TRAVEL MEDICINE ADVISOR

This Month's Compendium of Articles from Other Thomson American Health Consultants Publications

THOMSON
AMERICAN HEALTH CONSULTANTS

INSIDE

Volume 16, No. 3
March 2006

Financial Disclosure:

Travel Medicine Advisor's physician editor, Frank Bia, MD, MPH, is a consultant for GlaxoSmithKline and Aventis, and receives funds from Johnson & Johnson. The peer reviewer, Philip Fischer reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company related to this field of study.

Travel Medicine Advisor® is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd. NE, Six Piedmont Center, Suite 400, Atlanta, GA 30305. Periodicals postage paid at Atlanta, GA. POSTMASTER: Send address changes to *Travel Medicine Advisor®,* P.O. Box 740059, Atlanta, GA 30374.
Customer Service:
1-800-688-2421.
Subscription Information:
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Toxic Shock Syndrome After Medical Abortion

ABSTRACT & COMMENTARY

By Leon Speroff, MD
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Dr. Speroff is a consultant for Barr Laboratories.

Synopsis: *Rare cases of fatal toxic shock syndrome associated with* Clostridium sordellii *have been reported; clinicians are urged to be aware of warning signals.*

Source: Fischer M, et al. Fatal Toxic Shock Syndrome Associated with *Clostridium sordellii* After Medical Abortion. *N Engl J Med.* 2005;353:2352-2360.

THE CDC REPORTED 4 CASES OF FATAL TOXIC SHOCK SYNDROME IN CALIFORNIA ASSOCIATED with *Clostridium sordellii* that occurred within one week after medical abortions (induced with 200 mg of oral mifepristone and 800 µg of vaginal misoprostol).[1]

Patient 1: A healthy 18-year-old woman underwent medical abortion at 47 days gestation and, 4 days later, was seen in an emergency ward with abdominal cramping. She was afebrile and there was no tenderness on physical examination. No laboratory studies or cultures were obtained. Three days later, the patient returned with nausea, vomiting, and weakness. She was again afebrile, but now had tachycardia, hypotension, an extremely elevated white count, blood cultures that later were negative, and bilateral infiltrates on chest X-ray. She still had no positive findings on physical examination. Despite treatment with antibiotics, the patient rapidly developed respiratory distress and died 10 hours after admission.

Patient 2: A healthy 21-year-old woman underwent medical abortion at 43 days gestation, and became unresponsive 6 days later. Resuscitation was unsuccessful. No laboratory studies or cultures were performed.

Patient 3: A healthy 22-year-old woman underwent medical abortion at 53 days gestation, and presented to an emergency ward 5 days later with nausea, vomiting, diarrhea, and abdominal pain. The patient had normal vital signs except for mild tachycardia. The patient was admitted to rule out an ectopic pregnancy, and the next day developed hypotension, diffuse abdominal tenderness, a white count of 120,200 cells/µL, and metabolic acidosis. Blood cultures before antibiotic treatment were negative. Within a few hours, the patient had a cardiopulmonary arrest. Emergency laparotomy revealed a large amount of serous peritoneal fluid that failed to grow aerobic or anaerobic bacteria. The patient died during surgery, 23 hours after coming to the hospital.

Patient 4: This healthy 34-year-old woman had her medical abortion at 45 days gesta-

tion, and presented to an emergency ward 4 days later with nausea, vomiting, and abdominal pain. Vital signs were normal, and the only finding on physical examination was abdominal tenderness. Her white count was elevated and cultures of blood and urine were later negative. Despite antibiotic treatment, the patient went into refractory hypotension and died 12 hours after presenting to the hospital.

The autopsies revealed pleural, pericardial, and peritoneal effusions, inflammation of endometrium and myometrium with multiple small abscesses, necrosis, and hemorrhage without gas formation. There were no retained fetal or placental tissues. Formalin-fixed tissues were obtained by the CDC, and *Clostridium sordellii* was identified in uterine tissues by a nonspecific polyclonal anti-clostridium antibody, followed by specific polymerase-chain-reaction assays on extracted DNA.

