



INFECTIOUS DISEASE

Four recent studies provide new data—with potential global impact—regarding birth defect rates in symptomatic and asymptomatic maternal Zika virus infection, dual-agent prophylaxis for postcesarean infection, tenofovir treatment of hepatitis B in pregnant women, and HIV transmission rates in patients receiving ART



>> Jessica R. Jackson, MD

Dr. Jackson is a third-year Maternal-Fetal Medicine Fellow in the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Florida College of Medicine, Gainesville.



>> Patrick Duff, MD

Dr. Duff is Associate Dean for Student Affairs and Professor of Obstetrics and Gynecology in the Division of Maternal-Fetal Medicine, University of Florida College of Medicine.

The authors report no financial relationships relevant to this article.

In this Update we review the results of 4 recent investigations that have important implications:

- the first analysis of the US Zika Virus Infection in Pregnancy Registry
- a study revealing an improved antibiotic

- regimen to prevent postcesarean infection
- an important new methodology for reducing the rate of perinatal transmission of hepatitis B virus (HBV) infection
- the risks and benefits of combination antiretroviral therapy (ART) in pregnancy.

Zika virus–associated birth defect rates similar regardless of symptom presence; first-trimester exposure has highest rate of anomalies

Honein MA, Dawson AL, Petersen EE, et al; US Zika Pregnancy Registry Collaboration. Birth defects among fetuses and infants of US women with evidence of

possible Zika virus infection during pregnancy. JAMA. 2017;317(1):59–68.

IN THIS ARTICLE

Prophylaxis for postcesarean infection

page 20

Reducing HBV transmission

page 21

ART regimens in pregnancy

page 22

Honein and colleagues provide a summary of the data from the US Zika Virus in Pregnancy Registry (a collaboration between the Centers for Disease Control and Prevention and state and local health departments), estimating the proportion of fetuses and infants with birth defects based on maternal symptoms of Zika virus infection and trimester of possible infection.

Details of the study

The authors evaluated the outcomes of 442 women who had laboratory evidence of a possible Zika virus infection during pregnancy. Overall, 26 infants (6%; 95% confidence interval (CI), 4%–8%) had evidence of birth defects related to the Zika virus. Of note, abnormalities were detected in 16 of the 271 children (6%; 95% CI, 4%–9%) born to women who were asymptomatic and 10 of 167 (6%; 95% CI, 3%–11%) children delivered to women with symptomatic infections.

The most common birth defect was microcephaly, although other serious central nervous system abnormalities were noted as well. Nine of 85 women (11%; 95% CI, 6%–19%) who had exposure only during the first trimester had infants with birth defects. There were no documented abnormalities in infants born to mothers who developed Zika virus infection only in the second or third trimester.

Key study findings

This article is important for several reasons. First, the authors describe the largest series of pregnant women in the United States with Zika virus infection. All of these patients developed Zika virus infection as a result of foreign travel or exposure to sexual partners who had traveled to Zika virus endemic areas. Second, the authors confirmed findings that previously had been based only on mathematical models rather than on actual case series. Specifically, they demonstrated that the risk of a serious birth defect following first-trimester exposure to Zika virus infection was approximately 11%, with a 95% CI that extended from 6% to 19%. Finally, Honein and colleagues



highlighted the key fact that the risk of a serious birth defect was comparable in mothers who had either an asymptomatic or a symptomatic infection, a finding that seems somewhat counterintuitive.

CONTINUED ON [PAGE 20](#)

WHAT THIS EVIDENCE MEANS FOR PRACTICE

This study's critical observations are a "call to action" for clinicians who provide prenatal care.^{1,2} Proactive steps include:

- For patients considering pregnancy, strongly advise against travel to any area of the world where Zika virus is endemic until an effective vaccine is available to protect against this infection.
- For any woman with a newly diagnosed pregnancy, ask about travel to an endemic area.
- Inquire also about a pregnant woman's exposure to partners who live in, or who have traveled to, areas of the world where Zika virus infection is endemic.
- Be aware that both asymptomatic and symptomatic infection in the first trimester of pregnancy pose a grave risk to the fetus.
- Recognize that, although microcephaly is the principal abnormality associated with Zika virus infection, other central nervous system anomalies also may occur in these children. These include ventriculomegaly, subcortical calcifications, abnormalities of the corpus callosum, cerebral atrophy, and cerebellar abnormalities. In addition, infected infants may have arthrogryposis.
- Finally, as Honein and colleagues noted, laboratory testing for Zika virus infection is imperfect. In the early stages of infection or exposure, testing for Zika virus infection by polymerase chain reaction (PCR) in both serum and urine is the preferred test. After a period of 2 weeks, the preferred laboratory test is an immunoglobulin M (IgM) assay. Positive tests on the IgM assay must be confirmed by the plaque neutralization reduction test—a very important test for differentiating Zika virus infection from infection caused by other arboviruses, such as those that cause dengue fever and chikungunya.



