ROUTINE FETAL ECHOCARDIOGRAPHY AT THE TIME of the FIRST TRIMESTER NUCHANT TRANSLUCENCY EXAMINATION: IS IT OF VALUE?

by Greggory DeVore, MD, FACOG, FAIUM
David Geffen School of Medicine, UCLA,
Fetal Diagnostic Centers and Providence Tarzana Medical Center

Figure 1: This is a 12-week fetus. The B-mode image does not identify the four-chamber view. Using power Doppler the following structures are identified: (1) symmetrical right (RV) and left (LV) ventricles correctly oriented within the chest; (2) left ventricular outflow tract (LVOT) identified exiting the left ventricle; (3) the main pulmonary artery (MPA), ductus arteriosus (DA), and the cross-section of the aorta (Ao) are observed in the 3-vessel view (4), the MPA and the transverse aortic arch (Ao) are identified in the tracheal view.

Over 30 years ago I had the opportunity to be one of the early investigators evaluating the potential use of ultrasound to examine the fetal heart. The early studies reported real-time views that could be obtained during the second and third trimesters of pregnancy, measured the dimensions of the four chambers and outflow tracts, and observed the association between an abnormal four-chamber view and congenital heart disease (1,2). When pulsed and color Doppler became available, it was found to be of assistance in the detection of fetuses with aneuploidy (3). Although there are several reports of first-trimester evaluation of the fetal heart, fetal echocardiography has been performed during the second and third trimesters of pregnancy because of imaging difficulties encountered earlier in pregnancy as the result of fetal access, small cardiac structures, and transducer frequencies (3-5 MHz) inappropriate for first-trimester imaging.
Although in 1987 we were the first to report the detection of a complex heart defect at 14 weeks of gestation, our colleagues in Europe were the first to report larger series of first-trimester detected congenital heart defects. (4) Since many fetal consultative sonologists in North America did not see a large number of fetuses during this gestational time period, because the majority of patients were referred for second trimester studies as the result of advanced maternal age and/or abnormal second-trimester maternal serum screening, first-trimester imaging of fetal anatomy lagged behind the European experience. When the results of the FASTER trial were published, first-trimester nuchal translucency (NT) screening was introduced to North America in a larger scale. As a result of the FASTER trial, our practice was inundated with first trimester screening requests for NT screening. As we began providing this service, I reflected on an editorial I wrote in 2005 entitled, “First-trimester fetal echocardiography: is the future now?”(5). Since the conclusion of the paper was that the fetal heart could be imaged during the first-trimester with both real-time and color / power Doppler, our group undertook a protocol in which the four-chamber view and the outflow tracts were imaged both transabdominally and endovaginally in each patient. We examined 2,412 consecutive patients who were referred for first-trimester NT screening. The following were our findings.

1. CRL ranged between 4.1 and 9.5 cm (mean 6.54 +/- 0.9 SD) and was normally distributed.

2. The four-chamber and outflow tract views were imaged in 98% of fetuses.

3. When using power Doppler ultrasound, the Thermal Index was less than or equal to 0.2 (<0.5 TIB appropriate for fetal evaluation).

4. Power Doppler was especially important at gestational ages between 11 and 13 weeks when the B-mode images may be inadequate as the result of imaging difficulties associated with fetal position and maternal adipose tissue (Figure 1).

5. Power Doppler was useful for identifying symmetry of the ventricular inflow tracts to exclude hypoplastic ventricles. This was even more crucial if only a transabdominal examination were to occur (Figure 1).

6. Power Doppler assisted us in identifying symmetry and crossing of the outflow tracts to exclude hypoplasia as well as transposition of the great arteries.

7. Complex cardiac malformations were identified in 4.1 / 1,000 fetuses.

8. 80% of complex heart defects were identified in fetuses with an NT of less than 3.5 mm.

9. The four-chamber and outflow tract views could be normal during the first-trimester, only to demonstrate an evolving hypoplastic left heart syndrome in the second-trimester (Figure 2).

Figure 2: The four-chamber view was normal in size and shape and demonstrated normal contractility at 13 weeks 1 day. At 17 weeks 5 days, the four-chamber view was abnormal, with the left ventricle (LV) dilated and poorly contractile. There was mitral regurgitation, aortic stenosis, and evolving endocardial fibroelastosis. This was an evolving hypoplastic left heart syndrome.
10. During the first-trimester NT screening examination we have detected the following malformations in low-risk fetuses: endocardial cushion defect, hypoplastic left ventricle, transposition of the great arteries, dextrocardia, right-sided aortic arch, pulmonary hypoplasia, single ventricle, coarctation of the aorta, and large ventricular septal defects (Figure 3).

