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*The author reports no financial relationships relevant to this article.*

Recent news and expert perspective on therapy for cesarean incision wounds, vaginal cleansing, managing skin abscesses, *C difficile* infection in obstetric patients, and risks of maternal Zika virus infection

In this Update I highlight 5 interesting investigations on infectious diseases. The first addresses the value of applying prophylactically a negative-pressure wound dressing to prevent surgical site infection (SSI) in obese women having cesarean delivery (CD). The second report assesses the effectiveness of a preoperative vaginal wash in reducing the frequency of postcesarean endometritis. The

third investigation examines the role of systemic antibiotics, combined with surgical drainage, for patients who have subcutaneous abscesses ranging in size up to 5 cm. The fourth study presents new information about the major risk factors for *Clostridium difficile* infections in obstetric patients. The final study presents valuable sobering new data about the risks of congenital Zika virus infection.

## Negative-pressure wound therapy after CD shows some benefit in preventing SSI

Yu L, Kronen RJ, Simon LE, Stoll CR, Colditz GA, Tuuli MG. Prophylactic negative-pressure wound therapy after cesarean is associated with reduced risk of surgical site infection: a systematic review and meta-analysis. *Am J Obstet Gynecol.* 2018;218(2):200-210.e1.

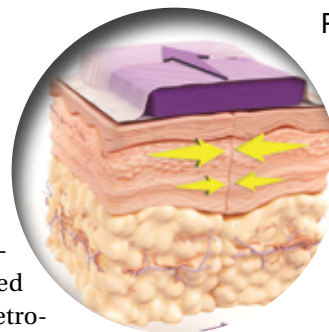
**Y**u and colleagues sought to determine if the prophylactic use of negative-pressure devices, compared with standard wound dressing, was effective in reducing the frequency of SSI after CD.

The authors searched multiple databases and initially identified 161 randomized controlled trials and cohort studies for further assessment. After applying rigorous exclusion criteria, they ultimately selected 9 studies for systematic review and meta-analysis.

Six studies were randomized controlled trials (RCTs), 2 were retrospective cohort studies, and 1 was a prospective cohort study. Five studies were considered high quality; 4 were of low quality.

### Details of the study

Several types of negative-pressure devices were used, but the 2 most common were the Prevena incision management system (KCI, San Antonio, Texas) and PICO negative-pressure wound therapy (Smith & Nephew, St. Petersburg, Florida). The majority of patients in all groups were at high risk for wound complications because of obesity.



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Passive wound closure (left) compared with negative-pressure wound therapy with the Prevena incision management system (right).

The primary outcome of interest was the frequency of SSI. Secondary outcomes included dehiscence, seroma, endometritis, a composite measure for all wound complications, and hospital readmission.

The absolute risk of SSI in the intervention group was 5% (95% confidence interval [CI], 2.0%–7.0%) compared with 11% (95% CI, 7.0%–16.0%) in the standard dressing group. The pooled risk ratio was 0.45 (95% CI, 0.31–0.66). The absolute risk reduction was 6% (95% CI, -10.0% to -3.0%), and the number needed to treat was 17.

There were no significant differences in the rate of any of the secondary outcomes other than the composite of all wound complications. This difference was largely

accounted for by the difference in the rate of SSI.

### How negative-pressure devices aid wound healing

Yu and colleagues explained that negative-pressure devices exert their beneficial effects in various ways, including:

- shrinking the wound
- inducing cellular stretch
- removing extracellular fluids
- creating a favorable environment for healing
- promoting angiogenesis and neurogenesis.

Multiple studies in nonobstetric patients have shown that prophylactic use of negative-pressure devices is beneficial in reducing the rate of SSI.<sup>1</sup> Yu and colleagues' systematic review and meta-analysis confirms those findings in a high-risk population of women having CD.

### Study limitations

Before routinely adopting the use of negative-pressure devices for all women having CD, however, obstetricians should consider the following caveats:

- The investigations included in the study by Yu and colleagues did not consistently distinguish between scheduled versus unscheduled CDs.
- The reports did not systematically consider other major risk factors for wound complications besides obesity, and they did not control for these confounders in the statistical analyses.
- The studies included in the meta-analysis did not provide full descriptions of other measures that might influence the rate of SSIs, such as timing and selection of prophylactic antibiotics, selection of suture material, preoperative skin preparation, and closure techniques for the deep subcutaneous tissue and skin.
- None of the included studies systematically considered the cost-effectiveness of the negative-pressure devices. This is an important consideration given that the acquisition cost of these devices ranges from \$200 to \$500.

