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PRENATAL TESTING IN THE GENOMIC AGE: BALANCING CLINICAL OUTCOMES, QUALITY OF LIFE, AND COSTS

by Anjali J. Kaimal M.D.

Since amniocentesis was first introduced, prenatal testing has expanded exponentially to include a menu of screening and diagnostic testing options. In particular, the recent introductions of cell-free DNA screening and chromosomal microarray analysis have increased both the number of options available and the complexity of prenatal testing decision making as patients and providers weigh the trade-offs not only between screening and diagnostic testing, but also between multiple different screening options. In a recent publication, we used decision and cost-utility analysis to investigate the clinical outcomes, maternal quality-of-life effects, and cost-effectiveness of currently available screening and diagnostic prenatal testing strategies for detection of aneuploidy and pathogenic copy number variants.

We found that screening strategies starting with multiple marker approaches yielded the highest detection of significant chromosomal abnormalities, including copy number variants, with the lowest number of procedures performed per case diagnosed, the optimal maternal experience (based on the highest number of quality-adjusted life-years (QALYs)), and the lowest costs. While cell-free DNA as a primary screening test yielded a higher detection rate of trisomy 21, this was at the expense of detection of other significant abnormalities. Multiple marker screening with the option of either cell-free DNA analysis or diagnostic testing as follow up for positive results improved the detection of other chromosomal abnormalities in comparison to primary cell-free DNA screening, and decreased the rate of diagnostic procedures. This is in part because, based on the literature, we assumed that a significant minority of women would choose diagnostic testing after counseling regarding their positive screening results. While simultaneous testing with cell-free DNA and either NT or multiple marker screening is theoretically appealing, this approach always yielded lower QALYs than single test or contingent strategies and by definition has higher costs, making these strategies less optimal.

For several reasons, maternal age impacted our results. First, the rate of common aneuploidies increases with maternal age, while the incidence of less common chromosomal abnormalities and copy number variants does not. Because traditional multiple marker screening is less specific, it facilitates the detection of many of the uncommon chromosomal abnormalities not identified by cell-free DNA, which has a significant impact in younger women, who are at fairly low risk of common aneuploidies. Consequently, while multiple marker screening with diagnostic testing as the only option for follow up optimized quality of life outcomes for women under 35, cell-free DNA as the first-line test maximized QALYs in women aged 38 and older. It is important to consider that this analysis measured outcomes at a population level, while the balance between the value of information and risk aversion requires consideration at an individual level, as these may be valued differently. Therefore, we believe that age should be neither a necessary nor a sufficient criterion to constrain testing strategies at a population level.

In summary, we found that the current paradigm of traditional marker screening is the optimal initial strategy for most women who desire prenatal testing. As women approach 40, the larger proportion of chromosomal abnormalities represented by the common aneuploidies makes cell-free DNA a more reasonable first-line test, as it provides excellent detection of the chromosomal problems most common at older maternal ages. For women who desire the most comprehensive information available regarding fetal chromosomal abnormalities, diagnostic testing should be offered regardless of maternal age.

REFERENCE: Kaimal AJ, Norton ME, Kuppermann M. Prenatal testing in the genomic age: Clinical outcomes, quality of life, and costs. Obstet Gynecol. 2015;126(4):737-46.

IN THIS ISSUE

FETAL MONITORING CREDENTIALING: MAINTAINING EXAMINATION RELIABILITY

by Sara Brumbaugh, MS and
Marin O'Keeffe, RN

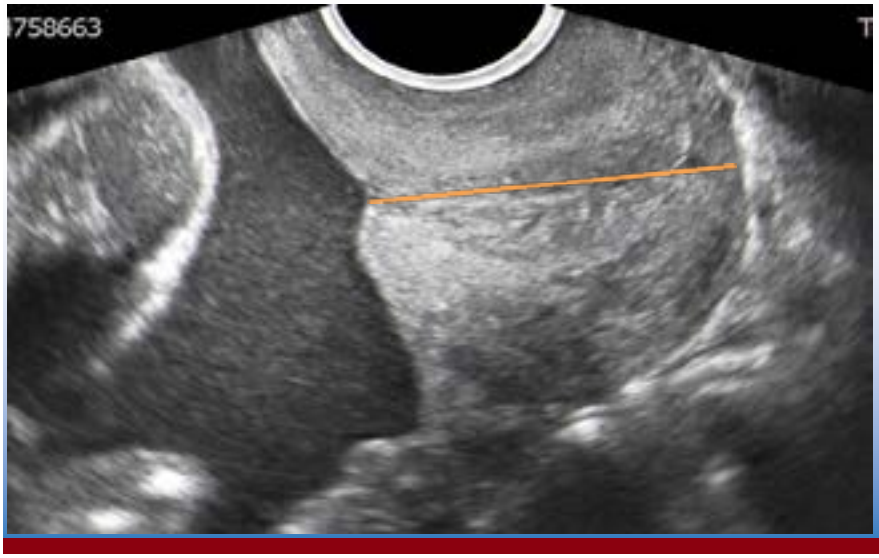
The Perinatal Quality Foundation developed the Fetal Monitoring Credentialing (FMC) examination to provide feedback to clinicians on their ability to manage laboring patients undergoing electronic fetal monitoring. Perinatal Quality Foundation's FMC exam has been available since 2014 and many institutions have since joined PQF with the aim of improving outcomes by measuring knowledge and judgment of intrapartum providers and providing feedback regarding weaknesses and incentives for additional education.

