OB/GYN CLINICAL ALERT®

Providing Evidence-based Clinical Information for 29 Years

A monthly update of developments in female reproductive medicine

AHC Media Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com

AHC Media

INSIDE

Testing for chlamydia and gonorrhea in pregnancy **page 42**

Intrauterine growth restriction **page 44**

CME test questions **page 48**

Financial Disclosure: *OB/GYN Clinical Alert's* editor, Jeffrey T. Jensen, MD, MPH, is a consultant for Agile Pharmaceuticals, Bayer Healthcare, HRA Pharma, and Merck; is a speaker for Bayer Healthcare and Merck; and receives research support from Agile Pharmaceuticals, Abbott Pharmaceuticals, Bayer Healthcare, HRA Pharma, and Medicines360. Peer reviewer Catherine Leclair, MD; executive editor Leslie Coplin, and managing editor Neill Kimball report no financial relationships relevant to this field of study.

The Changing Paradigm of Vulva Cancer Management

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

Professor, University of Texas; M.D. Anderson Cancer Center, Houston

Dr. Coleman reports no financial relationships relevant to this field of study.

Synopsis: *Among women with early-stage squamous cell carcinoma of the vulva, sentinel node biopsy is a reasonable alternative to inguinal femoral lymphadenectomy. Histological ultrastaging is an important adjuvant to sentinel node assessment for metastatic disease.*

Source: Levenback CF, et al. Lymphatic mapping and sentinel lymph node biopsy in women with squamous cell carcinoma of the vulva: A Gynecologic Oncology Group study. *J Clin Oncol* 2012;Jul 2 [Epub ahead of print].

Sentinel lymph node biopsy is an assessment tool for early metastatic nodal spread used in management of many solid tumors. To evaluate its safety as a replacement for inguinal femoral lymphadenectomy (IFN), a multi-institutional clinical trial was conducted proscribing sentinel lymph node (SLN) biopsy ahead of full IFN in women with early stage vulvar cancer. Eligible patients were to have invasive (≥ 1 mm) squamous cell carcinoma of the vulva between 2 and 6 cm in size and clinically non-suspicious groin nodes. Sentinel lymph node localization was performed using dye and radionuclide with optional lymphoscintigraphy. Identified SLNs were prepared using step sectioning and stained for cytokeratin using immunohistochemistry (IHC). In all, 452 patients underwent the procedure with SLNs being identified in 418 (92%). Nodal metastases were identified by routine pathological assessment in 102 and by IHC in 30 additional patients (node metastasis rate 29%). Among those where an SLN was identified, the false-negative rate (SLN histologically negative, but metastatic nodal disease positive on IFN) was 8% (11/132). The false-negative predictive value, a metric that also includes the majority population

VOLUME 29 • NUMBER 6 • OCTOBER 2012 • PAGES 41-48

OB/GYN CLINICAL ALERT IS AVAILABLE ONLINE
www.ahcmedia.com

of true-negative assessments (1- the negative-predictive value), was 3.7%. In women with primary tumors < 4 cm in size, the false-negative rate was 2%. The authors conclude that the procedure may be safely substituted for IFN in selected women with early-stage vulvar cancer.

■ COMMENTARY

Primary carcinoma of the vulva is a rare but debilitating disease of primarily elderly women. In the last 100 years, surgical excision following the Halsteadian approach for breast cancer led to disease cures, but with great morbidity and disfiguration. Significant milestones in contemporary management came with documentation of: 1) the safety of separating the primary radical excision of the vulva from the IFN (the "triple incision" technique),[1] 2) the recognition that lateralized primary tumors were rarely associated with bilateral groin metastases,[2] and 3) primary vulvar excision didn't require complete vulvectomy. Further advances came with introduction of radiation (and chemoradiation) both as adjuvant and neoadjuvant therapy.[3] Indeed, these modifications improved survival, reduced morbidity, and provided, in many cases, functionality to the vulva. SLN biopsy is the next great iteration in this continuum. The importance of the procedure is underscored by the observation that most women with early-stage disease will not have nodal spread and gain nothing other than morbidity, such as lymphedema, from IFN. The obvious concern in adopting a "minimalization" alternative to full IFN is missing prevalent disease without therapy,[4] particularly since recurrent groin disease is particularly difficult to manage and is often a fatal event.

SLN biopsy is not new to management of vulvar cancer; descriptions appeared in the early 1990s.[5] However, large-scale validation took the international community to assemble the collective experience of two organizations to highlight the safety of this approach. I have previously highlighted one of these, the GROINS-V study, which was reported about 4 years ago.[6] The latest, from the Gynecologic Oncology Group, largely recapitulates that experience, particularly when similar cohorts are examined. The primary difference between the studies, though, is the level of experience of the contributing members. The majority of contributors to the latter study were novices with the technique and did not have to undergo a competency evaluation prior to participating in the trial. This may have led to the higher than initially expected false-negative rate, but it provides external validity for the procedure in this rare disease. Under the identified constraints (tumors < 4 cm, squamous histology, and clinically negative groins), SLN appears to be safely substituted for IFN. Current investigation is prospectively assessing the merit of SLN-only groin dissection (node negative and node positive) for survival and morbidity, including quality of life. ■

References

1. Way S. Carcinoma of the vulva. *Am J Obstet Gynecol* 1960;79:692-697.
2. Parker RT, et al. Operative management of early invasive epidermoid carcinoma of the vulva. *Am J Obstet Gynecol* 1975;123:349-355.
3. Boronow RC. Combined therapy as an alternative to exenteration for locally advanced vulvo-vaginal cancer: Rationale and results. *Cancer* 1982;49:1085-1091.
4. Wharton J, et al. Microinvasive carcinoma of the vulva. *Am J Obstet Gynecol* 1974;118:159-162.
5. Levenback C, et al. Intraoperative lymphatic mapping for vulvar cancer. *Obstet Gynecol* 1994;84:163-167.
6. Van der Zee AG, et al. Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. *J Clin Oncol* 2008;26:884-889.

