OBSTETRICS

These experts discuss the practical clinical implications of new society recommendations for antenatal steroid administration, low-dose aspirin for preeclampsia prevention, chromosomal microarray analysis, and Zika virus infection and pregnancy

Jaimey M. Pauli, MD
Dr. Pauli is Associate Professor, Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Penn State University College of Medicine, and Attending Perinatologist at the Milton S. Hersey Medical Center in Hershey, Pennsylvania.

John T. Repke, MD
Dr. Repke is University Professor and Chairman, Department of Obstetrics and Gynecology, Penn State University College of Medicine, and Obstetrician-Gynecologist-In-Chief, The Milton S. Hershey Medical Center, Hershey, Pennsylvania. Dr. Repke serves on the OBG MANAGEMENT Board of Editors.

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IN THIS ARTICLE

In this Update we discuss several exciting new recommendations for preventive treatments in pregnancy and prenatal diagnostic tests. Our A-to-Z coverage includes:

- antenatal steroids in late preterm pregnancy
- expanded list of high-risk conditions warranting low-dose aspirin for preeclampsia prevention
- chromosomal microarray analysis versus karyotype for specific clinical situations
- Zika virus infection evolving information.

New recommendation offered for timing of late preterm antenatal steroids

Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al; for the NICHD Maternal-Fetal Medicine Units Network. Antenatal betamethasone for women at risk for late preterm delivery. N Engl J Med. 2016;374(14):1311–1320.

American College of Obstetricians and Gynecologists. Committee Opinion No. 677. Antenatal corticosteroid therapy for fetal maturation. Obstet Gynecol. 2016;128(4):e187–e194.

Kamath-Rayne BD, Rozance PJ, Goldenberg RL, Jobe AH. Antenatal corticosteroids beyond 34 weeks gestation: what do we do now? Am J Obstet Gynecol. 2016;215(4):423–430.

A dramatic recommendation for obstetric practice change occurred in 2016: the option of administering antenatal steroids for fetal lung maturity *after* 34 weeks. In the Antenatal Late Preterm Steroids (ALPS) trial of betamethasone in the late preterm period in patients at "high risk" of imminent delivery, Gyamfi-Bannerman and colleagues demonstrated that the treated group had a significant decrease in the rate of neonatal respiratory complications.

The primary outcome, a composite of respiratory morbidities (including transient tachypnea of the newborn, surfactant use, and need for resuscitation at birth) within the first 72 hours of life, had significant differences between groups, occurring in 165 of 1,427 infants (11.6%) in the betamethasone-treated group and 202 of 1,400 (14.4%) in the placebo group (relative risk in the betamethasone group, 0.80; 95% confidence interval, 0.66–0.97; P = .02). However, there was no statistically significant difference in respiratory distress syndrome, apnea, or pneumonia between groups, and the significant difference noted in bronchopulmonary dysplasia was based on a total number of 11 cases.

In response to these findings, both the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) released practice advisories and interim updates, culminating in a final recommendation for a single course of betamethasone in patients at high risk of preterm delivery between 34 and 36 6/7 weeks who have not received a previous course.

In a thorough review of the literature on antenatal steroid use, Kamath-Rayne and colleagues highlighted several factors that should be considered before adopting universal use of steroids at >34 weeks. These include:

- The definition of "high risk of imminent delivery" as preterm labor with at least 3-cm dilation or 75% effacement, or spontaneous rupture of membranes. The effect of less stringent inclusion criteria in real-world clinical practice is not known, and many patients who will go on to deliver at term will receive steroids unnecessarily.
- Multiple gestation, patients with preexisting diabetes, women who had previously received a course of steroids, and fetuses with anomalies were excluded from the ALPS study. Use of antenatal steroids in these groups at >34 weeks should be

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evaluated before universal adoption.

- The incidence of neonatal hypoglycemia in the treated group was significantly increased. This affects our colleagues in pediatrics considerably from a systems standpoint (need for changes to newborn protocols and communication between services).
- The long-term outcomes of patients exposed to steroids in the late preterm period are yet to be delineated, specifically, the potential neurodevelopmental effects of a medication known to alter preterm brain development as well as cardiovascular and metabolic consequences.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Kamath-Rayne and colleagues reminded us that it took almost 20 years to adopt antenatal steroid use between 24 and 33 6/7 weeks, a process that is essentially unquestioned in clinical practice today. Use of antenatal steroids at >34 weeks in patients who meet the inclusion/exclusion criteria of the ALPS study is appropriate if the risk of hypoglycemia is addressed, but caution should be exercised in adopting universal use given the still-unanswered questions that warrant further study.

