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REVIEW

Non-invasive prenatal screening for chromosomal abnormalities using circulating cell-free fetal DNA in maternal plasma: Current applications, limitations and prospects

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KEYWORDS

Prenatal screening;
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Abstract *Background:* Prenatal screening for chromosomal aneuploidies was initiated in the 1970s, based in maternal age. With the introduction of serum and ultrasound biomarkers, new screening methodologies, with higher detection rates and lower false-positive rates, were implemented. More recently, cell-free fetal DNA testing was presented as a non-invasive test that uses maternal plasma to obtain fetal DNA in order to search for fetal aneuploidies or other chromosomal imbalances.

Methodology: Searches of PubMed were performed, being restricted to English-language publications and to humans. The search period was from January 2010 to July 2016. A total of 3416 citations were examined by title and abstract, 159 were analyzed integrally and a backward search of relevant studies led to the analyses of an additional 67 articles.

Results: When compared to other prenatal screening methods of common aneuploidies, cell-free fetal DNA testing has the best performance. However, its high cost and failure rate prevent at present time its implementation as a universal prenatal aneuploidy screening. Recent inclusion of microdeletions and microduplications in the panel of chromosomal anomalies to be screened by cell-free fetal DNA testing is a matter of concern, because of the low positive predictive value for these changes, and the associated significant cumulative false-positive rate.

Discussion: Cell-free fetal DNA testing represents the best screening method for common aneuploidies, and should its cost decrease, its use may be more widespread. But presently, contingent screening strategies may represent a cost-effective alternative. This review provides a current overview of this relevant theme.

Abbreviations: aCGH, array comparative genomic hybridization; cffDNA, cell-free fetal DNA; CMA, chromosomal microarray analysis; FISH, fluorescence in situ hybridization; hCG, human chorionic gonadotropin; NIPS, non-invasive prenatal screening; NIPT, non-invasive prenatal testing; PAPP-A, pregnancy-associated plasma protein A; PPV, positive predictive value; QF-PCR, quantitative fluorescent polymerase chain reaction

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Contents

1. Introduction

The presence of fetal cells in maternal plasma was first identified in the 1950s but its isolation had limited success [1]. However, the discovery of cell-free fetal DNA in maternal plasma in 1997 completely altered non-invasive prenatal screening applications [1]. The cell-free DNA present in the plasma normally has approximately 150–180 base pairs in length and its majority originated from apoptotic cells. [2] Particularly, cell-free fetal DNA (cffDNA) has its origin in the placental cytotrophoblastic cells, which are released into maternal bloodstream during pregnancy [2] and usually accounts for approximately 10–20% of the average of cell-free DNA in the maternal plasma in the second trimester of gestation [3]. Despite several reports describing a 1% increase in cffDNA fraction per gestational week, some authors observed stabilization or even decrease in cffDNA fraction along the pregnancy [4]. Some variables are known to affect cffDNA concentration in maternal plasma, for example maternal weight, number of previous gestations and gestational age [3]. However, it is still impossible to predict which patients will present higher or lower levels of cffDNA, which suggests that other factors control the amounts of fetal and maternal DNA circulating in the plasma of each pregnant woman [4]. There are well documented cases of false non-invasive prenatal screening (NIPS) results, which may derive mostly from fetoplacental mosaicism, maternal chromosomal abnormalities, low DNA fetal fraction, vanishing twin and/or errors associated with the procedures [3]. Currently, non-invasive prenatal screening is usually performed at or after 10 weeks of gestational age until the end of the first trimester, but can be done later in the pregnancy [3].

Non-invasive prenatal screening is usually based on massive parallel sequencing or on single nucleotide polymorphism pattern analysis of cell-free fetal DNA in maternal plasma [2,5–10]. The quantity of cffDNA present in the maternal plasma determines the test accuracy, the lowest accepted being approximately 4% [4]. Non-invasive prenatal screening applications are multiple and their value was first demonstrated in the determination of fetal sex, Rhesus D status and monogenic disorders [1].

In the last five years, it was found that detection of fetal aneuploidies was also possible through the study of circulating fetal cell-free DNA in the maternal plasma, with a very high sensitivity and specificity for the detection of trisomy 21, and slightly lower performance for trisomy 18, trisomy 13 and sex chromosome aneuploidies (SCAs: 45, X; 47, XXX; 47, XXY; 47, XYY) [2].

More recently, companies started promoting non-invasive prenatal screening also for microdeletions [2] and microduplications [11].

Since the demonstration of the feasibility of non-invasive analysis of fetal DNA to screen for chromosomal anomalies, non-invasive prenatal screening has gained a growing role in prenatal testing and it is essential to review its applications, major limitations and likely developments in the future.

2. Methods

Searches of PubMed were performed using the following search terms: ‘‘non invasive DNA prenatal screening’’, ‘‘non invasive prenatal test accuracy’’, ‘‘cell-free DNA analysis trisomy’’, ‘‘NIPS for fetal abnormalities’’, ‘‘noninvasive prenatal diagnosis and standard screening’’, ‘‘Prenatal screening review’’ and ‘‘massive parallel sequencing’’. These were restricted to English-language publications and to humans. The search period was from January 2010 to February 2016. Then, a total of 3416 citations were examined by title and abstract in order to identify all relevant articles. A sum of 159 were analyzed integrally, including a backward search of relevant studies, which led to the analyses of an additional 67 articles.

3. Prenatal diagnosis of chromosomal anomalies

Since, in 1966, it was demonstrated that fetal cells obtained through amniocentesis could be cultured in vitro to obtain a fetal karyotype, the era of prenatal diagnosis started.

A few years later, other prenatal invasive procedures, such as chorionic villus sampling and cordocentesis, became available and were used initially for the study of fetal chromosomes, originally for the detection of aneuploidies and, after banding techniques were discovered, also for the diagnosis of balanced and unbalanced structural abnormalities [12,13].

Prenatal diagnosis of chromosomal anomalies remained based on fetal karyotyping for several decades, which in turn required that at-risk women would be subjected to an invasive procedure, either chorionic villous biopsy (usually performed between the 10th and the 13th gestational week), amniocentesis (usually carried out at 16 plus weeks) or, rarely, cordocentesis (later in pregnancy), each of these procedures having a risk of fetal loss that ranges from 0.5% to 1% for amniocente-