### WHAT THIS EVIDENCE MEANS FOR PRACTICE

Results of the systematic review and meta-analysis by Yu and colleagues suggest that prophylactic negative-pressure wound therapy in high-risk mostly obese women after CD reduces SSI and overall wound complications. The study's limitations, however, must be kept in mind, and more data are needed. It would be most helpful if a large, well-designed RCT was conducted and included 2 groups with comparable multiple major risk factors for wound complications, and in which all women received the following important interventions<sup>2-4</sup>:

- removal of hair in the surgical site with a clipper, not a razor
- cleansing of the skin with a chlorhexidine rather than an iodophor solution
- closure of the deep subcutaneous tissue if the total subcutaneous layer exceeds 2 cm in depth
- closure of the skin with suture rather than staples
- administration of antibiotic prophylaxis, ideally with a combination of cefazolin plus azithromycin, prior to the surgical incision.

# Vaginal cleansing before CD lowers risk of postop endometritis

Caissutti C, Saccone G, Zullo F, et al. *Vaginal cleansing before cesarean delivery: a systematic review and meta-analysis. Obstet Gynecol. 2017;130(3):527–538.*

**C**aissutti and colleagues aimed to determine if cleansing the vagina with an antiseptic solution prior to surgery reduced the frequency of postcesarean endometritis. They included 16 RCTs (4,837 patients) in their systematic review and meta-analysis. The primary outcome was the frequency of postoperative endometritis.

## Details of the study

The studies were conducted in several countries and included patients of various socioeconomic classes. Six trials included only patients having a scheduled CD; 9 included both scheduled and unscheduled cesareans; and 1 included only unscheduled cesareans. In 11 studies, povidone-iodine was the antiseptic solution used. Two trials used chlorhexidine diacetate 0.2%, and 1 used chlorhexidine diacetate 0.4%. One trial used metronidazole 0.5% gel, and another used the antiseptic cetrimide, which is a mixture of different quaternary ammonium salts, including cetrimonium bromide.

In all trials, patients received prophylactic antibiotics. The antibiotics were administered prior to the surgical incision in 6 trials; they were given after the umbilical cord was clamped in 6 trials. In 2 trials, the antibiotics were given at varying times, and in the final 2 trials, the timing of antibiotic administration was not reported. Of note, no trials described the method of placenta removal, a factor of considerable significance in influencing the rate of postoperative endometritis.<sup>5,6</sup>

**Endometritis frequency reduced with vaginal cleansing; benefit greater in certain groups.** Overall, in the 15 trials in which vaginal cleansing was compared with

placebo or with no treatment, women in the treatment group had a significantly lower rate of endometritis (4.5% compared with 8.8%; relative risk [RR], 0.52; 95% CI, 0.37–0.72). When only women in labor were considered, the frequency of endometritis was 8.1% in the intervention group compared with 13.8% in the control group (RR, 0.52; 95% CI, 0.28–0.97). In the women who were not in labor, the difference in the incidence of endometritis was not statistically significant (3.5% vs 6.6%; RR, 0.62; 95% CI, 0.34–1.15).

In the subgroup analysis of women with ruptured membranes at the time of surgery, the incidence of endometritis was 4.3% in the treatment group compared with 20.1% in the control group (RR, 0.23; 95% CI, 0.10–0.52). In women with intact membranes at the time of surgery, the incidence of endometritis was not significantly reduced in the treatment group.

Interestingly, in the subgroup analysis of the 10 trials that used povidone-iodine, the reduction in the frequency of postcesarean endometritis was statistically significant (2.8% vs 6.3%; RR, 0.42; 95% CI, 0.25–0.71). However, this same protective effect was not observed in the women treated with chlorhexidine. In the 1 trial that directly compared povidone-iodine with chlorhexidine, there was no statistically significant difference in outcome.

