Suppression of Herpes Simplex Virus During Pregnancy

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Transmission of maternal genital herpes to a neonate is an uncommon yet serious outcome of infection with herpes simplex virus (HSV) during pregnancy. Exposure of infants to HSV during delivery through the genital tract can result in neonatal herpes. Neonatal herpes affects 1 in 3000 infants born in the United States.[1] Newborns infected with HSV can develop severe complications, including vesicular skin lesions, keratoconjunctivitis, meningoencephalitis, and sepsis. A significant number of infants do not survive neonatal HSV disease, and in survivors, severe neurologic impairment may persist despite treatment. Maternal HSV infection has also been associated with preterm labor, preterm delivery, intrauterine growth retardation, and spontaneous abortion,[2,3] although these adverse outcomes were not demonstrated in a more recent study.[4] To improve the rates of perinatal morbidity and mortality related to genital herpes during pregnancy and to alleviate maternal symptoms, the recognition and treatment of HSV infection—especially asymptomatic infection—is essential in the care of the pregnant woman.

HERPES SIMPLEX VIRUS

Herpes simplex infection may be caused by either HSV type 1 or type 2 (also called human herpesvirus 1 and 2). Genital herpes is typically caused by HSV-2. HSV-1, commonly the cause of oral herpetic lesions, has increasingly become a cause of genital herpes as a result of oral-genital contact. HSV-1 is clinically indistinguishable from HSV-2, and it was demonstrated in one study that new genital infections with HSV-1 were as common as new oral HSV-1 infections.[5]

Symptoms related to genital herpes infection consist of a prodromal phase of malaise and fever that is followed by local pain and the development of vesicular and ulcerated lesions. Many persons are unaware of their acquisition of HSV infection and do not experience any symptoms with primary infection. As many as 60% of individuals with newly acquired HSV-2 and 35% of those with new HSV-1 are asymptomatic.[5] Conversely, most patients with a first symptomatic episode of genital HSV have already developed antibodies.[6] Therefore, a first clinical episode of genital herpes does not necessarily indicate a recent primary infection.

Transmission between individuals results from direct contact with an infected area of the body, usually through genital contact. After initial infection with HSV, the virus remains dormant in ganglion cells and can reactivate at a later time to cause a clinical recurrence. Subclinical viral shedding and horizontal transmission can occur during asymptomatic periods before a patient is aware they have acquired HSV infection or between clinical outbreaks.[7,8] Approximately 2% of HSV-2–infected individuals will shed virus asymptomatically on any given day.[7] Asymptomatic viral shedding may occur anytime in any infected person, and is likely to occur in those who have recently acquired HSV and those with more frequent recurrences.[7,9]

The prevalence of genital herpes has risen in recent decades. According to the most recent data, approximately 22% of Americans older than 12 years are seropositive for HSV-2 antibodies, yet only an estimated 2.6% of individuals report having ever experienced a clinical episode of genital herpes.[10] This suggests that many individuals are unaware that they are at risk for transmitting HSV. Rates of infection are higher among women, blacks, older persons, and persons with lower economic status, less education, earlier age of first intercourse, and greater number of sexual partners.[10,11] From the mid-1970s to the mid-1990s, the greatest increase in HSV-2 seropositivity was among whites in their teens and twenties.[10]

HSV INFECTION DURING PREGNANCY

Clinicians must be particularly alert to a patient's past history of genital herpes or symptoms of infection

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during pregnancy. An estimated 2% of women will acquire HSV-1 or -2 while pregnant,[4] and there is an increased rate of recurrence during pregnancy.[9,12] Maternal-fetal transmission of HSV mostly occurs due to the presence of the virus in the genital tract during delivery, although transmission may also occur prenatally. Viral shedding can be detected from viral cultures of the cervix, labia, or both.[9,12]

The greatest risk of perinatal transmission exists when primary infection with HSV-1 or HSV-2 occurs close to the time of labor. Primary infection is defined by the absence of maternal HSV antibodies. One study demonstrated a 10-fold increase in the rate of vertical transmission during a primary episode of genital herpes compared with transmission in women with a recurrent episode.[12] In a large study of 7046 HSV antibody–seronegative pregnant women, 94 women developed HSV antibodies during the course of pregnancy. There were no cases of neonatal herpes among the infants born to these 94 women. However, 9 women in the study acquired HSV near the time of delivery and did not develop antibodies. Four of the newborns born to these women did acquire neonatal herpes, including 1 neonate who died.[4] It appears that the development of maternal antibodies to HSV is protective to the infant.[13] A history of first-episode genital herpes infection late in pregnancy should concern the physician, but history and clinical symptoms alone cannot distinguish primary infection from a prior asymptomatic infection with recurrence.[6]

Most mothers with infants exposed to HSV during delivery do not have a history of symptomatic genital herpes.[14,15] Asymptomatic viral shedding in patients with a negative history of HSV infection presents a dilemma for clinicians because it is not predictable who will shed virus at the time of delivery.

LABOR AND DELIVERY

Current guidelines recommend cesarean delivery for any pregnant women with prodromal symptoms or herpetic lesions at the time of delivery.[16] This recommendation applies to women with first-episode genital herpes and women with a history of lesions who experience a recurrence at the time of delivery. Although the risk of perinatal transmission with recurrent genital HSV is low, cesarean delivery may even further reduce the possibility of infant morbidity and mortality. Critics of this recommendation cite the increased financial burden and maternal risks of performing a cesarean section for all women with active lesions at the time of delivery. A cost analysis demonstrated that more than 1500 cesarean sections need to be performed in women with recurrent genital herpes for each case of severe neonatal HSV prevented.[17] To effectively reduce the cesarean section rate in HSV-positive women, it is important to adequately diagnose, treat, and suppress HSV during pregnancy.

