Perspective
Volume 8:1, 2023

Journal of Pediatric Neurology and Medicine

ISSN: 2472-100X

Open Access

Analysis of Cell-Free Foetal DNA for Continuous Prenatal Screening for Frequent Aneuploidies

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Introduction

One quarter of newborns have chromosomopathies, which account for about 3% of all congenital anomalies. Aneuploidies, which are characterized by an abnormal number of chromosomes, are the most prevalent of the chromosomal disorders. Trisomy 21 (T21), also known as Down syndrome, is the most common aneuploidy and the most common cause of mental retardation in live newborns. Trisomies 18 (T18) and 13 (T13) are the next most common causes. There are a number of ways to screen for aneuploidies before a baby is born. With detection rates of up to 80%–90%, it is currently recommended to combine ultrasound and biochemical methods for better results [1].

Description

Based on the results of these markers, these screening programs make it possible to determine each pregnant woman's risk of certain chromosomal anomalies. When it comes to diagnosing aneuploidies in high-risk women, only QF-PCR and karyotyping in chorionic villi or amniotic fluid can be used. In addition to the high emotional cost, obtaining these samples requires an invasive procedure (chorionic biopsy or amniocentesis) with a 0.5% chance of complications (fetal loss and/or premature membrane rupture). There is currently no established national program for screening for genetic anomalies in Spain. In Spain's 17 autonomous communities, various diagnostic and screening methods are available [2].

Following the guidelines of NICE (National Institute for Health and Care Excellence) and SEGO (Spanish Society of Gynecology and Obstetrics), the Andalusian Program for the Screening of Congenital Anomalies (PACAC) was launched in 2009 as a combined first-trimester screening program throughout Andalusia. Pregnancy-associated plasma protein A (PAPP-A), a free beta subunit of human chorionic gonadotropin (fhCG), and nuchal translucency (NT) are measured during the first trimester of pregnancy in order to determine the likelihood of common aneuploidies. For the purpose of identifying women at high risk, f-HCG and alpha-fetoprotein (AFP) were also measured in women who first entered the healthcare system during their second trimester. In the first and second trimesters, the SIPACAC computer tool is used to estimate the risk of aneuploidies [3].

In 2011, cell-free DNA (cfDNA) testing became commercially available. It was developed in the field of molecular biology as a method for prenatal screening that makes it possible to detect the primary chromosomal alterations of the fetus—the Down, Edwards, and Patau syndromes-in the maternal blood as early as the tenth week of gestation. With a sensitivity of 99 percent and a false positive rate of 0.1 percent, this method has a high diagnostic efficiency for T21. Some authors suggest using it as contingent screening to cut down on the number of false positives in combined screening because of its high cost. The results of a pilot study in Andalusia using non-invasive prenatal testing (NIPT) as a contingent screening method are presented in this study.

The screening test takes into account maternal age, NT measurement, and PAPP-A and hCG levels in the first trimester of pregnancy. According to the Fetal Medicine Foundation's recommendations, ultrasound evaluation of the NT measurement was performed on patients whose crown rump length (CRL) was between 45 and 84 millimeters. The Cobas 8000 modular system was used to analyze blood samples for biochemical analysis that were taken between 9 and 13 plus 6 weeks of gestation. Women who entered the healthcare system for the first time during the second trimester were offered a second-trimester double test screening. The Cobas 8000 modular system was used to measure alpha-fetoprotein and free hCG in these cases between 14 and 18 weeks of pregnancy. Age at delivery was another factor.

The SIPACAC program was used to calculate the women's risk estimation for T21, T18, and T13 in both instances. Prenatal Cf-DNA testing The Harmony test was used in the Megalab, S.A. laboratory for Cf-DNA testing. Before NIPT, each participant received in-depth and careful pre-test counseling. Every patient gave written, informed consent. In a cell-free DNA collection tube approximately 10 milliliters of blood were taken from each subject. A double centrifugation procedure at 15′ 1600 rpm was used to separate plasma from blood. Using specialized circulating DNA extraction protocols, cell-free DNA was extracted with the QiaSymphony SP/AS platform. All extractions were performed in accordance with the Ariosa Clinical Laboratory's approved and validated protocols or the instructions provided by the manufacturer. For immediate use in the Harmony test on the Ariosa cell-free DNA System, the cell-free DNA that was produced was eluted to a final volume of 150 L and transferred to 96-well plates.

Only samples that met the Harmony test's quality metric thresholds by either method were used to generate probabilities for T21, T18, T13, and sex chromosome aneuploidies. More than 4% of the fetal cfDNA should be present. The Harmony test has previously been described in great detail. After the sample was collected, cfDNA testing results were available eight business days later. It is essential to emphasize that a 2% residual risk of a chromosomal abnormality has been reported in patients with a normal cf-DNA result following an abnormal traditional screening test. Additionally, our findings demonstrate that this patient group experiences some adverse perinatal outcomes [4].

One of the appropriate options being considered by the International Society for Prenatal Diagnosis is providing high-risk women with cDNA testing, along with the following two: cfDNA screening as a primary test for all pregnant women, and cf-DNA contingently for women identified by conventional screening as having high or intermediate risks. The SEGO's Ultrasound and Perinatal Medicine sections have developed a consensual strategy for implementing the cfDNA in Spain, taking into account the country's social needs and economic situation. It recommends using the contingent model for patients with a risk index of one in fifty and one in 250 without an associated ultrasound anomaly. Direct amniocentesis, in addition to karyotyping and QF-PCR, is recommended for pregnant women with risks greater than 1 in 50 [5].

Conclusion

We do not believe that direct invasive tests should be offered for pregnancies with risks greater than 1 in 50 and no fetal structural anomaly or NT greater than or equal to 3.5 mm. If the non-invasive test is offered first, it is important to reduce the number of amniocenteses, and the invasive test will probably not provide additional information if the Qf-PCR and karyotype are performed. On the other hand, our findings raise the question of whether women at intermediate risk up to 1 in 1000 should also receive cfDNA testing. If it had been given to 715 more pregnant women with intermediate risk, four false negative cases, including one

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Received: 02 January 2023, Manuscript No. JPNM-23-90689; **Editor assigned:** 04 January 2023, Pre QC No. P-90689; **Reviewed:** 16 January 2023, QC No. Q-90689; **Revised:** 21 January 2023, Manuscript No. R-90689; **Published:** 28 January 2023, DOI: 10.37421/2472-100X.2023.8.212

T21, would have been detected in our cohort. Expanding the use of cfDNA testing to lower-risk groups would, in our case, be contingent on regional health policies and financial resources.

Acknowledgement

None.

Conflict of Interest

None.

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How to cite this article: Ortiz, Siegel. “Analysis of Cell-Free Foetal DNA for Continuous Prenatal Screening for Frequent Aneuploidies.” *J Pediatr Neurol Med* 8 (2023): 212.