COMMENTARY

Clostridium sordellii is a Gram-positive anaerobic bacillus that has been previously identified as a cause of fatal toxic shock syndrome in 10 cases in the United States, 8 within one week after delivery of live-born infants, one within a week after a medical abortion, and one not associated with pregnancy (and one more case in Canada following medical abortion). The clinical and pathological findings (responses to exotoxins) in the 4 new cases and the 10 previous cases were similar. Clostridium species are known to colonize the vagina and to be associated with postpartum endometritis and septic abortion. Recognized infections with *Clostridium sordellii*, however, are very rare, although this rare prevalence may be partly due to the difficulty in the isolation and identification of this organism. The usual anaerobic culture techniques seem to be insufficient for timely diagnosis. The FDA has reported that testing the manufacturing lots of mifepristone and misoprostol has indicated no evidence of bacterial contamination.

How great is the risk? The 4 patients in this report and the one previous case (whose death was attributed to a ruptured ectopic pregnancy) represent the only fatal cases recognized after nearly 500,000 uses of medical abortion in the United States since mifepristone was approved in 2000. The mortality rate is estimated to be from 1.0 to 1.5 per 100,000, a rate that would be higher than that associated with legal surgical abortions. The number of American women reported as dying from abortion declined from nearly 300 deaths in 1961, to only 6 in 1985, 10 in 1992, and 4 in 1999, or about 0.6 deaths for every 100,000 legal abortions.[2,3] The risk of death from any cause associated with pregnancy is higher. For comparison, in 1990, the maternal death rate for childbirth in the United States was 10 per 100,000 births, and for ectopic pregnancy, approximately 50 per 100,000 cases[4-6] and, in 1992, 17 deaths were associated with spontaneous miscarriage.[2]

Why haven't similar cases been reported in Europe? Philip Darney has speculated regarding the possibilities.[7] Because of equivalent efficacy and safety, the currently accepted method of medical abortion, supported by the recommendation of the World Health Organization, uses 200 mg mifepristone orally followed the next day by 800 µg misoprostol vaginally; this differs from

the FDA-approved regimen of 600 mg mifepristone orally followed by 400 µg misoprostol also given orally. Thus, one might suspect different American and European experiences to reflect the different dose of mifepristone; however, American clinicians have not followed the FDA-approved regimen, but instead, used the European lower-dose regimen that has solid clinical trial support. The use of self-administered vaginal misoprostol in America is different compared with the European practice of administering misoprostol by health care personnel in a clinic setting. Darney questions whether the misoprostol oral route, with its equivalent pharmacokinetic behavior, might be preferable.

Is there an alteration in immunity secondary to one of the drugs. McGregor and Equiles suggest that mifepristone may impair stress responses by blocking both progesterone and glucocorticoid receptors.[8] On the other hand, Grimes points out that infection with *Clostridium sordellii* has occurred without exposure to mifepristone.[9]

At this point in time, no changes have been suggested in the regimen used for medical abortion. The best prevention of fatal toxic shock with this rare infection is awareness of the possibility and early recognition. Abdominal cramping as a presenting complaint makes the diagnosis difficult because this is a common symptom following medical abortion. Unique characteristics include: the absence of fever, markedly elevated white counts, fluid effusions sufficient to produce hemoconcentration, and eventually tachycardia and hypotension. Specific antibiotics with demonstrated efficacy against *Clostridium sordellii* have not been identified. Early recognition of this rare infection would mandate consideration of aggressive surgery with hysterectomy, a lesson learned from the experience with septic abortions in the years before legalized abortion. ■

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Aim Toward Success in Oral Contraceptives Compliance; Better Communication Improves Use

By Rebecca Bowers, Author

Rebecca Bowers reports no relationship with any company having ties to this field of study.

