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Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

Does Childhood Adversity Affect the Menopausal Transition?

By Chiara Ghetti, MD

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

SYNOPSIS: The number and timing of adverse childhood experiences in relation to puberty affect the risk of incident major depressive disorder in the menopausal transition.

SOURCE: Epperson CN, et al. Adverse childhood experiences and risk for first-episode major depression during the menopause transition. *J Clin Psychiatry* 2017;78:e298-e307.

The objective of this study was to determine the effect of early-life stress on the risk of having a first episode of major depressive disorder (MDD) during the menopause transition (incident depression) among participants in the Penn Ovarian Aging Study (POAS). In addition, the study authors explored whether the timing of adverse childhood experiences (ACEs) in relationship to puberty affects the risk of lifetime MDD and incident MDD at time of the menopausal transition. This was a cohort study of the POAS cohort, which is a population-based longitudinal cohort of cycling premenopausal women between the ages of 35 and 47 years. The cohort initially was identified by random-digit dialing in Philadelphia County, Penn., in 1996-1997, and was stratified to obtain equal numbers of white and African-American women. Exclusion criteria included hysterectomy, the use of hormonal contraception or psychotropic medication, the presence of a serious health problem, or alcohol or drug abuse in the previous year. The initial cohort consisted of 436 women. The current study is the analysis of 293 women who remained active in the cohort between June 2012 and August 2012. The main outcomes included: menopausal status obtained by menstrual diaries; ACE, measured using the ACE-Q questionnaire; and history of major depression diagnosis and depressive symptoms, as measured by Center for Epidemiologic Studies Depression (CES-D) scale scores.

The ACE-Q focuses on three general categories of childhood adversity (abuse, neglect, and household/family dysfunction), which are broken down into subcategories that include physical, sexual, and emotional abuse;

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emotional and physical neglect; parental separation; household violence; parental substance abuse or psychiatric disorders; and household member in prison. A CES-D score of ≥ 16 corresponds to a clinically meaningful level of depressive symptoms, while a score of ≥ 25 is suggestive of a clinical diagnosis of MDD.

Of the women active in the POAS in the cohort, 243 had completed ACE-Q data. The mean age of these women was 41.6 years, and 47% were African American with the remainder Caucasian. Forty percent of women had not experienced an ACE, 22% had experienced one ACE, and 38% had experienced two or more ACEs. Most ACEs occurred in the prepubertal window. Groups with high vs. low ACEs differed by race, with African-American women more likely to be in the high ACE group. Women with two or more postpubertal ACEs were significantly more likely to have baseline CES-D scores ≥ 16 or ≥ 25 and body mass index (BMI) ≥ 30 kg/m^2. Of the women at risk for incident menopause MDD, 22.4% were diagnosed with MDD during premenopause, while 20.7% had incident menopause MDD. In logistic regression models adjusted for race, smoking, BMI ≥ 30 kg/m^2, and employment status, subjects with two or more ACEs, compared to subjects with no ACE, were two times more likely to experience a lifetime MDD and incident menopause MDD. Women with ≥ 2 postpubertal ACEs were at greater risk of incident menopause MDD but not lifetime MDD when compared to those with no postpubertal ACEs. Women who reported one ACE had significantly reduced MDD risk compared to women who reported two or more ACEs.

■ COMMENTARY

Major depression is very prevalent and is a major cause for disability. The World Health Organization has ranked depression the fourth leading cause of disability worldwide and has estimated that it will be the second leading cause by 2020.[1,2] Lifetime prevalence estimates vary worldwide and are estimated to be 16.9% but are as high as 21% in the United States.[1,2,3] Women are at higher risk for MDD and are more susceptible during certain reproductive milestones. As obstetricians, we may be most familiar with postpartum depression. However, depression also is common in young women and in women during the menopausal transition. Women with no prior history of depression are two to three times more likely to experience a first episode of depression during perimenopause and early menopause.[4,5]

Although a role of childhood adversity has been established in mood disorders, this is the first study examining the role of childhood adversity and the onset of MDD during the menopausal transition.

Chapman et al found that the exposure to ACEs was associated with an increased risk of adult depressive disorders and established the role of childhood adversity in major depression.[6] In their study, the most commonly reported adverse experiences were household substance, physical, and sexual abuse, with emotional abuse posing the largest risk for lifetime or recent depression among women. Limitations include the inability to provide more details about specific ACEs. This study has some data points that may be influenced by recall bias. In addition, this authors were not able to explore the relationships between depression, ACE, and hormone therapy.