Low-dose aspirin clearly is effective for reducing the risk of preeclampsia

FAST TRACK

Women at high risk of preeclampsia and certain high-risk conditions (eg, prior preeclampsia, multifetal gestation, diabetes) should receive low-dose aspirin starting between 12 and 28 weeks

American College of Obstetricians and Gynecologists. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013;122(5):1122–1131.

Henderson JT, Whitlock EP, O'Connor E, Senger CA, Thompson JH, Rowland MG. Low-dose aspirin for prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the US Preventive Services Task Force. Ann Intern Med. 2014;160(10):695–703.

LeFevre ML; US Preventive Services Task Force. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: US Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161(11):819–826.

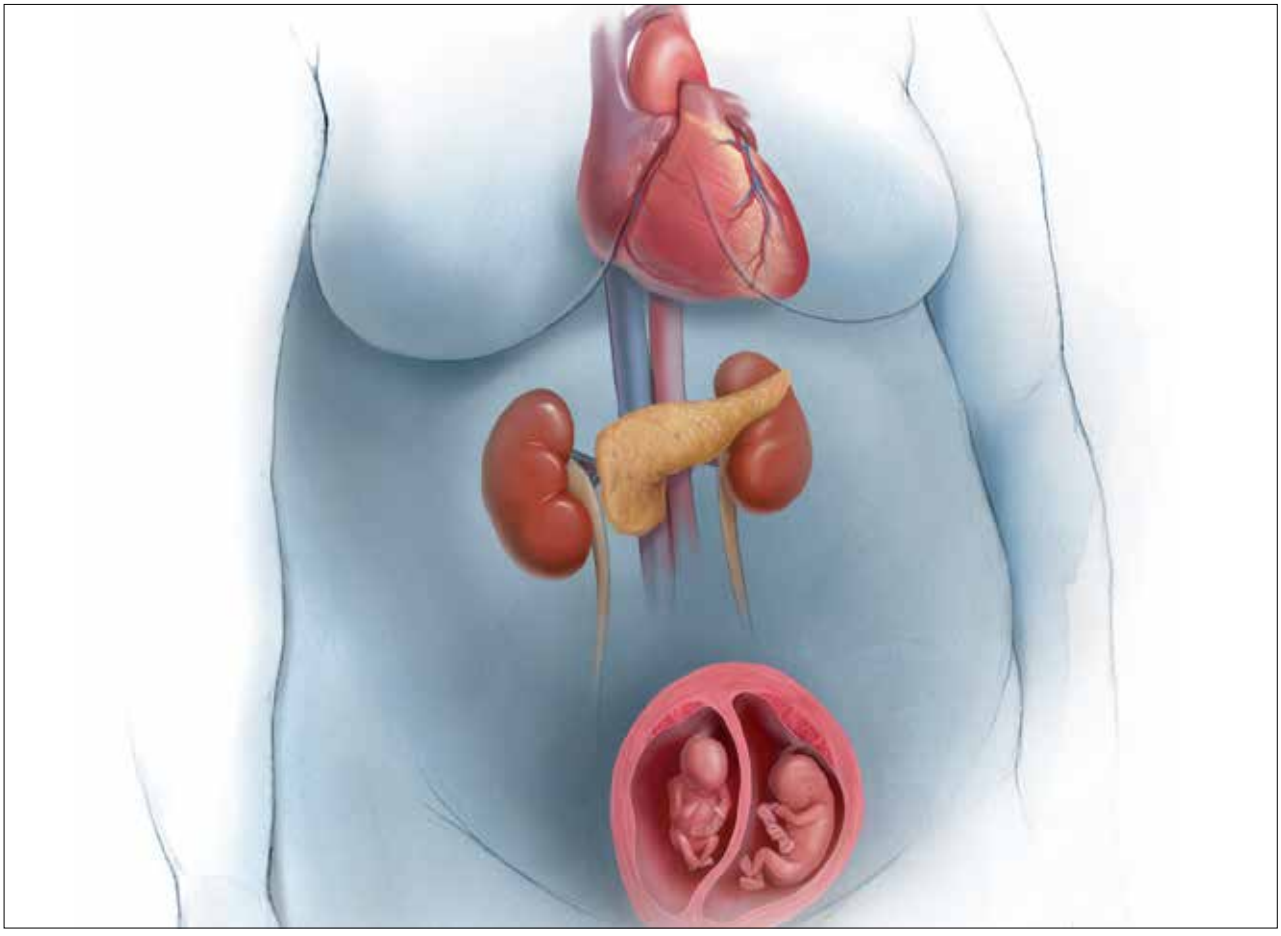
American College of Obstetricians and Gynecologists. Practice advisory on low-dose aspirin and prevention of preeclampsia: updated recommendations. http://www.acog.org/About-ACOG/News-Room/Practice-Advisories/Practice-Advisory-Low-Dose-Aspirin-and-Prevention-of-Preeclampsia-Updated-Recommendations. Published July 11, 2016. Accessed December 6, 2016.