THE NEXT WOMAN IN YOUR EXAMINATION ROOM HAS BEEN using oral contraceptives (OCs) as her chosen method of birth control for the past three months. During her checkup, she tells you that she often misses a pill in her pack, but doesn't take further precautions for protection.

This woman is not alone in her dilemma. According to a new international study, more than one-third of women continue to have unprotected sexual intercourse when they know the Pill's reliability may be compromised.[1] What can providers do to help women achieve success with daily pill-taking?

About 60% of the 62 million women ages 15-44 in the United States are using a contraceptive method; about 30% of those women are using the Pill for birth control.[2] The Pill represents a very effective form of contraception. When used correctly, for every 1000 women who take pills for one year, just 3 will become pregnant in the first year of use.[3] But in a typical use setting, the Pill's failure rate rises to 8% in the first year.[3]

What can you do to help women achieve success with oral contraceptives? Know that the office/clinic visit is just the start of the patient's/ client's process of effective contraceptive use, says Deborah Oakley, PhD, professor emeritus in the University of Michigan School of Nursing in Ann Arbor. "The provider can help with this future behavioral process by asking about whether the woman has a plan for how she is going to use her method effectively, what that plan is, and how she is going to overcome barriers and solve problems," says Oakley, who has studied Pill use.[4-7]

Many women experience difficulty in taking the Pill correctly, according to results from the new survey.[1] To perform the analysis, researchers questioned 8531 heterosexual men and women ages 16-40 years in 14 countries about their contraceptive use and experience. A previous survey shows that more than two-thirds of women regularly miss pills, and one in 5 Pill users miss a pill every month.[8]

Problems with pill-taking can lead to fears. More than half of Pill users and 40% of men whose partner used the Pill had thought they/their partner might be pregnant while on the Pill, according to results from the new survey.[1] Overall, 67% of women and 59% of men reported that pregnancy scares had a negative impact on their emotional life, rising to 72% and 67%, respectively, if their career was important to them. About 25% of women and men reported a negative impact on their work or studies, with figures rising to 34% and 42%, respectively among respondents who said their career or studies were important to them.[1]

Who Can Take OCs Daily?

What are some ways to assess a woman's ability to take a pill every day? Findings from research performed by Oakley and family planning colleagues suggest that 2 of the most powerful predictors of those who especially need to be asked about future plans for effective use are:

- women who have had an abortion
- women who are not especially strong in their resolve to avoid pregnancy for the next 6 months

Contrary to many clinicians' beliefs, risky OC use is not necessarily related to socioeconomic status or age, says Oakley. Recent research confirms that compliance problems are common among all age groups, with 47% of women missing one or more pills per cycle, and almost a quarter (22%) missing 2 or more pills per cycle.[9]

Help women to formulate a game plan for success with oral contraceptives, says Oakley. Help them to identify potential barriers and discuss how to solve such problems—use the following problem areas as discussion triggers:

- staying overnight at a friend or relative's house and forgetting to take her pill pack;
- forgetting to take a pill during a stressful time at work or school;
- drinking too much or getting sick so that no protection is used or severe vomiting occurs;
- not having money to refill a prescription.

"Listening is such a powerful tool, and more of the provider-client/patient interaction needs to be focused on asking questions about how the future will unfold for the contraceptive user," says Oakley.

Educate on Side Effects

Aside from providing basic information about OCs, provide anticipatory guidance as part of the counseling process, says Mimi Zieman, MD, adjunct associate professor at Emory University in Atlanta. Although many women never experience adverse events related to Pill use, others may have episodes of breakthrough bleeding or may skip an entire period.[10]

"It is very important when a woman is starting oral contraceptives to know in advance what side effects she may have and the usual time course of those side effects, because many improve with time," says Zieman. "The most important message is that if she is experiencing anything that she is worried about, or she doesn't like, that she needs to call [the provider's office] before just stopping using the method."