OB/GYN Clinical Alert, ISSN 0743-8354, is published monthly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

EXECUTIVE EDITOR: Leslie G. Coplin
MANAGING EDITOR: Neill L. Kimball
SENIOR VICE PRESIDENT/GROUP PUBLISHER: Donald R. Johnston
GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***OB/GYN Clinical Alert***, P.O. Box 105109, Atlanta, GA 30348.

Back Issues: $42.

Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.
This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

AHC Media

Subscriber Information

Customer Service: 1-800-688-2421.
Editorial E-Mail: leslie.coplin@ahcmedia.com
Customer Service E-Mail: customerservice@ahcmedia.com

Subscription Prices

United States
1 year with free AMA Category 1 credits: $319
Add $17.95 for shipping & handling.
(Student/Resident rate: $125)

Multiple Copies
Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

Canada
Add 7% GST and $30 shipping.

Elsewhere
Add $30 shipping.

Accreditation

AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of *25 AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity is intended for the OB/GYN. It is in effect for 36 months from the date of the publication.

Questions & Comments
Contact **Leslie Coplin**, Executive Editor, at leslie.coplin@ahcmedia.com.

Testing for Chlamydia and Gonorrhea in Pregnancy

ABSTRACT & COMMENTARY

By Rebecca H. Allen, MD, MPH

Assistant Professor, Department of Obstetrics and Gynecology, Warren Alpert Medical School of Brown University, Women and Infants Hospital, Providence, RI

Dr. Allen reports no financial relationships relevant to this field of study.

Synopsis: *In this national retrospective study, 59% and 57% of women were tested at least once during pregnancy for* Chlamydia trachomatis *or for* Neisseria gonorrhoeae*, respectively. Of those women testing positive, 78% and 76% underwent a test of cure for* C. trachomatis *and* N. gonorrhoeae*, respectively.*

Source: Blatt AJ, et al. Chlamydial and gonococcal testing during pregnancy in the United States. *Am J Obstet Gynecol* 2012;207:55.e1-8.

THE AUTHORS PERFORMED A RETROSPECTIVE COHORT STUDY of 1,293,423 pregnant women aged 16 to 40 in the United States from June 1, 2005 to May 30, 2008, using data from the Quest Diagnostics Informatics Data Warehouse. Women aged 16-40 years who had an obstetrical panel (that included a rubella antibody test) performed at Quest Diagnostics were assumed to be pregnant, and those who had any further laboratory tests at Quest Diagnostics during what was estimated to be the third trimester (to ensure continuity) were enrolled as subjects. Of these women, 525,258 (41%) had race data available through the maternal serum screen test. In addition, the authors identified Medicaid insurance as a marker of socioeconomic status. Chlamydial and gonoccocal testing results were then extracted, and testing was determined to be at the first prenatal visit if it occurred shortly before or during the visit when the obstetric lab panel test was performed.

The study population was similar in race and proportion on Medicaid (18.1%) to the total U.S. pregnant population. Although the study population was older than the total U.S. pregnant population, the authors adjusted for this in the results. The authors found that 761,315 (59%) and 730,796 (57%) of women were tested at least once during pregnancy for *Chlamydia trachomatis* or for *Neisseria gonorrhoeae*, respectively (the age-adjusted rates were 60% and 58%, respectively). In addition, 37% of women were tested for *C. trachomatis* during the first prenatal visit. Testing rates for chlamydia were highest for younger women (71.5% for age 16 to 24 compared to 58.5% for age 35 to 40) and African American women (74% compared to 59.2% for whites). Of those tested at least once, the prevalence of *C. trachomatis* was 3.5% and the prevalence of *N gonorrhoeae* was 0.6% (the age-adjusted rates were 4.6% and 0.8%, respectively). Not surprisingly, the prevalence of infection was highest among younger ages with 16% of 16-year-olds testing positive compared to < 1% of women older than age 35 years. A test of cure was performed for 78% of chlamydia-positive women and 76% for gonorrhea-positive women. Test of cures were positive among 6% of women with chlamydia and 3.8% of women with gonorrhea.

