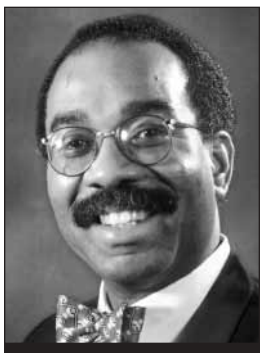
MASTER CLASS

Prenatal Screening

There was a time when pregnancy and its outcome were clouded in mystery, when fetal outcome was known only at birth. Over many years, that mystery has dissipated as an evolution of technological developments occurred, eventually leading to the discipline of prenatal diagnosis.

In the 1800s, fetal assessment using the Pinard stethoscope was introduced. This was followed by the introduction and use of more refined instruments that similarly focused on assessment of fetal movement and the fetal heart rate. In 1958, Dr. E.H. Hon introduced electronic fetal monitoring—a technology that enabled us to attempt to assess fetal well-being by attributing illness or lack of health to significant changes in the heart rate. After Dr. Ian Donald of the United Kingdom introduced obstetric ultrasound in the late 1950s and early 1960s, we began using more sophisticated technology to assess the global appearance of the in utero environment.



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

As this succession of technological innovations occurred, the desire of parents and families to know about the well-being of the fetus grew. Parents welcomed the development of more sophisticated ultrasound and their new ability to scrutinize the fetus in even greater detail, assessing not only its anatomical development but also its behavioral and functional states.

Other methods of fetal assessment were introduced, including biochemical analysis of the maternal and fetal blood. We soon reached the point at which we could use an algorithm that incorporated the biophysical findings of ultrasound and the biochemical assessment of maternal blood to gain significant insight about fetal status very early in gestation.

The culmination of this technological evolution has been the development of first-trimester fetal screening. Using various algorithms, we are now able to gain a significant amount of information on fetal development and outcomes early on.

Our guest professor for Master Class this month, Dr. Mark I. Evans, will elucidate the application of first-trimester prenatal diagnosis. Dr. Evans is professor of obstetrics and gynecology at the Mount Sinai School of Medicine, New York, and president of the Fetal Medicine Foundation of America. He is a national leader in prenatal diagnosis and genetics. ■

DR. REECE, *who specializes in maternal-fetal medicine, is the vice chancellor and dean of the college of medicine at the University of Arkansas in Little Rock. He is the medical editor of this column.*

Let's Incorporate First-Trimester Screening Into Obstetric Practice

We are in the midst of a significant shift in our approach to prenatal screening for Down syndrome and other major chromosomal abnormalities. We now know, without doubt, that first-trimester screening that combines maternal serum free β–human chorionic gonadotropin and pregnancy-associated plasma protein–A with fetal nuchal translucency measurement is better than second-trimester screening, and we must embrace this new knowledge.

BY MARK I. EVANS, M.D.

A host of studies, conducted at the front lines of clinical practice as well as at major medical centers, has provided more-than-sufficient evidence that first-trimester screening is ready for implementation in obstetric practice. Major organizations—such as the American College of Obstetricians and Gynecologists, the Society for Maternal-Fetal Medicine, and the National Institutes of Health—are supportive of the shift. For our own patients and as part of an overall public health strategy, we should be rapidly moving away from second-trimester screening and away from using advanced maternal age as the main criterion for deciding who is at risk; instead, we should move toward incorporating the tests and referrals necessary for effective first-trimester screening.

In our practice, we see hundreds of patients who, in previous pregnancies, did not learn until the 18th, 19th, or 20th weeks that they had a baby with a serious problem. They had to go through emotionally wrenching experiences regardless of what they chose to do. With their new pregnancies, they want answers, privately and urgently.

Giving our patients the opportunity to get information and make decisions privately, at a time when their pregnancies are not yet obvious, was always one of the principal driving forces behind the desire for earlier prenatal screening. Now, with first-trimester screening a reality, obstetricians need to be even better prepared to counsel patients and to accept and fully respect their various opinions and decisions.

