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ABSTRACT & COMMENTARY

Is Nitrous Oxide an Effective Analgesic During Labor?

By Rebecca H. Allen, MD, MPH, Editor

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SYNOPSIS: In this prospective cohort study at one large academic medical center in Colorado, 31% of women who opted for nitrous oxide for analgesia during labor did not require any other source of analgesia, such as an epidural or intravenous opioids. Risk factors for conversion to other modalities included labor induction, oxytocin augmentation, and labor after cesarean.

SOURCE: Nodine PM, Collins MR, Wood CL, et al. Nitrous oxide use during labor: Satisfaction, adverse effects, and predictors of conversion to neuraxial analgesia. *J Midwifery Womens Health* 2020; May 26. doi: 10.1111/jmwh.13124. [Online ahead of print].

This prospective cohort study was conducted at a large, urban, tertiary care academic medical center in Colorado between March 2016 and July 2017. Adult women were enrolled in the study during the first or second stage of labor if they opted for nitrous oxide for pain management and were at term (37 to 42 weeks' gestation).

All women presenting in labor were counseled about the option to receive epidural analgesia, intravenous opioids, or nitrous oxide. Exclusion criteria included women with planned cesarean deliveries. Multiple data variables were collected, including demographic information, medical history, obstetric history, intrapartum course, and specifics of nitrous oxide use. Maternal adverse effects and satisfaction levels also were recorded.

A total of 463 women were enrolled and had complete data for analysis. The majority of participants were nulliparous (60.9%), and the average age was 27.3 years (standard deviation [SD] = 6.3). One hundred eighty-six women (40%) were admitted for labor induction and 101 (22%) underwent oxytocin augmentation of labor. Overall, of the women who used nitrous oxide as their initial pain relief modality, 144 (31%) used it during the entire course of labor. The remainder converted to another option. The mean time of using nitrous oxide was 178 minutes (SD = 213) and the mean

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satisfaction score on a scale of 0 to 10 was 7.4 (SD = 2.9). The most common adverse effects reported during use were nausea (3.7%) and dizziness (1.7%). There were no reports of excessive sedation. The mode of delivery among the sample was 81% spontaneous vaginal, 0.9% vacuum, 4.5% forceps, and 13.6% cesarean.

Of the 319 women who converted to another method of pain relief, the most common reason cited was inadequate pain relief (96%), followed by a minority for adverse effects (1.6%). Most who converted to another method chose epidural anesthesia (91%). In multivariable analysis, higher odds of converting to another pain control method were found with labor induction (adjusted odds ratio [aOR], 2.9; 95% confidence interval [CI], 1.7-4.9), oxytocin augmentation (aOR, 3.1; 95% CI, 1.6-6.0), and labor after cesarean (aOR, 6.4; 95% CI, 2.5-16.5). Multiparity was protective and decreased the odds of analgesia method conversion (aOR, 0.4; 95% CI, 0.2-0.6).

■ COMMENTARY

Epidural analgesia is the most common pain control method employed during labor and delivery in the United States. In the past, other options included only intravenous opioids, which are limited in utility because of adverse maternal and fetal effects. However, nitrous oxide recently has become available as another option on many labor and delivery units. The advantages of nitrous oxide (50% N_2O and 50% O_2) include rapid onset and offset, no need for additional monitoring because of the minimal effects on the maternal cardiovascular and respiratory system, and control by the patient.[1] Although it is not considered as effective as epidural analgesia in terms of pain scores, patients may prefer it as an alternative.

Although nitrous oxide has been used for labor pain in other countries for many years, it is relatively new to the United States. The authors of this study wanted to explore the use of nitrous oxide at their institution in Colorado and found a 69% conversion rate from nitrous oxide to another form of pain control. Two other studies from the United States found conversion rates ranging from 40% to 63%, which correspond with the findings from the Nodine et al study.[2,3] The finding that oxytocin augmentation and labor induction increased conversion rates is not surprising to me, given that these factors likely are associated with longer labors. Similarly, multiparous women likely do better with nitrous oxide alone, since their labors typically are faster, and they may have a higher tolerance for labor pain because of their past experience.

This study also found a higher rate of conversion among women with a previous cesarean delivery, which the authors suspected may be related to increased anxiety and fear of labor or a slower labor progress. The mean time of nitrous oxide use was 178 minutes in this study, with a wide range reported (five to 1,508 minutes). The authors thought that better education and communication regarding the expected effect for patients who start using nitrous oxide would be beneficial in prolonging use times.

