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Editorial

Non-Invasive Prenatal Test with CffDNA (NIPT)

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Conventional prenatal screening tests for detection of Tri 21 are based on biochemical and sonographic measurements in first and second trimester with a 5% false positive rate and 60-95% detection rate [1]. Recently, a new prenatal test is arised and is being attended to prenatal screening programs and changing the prenatal testing paradigm. Non-invasive prenatal testing (NIPT) can be placed to an intermediate step between conventional serum screening and invasive diagnostic testing. In 16 years period, after detection of cell free fetal DNA (cffDNA) in maternal blood in 1997 by Lo YM et al [2], studies on this area is concentrated more and cffDNA is entered to clinical practice from the year 2012. In the coming years it is expected to enter daily clinical use increasingly. NIPT involves analyzing the cffDNA present in a sample of maternal blood to determine the likelihood of a fetal aneuploidy. CffDNA can be detected in maternal plasma as early as 5-7 weeks of gestation [3]; however, test results are more accurate after 10 weeks because the amount of cffDNA increases by gestational age. The primary source of cffDNA in the maternal circulation is placental cells (syncytiotrophoblast) that undergone apoptosis. Also maternal originated cell free DNA is present in blood. Circulating DNA, whatever its origin, is highly fragmented; each fragment is between 50 and 200 base pairs [4]. CffDNA ratio that is approximately 10% at 11-3 week's gestation increases with advancing gestation and generally ranges between 3-20%. The amount decreases rapidly after birth and postpartum cannot be detected in maternal blood after two hours [5]. NIPT is generally being used as a screening test for chromosomal abnormalities like trisomy 21 (T21), trisomy 18 (T18), trisomy 13 (T13). Detection success for T21 and T18 is better than T13. Detection rates are 98.6, 94.9, 91.3%, false positive rates are 1.01, 0.14 and 0.14%, false negative rates are 1.01, 5.04 and 8.7% for Tri 21, Tri 18 and Tri 13 respectively. Detection rates for sex chromosome aneuploidies are lower and detection rate for Turner Syndrome is reported as 90,3% [6]. Test failure problem (i.e., no result) is another problem for cffDNA tests. It is reported as 1-5% in various studies [7]. In this situation test can be repeated, another screening test can be applied or invasive test can be applied. False positive test results depend on placental mosaicism, demised twin, maternal mosaicism, maternal cancer, transplant recipient mother or technical problems. NIPT is not recommended for multiple gestation pregnancies. False negative results may depend on again mosaicism, technical problems but especially low fetal fraction is the main reason. In 2, 2% cases test failure depends on low fetal fraction lower than 4% [8].

There is not a certain recommendation for clinical use of cffDNA in follow up. Currently, NIPT has only been validated in women with an increased risk of fetal aneuploidies; according to the American Congress of Obstetricians and Gynecologists (ACOG), risk factors include: 1) maternal age 35 years or older at delivery; 2) fetal ultrasonographic findings indicating an increased risk of aneuploidy; 3) history of a prior pregnancy with a trisomy; 4) positive test result for aneuploidy, including first trimester, sequential, or integrated screen, or a quadruple screen; or 5) a parental balanced Robertsonian translocation with increased risk of fetal trisomy 13 or trisomy 21 [9].

Various screening strategies defined recently with addition of cffDNA to prenatal screening programs. In contingent model al pregnant women are offered for first trimester screening. The "high risk" (eg, >1:150) identifies a group that could choose between going directly to invasive testing or to secondary cffDNA screening (or no further testing). The low-risk group (eg, <1:1000) would receive routine prenatal care with no options for further testing. The newly defined intermediate-risk group (eg, 1:151 to 1:1000) represents about 8 to 10 percent of the screened population and about 10 to 12 percent of all Down syndrome cases. These women are informed of their intermediate risk and offered cffDNA screening after counseling. If the cfDNA test is positive, the women are offered invasive testing. 99% of all Tri 21s are expected to be detected with this model. 3-5% will undergo invasive testing and 10% will undergo NIPT. In reflexive model maternal plasma is being collected at the same time with first trimester screening. If first trimester results indicate an intermediate risk, NIPT is being applied from previously collected sample negating the need for a call-back or counseling session. cffDNA is not commonly used as a primary screening test but in some countries it is being used as primary screening for high risk population. Higher cost of the test compared with serum immunoassays is a meaningful reason for this. Also, test failures up to 5% in low risk population seems confusing about the advantage of NIPT.

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