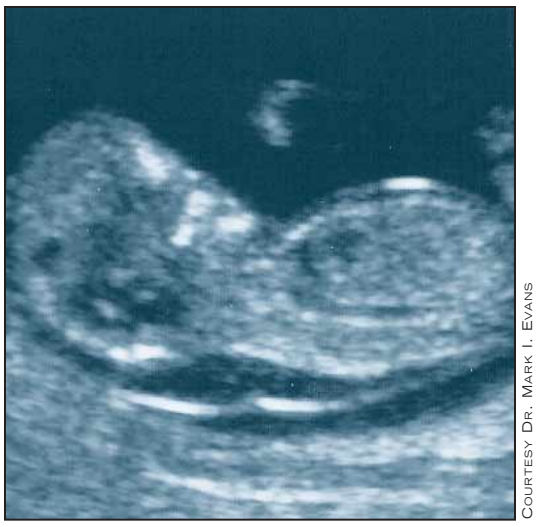
To effectively incorporate first-trimester screening into practice, we face two other responsibilities. First, we must appreciate—and reassure patients of—the fact that, when done by experienced physicians and at the proper gestational age, chorionic villi sampling (CVS) is safe. When it is done beyond 9 weeks' gestation, the incidence of birth defects after CVS is the same as it is in patients who had no procedure. Second, we must ensure the quality of obstetric ultrasound and, specifically, the measuring of nuchal translucency.

The Road to First-Trimester Screening

We have come a long way in the past 40 years. Once, the best we could do was tell a woman that, as she got older, she had an increased risk of having a baby with a chromosomal abnormality. Then we began to understand that levels of risk were generally clumped together into 5-year cohorts, with a big jump in risk occurring between the 30- to 34-year-old cohort and the 35- to 39-year-olds. As we looked further, we saw that the slope of the curve begins to go up at about age 32 years.

Once amniocentesis was developed, it evolved from a procedure offered only to women at the very highest risk—mainly those who were older than 40 or who had a child with an abnormality—to one that was offered widely to women older than 35 years. In the 1980s, however, it took almost a month for results to come back. By that time, at 21-22 weeks, patients were visibly pregnant, and the bonding process had accelerated.

The angst faced by women at this point in their pregnancies led to the notion of trying to move prenatal diagnosis into the first trimester with CVS. By the end of the 1980s, the procedure was deemed safe and effective. We were stymied, unfortunately, by the limb reduction scare of the early 1990s—an assertion that babies born after CVS had a higher risk of certain limb defects. When this procedure is done in experienced hands and later than 9 weeks' gestation, however, the procedure carries no such risks. The quality of chromosomal study with CVS, moreover, is virtually identical to that with amniocentesis. The risk of miscarriage is also the same.



COURTESY DR. MARK I. EVANS

A trisomy 18 fetus with enlarged nuchal translucency is seen on ultrasound.

If all we did was offer CVS and amniocentesis to women aged 35 years and older, however, we would detect only about one-third of the babies born with chromosomal anomalies like Down syndrome. Significantly more pregnancies occur among younger women, and the vast majority of chromosomal abnormalities therefore occur in this "low-risk" group. For this reason—and in an effort to avoid invasive procedures when possible and when desired among older women—physicians and patients clamored for an effective screening test.

Our first obstetric prenatal screening test—the measurement of maternal serum alpha fetoprotein (AFP)—enabled us to detect about one-third of the chromosomal anomalies in women under 35.

The addition of human chorionic gonadotropin and sometimes unconjugated estriol levels measured at 15-18 weeks (the double- and triple-screening protocols) raised the detection rate to approximately 50% in women younger than 35. Yet another measurement—inhibin A—later raised it even more, although we know now that the detection rate is still not as high as that achieved with the first-trimester screening protocol.

These were second-trimester screening tests, however, so women faced the often difficult choice of either having a first-trimester diagnosis by CVS or waiting for screening.

Biochemists experimented with first-trimester measurements and found that AFP and estriol were useless when measured this early. Free β-HCG, however, showed promise, as did measurement of another analyte, pregnancy-associated plasma protein–A (PAPP-A).

(There are two ways of measuring HCG, however, and it is important to understand that virtually all studies done on first-trimester biochemistry have used the so-called free β subunit of HCG—the dissociated part of HCG's β chain. Despite the fact that measurement of the intact β chain is not nearly as useful or accurate, some laboratories still market total β-HCG measurements. It is free β-HCG that we need to measure.)

Meanwhile, ultrasound had become more sophisticated, and it also became apparent that nuchal translucency (the thickness of the back of the fetal neck) in the late first trimester was the strongest indicator of fetal abnormalities identified thus far. It was clear that the bigger the NT measurement, the larger the risk of major chromosomal anomalies.