Two antibiotics before cesarean delivery reduce infection rates further than one agent

Tita AT, Szychowski JM, Boggess K, et al; for the C/SOAP Trial Consortium. Adjunctive azithromycin prophylaxis for cesarean delivery. N Engl J Med. 2016;375(13):1231-1241.

the groups in the frequency of the secondary neonatal composite outcome, which included neonatal death and serious neonatal complications.

Tita and colleagues reported the results of a multicenter trial that was designed to assess whether a combination of 2 antibiotics, including one that specifically targets ureaplasma species, provided more effective prophylaxis against postcesarean infection than single-agent prophylaxis.

Details of the study

The Cesarean Section Optimal Antibiotic Prophylaxis (C/SOAP) trial was conducted at 14 centers in the United States and included 2,013 women who were at least at 24 weeks' gestation and who had a cesarean delivery during labor or after membrane rupture.

The authors randomly assigned 1,019 women to receive 500 mg of intravenous azithromycin plus conventional single-agent prophylaxis (usually cefazolin) and 994 women to receive a placebo plus conventional prophylaxis. The primary outcome was the composite of endometritis, wound infection, or other infection occurring within 6 weeks.

The authors observed that the primary outcome occurred in 62 women (6.1%) who received azithromycin plus conventional prophylaxis and in 119 women (12%) who received only single-agent prophylaxis. The relative risk of developing a postoperative infection was 0.51 in women who received the combined therapy. There were significant differences between the 2 groups in both the rates of endometritis (3.8% vs 6.1%, $P = .02$) and wound infection (2.4% vs 6.6%, $P < .001$). There were no differences between

Efficacy of dual-agent prophylaxis

At present, the standard of care is to administer prophylactic antibiotics to all women having cesarean delivery, including women having a scheduled cesarean in the absence of labor or ruptured membranes. Multiple studies have shown clearly that prophylaxis reduces the frequency of endometritis and, in high-risk patient populations, wound infection, and that prophylaxis is most beneficial when administered prior to the time the surgical incision is made. The most commonly used drug for prophylaxis is cefazolin, a first-generation cephalosporin. The usual recommended dose is 2 g, administered immediately prior to surgery.^{3,4}

Although most centers in the United States traditionally have used just a single antibiotic for prophylaxis, selected recent reports indicate that expanding the spectrum of activity of prophylactic antibiotics can result in additional beneficial effects. Specifically, Tita and colleagues evaluated an indigent patient population with an inherently high rate of postoperative infection.⁵ They showed that adding azithromycin 500 mg to cefazolin significantly reduced the rate of postcesarean endometritis. In a follow-up report from the same institution, Tita and colleagues demonstrated that adding azithromycin also significantly reduced the frequency of wound infection.⁶ Of note, in both these investigations, the antibiotics were administered after cord clamping. In a subsequent report, Ward and Duff showed

FAST TRACK

Previous studies showed that adding azithromycin to a usual antibiotic regimen reduced the rates of postcesarean endometritis and wound infection

that the combination of azithromycin plus cefazolin administered preoperatively resulted in a combined rate of endometritis and wound infection that was less than 3%.⁷

C/SOAP trial confirmed lower infection rates with combined regimen

Results of the present study confirm the findings of these 3 investigations. The trial included a large sample size. The study was carefully designed, and the end points were clearly defined. It included only patients at increased risk for postoperative infection by virtue of being in labor or having ruptured membranes at the time of cesarean delivery. Patients who received standard prophylaxis,

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Based on the results of the C/SOAP trial, considered in conjunction with the 3 previously cited investigations,⁵⁻⁷ we believe that the standard approach to antibiotic prophylaxis should be to administer both cefazolin, in a dose of 2 g, plus azithromycin, in a dose of 500 mg, prior to surgery. Cefazolin can be administered as an intravenous bolus; azithromycin should be administered as a continuous infusion over a 60-minute period prior to surgery. Clinicians may anticipate very low rates of both endometritis and wound infection with this regimen.

usually cefazolin, *plus* azithromycin had a significantly lower risk of postcesarean endometritis and wound infection compared with patients who received a single antibiotic. The overall risk of infection was reduced by an impressive 50%.

