MASTER CLASS

The Evolution of Prenatal Assessment

E. ALBERT REECE, M.D., PH.D., M.B.A.

It is astonishing how much obstetrics and maternal-fetal medicine have grown. There was a time not too long ago when obstetric care was primarily delivered to the mother, with the fetus being a hopeful beneficiary. We could listen to the fetal heart rate using the fetoscope, but access to the fetus for its early developmental analysis was otherwise off-limits; its growth and development were assumed as part of maternal-focused obstetric care.

The introduction of electronic fetal monitoring gave us the opportunity to see a recording of the fetal heart rate pattern – its rhythm, and its quality – and we used that as an indirect measure of fetal well-being. Subsequently, ultrasound became available, and we could then evaluate the anatomy of the fetus – though usually in the latter part of pregnancy – and appreciate the morphology and overall growth performance.

It was not until relatively recently that the focus of prenatal assessment has shifted to the first trimester. In large measure, this change has been consumer driven. Families have become very interested in the development of their unborn children, and that interest increasingly has centered on obtaining more information earlier on. Such demand has pushed physician scientists working in the field to adapt their technologies to the first trimester. Recent research has, in large measure, advanced in response to parental interests.

Fetal diagnosis in the first trimester was thus born of this great desire and has evolved to the point where, as stated in this month's Master Class, it is becoming the standard of care. The field of first-trimester fetal diagnosis now consists of a series of biochemical and biophysical assessments that can truly evaluate fetal well-being at the current time and can contribute to the prediction of later development and later fetal well-being, or more importantly, the loss of fetal well-being.

It is in light of this burgeoning field of first-trimester evaluation that we decided to develop a Master Class to review this new state of the art. I have invited Dr. Christopher R. Harman, an international expert in the field of ultrasound and Doppler technology, to serve as this month's guest professor.

Dr. Harman is professor and interim chair of the department of obstetrics, gynecology, and reproductive sciences at the University of Maryland, Baltimore, as well as director of the school's maternal-fetal medicine division. He will explain how research is honing in on a first-trimester platform of assessments that holds even more potential for predicting risks and complications than we realized with the first-trimester screening algorithm that took hold more than 5 years ago. ■

Dr. Reece, who specializes in maternal-fetal medicine, is vice president for medical affairs at the University of Maryland, Baltimore, as well as the John Z. and Akiko K. Bowers Distinguished Professor and dean of the school of medicine. He said he had no relevant financial disclosures. He is the medical editor of this column. Contact him at obnews@elsevier.com.

First-Trimester Screening: State of the Art Is Standard of Care

The decades-long shift in our approach to prenatal screening which brought us from a point that maternal age was the main criterion for assessing risk of chromosomal abnormalities to a more precise first-trimester screening approach – one that combines biochemistry and imaging – is continuing to evolve.

CHRISTOPHER R. HARMAN, M.D.

Indeed, researchers are honing in on a "platform" of first-trimester assessments that can screen for an even wider array of risks and pregnancy complications than previously envisioned – an array that extends far beyond chromosomal abnormalities. Much of this first-trimester screening platform is currently being applied and is poised to become a new standard of care.

The continued evolution of first-trimester screening is critical, as a massive amount of time and resources is spent trying to identify problem pregnancies. Many of these resources still are used inefficiently because detection is incomplete or too late to make a difference. With an expanded and precise first-trimester platform for assessment, we can offer women and their physicians significantly more information early on. This will enable us to channel our resources to improve decision making, direct management, and enhance pregnancy outcome.

Early Screening's Development

Prenatal screening used to be all about maternal age. Our early methods were based on the fact that risk increases with age, and then on the idea that particular age cut-offs may signify varying levels of risk.

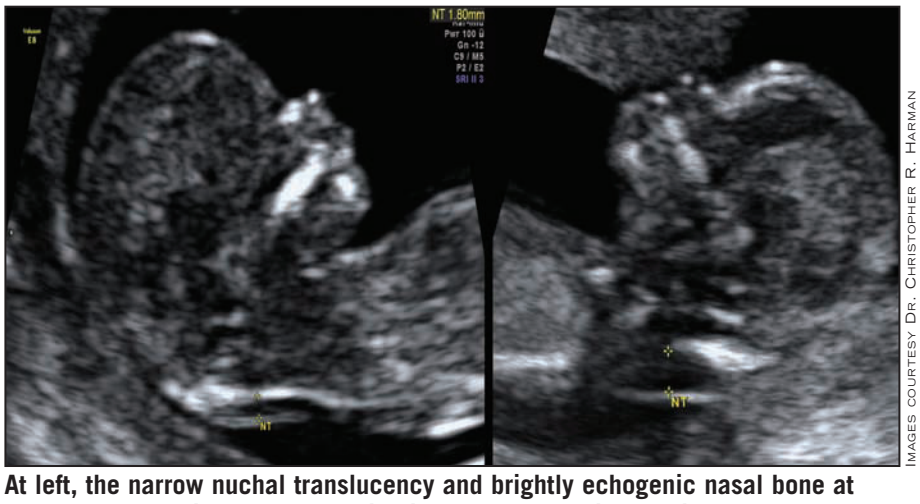
However, advances in ultrasound, and the identification of four pregnancy-related maternal blood analytes, provided us new and exciting insights on fetal status. These chemicals became part of a second-trimester screening process focused largely on trisomy 21. Although we still used age as a factor to assess risk, we learned that the cut-offs we had identified earlier were arbitrary and that risk could now be individualized.

