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INFECTIOUS DISEASE

How to respond to a CMV diagnosis in pregnancy; worries over methicillin-resistant *S. aureus* infection in and out of pregnancy; more on HPV vaccination

Four studies caught my eye this past year. The first describes the use of systematic methodology to confirm the diagnosis of primary cytomegalovirus (CMV) infection in pregnancy and lower the rate of unnecessary pregnancy termination. Investigators were able to reclassify approximately 70% of women who had been diagnosed with CMV infection and reduce the number of pregnancy terminations by 73%.

Two other studies help define the emerging problem of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infection, when to look for it, and how to treat it. In the first, researchers isolated *S. aureus* from the wounds of 320 patients with community-acquired infection and tested the samples for methicillin resistance, finding a prevalence of 59%. In the second study, investigators analyzed culture specimens from pregnant women for the presence of group B streptococci and *S. aureus* colonization. They found colonization with group B streptococci to be significantly associated with *S. aureus* colonization, with a prevalence odds ratio of 2.1.

The fourth study concerns the human papillomavirus (HPV) vaccine. Women given an HPV-16 L1 virus-like particle vaccine and followed for 4 years remained 100% free of cervical intraepithelial neoplasia (CIN) grades 2 and 3, unlike women who received placebo.

I believe these 4 studies represent the most significant developments of the past year in the field of infectious disease.

IN THIS ARTICLE

Don't rush a diagnosis of CMV infection in pregnancy

Guerra B, Simonazzi G, Banfi A, et al. Impact of diagnostic and confirmatory tests and prenatal counseling on the rate of pregnancy termination among women with positive cytomegalovirus immunoglobulin M antibody titers. Am J Obstet Gynecol. 2007;196:221.e1–6.

CMV infection is a common and important perinatal pathogen. Each year in the United States, approximately 1% of gravidas acquire primary infection. Of these, about 40% transmit infection to the fetus. The rate of transmission is highest when maternal infection occurs in the third trimester, but the risk of serious fetal injury is greatest when maternal infection occurs in the first trimester. Ten percent to 20% of congenitally infected infants are acutely symptomatic at birth.

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Approximately 20% of these newborns die; most survivors have serious long-term complications. In contrast, CMV infection that recurs during pregnancy poses only minimal risk to the baby.[1]

Many women choose to have their pregnancy terminated when they learn they have a primary CMV infection.

Details of the study

This retrospective study was designed to determine whether a systematic diagnostic algorithm reduces the rate of unnecessary abortion in women who have apparent acute CMV infection during pregnancy. Guerra and colleagues evaluated 1,857 consecutive patients in practices in Italy who had a positive anti-CMV immunoglobulin M (IgM) antibody assay in the first or second trimester and were referred to a tertiary care facility for further diagnostic testing. Universal screening for CMV is now common among practitioners in Italy, and virtually all of these patients were completely asymptomatic.

At the tertiary facility, investigators tested again for CMV-specific IgM, as well as IgG, by enzyme immunoassay. They also tested for IgM by immunoblot and determined the avidity of anti-CMV IgG. Women who had IgG of low or moderate avidity with confirmed IgM, and those who clearly seroconverted to IgG were assumed to have a primary infection.

Women who were positive for IgM with high-avidity IgG were assumed to have nonprimary infection. Women who were seronegative for both antibodies were classified as uninfected. Those who were IgM-negative with high-avidity IgG were classified as previously infected. Women with an acute infection were then counseled by a specialist and offered amniocentesis and targeted ultrasonography.

Only 11.9% of women with primary infection chose abortion

Of the 1,857 women in this study, 445 were classified as having primary infection (group 1); 53 (11.9%) women elected to terminate their pregnancy. At autopsy, 38 of the 53 fetuses were found to be infected. In the other 15 cases, the pregnancy was terminated in the first trimester, and postmortem examination was not performed.

In the 1,205 women found to have nonprimary infection or previous infection (group 2), only 5 (0.4%) had the pregnancy terminated in the first trimester, and no postmortem examinations were performed. The difference in the observed rates of abortion between groups 1 and 2 was highly significant ($P<.001$).

Given their observations in group 1, the authors estimated that, on the basis of the initial screening tests at the referring institutions, approximately 196 (11.9%) of all patients in groups 1 and 2 would have elected abortion. By using confirmatory tests combined with counseling by a specialist, the authors were able to reduce the number of abortions from 196 to 53, a 73% decrease.

