



## MAKING THE CASE FOR FIRST TRIMESTER SCREENING

by

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Noninvasive prenatal testing (NIPT) has dramatically improved the detection rate for Trisomy 21, 18, 13, and sex chromosomal abnormalities. However, this improved performance raises the question of the value of continuing to do first trimester screening using nuchal translucency (NT) measurement and biochemistry. Presently, there is still value in this testing both to identify chromosomal abnormalities not amenable to NIPT as well as other fetal genetic disorders and structural malformations.

The overall frequency of the common aneuploidies (Trisomy 21, 18, 13) screened for by NIPT is approximately two per thousand pregnancies and these common aneuploidies account for only a small percentage of all fetal structural and genetic disorders. Depending on the mother's age, chromosomal abnormalities other than the common trisomies may occur more frequently, and - if one considers clinically relevant microdeletions and duplications - the frequency of cytogenetic abnormalities not identifiable by NIPT exceeds 1% of pregnancies. In addition, Mendelian genetic disorders occur at a rate of four per thousand pregnancies. Unlike NIPT, first trimester screening can identify some of the pregnancies with chromosomal abnormalities other than the common aneuploidies. A recent study from the California Prenatal Diagnosis Program has shown that among pregnancies with a "positive" first trimester screen result, approximately 20% of the chromosomal abnormalities would not be identified with NIPT, and the residual risk of a chromosomal abnormality after negative NIPT is approximately 1:50.<sup>1</sup>

Nuchal translucency enlargement is also an excellent marker for other genetic disorders and for fetal structural malformations. Studies have demonstrated that up to 6% of euploid fetuses with an enlarged nuchal translucency are diagnosed with a genetic disorder.<sup>2</sup> Of particular interest is the association between an elevated nuchal translucency and Noonan's syndrome. We recently looked at a large series of pregnancies with NTs greater than 4.0 mm and found that approximately 5% have pathogenic mutations for Noonan's and another 2.3% had a variant of unknown significance in the Noonan's gene.<sup>3</sup> Furthermore, among fetuses with an NT > 3.5 mm, there was also a 3% incidence of pathogenic copy number variants.<sup>3</sup> Lastly, an enlarged NT is associated with an increased risk of fetal structural malformations, many of which may be diagnosed at the time of the first

trimester ultrasound. Specifically, an NT measuring between 3.5 and 4.5 mm carries a 10% risk of fetal structural anomaly; between 4.5 and 5.4 mm, this risk doubles, and for NTs greater than 6.5, almost 50% of pregnancies will have a structural abnormality.<sup>4</sup>

In conclusion, first trimester biochemical and NT screening has a much broader role to play than to simply screen for specific fetal aneuploidies. The advent of NIPT has been a major advance in Down Syndrome screening, but the early identification of other fetal genetic conditions is equally important. Continued performance of NT and biochemistry is recommended

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to maximize the early detection of fetal disorders. With time, it is likely that NIPT will expand to identify a wider spectrum of cytogenetic abnormalities including microdeletions. Simultaneously, first trimester screening for adverse pregnancy outcomes such as preeclampsia and preterm birth may become a reality. Early pregnancy screening is evolving, and as it does, our approach will also evolve.

1. Norton M et al. Rare chromosome abnormalities detected by current prenatal screening compared to expected performance using non-invasive prenatal testing (NIPT). *AJOG* 2014 Jan;208(1): S3-4.
2. Bilardo CM, et al. Increased nuchal translucency in euploid fetuses--what should we be telling the parents? *Prenat Diagn.* 2010 Feb;30(2):93-102.
3. Coletta Lucas J, et al. Increased nuchal translucency and normal karyotype: Value of additional testing. *AJOG* 2014 Jan;208(1): S87.
4. Souka AP, et al. Increased nuchal translucency with normal karyotype. *Am J Obstet Gynecol.* 2005

## EARLY FETAL ANATOMIC IMAGING

by

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Approximately 2 to 5% of all pregnancies are complicated by fetal congenital anomalies. Congenital anomalies are one of the major causes of neonatal morbidity and mortality, and early detection can increase time for evaluation and counseling for families. Recently, prenatal screening tests have shifted from the second trimester to the first trimester as the benefits of early detection have become evident. First trimester ultrasound was originally used for evaluation of fetal viability and determination of pregnancy dating. Nuchal translucency measurement in the first trimester was then developed as a method of screening for chromosomal anomalies. Over the last 20 years, advancements in ultrasound resolution and the introduction of high-frequency transducers have allowed for assessment of fetal anatomy in the first trimester.<sup>1</sup>

As fetal anatomy is evaluated earlier in pregnancy, it is important to remain mindful of the normal development of the fetus. Specific anatomic findings may be considered normal or abnormal depending on the gestational age of the fetus.<sup>2</sup> For example, gut herniation into the umbilical cord is normal prior to 10-11 weeks. Similarly, absence of the corpus callosum in the first trimester is a normal finding, as the corpus callosum does not develop until between 14 and 19 weeks gestation. There are, however, many anomalies like anencephaly, gastroschisis, holoprosencephaly, and heterotaxia that could be routinely identified during the first trimester ultrasound.

