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Screening for fetal chromosomal and subchromosomal disorders

Sarah Harris [a, *], Dallas Reed [b], Neeta L. Vora [c]

[a] University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC, USA
[b] Tufts Medical Center and the Floating Hospital for Children, Department of Obstetrics and Gynecology, Division of Genetics and Metabolism, Department of Pediatrics, Boston, MA, USA
[c] University of North Carolina at Chapel Hill School of Medicine, Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Chapel Hill, NC, USA

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A B S T R A C T

Screening for fetal chromosomal disorders has evolved greatly over the last four decades. Initially, only maternal age-related risks of aneuploidy were provided to patients. This was followed by screening with maternal serum analytes and ultrasound markers, followed by the introduction and rapid uptake of maternal plasma cell-free DNA-based screening. Studies continue to demonstrate that cfDNA screening for common aneuploidies has impressive detection rates with low false-positive rates. The technology continues to push the boundaries of prenatal screening as it is now possible to screen for less common aneuploidies and subchromosomal disorders. The optimal method for incorporating cfDNA screening into existing programs continues to be debated. It is important that obstetricians understand the biological foundations and limitations of this technology and provide patients with up-to-date information regarding cfDNA screening.

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* Corresponding author. University of North Carolina at Chapel Hill School of Medicine, 3010 Old Clinic Building, CB 7516, Chapel Hill, NC 27516, USA.
E-mail address: sally_harris@med.unc.edu (S. Harris).

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1. Introduction

Prenatal screening for fetal chromosomal disorders has been offered clinically for more than 40 years. The goal of aneuploidy screening is to identify pregnancies at increased risk for chromosomal disorders using screening tests that have high detection rates while minimizing the number of false-positive results. Individuals identified to be at increased risk are subsequently offered diagnostic testing. Diagnostic confirmation of fetal chromosomal disorders requires obtaining fetal cells through invasive procedures, such as amniocentesis or chorionic villus sampling. Whereas these procedures are relatively safe, they carry a small risk for miscarriage [1]. Prenatal screening and diagnostic testing give women the opportunity to make informed reproductive decisions and optimize their pregnancy outcomes. In this review, we discuss the evolution of screening for chromosomal disorders from its modest beginnings with maternal serum analytes through the development of cell-free DNA (cfDNA) screening. We focus our discussion on the clinical applications of cfDNA, its limitations, and how it continues to revolutionize the field of prenatal screening.

2. Historical perspective

Traditionally, prenatal screening has focused on detecting cases of trisomy 21 (Down syndrome), the most common chromosome condition affecting live births. It is well established that the risk for trisomy 21 increases with maternal age. The risk of a live term infant with trisomy 21 increases from ~1 in 1500 at age 20 years to 1 in 85 at age 40 years [2]. In the USA and other high-income countries, pregnant women aged >35 years have been offered amniocentesis based on their age-related risk of trisomy 21 since the 1970s. At that time, screening based solely on maternal age allowed the detection of 30% of fetuses with trisomy 21 by offering diagnostic testing to ~6% of pregnant women [3]. Now, with the availability of maternal blood and ultrasound-based markers, screening and follow-up diagnostic testing is offered to all pregnant women regardless of age, based on the patient's desire for information about genetic conditions.

Screening for chromosomal abnormalities in women age <35 years was introduced in the 1980s when reports were published linking low alpha-fetoprotein levels in maternal serum to pregnancies with trisomy 21 [3]. Over time, additional maternal serum markers, including human chorionic gonadotropin (hCG), dimeric inhibin A (DIA), and unconjugated estriol (uE3), were added to the screening algorithm to improve detection rates. Combined first-trimester screening further improved detection rates by incorporating analysis of serum free β-hCG or total hCG along with pregnancy-associated plasma protein A (PAPP-A) in addition to an ultrasound measurement of the nuchal translucency [4,5]. Table 1 summarizes the evolution of screening for trisomy 21.

While conventional screening methods were developed to identify fetuses with trisomy 21, other aneuploidies, including trisomy 18 (Edwards syndrome), trisomy 13 (Patau syndrome) and monosomy X (Turner syndrome), were also being detected with the widespread use of these screening tests. Screening algorithms were developed for trisomy 18 using the analytes and ultrasound components developed for trisomy 21 detection [6]. However, screening for trisomy 13 and monosomy X remained more difficult.

In 2011, the paradigm of prenatal screening shifted with the introduction of cell-free DNA (cfDNA) screening. This new technology allowed for significant improvements in the detection of pregnancies with trisomy 21 as well as the less common chromosomal disorders.

3. Development of cell-free DNA screening

Driven by the desire to produce an accurate test without risk, researchers have worked towards developing a non-invasive

Table 1
Evolution of screening tests for trisomy 21.

Year	Event
1970s	Maternal age >35 years Detection rate: 30%
1980s	Introduction of maternal serum screening with AFP AFP and maternal age Detection rate 25–30%
1990s	Addition of multiple maternal serum markers Triple screen (hCG, AFP, uE3) Detection rate: 69% GA: 15–22 weeks Quadruple screen (hCG, AFP, uE3, DIA) Detection rate 81% GA: 15–22 weeks
2000s	First trimester screening First trimester combined screening (hCG, PAPP-A + NT measurement) Detection rate: 82–87% GA: 10–$13^{6/7}$ weeks
2011	cfDNA screening introduced to clinical practice cfDNA measured in maternal plasma Detection rate: >99%

AFP, alpha-fetoprotein; hCG, human chorionic gonadotropin; uE3, unconjugated estriol; GA, gestational age; DIA, dimeric inhibin-A; PAPP-A, pregnancy-associated plasma protein A; NT, nuchal translucency; cfDNA, cell-free DNA.

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