Tenofovir treatment in pregnant women with HBV reduces vertical transmission

Pan CQ, Duan Z, Dai E, et al; China Study Group for the Mother-to-Child Transmission of Hepatitis B. Tenofovir to prevent hepatitis B transmission in mothers with high viral load. N Engl J Med. 2016;374(24):2324-2334.

A multicenter, open-label, randomized, parallel-group investigation was conducted from March 2012 to June 2013 at academic tertiary care centers in 5 geographic regions of China. Two hundred mothers, who were positive for both hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) and who had HBV DNA concentrations of 200,000 IU/mL or greater, were randomly assigned in a 1:1 ratio to either tenofovir or to usual treatment. Exclusion criteria were coexistent viral infections or medical conditions, renal failure, laboratory abnormalities, fetal deformities, and use of many medications.

Details of the study

Women in the active treatment group received tenofovir 300 mg by mouth daily from 30 to 32 weeks' gestation until postpartum week 4. Patients were monitored every 4 weeks in the antepartum period for adverse events and laboratory abnormalities. In the postpartum period, mother-infant dyads were evaluated at weeks 4, 12, 24, and 28.

Primary outcomes were the rates of mother-to-child transmission and birth defects with, or without, tenofovir exposure. Secondary outcomes were the percentage of mothers who had an HBV DNA serum concentration of less than 200,000 IU/mL at delivery and the percentage of mothers with HBeAg or HBsAg loss or seroconversion at postpartum week 28. Safety outcomes included the adverse event profile of tenofovir in mothers and safety events in the mother-infant dyads. These outcomes encompassed

FAST TRACK

We believe that the standard approach to antibiotic prophylaxis for cesarean delivery should be to administer cefazolin 2 g plus azithromycin 500 mg before surgery



all adverse events and drug discontinuations in patients who received at least one dose of tenofovir.

Sixty-eight percent of mothers in the tenofovir group, compared with 2% of mothers in the control group, had HBV levels less than 200,000 IU/mL at delivery ($P < .001$). The rate of mother-to-child HBV transmission at postpartum week 28 was lower in the tenofovir group. In the intention-to-treat analysis, the rate was 5% (95% CI, 1–10; 5 of 97 infants) in the tenofovir group versus 18% (95% CI, 10–26; 18 of 100 infants) in the control group ($P = .007$). In the per-protocol analysis, the rate was 0% (95% CI, 0–3; 0 of 92 infants) in the tenofovir group versus 7% (95% CI, 2–12; 6 of 88 infants) in the control group ($P = .01$). Maternal and infant safety profiles were similar between the 2 groups, with the exception of elevated creatinine kinase and alanine aminotransferase levels in mothers treated with tenofovir. Maternal HBV serologic titers did not differ significantly between the 2 groups.

Study strengths and limitations

This study's strengths include a multicenter, randomized controlled design, with strict inclusion and exclusion criteria. The results are clinically relevant and of global impact, with potential to decrease morbidity and

WHAT THIS EVIDENCE MEANS FOR PRACTICE

HBV is a serious infection that can lead to liver failure and cirrhosis. HBV infection is most likely to have long-term sequelae if acquired in the perinatal period. If untreated, chronic HBV infection will develop in 80% to 90% of infants born to mothers positive for HBeAg. Current immunoprophylaxis for at-risk neonates is postnatal HBV vaccine in combination with hepatitis B immune globulin. Unfortunately, this immunoprophylaxis fails in 10% to 30% of infants born to mothers with an HBV DNA level of greater than 6 log 10 copies/mL. Thus, the observations of Pan and colleagues are welcome findings.

Based on the results of this study, we recommend the use of tenofovir to decrease HBV transmission during pregnancy for women with high viral loads.

mortality from HBV infection in children born to infected mothers.

A limitation, however, is that the study was probably underpowered to detect small differences in the rate of birth defects between the tenofovir and usual-care treatment groups. Additionally, some patients ceased taking tenofovir in the postpartum time period. Abrupt cessation may be associated with acute, severe HBV exacerbation.

Benefits of ART for reducing mother-to-baby HIV transmission outweigh higher risk of adverse outcomes

Fowler MG, Qin M, Fiscus SA, et al; IMPAACT 1077BF/1077FF PROMISE Study Team. Benefits and risks of antiretroviral therapy for perinatal HIV prevention. *N Engl J Med*. 2016;375(18):1726–1737.

