



INFECTIOUS DISEASE

Here is a practical look at 1 year's advances in managing disseminated gonococcal disease, infection associated with cesarean delivery, hepatitis C, and chorioamnionitis



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In this Update, I've highlighted four interesting articles about infectious disease management in obstetric and gyn practice that appeared in the medical literature over the past 12 months:

- One describes a study that reminds physicians of the importance of an unusual manifestation of gonococcal infection
- A second article demonstrates the importance of making a change in the

prophylactic antibiotic regimen provided to morbidly obese patients who are having a cesarean delivery

- A third describes an exciting development in the treatment of chronic hepatitis C virus infection
- The final article makes interesting observations about the proper duration of treatment for patients who have chorioamnionitis.

N gonorrhoeae causes illness beyond the urogenital tract

Bleich AT, Sheffield JS, Wendel GD, Sigman A, Cunningham FG. Disseminated gonococcal infection in women. Obstet Gynecol. 2012;119(3):597-602.

This article describes a retrospective review of 112 women who were admitted to Parkland Memorial Hospital in Dallas, Texas, from January 1975 through December 2008 and given a diagnosis of disseminated infection with *Neisseria gonorrhoeae*. Eighty (71%) of these women were *not* pregnant and were cared for on the internal medicine service; 32 (29%) were pregnant and were treated by faculty members and residents on the ObGyn service.

Over the course of the study, the frequency of disseminated gonococcal infection decreased significantly. Among pregnant women, the rate of infection was 11 for every 100,000 deliveries before 1980 and, after 1985, five for every 100,000 deliveries.

The most common clinical manifestation of disseminated gonococcal infection was arthritis. The most commonly affected joints were the knee, wrist, elbow, and ankle.

Other common clinical manifestations included dermatitis, fever, chills, and a purulent cervical discharge. Notably, the frequency of a purulent joint effusion was 50% in pregnant women and 70% in nonpregnant women—reflecting the fact that the duration

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of symptoms was approximately 3 days shorter in pregnant women than in nonpregnant women. Otherwise, the clinical presentation in pregnant women did not differ significantly from that of nonpregnant women.

In addition, the clinical course and the response to intravenous (IV) antibiotic therapy did not differ significantly between pregnant and nonpregnant women.

The authors were unable to document that disseminated gonococcal infection had any deleterious effect on the outcome of pregnancy among the patients studied. Although four of the 32 women delivered preterm, in only one instance was delivery related temporally to the disseminated gonococcal infection.

Commentary

Because of their experience treating women who have gonorrhea, I would say that most ObGyns think of *N gonorrhoeae* as causing localized infection in the lower genital tract (urethritis, endocervicitis, inflammatory proctitis) or upper genital tract (pelvic inflammatory disease). We should recognize, however, that gonorrhea also can cause prominent extra-pelvic findings, such as severe pharyngitis (in patients who practice orogenital intercourse) and perihepatitis (Fitz-Hugh-Curtis syndrome).

In addition, always bear in mind that, in rare instances, gonorrhea can become disseminated, causing quite serious illness. The most common extra-pelvic manifestation

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Disseminated gonococcal infection usually responds promptly to intravenous antibiotic therapy.

Recommended therapy is **ceftriaxone**:

- 25 to 50 mg/kg/d IV for 7 days

or

- a single, daily, 25 to 50 mg/kg intramuscular dose, also for 7 days. Continue therapy for 10 to 14 days if the patient has meningitis.

An alternative regimen is **cefotaxime**:

- 25 mg/kg/d IV for 7 days

or

- 25 mg/kg IM every 12 hours, also for 7 days.

Extend treatment for 10 to 14 days if meningitis is present.¹

of disseminated gonococcal infection is **arthritis**. As noted in this study of a series of patients, the arthritis is usually polyarticular and affects medium or small joints.

The second most common manifestation of disseminated gonococcal infection is **dermatitis**. Characteristic lesions are raised, red or purple papules. These lesions are not a simple vasculitis; rather, they contain a high concentration of microorganisms.

