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Management of Genital Herpes in Pregnancy

Genital herpes simplex virus (HSV) infection during pregnancy poses a risk to the developing fetus and newborn. Genital herpes is common in the United States. Among 14- to 49-year-old females, the prevalence of HSV-2 infection is 15.9%. However, the prevalence of genital herpes infection is higher than that because genital herpes is also caused by HSV-1 (1). Because many women of childbearing age are infected or will be infected with HSV, the risk of maternal transmission of this virus to the fetus or newborn is a major health concern. This document has been revised to include that for women with a primary or nonprimary first-episode genital HSV infection during the third trimester of pregnancy, cesarean delivery may be offered due to the possibility of prolonged viral shedding.

Background

Etiology

Herpes simplex virus is a double-stranded DNA virus that can be differentiated into HSV type 1 (HSV-1) and HSV type 2 (HSV-2) based on the glycoproteins in the lipid bilayer envelope. Glycoprotein G1 is associated with HSV-1 and glycoprotein G2 is associated with HSV-2. Herpes simplex virus type 1 is the primary etiologic agent of herpes labialis, gingivostomatitis, and keratoconjunctivitis. Herpes simplex virus type 2 is virtually always a genital pathogen, and most genital infections with HSV are caused by HSV-2. However, HSV-1 infections are becoming increasingly common as a cause of oral and genital infections, particularly among adolescent women and young women (2, 3).

Herpes simplex virus is transmitted from person to person through direct contact. Infection is initiated when the virus contacts mucosa or abraded skin. The incubation period after acquisition of HSV-1 or HSV-2 ranges from 2 days to 12 days. Herpes simplex virus then replicates in the epidermis and dermis, which causes cellular destruction and inflammation. During the initial infection, the virus gains access to the sensory neurons, and then the infection becomes latent in the sensory ganglia. Reactivation of viral replication occurs and may manifest clinically as recurrent ulcerative lesions or subclinically as asymptomatic viral shedding. Both the cellular and humoral immune systems play an important role in controlling this viral infection (4).

Herpes virus has a characteristic protein coat, and each viral type has identifiable proteins. Type-specific antibodies to the viral proteins develop within 2–3 weeks of infection and persist (5).

A clinical suspicion of primary infection is confirmed when HSV-1 or HSV-2 is detected from lesions in individuals who do not have evidence of antibodies to either viral type in the serum. A nonprimary first-episode infection is confirmed when one viral type is detected in lesions from individuals with evidence of antibodies to the other viral type in the serum. Recurrent infection is confirmed when HSV-1 or HSV-2 is detected in lesions from individuals with evidence of antibodies to the same viral type in the serum.

Incidence

Herpes simplex virus infection of the genital tract is one of the most common sexually transmitted infections. The

true incidence of genital HSV infection is not known because it is not a reportable disease. In addition, most individuals who are infected with HSV are unaware that they have contracted the virus. Only approximately 5–15% of infected individuals report recognition of their infections (6, 7). An estimated 1.6 million new HSV-2 infections occur annually in the United States (8), and there are approximately 50 million prevalent HSV-2 infections among adolescent and adult individuals in the United States (9). A large, national serologic study found that approximately 21% of women had serologic evidence of HSV-2 infection (10). Serologic studies of HSV-2 underestimate the prevalence of genital herpes because HSV-1 also causes genital disease.

Among women with serologic test results that indicate susceptibility to HSV infection, the incidence of new HSV-1 or HSV-2 infection during pregnancy is approximately 2% (11). Approximately 10% of women who are HSV-2 seronegative have partners who are seropositive and are at risk for transmission of HSV-2 during the pregnancy (12). Consistent with nonpregnant patients, most new infections in pregnant patients are asymptomatic (11). The timing of infection is relatively evenly distributed, with approximately one third of women becoming infected in each trimester (11). Among women with recurrent genital HSV, approximately 75% can expect at least one recurrence during pregnancy, and approximately 14% of patients will have prodromal symptoms or clinical recurrence at delivery (13, 14).

