

INFECTIOUS DISEASES

CMV vaccine ... Outpatient PID therapy ... C-section healing in the obese ... 2 useful antibiotics now unavailable

For the 2006 Update, I have chosen to focus on 3 important new clinical reports that stand to improve patient care, and another development that necessitates a change in how we treat gonorrhea in pregnant women:

CMV vaccine. A new immunologic agent for the treatment and prevention of congenital cytomegalovirus (CMV) infection is extremely promising. Until now, no consistently effective therapy for this serious congenital infection has been identified.

- Recommended hygiene measures to prevent transmission—*Page 64*

Outpatient treatment of PID. Relatively inexpensive outpatient therapy for mild to moderately severe pelvic inflammatory

disease was demonstrated to be equal to inpatient therapy in efficacy and safety.

- Whom to hospitalize—*Page 68*

Wound complications after cesarean delivery in the obese were reduced by use of subcutaneous closure and avoidance of surgical drains.

- Recommended technique—*Page 70*

2 antibiotics with unique application in the treatment of uncomplicated gonococcal infections in pregnant women—cefixime and spectinomycin—were recently withdrawn from the market. This unfortunate development is a special dilemma in pregnant women with allergy to beta-lactams.

- Alternative regimens, using other antibiotics—*Page 75*

A promising therapy for congenital CMV

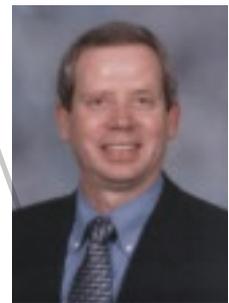
For now, emphasize prevention

Nigro G, Adler SP, LaTorre R, Best AM. Passive immunization during pregnancy for congenital cytomegalovirus infection. N Engl J Med. 2005;353:1350–1362.

I Although anti-cytomegalovirus hyper-immune globulin appears to have great promise for prevention and treatment of congenital CMV infection, I propose that obstetricians avoid a rush to judgment and maintain their focus on simple measures to prevent horizontal transmission of CMV

SUMMARY

Nigro and colleagues present a provocative report of a promising new treatment for congenital cytomegalovirus (CMV) infection. Their prospective cohort study at 8 Italian medical centers involved 157 pregnant women with confirmed primary CMV infection: 148 women were asymptomatic



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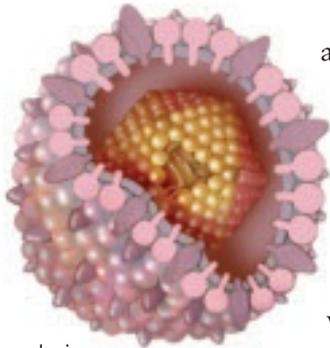
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and were identified by routine serologic screening; 8 had symptomatic infections and 1 had ultrasound findings consistent with congenital CMV infection.



Cytomegalovirus

CMV was detected in the amniotic fluid of 45 women who had a primary infection more than 6 weeks before enrollment, and 31 of these women agreed to receive CMV-specific hyperimmune globulin (200 units per kilogram of maternal body weight). Nine of the 31 women received 1 or 2 additional infusions into either the amniotic fluid or umbilical cord because of persistent fetal abnormalities on ultrasound.

- Only 1 of the 31 treated women delivered an infected infant (adjusted odds ratio, 0.02; $P < .001$).
- In contrast, of the 14 women who declined treatment, 7 had infants who were symptomatically infected at birth.

There were 84 additional women who did not have an amniocentesis because their infection occurred within 6 weeks of enrollment, their gestational age was less than 20 weeks, or they declined the procedure. Of these, 37 agreed to treatment with 100 U of hyperimmune globulin per kilogram of maternal weight every month until delivery.

- 6 of these treated women delivered infected infants.
- In contrast, 19 of the untreated women (adjusted odds ratio 0.32; $P = .04$) delivered infected infants.

No adverse effects of hyperimmune globulin were noted in either treatment group.

COMMENTARY

This study is remarkable because, until now, no consistently effective therapy for this serious congenital infection has been available. However, before we fully embrace the findings, 3 caveats should be considered.¹ **1. Although the study was prospective, it was neither randomized nor controlled.** The lack of strict randomization resulted in a curious blend of 2 cohorts—a treatment group and

a prevention group. The dosage regimens were different both within and between the 2 groups.