Epperson et al built on prior work and established a link between childhood adversity and increased risk of depression in women experiencing the menopausal transition decades after the ACEs. This provides another window into the relationship of depression, stress, and hormonal fluctuations. Although they did not discuss the clinical management of depression, the discussion further underscores the lasting effect of childhood trauma and its role in adult depression even during the menopausal transition.[7,8,9] As clinicians, awareness of the relationship between trauma and depression may aid us to better care for women with depression throughout the lifespan. ■

REFERENCES

1. Kessler RC, Bromet EJ. The epidemiology of depression across cultures. *Ann Rev Public Health* 2013;34:119-138.
2. Whiteford HA, et al. Global burden of disease attributable to mental and substance use disorders: Findings from the Global Burden of Disease Study 2010. *Lancet* 2013;382:1575-1586.
3. Kessler RC, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994;51:8-19.
4. Bromberger JT, et al. Major depression during and after the menopausal transition: Study of Women's Health Across the Nation (SWAN). *Psychol Med* 2011;41:1879-1888.
5. Cohen LS, et al. Risk for new onset of depression during the menopausal transition: The Harvard study of moods and cycles. *Arch Gen Psychiatry* 2006;63: 385-390.
6. Chapman DP, et al. Adverse childhood experiences and the risk of depressive disorders in adulthood. *J Affect Disord* 2004;82:217-225.

7. Schussler-Fiorenza Rose SM, et al. Adverse childhood experiences and disability in U.S. adults. *PM R* 2014;6:670-680.
8. Cheong EV, et al. Adverse childhood experiences (ACEs) and later-life depression: Perceived social support as a potential protective factor. *BMJ Open* 2017;7:e013228.
9. Brinker J, Cheruvu VK. Social and emotional support as a protective factor against current depression among individuals with adverse childhood experiences. *Prev Med Rep* 2016;5:127-133.

ABSTRACT & COMMENTARY

An Arcuate Uterus (Apparently) Does Not Impair Fertility

By Robert W. Rebar, MD

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

SYNOPSIS: No decreases in implantation rates and live birth rates were present in a retrospective study from a single fertility center examining outcomes of in vitro fertilization in women with an arcuate uterus.

SOURCE: Surrey ES, et al. The arcuate uterus: Is there an impact on in vitro fertilization outcomes after euploid embryo transfer? *Fertil Steril* 2018;109:638-643.

The arcuate uterus is one of the most common congenital uterine anomalies. Although, generally, it is believed that the arcuate uterus does not affect fertility, data are scanty and conflicting. Confusing the issue even more is the fact that there is no standardized definition for an arcuate uterus. Despite these difficulties, investigators at a single in vitro fertilization (IVF) center conducted a retrospective review of consecutive patients undergoing IVF and comprehensive chromosomal screening (CCS), with subsequent transfer of thawed euploid embryos in a later artificial menstrual cycle during the 2014 calendar year, to examine the effect of an arcuate uterus on implantation and live birth rates. They chose to include only individual patients undergoing CCS to control for the possible confounding variable of embryo aneuploidy. In addition, as part of their evaluation, all patients underwent three-dimensional ultrasound examination and office flexible hysteroscopy performed in the early follicular phase. An arcuate uterus was defined as existing when the myometrium extended perpendicularly below an interstitial line connecting the cornua on ultrasound by 4 to 10 mm with a myometrial angle > 90 degrees and was confirmed by hysteroscopy. This definition was based on a recent practice committee guideline from the American Society for Reproductive Medicine (ASRM).[1]

Eighty-three transfer cycles were performed in 78 patients with an arcuate uterus, and 378 transfer cycles were performed in 354 women with a normal uterine cavity. In the women with an arcuate uterus, the mean depth of the fundal indentation was 5.43 ± 1.81 mm (standard deviation), with a range of 4 mm to 9.5 mm. The two groups did not differ regarding age or follicular reserve as assessed by anti-Müllerian hormone levels, follicle-stimulating hormone levels on cycle day 3, or antral follicle count. Similarly, there were no differences in numbers of blastocysts biopsied, percentage of euploid embryos (~59%), or numbers of euploid embryos transferred (~1.5 per transfer). There were no differences in outcomes either. The live-birth rate (defined as the number of live births > 26 gestational weeks per embryo transfer procedure) was 68.7% in women with an arcuate uterus and 68.7% in those with a normal uterus. The implantation rate (defined as the number of gestational sacs with ultrasound evidence of cardiac activity per number of embryos transferred) was 63.7% in women with an arcuate uterus and 65.4% in the control group (normal uterus). Spontaneous miscarriages after ultrasound visualization of a gestational sac also did not differ between the two groups (4.8% vs. 4.3%).