■ COMMENTARY

The American College of Obstetricians and Gynecologists (ACOG) recommends that all pregnant women be screened for chlamydial infection during their first prenatal care visit.[1] The rationale for universal screening is the relatively high prevalence of infection (2 -13%), the existence of effective treatment options, and the negative sequelae of chlamydial infection for the pregnancy and neonate. If negative, the test should be repeated for pregnant women at increased risk (women aged 25 years or younger, or women who have a new, or more than one, sexual partner) in the third trimester. If positive, a test of cure should be performed 3 weeks after completing therapy to confirm successful treatment, and the woman should be rescreened in the third trimester. The Centers for Disease Control and Prevention (CDC) issued similar recommendations.[2] For gonorrhea, ACOG and the CDC recommend screening only for pregnant women at increased risk for infection.[1,2] However, in clinical practice, commercially available assays most frequently test for both infections simultaneously. Therefore, testing rates for both infections are usually identical, as this study demonstrates.

The authors of this study report the prevalence of chlamydia and gonorrhea among pregnant women and compliance with ACOG and CDC recommendations. The study population was similar to the population of pregnant women in the United States; therefore, the results are generalizable to those women with access to health care. As a retrospective study, the most important limitation is lack of access to the clinical records of participants to determine why they were not screened or whether follow-up took place at another laboratory. Nevertheless, the report provides a picture of compliance, with ACOG and CDC recommendations among insured pregnant women. Unfortunately, compliance was not ideal with 40% of pregnant women not tested at all for chlamydia. Test of cures also were not performed according to recommendations. The fact that younger women were more likely to be tested indicates that clinicians were probably using a risk-based screening strategy, which was ACOG's position prior to 2007 and is the recommendation for nonpregnant women. In defense of these clinicians, screening guidelines were changed during the study period.

Not all organizations agree with ACOG and the CDC regarding universal testing for chlamydia among pregnant women. One might ask whether a 36-year-old, pregnant woman in a monogamous sexual relationship really needs to be screened for chlamydia. There is a significant harm from a false-positive diagnosis for the pregnant woman's relationship, and false-positive results increase when the prevalence is low. This study showed a very low prevalence in older women. The United States Preventive Services Task Force (USPSTF) only recommends chlamydial screening among pregnant women aged 24 and

younger and among older pregnant women at increased risk.[3] The USPSTF recommends against routine screening of women age 25 and older, whether pregnant or not, who have no risk factors. Clinical practice likely varies within and between communities. In our hospital, the low-income prenatal care clinic where I work always has screened universally for chlamydia. In contrast, a few of the private OB/GYN practices are only now beginning to adopt universal testing of pregnant women. Which testing strategy you employ depends on which organization you adhere to, with ACOG and the CDC on one side and the more conservative USPSTF on the other. Clinical judgment is paramount and screening can be individualized according to the USPSTF. Nonetheless, since a pelvic exam is routinely performed at the first prenatal visit, it is not difficult to collect a cervical sample for chlamydia (and gonorrhea). ■

References

1. *Guidelines for Perinatal Care*, 6th ed. Washington DC: American Academy of Pediatrics, American College of Obstetrician Gynecologists; 2007.
2. Workowski KA, et al; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep* 2010;59:1-110.
3. United States Preventive Services Task Force. Screening for chlamydial infection. Available at: www.uspreventiveservicestaskforce.org/uspstf/uspschlm.htm. Accessed Aug. 24, 2012.

Special Feature

Intrauterine Growth Restriction

By John C. Hobbins, MD

Professor of Obstetrics and Gynecology, University of Colorado Anschutz Medical Campus, Aurora, Colorado

Dr. Hobbins reports no financial relationships relevant to this field of study.

Synopsis: *Intrauterine growth restriction represents immediate and long-term threats to infants with this condition. New information from Doppler studies now provides very useful information with which to optimize management of these infants and to improve outcome.*

Recently, there has been an increased focus on the identification of fetal anomalies and aneuploidy through first and early second trimester maternal testing, which has improved early identification of these disorders. However, even lumped together, fetal anomalies and aneupoloidy complicate only 1-2% of all pregnancies. Intrauterine growth restriction (IUGR) is a far more common condition that complicates 5-10% of all pregnancies and accounts for 400,000 pregnancies in the United States. IUGR should garner at least as much attention as fetal anomalies and aneuploidy because diagnosis and strategic management can have a life-long impact on infants affected by this condition.

The consequences of being born small are well documented. Smaller than average babies are subject to higher rates of perinatal death, neonatal morbidity, later cognitive and developmental problems, and even higher rates of diabetes and cardiovascular disease in adult life.

Today's standard obstetrical care includes the assessment of uterine size and, generally, at least one ultrasound examination. Unfortunately, many cases of IUGR elude detection until late in pregnancy. Lindqvist et al have found that just knowing a fetus is under-grown will decrease neonatal mortality and morbidity four-fold.[1]

Predisposing risk factors for IUGR are:

1. Fetal growth restriction in a previous pregnancy.
2. History of hypertension or preeclampsia in the current or a previous pregnancy.
3. A quad screen showing increased levels of AFP, hCG, or inhibin.
4. Abnormal uterine artery waveforms.
5. Insufficient maternal weight gain (< 10 lb).
6. A fall off in fundal height growth.

Diagnosis of IUGR

For some clinicians the terms "small-for-gestational age" (SGA) and "intrauterine growth restriction" are synonymous. Many have considered SGA to be only a neonatal label. However, for others (myself included) IUGR is reserved for those fetuses who are small and deprived (as documented by abnormal Doppler studies).