Neonatal herpes usually is acquired during the intrapartum period through exposure to the virus in the maternal genital tract; in utero and postnatal infections are rare but can occur. Before the availability of testing became more widespread, approximately 80% of infected infants were born to women with no reported history of HSV infection (15). Current estimates are not available. Although the actual incidence is unknown because neonatal herpes infection is not a reportable disease, estimates suggest that approximately 1,200–1,500 cases occur annually in the United States (16). Approximately one third to one half of cases of neonatal herpes are caused by HSV-1 (16, 17). Neonatal HSV infections can be classified as disseminated disease (25%); central nervous system disease (30%); and disease limited to the skin, eyes, or mouth (45%) (15). Mortality has decreased substantially over the past 2 decades, decreasing to 30% for disseminated disease and 4% for central nervous system disease. Approximately 20% of survivors of neonatal herpes have long-term neurologic sequelae (18).

Clinical Considerations and Recommendations

▶ *How can the diagnosis of herpes simplex virus be established?*

In pregnancy, suspected genital herpes virus infections should be confirmed with type-specific laboratory testing. However, retesting is not warranted in pregnant women with a history of laboratory-confirmed genital HSV. The tests used to confirm the presence of HSV infection can be divided into two basic groups: 1) viral detection techniques and 2) antibody detection techniques (19).

Virologic tests are preferred for patients who present with genital vesicles, ulcers, or other mucocutaneous lesions and include viral culture and HSV antigen detection by polymerase chain reaction (PCR). When a genital specimen is collected for HSV culture, the vesicles should be unroofed, if present, and vesicular fluid should be collected. The sensitivity of viral culture is low, especially for recurrent or healing lesions. Primary lesions are more likely than recurrent lesions to yield positive cultures (80% versus 40% of patients, respectively) (20, 21). Thus, a negative result does not exclude the presence of infection; however, a positive genital culture provides conclusive evidence of genital HSV infection. Polymerase chain reaction techniques involve the amplification of particular sequences of DNA and, thus, can detect evidence of viral DNA at low concentrations. In one large study, PCR results were three to five times more likely to be positive than were cultures (22).

For patients who have a clinical history that suggests HSV but who do not present with active lesions or whose lesions have negative culture or PCR test results, type-specific serologic assays that accurately distinguish between HSV-1 and HSV-2 antibodies may be helpful. The antibody detection techniques include the use of laboratory-based and point-of-care serologic tests to detect the presence of antibodies to HSV-1 or HSV-2. Antibodies to HSV develop during the first weeks after infection and persist indefinitely. Therefore, if clinical suspicion for herpes is high and recent infection is suspected, repeat serologic testing may be indicated.

Because HSV-2 is an uncommon cause of oral infection, detection of HSV-2 antibodies is virtually diagnostic of genital HSV infection. Conversely, detection of HSV-1 antibodies alone may represent orolabial infection or may indicate genital infection (19).

▶ *How can primary herpes simplex virus infection be distinguished from a nonprimary first episode during pregnancy?*

It is not possible to distinguish primary from nonprimary HSV infection based only on signs and symptoms (23). Up to 15% of first-episode infections during pregnancy are recurrent infections. Diagnosis of a primary infection is based on the combination of positive viral detection and negative serologic test results or evidence of seroconversion.

A primary outbreak in the first trimester of pregnancy has been associated with neonatal chorioretinitis, microcephaly, and skin lesions in some cases (24). Although HSV has been associated with an increased risk of spontaneous abortion, recent studies do not support such a risk (25).

▶ *Is there a role for routine screening for genital herpes during pregnancy?*

For women with a known history of genital herpes, symptomatic shedding during the antepartum period does not predict asymptomatic shedding at delivery (26, 27). Thus, routine antepartum genital HSV cultures in asymptomatic patients with recurrent disease are not recommended.