In the 2013 ACOG Task Force on Hypertension in Pregnancy report, low-dose aspirin (60–80 mg) was recommended to be initiated in the late first trimester to reduce preeclampsia risk for women with:

- prior early onset preeclampsia with preterm delivery at <34 weeks' gestation, or
- preeclampsia in more than one prior pregnancy.

This recommendation was based on several meta-analyses that demonstrated a 10% to 17% reduction in risk with no increase in bleeding, placental abruption, or other adverse events.

In 2014, the US Preventive Services Task Force (USPSTF) conducted a systematic evidence review of low-dose aspirin use for prevention of morbidity and mortality from preeclampsia. That report revealed a 24% risk reduction of preeclampsia in high-risk women treated with low-dose aspirin, as well as a 14% reduction in preterm birth and a 20% reduction in fetal growth restriction. A final statement from the USPSTF in 2014 recommended low-dose aspirin (60–150 mg) starting between 12 and 28 weeks' gestation for women at "high" risk who have:



A patient with type 2 diabetes, chronic hypertension, and multifetal gestation should be offered low-dose aspirin beginning at 12 weeks' gestation to reduce her risk of preeclampsia.

- a history of preeclampsia, especially if accompanied by an adverse outcome
- multifetal gestation
- chronic hypertension
- diabetes (type 1 or type 2)
- renal disease
- autoimmune disease (such as systematic lupus erythematosus, antiphospholipid syndrome).

As of July 11, 2016, ACOG supports this expanded list of high-risk conditions. Additionally, the USPSTF identified a "moderate" risk group in which low-dose aspirin may be considered if a patient has several risk factors, such as obesity, nulliparity, family history of preeclampsia, age 35 years or older, or another poor pregnancy outcome. ACOG notes, however, that the evidence supporting this practice is uncertain and does not make a recommendation regarding aspirin use in this population. Further study should be conducted to determine the benefit of low-dose aspirin in these patients as well as the long-term effects of treatment on maternal and child outcomes.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Offer low-dose aspirin (81 mg is the dose available in the United States) starting at 12 weeks' gestation to women with the expanded number of conditions listed at left to reduce the risk of preeclampsia and other associated adverse perinatal outcomes.

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ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

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Chromosomal microarray analysis is preferable to karyotype in certain situations

Pauli JM, Repke JT. Update on obstetrics. OBG Manag. 2013;25(1):28–32.

Society for Maternal-Fetal Medicine (SMFM), Dugoff L, Norton ME, Kuller JA. The use of chromosomal microarray for prenatal diagnosis. Am J Obstet Gynecol. 2016;215(4):B2–B9.

American College of Obstetricians and Gynecologists. Committee Opinion No. 682. Microarrays and next-generation sequencing technology: the use of advanced genetic diagnostic tools in obstetrics and gynecology. Obstet Gynecol. 2016;128(6):e262–e268.

FAST TRACK

For prenatal genetic diagnosis, only karyotype can detect balanced translocations/inversions; only CMA can detect copy number variants

We previously addressed the use of chromosomal microarray analysis (CMA) for prenatal diagnosis in our 2013 "Update on obstetrics," specifically, the question of whether CMA could replace karyotype. The main differences between karyotype and CMA are that 1) only karyotype can detect balanced translocations/inversions and 2) only CMA can detect copy number variants (CNV). There are some differences in the technology and capabilities of the 2 types of CMA currently available as well.

In our 2013 article we concluded that "The total costs of such an approach—test, interpretation, counseling, and long-term follow-up of uncertain results—are unknown at this time and may prove to be unaffordable on a population-wide basis." Today, the cost of CMA is still higher than karyotype, but it is expected to decrease and insurance coverage for this test is expected to increase.

