

PERINATAL QUALITY FOUNDATION FIRST TRIMESTER IMAGE BANK

The first trimester combined screening test for aneuploidy has led to increased numbers of and greater to first trimester ultrasound examinations. It is important that the additional benefits seen with first trimester examinations are not lost as alternative screening methods become more available.

Early anatomic diagnosis is an emerging field made possible by advances in sonographic technology. Although the use of first trimester ultrasound as an initial screen for anatomic anomalies is growing, the diagnostic certainty for many conditions is lower in the first trimester than in the second; and sensitivities, specificities, and natural history of many early findings have not yet been well established. The limitations of first trimester ultrasound for diagnosis of fetal anomalies must be taken into consideration when counseling patients and planning pregnancy management.

The Perinatal Quality Foundation has collected cases to demonstrate the potential of first trimester ultrasound examination for diagnosis of anatomic abnormalities. The case images and accompanying questions will allow visitors to the PerinatalQuality.org website to test and enhance their diagnostic skills and knowledge.

The Perinatal Quality Foundation will continue to collect these cases and provide a rotation of information and images. If you would like to submit images for possible inclusion in the First Trimester Image Bank, please remove any identifying information, and send the images along with a description of the case to Jean Spitz at jspitz@perinatalquality.org. Images should be of high resolution; videos cannot be included at this time.

An example case is displayed below.

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This fetus was referred for an NT measurement with a CRL of 77mm. The fetus has a poorly imaged NT, with markedly abnormal head shape and 'floppy' appearing neural tissue above the face. No visible cranium is seen. To confirm the diagnosis go to <http://www.perinatalquality.org>.

USEFUL APPS AND WEBSITES FOR THE BUSY CLINICIAN

by Lorelei Thornburg, MD
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With the increasing emphasis on evidenced-based care and avoiding unnecessary testing, there are so many new guidelines and updated protocols to know, it can be hard to keep all the data straight. Although electronic records are being used more widely, few have incorporated practice guidelines to assist providers. Fortunately, there are a number of smartphone apps and websites that can make a busy clinician's life easier. Some of my favorites are listed below:

For pelvic floor/pelvic anatomy understanding: *POP-Q* is an app (also at pelvic-floor-institute.com) focused on prolapse and incontinence; interactive examples allow input of specific *Pop-Q* measurements and alteration of pelvic prolapse findings based on *POP-Q* score and therapeutic options. *drawMD* has a number of different apps, including one for female pelvic surgery and one for general ob/gyn (*drawMD female pelvic surgery, drawMD OBGYN*) which provide clear, simple drawings of common obstetrical and gynecologic conditions and allow freehand modification of drawing that can then be emailed or saved in the patient's record.

For pap smear guidelines: The website for the American Society for Colposcopy and Cervical Pathology (ASCCP), asccp.org, provides current screening and treatment protocols. *Pap Guide* is a free app which allows you to input the patient's age, relevant clinical history, and recent pap results and then generates the applicable 2012 consensus guideline...

For infection treatment and prevention: *STD2010* covers treatment for common sexually-transmitted diseases, and is especially helpful if a patient has multiple allergies, is pregnant, or cannot follow regular treatment protocols. cdc.gov/vaccines/parents/pregnant.html has current information related to pregnancy and vaccinations. *ACP immunization advisor* is another free app that outlines recommended vaccinations based on a patient's current age, risk factors, and other activities (i.e. international travel, adoption, or work settings). *GBS guide* distills the latest CDC recommendations including recommendations for patients with allergies.

For pregnancy dating: *Perfect wheel* and *Preg Wheel* are apps that allow gestational age to be calculated from a variety of reference dates (i.e. EDD, LMP, conception, ART). *eSnurra* is helpful for determining gestational age based on bedside biometry when an obstetrical package is not loaded on an ultrasound machine.

For general OB: *Bishop's Score Calc* is an app that includes not just a scoring tool but also gives a favorable/unfavorable rating and reports the expected C-section rate. *Perinatology.com* (<http://www.perinatology.com/calculators2.htm>) is an invaluable site that has numerous perinatology calculators as well as links to a VBAC success calculator and the NICHD prematurity calculator.

For fetal anomalies: *OMIM* - Online Mendelian Inheritance in Man - is the place for clinicians to obtain information related to genetic disorders. For affected patients, aheartbreakingchoice.com and nowllaymedowntosleep.org can be wonderful sources of support.

In the interest of full disclosure, I have NO personal financial stake in any of these apps. Enjoy!

PRENATAL MICROARRAY FOLLOW-UP STUDY

by Laird Jackson, MD
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The Prenatal Chromosomal Diagnosis by Microarray study group would like to inform you of an ongoing project and ask for your assistance. The original chromosomal prenatal diagnosis microarray study was published in December 2012 (Wapner et al. N Engl J Med 2012;367:2175-84) and showed that microarray copy-number analysis was equivalent to conventional karyotype analysis for prenatal diagnosis of all common aneuploidies, large deletions/duplications, and unbalanced rearrangements. In addition, in samples with a normal karyotype, the microarray analysis found clinically significant copy-number changes in 6% of fetuses with a structural anomaly and in 1.7% of those whose indications were advanced maternal age or positive screening results. Many of these copy-number changes are firmly diagnostic, but the clinical phenotype associated with these changes can vary widely in both severity and breadth of findings. In addition, some copy-number changes are predictive of an increased risk of development of a clinical condition, but do not absolutely predict development of the condition (e.g. autism-spectrum-disorder or autism). After appropriate genetic counseling and discussion, many of these parents will elect to accept these variable risks and will continue their pregnancies.