The FMC examination tool utilizes Script Concordance Testing (SCT) as a measurement of clinical reasoning, and the exam is continually assessed to confirm that it is a relevant and reliable measure of individuals' knowledge and judgment around electronic fetal monitoring. The FMC Task Force recently met over several days to review questions and ensure maximum validity of the examination.

The Task Force's review of the FMC examination included a substantive assessment of questions and resulting answer patterns. If virtually all examinees were to answer a question correctly, then the task force would review the question to ensure that it represents essential knowledge fundamental to basic practice and that the answer is not obvious even to a non-practitioner.

Review also included statistical analysis of exam from perspectives of both Classical Test Theory and Item Response Theory. Classical Test Theory supports measurement of overall exam reliability whereas Item Response Theory measures the difficulty of each question along with its effectiveness in distinguishing examinees' proficiency.

Be evaluating the exam from these three different perspectives - substantive assessment, Classical Test Theory and Item Response Theory - the FMC Task Force has ensured continuing validity of the exam. Further information regarding FMC can be found at http://fmc.perinatalquality.org.



WHAT'S WRONG WITH THIS CERVICAL LENGTH MEASUREMENT?

Turn to page 4 to find out!

INCREASED NUCHAL TRANSLUCENCY: BEYOND THE KARYOTYPE - CHROMOSOMAL MICROARRAY

by Renee Chard, MSc, CGC

The association between an increased first trimester nuchal translucency (NT) measurement and fetal aneuploidy is well known and standard of care includes the offer of fetal karyotyping by chorionic villi sampling or amniocentesis. Chromosomal microarray is a laboratory technique that allows for much higher resolution than a standard karyotype. Thus, while still ruling out major aneuploidies, chromosomal microarray allows a specimen to be tested for submicroscopic chromosomal deletions and duplications throughout the genome.

In 2011, Leung[1] reported 48 cases of increased NT (> 3.5 mm) with normal standard karyotypes on which microarray analysis was then performed on stored chorionic villi specimens. Of the 10 fetuses with other abnormalities detected on ultrasound, 20.0% (2/10) were noted to have a clinically significant copy number variant. Among the 38 fetuses with no other sonographic abnormality, two (5.3%) had clinically significant copy number variants. In 2012, Wapner et al[2] published the results of a multicenter study in which chromosomal microarray was performed on 4340 prenatal specimens collected from amniocenteses and chorionic villi sampling procedures performed for common indications including advanced maternal age, positive maternal serum screening test results and abnormal ultrasound findings. Of those with normal standard karyotype, a clinically significant duplication or deletion was identified in 6.0% of specimens associated with a chromosome abnormality and in 1.7% of tests done for advanced maternal age or positive screening test result. A 2015 meta-analysis of 17 studies by Grande[3] designed to evaluate the efficacy of chromosomal microarray in euploid fetuses with increased first trimester nuchal translucency, demonstrated that chromosomal microarray resulted in a 5% incremental yield over karyotyping. The incremental yield was 4% in cases of isolated increased NT and 7% when the increased NT was associated with other ultrasound findings.

For a variety of reasons, genetic counseling should be offered prior to performance of diagnostic testing in the setting of increased nuchal translucency. Since the majority of chromosome abnormalities associated with increased NT are the common trisomies and Turner syndrome, a patient may want to consider a test with rapid turn-around time such as aneuploidy FISH as a first tier test to be followed by microarray if FISH results are normal. When pursuing microarray testing, discovery of a variant of unknown significance is a possible outcome in ~ 1% of cases.[3] For this reason it is important that chromosomal microarray be offered in the context of comprehensive pretest counseling. In addition, microdeletion and microduplication syndromes vary widely in terms of severity. Some are associated with structural findings that are detectable by ultrasound examination, and some are associated with neurodevelopmental findings including developmental delay, intellectual disability and autism. In many cases, parental studies are indicated. For those without one in their clinical practice, a genetic counselor can be found by clicking on the 'Find A Genetic Counselor' link on the website of the National Society of Genetic Counselors (http://ww.nsgc.org).

It is also important to remember that increased nuchal translucency is also associated with an increased risk for structural birth defects, especially congenital heart disease, as well as a number of single gene disorders that would not be identified by fetal karyotype or microarray; these will be covered in future issues by our "Increased Nuchal Translucency: Beyond the Karyotype" series.

