A woman at 26 weeks of gestation presented with 2 days of nausea, vomiting, fevers, and abdominal pain. She had no recent travel or sick contacts. Her medical history was significant for gonorrhea and cholecystectomy. On physical examination her temperature was 38.5°C and she had right abdominal tenderness with a normal pelvic examination and no signs of preterm labor. The nonstress test was reactive. Initial laboratory evaluation revealed a leukocytosis of 15.8×10⁹/L with left shift, normal hemolysis, elevated liver enzymes, and low platelet count laboratory results, negative gonorrhea and chlamydia tests, and urinalysis. A wet mount was positive for *Trichomonas* infection. Given the severe pain, a magnetic resonance image of the abdomen and pelvis was ordered and preliminary reading was negative for appendicitis. After observation and treatment with metronidazole and acetaminophen, she improved and was discharged home.

The next day, she returned with fevers of up to 39.4°C and abdominal pain with rebound and guarding. The leukocytosis had resolved, but a nonstress test revealed a fetal heart rate in the 170s. Broad-spectrum antibiotics were started. The prior day’s magnetic resonance image final read did not identify the appendix but showed right ovarian compression and enlargement of the right uterine vessels. Given the significant fundal tenderness, an amniocentesis was performed with initial results being inconsistent with infection. Final cultures were subsequently negative. With worsening right abdominal pain, a surgeon was consulted who recommended exploratory laparotomy. An appendectomy was performed, and both general surgeons and obstetrician–gynecologists confirmed normal bilateral adnexa. The pathology findings were not consistent with appendicitis.

Through hospital day 4, the negative laboratory work-up included: amniotic fluid, blood, and urine cultures, rapid plasma reagin, human immunodeficiency virus AG/AB, cytomegalovirus immunoglobulin (Ig)M/IgG, herpes simplex virus (HSV) IgG, hepatitis A/B/C serologies, and tests for influenza A/B/H1N1, mycoplasma, ureaplasma, toxoplasmosis, parovirus, tuberculosis, ehrlichiosis, Rocky Mountain spotted fever, and Lyme disease. The echocardiogram and chest radiograph results were negative.

At the recommendation of an infectious disease consultant, her antimicrobials were broadened from ampicillin and gentamicin and metronidazole to piperacillin and tazobactam and vancomycin. She received heparin for potential septic thrombophlebitis. She remained febrile to greater than 40.0°C with persistent fetal tachycardia.

On hospital day 4, while obtaining a urine specimen, the nurse observed a solitary 1-cm painless ulcer on the labium. Tests from the lesion revealed HSV-2 DNA. Intravenous acyclovir was initiated, and she became afebrile within 12 hours. Herpes simplex virus-2 DNA from her blood confirmed dissemination. Outpatient acyclovir prophylaxis was continued. However, at 37 weeks of gestation, three painless labial lesions were found to be HSV-2 polymerase chain reaction-positive and she presented in labor at 38 weeks of gestation and was delivered by cesarean. Her neonate was healthy and without evidence of HSV infection. A representative HSV lesion is shown in Figure 1.

**QUESTIONS FOR THE COMMENTATORS**
Fever, nausea, and abdominal pain in pregnancy present a large differential diagnosis and require a careful, step-wise approach. The late discovery of a painless genital lesion was especially unusual for disseminated HSV. Given the wide differential diagnosis and the nonspecific presentation of disseminated HSV, the authors review febrile illness and disseminated HSV in pregnancy to...
provide a logical, stepwise approach for obstetrician–gynecologists.

**What Is the Appropriate Work-Up for Febrile Illness in Pregnancy?**

The work-up of febrile illness in pregnancy can be exhaustive and should be directed in a stepwise fashion by a complete history and repeated physical examinations. We suggest an initial work-up as detailed in Box 1. Laboratory work-up can be divided into sexually transmitted, viral, and other bacterial infections. Specific laboratory tests for sexually transmitted and viral infections are summarized in Table 1. As illustrated by this case, diagnosis is often dependent on serial examinations. Appropriate specialist consultations should be sought if there is evidence of hemodynamic or respiratory compromise and is recommended if evaluation and treatment remain unsuccessful after 48 hours.

**What Are the Most Common Causes of Febrile Illness in Pregnancy?**

The most common severe antenatal infections are septic abortion, intraamniotic infection (chorioamnionitis), complicated pyelonephritis, and influenza. A classification of febrile illnesses in pregnancy is summarized in Box 2.