## Simple intervention, solid benefit

Endometritis is the most common complication following CD. The infection is polymicrobial, with mixed aerobic and anaerobic organisms. The principal risk factors for postcesarean endometritis are low socioeconomic status, extended duration of labor and ruptured membranes, multiple vaginal



## FAST TRACK

*Women treated with vaginal cleansing before cesarean had a significantly lower rate of endometritis compared with those who received placebo or no treatment—4.5% vs 8.8% (RR, 0.52; 95% CI, 0.37–0.72)*

## WHAT THIS EVIDENCE MEANS FOR PRACTICE

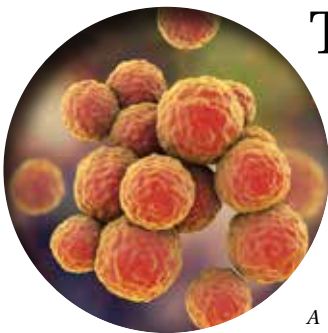
From my perspective, the interesting unanswered question is why a chlorhexidine solution with low alcohol content was not more effective than povidone-iodine, given that a chlorhexidine abdominal wash is superior to povidone-iodine in preventing wound infection after cesarean delivery.<sup>7</sup> Until additional studies confirm the effectiveness of vaginal cleansing with chlorhexidine, I recommend the routine use of the povidone-iodine solution in all women having CD.

examinations, internal fetal monitoring, and pre-existing vaginal infections (principally, bacterial vaginosis and group B streptococcal colonization).

Two interventions are clearly of value

in reducing the incidence of endometritis: administration of prophylactic antibiotics prior to the surgical incision and removal of the placenta by traction on the cord as opposed to manual extraction.<sup>5,6</sup>

The assessment by Caissutti and colleagues confirms that a third measure—preoperative vaginal cleansing—also helps reduce the incidence of postcesarean endometritis. The principal benefit is seen in women who have been in labor with ruptured membranes, although certainly it is not harmful in lower-risk patients. The intervention is simple and straightforward: a 30-second vaginal wash with a povidone-iodine solution just prior to surgery.



## Treat smaller skin abscesses with antibiotics after surgical drainage? Yes.

Daum RS, Miller LG, Immergluck L, et al; for the DMID 07-0051 Team.

A placebo-controlled trial of antibiotics for smaller skin abscesses. *N Engl J Med.* 2017;376(26):2545-2555.

**F**or treatment of subcutaneous abscesses that were 5 cm or smaller in diameter, investigators sought to determine if surgical drainage alone was equivalent to surgical drainage plus systemic antibiotics. After their abscess was drained, patients were randomly assigned to receive either clindamycin (300 mg 3 times daily) or trimethoprim-sulfamethoxazole (80 mg/400 mg twice daily) or placebo for 10 days. The primary outcome was clinical cure 7 to 10 days after treatment.

### Details of the study

Daum and colleagues enrolled 786 participants (505 adults, 281 children) in the prospective double-blind study. *Staphylococcus aureus* was isolated from 527 patients (67.0%); methicillin-resistant *S aureus* (MRSA) was

isolated from 388 (49.4%). The cure rate was similar in patients in the clindamycin group (83.1%) and the trimethoprim-sulfamethoxazole group (81.7%), and the cure rate in each antibiotic group was significantly higher than that in the placebo group (68.9%;  $P < .001$  for both comparisons). The difference in treatment effect was specifically limited to patients who had *S aureus* isolated from their lesions.

**Findings at follow-up.** At 1 month of follow-up, new infections were less common in the clindamycin group (6.8%) than in the trimethoprim-sulfamethoxazole group (13.5%;  $P = .03$ ) or the placebo group (12.4%;  $P = .06$ ). However, the highest frequency of adverse effects occurred in the patients who received clindamycin (21.9% vs 11.1% vs 12.5%). No adverse effects were judged to be serious, and all resolved without sequela.

### Controversy remains on antibiotic use after drainage

This study is important for 2 major reasons. First, soft tissue infections are quite common



## WHAT THIS EVIDENCE MEANS FOR PRACTICE

In my opinion, this investigation by Daum and colleagues supports a role for consistent use of systemic antibiotics following surgical drainage of clinically significant subcutaneous abscesses that have a 5 cm or smaller diameter. Several oral antibiotics are effective against *S aureus*, including MRSA.<sup>10</sup> These drugs include trimethoprim-sulfamethoxazole (1 double-strength tablet orally twice daily), clindamycin (300–450 mg 3 times daily), doxycycline (100 mg twice daily), and minocycline (200 mg initially, then 100 mg every 12 hours).