Overall, women were satisfied with nitrous oxide use in this study, even though the pain control was not optimal for the majority. Nevertheless, the method may be satisfactory for other reasons, including the ability to ambulate and the control that the patient has over its use. Even if the patient does not use nitrous oxide for the entire labor, it may be a helpful adjunct and may increase satisfaction with the overall delivery experience. Most patients prefer to have multiple options available for pain control.

During the COVID-19 pandemic, our hospital suspended use of nitrous oxide for labor pain because of the concern for aerosolizing the virus if the patient was infected. It is hoped that nitrous oxide will be reinstated for patient use at some point. ■

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ABSTRACT & COMMENTARY

Macrolides During Pregnancy — Behind the Headlines

By Philip R. Fischer, MD, DTM&H

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

SYNOPSIS: Despite published concerns, there is no good evidence that macrolide use during pregnancy causes birth defects.

SOURCE: Fan H, Gilbert R, O'Callaghan F, Li L. Associations between macrolide antibiotics prescribing during pregnancy and adverse child outcomes in the UK: Population based cohort study. *BMJ* 2020;368:m331.

The macrolide antibiotics, erythromycin, clarithromycin, and azithromycin, are used commonly during pregnancy. However, safety concerns have been raised. Thus, Fan and colleagues reviewed data from a large cohort of primary care patients, including, in fact, approximately 7% of people in the United Kingdom. This database is thought to be representative of the diverse population of the United Kingdom. Children born from January 1990 through June 2016 were included if they were registered within six months of birth. Stillborn babies were excluded, as were babies with known genetic syndromes and offspring of mothers who received a "known" teratogen during pregnancy.

Fan and colleagues looked particularly at those mothers who received a prescription for a macrolide between the fifth and final weeks of their gestation. Comparison groups included those who had been treated with penicillin, those who had received a macrolide or a penicillin prescription between 50 and 10 weeks prior to the pregnancy, and siblings of the children included in the study cohort.

The primary outcome measures were malformations and neurodevelopmental disorders (cerebral palsy, epilepsy, attention deficit disorder, and autism spectrum disorder). There were 1,071,379 live births in the database during the study period, and 726,274 had adequate data for inclusion without meeting exclusion criteria. (Most of the excluded subjects were excluded because adequate pre-pregnancy data were not available to complete all aspects of the study.) A total of 621,669 were excluded since they did not receive antibiotics during pregnancy. For comparison, that left 104,605 who had received a macrolide or penicillin, and comparison groups of 82,314 who had received a macrolide or penicillin prior to pregnancy and 53,735 siblings of treated mothers. Of the treated cohort, 24,714 were treated in the first trimester, and 79,891 were treated during subsequent trimesters. Penicillin antibiotics were given approximately 10 times as often as macrolides.

Major malformations were seen in 27.7 per 1,000 children born to mothers who had received a macrolide in the first trimester and in 17.7 per 1,000 children of the mothers who received a penicillin during the first trimester. Corresponding prevalence rates for the subsequent two trimesters of pregnancy were 19.5 for macrolides and 17.3 for penicillins. Specifically, cardiovascular malformations were seen in 10.6 per 1,000 live births for macrolides vs. 6.6 for penicillins.

Genital malformations, such as hypospadias, were reportedly more common with macrolide use than with penicillin use in all trimesters. Based on these data, the authors proposed that, until further data are available, macrolide use in pregnancy be replaced by the use of other antibiotics whenever feasible.

■ COMMENTARY

Fan and colleagues did a rigorous retrospective study to determine whether macrolide use during pregnancy is associated with increased risks for birth defects and neurodevelopmental problems in the children born to macrolide-treated mothers. The study had a large enough population base to be adequately powered to identify relevant risks. The investigators wisely used several different comparison groups to help readers infer risks actually due to macrolide use, as opposed to other coincident pregnancy-related situations. They concluded that: "prescribing macrolide antibiotics during the first trimester of pregnancy was associated with an increased risk of any major malformation," and, "macrolide prescribing in any trimester was associated with an increased risk of genital malformations."