**What Is the Definition of Sepsis and Its Prevalence in Pregnancy?**

Systemic inflammatory response syndrome describes the clinical response to either an infective or a noninfective insult. On confirming an infection, the process is referred to as “sepsis.” In 1991, the American College of Chest Physicians and the Society of Critical Care Medicine defined systemic inflammatory response syndrome, sepsis, severe sepsis, and septic shock based on the severity of response (Box 3). In 2001, the multidisciplinary Sepsis Consensus Conference introduced the Predisposition, Insult/Infection, Response, and Organ Dysfunction system as a more robust definition of systemic response to infection. It focuses on predisposing factors, infectious insult, and response of the host and organ dysfunction (Box 4).

Sepsis was the most common cause of maternal mortality in the 19th century, accounting for nearly 50% of cases. Introduction of antisepsis measures have improved outcomes; however, sepsis-related maternal morbidity and mortality remain a significant and persistent problem. In the United States, the estimated prevalence of bacteremia in obstetric patients is 7.5 per 1,000 admissions, and the rate of sepsis in this population is approximately 8–10%. The rates of septic shock are variable in the obstetric

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**Box 1. Work-Up of Febrile Illness in Pregnancy**

**History**
- Localizing symptoms
- Travel and sick contacts
- Animal exposure (e.g., pets, occupation)
- Immunosuppression (illness, medications)
- Medication and toxin history

**Repeated physical examination**

- Complete blood count with differential
- Blood cultures (three sets drawn from different sites before administrations of antibiotics*)
- Routine blood chemistries including liver function tests
- Hepatitis (if liver tests abnormal), syphilis, influenza, tuberculosis, and human immunodeficiency virus testing
- Urine microscopy and culture

Based on clinical presentation:
- Chest radiograph
- Amniocentesis
- Maternal echocardiogram

Proceed with further evaluation of abnormalities detected with these tests. Consider noninfectious etiologies (malignancy and autoimmune disease).

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*Of unimicrobial cases, 73.1% were detected with the first blood culture, 89.7% were detected with the first two blood cultures, 98.2% were detected with the first three blood cultures, and 99.8% were detected with the first four blood cultures.
population, ranging from 3% to 12% in patients with confirmed bacteremia.\(^5\)

**Who Is at Risk for Disseminated Herpes Simplex Virus?**

In healthy populations with primary genital HSV, up to 24% have polymerase chain reaction-detectable viremia. This is most common among whites and women. Multiple studies have found constitutional and meningeal symptoms positively correlate with viremia; however, clinically significant disease, with complications from dissemination of HSV into the bloodstream or viscera, is more common in immunocompromised populations.\(^6\)

Herpes simplex virus viremia has been described with hematologic malignancy, immunosuppression resulting from medications, and with both bone marrow and solid organ transplant.\(^6\) Rarely, cases have also been reported in previously healthy immunocompetent individuals with a disproportionate number of these occurring in pregnant women.\(^7\) Since the first instance was reported in 1969,\(^8\) 33 cases of disseminated HSV during pregnancy have been reported in the literature. Similar to nonpregnant populations, HSV viremia in pregnancy is more commonly associated with HSV-2.\(^6,7\)

It has previously been postulated that the unique immunomodulation of pregnancy may increase the risk for systemic spread of HSV. The overwhelming majority of disseminated HSV cases in pregnancy are primary infections that occurred in the third trimester. It is during this setting that prior studies have shown alterations in both humoral and cell-mediated immunity.\(^7,8\)

**How Does Disseminated Herpes Simplex Virus Present? Is Presentation Different in Pregnant Women?**

In all populations, the most common findings associated with HSV viremia are constitutional symptoms and central nervous system alterations; abdominal pain, dysuria, vaginal discharge, urinary retention, and skin lesions occur less frequently.\(^6\) Aseptic meningitis and sepsis syndrome were more significant presentations found in immunocompromised patients, with sepsis also being the most common cause of death.\(^6\)

In a previous review of disseminated HSV in pregnancy, fever occurred in 96% of cases. As in this case report, the majority of patients reported a flu-like prodrome of fever, chills, malaise, myalgias, and anorexia;\(^7\) and 41–50% had no lesions at the time of presentation.\(^7,9\) Hepatitis was also common in this population, occurring in 52% of pregnant patients. Other presenting signs and symptoms are seen in Box 5. Given the nonspecific nature and lack of mucocutaneous lesions at initial presentation, repeated complete physical examinations should be performed in women with unexplained fever and a high index of suspicion.