Always confirm an initial diagnosis

Given the ominous prognosis for congenital CMV infection and the major psychological implications and sobering finality of abortion, it is imperative that clinicians confirm the diagnosis of primary CMV infection. Because most cases of CMV infection in immunocompetent adults are asymptomatic, the diagnosis is typically confirmed by serology. Unfortunately, the serologic tests for CMV are not as straightforward and reliable as tests for other viral infections such as rubella. Commercially available tests for anti-CMV IgM often have false-positive and false-negative results. In addition, IgM antibody may be detected as long as 9 months after a primary infection and may subsequently reappear during reactivation of a latent infection or reinfection.[2,3]

Routine screening is not necessary

The authors' findings vividly illustrate the potential errors that can occur when a large number of asymptomatic patients are routinely screened for CMV. Because of these pitfalls, I do not recommend rou-

Be selective, on the basis of risk factors and clinical manifestations, when screening pregnant women for **cytomegalovirus** infection.

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You must accurately confirm the diagnosis of a primary CMV infection—despite the unreliability of CMV serology

tine screening. Rather, screening should be selective, directed at women who:

- have clinical manifestations of CMV infection
- are immunosuppressed
- have small children in daycare or work in daycare themselves or
- have documented exposure to someone with CMV infection.

If the initial immunoassay for CMV IgM is positive, a confirmatory immunoblot test for IgM should be performed, as well as avidity testing for IgG.

If primary infection is confirmed, the patient should undergo targeted ultrasonography and amniocentesis to assess for manifestations of congenital infection and to detect CMV in amniotic fluid by culture or polymerase chain reaction (PCR) testing. If the sonogram shows signs of fetal injury, or the PCR test is positive, the woman should be counseled about the options, which include experimental immunotherapy with hyperimmune anti-CMV globulin[4] and pregnancy termination.

The study by Guerra and colleagues is a welcome addition to the obstetric literature. By using a systematic diagnostic algorithm that included an enzyme-linked immunosorbent assay and an immunoblot assay for IgM antibody and avidity testing for IgG antibody, the authors were able to reclassify approximately 70% of patients as either uninfected or previously infected. As a result, they reduced the number of pregnancy terminations by 73%, an objective endpoint that clearly has great social, economic, and medical impact.

Most community *S. aureus* infections are methicillin-resistant

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The prevalence of methicillin resistance in community-acquired *S. aureus* infections was 59%

Moran GJ, Krishnadasan A, Gorwitz RJ, et al. Methicillin-resistant *S. aureus* infections among patients in the emergency department. N Engl J Med. 2006;355:666–674.

Moran and colleagues reviewed the records of 422 adults with acute purulent and soft-tissue infections who were evaluated in 11 university-affiliated emergency departments in August 2004. Wounds were routinely cultured. When *S. aureus* was isolated, the organisms were tested for antimicrobial susceptibility to identify those that were methicillin-resistant. The PCR test was used to identify genes for staphylococcal enterotoxins A through E and H, toxic shock syndrome toxin, and Panton–Valentin leukocidin. The same methodology was used to identify the gene complex staphylococcal cassette chromosome mec (SCCmec). This complex contains the mecA gene that confers methicillin resistance.

Of the 422 patients, 320 (76%) had *S. aureus* isolated from their wound. The prevalence of methicillin resistance was 59%. Ninety-seven percent of MRSA isolates were pulsed-field type USA 300. SCCmec type IV and the Panton–Valentin leukocidin gene were detected in 98% of MRSA isolates. Other toxin genes were rare.

Only 2 drugs were 100% effective

Among MRSA isolates, 100% were susceptible to rifampin and trimethoprim-sulfamethoxazole (TMP-SMX), 95% were susceptible to clindamycin, and 92% were sensitive to tetracycline. Only 60% were sensitive to fluoroquinolones, and only 6% were sensitive to erythromycin. Only 43% of patients received initial empiric therapy with antibiotics to which their organisms were sensitive.

Reason to worry

S. aureus is an important pathogen in obstetric patients. It is the causative or-

ganism of toxic shock syndrome and the dominant pathogen in patients with puerperal mastitis, as well as one of the key causes of postoperative wound infection. When penicillin was developed in 1941, all strains of *S. aureus* were sensitive to the drug. Within a few short years, however, most hospital-acquired strains became resistant.