Their work has already prompted a published warning about macrolide use during pregnancy in the nursing literature.[1] If true, these conclusions should prompt "caution" and a decision to use alternative antibiotics "if feasible," as the authors suggested. However, several thought processes cast doubt on the appropriateness of the published conclusions.

As originally published, the paper suggested that the authors' recommendation to restrict the use of macrolide antibiotics during pregnancy was in line with published British guidelines. However, as noted in a correction subsequently published online, those British guidelines actually had merely advised to use macrolides only when the benefit outweighs the risk,[2] similar to guidelines for any medication. The authors concluded that macrolide use "in any trimester" was associated with the risk of malformations.

This conclusion runs counter to consideration of plausibility. The malformations evaluated, specifically genital malformations such as hypospadias, result from alterations in fetal development taking place early in pregnancy. Genital structures are already formed before the third trimester,[3] and it is not plausible that a treatment in the third trimester could reverse aspects of formation/development that are completed already. Nonetheless, Fan and colleagues used their data to conclude that second- and third-trimester exposure to macrolides does increase the risk of hypospadias.

In addition, Fan and colleagues reached their "any trimester" conclusions when combining data from each trimester. When there was a strongly significant statistical association during one part of pregnancy, statistical significance ($P < 0.05$) still was present when including data from trimesters during which there was no significant difference. Such was the case with genital malformations, mostly hypospadias, when the researchers found a "significant" P value in one trimester and then combined data from the other trimesters to conclude that the "risk" related to all trimesters.

Statisticians also would remind us that "statistical significance" actually just means that there is more than a 5% chance of a meaningful difference between groups. When 20 different unassociated variables are evaluated, one would expect, statistically, that at least one of those variables would rank in that "$P < 0.05$" significance range. Fan and colleagues made scores of comparisons, without using a Bonferroni or other "correction factor" in testing significance, and found only a very small number that "reached significance." It is possible that the identified risk of 10.6 per 1,000 incidence of cardiac malformations with macrolide use during the first trimester, compared to a 6.6 per 1,000 incidence in penicillin-treated mothers ($P = 0.03$), with a total of 172 incident cases among the whole database, was the result of the "random chance" of finding some variables with low P values when testing scores of factors.

Similarly, it is not surprising that an apparently random "risk" was found (with a P value of 0.018) of urinary malformations in siblings of children whose mothers received macrolides vs. penicillin during pregnancy.

Of course, one could wonder if the illness prompting antimicrobial use, rather than the antimicrobial itself, might have triggered the risk of poor fetal outcomes. Wisely, Fan and colleagues provided indication-based data about their findings. In a supplemental table, they showed that macrolide vs. penicillin use for respiratory infections during the first trimester was associated only with a risk of cardiac malformations (95% confidence interval for risk, 1.05-2.51). However, there was no increased risk specifically for ventricular septal defects, atrial septal defects, or patent ductus arteriosus. Also, there was no difference in risk between these groups for other malformations or other poor neurodevelopmental outcomes.

In fact, the clearly negative findings of this study are valuable. Macrolide use in pregnancy was not associated with any risk of cerebral palsy, autism spectrum disorder, attention deficit hyperactivity disorder, or epilepsy. In a recent meta-analysis, macrolide use during pregnancy had only a "weak association" with any risk of congenital malformations, and that was only with first-trimester exposure and with either gastrointestinal or musculoskeletal malformations.[4] A separate systematic review published last year by Fan and colleagues found hints only of macrolide-related risk of miscarriage, cerebral palsy, epilepsy, and gastrointestinal malformations — but not other malformations, stillbirths, or neonatal deaths.[5]

Interestingly, 25% of the 726,274 children in this study were exposed to prenatal macrolides or penicillins, and an additional 7% were exposed to other antibiotics. Thus, approximately one-third of women received antibiotic treatment during pregnancy. For those for whom an indication for antimicrobial therapy was identified in the medical record, 75% were treated for respiratory infections. One reasonably could wonder if bacterial respiratory infections truly required antimicrobial treatment in such a large proportion of pregnant women. Doubt about all the treatment actually being necessary certainly adds support to the notion that antimicrobials should be used judiciously and only when truly indicated, whether or not specific risks of treatment are identified. Thus, these new data from Fan and colleagues provide significant reassurance about problems that are likely not due to macrolide use during pregnancy. They do not provide evidence of much significant risk for even cardiac and genital malformations being due to macrolide use. At the same time, these new data do provide good reminders that antimicrobials should be used judiciously during pregnancy. ■

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ABSTRACT & COMMENTARY

Many Serious Cardiac Complications of Pregnancy Are Preventable

By Jamie L. W. Kennedy, MD, FACC

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

SYNOPSIS: Investigators determined about half of serious cardiac complications of pregnancy are preventable.