There are a variety of methods for evaluating early fetal anatomy. The majority of these use a systematic approach similar to the second-trimester fetal anatomy ultrasound. The early anatomy scan should visualize the fetal brain, profile, spine, heart, umbilical cord insertion, stomach, bladder, and extremities. A study evaluating the feasibility of performing a fetal anatomic survey at the time of nuchal translucency measurement found that they were successful in completing the anatomic survey in 33% of pregnancies in the first trimester.<sup>3</sup> Fetal echocardiography can also be performed in early pregnancy, but it likely should be reserved for patients at the highest risk of cardiac anomalies including those with increased nuchal translucency, history of cardiac defects, and presence of other anatomic anomalies.<sup>2</sup>



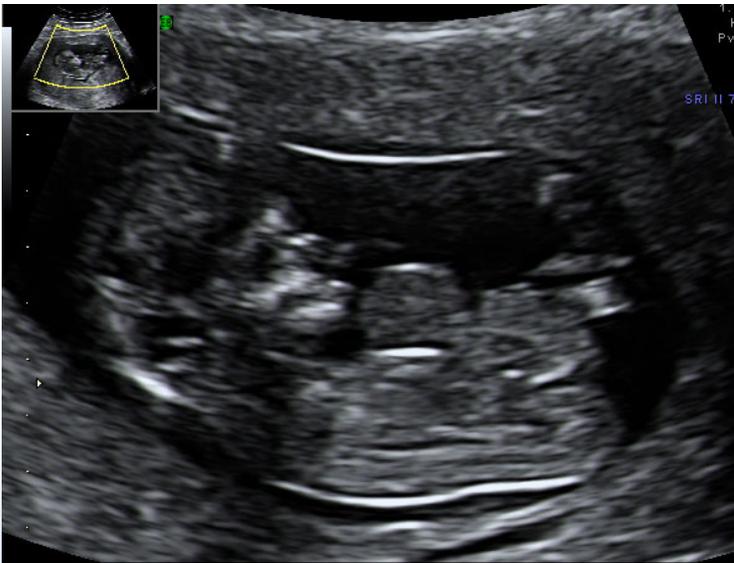
**TRAP Syndrome First Trimester**

There are conflicting reports of congenital anomaly detection rates with early anatomic imaging. Early pregnancy imaging is limited in detecting anomalies, especially those that do not manifest until later in pregnancy (ie some skeletal dysplasias and brain anomalies).<sup>4</sup> A large randomized trial found that the antenatal detection rate of major fetal malformations was lower in anatomic ultrasounds performed at 12-14 weeks compared to ultrasounds performed at 15-22 weeks.<sup>5</sup> A systematic review of the literature addressing the efficacy of early ultrasonography in identifying fetal anomalies found an overall detection rate of 51%. The highest detection rates were achieved for fetal neck and abdomen anomalies, and the lowest detection rates were seen with limb, face, and genitourinary anomalies. The detection rate was highest when using a combination of both transabdominal and transvaginal imaging techniques compared to either technique alone.<sup>4</sup>

Potential advantages of early anatomic ultrasound include early detection of congenital anomalies, reassurance in high risk patients, prompt genetic testing, and time for consideration of pregnancy management options including termination and referral to a tertiary care center.<sup>1,2</sup> If a congenital anomaly is detected by early ultrasound and the patient desires a termination of pregnancy, the morbidity of the procedure is reduced in early pregnancy.<sup>5</sup> Early anatomic imaging may also be beneficial in obese patients. Studies have demonstrated a reduced detection rate of structural anomalies in obese women secondary to poor visualization and decreased image quality. Early transvaginal anatomic imaging in obese patients has the potential to improve the detection rate of fetal anomalies.<sup>6</sup> Limitations of early anatomic imaging include sonographer experience requirements and high costs of both time and equipment.<sup>4</sup>



**Limb Anomaly seen first trimester**



**Pentalogy diagnosed at 12 weeks**

The sensitivity of early anatomic ultrasound increases with sonographer experience, so sonographers will require appropriate training and equipment if early anatomic ultrasound becomes standard of care.<sup>2</sup> The cost effectiveness of early anatomic imaging remains unclear.<sup>1</sup>

It is unlikely that early anatomic ultrasonography will replace the “gold standard” second-trimester anatomic survey given decreased detection rates in early pregnancy and delayed onset of many anomalies. The American Institute of Ultrasound (AIUM) recommends that “fetal anatomy appropriate for the first trimester should be assessed” during any first trimester ultrasound. The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) has also confirmed this, and they provide a suggested list of anatomical assessment during the 11-13 week ultrasound including head, neck, face, spine, chest, heart, abdomen, abdominal wall, extremities, placenta, and umbilical cord.<sup>1</sup> As the demand for early

anatomic imaging grows and technology continues to improve, a standardized protocol for early ultrasonography should be established.<sup>4</sup> Given that it is not possible to recognize some congenital anomalies in the first trimester, a follow up ultrasound in the second trimester is always recommended. Regardless, evaluation of at least basic fetal anatomy in the first trimester should be part of any nuchal translucency scan.