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**Table 1. Sexually Transmitted Infection and Viral Infection Diagnosis in Perinatal Fever**

<table>
<thead>
<tr>
<th>Infectious Etiology</th>
<th>Diagnostic Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexually transmitted infections</td>
<td>Isolation by culture, antigen-detection by enzyme immunoassays or direct fluorescence assays, nucleic acid amplification tests</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>Isolation by culture, nucleic acid amplification tests</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>Screening: RPR, VDRL. Confirmation: microhemagglutination assay-T pallidum, fluorescent treponemal antibody absorption test</td>
</tr>
<tr>
<td>Treponema pallidum</td>
<td></td>
</tr>
<tr>
<td>Major perinatal viral infections</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>Antibody detection</td>
</tr>
<tr>
<td>Parvovirus</td>
<td>Antibody detection</td>
</tr>
<tr>
<td>Rubeola</td>
<td>Antibody detection</td>
</tr>
<tr>
<td>Rubella</td>
<td>Antibody detection</td>
</tr>
<tr>
<td>CMV</td>
<td>Antibody detection, PCR</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>Clinical examination, viral culture, PCR</td>
</tr>
<tr>
<td>Varicella</td>
<td>Clinical examination, antibody detection, PCR</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Antibody detection</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Detection of surface antigen</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Antibody detection</td>
</tr>
<tr>
<td>Hepatitis D</td>
<td>Antibody detection, antigen detection</td>
</tr>
<tr>
<td>Hepatitis E</td>
<td>Antibody detection, RT-PCR</td>
</tr>
</tbody>
</table>

RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratories; HIV, human immunodeficiency virus; CMV, cytomegalovirus; PCR, polymerase chain reaction RT-PCR, reverse transcription-polymerase chain reaction.
How Is Herpes Simplex Virus Diagnosed?

Clinical diagnosis of genital herpes is both insensitive and nonspecific with sensitivity of 39% and a false-positive rate of 20%. Additionally, the clinical course, prognosis, and counseling vary depending on infection with HSV-1 compared with HSV-2. Therefore, clinical suspicion of genital herpes should always be confirmed with laboratory tests.

When vesicles are present, sampling an unroofed lesion with isolation of HSV by cell culture has historically been the preferred test. However, tissue culture has low sensitivity, identifying only 80% of primary infections and is prone to technical error. In recurrent illness and healing lesions, the detection rate can be as low as 25–50%. Polymerase chain reaction assay for HSV DNA is four times more

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**Box 2. Classification of Infections in Critically Ill Obstetric Patients**

**Pregnancy-related infections**
- Chorioamnionitis
- Puerperal sepsis
- Septic abortion
- Episiotomy infection (necrotizing fasciitis)
- Pelvic septic thrombophlebitis

**Nonpregnancy-related infections**

Increased predisposition in pregnancy
- Urinary tract infection or pyelonephritis
- Malaria
- Listeriosis
- Viral hepatitis (E)
- Varicella pneumonia
- Coccidiomycosis

Infection incidental to pregnancy
- Community-acquired pneumonia (bacterial, fungal, viral)
- Influenza virus
- Human immunodeficiency virus infection
- Toxoplasmosis
- Cytomegalovirus
- Appendicitis
- Cholecystitis
- Disseminated herpes

**Nosocomial infection**
- Hospital-acquired infection
  - Intensive care unit–acquired infection
    - Ventilator-acquired pneumonia
    - Other respiratory tract infections
    - Urinary tract infection
    - Catheter-related bloodstream infection
    - Skin, soft tissue, wound infections
    - Gastrointestinal tract
    - Central nervous system
    - Cardiovascular

**Box 3. Spectrum of Systemic Inflammatory Response**

**SIRS**
- Two of the following:
  - Temperature greater than 38°C or less than 36°C
  - Heart rate higher than 90 beats per min
  - Respiratory rate greater than 20 breaths per min or PaCO₂ lower than 32 mmHg (4.3 kPa)
  - White cell count
    - Greater than 12,000 cells/mm³ or
    - Less than 4,000 cells/mm³ or
    - 10% immature or band forms

**Sepsis**
- SIRS with infection

**Severe sepsis**
- Sepsis associated with organ dysfunction, hypoperfusion or hypotension; hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status

**Septic shock**
- Sepsis associated with hypotension, despite adequate fluid resuscitation along with the presence of perfusion abnormalities as listed for severe sepsis; patients who are on inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured

**Multiple organ dysfunction syndrome**
- Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention

SIRS, systemic inflammatory response syndrome.