SOURCE: Pfaller B, Sathananthan G, Grewal J, et al. Preventing complications in pregnant women with cardiac disease. *J Am Coll Cardiol* 2020;75:1443-1452.

Cardiovascular disease is the leading cause of maternal mortality in the United States, accounting for more than one-third of all pregnancy-related deaths.[1] The rate of adverse fetal events also is much higher in women with heart disease, including premature birth, small for gestational age infants, and fetal death. Pfaller et al sought to characterize serious cardiac events in pregnant women with heart disease.

Pregnant women with heart disease were prospectively enrolled in the Canadian Cardiac Disease in Pregnancy (CARPREG) study. Some patients were known to have heart disease prior to conception, while others were diagnosed during pregnancy. This substudy concerned the cohort of patients followed at two centers, one in Vancouver and one in Toronto, between 2004 and 2014. Serious events during pregnancy and up to six months postpartum were recorded. Cardiac events included heart failure, cardiac death, arrest, arrhythmias requiring intensive care unit admission, myocardial infarction, aortic dissection, mechanical valve thrombosis, endocarditis, cerebrovascular events, and need for urgent cardiac intervention. At least two cardiologists reviewed serious cardiac events to determine preventability and contributing factors.

Of the 1,315 pregnancies followed in this study, 17% were complicated by cardiac events, 3.6% of them serious, including five maternal deaths and four resuscitated cardiac arrests. Patients with acquired heart disease, mechanical valves, high-risk native valve lesions, systemic ventricular dysfunction, cyanosis, and New York Heart Association class III or IV symptoms were more likely to experience serious cardiac events. The need for urgent cardiovascular intervention was the most common serious cardiac event, occurring in 0.7% of pregnancies and including valve intervention, resection of cardiac tumor, atrial septal defect closure, and aortic root replacement. Two-thirds of events occurred during pregnancy: one-quarter postpartum, and the remaining during labor and delivery.

Of the 47 pregnancies complicated by severe cardiac events, 42 resulted in live births (45% were preterm deliveries). The overall rate of adverse fetal events in pregnancies with severe cardiac events was 62%, compared to 29% in pregnancies without cardiac events and 32% in pregnancies with nonserious cardiac events. There were 22 severe obstetric events, none fatal, most commonly severe pre-eclampsia. Overall, 5.1% of pregnancies were complicated by pre-eclampsia. Fortunately, only two pregnancies were complicated by both severe cardiac and obstetric events. On chart review, 49% of severe cardiac events were considered definitely, probably, or possibly preventable, including two maternal deaths and three cardiac arrests. Most preventable events occurred in the antepartum period. Provider management-related factors were the largest group of preventable events (74%), including failure to identify cardiac disease, failure to recognize high-risk patients, delays in diagnosis and intervention, and inappropriate treatment. Many preventable events occurred in women who had not been diagnosed with heart disease and patients initially managed at smaller centers. Patient-related factors were identified

in 17% of events, including failure to seek care, noncompliance, and lack of access to healthcare. The authors concluded that although uncommon, about half of serious cardiac complications of pregnancy are preventable.

■ COMMENTARY

The Centers for Disease Control and Prevention reports pregnancy-related mortality in the United States was 17.4 per 100,000 live births in 2018, up from 7.2 per 100,000 in 1987.[2,3] In Canada, the rate has been fairly stable at between 9 and 11 deaths per 100,000 live births between 2000 and 2017.[4] The reasons for the increase in the United States are many and poorly understood. More women conceiving and delivering at an older age (and more likely to do so with comorbid conditions) and improved survival to adulthood for patients with congenital heart disease are two likely contributors. Comorbid conditions in Canadian women also have increased over time without a corresponding increase in mortality, raising the possibility that the Canadian healthcare system is better equipped to care for pregnant women with heart disease.