As research continued, it became apparent that versions of the biochemical tests used in second-trimester screening could be done in the first trimester – even by 12-14 weeks of gestation – and could be used to assess the risks not only of Down syndrome, but of other chromosomal abnormalities and some physical abnormalities. These biochemical tests (free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A) were combined with first-trimester ultrasound measurements of nuchal translucency into a screening algorithm that took hold more than 5 years ago and has steadily gained acceptance.

Since then, a number of parameters have been added to first-trimester screening to make the prediction of normality, or abnormality, even more precise. Assessment of the nasal bone, of the frontonasal facial angle, and of various structures inside the brain have become part of an anatomic review, for instance, that help us better define which babies we should be most concerned about.

Additionally, Doppler assessment of blood flow measurement – specifically of tricuspid regurgitation and of flow through the ductus venosus, a small fetal blood vessel that leads to the heart – can provide valuable information about fetal cardiac status and can easily be done in the context of the first-trimester ultrasound evaluation. Abnormal first-trimester Doppler findings also appear to predict Down syndrome and other adverse outcomes independently of a normal nuchal translucency measurement.

Combined with additional, early biochemical tests on maternal serum, these imaging advances (for fetal anatomic reviews and blood flow measurements) have led to an improved detection rate as high as 90% for trisomy 21 and other chromosomal abnormalities. More importantly, this detection rate is achieved without invasive testing, enabling us to reserve invasive procedures such as chorionic villus sampling (CVS) or amniocentesis for women with higher identified risks.



IMAGES COURTESY DR. CHRISTOPHER R. HARMAN

At left, the narrow nuchal translucency and brightly echogenic nasal bone at 12 weeks' gestation reduce the likelihood of aneuploidy. At right, the fetus has a NT over 4 mm and nonvisualizing nasal bone. CVS on the second fetus revealed Down syndrome.

A New Cardiac Focus

The nuchal translucency test, which measures levels of fluid in a small area in the back of the fetal neck, has been available in the United States for approximately 15 years. With time, we have come to appreciate that a number of problems, in addition to Down syndrome, are associated with increases in nuchal translucency. We also better understand that abnormal nuchal translucency measurements are not always indicative of a problem, and that when there is a problem, the issue is not always chromosomal in nature.

The quest to detect other kinds of problems (mainly structural abnormalities, and congenital heart defects, in particular) as early as we can detect chromosomal problems has taken on added urgency in recent years.

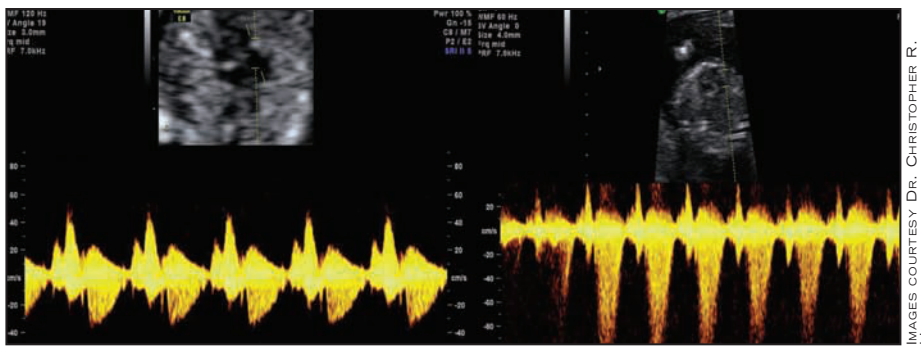
Indeed, significant improvements in the overall computing capability of modern ultrasound equipment, in three-dimensional color ultrasonography, and in ultrasound image resolution – as well as specific new technologic developments such as tomographic imaging and spatiotemporal image correlation – have opened the door to first-trimester cardiac screening.