Other possible manifestations of disseminated infection include **pericarditis**, **endocarditis**, and **meningitis**.

The diagnosis of disseminated gonococcal infection is usually made by clinical examination and culture of specimens from the genital tract, blood, or joint effusion.



In rare instances, gonorrhea can become disseminated, causing serious illness

Obesity curtails effectiveness of antibiotic prophylaxis in cesarean delivery

Pevzner L, Swank M, Krepel C, Wing DA, Chan K, Edmiston CE Jr. Effects of maternal obesity on tissue concentrations of prophylactic cefazolin during cesarean delivery. Obstet Gynecol. 2011;117(4):877-882.

In this prospective study of the influence of an obese habitus on antibiotic prophylaxis during cesarean delivery, researchers divided 29 patients who were scheduled for cesarean into three groups, by body mass index (BMI):



WHAT THIS EVIDENCE MEANS FOR PRACTICE

Pending further investigation, I strongly recommend that *all* women who have a BMI greater than 30 receive a 2-g dose of cefazolin 30 to 60 minutes before cesarean delivery. Future research is needed to determine whether an even higher dosage is necessary to achieve a therapeutic concentration in the subcutaneous tissue of morbidly obese patients.

- lean (BMI, <30; n = 10)
- obese (30–39.9; n = 10)
- extremely obese (>40; n = 9).

All patients were given a 2-g dose of IV cefazolin 30 to 60 minutes before surgery.

During delivery, the team took two specimens of adipose tissue: one immediately after the skin incision and one later, after fascia was closed. They also obtained a specimen of myometrial tissue after delivery and a blood specimen after surgery was completed.

The concentration of cefazolin was then measured in adipose and myometrial tissue and in serum.

Findings. The researchers demonstrated that the mean concentration of cefazolin in the initial specimen of adipose tissue was significantly higher in lean patients than in obese and extremely obese patients. All 10 women who had a BMI less than 30 had a serum cefazolin concentration greater than 4 µg/g—the theoretical break-point for defining resistance to cefazolin. The initial adipose tissue specimen from two of the 10 obese patients and three of the nine extremely obese patients showed

cefazolin concentrations less than 4 µg/g.

Of particular interest, two women—both of whom had a BMI greater than 40—developed a wound infection that required antibiotic therapy. Their initial and subsequent adipose tissue concentrations of cefazolin were less than 4 µg/g break-point for resistance.

The concentration of cefazolin in the patients’ myometrial and serum specimens demonstrated a pattern similar to what the researchers observed in adipose tissue, but these results were *not* statistically significant across BMI groups. In fact, the cefazolin concentration in all groups’ myometrial and serum specimens exceeded the minimum inhibitory concentration for most potential pathogens in the setting of cesarean delivery.

Commentary

Clearly, prophylactic antibiotics are indicated for all women who are having a cesarean delivery. Antibiotics have their greatest impact when administered *before* the surgical incision is made; to exert their full protective effect against endometritis and wound infection, however, antibiotics should reach a recognized therapeutic concentration—not only in serum and myometrium but in the subcutaneous tissue.

The customary dosage of cefazolin for cesarean delivery prophylaxis has been 1 g. This study demonstrated that, although a 2-g dose of cefazolin reached a therapeutic concentration in myometrial tissue and serum, it did not consistently do so in the adipose tissue of obese and extremely obese patients.



Women who have a BMI >30 should receive a 2-g dose of cefazolin 30 to 60 minutes before cesarean delivery

New therapies promise a better outcome in hepatitis C

Jacobson IM, McHutchison JG, Dusheiko G, et al; ADVANCE Study Team. Telaprevir for previously untreated hepatitis C virus infection. N Engl J Med. 2011;364(25):2405-2416.