The most commonly used definition of SGA is a fetus/neonate whose estimated fetal weight (EFW) is below the 10th percentile. However, another definition, favored by European clinicians, is a fetus whose abdominal circumference (AC) is below the 5th percentile. Using the AC as the defining factor makes sense, since the liver is the organ most affected by deprivation, and IUGR fetuses have minimal deposits of subcutaneous fat around their abdominal cavities (for later thermal stability).

Estimated Fetal Weight

There are more than 50 formulas in the literature for estimated fetal weight (EFW), which put into play various measurements of the fetus; now even 3-dimension-

al (3-D) estimates of fetal volume have been described. Despite the smorgasbord of formulas available, the one most commonly used in the United States is a formula by Hadlock[2] involving the biparietal diameter, head circumference, AC, and femur length. This four-variable formula provides a reasonable estimate of fetal weight, but with fine-tuning from 3-D ultrasound, the accuracy can be further improved. For example, Lee et al found that in 66% of cases, the 3-D formula was within 5% of the fetal weight.[3] Nevertheless, with 2-D, a rough rule of thumb is that in 80% of cases, the estimated weight is within 10% of the true fetal weight.[4]

Other Diagnostic Avenues

Oligohydramnios. Oligohydramnios frequently accompanies IUGR, but not SGA — a useful diagnostic distinction. The logical explanation for the presence of oligohydramnios is that when the fetus spares the brain, it is at the expense of flow going downward to the kidneys. However, oligohydramnios represents a diagnostic wild card because the timing of its appearance is variable and, occasionally, it is unassociated with brain sparing. However, oligohydramnios is rarely found without severe IUGR.

Some have advocated delivery if an SGA pregnancy is associated with oligohydramnios. However, oligohydramnios is a basic sign of this condition, not the cause, nor is oligohydramnios responsible for the aftermath. Since it can appear before there is Doppler evidence of compromise, many unnecessary early deliveries would occur if this were the only reason for intervention.

We have abandoned the amniotic fluid index (AFI) in favor of a maximal vertical pocket (MVP) method for diagnosing oligohydramnios. The AFI technique, compared with the MVP, over-calls true oligohydramnios and is associated with a doubling of (unnecessary) inductions and cesarean sections without improving perinatal outcome.[5]

Head-to-body ratio. Years ago, Stuart Campbell described two types of IUGR based on the head-to-body (H/B) ratio.[6] Generally, fetuses suffering from placentally mediated IUGR are asymmetrically small since they have relatively normal size heads but small ACs (because the liver gets shortchanged). On the other hand, constitutionally small fetuses have normal H/B ratios because they are not deprived. Unfortunately, to confuse the issue, fetuses with aneuploidy and intrauterine infection-related IUGR tend to be symmetrically small. Although this concept is often forgotten because of the overlap between various types of IUGR fetuses, it still is a useful parameter to keep in mind when sorting out SGA from IUGR.

Thigh circumference. This measurement can be done with 2-D or 3-D and, although the method has not caught on, it does represent how "beefy" the fetus is. It has been used in fetal macrosomia and, as an adjunctive variable, thigh circumference has enhanced the accuracy of formulas for EFW.[7]

Serial biometric evaluations. With two or more appropriately spaced ultrasound exams, a growth trajectory can be plotted for individual fetuses to determine if there is plateauing of growth. Gardosi et al elegantly enchanced the concept of diagnosing IUGR by determining whether an individual fetus matches up to his/her own ideal weight expectations according to a "customized growth potential"[8] — a calculation that is based on maternal height, weight, ethnicity, and parity.

Exploring Possible Causes of IUGR

Once a fetus is determined to be SGA, there are only a few diagnoses, most of which can be sorted out from the start.

Off on dates. This is one of the most common reasons for a fetus to be seemingly small, especially in patients who present for late care. Therefore, every effort should be made through menstrual history, possible dates of conception, and early ultrasound information or pregnancy test dating, to separate the "on dates" SGA fetus from the "off on dates" appropriate for gestation (AGA) fetus. We have continued to find the trans-cerebellar diameter to be extremely useful in solving this diagnostic problem because it is the last biometric measurement to be affected by fetal deprivation — except in aneuploidy or infection. In other words, it is the closest measurement to the true gestational age.

Aneuploidy. Every SGA fetus should have a detailed ultrasonic survey looking for anomalies or markers of aneploidy. With today's comprehensive ultrasonic exams, most anomalies can be excluded. Although older screening studies have shown less than stellar identification rates for anomalies,[9] there is a detection difference between the low-risk population and the high-risk population.

Once structural anomalies or aneuploidy markers have been excluded in an SGA fetus, the chance of a common chromosome abnormality is, in most cases, not worth the risk of amniocentesis. New maternal DNA tests for fetal aneuploidy are essentially risk-free. However, these newer tests only include screening for trisomies 13, 18, and 21. Trisomy 18 and 13 can be excluded by ultrasound alone. Although an occasional trisomy 21 fetus slips through without ultrasound detection, the slightly short femur of a Trisomy 21 fetus is not enough to make the fetus officially SGA.