■ COMMENTARY

Although far from perfect, these are perhaps the best data yet suggesting that the presence of an arcuate uterus should be treated as an incidental finding without any effect on fertility, miscarriage rates, or the outcomes of pregnancy. One editorialist noted several reasons to question the findings.[2] The women in this study had mild anomalies, even with the definition of the arcuate uterus used. The patients were highly selected, being infertile and undergoing IVF. The method of defining an arcuate uterus by ultrasound required skill on the part of the examiners, and there is no real way to confirm the presence of an arcuate uterus by office hysteroscopy. Still, the findings agree with many but not all studies examining outcomes in women with an arcuate uterus.

The difficulty rests in distinguishing an arcuate from a septate uterus. The ASRM practice guideline defined a septate uterus as one with an acute angle of < 90 degrees at the central point of the septum (to differentiate from the obtuse angle of > 90 degrees seen with an arcuate configuration) and with the length of the septum > 1.5 cm. The guideline left undefined those individuals with a

septum extending perpendicularly from a line between the cornua that is > 1.0 cm and < 1.5 cm in length. It is just this ambiguity that confuses the literature. As noted within the guideline, the septate uterus has been associated with increases in the risks of miscarriage, premature delivery, and malpresentation, but there is insufficient evidence to associate a septum with infertility.[2] Variations in definitions distinguishing arcuate from septate uteri may well account for some studies, such as one meta-analysis reporting that arcuate uteri are associated with increased incidences of both second trimester loss (pooled risk ratio, 2.39) and fetal malpresentation at delivery (pooled risk ratio, 2.53).[3]

We all recognize that uterine anomalies constitute a spectrum of disorders extending from the normal to the arcuate to the septate and finally to the bicornuate uterus and uterus didelphys. Surrey et al demonstrated that minor abnormalities indeed are trivial and are unlikely to affect fertility and the outcomes of any resulting pregnancies. We must await further studies using three-dimensional ultrasound and MRI to define just when a uterine anomaly becomes clinically significant. Even then, it may well be that there is no sharp limit separating uterine malformations that affect fertility and pregnancy and those that do not. However, it is clear that surgical correction of all uterine malformations is not required. ■

REFERENCES

1. Practice Committee of the American Society for Reproductive Medicine. Uterine septum: A guideline. *Fertil Steril* 2016;106:530-540.
2. Donnez J. Arcuate uterus: A legitimate pathological entity? *Fertil Steril* 2018;109:610.
3. Chan Y, et al. Reproductive uterine outcomes in women with congenital uterine anomalies: A systemic review. *Ultrasound Obstet Gynecol* 2011;38:371-382.

ABSTRACT & COMMENTARY

Ovarian Function: Use It or Lose It

By Jeffrey T. Jensen, MD, MPH

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Dr. Jensen reports he is a consultant for and receives grant/research support from Bayer, Merck, ContraMed, and FHI360; receives grant/research support from Abbvie, HRA Pharma, Medicines 360, and CONRAD; and is a consultant for the Population Council.

SYNOPSIS: A larger epidemiologic study from Norway found no association between early menarche and age of menopause. Women with early menarche experience a longer fertility window, which may increase certain risks.

SOURCE: Bjelland EK, et al. The relation of age at menarche with age at natural menopause: A population study of 336 788 women in Norway. *Hum Reprod* 2018;33:1149-1157.

Age at menarche and menopause may influence a variety of health outcomes, including fertility and cancer. Bjelland and colleagues used the BreastScreen Norway cohort to determine if the age of menarche predicted the age of natural menopause and the reproductive period (duration of fertility). The Cancer Registry of Norway administers the BreastScreen Norway program, enrolling women 50 to 69 years of age into a screening program that includes biannual mammograms. More than 75% of eligible women participate in the program. During 2006-2014, enrolled women also received questionnaires about health history and current lifestyle as part of the screening program. The mean age at screening of this cohort was 57 years. A total of 392,238 women completed the questionnaire, and 336,788 provided information on age of menarche. Of these, 220,779 had undergone a natural menopause. The authors estimated the associations of age at menarche and reproductive period (in years) with menopause as crude hazard ratios with 95% confidence interval by applying Cox proportional hazard models and adjusted the data for year of birth. Then they adjusted for smoking, body mass index (BMI), and hormonal therapies.