Part of the larger PROMISE (Promoting Maternal and Infant Survival Everywhere) trial, a study by Fowler and colleagues compared the relative efficacy and safety of various proven ART strategies for

FAST TRACK

In the intention-to-treat analysis, the rate of mother-to-child HBV transmission was 5% in the tenofovir-treated group versus 18% in the control group ($P = .007$)

prevention of mother-to-child transmission of HIV infection in women with relatively high CD4 counts.

Details of the study

The trial was conducted at 14 sites in 7 countries. Patients were stratified according to HBV coinfection status and country of origin. The primary efficacy outcome was frequency of early infant HIV infection.

Women were randomly assigned to 1 of 3 treatment categories:

- zidovudine alone (zidovudine plus a single intrapartum dose of nevirapine, followed by 6 to 14 days of tenofovir plus emtricitabine postpartum)
- zidovudine-based ART (zidovudine in combination with lamivudine and lopinavir-ritonavir)
- tenofovir-based ART (tenofovir in combination with emtricitabine and lopinavir-ritonavir).

All regimens were continued through 6 to 14 days postpartum. All infants received nevirapine at birth and in the immediate postpartum period.

Two trial periods. During period 1 (April 2011–September 2012), safety data on tenofovir in pregnancy were limited. Women without HBV coinfection were assigned only to zidovudine alone or zidovudine-based ART. During period 2 (October 2012–October 2014), since more information about tenofovir use in pregnancy was available, the study protocol was modified to allow women to be assigned to any of the 3 regimens, regardless of their HBV status.

Inclusion criteria were as follows: CD4 count of at least 350 cells/mm³ (or country-specific threshold for initiating triple-drug ART, if that threshold was higher), gestation of at least 14 weeks and not in labor, no previous use of triple-drug ART, no clinical or immune-related indication for triple-drug ART, hemoglobin level of at least 6.5 g/dL, an absolute neutrophil count of at least 750 cells/mm³, an alanine aminotransferase level of less than 2.5 times the upper limit of normal range, an estimated creatinine

clearance of greater than 60 mL/min, and no serious pregnancy complications. Patients were excluded if they had active tuberculosis, HBV infection requiring treatment, a structural or conduction heart defect, or a fetus with a serious congenital malformation.

Primary outcomes. The primary efficacy outcome was early infant HIV infection, defined as a positive infant HIV nucleic acid test result at birth or at 1 week postpartum. The primary safety outcome was a composite of adverse events.

Adverse events in mothers were defined as hematologic abnormalities, abnormal blood chemical values, or abnormal signs/symptoms during pregnancy through 1 week postpartum. Severe pregnancy composite outcomes were low birth weight (<2,500 g), preterm delivery before 37 weeks' gestation, spontaneous abortion (<20 weeks), stillbirth (≥20 weeks), or congenital anomaly. Adverse events in infants were defined as death from any cause, hematologic abnormalities or abnormal blood chemical values, and abnormal signs/symptoms through 1 week postpartum.

A total of 3,490 mother-infant sets were included in the analysis (2,261 during trial period 1 and 1,229 during trial period 2). Baseline maternal characteristics were well balanced between groups. Most women were African, young (median age, 26 years), and asymptomatic.

Study results

The combined maternal ART-treated groups had significantly lower rates of early transmission of HIV infection compared with the zidovudine-alone group (0.5% vs 1.8%, -1.3 percentage points; CI, -2.1 to -0.4). The zidovudine-based ART-treated group had a significantly higher rate of infant HIV-free survival through postpartum week 1 than did the zidovudine-alone group ($P = .001$) or the tenofovir-based ART group ($P = .002$).

When examining trial periods 1 and 2 combined, the zidovudine-based ART group experienced significantly higher rates of any adverse event than those receiving



Significantly lower rates of early transmission of HIV infection were found in the combined maternal ART-treated groups compared with the mothers treated with zidovudine alone (0.5% vs 1.8%)



WHAT THIS EVIDENCE MEANS FOR PRACTICE

Although antenatal ART was associated with a higher risk of adverse maternal and neonatal outcomes when compared with zidovudine alone, these risks are outweighed by the benefit of significantly lower rates of early HIV transmission. Therefore, women who meet the World Health Organization's (WHO) eligibility criteria should be treated with combination ART during pregnancy. The WHO major eligibility criteria for ART during pregnancy are:

1. CD4 count of ≤ 350 cells/mm³, irrespective of clinical staging
 2. clinical stage 3 or stage 4 disease, irrespective of CD4 cell count.
- The WHO recommends starting ART at 14 weeks' gestation.⁸

zidovudine alone (21.1% vs 17.3%, $P = .008$) and higher rates of abnormal blood chemical values (5.8% vs 1.3%, $P < .001$). During period 2 alone, the tenofovir-based ART group had significantly higher rates of abnormal blood chemical values than did the zidovudine-alone group (2.9% vs 0.8%, $P = .03$). There were no significant differences between the 2 ART treatment groups. No maternal deaths occurred during the study, and the trial-drug discontinuation rate was low (2%–5%) and did not vary among the 3 groups.

During trial periods 1 and 2, the zidovudine-based ART group had significantly higher rates of adverse pregnancy outcomes than did the zidovudine-alone group (40% vs 27.5%, $P < .001$). These included low birth weight less than 2,500 g (23% vs 12%) and preterm delivery before 37 weeks (20.5% vs 13.1%). During trial period 2, the tenofovir-based ART group had significantly higher rates of adverse pregnancy outcomes than did the zidovudine-alone group (34.7% vs 27.2%, $P = .04$). There were no significant differences for any outcome between the 2 ART-treated groups, and there were no significant

differences in stillbirth or spontaneous abortion and congenital anomalies among the 3 groups.

Regarding severe pregnancy outcomes, there were no significant differences (composite or individual) between the zidovudine-based ART group and the zidovudine-alone group. The tenofovir-based ART group experienced significantly higher rates of composite severe adverse pregnancy outcomes compared with the zidovudine-based ART group (9.2% vs 4.3%, $P = .02$), and very preterm birth before 34 weeks (6.0% vs 2.6%, $P = .04$).

Infant safety outcomes were also examined. There were no significant differences for composite or individual adverse neonatal outcomes other than death. The tenofovir-based ART group experienced a significantly higher rate of infant death than did the zidovudine-based ART group (4.4% vs 0.6%, $P < .001$). However, a post hoc analysis suggested that extreme prematurity contributed to the infant mortality.

Limitations of the study

This study had minor limitations. It divided patients into only 2 major categories with respect to gestational age—more than or less than 34 weeks. Some maternal medical conditions, such as malaria, were not controlled for. In addition, breastfeeding and formula feeding were combined for analysis, and we know that breastfeeding would inherently confer a higher risk of HIV transmission.

Nevertheless, this study was thoughtfully designed and carefully conducted, and the results are of significant global impact.

References

1. Chelliah A, Duff P. Zika virus: counseling considerations for this emerging perinatal threat. *OBG Manag.* 2016;28(3):28–34.
2. Chelliah A, Duff P. Zika virus update: a rapidly moving target. *OBG Manag.* 2016;28(8):17–26.
3. Patrick KE, Deatsman SL, Duff P. Preventing infection after cesarean delivery: evidence-based guidance. *OBG Manag.* 2016;28(11):41–47.
4. Patrick KE, Deatsman SL, Duff P. Preventing infection after cesarean delivery: 5 more evidenced-based methods to consider. *OBG Manag.* 2016;28(12):18–22.
5. Tita AT, Hauth JC, Grimes A, Owen J, Stamm AM, Andrews WW. Decreasing incidence of postcesarean endometritis with extended-spectrum antibiotic prophylaxis. *Obstet Gynecol.* 2008;111(1):51–56.
6. Tita AT, Owen J, Stamm AM, Grimes A, Hauth JC, Andrews WW. Impact of extended-spectrum antibiotic prophylaxis on incidence of postcesarean surgical wound infection. *Am J Obstet Gynecol.* 2008;199(3):303.e1–e3.
7. Ward E, Duff P. A comparison of 3 antibiotic regimens for prevention of postcesarean endometritis: an historical cohort study. *Am J Obstet Gynecol.* 2016;214(6):751.e1–e4.
8. New guidance on prevention of mother-to-child transmission of HIV and infant feeding in the context of HIV. World Health Organization website. <http://www.who.int/hiv/pub/mtct/PMTCTfactsheet/en/>. Published July 20, 2010. Accessed June 16, 2017.

FAST TRACK

The benefit of significantly lower rates of early HIV transmission with antenatal ART compared with zidovudine alone outweigh the higher risk of adverse maternal and neonatal outcomes