First results of non invasive prenatal testing in France after 18 months of analysis

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Objective

Detection of circulating cell-free DNA (ccfDNA) has been reported since 1997 by Lo. This ccfDNA principally comes from trophoblastic cells and can reach more than 10% of total DNA. This quantity increases with gestational age. DNA sequencing allows us to determine the fetal sex and Rhesus genotyping by non-invasive means. The detection of fetal DNA in maternal blood and the improvement in molecular genetic methods using NGS ("Next Generation Sequencing") has enabled Non Invasive Prenatal Testing (NIPT) of trisomy. This approach has been offered since 2011 to women with a higher age, history of trisomy or who have tested positive for aneuploidy or in cases of parental balanced translocation involving chromosomes 13, 18, 21. Fetal ccfDNA of chromosomes 13, 18, 21 can be detected and amplified by specific primers and quantified by a "massively parallel sequencing" (MaterniT21 PLUS LDT) at Sequenom CMM laboratory. Sexual chromosomal and microdeletion syndromes, such as Del22q, Del4p, Cri du Chat or Prader-Willi-Angelman syndromes are also detected by this screening. This test has a sensitivity of 99. 1% for T21. Each positive test is follow up by a fetal karyotype.

Methods

The main indication remains an integrated risk beyond 1/250 for first trimester serum markers as an alternative to invasive fetal puncture. An intermediary risk between 1/250 and 1/500 could be a very good target because of risk's residual of trisomy in this group, as well as cases of personal history of robertsonian translocation. The low-risk group is an interesting population due to high sensitivity and a poor rate of false-positives using this test. Ultrasound fetal abnormalities are excluded because they require a complete karyotype. Nevertheless, in case of "soft-signs" in intermediary-risk population or at a critical gestational age, NIPD may be really helpful.

Results

For the last 18 months in France, women could use this test at the American Hospital of Paris. Between first of January 2013 and fifth of June 2014, 1220 tests have been carried out. For 18 women (1, 5%) the results for Trisomy 21 were positive and one for Trisomy 18. In all cases, the indication was result beyond 1/250 for the first trimester serum markers. 16 of the detected Trisomy 21 were confirmed with amniocentesis. There were two false positive results (one for T21 and one for T18). Sex sexual chromosome abnormalities were detected with two Klinefelter syndromes, two Turner syndromes and two 47, XXX. For 7 women (0, 6%) the first results were non reportable. In this case, an additional blood test was performed but the results remained non conclusive for 2 of them (0. 02%). No false negative cases have been reported.

Conclusion

This test offers a high sensitivity method of screening but is not a diagnostical method for trisomy. An insufficient quantity of circulating DNA (less than 4%) can occur, particularly in case of maternal obesity or at an early gestational age and then requires a second test to reach a conclusion. The comparative approach doesn't allow detection of mosaicism, structural or molecular abnormalities, neither chromosomal discordance between fetus and placenta. Difficulties in interpreting the data can also occur in case of vanishing twin or in the presence of myoma or neoplasia. This very sensitive approach helps to reduce invasive test and the rate of induced miscarriages. This performance in low-risk women needs a large-scale assessment. The indications, contraindications and features must be explained in detail by dedicated genetic counseling before this promising and new method is exercised on a broader scale.