The median ages at menarche and menopause in the study cohort were 13 and 51 years. Compared to those women with menarche at age ≤ 13 years, women who reported menarche at age ≥ 16 years reported onset of menopause one year later (e.g., 52 vs. 51 years). Overall, age at menarche was not associated linearly with age at menopause, and the absolute difference in mean age at menopause between any menarche age group did not exceed one year. Use of menopausal hormone therapy did not change the results. However, smoking reduced the median age at menopause by two years (50 vs. 52 years), and women with a BMI < 25 kg/m^2 were one year younger at menopause (51 years) than women with BMI ≥ 25 kg/m^2 (52 years).

Overall, the median duration of the reproductive period was 38 years (interquartile range, 35 to 41 years). The later menarche occurred, the shorter the median reproductive period — a decrease by one year for every one-year increase in age at menarche. This longer reproductive period of women with early menarche has bearing on contraceptive decisions, as well as health conditions influenced by hormonal exposure.

■ COMMENTARY

Our patients frequently request that we predict the future. In obstetrics, we can confidently predict that pregnancy will end around 38 weeks following conception. For menopause, 51 to 52 years of age provides another benchmark. The devil is always in the details for individuals, as these represent median values and not guarantees. All the recent advances in medical informatics have not yielded the crystal ball or retrospectoscope. For this reason, large population-based surveys continue to add value as we seek to improve the precision of our estimates.

This large cross-sectional survey from Norway provides additional information regarding the reproductive lifespan, at least for women of Northern European ancestry. The cohort included only a small number of women born outside Norway: 1.4% born in Asia and 0.2% in Africa. While this should make us question generalizability, other studies have shown similar results. Dorjgochoo and colleagues analyzed data from the Shanghai Women's Health Study, a prospective cohort study designed to investigate associations of diet and lifestyle with chronic diseases.[1] Chinese women reported menopause at an earlier age (mean, 49.2 years).

Although the authors reported a significant trend of later menopause associated with late menarche, the absolute differences were not clinically important: a four-month difference for menarche at ≤ 11 years of age compared to ≥ 16 years of age. Similar to the Norwegian study, they did see a significant reduction in the reproductive span of over five years for women in the latest menarche group compared to the youngest. Results from 64,500 U.S. women aged 21 to 69 years who participated in the Black Women's Health Study provide comparator data for an African-American population: mean (49.6) and median (50) age of menopause and no difference in onset with age of menarche.[2]

These results should not surprise us. Primordial germ cells end mitotic activity early in fetal life, reaching 6-7 million oogonia by 16-20 weeks. Beginning at 11-12 weeks, oogonia begin to undergo meiosis, become arrested at prophase I, and become primary oocytes. Over the next 20 weeks, the number of oocytes declines precipitously, such that about 500,000 to 2 million are present at birth. Loss of oocytes continues unchecked through childhood, with fewer than 300,000 to 500,000 remaining by the onset of puberty. At this point, gonadotropins contribute to the maturation of a pool of small antral follicles sensitive to follicle-stimulating hormone, and a complex feedback system results in selection and ovulation of a single dominate follicle. The rest of these developing follicles undergo apoptosis. Ovarian stimulation protocols can promote maturation of more than one of these follicles. Hormonal contraception can prevent maturation of any of them. But the vast majority continue down an apoptotic path at a highly predictable rate. Among populations of women, the math is the same. Menopause will occur between 49 and 52 years of age, and fertility declines years before this.

Women face complex decisions to balance fertility and career. Modern societies must do everything possible to make these decisions easier. Providing highly effective reversible options for contraception allows women to enjoy intimate relationships and delay childbearing. But our obligation as women's health providers includes a responsibility to provide a check in about fertility aspirations. We don't have a strategy to prevent ovarian aging. You use it, or you lose it. ■

REFERENCES

1. Dorjgochoo T, et al. Dietary and lifestyle predictors of age at natural menopause and reproductive span in the Shanghai Women's Health Study. *Menopause* 2008;15:924-933.
2. Palmer JR, et al. Onset of natural menopause in African American women. *Am J Public Health* 2003;93:299-306.