The authors conducted an international Phase-3, randomized, double-blind, placebo-controlled trial of two different treatment modalities for chronic hepatitis C virus (HCV) infection. The authors assigned

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1,088 patients who had HCV genotype-1 infection and who had *not* received prior therapy to one of three treatment groups:

- **telaprevir** (Incivek, Vertex Pharmaceuticals), an HCV genotype-1 protease inhibitor, combined with **peginterferon alfa-2a** (Pegasys, Genetech) plus **ribavirin** (Copegus, Genetech; Rebetol, Merck; etc.) for 12 weeks; patients then were given peginterferon alfa-2a plus ribavirin only for 12 additional weeks if HCV RNA was *undetectable* at weeks 4 and 12 *or* peginterferon alfa-2a plus ribavirin only for 36 weeks if HCV RNA was *detectable* at either time point (*Group 1*)
- telaprevir with peginterferon alfa-2a plus ribavirin for 8 weeks, then placebo with peginterferon alfa-2a plus ribavirin for 4 weeks, followed by 12 to 36 weeks of peginterferon alfa-2a plus ribavirin using the HCV RNA criteria applied to Group 1 (*Group 2*)
- placebo with peginterferon alfa-2a plus ribavirin for 12 weeks, followed by 36 weeks of peginterferon alfa-2a plus ribavirin (*Group 3*).

The primary endpoint of the trial was the percentage of patients who had undetectable plasma HCV RNA at 24 weeks after the last planned dose of the study drugs. The investigators considered that this endpoint represented a sustained virologic response.

Findings. Seventy-five percent of patients in Group 1 and 69% of those in Group 2 had a sustained virologic response. By comparison, only 44% of patients in Group 3 had a sustained response. The differences in outcome between Group 1 and Group 3, and between Group 2 and Group 3, were highly significant ($P < .001$). Virologic failure was more common among patients who had HCV genotype-1a infection than among those who had HCV genotype-1b infection.

The most common side effects noted by patients who received telaprevir were

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The lesson here for ObGyns? Screen at-risk patients and then refer the hepatitis C-seropositive ones to a specialist in gastroenterology, who can determine candidacy for one of the new treatment regimens.

Clearly, the prognosis for people who have hepatitis C is much better today than it was 20 years ago.

gastrointestinal irritation, rash, and anemia. Ten percent of patients in the telaprevir group discontinued therapy, compared with 7% in the peginterferon-ribavirin-alone group.

Commentary

Worldwide, approximately 170 million people have chronic hepatitis C, which is the most common indication for liver transplantation. Until recently, the principal treatments for hepatitis C were pegylated interferon alfa with ribavirin and without ribavirin; the response rate with these regimens was in the range of 55%. This study shows that adding telaprevir to regimens for HCV infection significantly improves prospects for long-term resolution of infection.

In some obstetric and gynecologic populations, HCV is more common than hepatitis B virus. Risk factors for hepatitis C include hepatitis B, intravenous drug abuse, and human immunodeficiency virus infection. HCV-infected women pose a risk to their sex partners; infected pregnant women can transmit the virus to their baby.

Unlike hepatitis A and hepatitis B, immunoprophylaxis is not available for hepatitis C. That reality is what makes the study by Jacobsen and colleagues so compelling: They have clearly demonstrated that multi-agent antiviral therapy might be able to truly cure this infection.



Adding telaprevir to regimens for HCV infection significantly improves prospects for long-term resolution of infection

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For how long should chorioamnionitis be treated?

Black LP, Hinson L, Duff P. Limited course of antibiotic treatment for chorioamnionitis. Obstet Gynecol (in press).

The authors conducted a retrospective review of 423 women who had been treated for chorioamnionitis at the University of Florida from 2005 to 2009.

Patients had been given IV ampicillin (2 g every 6 h) plus IV gentamicin (1.5 mg/kg every 8 h) as soon as the diagnosis of chorioamnionitis was established; postpartum, they were given only the one next scheduled dose of each antibiotic. Patients who had a cesarean received either metronidazole (500 mg) or clindamycin (900 mg) immediately after cord clamping to enhance coverage of anaerobic organisms.