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## ***GENOMICS IN CLINICAL PRACTICE***

**produced by the**

**American College of Medical Genetics and Genomics**

The American College of Medical Genetics and Genomics (ACMG) has developed a series of web-based CME modules entitled *Genomics in Clinical Practice*. Aimed at providers, the four modules listed below each focus on a different aspect of medical genetics and genomics relevant to perinatal medicine.

- The *Understanding Your Genome: Genomics in Clinical Practice* module focuses on the role and use of genome and exome sequencing technologies, and not only describes their indications but also explains the procedures for ordering each test and the format of the results.
- *Preimplantation Genetic Diagnosis and Screening* covers the expanding range of genetic abnormalities amenable to PGD testing, the interpretation of prenatal genomic testing results, impact of genetic information on embryo selection, and the limitations in single cell testing.
- The *Preconception and Prenatal Cystic Fibrosis Carrier Screening* module reviews the preconceptional and prenatal carrier screening for cystic fibrosis including a discussion of testing for CFTR variants and pre-test and post-test genetic counseling processes.
- The module on *Noninvasive Prenatal Screening (NIPS)* explains the different types of NIPS, including use of cell free fetal DNA and fetal cells separated from maternal circulation, and describes patient selection, clinical performance characteristics, and limitations of NIPS.

These informative modules can be found at [www.acmg.net/Education](http://www.acmg.net/Education), and more information is available by contacting ACMG at 301-718-9603.

## LITERATURE HIGHLIGHTS

### **Simplified first-trimester fetal cardiac screening (four chamber view and ventricular outflow tracts) in a low-risk population.**

E Orlandi et al.

Prenat Diagn. 2014 Jun;34(6):558-63.

In this prospective study of over 4000 women, authors demonstrate utility of a simplified fetal cardiac study at 11-14 weeks in screening for congenital heart disease. Using transabdominal ultrasound to image the 4 chamber view, outflows, and abdominal situs, over 70% of the cardiac anomalies were detected in the first trimester including 90% of the cases of major congenital heart disease.

### **High macrosomia rate in healthy fetuses after enlarged nuchal translucency.**

E Timmerman et al.

Prenat Diagn. 2014 Feb;34(2):103-8.

In this retrospective study of 6503 singletons, authors sought to investigate the association of nuchal translucency (NT) and first trimester serum analytes with birthweight. Birthweight centiles were positively correlated with NT multiples of the median (MoM) and pregnancy associated plasma protein (PAPP-A) MoM. Furthermore, NT >95th percentile was associated with an increased likelihood of birthweight >95th percentile.

### **Accuracy of nuchal translucency measurement depends on equipment used and its calibration.**

RG Axell et al.

Ultrasound Obstet Gynecol. 2014 Jul;44(1):31-7.

In this study, authors sought to determine the difference in NT measurements obtained on various combinations of ultrasound equipment, and to assess the impact of this variation on calculated risk of Trisomy 21. Specifically, they utilized sixteen different ultrasound machine-probe combinations to measure 2 mm, 3 mm, and 4 mm targets within an ultrasound phantom. The authors found that differences observed using different machine-probe combinations exceeded those due to intraobserver variability, and that the specific machine-probe combination used significantly affected the calculated screening risk. This paper, and the subsequent editorial (J. D. Sonek; Ultrasound Obstet Gynecol. 2014 Jul;44(1):6), highlight the importance of adjusting machine settings and calibration of ultrasound equipment.

### **ISUOG consensus statement on the impact of non-invasive prenatal testing (NIPT) on prenatal ultrasound practice.**

LJ Salomon et al.

Ultrasound Obstet Gynecol. 2014 Jul;44(1):122-3.

The logo for CLEAR (Cervical Length Education & Review) features the word "clear" in a lowercase, sans-serif font. Each letter is a different color: 'c' is pink, 'l' is orange, 'e' is green, 'a' is blue, and 'r' is dark blue.

*Cervical Length Education & Review*

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or 3 hours SDMS CME  
for sonographers**

## FIRST TRIMESTER SCREENING COURSE TO BE OFFERED AT SMFM / THE PREGNANCY MEETING 2015

The Perinatal Quality Foundation will present a revised first trimester screening course at the SMFM Pregnancy Meeting in San Diego. The course will be held Wednesday morning, February 4, 2015. The goal of the course is to discuss the performance and interpretation of first trimester screening techniques and how to integrate results from the nuchal translucency combined test, analytes, cell-free DNA analysis, fetal structural anatomy imaging, and second trimester testing. The four hour course consists of six lectures including the following:

- Screening Principles
- NT and NB Techniques
- First Trimester Fetal Anatomy Imaging
- Follow-up and Confirmatory Testing including NIPT
- Quality Assessment
- Clinical Scenarios

A course cannot teach participants in four hours how to provide screening options for every patient, however, the Perinatal Quality Foundation course presents an overview of the tools available and how to integrate testing in the interest of the patient. The course content and format was developed by the Education Committee and the Board of Directors of the PQF.

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