For women without a known history of genital herpes, maternal HSV screening has been proposed to reduce neonatal herpes by identifying women infected (seropositive) with genital herpes and offering suppressive antiviral therapy near term. It also may identify susceptible women (seronegative) whose partners could be offered screening, allowing for counseling of at-risk couples about strategies to reduce the possibility of new maternal infection during pregnancy. Several analyses have evaluated the cost effectiveness of various screening protocols for pregnant patients to reduce the incidence of neonatal HSV infection (28–32). The results from these analyses are highly variable—estimates of the cost to prevent one case of neonatal herpes range from $200,000 to $4,000,000. Several factors influence these cost estimates, including the costs of testing and counseling, effectiveness of antiviral therapy, the probability of lesions or shedding at delivery in asymptomatic women in whom HSV has been diagnosed only by the screening test, and the likelihood of neonatal herpes with vaginal delivery (27, 28). Currently, there is no evidence from clinical trials or well-designed cohort studies in pregnancy of cost-effectiveness of screening strategies. Routine HSV screening of pregnant women is not recommended. In addition, routine antepartum genital HSV cultures in asymptomatic patients with recurrent disease are not recommended.

▶ *What antiviral medications are available for treatment of herpes simplex virus infection during pregnancy?*

The three oral antiviral agents that are commonly used to treat HSV infections are acyclovir, valacyclovir, and famciclovir. These drugs are approved for the treatment of primary genital herpes, the treatment of episodes of recurrent disease, and the daily treatment for suppression of outbreaks of recurrent genital herpes. Topical antiviral therapy has not been shown to be of benefit.

Of the three medications, acyclovir is the most well-studied in pregnancy, and animal and human data suggest that it is safe in pregnancy, including in the first trimester, and can effectively reduce viral shedding and persistence of lesions. Acyclovir is a nucleoside analogue that enters virally infected cells and acts specifically to inhibit the viral thymidine kinase and, thus, DNA replication. Valacyclovir is a prodrug of acyclovir and is rapidly converted to acyclovir after metabolism in the liver. Therefore, valacyclovir is presumed to have a safety profile that is similar to acyclovir. Because valacyclovir has increased bioavailability and can be taken less often, patient adherence with valacyclovir may be increased compared with acyclovir. However, valacyclovir is generally more expensive than acyclovir (33). The pharmacokinetics of both drugs have been evaluated in pregnancy. After doses of acyclovir and valacyclovir, there was evidence of acyclovir concentration in the amniotic fluid but no evidence of preferential fetal drug accumulation (34, 35). There are no published data on the use of famciclovir in pregnancy. There are no documented increases in adverse fetal or neonatal effects because of acyclovir exposure (36–38).

Development of viral resistance to acyclovir has not been a problem in immunocompetent patients. In two large, laboratory-based studies, a low prevalence of acyclovir resistance in viruses isolated from immunocompetent patients has been estimated (0.3–0.6%), whereas acyclovir-resistant HSV infections occur more commonly among patients who are immunocompromised (6–7%) (37, 39).

▶ *What antiviral therapy is recommended for a primary or a nonprimary first-episode herpes simplex virus outbreak in pregnancy?*

At the time of the initial outbreak, antiviral treatment should be administered orally to pregnant women to reduce the duration and the severity of the symptoms as well as reduce the duration of viral shedding (Table 1) (40). In patients who have severe disease, oral treatment can be extended for more than 10 days if lesions are incompletely healed at that time (19). Acyclovir may be administered intravenously to pregnant women with severe genital HSV infection or with disseminated herpetic infections. Women with a primary or

Table 1. Recommended Doses of Antiviral Medications for Herpes in Pregnancy.

Indication	Acyclovir	Valacyclovir
Primary or first-episode infection	400 mg orally, three times daily, for 7–10 days*	1 g orally, twice daily, for 7–10 days*
Symptomatic recurrent episode	400 mg orally, three times daily, for 5 days or 800 mg orally, twice daily, for 5 days	500 mg orally, twice daily, for 3 days or 1 g orally, daily, for 5 days
Daily suppression	400 mg orally, three times daily, from 36 weeks estimated gestational age until delivery	500 mg orally, twice daily, from 36 weeks estimated gestational age until delivery
Severe or disseminated disease	5–10 mg/kg, intravenously, every 8 hours for 2–7 days, then oral therapy for primary infection to complete 10 days	

*Treatment may be extended if healing is incomplete after 10 days of therapy.

Data from Centers for Disease Control and Prevention. Genital HSV infections. In: 2015 sexually transmitted diseases treatment guidelines. Atlanta, GA: CDC; 2015. Available at: https://www.cdc.gov/std/tg2015/herpes.htm. Retrieved January 6, 2020.

nonprimary first-episode outbreak in pregnancy, as well as women with a clinical history of genital herpes, should be offered suppressive therapy beginning at 36 weeks of gestation. Alternatively, for primary outbreaks that occur in the third trimester, continuing antiviral therapy until delivery may be considered.