In conclusion, it was our experience that significant congenital heart defects can be detected during the first-trimester NT screening examination. Only evaluating fetuses with an increased NT for congenital heart defects would result in detection of fewer fetuses with cardiac malformations than when all fetuses are screened as described in this communication. The opinion paper authored in 2005 entitled, “First-trimester fetal echocardiography: is the future now?,” is even more true today since we believe the FUTURE IS NOW!

Figure 3: The image on the left is the B-mode of the four-chamber view using a high-resolution endovaginal probe. The ventricular septal defect (VSD) is identified. The image on the right illustrates shunting from the left to the right ventricle. There is disproportion, with the right ventricle (RV) larger than the left ventricle (LV). RA=right atrium, LA=left atrium.

References
The Cervical Length and Review (CLEAR) program was developed by a task force representing the Perinatal Quality Foundation, as well as ACOG, ACOOG, ACR, AIUM, SDMS, and SMFM, in response to the recent marked demand for cervical length measurement in clinical practice. Its purpose is to provide standardized measurement criteria and education, because it has been shown that 20% of practitioners perform the measurement incorrectly (even in highly controlled academic research settings). The CLEAR program includes web-based lectures, an examination, and criterion-based image review. More information can be found at www.perinatalquality.org

RISKS OF INVASIVE PRENATAL TESTING

by Jennifer C. Donnelly MD
Ronald J. Wapner MD, Director of Reproductive Genetics
Department OB/GYN, Columbia University Medical Center
New York, New York

The field of diagnostic prenatal diagnosis is changing at a rapid rate. Less than ten years ago, the hot topic was the transition of aneuploidy screening from the second to the first trimester with the advent of reliable first trimester screening (1) and increased confidence and acceptance of chorionic villus sampling. With the introduction of cell free fetal DNA (cffDNA) into clinical practice, we are likely to see another paradigm shift in screening and diagnosis of prenatal aneuploidies. Many researchers speculate whether invasive fetal testing will ultimately be supplanted by non-invasive methods (2,3). As the prenatal diagnosis community determines how best to integrate these new technologies into clinical practice, it is an appropriate time to review the risks and safety of invasive prenatal diagnostic techniques.

Amniocentesis

Amniocentesis has been the gold standard for second trimester invasive testing since its introduction into clinical practice almost forty years ago. One of the most statistically robust studies of miscarriage risk with amniocentesis comes from Denmark in 1986 and would be difficult to justify performing today (4). This study randomized 4606 women at low risk of miscarriage and aged between 24-35 years to ultrasound-guided amniocentesis or no procedure. The amniocentesis group had a loss rate which exceeded the control group by 1%.

More recently, several large cohort studies suggested significantly lower procedure-related loss rates after amniocentesis (1,5). In a recent systematic review, Alfirevic et al (8) report an overall risk of pregnancy loss following amniocentesis of 0.6% up to 14 days and increasing to 1.9% total loss until term. The majority of this data comes from cohort studies of which only a few contain controls. In those with controls, the best estimate of a procedure induced risk of pregnancy loss is approximately 0.6%; far less than that suggested in the Danish randomized study. This risk is consistent with the risk of 0.6% reported by Seeds et al in a similar analysis (6).

Some studies have suggested even a lower risk of loss. For example, in the FASTER study(1), the overall spontaneous loss rate in the amniocentesis group was not significantly different (p=0.74) than the group not having a procedure, with loss rates of 1.0% and 0.94% respectively (7). They assumed that the 0.94% rate of pregnancy loss in the control group (no amniocentesis) was the “background” loss rate, therefore the loss...
rate attributable to amniocentesis was calculated at 0.06% (1.0% minus 0.94%). As all patients recruited to this study had to reach 15 weeks gestation, this provided a well-matched control group to allow for valid comparisons. There are, however, concerns with this analysis since patients terminating pregnancies identified with fetal aneuploidy were extracted from the sample group but retained in the control group accounting for some of the pregnancy losses in this group.

There is evidence to suggest that operators who perform procedures more frequently, have lower miscarriage rates (8). Physicians should be aware of these issues and are advised to carefully evaluate the adequacy of their own follow-up data.