Both SMFM and ACOG released recommendations in 2016 regarding the use of CMA in prenatal genetic diagnosis, summarized as follows:

- CMA is recommended over karyotype for fetuses with structural abnormalities on ultrasound
  - —The detection rate for clinically relevant abnormal CNVs in this population is about 6%
- CMA is recommended for diagnosis for stillbirth specimens
  - —CMA does not require dividing cells and may be a quicker and more reliable test in this population
- Karotype or fluorescence in situ hybridization (FISH) is recommended for fetuses with ultrasound findings suggestive of aneuploidy
  - —If it is negative, then CMA is recommended
- Karyotype or CMA is recommended for patients desiring prenatal diagnostic testing with a normal fetal ultrasound
  - —The detection rate for clinically relevant CNVs in this population (advanced maternal age, abnormal serum screening, prior aneuploidy, parental anxiety) is about 1%
- Pretest and posttest counseling about the limitations of CMA and a 2% risk of detection of variants of unknown significance (VUS) should be performed by a provider who has expertise in CMA and who has access to databases with genotype/phenotype information for VUS
  - —This counseling should also include the possibility of diagnosis of nonpaternity, consanguinity, and adult-onset disease
- Karyotype is recommended for couples with recurrent pregnancy loss
  - —The identification of balanced translocations in this population is most relevant in this patient population
- Prenatal diagnosis with routine use of whole-genome or whole-exome sequencing is not recommended.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

CMA does not completely replace karyotype for prenatal diagnosis, but it is the preferred test in prenatal diagnosis in certain patient populations. Cost remains an issue.

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Zika virus infection: Check often for the latest updates

American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine. Practice advisory on Zika virus. http://www.acog.org/About-ACOG/News-Room/Practice-Advisories/Practice-Advisory-Interim-Guidance-for-Care-of-Obstetric-Patients-During-a-Zika-Virus-Outbreak. Published December 5, 2016. Accessed December 6, 2016.

Centers for Disease Control and Prevention. Zika virus. http://www.cdc.gov/zika/pregnancy/index.html. Updated August 22, 2016. Accessed December 6, 2016.

Petersen EE, Meaney-Delman D, Neblett-Fanfair R, et al. Update: interim guidance for preconception counseling and prevention of sexual transmission of Zika virus for persons with possible Zika virus exposure—United States, September 2016. MMWR Morbid Mortal Wkly Rep. 2016;65(39):1077–1081.

FAST TRACK

Women with Zika infection should postpone conception for at least 8 weeks, and men for at least 6 months

A yearly update on obstetrics would be remiss without mention of the Zika virus and its impact on pregnancy and reproduction. That being said, any recommendations we offer may be out of date by the time this article is published given the rapidly changing picture of Zika virus since it first dominated the headlines in 2016. Here are the basics as summarized from ACOG and the Centers for Disease Control and Prevention (CDC):

Viral spread. Zika virus may be spread in several ways: by an infected *Aedes* species mosquito, mother to fetus, sexual contact, blood transfusion, or laboratory exposure.

Symptoms of infection include conjunctivitis, fever, rash, and arthralgia, but most patients (4/5) are asymptomatic.

Sequelae. Zika virus infection during pregnancy is believed to cause fetal and neonatal microcephaly, intracranial calcifications, and brain and eye abnormalities. The rate of these findings in infected individuals, as well as the rate of vertical transmission, is not known.

Travel advisory. Pregnant women should not travel to areas with active Zika infection (the CDC website regularly updates these restricted areas).

Preventive measures. If traveling to an area of active Zika infection, pregnant women should take preventative measures day and night against mosquito bites, such as use of insect repellents approved by the Environmental Protection Agency, clothing that covers exposed skin, and staying indoors.

Safe sex. Abstinence or consistent condom use is recommended for pregnant women with partners who travel to or live in areas of active Zika infection.

Delay conception. Conception should be postponed for at least 6 months in men with Zika infection and at least 8 weeks in women with Zika infection.

Testing recommendations. Pregnant women with Zika virus exposure should be tested, regardless of symptoms. Symptomatic exposed nonpregnant women and all men should be tested.

Prenatal surveillance. High-risk consultation and serial ultrasounds for fetal anatomy and growth should be considered in patients with Zika virus infection during pregnancy. Amniocentesis can be considered on a case-by-case basis.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Prevention of Zika virus infection in pregnant women is imperative as information continuously unfolds regarding new areas of transmission, expanding fetal and neonatal effects, and the current lack of treatment options.