Moreover, and somewhat counterintuitively, the mothers in the prevention group seemingly received more intensive therapy than those in the treatment group yet had somewhat less successful outcomes.

2. There are biological reasons to question the remarkable success rates reported by the authors. For example, administration of anti-HIV hyperimmune globulin has not protected neonates against perinatal transmission of HIV.² Moreover, the presence of naturally acquired antibody against CMV does not fully protect a mother or her fetus against reactivation and subsequent perinatal transmission of CMV infection.¹ This latter observation is particularly important in assessing the authors' observations that major abnormalities identified by ultrasound, such as ascites, ventriculomegaly, intracerebral and intraabdominal echodensities, and intrauterine growth restriction apparently resolved completely in 14 fetuses after maternal treatment.

3. The study did not address the financial and logistic issues of screening large obstetric populations for CMV infection, triaging patients with inevitable false-positive test results, performing targeted sonography and amniocentesis in affected women, and then treating at-risk women with hyperimmune globulin.

RECOMMENDATIONS

Hyperimmune globulin appears to be very safe and to have great promise for treatment and prevention of congenital CMV infection. However, additional investigations are needed to delineate the appropriate dose, method of administration, and timing of immunoprophylaxis and to define its precise level of effectiveness.

Meanwhile, focus on simple hygiene measures

Until confirmatory studies are reported, I propose that obstetricians avoid a rush to judgment and maintain their focus on simple measures to prevent horizontal

FAST TRACK

To help prevent CMV transmission:

- Use CMV-negative blood products
- Encourage safe sex practices
- Encourage expectant mothers to use careful handwashing techniques after handling infants' diapers or toys

transmission of CMV, such as:

- using **CMV-negative blood products** when transfusing pregnant women or fetuses
- encouraging expectant mothers to

adopt **safe sex practices**

- encouraging expectant mothers to use **careful handwashing** techniques after handling infants' diapers and toys.

Outpatient treatment of PID is effective, safe, and economical

Fertility and recurrence rates similar to inpatient therapy

Ness RB, Trautmann G, Richter HE, Randall H, Peipert JF, Nelson DB, et al. Effectiveness of treatment strategies of some women with pelvic inflammatory disease. *Obstet Gynecol.* 2005;106:573-580.

I Outpatient treatment is an effective and economically attractive alternative to inpatient therapy for women with mild to moderately severe pelvic inflammatory disease

SUMMARY

Relatively inexpensive outpatient therapy for mild to moderately severe pelvic inflammatory disease (PID) proved effective and equivalent to inpatient treatment in key respects, in this long-term follow-up study.

Ness and colleagues describe 831 patients who had participated in a prospective, randomized, unblinded multicenter trial of outpatient versus inpatient treatment for mild-to-moderate PID.³ The patients were followed for a mean of 84 months (range 64-100 months).

- **The inpatient treatment group** received intravenous cefoxitin (2 grams every 6 hours) and either intravenous or oral doxycycline (100 mg twice daily) for at least 72 hours, followed by oral doxycycline (100 mg twice daily) to complete a 14-day course.
- **The outpatient treatment group** received a single 2-g intramuscular injection of cefoxitin plus a single 1-g oral dose of probenecid, followed by oral doxycycline (100 mg twice daily) for 14 days.

Equivalent outcomes

Outpatient treatment did not adversely affect subsequent fertility or increase the frequency of recurrent PID or chronic pelvic pain. The equivalence of outpatient

compared with inpatient therapy extended to women of all races and to those with a history of PID; those colonized by *Neisseria gonorrhoeae* and/or *Chlamydia trachomatis*; and those with a high temperature, high white count, and high pelvic tenderness score.

Even in teenage women and women who had never had a live birth, outpatient and inpatient therapy were equivalent.

Risk of ectopic pregnancy was increased in outpatients (odds ratio 4.91); however, ectopic pregnancy was such a rare event that the 95% confidence interval was quite wide, ranging from 0.57 to 42.25.

COMMENTARY

The initial encouraging results of the authors' 2002 landmark Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) Randomized Trial³ led to this long-term follow-up study. In the women who were treated as described above, the short-term clinical outcomes and markers of micro-biologic improvement were similar in the outpatient and inpatient groups. After a mean follow-up of 35 months, pregnancy rates were essentially equal (42%) in both groups. Moreover, the groups did not differ significantly in risk of recurrent PID, chronic pelvic pain, or ectopic pregnancy.