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sensitive than cell culture and less dependent on collection conditions;\textsuperscript{11,12} polymerase chain reaction is not yet approved by the U.S. Food and Drug Administration for the testing of genital lesions but is considered the test of choice for detecting HSV in spinal fluid or serum.\textsuperscript{13}

Serologic testing is useful in asymptomatic partner testing and in cases of high clinical suspicion with either absence of lesions or negative virus culture.\textsuperscript{13} Type-specific IgG enzyme-linked immunosorbent assay testing can correctly distinguish HSV-1 or HSV-2 with a sensitivity of 97–100% and specificity of 94–98%. Type-specific serology and direct virus testing help differentiate among primary infection, nonprimary first infection, and recurrent infection, which may help guide treatment and counseling.\textsuperscript{14}

Because type-specific IgG HSV antibodies can take 2 weeks to 3 months to be detected, initially negative patients should be retested for seroconversion.\textsuperscript{12} IgM antibodies are not considered reliable, because they exhibit a high degree of crossreactivity and may be present with recurrent infection.\textsuperscript{13}

**What Are Potential Consequences of Disseminated Herpes Simplex Virus in Pregnancy?**

Hepatitis is the most frequent complication of disseminated HSV in all populations and may lead to coagulopathy.\textsuperscript{7,10} Its overall mortality rate is

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**Box 4. Predisposition, Insult or Infection, Response, and Organ Dysfunction System for the Diagnosis of Sepsis**

**General**
- Temperature higher than 38.3°C or lower than 36°C
- Heart rate greater than 90 beats per min or more than 2 SD above the normal value for age
- Tachypnea
- Altered mental status
- Significant edema or positive fluid balance (greater than 20 mL/kg/24 h)
- Hyperglycemia (greater than 120 mg/dL or more than 7.7 mmol/L)

**Inflammatory**
- White blood cell count higher than 12,000/microliter or lower than 4,000/microliter
- Normal white blood cell count with more than 10% immature forms
- Plasma C-reactive protein greater than 2 SD above the normal value
- Plasma procalcitonin greater than 2 SD above the normal value

**Hemodynamic**
- SBP lower than 90 mmHg or MAP lower than 70 mmHg, or a decrease in SBP of more than 40 mmHg or greater than 2 SD below normal for age
- Central venous oxygen saturation greater than 70%
- Cardiac index greater than 3.5 L/min/m\(^2\)

**Organ dysfunction**
- Arterial oxygen tension or fraction of inspired oxygen less than 300
- Urine output less than 0.5 mL/kg/h
- Creatinine increase greater than 0.5 mg/dL
- International normalized ratio greater than 1.5 or activated partial thromboplastin time longer than 60 sec
- Platelet count below 100,000/microliter
- Absent bowel sounds (ileus)
- Plasma total bilirubin higher than 4 mg/dL or higher than 70 mmol/L

**Tissue perfusion**
- Lactate greater than 1 mmol/L
- Decreased capillary refill or mottling

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SD, standard deviation; SBP, systolic blood pressure; MAP, mean arterial pressure.
approximately 39%. Although maternal and fetal mortality rates in HSV hepatitis are also high, they are thought to be lower than nonpregnant individuals, possibly as a result of higher suspicion and earlier treatment or compared with those with true immunocompromise.9 Although uncommon with HSV infection, pericarditis, myocarditis, pancreatitis, and bone marrow suppression have also been reported.9 Central nervous system involvement has been confirmed in multiple cases. However, meningeal symptoms are reported more frequently than HSV meningitis verified with cerebrospinal fluid or brain biopsy.7,15 If the brain is involved, seizure activity is common.7

Fetal risks include sequelae from maternal compromise such as high fever, sepsis, and hypotension or by transplacental transmission of the virus. Fetal outcomes are variable and include stillbirth, subsequent death from neonatal HSV infection, infected survivors, and uninfected survivors.15 Amniocentesis has not proven beneficial as a prenatal predictor of infection.15 Recent epidemiologic data show rates of neonatal HSV infection are approximately 13 per 100,000 live births.16

What Is the Best Treatment for Disseminated Herpes Simplex Virus in Pregnancy?