Primary genital herpes infection during pregnancy constitutes a higher risk of perinatal transmission than does recurrent infection. Among neonates delivered vaginally, the risk of vertical transmission to the neonate when a primary outbreak occurs at the time of delivery is approximately 40–80% (11, 16). Several factors likely contribute to the increased risk. First, when women have acquired infection near the time of delivery, there is likely reduced transplacental passage of protective HSV-2 specific antibodies. Higher titers of neutralizing antibodies in the neonate have been associated with a reduced risk of neonatal infection (41). Second, neonatal exposure to the virus in the genital tract may be increased. The genital viral shedding in women with primary infection is of higher concentration and longer duration than shedding that occurs with recurrent episodes. Women with primary herpes that is untreated have a mean duration of viral shedding of 15 days (40). In addition, cervical shedding was detected by viral culture in 90% of women with primary infection (40).

▶ *What antiviral therapy is recommended for a recurrent herpes simplex virus infection in pregnancy?*

In women with a recurrent HSV outbreak during pregnancy, antiviral treatment should be administered orally to reduce the duration and the severity of the symptoms and to reduce the duration of viral shedding (Table 1). Women with a clinical history of genital herpes should be offered suppressive viral therapy at or beyond 36 weeks of gestation. For primary outbreaks that occur in the third trimester, continuing antiviral therapy until delivery may be considered. Suppressive therapy beginning at 36 weeks of gestation in women diagnosed with herpes before or during pregnancy has been shown to reduce the risk of clinical recurrence of HSV at the time of delivery, cesarean birth for recurrent herpes, and asymptomatic shedding (42).

Because of enhanced renal clearance, the doses of antiviral medication used for suppressive therapy for recurrent HSV infection in pregnancy are higher than the corresponding doses in nonpregnant women (Table 1). Although neutropenia is a recognized, transient complication of acyclovir treatment of neonatal HSV infection, it has not been reported after maternal suppressive therapy (18). The acyclovir concentrations at which neutropenia occurred were approximately 5–30 times greater than were observed in umbilical vein plasma in a pharmacokinetic study of valacyclovir in pregnancy (34).

▶ *When should cesarean delivery be performed to prevent perinatal herpes simplex virus transmission?*

Cesarean delivery is indicated in women with active genital lesions or prodromal symptoms, such as vulvar pain or burning at delivery, because these symptoms may indicate viral shedding. Although in the setting of recurrent active maternal disease the incidence of neonatal disease is low, cesarean birth is recommended because of the potentially serious nature of the disease. Overall,

among women with HSV isolated from genital secretions at delivery, neonatal herpes occurred in 1.2% of infants delivered by cesarean birth compared with 7.7% of infants delivered vaginally (16). Cesarean birth does not completely prevent vertical transmission to the neonate. Transmission has been documented in the setting of cesarean delivery performed before membrane rupture (15, 43).

All women should be asked early in pregnancy about symptoms of genital herpes including prodromal symptoms. Women with a history of herpes should be examined for herpetic lesions when they present for evaluation in labor and delivery. In general, cesarean delivery is not recommended for women with a history of HSV infection but no active genital lesions or prodromal symptoms during labor (44). However, for women with a primary or nonprimary first-episode genital HSV infection during the third trimester of pregnancy, cesarean delivery may be offered due to the possibility of prolonged viral shedding (45).

▶ ***Is cesarean delivery recommended for women with recurrent herpes simplex virus lesions on the back, thigh, or buttock?***

Cesarean delivery is not recommended for women with nongenital lesions (eg, lesions on back, thigh, buttock). These lesions may be covered with an occlusive dressing and the patient can give birth vaginally. However, women with nongenital lesions should be examined carefully for herpetic lesions of the genital region.