Extended follow-up is reassuring

PID, a common and potentially serious illness, is the single most common predisposing factor for ectopic pregnancy and one of

FAST TRACK

Outpatient therapy makes good sense in women with PID who are not seriously ill

the principal causes of infertility and chronic pelvic pain. The direct and indirect expenses of PID are enormous, and the PEACH trial provides great reassurance that women who are not seriously ill can be safely, effectively, and inexpensively treated as outpatients.

The additional 4 years of follow-up reassures us that outpatient treatment did not adversely affect long-term outcome. Moreover, outpatient therapy was not less effective in women who initially appeared to be at higher risk for adverse sequelae: teens, African-Americans, women with a history of PID, and women colonized with *N gonorrhoeae* and/or *C trachomatis*.

Cost comparison

A 14-day prescription for doxycycline should cost less than \$25. The single 2-g dose of cefoxitin, combined with the administration charge, should not exceed \$100. If cefotetan (2 g) were substituted for cefoxitin (the 2 drugs should be therapeutically equivalent in this clinical situation), the cost would be even less. Conservatively,

the charges for a single day in the hospital combined with charges for intravenous antibiotics would be at least \$300 to \$400.

Beyond the issue of expense are considerations of patient and physician convenience, ease of management, and conservation of scarce resources.

RECOMMENDATIONS

In carefully selected patients, outpatient treatment makes good sense, economically and clinically.

Whom to hospitalize

Patients judged to be seriously ill, particularly those in whom a tubo-ovarian abscess is suspected, should be treated in the hospital. Even with modern antibiotics and sophisticated intensive care, mortalities still occur in women with severe PID complicated by a ruptured abscess.

In addition, patients should be hospitalized for treatment if they are judged to be at risk for noncompliance, lack a reliable support system at home, or have previously failed outpatient management.

FAST TRACK

Adding a closed drain did not improve outcome beyond that achieved by subcutaneous closure

A technique that reduces C-section wound complications in the obese

Closure method, but not surgical drains, lowers morbidity

Ramsey PS, White AM, Guinn D, et al. Subcutaneous tissue reapproximation, alone or in combination with drain, in obese women undergoing cesarean delivery. Obstet Gynecol. 2005;105:967-973.

In obese women having cesarean delivery, closure of the subcutaneous layer reduces risk of wound complications such as seroma, hematoma, incisional abscess, and fascial dehiscence. Addition of a closed system drain did not improve outcome beyond that achieved with subcutaneous closure alone.

SUMMARY

This prospective randomized trial at 5 medical centers assessed the role of 2 surgical techniques in decreasing the risk of wound complications after cesarean deliv-

ery in 280 obese women. Patients with subcutaneous thickness greater than or equal to 4 cm were randomized to either subcutaneous suture closure alone (149 women) or suture plus drain (131 women).

The primary study outcome was composite wound morbidity rate, defined by any of the following: subcutaneous tissue dehiscence, seroma, hematoma, incisional abscess, or fascial dehiscence.

Addition of drain did not improve wound morbidity

A running, nonlocking suture of 3-0 Vicryl was used for closure of the subcutaneous

layer. The drain used was the Jackson-Pratt surgical drain (10 mm), and it was placed below the layer of subcutaneous suture and then connected to bulb suction. The drain was removed on the third postoperative day, or sooner, if drain output was less than 30 mL in 24 hours. The drain exited the wound via a separate stab site lateral to the incision. All of the skin incisions were closed with staples, which were removed 7 to 14 days after surgery. All patients received standard skin preparations and prophylactic antibiotics.

The composite wound morbidity rate was 17.4% in the suture group and 22.7% in the suture plus drain group ($P=NS$). Individual wound complication rates were similar in the 2 groups. The authors concluded that the surgical drain did not improve outcome beyond that achieved by closure of the subcutaneous layer.

COMMENTARY

Endometritis and wound disruption are the most common complications of cesarean delivery. Wound complications clearly are the more serious, for they inevitably lead to persistent patient discomfort, prolonged hospitalization, and increased expense. Moreover, they may necessitate additional surgical intervention to drain a seroma, hematoma or abscess or to repair a fascial dehiscence.