Any of three agents is recommended by the Centers for Disease Control and Prevention (CDC) for treatment of HSV: acyclovir, valacyclovir, and famciclovir. Valacyclovir and famciclovir have higher oral bioavailability, and acyclovir is available in intravenous preparation. Oral therapy is sufficient for primary and recurrent genital infections, but intravenous acyclovir is recommended for serious or disseminated illness. The recommended regimen is 5–10 mg/kg acyclovir body weight intravenously every 8 hours for 2–7 days or until clinical improvement followed by oral antiviral treatment to complete at least 10 days of total therapy.13 Immunocompromised patients often require longer therapy at higher doses to heal mucocutaneous disease.12 Given the specific immunomodulation of pregnancy, extended therapy should also be considered in these patients. It is important to note that although suppressive therapy is effective, it does not prevent all neonatal HSV disease and clear communication with the pediatric team is important.17

Although data on its safety in pregnancy are limited, the CDC endorse using intravenous acyclovir in pregnant women with disseminated disease due to the possible severe consequences of the disease.13 Preliminary data show no increased risk of major birth defects in women treated with systemic acyclovir (either oral or intravenous) during the first trimester.13,14,18 In those with HSV hepatitis, acyclovir has been shown to prolong the interval between onset of illness and delivery.19 Additionally, a 1996 review of 27 cases showed mortality among women and their neonates to be 73% and 69%, respectively, without antiviral therapy. With therapy, the mortality rate dropped to 18% for both mothers and neonates.7 Although this review does not clarify the cause of deaths, the older data more likely reflect the natural history of disease. With earlier detection and treatment today, the survival rate should be improved.

Although no cases of acyclovir resistance have been reported in pregnancy to date, the prevalence of

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**Box 5. Findings Seen With Disseminated Herpes Simplex Virus**

### Common symptoms
- Fever or chills
- Headache
- Abdominal pain
- Myalgias

### Examination findings
- Fever
- Lesions—may be present on presentation or later in course
  - Genital (most common)
  - Oropharyngeal
  - Skin
- Nuchal rigidity
- Altered mental status
- Seizures

### Laboratory findings
- Hepatitis
- Coagulopathy or thrombocytopenia
- Abnormal cerebral spinal fluid
- Pancreatitis

### Other study findings
- Pulmonary infiltrates
- Pulmonary edema or Cardiomegaly
- Myocarditis
- Abnormal EEG
- Abnormal head CT
- Abnormal liver CT

EEG, electroencephalogram; CT, computed tomography.

resistance is 5–12% in immunocompromised patients. The CDC currently recommend Foscarnet until clinical resolution is attained for acyclovir-resistant HSV; however, there are no recommendations for pregnant populations, and Foscarnet is pregnancy category C. Decisions for treatment in this scenario should be made with infectious disease colleagues.

How Should a Woman With Primary Herpes Simplex Virus Diagnosed in Pregnancy Be Delivered?

Although recurrent episodes are more common than primary HSV in pregnancy, the risk of neonatal infection is more substantial with primary HSV. With late acquisition, transmission rates are as high as 30–50% and perinatal transmission is 10 times more likely than among those who acquire HSV early or with recurrent HSV.

Patients with active genital lesions or prodromal symptoms such as vulvar pain or burning should have a cesarean delivery to reduce the risk of transmission. As a result of the higher risk of transmission with primary HSV acquired in late pregnancy and the knowledge that most cases of neonatal herpes result from mothers with asymptomatic shedding, continued prophylactic therapy through the remainder of pregnancy is recommended. Among those with late primary HSV consideration for cesarean delivery is reasonable, although adequate specific evidence in this regard is lacking.

The protective effect of cesarean delivery is undermined in cases when additional risk factors for transmission such as rupture of membranes and internal monitoring are present. This was illustrated in a recent case series in which 37.5% (27/72) of cases of neonatal HSV occurred in the setting of a cesarean delivery. At least one risk factor for HSV transmission (greater than 4 hours between rupture of membranes and delivery, artificial rupture of membranes, or invasive instrumentation) was present in 80% of cases.

REFERENCES