Of these drugs, I prefer trimethoprim-sulfamethoxazole, provided that the patient does not have an allergy to sulfonamides. Trimethoprim-sulfamethoxazole is significantly less expensive than the other 3 drugs and usually is better tolerated. In particular, compared with clindamycin, trimethoprim-sulfamethoxazole is less likely to cause antibiotic-associated diarrhea, including *Clostridium difficile* infection. Trimethoprim-sulfamethoxazole should not be used in the first trimester of pregnancy because of concerns about fetal teratogenicity.

and can evolve into serious problems, especially when the offending pathogen is MRSA. Second, controversy exists about whether systemic antibiotics are indicated if the subcutaneous abscess is relatively small and is adequately drained. For example, Talan and colleagues demonstrated that, in settings with a high prevalence of MRSA, surgical drainage combined with trimethoprim-sulfamethoxazole (1 double-strength tablet orally twice daily) was superior to drainage plus placebo.<sup>8</sup> However, Daum and Gold recently debated the issue of drainage plus antibiotics in a case vignette and reached opposite conclusions.<sup>9</sup>



## Antibiotic use, common in the obstetric population, raises risk for *C difficile* infection

Ruiter-Ligeti J, Vincent S, Czuzoj-Shulman N, Abenhaim HA. Risk factors, incidence, and morbidity associated with obstetric *Clostridium difficile* infection. *Obstet Gynecol*. 2018;131(2):387–391.

**T**he objective of this investigation was to identify risk factors for *Clostridium difficile* infection (previously termed pseudomembranous enterocolitis) in obstetric patients. The authors performed a retrospective cohort study using information from a large database maintained by the Agency for Healthcare Research and Quality. This database provides information about inpatient hospital stays in the United States, and it is the largest repository of its kind. It includes data from a sample of 1,000 US hospitals.

### Details of the study

Ruiter-Ligeti and colleagues reviewed

13,881,592 births during 1999–2013 and identified 2,757 (0.02%) admissions for delivery complicated by *C difficile* infection, a rate of 20 admissions per 100,000 deliveries per year (95% CI, 19.13–20.62). The rate of admissions with this diagnosis doubled from 1999 (15 per 100,000) to 2013 (30 per 100,000,  $P < .001$ ).

Among these obstetric patients, the principal risk factors for *C difficile* infection were older age, multiple gestation, long-term antibiotic use (not precisely defined), and concurrent diagnosis of inflammatory bowel disease. In addition, patients with pyelonephritis, perineal or cesarean wound infections, or pneumonia also were at increased risk, presumably because those patients required longer courses of broad-spectrum antibiotics.

Of additional note, when compared with women who did not have *C difficile* infection,

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patients with infection were more likely to develop a thromboembolic event (38.4 per 1,000), paralytic ileus (58.0 per 1,000), sepsis (46.4 per 1,000), and death (8.0 per 1,000).

### Be on guard for *C difficile* infection in antibiotic-treated obstetric patients

*C difficile* infection is an uncommon but potentially very serious complication of antibiotic therapy. Given that approximately half of all women admitted for delivery are exposed to antibiotics because of prophylaxis for group B streptococcus infection, prophylaxis for CD, and treatment of chorioamnionitis and puerperal endometritis, clinicians constantly need to be vigilant for this complication.<sup>11</sup>

Affected patients typically present with frequent loose, watery stools and lower abdominal cramping. In severe cases, blood may be present in the stool, and signs of intestinal distention and even acute peritonitis may be evident. The diagnosis can be established by documenting a positive culture or polymerase chain reaction (PCR) assay for *C difficile* and a positive cytotoxin assay for toxins A and/or B. In addition, if endoscopy is performed, the characteristic gray membranous plaques can be visualized on the rectal and colonic mucosa.<sup>11</sup>

**Discontinue antibiotic therapy.** The first step in managing affected patients is to stop all antibiotics, if possible, or at least the one

### WHAT THIS EVIDENCE MEANS FOR PRACTICE

Clearly, clinicians should make every effort to prevent *C difficile* infection in the first place. The following preventive measures are essential:

- Avoid the use of extremely broad-spectrum antibiotics for prophylaxis for CD.
- When using therapeutic antibiotics, keep the spectrum as narrow as possible, consistent with adequately treating the pathogens causing the infection.
- Administer antibiotics for the shortest time possible, consistent with achieving a clinical cure or providing appropriate prophylaxis for surgical procedures (usually, a maximum of 3 doses).
- If a patient receiving antibiotics experiences more than 3 loose stools in 24 hours, either discontinue all antibiotics or substitute another drug for the most likely offending agent, depending on the clinical situation.
- If, after stopping or changing antibiotics, the clinical findings do not resolve promptly, perform a culture or PCR assay for *C difficile* and assays for the *C difficile* toxin. Treat as outlined above if these tests are positive.

most likely to be the causative agent of *C difficile* infection. Patients with relatively mild clinical findings should be treated with oral metronidazole, 500 mg every 8 hours for 10 to 14 days. Patients with severe findings should be treated with oral vancomycin, 500 mg every 6 hours, plus IV metronidazole, 500 mg every 8 hours. The more seriously ill patient must be observed carefully for signs of bowel obstruction, intestinal perforation, peritonitis, and sepsis.