TREATMENT AND SUPPRESSION OF HSV

Antiviral Agents

Several antiviral agents are available to decrease the occurrence and duration of symptoms of genital herpes. Acyclovir, the most widely studied antiviral agent in the treatment of HSV, is a guanine analog that is activated intracellularly by viral thymidine kinase and selectively inhibits viral DNA polymerase. Because acyclovir is activated by cells infected with virus and does not affect native cell enzymes, it is relatively well tolerated. Acyclovir was approved in 1984 for the treatment of herpes simplex infections in nonpregnant adults. Its use was determined to be effective in treating first episodes of HSV[18] and in reducing the number of herpetic outbreaks in patients with recurrent genital herpes.[19,20] In a 5-year study of patients receiving daily acyclovir, many individuals did not experience a single recurrence, and the drug appeared to be safe for prolonged daily suppressive therapy.[20]

Acyclovir was subsequently researched in pregnant women with a history of genital herpes. The administration of 200 mg of oral acyclovir 5 times daily compared with placebo was safe and effective in reducing symptomatic HSV recurrences and subclinical viral shedding in women near term.[21,22] Further studies revealed that the use of 400 mg of acyclovir 3 times daily reduced the frequency of cesarean sections in women who experienced a first episode of genital herpes during pregnancy.[23]

A more recently available antiviral agent is valacyclovir, the *L*-valine ester of acyclovir. Valacyclovir is rapidly converted to acyclovir in the liver. Oral administration of valacyclovir has 2 to 3 times greater bioavailability and a longer plasma half-life than oral acyclovir and therefore requires less frequent dosing.[24] When compared, twice-daily valacyclovir and 5-times daily acyclovir were equally effective in reducing the symptoms and number of outbreaks of genital herpes.[25] Further studies of valacyclovir have demonstrated that once-daily dosing is effective and increases compliance.[26] Data suggests beginning suppression therapy at 36 weeks of gestation and continuing therapy until delivery occurs.

Famciclovir, the oral form of penciclovir, is an alternative to acyclovir and valacyclovir. Its mechanism of action is similar to acyclovir, but, like valacyclovir, it has an increased bioavailability. It has been shown to be

effective in reducing the signs and symptoms of acute and recurrent genital herpes in a twice-daily or thrice-daily regimen.[27,28]

Subclinical Viral Shedding

Because many patients with genital herpes shed viral particles in the absence of symptoms of infection, it is important to recognize that antiviral suppressive therapy can also reduce asymptomatic shedding of HSV-2.[28,29] This has important implications in the prevention of neonatal transmission in women who have viral shedding but do not have active lesions at the time of delivery. Cesarean section would not be performed in the absence of clinical symptoms, yet transmission could still occur.[12,15] A study of women with a history of recurrent genital herpes that compared the costs of cesarean delivery in women with lesions versus suppressive therapy during late pregnancy revealed suppression to be significantly more cost effective.[30]

Fetal Risks with Antiviral Therapy

Concern regarding fetal effects is warranted for any drug used during pregnancy. The pharmacokinetics of antiviral agents in pregnant women appear to be similar to those in nonpregnant adults.[24] Although acyclovir accumulates in the amniotic fluid through fetal urine, it does not concentrate in the fetus.[31] In utero exposure to acyclovir or valacyclovir has not been associated with increased risk of neonatal complications or congenital malformations.[22,23,32]

Acyclovir does concentrate in breast milk after oral administration, but the concentration is substantially less than that in neonates receiving treatment for exposure to HSV. Its use in the postpartum period is compatible with breastfeeding.[33]

SCREENING FOR HSV DURING PREGNANCY

According to current American College of Obstetricians and Gynecologists guidelines, routine screening for HSV is not recommended in asymptomatic pregnant women.[16] High costs, low sensitivity, and delays in obtaining test results preclude the regular use of viral cultures at the time of delivery.[34] Viral cultures overall are not as accurate as serologic testing.[35] An effective screening program would need to include all pregnant women because most cases of neonatal herpes occur in infants born to women without a known history of HSV. The presence of HSV antibody could identify women exposed to HSV. Seropositivity would not, however, identify women with primary infection. Based on a recent study, it may be cost effective to offer serologic testing to all pregnant women.[36]

CONCLUSION

The prevalence of genital herpes is increasing in the United States, and most individuals are unaware of their infection. Pregnant women should be counseled regarding the risks of HSV acquisition during pregnancy, including acquisition through oral-genital contact. HSV infections carry a risk of neonatal transmission; unfortunately, most cases of neonatal herpes occur in women who do not have a known history of genital herpes.

Antiviral therapy given in pregnancy successfully treats active lesions. Suppressive therapy beginning at 36 weeks of gestation decreases the incidence of recurrent lesions at the time of vaginal delivery, and thus may reduce the rate of cesarean delivery. It is extremely important to consider serologic testing for pregnant women and suppression therapy during pregnancy in order to decrease maternal infection and surgical risk due to cesarean delivery, as well as neonatal morbidity and mortality. **HP**

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