Sadly, there are significant racial and ethnic disparities in outcomes. Black women exhibit the highest maternal mortality rate in the United States at 42.2 deaths per 100,000 live births.[2] Disadvantages that Black women experience at many levels contribute to this discrepancy, including the rate of unintended pregnancy, burden of comorbid conditions, and limited healthcare access. Of note, Black women are affcted more frequently by peripartum cardiomyopathy for unclear reasons. The reported number of serious cardiac events in this population of pregnant women with heart disease is not un-expected, although the high number of potentially preventable events is surprising. Regardless, there is an opportunity for improvement. Women with known heart disease are somewhat easier to target, with interventions such as preconception counseling, referral to an expert center, and close monitoring throughout pregnancy and the postpartum period by both obstetrician and cardiologist. Interpreting the many physiological changes of pregnancy can be challenging for both patient and physician. Serial biomarkers such as brain natriuretic peptide and even echocardiograms to monitor left ventricular function can be helpful. Faster diagnosis of heart disease during pregnancy requires higher suspicion from treating physicians, primarily in obstetrics, primary care, and emergency medicine, followed by the cardiologists who receive these referrals. Dyspnea at rest, orthopnea, and severe chest pain always are abnormal and warrant full evaluation. ■

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ABSTRACT & COMMENTARY

Malaria Prophylaxis During Pregnancy

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

SYNOPSIS: In a retrospective study of American military women involving 50 treated with atovaquone-proguanil and 156 exposed to mefloquine, no increase in risk of fetal loss or adverse infant outcomes was identified. Atovaquone-proguanil seems safe for use in pregnancy, but data are limited.

SOURCE: Gutman JR, Hall C, Khodr ZG, et al. Atovaquone-proguanil exposure in pregnancy and risk for adverse fetal and infant outcomes: A retrospective analysis. *Travel Med Infect Dis* 2019;32:101519.

Gestational malaria is associated with significant risks to both the mother and the baby. Travel by pregnant women to malaria-endemic areas is not always avoidable. Chloroquine has been used widely in pregnancy without evidence of adverse effects, but it is ineffective against the malaria found in many parts of the world. Mefloquine is thought to be safe in pregnancy, but resistance is increasing. The typical expert advice is to avoid atovaquone-proguanil during pregnancy because of an uncertain safety profile, but the actual risks are unknown.

Gutman and colleagues reviewed data from 198,164 pregnancies of U.S. military women from 2003

to 2014. During that time, 50 women received atovaquone-proguanil during pregnancy, 156 received mefloquine, and 131 received chloroquine. Those who received atovaquone-proguanil were older and more likely to be in the first trimester of pregnancy (since the treatment policy was not to use atovaquone-proguanil when the woman was known to be pregnant).

Women receiving atovaquone-proguanil or mefloquine demonstrated no increased risk of either pregnancy loss (spontaneous abortion, stillbirth) or adverse infant outcome (preterm birth, small for gestational age, large for gestational age, or birth defects). Although the differences were not statistically significant, miscarriage and stillbirth were seen in 28% of women treated with atovaquone-proguanil and 16% of those treated with mefloquine. Pregnancy loss was seen in 6.1% of women treated with chloroquine. Statistically, the use of chloroquine was protective against pregnancy loss.

The authors summarized their findings by saying that a true assessment of the safety of atovaquone-proguanil was not possible with the small number of women included in the study. They suggested that further observational studies be done but, because of concerns for risk, they do not advocate for a randomized prospective study.

■ COMMENTARY

Pregnant women are at particular risk of contracting malaria. With pregnancy, women produce more exhaled carbon dioxide and release different concentrations of transcutaneous substances, making them more attractive to mosquito chemoreceptors.[1] In addition, related to pregnancy-induced changes in immunity and specific parasite-placenta interactions, pregnant women are at risk of severe malaria and serious consequences of malarial infection.[2]

Malaria is dangerous for pregnant women and their babies. Mothers risk pregnancy loss, severe illness, anemia, premature labor, and death.[1] Babies born to women with gestational malaria are at increased risk of congenital malaria, low birthweight, neonatal fever, neonatal death, infantile anemia, infantile malaria, and death during the first year of life.[3] Thus, it is wise to try to prevent malaria during pregnancy.[4] For women who must be in areas where malaria is endemic, mosquito bites should be avoided by wisely using insecticide-impregnated clothing to cover skin, insect repellents such as diethyl-meta-toluamide (DEET) or picaridin, and insecticide-impregnated bed nets. Behaviorally, pregnant women also can try to stay away from areas where *Anopheles* mosquitoes are active, especially during evening and night hours. In addition, because of the risk of malaria and its severe consequences, they should take chemoprophylaxis.