## Danger for birth defects with maternal Zika infection present in all trimesters, but greatest in first

Hoen B, Schaub B, Funk AL, et al. Pregnancy outcomes after ZIKV infection in French territories in the Americas. *N Engl J Med*. 2018;378(11):985-994.

**T**o estimate the risk of congenital neurologic defects associated with Zika virus infection, Hoen and colleagues conducted a prospective



cohort study of pregnant women with symptomatic Zika virus infection who were enrolled during March through November 2016 in French Guiana, Guadeloupe, and Martinique. All women had Zika virus infection confirmed by PCR assay.

### Details of the study

The investigators reviewed 546 pregnancies, which resulted in the birth of 555 fetuses and infants. Thirty-nine fetuses and neonates (7%; 95% CI, 5.0–9.5) had neurologic and ocular findings known to be associated with Zika virus infection. Of these, 10 pregnancies were terminated, 1 fetus was stillborn, and 28 were live-born.

Microcephaly (defined as head circumference more than 2 SD below the mean) was present in 32 fetuses and infants (5.8%); 9 had severe microcephaly, defined as head circumference more than 3 SD below the mean. Neurologic and ocular abnormalities were more common when maternal infection occurred during the first trimester (24 of 189 fetuses and infants, 12.7%) compared with infection during the second trimester (9 of 252, 3.6%) or third trimester (6 of 114, 5.3%) ( $P = .001$ ).

### Studies report similar rates of fetal injury

Zika virus infection primarily is caused by a bite from the *Aedes aegypti* mosquito. The infection also can be transmitted by sexual contact, laboratory accident, and blood transfusion. Eighty percent of infected persons are asymptomatic. In symptomatic patients, the most common clinical manifestations are low-grade fever, a disseminated maculopapular rash, arthralgias, swelling of the hands and feet, and nonpurulent conjunctivitis.

The most ominous manifestation of congenital Zika virus infection is microcephaly. Other important manifestations include lissencephaly, pachygyria, cortical atrophy, ventriculomegaly, subcortical calcifications, ocular abnormalities, and arthrogryposis. Although most of these abnormalities are immediately visible in the neonate, some

may not appear until the child is older.

The present study is an excellent complement to 2 recent reports that defined the risk of Zika virus–related fetal injury in patients in the United States and its territories. Based on an analysis of data from the US Zika Pregnancy Registry, Honein and colleagues reported an overall rate of congenital infection of 6%.<sup>12</sup> The rate of fetal injury was 11% when the mother was infected in the first trimester and 0% when the infection occurred in the second or third trimester. The overall rate of infection and the first trimester rate of infection were similar to those reported by Hoen and colleagues.

Conversely, Shapiro-Mendoza and colleagues evaluated rates of infection in US territories (American Samoa, Puerto Rico, and the US Virgin Islands) and observed cases of fetal injury associated with second- and third-trimester maternal infection.<sup>13</sup> These authors reported an overall rate of infection of 5% and an 8% rate of infection with first-trimester maternal infection. When maternal infection occurred in the second and third trimesters, the rates of fetal injury were 5% and 4%, respectively, figures almost identical to those reported by Hoen and colleagues. Of note, the investigations by Honein and Shapiro-Mendoza included women with both symptomatic and asymptomatic infection. ●

### WHAT THIS EVIDENCE MEANS FOR PRACTICE

Taken together, the studies discussed provide 2 clear take-home messages:

- Both symptomatic and asymptomatic maternal infection pose a significant risk of injury to the fetus and neonate.
- Although the risk of fetal injury is greatest when maternal infection occurs in the first trimester, exposure in the second and third trimesters is still dangerous. The Zika virus is quite pathogenic and can cause debilitating injury to the developing fetus at any stage of gestation.

### FAST TRACK

*The Zika virus is quite pathogenic and can cause debilitating injury to the developing fetus at any stage of gestation*

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