SPECIAL FEATURE

Management of IUGR: Revisited

By John C. Hobbins, MD

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

In 2012, a special feature was devoted to the management of intrauterine growth restriction (IUGR). Since then, enough enlightening information has surfaced to necessitate our covering the topic again — with a few new twists. Most obstetric clinicians deal with IUGR on an almost daily basis, and since it can end with serious consequences for the affected fetus/child, it needs to be managed in a comprehensive way. Fetuses who are under-grown are subject to higher rates of perinatal mortality,[1] immediate neonatal morbidity,[2] and increased risks of later cardiovascular disease[3] and neurodevelopmental abnormalities.[4]

DIAGNOSING AN SGA FETUS

Small for gestational age (SGA) is defined as a fetus whose estimated fetal weight (EFW) is less than the 10th percentile or abdominal circumference (AC) is below the fifth percentile. Among the many formulas in the literature, the most commonly used is the Hadlock formula, which incorporates the head circumference, biparietal diameter, femur length, and AC.[5] Through the years, this has been a serviceable method to assess fetal weight, but it is fraught with some inaccuracies. The AC is easier to acquire, and it adds the dimension of fetal deprivation because growth-restricted fetuses have smaller livers and less subcutaneous

fat. Three-dimensional (3D) formulas for EFW enhance the predictability, but these formulas can be cumbersome and most require the addition of 3D thigh volumes.[6]

Once an EFW is calculated, it is plotted into nomograms based on gestational age. Here, the choices expand. The usual fire-up nomogram in ultrasound machines is the Hadlock curve,[7] based on 372 mostly Caucasians from Texas. Other curves include a National Institute of Child Health and Human Development nomogram,[8] constructed from four ethnic populations in the United States; the INTERGROWTH-21st Fetal Growth Standards Curve, which was based on World Health Organization data from eight countries;[9] or homegrown formulas based on local populations. In vogue are curves that are based on maternal height, weight, sex, parity, and ethnicity and are customized to fit individual fetuses.[10] Customized formulas are better at predicting perinatal outcome, such as preterm birth, need for emergency cesarean delivery, and newborn special care admissions.[11]

Interestingly, some researchers have questioned the benefit of the newer growth standard approaches, such as the INTERGROWTH-21 formula, when compared with the standard Hadlock formula.[12] Although customized formulas are better at predicting short-term outcome, my preference is to deal with a method that leans toward over-predicting EFW < 10th percentile, since the false positives may include some deprived fetuses in the lower quartile who, while avoiding immediate perinatal morbidity, may be destined for neonatal or childhood morbidity.[13]

POTENTIAL FOR FETAL COMPROMISE

Once the fetus is determined to be SGA, the next step has been to sort out the "constitutionally" small fetus from the growth-restricted (IUGR) one. This has been done by various Doppler and biomechanical methods. Many consider a fetus whose EFW is below the third percentile or whose mother had an abnormal uterine artery waveform earlier in pregnancy to have IUGR. There are two types of IUGR. The "early" variant usually is associated with severe growth restriction, often in patients with histories of stillbirth, preeclampsia, hypertension, previous IUGR, and in smokers. In these pregnancies, fetal growth falls off as early as 20 weeks and femur length can be curtailed almost as much as the AC, the latter always the first to be affected by intrauterine deprivation. Late IUGR usually becomes apparent after the 32nd week of gestation. The AC may be the only biometric measurement affected significantly, and these fetuses may show no sign of compromise until after 34 to 35 weeks, when the first Doppler sign is brain sparing. These babies generally are not at risk for stillbirth or severe neonatal morbidity, but often they tolerate labor poorly[14] and can develop neurodevelopmental abnormalities in childhood[15] and cardiovascular disease that can extend into adulthood.[16]

SURVEILLANCE OF IUGR

Once a fetus has EFW below the 10th percentile, a variety of Doppler waveform analyses have been used to assess fetal condition. Data from recent studies have allowed a more enlightened approach to their place and worth in a diagnostic panel.

Umbilical Artery (UA) Doppler. The UAs reflect the richness of the placental circulation and often are the first sign of compromise in early IUGR when resistance is encountered from inadequate villus development, especially the terminal villi, and/or infarction. Absent/reversed end-diastolic flow is a sign of severe placental insufficiency and often is preceded by a sequential decrease in end-diastolic flow, resulting in an upward trend in the systolic to diastolic (S/D) ratio or pulsatility index (PI). Alone, UA results are not an indicator for interruption of pregnancy, but an increase in PI will alert the clinician to a placental problem to which fetuses may or may not be able to adapt.