The primary outcome was treatment failure, defined as persistent fever requiring continued antibiotics, surgical intervention, or administration of heparin for septic pelvic-vein thrombophlebitis.

Findings. Here is a breakdown of what the investigators found regarding the 282 women who delivered vaginally and the 141 who underwent cesarean delivery:

- Overall, 399 of the patients (94%; 95% confidence interval [CI], 92% and 96%) were treated successfully; 24 (6%; 95% CI, 3.7% and 8.3%) failed short-course treatment
- Of the 282 patients who delivered vaginally, 279 (99%; 95% CI, 98% and 100%) were cured with short-term therapy
- Of the 141 who delivered by cesarean, 120

(85%; 95% CI, 79% and 91%) were cured ($P < .001$).

- Seventeen of the total treatment failures had endometritis and responded quickly to continuation of antibiotics. Of the 17 patients with endometritis, 14 had a cesarean delivery.
- Seven patients had more serious complications: four, wound infection; three, septic pelvic-vein thrombophlebitis. All serious complications occurred *after* cesarean delivery.
- Of the four patients who had a wound infection, three had labor induced by misoprostol; their BMI was 44.8, 31.1, and 48.5, respectively. The fourth had a cesarean delivery at 29 weeks for preterm premature rupture of membranes (PPROM), chorioamnionitis, and malpresentation.
- Of the three patients who had septic pelvic-vein thrombophlebitis, two had labor induced by misoprostol. One had a BMI of 29.2; the other, 31.1. The third patient was delivered secondary to PPRM; her BMI was 40.3.

In addition, of the 21 treatment failures in the cesarean delivery group, 6 had prolonged rupture of membranes (ROM) and 10 had a BMI greater than 30. Six patients had both prolonged ROM and were obese or morbidly obese.

Of the 120 women who had a cesarean delivery and were treated successfully, 3 had prolonged ROM and 39 had a BMI greater than 30. None had both prolonged ROM *and* a BMI greater than 30.

Last, the difference between treatment failures and treatment successes in regard to the frequency of prolonged ROM or a BMI greater than 30 was highly significant ($P < .01$).

Commentary

In most published reports of patients who have chorioamnionitis, antibiotic treatment continues until the patient is afebrile and asymptomatic for 24 to 48 hours. This

FAST TRACK

A limited course of antibiotic therapy (ampicillin plus gentamicin) for women with chorioamnionitis who deliver vaginally is strongly recommended

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Based on this investigation, I strongly recommend a limited course of antibiotic therapy (ampicillin plus gentamicin) for women with chorioamnionitis who deliver vaginally. Patients who have had a cesarean delivery—particularly those who are obese or have had an extended duration of labor, or both—should be treated with antibiotics until they have been afebrile and asymptomatic for 24 hours.

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treatment approach has been based largely on expert opinion, however, not on Level-1 or Level-2 evidence.

In 2003, Edwards and Duff published a study of chorioamnionitis antibiotic regimens that compared single-dose postpartum treatment to extended treatment.² This randomized controlled trial demonstrated that there was no statistically significant difference between patients who had only a single dose of postpartum antibiotics and those who received an extended course of medication (i.e., who were treated until they had been afebrile and asymptomatic for a minimum of 24 hours) *in regard to adverse outcomes* (2.9% and 4.3%, respectively). The study discussed here extends and refines the observations made in the 2003 Edwards and Duff randomized controlled trial.

The new study shows that **a limited course of antibiotics was, overall, effective in treating 94% of patients with chorioamnionitis** (95% CI, 92% and 96%). Only 1% of patients who delivered vaginally failed therapy, compared with 15% of patients who delivered by cesarean ($P<.001$). In the cesarean group, women who failed therapy were likely to **1)** be obese or **2)** have a relatively long duration of labor or ruptured membranes, or both. These patients may have benefitted from a more extended course of antibiotic therapy. 📌

References

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2. Edwards RK, Duff P. Single dose postpartum therapy for women with chorioamnionitis. *Obstet Gynecol.* 2003;102(5 Pt 1):957-961.