Infection. Occasionally IUGR can be caused by an infectious process, particularly cytomegalovirus (CMV), and, therefore, when it is unclear if the placenta is responsible for SGA, considering an infectious etiology is important. An infectious cause for SGA is considered when

there are ultrasound clues for a central nervous system abnormality, echogenic bowel, or if the clinician simply has a hunch. Under these circumstances, today's standard workup usually involves a full "TORCH titer." However, each part of the TORCH acronym represents a diagnostic long shot, other than CMV.

Management of IUGR

Only recently has it become apparent that there are two types of IUGR. The early IUGR has long been the center of investigative scrutiny. However, now it is quite clear that late IUGR is just as worthy of attention. Each has its own pathway to trouble.

Early IUGR — The Pathogenesis

Early IUGR is largely due to placental insufficiency, and the earlier the supply/demand mismatch occurs, the earlier IUGR manifests. Usually, in this condition, the placenta has fewer terminal villi, fewer villus branches, and smaller vascular lumens than an AGA placenta. With a compromised ability to deliver oxygen and essential nutrients to the fetus by the placenta, fetal growth falls off, leading to the diagnosis of SGA by routine ultrasound examination. Doppler investigation plays a primary role in the diagnosis of IUGR, as well as in the timing of delivery. Importantly, the risks of prematurity must be weighed against the risks of hostile intrauterine environment for this at-risk fetus.

The umbilical arteries. The two umbilical arteries encounter increased resistance in early IUGR, which can be assessed by the amount of flow during diastole. Although this is quantified by the distance (or ratio) between systole and diastole, for practical purposes the obstetrician only needs to know if there is low (more favorable), absent, or reversed flow during diastole (most ominous). Most investigators only evaluate one umbilical artery, but assessing both may be valuable since a discrepancy between the two arteries may represent under-perfusion in one portion of the placenta which, in turn, could foretell IUGR.

Middle cerebral artery (MCA). As a tributary of the internal carotid artery, the MCA is responsible for sending blood to the cortex, an area in the brain that the fetal circulation attempts to protect first when in a damage-control mode. Actually, the frontal lobe gets first priority, as evidenced by waveforms from the anterior cerebral artery.[10] The cortex is next in line, and, last, the cerebellum and brainstem, which are seemingly most resistant to hypoxia. The latter can be monitored by waveforms from the vertebral artery, a spoke of the subclavian artery.[11]

The MCA is sampled just after it leaves the circle of Willis. As opposed to the umbilical artery, normally there is low-end diastolic flow. However, when brain-sparing occurs, resistance is lowered and end diastolic flow rises. This results in a lowered systolic/diastolic (S/D) ratio, where actual threshold values depend on gestational age. When the MCA waveform begins to look like a normal umbilical artery waveform, autoregulation has occurred and the fetus has opened up his/her cerebral vascular bed.

Simplistically, it originally had been assumed that if the brain was "spared" by the fetus, the cortex would be protected, but, as noted below, the protection is imperfect. There is now evidence of an association between brain sparing and adverse neurobehavioral outcomes.

The cerebral/placental ratio (C/P ratio). When resistance in the umbilical artery rises (but not enough to exceed preset thresholds for gestational age) and the MCA resistance drops, the relationship between the two S/D ratios (or pulsatility indices) changes. Some have found the C/P ratio to be a more sensitive index of early compromise compared to either cerebral or placental flow separately.[12] However, while the method may single out pregnancies in need of further surveillance, changes in the C/P ratio occur too early for this indice to have a major role in delivery decision-making.

Ductus venosus (DV). This small vessel is the main conduit for the delivery of oxygenated blood to the right heart and sends this enriched blood across the foramen ovale to the left heart, giving a more direct access to the brain via the aorta. The DV waveform indirectly reflects intra-cardiac pressures, which in advanced IUGR are elevated because of increased afterload, inadequate perfusion of the coronary arteries, and decreased ventricular compliance. The DV goes through predictable waveform changes as the fetal condition worsens — first with decreased flow during atrial contraction, then absent flow, and, finally, reversed flow (a pre-demise finding). Earlier studies in severe IUGR employing percutaneous umbilical blood testing[13] have shown that abnormal DV waveforms are associated with fetal academia, which is strongly related to neurological deficit.

Summary of data shows a common sequence of events leading to perinatal death or morbidity. There have been a few studies in which severely affected early IUGR fetuses have been followed with serial Doppler evaluation.[14,15,16] In these studies, the timing of delivery had been based on non-reassuring fetal heart rate patterns alone (the standard at that time), so it was possible to follow Doppler patterns as the fetal condition worsened.

Stepwise, the first Doppler parameter to become abnormal is the umbilical artery waveform. In the mid or early third trimester, a normal umbilical artery waveform is a reasonable excluder of compromise in an SGA fetus. Decreased flow in the umbilical artery will generally occur 3 weeks or more prior to changes noted in fetal heart rate pattern — the criteria that most use for an indication for delivery.[15]

The next waveform to become abnormal is the MCA, showing an increase in end diastolic flow. This finding is quite variable in appearance and may never happen in less severely affected IUGR fetus.