Methicillin was introduced in 1961 to treat these resistant staphylococcal species. Unfortunately, by the mid-1960s, methicillin-resistant *S. aureus* (MRSA) infections began to appear. By the 1990s, MRSA infections were common in hospitalized patients, particularly in intensive care units. Hospital-acquired MRSA isolates are often sensitive to only a few select antibiotics such as vancomycin, linezolid, and quinupristin/dalfopristin.[5]

In the late 1990s and early 2000s, MRSA began to appear in community-acquired infections in both adults and children. Most of these isolates have been implicated in skin and soft-tissue infections, but some have been responsible for invasive infection, bacteremia, and even death.[6] Compared with hospital-acquired MRSA, these community isolates are more likely to be sensitive to commonly used antibiotics.

Always culture an infected wound

Knowledge of these sensitivity patterns is of great importance. Regrettably, as noted by Moran and associates, more than half of the patients (57%) were initially treated with antibiotics to which their infecting organism was resistant.

The clinical implications are clear:

- We must be aware that many community-acquired soft-tissue infections will be caused by drug-resistant staphylococci.
- Because antibiotic resistance is so prevalent, a culture of the infected wound should be obtained routinely so that antimicrobial therapy can be modified if the patient fails to respond to initial treatment.
- Antibiotic therapy alone is rarely sufficient for abscesses in the soft tissue and skin; adequate surgical drainage is essential.
- Fundamental infection-control measures, such as careful handwashing, adequate skin preparation prior to surgery, and local wound care, are of greater importance than ever.

Most cases of community-acquired **MRSA** have been isolated from skin and soft tissue; surgical drainage is necessary when infection advances to abscess in those sites.

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Make it routine practice to culture an infected wound

In gravidas with group B strep, look for *S. aureus*

Chen KT, Huard RC, Della-Latta P, Saiman L. Prevalence of methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* in pregnant women. Obstet Gynecol. 2006;108:482–487.

To assess the prevalence of methicillin-sensitive and community-acquired methicillin-resistant *S. aureus* colonization in pregnant women, Chen and colleagues evaluated de-identified culture specimens that had originally been submitted to the microbiology laboratory for identification of group B streptococcal infection. As opposed to hospital-associated MRSA isolates, community-associated methicillin-resistant strains were defined as those possessing the type IV or V staphylococcal chromosomal cassette mec element and lacking a multidrug-resistant phenotype.

Of the 2,963 culture specimens in the prospective surveillance study, 743 (25%) were positive for group B streptococci, and 507 (17%) were positive for *S. aureus*. Group B streptococcal colonization was significantly associated with *S. aureus* colonization; the prevalence odds ratio was 2.1. Fourteen of the 507 *S. aureus* isolates were methicillin-resistant

(2.8%; 95% confidence interval [CI] 1.4–4.2%). Thirteen of the 14 strains (93%) were community-acquired.

S. aureus may cause sepsis, wound infection, bacteremia, and other ills

The unique feature of this study is the observation that vaginal colonization with group B streptococci was significantly associated with colonization with *S. aureus*—one of the possible causative pathogens in chorioamnionitis, endometritis, wound infection, bacteremia, puerperal mastitis, and toxic shock syndrome. The organism also may cause serious neonatal infection, particularly sepsis.

The prevalence of group B streptococcal colonization in this study (25.1%, 95% CI 23.5–26.7%) is comparable to data reported from several other investigators.[7] Colonized women are at increased risk for chorioamnionitis and puerperal endometritis, and their infants are at increased risk of sepsis, pneumonia, and meningitis. Fortunately, intrapartum antibiotic prophylaxis significantly reduces the risk of both maternal and neonatal group B streptococcal infection.[8]

As I noted earlier in this update, the antimicrobial susceptibility of *S. aureus* has become increasingly limited, particularly in light of the recent increase in both hospital- and community-acquired methicillin-resistant strains. In this study by Chen and colleagues, 2.8% of *S. aureus* isolates were methicillin-resistant. Of these, all but one were community-acquired.

Clinical suggestions

These findings certainly do not indicate the need for routine cultures for *S. aureus* vaginal colonization in all pregnant women. Nor are cultures needed in women who test positive for group B streptococci at 35 to 37 weeks. However, clinicians should be alert for possible staphylococcal infections, such as wound abscess, furuncle, carbuncle, or mastitis, in these women. If such an infection appears, obtain a culture of the purulent collection. Pending the result, treat the patient empirically with a drug that is likely to be effective against community-acquired MRSA. One hundred percent of these strains are sensitive to rifampin and TMP-SMX, and 90% to 95% are sensitive to tetracycline.[9]

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Be alert for possible staph infection in pregnant women who test positive for group B strep at 35 to 37 weeks

Univalent HPV vaccine is 100% effective against CIN grades 2, 3

Mao C, Koutsky LA, Ault KA, et al. Efficacy of human papillomavirus-16 vaccine to prevent cervical intraepithelial neoplasia. Obstet Gynecol. 2006;107:18–27.