Because ultrasound and biochemistry are independent markers, a consensus quickly developed that first-trimester screening should utilize both.

It is interesting to note that biochemistry alone is problematic because it does not work as well with multiples and because values are commonly dependent upon gestational age, the determination of which really requires ultrasound. In fact, the late first-trimester ultrasound is the most accurate indicator of gestational age, and in this sense, it offers tremendous obstetric advantages.

We also now know that if NT values are increased and there is not a chromosomal etiology, there may be other congenital problems, principally cardiac anomalies. Early detection of such problems allows not only for reproductive choice but also for planned delivery in appropriate facilities with the best subspecialists.

The Evidence

The person who deserves the lion's share of credit for our shift to first-trimester screening is Dr. Kypros Nicolaides of Kings' College London. Through the second half of the 1990s and continuing on to this point, his group has repeatedly shown that when ultrasound is done correctly and is combined with the proper biochemistry, about 90% of fetuses with trisomy 21 syndrome and other major chromosomal abnormalities can be identified with a 5% false-positive rate.

Investigators of the main American trial on first-trimester screening, called the BUN (Biochemistry, Ultrasound, Nuchal Translucency) study, reported an 83% detection rate with an 8% false-positive rate. Detection rates were similar—even higher—in the FASTER (First- and Second-Trimester Evaluation of Risk) trial published late last year.

In addition to examining first-trimester screening, the FASTER trial addressed the idea of integrating first- and second-trimester screening results. Everyone agrees that the FASTER trial results showed that first-trimester screening works far better than second-trimester screening, and that some patients can modify their first-trimester risk by adding second-trimester protocols. My interpretation, however, is that the vast majority of patients do not need to wait for additional screening. They can have superb results in the first trimester.

Biochemistry can be done anytime between 9 and 13 weeks, but it is best done at weeks 9 or 10. Nuchal translucency, on the other hand, is only interpretable during weeks 11, 12, or 13. Before week 11 or after week 13, we cannot use the data.

Some experts have pointed to the possible added value of the fetal nasal bone measurement, but it is a much harder measurement to perform, and I believe it is unlikely that a large percentage of physicians will be able to do it competently. When it can be correctly obtained, however, it can be a good adjunct to the risk calculation. I consider it a second-line screening test that can be used if there is confusion or ambiguity about the first round of tests.

Ultrasound Quality

Successful first-trimester screening is contingent upon accurate nuchal translucency measurement. There are a number of ways to do the measurement, and frankly, the way in which a standard method was chosen was, in essence, arbitrary. Standardization is necessary, however. NT measurement is not an art.

If we're going to use ultrasound numbers in an algorithm—as we are in our new screening protocols—we must employ the same quality control we expect of any other laboratory measurement. Although the issue of ultrasound certification as a prerequisite of the performance of NT measurement has been debated, several organizations perform quality review.

Nuchal translucency measurement will not be a procedure that everyone does in his or her own office. I see more of a "centers of excellence" model or process evolving, in which a patient who is 9-10 weeks pregnant has blood drawn in her obstetrician's office and then goes to another specialized center for the NT measurement. There, the specialist retrieves the lab results electronically, plugs the NT measurement and lab results into the algorithm, and then—on the spot—tells the patient what her risk is. If the patient decides she wants CVS, the procedure could even be done that day.

As in many other parts of health care, patients in rural areas can be at a disadvantage. To physicians in remote areas, I would say, rely on the biochemistry as a first step.

"Accept and Respect"

As a geneticist, I tell all patients that we try to provide information only, and that what they choose to do with that information is their decision. Faced with screening information and the fact that it adjusts odds and does not provide definitive answers, many patients will decide they are happy with an odds adjustment. Others will say, "I don't care what the risk is, I want a definitive answer."

Both decisions have to be equally respected. With prenatal screening undergoing such significant change, it is all the more important that we accept the fact that intelligent and reasonable people will look at the same data and reach opposing conclusions. We have to accept and respect this diversity.

During my 25 years in the field, I have found that what patients actually do when they are faced with information is often diametrically the opposite—in both directions—of what they thought they would do if confronted with a problem. That's why I believe that one of the most important things we can do is to reassure patients that everything—any decision—is fine. ■