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Cell Free Fetal DNA (CffDNA): A New Tool to Decrease the Severity of Chromosomal Abnormality and Single Gene Disorder

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Chromosomal abnormalities in pregnancy occur when a fetus has an abnormal number or structure of chromosome. Single gene disorders are inherited diseases caused by a mutation in a single gene. These can cause a variety of health issues for the baby and the mother. Moreover these disorders can cause birth defects and other complications. Prenatal screening tests help determine the risk of a baby having chromosomal abnormalities and genetic disorder. It is applied to a mother with high-risk pregnancy, such as a too-old mother or a too-young mother and having a certain disease in her medical history.

Here, a variety of tests can be performed ranging from simple blood test, ultrasonography to see trimester specific soft tissue marker to invasive tests like chorionic villus sampling (CVS), amniocentesis or cordocentesis. The accuracy of genetic testing depends on the type of test. CVS, amniocentesis can detect chromosomal abnormality with greater than 99.9% accuracy. Invasive prenatal diagnosis is not a low-risk option for all mothers, because there are many limitations that need to be improved.

Since the discovery of cell-free fetal DNA (cffDNA) in maternal plasma in 1997 there has been rapid progress in harnessing this as a source of fetal genetic material for prenatal diagnosis.[1] The majority of cell-free DNA is maternal in origin,[2] with the fetal proportion emanating from the placenta,[3] detectable in the maternal circulation from around 5 weeks gestation.

During pregnancy, fetal cells flow across the placenta to the maternal circulation and vice versa, and the fetal cells can be identified as stem cells.[4] Cell free fetal DNA is from trophoblast cells. Hence, the fragment of fetal DNA is released to the maternal circulation after the degradation of trophoblasts, the apoptotic fetal cells circulating in maternal blood can be the minor source of cffDNA.[5,6]

The earliest clinical use of cffDNA was for the determination of fetal sex.[1] This relies on the detection of sequences, SRY (sex determining region of Y chromosome), in the maternal plasma that derive from the Y-chromosome. The technique has already become incorporated into standard care in several European countries, including the UK, for management of pregnancies at risk of severe X-linked genetic disorders, such as Duchenne muscular dystrophy (DMD).[7,8] DMD primarily affects boys. It has the potential to reduce the incidence of invasive testing for such conditions by up to 50% by allowing targeted testing in male bearing pregnancies.[8]

The second clinical application of cffDNA testing was for the determination of fetal RhD status in pregnant RhD-negative mothers.[9] As with fetal sex determination, this is possible because an RhD-negative mother does not produce any copies of the RhD gene (RHD), and thus the RHD identified in maternal blood originates from the fetus who has inherited the gene from the father. This approach to management of these high-risk pregnancies has avoided the need for invasive testing that was required previously.

The NIPT (non-invasive prenatal testing) method refers to circulating cffDNA testing and it can be used for fetal gender, the identification of specific single-gene disorders, blood type, paternity determination and the potency of routine use for testing Down Syndrome in all pregnancies[5]. Several latest studies showed that the screening method is the most effective way for Down syndrome (trisomy 21), with a detection level of more than 99% and a false positive rate of around 0.1% coming from cffDNA testing.[10]

Early diagnosis and timely intervention and planning future course of action are crucial in managing chromosomal abnormality and genetic disorder. The use of cffDNA for the diagnosis of fetal genetic and chromosomal conditions is having a profound effect on the practice of fetal medicine worldwide. Prenatal testing has beneficial for both parents and health care providers. Babies born with chromosomal abnormality poses economic and psychological burden for parents. It provides parents information about baby's health so that they can take correct decision whether to terminate or continue the pregnancy. It also helps healthcare providers determine the best course of action for baby's health.

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