4	95.5%
• Trisomy 21	12	11	1	8.8	91.7
• Trisomy 18	3	3	0	7.4	100%
• Trisomy 13	2	2	0	5.1	100%
• Monosomy x	2	2	0	8.4	100%
• XYY (Jacob's syndrome)	1	1	0	6.4	100%

FP-false positive, FF-fetal fraction, PPV- positive predictive value

4. DISCUSSION

NIPTs are gaining more popularity due to their reputation of being low risk and highly accurate. Despite the advancement in NIPTs technology, the accuracy of these tests is not perfect, leading to the possibility of false-positive and false-negative results. This inaccuracy can be attributed to a variety of factors, such as technical limitations, biological variation, and maternal factors, which may affect the reliability of the test.

Our study showed, that overall PPV of NIPT for all chromosomal abnormalities was very high 95%. We received only one discordant case for trisomy 21. Previous publications showed that "PPV was 97.4% for trisomy 21 and 88.9% for trisomy 18 [6]. However, an Indian study estimated PPV of trisomy 21 and sex chromosome abnormalities XXX, XXY (80% and 50%, respectively) which was much lower compared with our results, but PPV of trisomy 18 was identical to the findings obtained from our research (100%)" [7]. "An important issue is, that any high-risk score in NIPT should be confirmed by invasive prenatal diagnosis before any decisions about pregnancy" [7]. So NIPT testing is much more precise that biochemical screening from maternal blood. According to recent data false positive rats in first trimester prenatal screening may be up to 4% [8].

Grobman et al. (2018) advocates for support and education for mothers who receive a high risk result [9]. Leung et al. (2016) found that false negatives can cause negative psychological responses such as anxiety, depression, and stress reactions as well as feelings of guilt towards themselves [10].

It is interesting to note that Leung et al. (2016) also found that women receiving a false positive displace higher levels of worry and stress than women receiving a true positive. These negative feelings can even persist throughout the pregnancy and can go as far as affecting the feelings of attachments the mother forms with her child once it is born. Furthermore, the relationship of the parents can also be damaged. Both studies showcase the importance of providing proper psychological support to not only the women but the entire family due to the negative impact this situation could have on the relationships among the family members. However, it also demonstrates the current lack of support provided.

The adverse psychological reactions experienced by women are not solely attributable to the prospect of having an unhealthy child and the associated emotional burden. Rather, it is also attributed to the need for additional testing to validate the initial findings. Such testing is usually invasive and has the potential to harm the fetus, thereby increasing the anxiety and distress experienced by the mother. In severe cases, invasive procedures could result in the termination of the pregnancy.

Aite et al. (2019) conducted a research questioning a sample of 269 women who received a false positive result for either Down Syndrome, Edwards Syndrome or Patau Syndrome using NIPTs [11]. The women reported increased feelings of anxiety, stress, anger, as well as depression amongst others and expressed their disappointment with the lack of provided psychological health care. On the other hand studies show that "short term anxiety decreased when women received low risk NIPT results and that decisional regret was generally low" [12].

"NIPT is likely to be used in prenatal screening at the first trimester due to its high PPV. While reducing the invasive testing rates, NIPT saves life to a lot of fetuses who could potentially be miscarriaged as a result of the diagnostic testing with CVS or amniocentesis" [13].

Because of possible false positive high risk results pregnant women have to receive proper informed consent even before testing. And all high risk cases must be counselled by experienced clinical geneticist [14].

5. CONCLUSION

Our study detected only one case of false positive result, but generally discordant results in prenatal diagnostics may be big psychological stressor. Providing comprehensive education to families regarding the implications of a prenatal diagnosis and equipping them with the necessary tools to navigate the unique psychological and emotional challenges associated with such diagnoses is a critical but often overlooked aspect of healthcare. It is essential to recognize that the impact of a prenatal diagnosis extends beyond the medical implications and can have a profound effect on the psychological and emotional well-being of the family. Therefore, healthcare professionals must prioritize the provision of holistic care that addresses the multifaceted needs of the families affected by a high-risk pregnancy.

CONSENT

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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