In the majority of patients, up to 12 parameters of fetal cardiac structure can be visualized. Each of the three segments of the exam takes only a few seconds to perform, so the actual collection of information is rapid. The technologic

Continued on following page

Continued from previous page

advances have also made the acquisition of images easier and less operator dependent. Moreover, the analysis is then performed offline, so the mother can go home afterward. Offline analysis of images also means that the ultrasound scan itself can be performed by trained sonographers at a distance from a cardiac center, with the information transmitted to the center for expert analysis.



IMAGES COURTESY DR. CHRISTOPHER R. HARMAN

In another pair of fetuses appearing at 12 weeks' gestation for nucal translucency screening, tricuspid valve Doppler shows normal flow on the left. The fetus on the right has a large downward jet of tricuspid regurgitation, suggesting possible abnormalities; pulmonary stenosis was later diagnosed.

It wasn't long ago that second-trimester fetal echocardiography was the gold standard for any prenatal evaluation of fetal cardiac structure and function. Now, with an early and integrated screening approach that utilizes first-trimester fetal cardiac examination, we can in fact diagnose many of the most severe heart defects as early as 12 weeks of gestation. At this stage, the fetal heart is as small as the tip of the little finger.

This component of first-trimester screening is just now coming to the forefront. Its availability can benefit populations at high risk of cardiac anomalies (such as women who have long-standing diabetes). It may be especially beneficial to those who were in poor glycemic control at the beginning of their pregnancy. It appears, though, that the exam can be meaningfully applied in low-risk populations as well. Research is underway to determine the best approaches to counseling and to determine which patients should have subsequent invasive testing.

Other New Frontiers

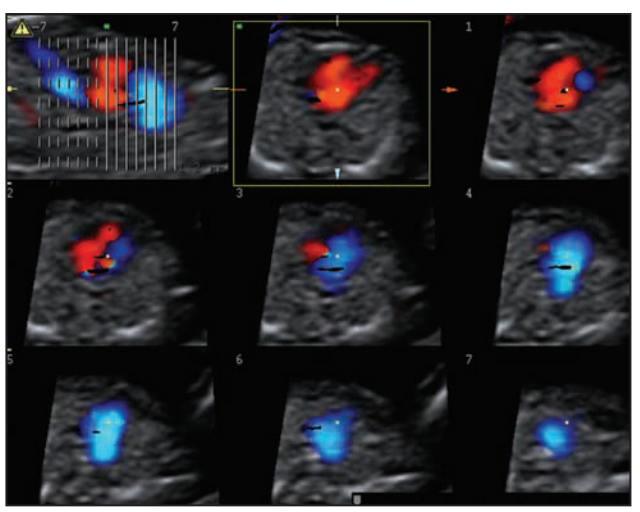
Another area of interest is the potential ability to predict which women will develop preeclampsia later in pregnancy based on how the fetus and placenta are faring at approximately 12 weeks' gestation.

Doppler investigations have shown us that placental abnormalities are difficult to distinguish from normal placental development early in pregnancy. In the first trimester, therefore, Doppler alone is a fair mechanism for knowing whether placental development is deficient enough to put the mother at high risk for developing preeclampsia or isolated hypertension.

However, when Doppler is combined with measurement of a family of maternal serum analytes – some of them inflammatory substances and some of them chemicals that regulate the formation of blood vessels – it can be employed to predict who will develop early hypertensive complications. And when other factors such as maternal weight and blood pressure at the time of first-trimester assessment are added to the equation, the accuracy of our predictions increases further.

We are proceeding in this area with a bit of caution, as we cannot yet predict the onset of preeclampsia later on in pregnancy. The predictive value of the first-trimester assessment for hypertensive problems that occur closer to term is not very good, so patients with normal early assessments still need careful prenatal care.

Still, in many ways we can tackle the most severe problems through early detection. There is some evidence that the administration of low-dose aspirin can reduce the incidence of hypertension and preeclampsia, as well as complications with the baby's growth, in women with detected placental abnormalities. This means that not only are we able to define and identify those women at highest risk, but we also have the ability to potentially modify the course of placental development and perhaps even eliminate hypertensive complications.



3-D blocks analyzed by tomographic section in a systematic approach yield a complete catalogue of anatomic cardiac landmarks in over 80% of fetuses at 12 weeks.

Current research is aimed at defining who will best benefit from this approach, because while low-dose aspirin appears in some research to work when started early in high-risk women, benefits have not been duplicated in other studies.