Many teen OC users tend to skip pills, so anticipatory counseling also should include emergency contraception methods, use of backup contraceptives, and alternatives to sexual intercourse.[10]

Help patients to establish a regular pill-taking regimen, which may be cued to daily activities such as putting on earrings, brushing teeth, or showering. Another way women are reminding themselves to take their pill is by setting their cell phones to beep at a certain time each day. Research has looked at using daily e-mail reminders for pill-taking; 64% of women participating in the study said they found such reminders helpful.[11]

By gearing oral contraceptive counseling to a woman's individual needs, clinicians can increase the likelihood that patients will adhere to the prescribed regimen, says Zieman.

"Today, there are so many formulations and so many delivery systems that we can really work to make people as satisfied as possible with their chosen method," she states. ■

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Correction

In the January issue, we included a letter which marked the beginning of the next semester of CME. In the letter we stated that once the CME activity was complete, the activity would be valid for 6 months. It should have read that the CME activity would be valid for 36 months. We apologize for any inconvenience.

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Treating Opioid-Dependent Patients with OAT

A Perspective article in the Jan. 17 *Annals of Internal Medicine* reviews pain management in patients with a history of opioid addiction who are receiving opioid agonist therapy (OAT) with maintenance methadone or buprenorphine. These patients present unique challenges that frequently result in suboptimal treatment of acute pain.

The authors provide an excellent review of these challenging patients and point our 4 common misconceptions: 1) Maintenance opioids provide analgesia—not only is this not the case, but OAT may reduce the effectiveness of standard pain relief measures; 2) Opioids for analgesia may result in addiction relapse—there is no evidence that treatment of acute pain triggers relapse; 3) The additive effects of opioid analgesics and OAT may cause respiratory and CNS depression—tolerance to the respiratory and CNS effects of opioids develops rapidly and is not exacerbated by acute therapy; 4) Reporting pain is drug-seeking behavior—as long as there is clinical evidence of pain, or an acute injury, pain may be safely treated. Drug seeking and manipulation is more likely characterized by vague reports of long-term pain than requests for short term pain relief. Plus, patients on OAT are less likely to experience euphoria associated with coadministered opioids, so there is less incentive to drug seek.

The authors provide specific pain treatment recommendations for patients on methadone and buprenorphine. They conclude, "Addiction elicits neurophysiologic, behavioral, and social responses that worsen the pain experience and complicate provision of adequate analgesia. These complexities are heightened for patients with opioid dependency who are receiving OAT, for whom the neural responses of tolerance or hyperalgesia may alter the pain experience. As a consequence, opioid analgesics are less effective; higher doses administered at shortened intervals are required. Opioid agonist therapy provides little, if any, analgesia for acute pain. Fears that opioid analgesia will cause addiction relapse or respiratory and CNS depression are unfounded. Furthermore, clinicians should not allow concerns about being manipulated to cloud good clinical assessment or judgment about the patient's need for pain medications. Reassurance regarding uninterrupted OAT and aggressive pain management will mitigate anxiety and facilitate successful treatment of pain in patients receiving OAT" (Alford DP, et al. *Ann Intern Med*. 2006;144:127-134).

Long-Term Effects of Warfarin Use

Warfarin use may be associated with osteoporosis and fractures in men, but not women, with atrial fibrillation, according to new study. In a retrospective cohort study of Medicare benefici-

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5416. E-mail: leslie.hamlin@thomson.com.

aries with atrial fibrillation in United States, 4461 patients on long-term warfarin therapy were compared to 7587 patients who were not prescribed warfarin. The adjusted odds ratio of fracture was 1.25 in patients who took warfarin (95% CI, 1.06-1.48). The odds ratio for men was 1.63, and a nonsignificant 1.05 for women. In patients who were prescribed warfarin for less than one year, the risk of osteoporotic fracture was not increased significantly. The authors speculate that since warfarin blocks vitamin K dependent clotting factors, it may also block vitamin K dependent osteocalcin and other bone matrix proteins. Interestingly, use of beta blockers reduced the risk of fracture in this population. The authors conclude that long-term use of warfarin was associated with osteoporotic fractures in men with atrial fibrillation, and that beta-blockers may be somewhat protective (Gage BF, et al. *Arch Intern Med*. 2006;166:241-246).