**Chorionic Villus Sampling**

There are no studies comparing pregnancies sampled with CVS to unsampled pregnancies. The majority of studies, therefore, compare CVS at 10-12 weeks gestation to second trimester amniocentesis. According to a recent systematic review, the variation in pregnancy loss and complication rates following CVS is due to the heterogenous nature in which the studies have reported their outcomes (9). The authors reviewed 4 studies that reported loss within 14 days of the procedure and showed a similar level of risk to that of amniocentesis (0.7%) but with much wider confidence intervals (10-13). In an early study in 1989, the Canadian Collaborative CVS/Amniocentesis Clinical Trial Group reported a randomized trial in which participants were enrolled to either CVS or amniocentesis within the first trimester thus controlling for the bias inherent in the higher miscarriage rate associated with sampling at an earlier gestation (14). This study demonstrated equivalent safety between CVS and second trimester amniocentesis, with an overall (including pregnancy terminations for aneuploidy) loss rate of 7.6% in the CVS group and 7.0% in the amniocentesis group (RR 1.1; 95% CI 0.92, 1.30). A similar study performed in the United States in which patients chose the procedure rather than being randomized confirmed that the two procedures have equivalent pregnancy loss rates (15). Over time and with increasing confidence and experience with the procedures, either transvaginal or transabdominal, the post procedure loss rates now reported have declined compared to earlier studies. For counseling purposes, it is clear that in experienced centers, CVS and amniocentesis are equally safe.

As with amniocentesis, operator experience makes a difference. Repeated catheter insertions were identified as a significant factor in loss rates, with a large multicenter study in the United States showing that there was a 10.8% loss rate following cases which required 3 or more catheter insertions (15).

Given that abnormal placentation in early pregnancy contributes to the subsequent development of pre-eclampsia, a possible association between the performance of a CVS and pre-eclampsia has been investigated (16, 17). The evidence is conflicting, with the balance of studies, including a meta-analysis showing that performing a CVS in the first trimester is not linked to the subsequent development of hypertensive disorders of pregnancy (18-20).

**Conclusion:**

Invasive prenatal testing is carried out to obtain genetic information and ACOG recommends that all pregnant women are offered the opportunity to have testing performed. In recent years, there has been a dramatic increase in genetic information available from invasive testing which has changed the risk benefit ratio. Microdeletions and duplications may occur in over 1.5% of pregnancies (21). Simultaneously, non-invasive approaches now provide a portion of this information without requiring any procedural risk. At present, all patients should be counseled about the genetic information available through invasive testing. Patients should also be informed of the proportion of this information that can be identified using non-invasive screening approaches. Patients may then balance the personal benefit of information about the health of their fetus against the risk of procedure induced loss of the pregnancy. This analysis is a very personal one.
References:


The double line artifact is seen within the nuchal translucency boundary lines and the amnion in the image above. The artifact widens the boundary line and makes it difficult to determine the correct location for caliper placement. This artifact may be created by the interaction of various factors related to equipment settings and to sound beam propagation pathways to the fetus. If you see the artifact it is helpful to try the following techniques to eliminate it.

If you are using a 3D / 4D transducer, try imaging with a 2D transducer.
If you are imaging with harmonics on, try imaging with harmonics off.
If you are imaging with harmonics off, try imaging with harmonics on.
Reduce your overall gains.
Place the focal zone on the area of the nuchal space.
Try a different acoustic pathway to the nuchal measurement.

The techniques above may be helpful in eliminating the double-line artifact.

The output display for imaging fetuses after 10 weeks gestation should be set to Thermal Index Bone (TIB) and not Thermal Index Soft Tissue (TIS). ALARA recommendations suggest that the TIB is to be monitored and kept under 0.5 for obstetrical examinations. In the image above you can see TIS 0.1 at the center top. The equipment should be set to display TIB.
The Perinatal Quality Foundation is committed to improving the quality of Maternal-Fetal Medicine medical services by providing state of the art educational programs, and evidence-based, statistically valid monitoring systems to evaluate current practices and facilitate the transition of emerging technologies into clinical care.

The Perinatal Quality Foundation invites you to view a web-based demonstration of the fetal monitoring credentialing examination that is opening shortly.

The fetal monitoring credentialing program will allow participants to demonstrate knowledge and judgment of fetal heart rate monitoring principles defined by national consensus. The examination will be open to physicians, nurses, and others involved in the management of labor and delivery patients.