More broadly, first-trimester assessment of maternal characteristics (such as weight), serum analytes, and ultrasound features set the stage for ongoing maternal evaluation of characteristics such as weight gain during pregnancy to predict her risk of developing preeclampsia, diabetes, and other serious problems, including neonatal concerns requiring specialized newborn care.

The Big Picture

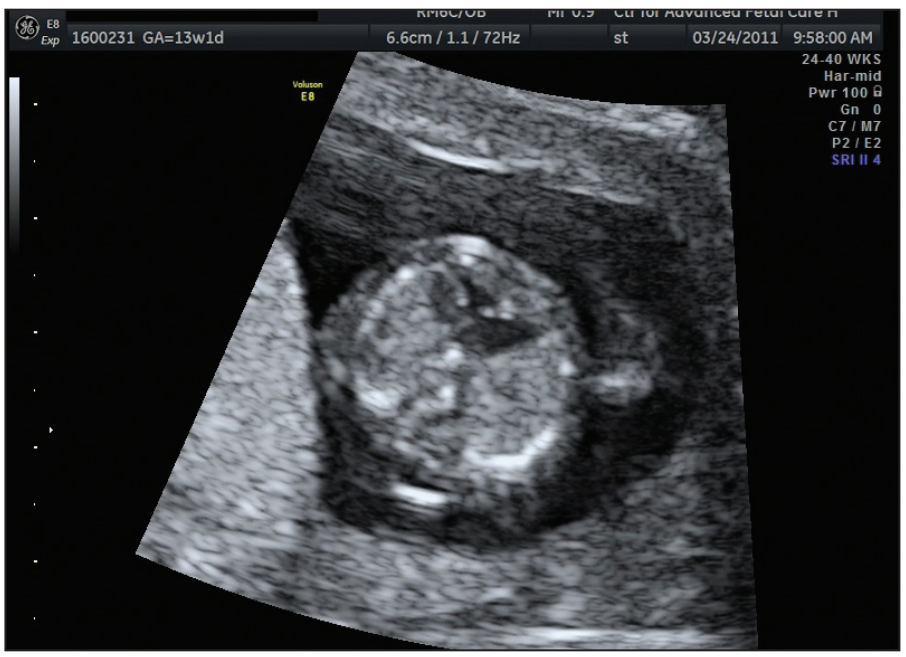
As first-trimester screening evolves with technologic developments to become more comprehensive and precise, one of its ever-important components involves the art of history taking, physician-patient dialogue, and the incorporation of low-tech risk assessments for coping with and possibly preventing preterm labor and delivery.

Measuring the cervix at this very early stage is not a good predictor of its ability to contain the pregnancy for the rest of the gestation or even until a reasonably mature gestation is reached. In the first trimester, the cervix generally is not under enough pressure from the weight of the pregnancy to disclose whether it is a strong or weak cervix or whether it has the potential to shorten in an extreme way or not. This is different from measuring the cervix later in pregnancy when the shortening process has already started, and when intervention is based on proven results.

The first trimester is an excellent time, however, to have the mother recount her history. It is also a good time to make decisions about the use of progesterone, which in weekly injections has been shown to reduce the incidence of preterm delivery, and to institute a serial monitoring program so that any changes may be detected before the patient presents with rapidly advancing preterm labor – i.e., before a clinical emergency.

Such dialogue and interaction emphasizes to me the importance of a team approach to first-trimester screening that involves the ob.gyn. physicians, well-trained sonographers, well-trained perinatal nurses, and perinatologists who specialize in high-risk maternal and fetal complications.

Prenatal screening is no longer an in-and-out assessment of two or three measures. That began to change more than 5 years ago with adoption of the first-trimester screening approach combining biochemistry and imaging. It continues to evolve as prenatal screening provides an even more thorough and comprehensive view of fetal, placental, and maternal function that allows us to thoroughly map out the care of our patients. For women who have normal pregnancies, this is incredibly reassuring. And for those with any kind of outlying results or overt complications, it provides a starting point for making the best of even the most challenging pregnancies. ■



Complete endocardial cushion defect was diagnosed at 12 weeks. First trimester echocardiography was triggered by abnormal ductus venosus alone during routine screening.

Dr. Harman said he had no relevant financial disclosures.

Maternal Serum Analytes in First Trimester Predictive of Early-Onset Severe Preeclampsia

Type	Example
Vascular growth	Low angiopoietin-2
Placental endothelium	Low placental growth factor
Placental growth	Low pregnancy-associated plasma protein A
Placental integrity	High inhibin A

Note: Probably not predictive are placental protein 13, A disintegrin, metalloproteinase 12, free beta human chorionic goadotrophin.

Source: Dr. Harman