The aim of our current project is to enroll women carrying a fetus with a prenatal diagnosis of a submicroscopic array abnormality and to follow these children from birth through 3 years of age. Our goal is to develop more accurate and comprehensive phenotypic “pictures” of these children, to develop understanding of the extent of variation of the phenotypes, and to gain insight into environmental-epigenetic influences on their development. In order to make this study possible, we are seeking your help in referring women who decide to continue a pregnancy after a microarray result of pathologic or uncertain significance has been reported in their fetus. Prenatal referral of these patients will allow us to enroll the mother before she gives birth, and the information gathered will be of enormous help in counseling parents who receive these prenatal diagnoses in the future.

We encourage you to join us in this important effort to better understand this emerging group of clinical conditions. If you have a patient with a prenatal diagnosis of a copy-number change, we ask that you inform them of our project and directing them to our website, www.prenatalarray.org and / or to our counselors/ advisors (1-855-77-ARRAY) for further information. Contact information for our study staff is listed below. We plan to develop a periodic web-based newsletter that will describe our ongoing findings and potentially helpful clinical correlates. We need your help!

Name	Role	Contact Information
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Ronald Wapner, MD <i>Study Primary Investigator</i>	Available for any concerns unable to be addressed by study team	rw2191@columbia.edu 212-305-1521
Wendy Chung, MD <i>Co-Investigator</i>	Available for contact regarding array results, potential genetic implications, study findings in similar cases	wkc15@columbia.edu 212-851-5313
Laird Jackson, MD <i>Co-Investigator</i>		Laird.Jackson@drexelmed.edu 267-432-2255
Andy Faucett, MS <i>Co-Investigator</i>	Available for problems / suggestions regarding the online resource center (www.prenatalarray.org)	wafaucett@geisinger.edu 570-214-4862

THE ROLE OF FIRST-TRIMESTER SCREENING IN THE ERA OF CELL-FREE DNA

by Lorraine Dugoff, MD

Noninvasive prenatal testing using cell free DNA (cfDNA) isolated from maternal plasma has recently been introduced in obstetrical practice as an effective primary method for fetal aneuploidy screening in women at increased risk for aneuploidy (1,2) (7-8). The purpose of this article is to contrast the role of cfDNA testing as compared to the first trimester screen, and to discuss potential benefits of the individual components of the first trimester combined screen.

Although a number of studies have demonstrated that cfDNA is an effective primary screening test for women at increased risk for aneuploidy (3-6), cfDNA has not been adequately validated in low risk women or in multiple gestations and therefore is not currently recommended in these populations (1,2). The first trimester screen or a first and second trimester combined test, however, are recommended screening tests for low risk women (7,8). Although the detection rates are lower than in singletons, maternal serum multiple marker testing has been validated in twin gestations. Similarly, nuchal translucency assessment alone may be used to assess risk in higher order multiples.

Even among women at increased risk of fetal aneuploidy, there are a number of reasons that some may elect not to pursue cfDNA testing. Financial or insurance considerations as yet unclear may impact test selection. Patients may choose accepted first trimester screening techniques based on experience in a previous pregnancy (9). Women with increased body mass index (BMI) may choose first trimester combined screening because of the increased risk of failure to obtain an assay result with cfDNA testing due to lower fetal fractions. Timing of testing may also influence a patient's choice to pursue cfDNA or first trimester combined screening.

Depending on which laboratory is used, it currently takes approximately 1 to 3 weeks to obtain a cfDNA test result and there is a 0.9% (3) to 4.6% (6) assay failure rate (failure to obtain a test result) associated with cfDNA testing. High risk women presenting at 12 to 13 weeks gestation may choose to have first trimester combined screening in order to obtain a risk result in time to have the option for CVS which is typically performed up to 14 weeks gestation.

A number of components of the first trimester screen may also offer relatively specific advantages over cfDNA testing. For example, first trimester nuchal translucency assessment may provide high risk women with immediate information that may help them to decide whether to proceed with CVS or cfDNA testing. If a NT is 3 mm or greater, there is a 1 in 6 incidence of fetal aneuploidy (10) and septated cystic hygromas are associated with a 51% incidence of fetal aneuploidy (11). Because addition of first trimester serum markers in cases with NT \geq 3 mm reduces the final trisomy 21 risk to less than 1 in 200 in only 8% of cases (8), women with NT measurements \geq 3 mm or cystic hygromas may opt for CVS or cfDNA rather than completion of the first trimester combined screen. It is well known that increased NT measurement is associated with an increased risk of fetal structural abnormalities in euploid fetuses (12-14), whereas cfDNA has no role in screening for fetal structural malformations. Similarly, low first trimester maternal serum PAPP-A levels have been associated with a number of adverse obstetric outcomes including preeclampsia, stillbirth and fetal growth restriction that would



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not be identified by cfDNA (15). Lastly, there are many potential benefits associated with first trimester ultrasound in addition to NT assessment including accurate assessment of gestational age, presence of multiple gestation and evaluation of chorionicity, and identification of some fetal anomalies.