Mao and colleagues set out to assess the long-term protection of a univalent HPV vaccine against CIN grades 2, 3. Their prospective, randomized, double-blind, placebo-controlled trial involved 2,391 women, aged 16 to 23 years, who received either 40 µg of HPV-16 L1 virus-like particle vaccine or placebo intramuscularly at day 1, month 2, and month 6. Genital samples for HPV-16 DNA and cervical cytology specimens were collected at day 1, month 7, and then every 6 months for 48 months. A radioimmunoassay was used to assess antibody titers to HPV-16.

Vaccinated women avoided CIN

Of the 750 women who received placebo, 6 developed HPV-16–related CIN 2, and 6 developed CIN 3. Among the 755 vaccinated women, no cases of CIN occurred. Thus, the vaccine was 100% effective in this trial (95% CI 65–100%).

Among women who received placebo, 111 cases of persistent HPV-16 infection occurred, compared with 7 cases in vaccinated women (vaccine efficacy 94%; 95% CI 88–98%).

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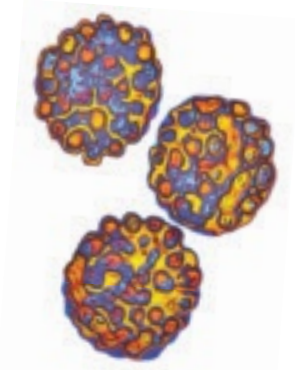

Emphasize to patients that preexisting cytologic abnormalities and genital warts don't respond to vaccination against **human papillomavirus.**

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HPV genotyping isn't indicated in an infected woman who will be given the vaccine

Following immunization, antibody to HPV-16 peaked at month 7, declined through month 18, and remained stable between months 30 and 48.

Any effective vaccine is important

Because 3,500 to 4,000 women still die from cervical cancer each year in the United States, and almost 274,000 die worldwide, the development of any HPV vaccine that provides lasting protection against CIN is important.

The vaccine evaluated by Mao and colleagues targeted a single strain of HPV, genotype 16. The recently approved quadrivalent vaccine, Gardasil, targets types 6, 11, 16, and 18. Of the more than 100 genotypes of HPV that have been discovered, approximately 30 are present in the mucosa of the genital tract, and 15 of these 30 are associated with cervical cancer. However, 2 HPV strains—types 16 and 18—are responsible for about two thirds of all cases of cervical cancer; 90% of genital warts cases result from infection with types 6 and 11.[10]

The Advisory Committee on Immunization Practices recommends that the quadrivalent vaccine be given to girls at age 11 or 12 years, prior to the onset of sexual activity, to be maximally effective against all 4 genotypes included in the vaccine.[10]

If a woman is infected with HPV prior to vaccination, she may develop abnormal cervical cytology related to the genotypes in the vaccine, as well as genotypes not included. Nevertheless, ACOG recommends that the vaccine be considered in all females ages 9 to 26.[11] HPV genotyping is not recommended before giving the vaccine because any type of routine screening reduces the cost-effectiveness of the vaccination program.[10]

Fundamentals of vaccination

The quadrivalent vaccine must be administered intramuscularly (0.5 mL) in 3 doses on day 1 and at 2 and 6 months. The principal adverse effect is a local reaction such as pain, swelling, or pruritus at the injection site. Low-grade fever occurs in approximately 10% of patients.

Although the vaccine is classified by the FDA as pregnancy category B, the manufacturer recommends against its use during pregnancy. It may be administered to lactating women, however. The approximate cost of the 3-dose series, including administration fees, is $400 to $500.

It's a vaccine, not a treatment

Patients need to understand that vaccination is not a treatment for preexisting cytologic abnormalities or genital warts. Nor can it be expected to be perfectly protective over a person's lifetime against infection caused by genotypes 6, 11, 16, and 18. Women must continue to have regular cytologic screening. No reliable scientific data suggest that vaccination of young girls will increase sexual promiscuity in the adolescent population.[10] ■

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