Middle Cerebral Artery (MCA) Doppler. In contrast to the UA, the MCA reflects a fetal attempt to adapt to relative hypoxia caused by a supply line problem. "Brain sparing" occurs when increased flow is directed to the brain because of vasodilation in arteries like the MCA and is triggered by a drop in the fetal pO_2. Doppler waveforms in the MCA usually show high resistance, but in IUGR the end-diastolic flow rises, resulting in a decrease in the S/D ratio and PI. In late IUGR, this may be the only sign of early fetal compromise and, even when isolated, has been associated with later neurodevelopmental problems.[4]

Cerebral placental ratio (CPR). This simply represents a ratio between the MCA and UA PIs. As fetal condition worsens, PIs move toward each other, and when the CPR approaches 1.0, there can be a cause for concern. CPRs below 1.08 or those plotted below the 10th percentile have been associated with higher rates of emergency cesarean delivery,[17] combined neonatal morbidity,[18] NICU admissions,[19] and compromised neonatal acid-base status.[20] Although this method appears to provide the best insight regarding fetal condition in IUGR, its value is enhanced when combined with the other tests described here.

Doppler of the Ductus Venosus (DV). The DV brings oxygenated blood from the umbilical vein to the right atrium and across the foramen ovale to the left atrium, the left ventricle, and then through the aorta to the brain. In the later stages of IUGR, the fetus attempts to adapt to hypoxia by shutting down the right lobe of the liver, thus directing more flow through the DV. Here, the oxygenated blood encounters more competition for entry into the right atrium from blood returning from the "spared" brain via the superior vena cava. What matters most is the ability of the fetal heart (which often is dysfunctional) to handle the increased preload. The waveform gradually will show a decrease in flow during atrial contraction (reflected by the a wave) when the fetus is severely compromised. When the a wave approaches zero, or dips below it, the fetus is in a pre-demise state. One study showed about a six-day average lag time between absent/reversed (A/R) flow during atrial contraction and fetal demise.[21] Longitudinal studies showed that in early IUGR, the DV becomes abnormal before the standard non-stress test becomes nonreactive.[22] The well-cited Trial of Randomized Umbilical and Fetal Flow in

Europe (TRUFFLE) study involved longitudinal surveillance of severely growth-restricted fetuses between 26 and 32 weeks of gestation. Delivery prior to 32 weeks was based on either abnormal fetal heart rate patterns (by computerized cardiotocography), early DV changes, or A/R DV flow. Two-year follow-up of live births showed that waiting to interrupt pregnancy based only on the latter finding prior to 32 weeks resulted in the best outcome.[23] In our experience, the DV never is affected in late IUGR.

Uterine Artery. Despite debate over the years, studies have shown uterine artery to be useful in predicting IUGR and preeclampsia, especially when combined in a screening strategy consisting of maternal historical factors and various biological markers. Since studies show a three- to nine-fold increased risk for IUGR with abnormal second trimester uterine artery wave forms,[24] some authors have advocated their use for screening high-risk patients (for IUGR) to fashion a timeline for surveillance studies. However, no existing guidelines in the literature include serial testing.

Fetal Cardiac Function. Since IUGR fetuses are prone to later cardiovascular dysfunction in childhood[3] and adulthood,[16] investigators have begun to study cardiac function in this condition using newer screening tests and more sophisticated techniques to evaluate myocardial contractility. Epigenetic influences during the intrauterine life of some IUGR fetuses render their cardiomyocytes particularly vulnerable to increased afterload in early growth restriction or relative hypoxia in late pregnancy. This results in a remodeling process that adversely affects systolic and diastolic function. Unfortunately, this can last throughout the lifespan of that individual. One of the earliest signs of cardiac dysfunction is a ballooning of the lateral ventricular walls, resulting in a more globular-shaped heart and general cardiac enlargement. Researchers have found assessments of cardiac area and global sphericity index to be useful screening tests.[25,26,27] Our group has found a majority of IUGR fetuses to have one or more parameters of cardiac dysfunction,[28] and since there has been no correlation between these abnormalities and standard Doppler results, there is a strong suggestion that cardiac dysfunction occurs in parallel with Doppler changes. Ongoing studies should allow a better understanding of the role of cardiac function studies in the management of IUGR. However, the potential to identify vulnerable fetuses may allow cardiovascular problems to be averted through preemptive dietetic and other measures in early childhood.[29,30]