Postcesarean wound complications are particularly likely in the obese, and, unfortunately, the prevalence of obesity is steadily increasing among obstetric patients.

In a landmark study of wound infections in many different types of surgery, Cruse and Foord⁴ demonstrated that sutures in the subcutaneous space actually increased the wound complication rate. DelValle and colleagues⁵ were among the first to challenge this observation and show

that, at least in women having cesarean delivery, reapproximation of Camper's fascia reduced risk of wound disruption.

Is thickness of subcutaneous layer a key determinant of wound morbidity?

Naumann et al⁶ and Vermillion and colleagues⁷ subsequently demonstrated that thickness of the subcutaneous layer was the key determinant of wound complications. Chelmon and colleagues⁸ recently published an excellent meta-analysis confirming that, in women with a subcutaneous layer greater than 2 cm, closure of the subcutaneous layer with suture significantly reduced the rate of wound disruption.

In the present study, the authors evaluated moderately to severely obese women who had a subcutaneous layer of 4 cm or greater. In light of the previous reports reviewed above, they were justified in omitting a treatment group in which no closure was done. The trial was well designed and included patients from varied populations. Not surprisingly, composite wound morbidity rates were high in both groups.

The addition of the surgical drain did not improve the morbidity rate, however. In fact, even though the drainage system was closed, women in the combined treatment group actually had slightly higher, although not statistically significant, rates of composite morbidity and individual morbidities.

RECOMMENDATIONS

When to omit drain

In view of the added time required to place the drain, greater patient discomfort, and the increased expense associated with the drain, this intervention should not be used in high-risk women having cesarean delivery.

UPDATE ON INFECTIOUS DISEASES

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CONTINUED

FAST TRACK

Drains should not be used in high-risk women having cesarean delivery

DRUG THERAPY

We've lost 2 key weapons in our antibiotics arsenal

Use ceftriaxone or azithromycin for gonorrhea, now that cefixime and spectinomycin are unavailable

I Cefixime and spectinomycin, antibiotics with unique application for treatment of uncomplicated gonorrhea in pregnant women, were recently withdrawn from the market. In their absence, use ceftriaxone, 125 mg intramuscularly in a single dose. Pregnant women who are allergic to beta-lactam antibiotics should be treated with a single 2-g oral dose of azithromycin.

Two antibiotics with unique application in treatment of uncomplicated gonococcal infections were recently withdrawn from the market. These drugs were not withdrawn because there were questions about their effectiveness or safety. Rather, the decisions to discontinue production appear to have been based on marketing and economic considerations.

- **Cefixime**, an oral cephalosporin that was highly effective in a single 400-mg dose against almost all strains of *N gonorrhoeae*.
- **Spectinomycin**, a parenteral agent (2 g, intramuscularly) that was the treatment of choice for uncomplicated gonorrhoeae in pregnant women allergic to beta-lactam antibiotics.

RECOMMENDATIONS

Nonpregnant women can be treated with either ceftriaxone, 125 mg IM in a single

dose, or with a single oral dose of a quinolone antibiotic; for example, 500 mg ciprofloxacin, 400 mg ofloxacin, or 250 mg levofloxacin.

Pregnant women who are not allergic to beta-lactam antibiotics should be treated with ceftriaxone, 125 mg IM in a single dose.

Dilemma: Beta-lactam allergy in pregnant women

The dilemma is how best to treat pregnant patients who are allergic to beta-lactam antibiotics, now that spectinomycin is unavailable. Doxycycline and tetracycline provide reasonable coverage against *N gonorrhoeae*, but both are considered FDA pregnancy category D. Quinolone antibiotics have excellent activity against this organism, but they are considered FDA pregnancy category C because of concern about their effect on fetal cartilage.

Azithromycin is an acceptable alternative. For the pregnant patient who has a true life-threatening allergy to beta-lactams, I believe the most reasonable alternative is azithromycin. This drug is usually used in a single oral dose of 1 g to treat uncomplicated chlamydial infections. However, in a dose of 2 g, azithromycin does have acceptable activity against *N gonorrhoeae*. At this dosage, gastrointestinal effects are more likely, and cost may exceed \$80. ■

FAST TRACK

Use azithromycin for gonorrhea in a pregnant patient with allergy to beta-lactams

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