The last Doppler waveform to become abnormal is the DV — first showing decreased diastolic flow, then eventually absent or reversed flow during atrial contraction. Often, this change occurs just prior to abnormal fetal heart rate changes. Turan et al have shown that the average time from absent or reverse flow during atrial contractions in the DV is 6 days until demise and 0 days for neurological morbidity.[16] Most importantly, in a study involving more than 600 IUGR pregnancies, Baschat et al showed that the best predictor of intact survival up until 29.5 weeks was gestational age, after which the DV was the best predictor.[17] In other words, the survival of infants born before 29.5 weeks is more dependent on how old they are at the time of birth, rather than on Doppler findings before birth. However, after that time DV waveforms are better at predicting survival in IUGR infants born preterm. Using another variable, biophysical profile (BPP), Baschat et al also showed an impressive relationship between beat to beat variability and fetal behavior with worsening Doppler findings, suggesting that the BPP is a useful adjunctive tool in assessing IUGR.[15]

Summary of sequential Doppler patterns in gradually worsening early IUGR:

1. Low end diastolic flow develops in the umbilical arteries.
2. C/P ratio becomes abnormal.
3. MCA shows increased flow during diastole.
4. There is absent or reversed end diastolic flow in the umbilical arteries.
5. DV shows decreased flow during atrial contraction.
6. DV show absent or reversed flow during atrial contraction.
7. Non-reassuring fetal heart rate pattern develops (this may happen at the same time as the last DV changes).

The most common dependent variables in the above studies were death or immediate severe neonatal morbidity. Turan et al have shown that DV was the most potent predictor of stillbirth, but with the other Doppler variables, gestational age correlated better with immediate outcome.[18] Regarding immediate neonatal morbidity, the DV again was the best predictor, but to asses later neurobehavioral outcome in survivors, the MCA may provide the best clues. For example, a recent study found that abnormal MCA, irrespective of other Doppler findings, impacted negatively on neurological assessment scales in preterm IUGR vs preterm AGA neonates.[19]

Late IUGR

This is defined as IUGR occurring after 34 weeks' gestation and represents a new arrival to IUGR investigation and knowledge — new, because earlier investigation strongly suggested that all placentally mediated IUGR fetuses behaved in a similar way. They don't. This is a variant of IUGR, which may be even more common than early IUGR. Late IUGR occurs when the placenta initially keeps up with fetal growth requirements throughout the early and middle portions of pregnancy, but toward the end, the fetus demands more than the placenta is capable of supplying. Consequently, the EFW falls off the normal growth curve and the AC (biometric measurement) becomes the most affected. Until recently, the umbilical artery (the first Doppler waveform to change in early IUGR) provided the warning sign as to impending IUGR. However, now there is evidence that many true late IUGR fetuses have normal umbilical artery waveforms because the problem is less about placental resistance and more about unmet fetal demand. Unfortunately, at this gestational age, the brain is vulnerable to hypoxia and recent studies show that the late IUGR fetus with normal umbilical artery waveform, but an abnormal MCA waveform, has a higher rate of neurological compromise,[20] later behavioral problems,[21] and a higher rate of nonreassuring fetal heart rate pattern in labor, often leading to an emergency cesarean section.[22] This information should get our attention — enough to obtain an MCA Doppler waveform in the SGA fetus in late pregnancy to help with the timing of delivery — irrespective of the umbilical artery findings.

The typical chain of diagnostic events occurring in late IUGR:

1. MCA shows increased EDF.
2. Umbilical arteries remain normal.
3. DV never shows decreased flow during atrial contractions.

Based on the above studies, I think that if the fetus is SGA, is over 35 weeks, and shows increased diastolic flow in the MCA, delivery should be a consideration. Why wait for the next shoe to drop? No, there have been no RCTs demonstrating the benefit of this approach in this type of patient, but we can no longer say that the IUGR fetus is successfully and adequately protecting the brain. ■

References

1. Lindqvist PG, Molin J. Does antenatal identification of small-for-gestational age fetuses significantly improve their outcome? *Ultrasound Obstet Gynecol* 2005;25:258-264.
2. Hadlock FP, et al. Sonographic estimation of fetal weight. The value of the femur length in addition to head and abdominal measurements. *Radiology* 1984;150:535-540.

