

Cell-Free Fetal DNA in the Maternal Circulation and its Future Uses in Obstetrics

This technical update has been prepared by the Genetics Committee and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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3. Diagnostic and screening techniques may be able to utilize this cell-free fetal DNA in the future to provide non-invasive screening and diagnosis opportunities. This DNA technique is already well established for fetal sexing in pregnancies at risk of an X-linked disorder and fetal rhesus-D evaluation. Other conditions with well-identified unique paternal mutations can also reliably apply this cell-free fetal DNA technology for prenatal diagnosis.

4. The overall use of this molecular technology is still limited and requires the identification of sex-independent DNA markers so that female fetal DNA can be distinguished from maternal DNA, allowing its use in the screening or diagnosis of fetal and placental disease in pregnancies of either fetal sex.

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INTRODUCTION

The discovery of fetal DNA in maternal plasma has opened an approach for non-invasive assessment of pregnancy in both fetal and fetal-initiated maternal disease. The knowledge of human genetics has increased dramatically in the past 2 decades, and as a result, there has been increasing interest in the analysis of circulating fetal nucleic acids DNA and (or) RNA in maternal blood plasma or serum as a clinical screening or diagnostic tool. Occasional reports suggested the existence of circulating nucleic acids, but the potential clinical implication was not realized until 1996, when DNA with tumour-specific characteristics was demonstrated in the plasma/serum of cancer patients.¹ This type of finding opened up opportunities to consider other applications such as prenatal diagnosis.²⁻⁴ This technical update will review those research findings related to obstetrics for screening and diagnostic applications.

In 1997 the presence of fetal DNA in maternal plasma was first discovered through the detection of Y-chromosome-specific sequences in the plasma of women who were carrying male fetuses.^{5,6} To date, there have been numerous reported applications,⁷ including fetal rhesus-D genotyping,^{8,9} fetal sexing for X-linked disorders,^{9,10} paternally inherited genetic diseases,¹¹⁻¹³ and pregnancy-associated conditions such as preeclampsia.¹⁴⁻¹⁶

Abstract

Objective: To provide an introduction to new technologies involving maternal plasma cell-free fetal DNA for non-invasive prenatal diagnosis and screening in obstetrics.

Options: Limited to introductory discussion of maternal plasma cell-free fetal DNA.

Evidence: MEDLINE was searched to identify publications related to the topic after 1996. This document represents an abstraction of the information.

Values: This update is a consensus of the Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC).

Benefits, Harms, and Costs: This update educates about new technology and its future use in obstetrics. At present, there is no harm or cost (research with limited clinical application) identified.

Conclusions:

1. Significant and measurable amounts of cell-free fetal DNA are present in the maternal circulation and increase throughout pregnancy.
2. Different fetal (trisomy 21, trisomy 13) and placental abnormalities can affect the levels of cell-free fetal DNA within the maternal plasma.

Key Words: Prenatal diagnosis, screening, cell-free fetal DNA, maternal plasma, maternal serum, obstetrical complications

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GENETICS 101¹⁷

The genome is the entire complement of genetic material in a chromosome set. The karyotype is a chromosome constitution of an individual. DNA is the double-helix structure composed of 2 coils of nucleotide chains connected by nitrogen bases. Messenger RNA (mRNA) is a single-stranded nucleotide chain of differing lengths, based on the length of the message. A gene is a unit of heredity responsible for the inheritance of a specific trait that occupies a fixed chromosomal site and corresponds to a sequence of nucleotides along a DNA molecule. An allele is 1 of 2 or more alternate gene forms. Within the gene, the exon is the region made up of DNA sequences that will be transcribed into RNA. The intron is the region made up of noncoding DNA sequences that lies between exons. Linkage is the association of genes on the same chromosome. A mutation is an alteration of DNA sequencing in a gene that results in a heritable change in protein structure or function that frequently has adverse effects. These mutations can be caused by a deletion, expansion, frame shift, insertion, inversion, or missense of the gene. Mutations can be identified by molecular DNA techniques that identify unique or changed DNA structure. Polymerase chain reaction (PCR) is a method for enzymatically amplifying a short sequence of DNA through repeated cycles of denaturation, binding with an oligonucleotide primer, and extension of the primers by a DNA polymerase. Complementary DNA (cDNA) probe is a DNA sequence that is exactly complementary to mRNA, lacking introns and regulatory regions. X-linked is an allele for a trait or disorder that is located on the X chromosome and may be either dominant or recessive. Sensitivity is the proportion of true positives (correctly identified disease) and specificity is the proportion of true negatives (correctly identified disease-free).