To view the demonstration, go to http://www.perinatalquality.org, click on fmc.
Noninvasive prenatal testing (NIPT) via circulating cell free fetal DNA in the maternal bloodstream has been available in the United States for over one year. The technology was highlighted in the last issue of “The Examiner” and provider-oriented educational materials may be found on the website for the National Coalition for Healthcare Provider Education in Genetics (www.nchpeg.org). In the December 2012 issue of Obstetrics and Gynecology, the American College of Obstetricians and Gynecologists (ACOG) in conjunction with the Society of Maternal-Fetal Medicine published joint committee opinion #545 “Noninvasive Prenatal Testing for Aneuploidy” (Obstet Gynecol 2012;120:1532-4). This document notes that pre-test patient counseling is integral to incorporating NIPT into clinical practice. The importance of this process cannot be over emphasized, as it will help to ensure that patients have the information they need to make decisions most appropriate for them, identify additional family history risk factors indicating additional screening or diagnosis, and informed patient choice regarding NIPT’s strengths, limitations, and pitfalls. The following case study illustrates the value of genetic counseling for women with increased fetal aneuploidy risk, the role and limitations of NIPT, and the continued importance of ultrasound and invasive prenatal diagnosis in a new era of NIPT.

Case
A 41-year-old woman was referred for genetic counseling after screening positive for trisomies 13 and 18 on the first part of a stepwise sequential test initiated by her obstetrician at 11 weeks gestation. The recorded nuchal translucency measurement was 1.7 mm. Following genetic counseling at 12 weeks, she declined diagnostic chorionic villus sampling, instead choosing NIPT. The initial laboratory report noted that the quantity of fetal DNA was insufficient to analyze. The patient had a second blood draw for NIPT, which was successful, resulting in a negative test with normal proportions of chromosomes 13, 18, and 21.

The patient returned to the office for a fetal survey at 19 weeks gestation. The ultrasound examination revealed low amniotic fluid, asymmetric fetal growth restriction, bilateral cerebral ventriculomegaly, hypoplastic cerebellum, and lemon-shaped skull. After counseling that the fetus remained at high risk for aneuploidy based on the ultrasound findings, diagnostic amniocentesis was performed. The fetal karyotype was 69, XXX (triploidy) and the patient opted to terminate the pregnancy.

Q: Could the patient have been offered NIPT initially?
A: Yes. Current indications for considering the use of cell free fetal DNA includes maternal age 35 years or older at delivery. Additional indications include history of a prior pregnancy with trisomy, parental balanced Robertsonian translocation with increased risk of fetal trisomy 13 or trisomy 21, positive test result for aneuploidy, including first trimester, sequential, integrated, or second trimester quadruple screen, and fetal ultrasonographic findings indicating an increased risk of aneuploidy. If the patient had received genetic counseling earlier, the option of NIPT could have been discussed.
Q: Did the fact of a triploid fetus cause the non-reportable result on the first sample submitted?
A: No, at this time there is no known correlation between other aneuploidy and no-call rates. Between 0.5 and 7 percent of submitted samples, depending on the laboratory, do not yield a result. The most common reason is an insufficient amount of cell free fetal DNA. This outcome is more common in obese woman. Of note, our patient had a BMI of 34.7. In such instances, one may resubmit a blood sample for a reattempt at NIPT or offer women invasive prenatal diagnosis.

Q: Why offer an NIPT when the patient tested positive on part 1 of her stepwise sequential screen rather than proceeding with prenatal diagnosis?
A: As noted, NIPT can serve as a second line screening test in patients found to be at increased risk for aneuploidy by a first line screening test. Alternatively, invasive prenatal diagnosis could be offered in this instance. CVS was offered, but declined due to associated increased risk for miscarriage.

Q: Why was amniocentesis offered when the ultrasound was abnormal, but NIPT was negative?
A: NIPT only screens for trisomy 21, and in some instances trisomies 13 and 18. Since ultrasound abnormalities can be associated with other aneuploidies, structural chromosome abnormalities and in some cases other genetic syndromes, counseling and invasive prenatal diagnosis for full karyotyping and when appropriate microarray and/or targeted mutation analysis should be offered.

Q: Why was NIPT negative in a triploid fetus, which has extra chromosomes 13, 18, and 21, in addition to an extra copy of all other chromosomes?
A: The technology currently being used by the majority of laboratories offering NIPT only detects the proportion of DNA for chromosomes 21, 18, and 13 relative to all others. In trisomy 21, 18, or 13, DNA from the extra single chromosome will be disproportionately increased, resulting in a positive test. In triploidy, since all chromosomes are present in the same proportion, although in abnormally increased absolute amounts, the NIPT is negative.

References