3. Lee W, et al. Birth weight prediction by three-dimensional ultrasonography: Fractional limb volume. *J Ultrasound Med* 2001;20:1283-1292.
4. Hobbins JC. Fetal Biometry. In: *Obstetric Ultrasound: Artistry in Practice.* Malden, MA: Blackwell Publishing; 2008.
5. Magann EF, et al. Biophysical profile with amniotic fluid volume assessments. *Obstet Gynecol* 2004;104:5-10.
6. Campbell S, Thoms A. Ultrasound measurement of the fetal head to abdominal circumference ratio in the assessment of growth retardation. *Br J Obstet Gynaecol* 1977;84:165-174.
7. Lee W, et al. New fetal weight estimation models using fractional limb volume. *Ultrasound Obstet Gynecol* 2009;34:556-565.
8. Gardosi J, et al. Prospective evaluation of customized fetal growth charts. *Ultrasound Obstet Gynecol* 1996;4(Supl 1):96.
9. Boyd PA, et al. The evolution of prenatal screening and diagnosis and its impact on in unselected population over an 18-year period. *BJOG* 2012;119:1131-1140.
10. Cruz-Martinez R, et al. Longitudinal brain perfusion changes in near-term small-for-gestational-age fetuses as measured by spectral Doppler indices of fractional moving blood volume. *Am J Obstet Gynecol* 2010;203:42.e1-6.
11. Morales-Roselló J, Peralta-Llorens N. Doppler study of the fetal vertebral artery in small for gestational age fetuses with intrauterine growth restriction. *J Ultrasound Med* 2012;31:1003-1010.
12. Baschat AA, Gembruch U. The cerebroplacental Doppler ratio revisited. *Ultrasound Obstet Gynecol* 2003;21:124-127.
13. Rizzo G, et al. The value of fetal arterial, cardiac, and venous flows in predicting the pH and blood gases measured in umbilical blood by cordocentesis in growth retarded fetuses. *Br J Obstet Gynaecol* 1995;102:963-969.
14. Hecher K, et al. Monitoring of fetuses with intrauterine growth restriction: A longitudinal study. *Ultrasound Obstet Gynecol* 2001;18:564-570.
15. Ferrazzi E, et al. Temporal sequence of abnormal Doppler changes in the peripheral and central circulatory systems of the severely growth-restricted fetus. *Ultrasound Obstet Gynecol* 2002;19:140-146.
16. Baschat AA, et al. Sequence of changes in Doppler and biophysical parameters as fetal growth restriction worsens. *Ultrasound Obstet Gynecol* 2001;18:571-577.
17. Turan OM, et al. Duration of persistent abnormal ductus venosus flow and its impact on perinatal outcome in fetal growth restriction. *Ultrasound Obstet Gynecol* 2011;38:295-302.
18. Baschat AA, et al. Predictors of neonatal outcome in early-onset placental dysfunction. *Obstet Gynecol* 2007;109:253-261.
19. Figueras F, et al. Neurobehavioral outcomes in preterm, growth-restricted infants with and without prenatal advanced signs of brain-sparing. *Ultrasound Obstet Gynecol* 2011;38:288-294.
20. Oros D, et al. Middle versus anterior cerebral artery Doppler for the prediction of perinatal outcome and neonatal neurobehavior in term small-for-gestational-age fetuses with normal umbilical artery Doppler. *Ultrasound Obstet Gynecol* 2010;35:456-461.
21. Eixarch E, et al. Neurodevelopmental outcome in 2-year-old infants who were small-for-gestational age term fetuses with cerebral blood flow redistribution. *Ultrasound Obstet Gynecol* 2008;32:894-899.
22. Cruz-Martinez R, et al. Fetal brain Doppler to predict cesarean delivery for nonreassuring fetal status in term small-for-gestational-age fetuses. *Obstet Gynecol* 2011;117:618-626.

CME Questions

1. **The false-negative predictive value was used as the primary validation metric in the study because it:**
   a. is a substitute for specificity in node negative patients.
   b. represents the rate of node positive patient in whom the sentinel lymph node was negative.
   c. predicts the false-negative rate.
   d. considers both correctly determined node positive and node negative patients.

2. **Pregnant women in the United States were more likely to be tested for chlamydia if they were:**
   a. older age.
   b. white.
   c. younger age.
   d. college-educated.

3. **What is the most important biometric measurement in the assessment of intrauterine growth restriction (IUGR)?**
   a. Biparietal diameter
   b. Abdominal circumference
   c. Femur length
   d. Head circumference
   e. The frontal lobe

4. **When sorting out a truly small fetus from an off-on-dates fetus, the best biometric measurement is the trans-cerebellar diameter.**
   a. True
   b. False

5. **In early IUGR, which of the following is the last Doppler finding before fetal/infant demise?**
   a. Absent or reversed diastolic flow in the umbilical arteries.
   b. Decreased diastolic flow in the umbilical arteries.
   c. Middle cerebral artery showing brain sparing.
   d. Absent or reversed flow in the ductus venosus.

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Statins and Cognition — More to the Story?

In this issue: Side effects of statins; effects of cannabis use; antihypertensives and lip cancer; and FDA actions.

Review challenges FDA warning

Do statins cause changes in cognition? In February, the FDA added warnings to statin labels regarding the risk of reversible memory loss and confusion. But a new review from the *Journal of the American College of Cardiology* reviews the evidence given to the FDA and concludes "that there is no increased risk of cognitive decline" with statin use. The State-of-the-Art Paper was a comprehensive review of case reports, observational research, and randomized, controlled trials of statins and cognitive change, as well as risk of cancer and diabetes. Most of the evidence for cognitive changes came from individual case reports, many of which were self-reported by consumers to the FDA. Observational studies gave mixed results on cognition with four of nine studies showing statins improved cognition, while three showed no change, and two studies found an increased risk of cognitive impairment. The authors suggest that these studies are inconclusive and prone to selection bias. Two large, randomized, controlled clinical trials specifically looked at the effect of statins on cognitive function as the major secondary endpoint. In both, no significant differences were seen between the study and control groups with regard to cognitive decline. Twelve smaller studies showed mixed results with the majority showing no change and only one in 12 showing a detrimental effect of statins on cognitive function, while two studies showed a benefit. Along with lack of evidence to suggest statins lead to cognitive decline, the authors also found no evidence that statins increase the risk of cancer. They did, however, find a small risk for development of diabetes, which they felt was "outweighed by the cardiovascular benefits in patients for whom statin therapy is recommended" (*J Am Coll Cardiol* published online August 15, 2012). ■