CLINICAL APPLICATIONS OF CELL-FREE DNA FROM MATERNAL PLASMA

1. Prenatal Diagnosis

In 1997 Lo *et al.*⁵ were the first to show the presence of high concentrations of cell-free fetal DNA in maternal plasma using real-time quantitative PCR. A recent review indicates this molecular test is highly accurate in determining fetal sex, fetal rhesus-D status in rhesus-D negative women, and single gene disorders of paternal origin.⁹ The sensitivity and specificity of fetal sexing from maternal plasma by detecting male fetal DNA in 676 published cases has a sensitivity of 96% (344/359) and a specificity of 100% (317/317), with gestational age varying from 5 weeks to 40 weeks and using different Y-chromosome sequences.⁹

When considering the best gestational age for plasma PCR for fetal sexing, the sensitivity increases substantially

between 5 weeks and 10 weeks and reaches its maximum at 10 weeks' gestational age.¹⁸ False-positive results of fetal sex determination in plasma are very low. This presents the possibility of fetal sexing in maternal plasma in fetuses at risk for recessive X-linked diseases or congenital adrenal hyperplasia.⁹

Molecular analysis of cell-free fetal DNA from maternal plasma to identify fetuses that are rhesus-D positive in sensitized rhesus-D negative women has a sensitivity close to 100%, with a specificity of 97% according to a recent series of 72 cases tested with no false-negative results and one false-positive result for rhesus-D typing, probably owing to the rhesus-D pseudogene.⁹ Avoiding false-negative results is crucial if these techniques are to be used in the clinical situation, especially in rhesus-D typing, because there is no way to secondarily confirm the results. In contrast, ultrasound can be used for anatomical confirmation of external genitalia when fetal sex determines risk.

An increasing number of individual case reports demonstrate that some paternal mutations, uniquely contributed to the fetus, could be assayed in maternal plasma samples. The genetic conditions that have been reported include cystic fibrosis,¹⁹ myotonic dystrophy,²⁰ achondroplasia,²¹ and congenital adrenal hyperplasia.¹²

Non-invasive prenatal diagnosis of beta thalassemia, one of the most common autosomal recessive diseases in the world, was performed by mass spectrometric analysis of DNA in maternal plasma. The paternally inherited fetal genotype was correctly identified in 20 of 23 pregnancies.¹³ The study demonstrated that fetal DNA can be robustly detected in maternal plasma by mass spectrometry and paves the way for high throughput, non-invasive prenatal diagnosis.

Fetal chromosomal abnormalities have also been shown to affect levels of cell-free fetal DNA in the maternal circulation. Down syndrome (trisomy 21) pregnancies exhibit 1.7-fold higher levels of maternal serum cell-free fetal DNA, compared with matched controls.²² Maternal serum cell-free fetal DNA levels are also increased in cases of trisomy 13 but not trisomy 18.²³ Combining quantification of cell-free fetal DNA using real-time quantitative PCR of Y-specific sequences with the usual second trimester maternal serum markers for Down syndrome modestly increases the screening performance with an estimated trisomy 21 detection rate rising from 81% to 86% at a 5% false-positive rate.²⁴ The present limitations of this type of chromosomal screening is that maternal serum fetal DNA measurements are currently based in quantifying Y-specific sequences and therefore can only apply to pregnancies with a male fetus. If a sex-independent DNA marker can be identified, cell-free

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