SUGGESTIONS FOR MANAGING IUGR

Management guidelines from official bodies often are slow to surface while the authors await the results of randomized trials to make sure that their recommendations are "evidence based." The following suggestions/opinions from this clinician are based on currently available meta-analyses, randomized, clinical trials, observational studies, and 50 years' worth of experience dealing with this vexing problem. If a fetus has either an EFW < 10th percentile or an AC below the fifth percentile, a first visit encounter should include Doppler waveform analysis of: 1) UA; 2) MCA; 3) CPR; and 4) uterine artery, which can be helpful. If Doppler studies are normal, there are no maternal preconditions for IUGR, and the EFW above the third percentile, the patient can return in three to four weeks. Between visits, the patient may begin fetal kick counts. Those with any Doppler measurements outside the normal range or with an EFW below the third percentile should return in two weeks for 1) UA; 2) MCA; 3) CPR; 4) repeat the AC; and 5) non-stress test/biophysical profile. If more than one Doppler finding is abnormal or there is no increase in AC, the DV should be added to the regimen and the patient should be seen at weekly intervals for all the above evaluations. EFW should be added to the protocol every three weeks.

SUGGESTIONS FOR DELIVERY IN IUGR

1. Not before 28 weeks in early IUGR, even if Doppler studies (including absent or reverse flow in the DV) are abnormal, since studies have suggested that prematurity under these circumstances is worse for the fetus than hypoxia associated with abnormal Doppler or non-stress test findings. Nevertheless, there can be mitigating circumstances, and this becomes a judgment call.
2. At 29 to 31 weeks if A/R flow in the DV.
3. At 32 to 34 weeks if weekly abnormal CPRs drop by > 20%.
4. At 34 to 36 weeks if any CPR value is abnormal (it is realized that this opinion is debatable).
5. At 37 to 39 weeks if any variable is abnormal or EFW below the third percentile.
6. At 39 weeks for all SGA fetuses. ■

REFERENCES

1. Caradeux J, et al. Risk of fetal death in growth-restricted fetuses with umbilical and/or ductus venosus absent or reversed end-diastolic velocities before 34 weeks of gestation: A systematic review and meta-analysis. *Am J Obstet Gynecol* 2018;218:S774-S782.e21.
2. Khalil AA, et al. The association between fetal Doppler and admission to neonatal unit at term. *Am J Obstet Gynecol* 2015;213:57.e1-7.
3. Cruz-Lemini M, et al. Fetal cardiovascular remodeling persists at 6 months in infants with intrauterine growth restriction. *Ultrasound Obstet Gynecol* 2016;48:349-356.
4. 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.
5. Hadlock FP, et al. Estimating fetal age: Computer-assisted analysis of multiple fetal growth parameters. *Radiology* 1984;152:497-501.
6. Lee W, et al. New fetal weight estimation models using fractional limb volume. *Ultrasound Obstet Gynecol* 2009;34:556-565.
7. Hadlock FP, et al. Estimation of fetal weight with the use of head, body, and femur measurements — a prospective study. *Am J Obstet Gynecol* 1985;151:333-337.
8. Buck Louis GM, et al. Racial/ethnic standards for fetal growth: The NICHD Fetal Growth Studies. *Am J Obstet Gynecol* 2015;213:449.
9. Papageorghiou AT, et al. International standards for fetal growth based on serial ultrasound measurements: The Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. *Lancet* 2014;384: 869-879.
10. Gardosi J, Francis A. A customized standard to assess fetal growth in a US population. *Am J Obstet Gynecol* 2009;201:25.e1-7.
11. Chiossi G, et al. Customized vs population-based growth charts to