There are several sorts of malarial prevention medications.[4,5] Chloroquine remains effective in parts of Central America but not in most other malarial areas of the world. Mefloquine is effective in most malarial areas, but it does cause bothersome side effects (nausea, unpleasant dreams) in nearly one-fifth of those who take it. It should not be used in those with active seizure disorders, cardiac rhythm disturbances, and psychiatric conditions. Atovaquone-proguanil is expensive but usually is well-tolerated and was the focus of Gutman's study. Doxycycline usually is avoided during pregnancy because of concerns about altered bone and tooth development in the growing fetus, but experts in some countries accept its use, when truly necessary, during pregnancy.[5] Finally, primaquine can be used to prevent malaria, but it carries a risk of triggering hemolysis in those with glucose-6-phosphate dehydrogenase deficiency (such as untested but affected fetuses). This summary of malaria preventive treatments serves as a reminder that atovaquone-proguanil, although incompletely tested, is the only agent without significant, proven risk (even though it is expensive). Thus, it was very helpful for Gutman and colleagues to try to determine through a retrospective observational study if atovaquone-proguanil actually is safe in pregnancy. Previously, a study of 149 Danish women inadvertently exposed to atovaquone-proguanil during early pregnancy showed no unusual risk of birth defects.[6] A retrospective review and a systematic review provided some (incompletely conclusive) optimism for the safety of atovaquone-proguanil.[7,8]

How should we interpret and apply the findings of the new study by Gutman and colleagues? Certainly, we can agree with the authors that the number of subjects was small and that a significant risk still could exist below the level of statistical significance of this study. Further studies are warranted.

At the same time, there are reasons to believe that the increased incidence of fetal loss with atovaquone-proguanil (28%) vs. mefloquine (16%) was not only statistically insignificant but, even if it is significant in larger studies, it likely is related to separate factors. First, the women in Gutman's study who received atovaquone-proguanil were older overall than the women who received mefloquine, and twice as many were older than 35 years of age. Older age during pregnancy can be associated with increased risks.

Second, more of the atovaquone-proguanil exposed women were in their first trimester of pregnancy, and essentially all were unaware of their pregnancy at the time of treatment. Miscarriage is most common during the first trimester, and it could be that the timing of treatment (earlier, first trimester), rather than the treatment itself, could prompt the women in the atovaquone-proguanil group to have more

miscarriages than those in the mefloquine group. Finally, it is not clear whether the women receiving atovaquone-proguanil might have been visiting geographical areas or participating in activities (such as brief, dangerous missions) during deployment that might have increased the risk of fetal loss separate from the medication use. Thus, the new study from Gutman provides reassurance that even more data demonstrate no significant risk of poor outcomes related to the use of atovaquone-proguanil during pregnancy. However, that reassurance is incomplete since some risk still could exist for an individual traveler. We must mitigate risk wisely by using non-pharmacologic protection against mosquito bites and by carefully considering the risks and benefits as we make specific chemoprophylaxis recommendations for women who are pregnant or might become pregnant during travel to malarial areas.

Statistically, the finding that chloroquine protected against pregnancy loss is fascinating. The authors attributed this protection to the known anti-inflammatory properties of chloroquine. Although no one should suggest using chloroquine to prevent miscarriage, pregnant travelers to areas of the Caribbean and Central America where malaria is sensitive to chloroquine certainly can use chloroquine with confidence. ■

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CME/CE QUESTIONS

1. **Which of the following is true regarding macrolide use in pregnancy?**
   a. It is strongly associated with epilepsy in exposed newborns.
   b. It is associated with gastrointestinal malformations in exposed newborns.
   c. It should be considered judiciously, as for any other antimicrobial agent.
   d. It is contraindicated.
2. **Most preventable serious cardiac events in pregnant women occur:**
   a. antepartum.
   b. during labor.
   c. during delivery.
   d. postpartum.
3. **In the study by Nodine et al, factors associated with increased odds of conversion to another pain control modality during labor after starting with nitrous oxide include all of the following *except*:**
   a. multiparity.
   b. labor induction.
   c. pitocin augmentation.
   d. a history of cesarean delivery.