▶ ***In a patient with active genital herpes simplex virus lesions and ruptured membranes at term, should cesarean delivery be performed to prevent perinatal transmission?***

In patients with active genital HSV lesions or prodromal symptoms and ruptured membranes at or near term, a cesarean delivery should be performed as soon as the necessary personnel and equipment can be readied. There is no evidence that there is a duration of rupture of membranes beyond which the fetus does not benefit from cesarean birth (46). At any time after rupture of membranes, cesarean delivery is recommended.

▶ ***How should a woman with active genital herpes simplex virus lesions and preterm prelabor rupture of membranes be managed?***

In a patient with prelabor rupture of membranes and active genital HSV lesions, the risks of prematurity should be weighed against the risk of neonatal HSV disease in considering expectant management. In pregnancies remote from term, especially in women with recurrent disease, there is increasing support for continuing the pregnancy to gain benefit from time and use of corticosteroids (47, 48). In women with preterm prelabor rupture of membranes, there is no consensus on the gestational age at which the risks of prematurity outweigh the risks of HSV. When expectant management is elected, treatment with an antiviral is recommended. The decision to use corticosteroids should be based on the balance between the risk of pulmonary immaturity and the risk of neonatal herpes.

▶ ***Are invasive procedures contraindicated in pregnant women with herpes simplex virus?***

Transabdominal invasive procedures, such as chorionic villus sampling, amniocentesis, and percutaneous umbilical cord blood sampling, may be performed even when genital HSV lesions are present. Because cervical shedding is associated with genital recurrences, it seems reasonable to delay transcervical procedures until lesions appear to have resolved. In women with a history of HSV and no active lesions who are undergoing a trial of labor, there is no evidence to alter usual obstetric management, including the use of invasive fetal monitoring and operative vaginal delivery when indicated.

▶ ***Should women with active herpes simplex virus breastfeed or handle their infants?***

Unless there is a lesion on the breast, breastfeeding is not contraindicated. To prevent postnatal transmission, women with herpetic lesions on any part of the body should be advised to take special consideration of handwashing with soap and water. Postnatally acquired disease can be as lethal as that acquired during delivery. Oropharyngeal or cutaneous lesions can be an effective source of virus for transmission to the newborn. Because the herpes virus is transmitted through direct contact (eg, hand-to-mouth), neonatal infection may be acquired from family members other than the woman and from sites other than the genital tract (49, 50). Most strains of HSV responsible for nosocomial neonatal disease are HSV-1 rather than HSV-2. Women with active lesions should use caution when handling their babies.

Valacyclovir appears to be safe for breastfeeding women. Although acyclovir was found in the breast milk in concentrations that were higher than the maternal serum, the amount of acyclovir in the breast milk was only 2% of that used for therapeutic doses in neonates (51).

Summary of Recommendations

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

▶ In pregnancy, suspected genital herpes virus infections should be confirmed with type-specific

laboratory testing. However, retesting is not warranted in pregnant women with a history of laboratory-confirmed genital HSV.

- Women with a clinical history of genital herpes should be offered suppressive viral therapy at or beyond 36 weeks of gestation. For primary outbreaks that occur in the third trimester, continuing antiviral therapy until delivery may be considered.
- Because of enhanced renal clearance, the doses of antiviral medication used for suppressive therapy for recurrent HSV infection in pregnancy are higher than the corresponding doses in nonpregnant women.
- Cesarean delivery is indicated in women with active genital lesions or prodromal symptoms, such as vulvar pain or burning at delivery, because these symptoms may indicate viral shedding.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- Routine HSV screening of pregnant women is not recommended. In addition, routine antepartum genital HSV cultures in asymptomatic patients with recurrent disease are not recommended.
- In general, cesarean birth is not recommended for women with a history of HSV infection but no active genital lesions or prodromal symptoms during labor. However, for women with a primary or nonprimary first-episode genital HSV infection during the third trimester of pregnancy, cesarean delivery may be offered due to the possibility of prolonged viral shedding.
- Cesarean delivery is not recommended for women with nongenital lesions (eg, lesions on back, thigh, buttock). These lesions may be covered with an occlusive dressing and the patient can give birth vaginally.
- In women with preterm prelabor rupture of membranes, there is no consensus on the gestational age at which the risks of prematurity outweigh the risks of HSV. When expectant management is elected, treatment with an antiviral is recommended.

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 2000–July 2019. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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