identify neonates at risk of adverse outcomes: Systematic review and Bayesian meta-analysis of observational studies. *Ultrasound Obstet Gynecol* 2017;50:156-166.
12. Nwabuobi C, et al. INTERGROWTH-21st and Hadlock growth standards to predict neonatal small for gestational age and short-term neonatal outcomes. SMFM abstract. *Am J Obstet Gynecol* 2018; January supplement, S310.
13. MacDonald TM, et al. Reduced growth velocity across the third trimester is associated with placental insufficiency in fetuses born at a normal birth weight: A prospective cohort study. *BMC Med* 2017;15:164.
14. Cruz-Martinez R, et al. Brain Doppler to predict cesarean delivery for nonreassuring fetal status in term SGA fetuses. *Obstet Gynecol* 2011;117:618-626.
15. Cruz-Martinez R, et al. Cerebral blood perfusion and neurobehavioral performance in full-term small-for-gestational-age fetuses. *Am J Obstet Gynecol* 2009;201:474.e1-7.
16. Barker DJP, et al. Weight in infancy and death from ischemic heart disease. *Lancet* 1989;2:577-580.
17. Prior T, et al. Prediction of fetal compromise in labor. *Obstet Gynecol* 2014;123:1263-1271.
18. Bakalis S, et al. Umbilical and fetal middle cerebral artery Doppler at 30-34 weeks' gestation in the prediction of adverse perinatal outcome. *Ultrasound Obstet Gynecol* 2015;45:409-420.
19. Khalil AA, et al. Is fetal cerebroplacental ratio an independent predictor of intrapartum fetal compromise and neonatal unit admission? *Am J Obstet Gynecol* 2015;213:54.e1–10.
20. Morales-Rosello J, et al. Poor neonatal acid-base status in term fetuses with low cerebroplacental ratio. *Ultrasound Obstet Gynecol* 2015;45:156-161.
21. Lees CC, et al. 2 year neurodevelopmental and intermediate perinatal outcomes in infants with very preterm fetal growth restriction (TRUFFLE): A randomized trial. *Lancet* 2015;385:2162-2172.
22. Turan OM, et al. Duration of persistent abnormal ductus venosus flow and its impact on perinatal outcome and fetal growth restriction. *Ultrasound Obstet Gynecol* 2011;38:295-302.
23. Ferrazzi E, et al. Temporal sequence of abnormal Doppler changes in the peripheral and central circulatory system of the severely growth restricted fetus. *Ultrasound Obstet Gynecol* 2002;19:140-146.
24. Cnossen JS, et al. Use of uterine artery Doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: A systematic review and bivariable meta-analysis. *CMAJ* 2008;178:701-711.
25. Rodríguez-López M, et al. Descriptive analysis of different phenotypes of cardiac remodeling in fetal growth restriction. *Ultrasound Obstet Gynecol* 2017;50:207-214.
26. DeVore GR, et al. Abnormal fetal findings associated with a global sphericity index of the 4-chamber view below the 5th centile. *J Ultrasound Med* 2017;36:2309-2318.
27. DeVore GR, et al. Area of the fetal heart four-chamber view: A practical screening tool to improve detection of cardiac abnormalities in a low-risk population. *Prenat Diagn* 2017;37:151-155.
28. Hobbins JC, et al. Measurements of cardiac shape and size in the four-chamber view of fetuses with intrauterine growth restriction: Correlation with Doppler waveforms from the umbilical and middle cerebral arteries. Manuscript submitted.
29. Vickers MH, et al. Neonatal leptin treatment reverses developmental programming. *Endocrinology* 2005;146:4211-4216.
30. Rodriguez-Lopez M, et al. Influence of breastfeeding and postnatal nutrition on cardiovascular remodeling induced by fetal growth restriction. *Pediatr Res* 2016;79:100-106.

CME/CE QUESTIONS

1. **Based on the study by Epperson et al, which of the following is true about depression during the menopausal transition?**
   a. It is not common.
   b. It is not related to adverse childhood experiences (ACE).
   c. It is more likely in the setting of two or more ACEs.
   d. It is as likely in women with one ACE as in women with two or more ACEs.
2. **Which of the following best predicts the age of onset of menopause?**
   a. Women with early onset of menarche (< 11 years of age) tend to have early menopause.
   b. Women with early menarche tend to have late menopause.
   c. Women with late menarche tend to have early menopause.
   d. Age of menarche is not related to age of menopause.
3. **Which of the following statements is *false* about umbilical artery waveforms?**
   a. Umbilical artery waveforms reflect the lushness of the placental circulation.
   b. Umbilical artery waveforms often are the first to be abnormal in early IUGR.
   c. Umbilical artery waveforms always are affected in late IUGR.
   d. Umbilical artery waveforms are not part of the fetal adaptive process in IUGR.

[IN FUTURE ISSUES]

Is Human Placentophagy Safe? What Patients Should Know