Cannabis use and cognitive decline

Persistent cannabis use — particularly in adolescence — may lead to permanent cognitive decline, according to a new study. Researchers looked at a birth cohort of 1037 healthy individuals in New Zealand who underwent neuropsychological testing in the mid 1980s before the onset of cannabis use, and then again in 2010-2012 after some had developed a persistent pattern of cannabis use. Persistent cannabis use over 20 years (at least 4 days per week) was associated with neuropsychological decline, with greater decline evidence for more persistent users. This effect was only seen in adolescent-onset cannabis users and was associated with an average 8 point loss in IQ by age 38. The effect persisted after controlling for education, other drugs, or tobacco. The effects were not seen among adult-onset cannabis users. The authors conclude that increasing efforts should be directed toward delaying the onset of cannabis use by young people, "particularly given the recent trend of younger ages of cannabis use initiation in the United States and

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

evidence that fewer adolescents believe that cannabis use is associated with serious health risk." (*Proc Natl Acad Sci U S A* published online August 27, 2012). This study and others are increasingly important as cannabis, the most widely used illicit drug in the world, is being considered for more medicinal uses as well as legalization. ■

Antihypertensives and lip cancer

Two photosensitizing antihypertensives, hydrochlorothiazide and nifedipine, may increase the risk for lip cancer in non-Hispanic white patients, according to a new study from Kaiser Permanente in California. From a large cohort of patients, 712 were identified with lip cancer along with nearly 23,000 matched controls. At least a 5-year supply of the drug resulted in the following odds ratios for lip cancer (95% confidence intervals) — hydrochlorothiazide 4.22 (2.82-6.31), hydrochlorothiazide-triamterene 2.82 (1.74-4.55), nifedipine 2.50 (1.29-4.84), and lisinopril 1.42 (0.95-2.13). When atenolol was given without other hypertensives, the odds ratio for lip cancer was 0.54 (0.07-4.08). The authors suggest that while antihypertensive therapy outweighs the risk of lip cancer, preventive measures should be taken for those at increased risk because of fair skin and long-term sun exposure (*Arch Intern Med* published online August 06, 2012). ■

FDA actions

The FDA has approved a delayed-release form of prednisone for the treatment of endocrine, inflammatory, and neoplastic conditions. Delayed-release prednisone should be taken once a day with timing to be determined by the disease being treated. For example, 10 p.m. dosing is recommended for rheumatoid arthritis, as it is more effective than immediate-release prednisone taken in the morning for treating morning stiffness associated with the disease. Dosing is based on the theory that both cytokines and endogenous cortisol follow a circadian rhythm, and that dosing the drug based on the condition being treated may afford more effective treatment than immediate-release prednisone. The new product delays the release of prednisone by approximately 4 hours. Side effects are the same as short-acting prednisone. Delayed-release prednisone will be marketed as RAYOS by Horizon Pharma.

The FDA has approved a new chlorofluorocarbon (CFC)-free, over-the-counter inhaled racepinephrine product for the treatment of asthma. The new product takes the place of the banned Primatene Mist, which was taken off the market at the end of 2011 because it contained CFCs. Inhaled epinephrine has been used for the treatment of asthma for more than 100 years. Marketed as Asthmanefrin, the new product will be sold as a starter kit and refill package. The starter kit will include 10 vials of racepinephrine along with the EZ Breathe Atomizer. The refill kit will include 30 vials of the drug. The drug is not without controversy, however, with many asthma experts feeling that the side effects of epinephrine are serious and well-documented, and over-the-counter use goes against published guidelines for treating asthma. Asthmanefrin will be marketed by Nephron Pharmaceuticals.

The FDA has approved linaclotide for the treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation. The drug is the first guanylate cyclase (GC-C) agonist that acts locally in the gut with minimal systemic exposure. The drug is taken once daily on an empty stomach at least 30 minutes before the first meal of the day. Safety and efficacy in the management of irritable bowel syndrome with constipation was established in two double-blind studies of nearly 1300 patients who were randomly assigned to linaclotide or placebo for 12 weeks. Patients taking the drug experienced more complete spontaneous bowel movements than those taking placebo. The drug should not be used in patients 17 years or younger. Linaclotide will be jointly marketed by Ironwood Pharmaceuticals and Forest Pharmaceuticals as Linzess.

Montelukast (Singulair), Merck's popular asthma and allergy medication, will soon be available as a generic. The leukotriene receptor antagonist will be manufactured by 10 generic companies in tablet form, oral granules, and chewable tablets. The FDA warns that montelukast should not be used for relief of sudden asthma attacks and further warns that patients should contact a clinic immediately if they are experiencing behavior and mood-related changes such as aggression, depression, or hallucinations.

The FDA has approved the first generic version of pioglitazone (Actos). The drug is approved along with diet and exercise to improve blood sugar control in adults with type 2 diabetes. This happens as thiazolidinediones have generally fallen out of favor for use in type 2 diabetes due to side effects including worsening heart failure and edema. The FDA also recently issued a warning for pioglitazone regarding increased risk of bladder cancer if the drug is taken for more than 1 year. The first generic pioglitazone will be manufactured by Mylan Pharmaceuticals. ■