Statins' Multiple Benefits

Mounting evidence suggest that statins have benefits beyond their ability to lower LDL cholesterol. Multiple studies show that statins reduce inflammation in patients without heart failure. Now, 2 new studies suggest that they also reduce inflammation in patients with heart failure. In a study from Emory University, 108 patients with nonischemic heart failure were randomized to atorvastatin 20 mg per day or placebo. Inflammatory markers such as C reactive protein, interleukin-6, and TNF-alpha were all reduced in the atorvastatin group. Atorvastatin treated patients also showed an improvement in LVEF from 0.33-0.37 over one year (P = 0.01) (Sola S, et al. *J Am Coll Cardiol*. 2006;47:332-337).

A second study, from Harvard, in patients with heart failure showed that atorvastatin 10 mg/ day led to an 8% reduction in TNF receptor 1, a 37% reduction in C reactive protein, and a 17% reduction in endothelin-1 (Mozaffarian D, et al. *Am J Cardiol*. 2005;96:1699-1704). Atorvastatin may also have anti-thrombotic effects in patients with unstable angina according to a study from Greece. Forty-five patients with normal cholesterol levels and unstable angina were randomized to 10 mg of atorvastatin or placebo, starting right after hospital admission and continuing for 6 weeks. After one week of treatment circulating levels of anti-thrombin III, factor V, and von Willebrand factor were all significantly reduced in the atorvastatin group (Tousoulis D, et al. *Int J Cardiol*. 2006;106:333-337).

FDA Actions

The FDA has approved the first inhaled insulin for the treatment of adults with type I and type 2 diabetes. Inhaled insulin, a powder form of recombinant human insulin, has been in development for over 10 years, and has been the subject of intense scrutiny by the FDA. Concerns over long-term safety, particularly in people with underlying lung disease, has delayed approval, and safety in children and teenagers is still under investigation. Inhaled insulin is delivered through a device that is significantly larger than an asthma inhaler and, even folded, is the size of a flashlight. A blister pack of insulin powder is inserted into the device, which is then triggered. It is not to be used by smokers or people who quit smoking within last 6 months, and is not recommended for people with asthma, bronchitis, or emphysema. The FDA also recommends pulmonary function testing prior to starting inhalation therapy, and every 6 to 12 months thereafter. Although the product is approved for treatment of both type I and type 2 diabetes, fewer than 30% of type I diabetics achieve adequate control with inhaled insulin alone. Inhaled insulin is a joint effort by Pfizer, Sanofi-Aventis, and Nektar Therapeutics. It will be marketed under the trade name Exubera.

The FDA has approved an intravenous form of Ibandronate that can be administered every 3 months for the treatment of postmenopausal osteoporosis. The 3 mg dose is injected intravenously over 15 to 30 seconds by a healthcare professional. The drug is an option for women who cannot take pills or are unable to sit upright for 30 to 60 minutes after taking an oral bisphosphonate. Efficacy with the injectable form of ibandronate was better than once-a-day oral dosing of Ibandronate 2.5 mg in a study of over 1300 women with osteoporosis. Intravenous and oral forms of the drug were equally well tolerated. The FDA is recommending measurement of serum creatinines prior to administration each dose. Ibandronate is also approved is a 2.5 mg once a day oral dose and a 150 mg monthly oral dose. All 3 formulations are marketed as Boniva.

Berlex's combination estradiol-levonorgestrel patch (Climara Pro) has been approved for the indication for prevention of postmenopausal osteoporosis in women with an intact uterus. The patch was previously approved for the indication of moderate to severe vasomotor symptoms associated with menopause. The osteoporosis indication was based on a 2-year, double-blind, randomized trial that showed that the estradiol-levonorgestrel patch was associated with significant maintenance of bone density compared to placebo. ■