In conclusion, there are currently multiple potential uses for the first trimester screen and its various components. The utility of first trimester screening may change as cfDNA testing is validated in low risk populations and multiple gestations and as the technology improves allowing for more rapid reporting of results and decreased assay failures.

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NTQR PARTICIPANTS

WHAT DOES IT MEAN TO HAVE A “LOW-SLOPE?”

The NTQR promotes quality monitoring of NT measurements by providing epidemiologic analysis for each individual performing NT exams. Specifically NTQR compares the distribution of an individual's measurements to the distribution seen in a large referent population. The NTQR quarterly reports compare the individuals' NT median MOM and the standard deviation to the referent curve. These reports categorize participants' measurements as “in-range” or “out-of-range-low” or “out-of-range-high.”

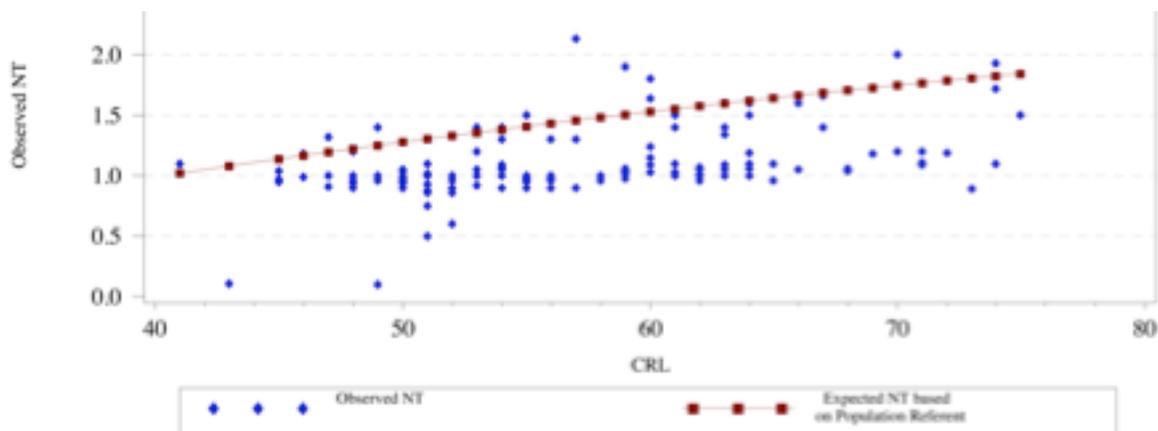
Recently the NTQR sent letters to participants who had a slope value less than 0.066 or less than the 5th percentile. These letters were sent for informational purposes only. A graph demonstrating measurements with a low slope value is seen above. The NT values do not increase with CRL values as expected.

A low slope may be caused by sub-optimal NT measurements. At times a particular NT value may be favored when the NT space appears small and the standard deviation will be low (less than 0.7) and the slope will be low. This is an example of how sub-optimal NT measurements are detected by NT median MOM or by standard deviation analysis. If these analyses are within the expected range and slope remains low, the cause may relate to CRL measurements.

Though we do not credential or monitor CRL measurements, this value is very important in risk assessment. The letters regarding low slope were sent to participants to remind of the importance of the CRL measurement. An acceptable CRL measurement has the following characteristics:

- The fetus is seen in a mid-sagittal plane
- The fetal neck is in a neutral position, neither hyperextended or flexed with the chin on the chest.
- The image magnification is such that the fetus occupies more than 50% of the image.
- The measurement is made from the crown to the rump, not to the posterior thigh, distal spine, or other location.

The information that the NTQR provides about measurements is intended to help participants, and practices monitor their own performance. An explanation of all of the statistics used by NTQR is available at <http://www.ntqr.org> under “Understanding Your Epidemiologic Reports.” Understanding the analysis provided and reviewing quarterly epidemiologic reports and additional correspondence is an important part of professional practice.





The Perinatal Quality Foundation invites you to view a web-based demonstration of the Fetal Monitoring Credentialing (FMC) examination program that will soon be available on our website. This program, developed by experts in the field, will be available to physicians, nurse practitioners, midwives, nurses, and other perinatal clinicians who are involved in the management of labor and delivery patients.

In addition to using recommended NICHD nomenclature and offering traditional knowledge-based questions, FMC also assesses provider judgment by using the script concordance test, an evidence-based tool that measures mental processes in uncertain clinical situations.

The PQF Fetal Monitoring Credentialing tool is intended to be adjunct to other educational programs. FMC provides a mechanism to measure provider proficiency, to determine if learning has taken place and to effect change.

To learn more and to view the demonstration go to <http://www.perinatalquality.org> and click on the FMC logo.



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