REFERENCES:

1. Leung TY, et al. Ultrasound Obstet Gynecol 2011;38:314-319.
2. Wapner RJ, et al. NEJM 2012;(367)23:2175-2184
3. Grande M, et al. Ultrasound Obstet Gynecol 2015; Dec;46(6):650-658.

INTRODUCING THE PQF APP SUITE

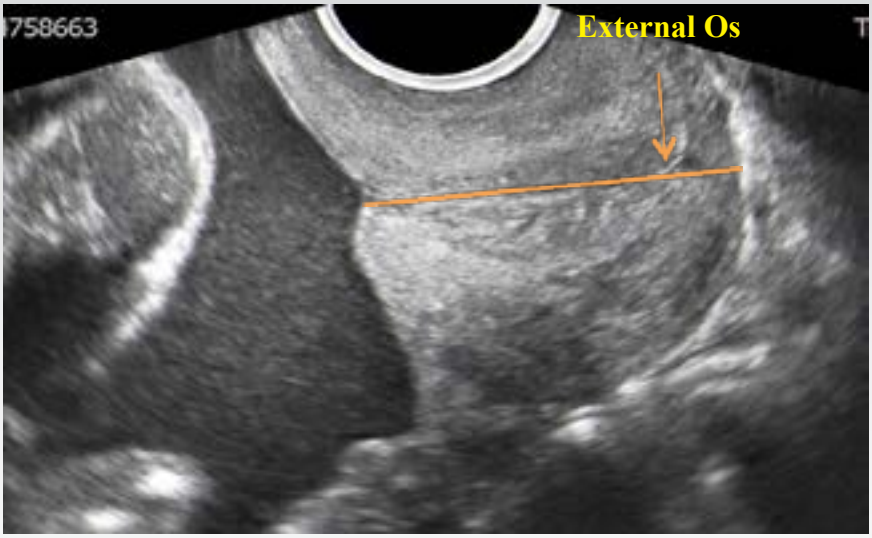
The Perinatal Quality Foundation (PQF) App provides a collection of smart device applications that put convenient calculators and OB practice tools right in your pocket. The apps include the Nuchal Translucency Calculator, Cell-free DNA/NIPT Predictive Value Calculator, and Cervical Length Algorithm with more to come.

Download on the App Store: http://tinyurl.com/h6vqvas

Download on the App Store

WHAT'S WRONG WITH THIS CERVICAL LENGTH MEASUREMENT?

(CONTINUED FROM PAGE 2)



ANSWER:

The image on page 2 is an incorrect measurement as it overmeasures the cervical length; the measurement should stop at the external os.

…For more information and education on measurement of cervical length, go to http://clear.perinatalquality.org

CLEAR
Cervical Length Education and Review

CLEAR.perinatalquality.org

2.5 hours AMA category 1 CME
or 3 hours SDMS CME
for sonographers

NOMENCLATURE REMINDER:
Use the term "cfDNA Screening"

Cell free DNA (cfDNA) technology is a valuable tool in screening for common aneuploidies. The terms "non-invasive prenatal testing (NIPT)", "non-invasive prenatal screening (NIPS)", or "cell-free fetal DNA testing (cffDNA)", however, may be misleading. The term "non-invasive" falsely implies benefit when compared to diagnostic testing procedures, and "testing" implies definitive diagnostic results rather than screening. Accordingly, when using cell free DNA technology in clinical practice, call it what it is and use the term "cfDNA screening."

PERINATAL QUALITY FOUNDATION ANNOUNCES THE GEM PROGRAM

The primary goal of the Perinatal Quality Foundation Genetic Education Module (GEM) is to provide unbiased and comprehensive information to health professionals, women, and their partners regarding prenatal genetic testing options. Recent developments in prenatal genetic technology, including the availability of cell free DNA (cfDNA) analysis for prenatal screening, expanded carrier screening, as well as the expansion of chromosomal microarray analysis have brought about significant changes in prenatal genetic testing. These rapidly evolving developments have created new challenges for many obstetric providers, and aggravated an existing shortage of prenatal genetic counselors and healthcare personnel with expertise in genetics. The GEM program aims to address these gaps by providing informational tools, talking points, standardized education, patient decision aids, regular updates, and a clinical results registry.

The creators of GEM are seeking provider feedback to ensure GEM includes the information desired by OB providers in a way that is useful to them. Be sure to provide your input by completing the GEM survey at http://www.surveymonkey.com/r/PQF-GEM-OBs. Those who complete the survey will be offered a chance to enter a drawing for monetary prizes.

GEM is Coming Soon -- Stay Tuned

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Editor - in - Chief

Karin M. Fuchs, MD
kmf2121@columbia.edu

Send letters to the editor and other inquiries to:

The Examiner
Perinatal Quality Foundation
12316A North May Avenue
Oklahoma City, OK 73120
e-mail: support@perinatalquality.org

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