

Neonatal Herpes Simplex Virus Infections

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Neonatal herpes simplex virus infections can result in serious morbidity and mortality. Many of the infections result from asymptomatic cervical shedding of virus after a primary episode of genital HSV in the third trimester. Antibodies to HSV-2 have been detected in approximately 20 percent of pregnant women, but only 5 percent report a history of symptomatic infection. All primary episodes of HSV and secondary episodes near term or at the time of delivery should be treated with antiviral therapy. If active HSV infection is present at the time of delivery, cesarean section should be performed. Symptomatic and asymptomatic primary genital HSV infections are associated with preterm labor and low-birth-weight infants. The diagnosis of neonatal HSV can be difficult, but it should be suspected in any newborn with irritability, lethargy, fever or poor feeding at one week of age. Diagnosis is made by culturing the blood, cerebrospinal fluid, urine and fluid from eyes, nose and mucous membranes. All newborns suspected to have or who are diagnosed with HSV infection should be treated with parenteral acyclovir. (Am Fam Physician 2002;65:1138-42,1143. Copyright© 2002 American Academy of Family Physicians.)

◉ A patient information handout on herpes in pregnancy, written by the authors of this article, is provided on page 1143.

Neonatal herpes simplex virus (HSV) infections are transmitted from an infected mother, usually vertically, during delivery. The incidence of infection is approximately one per 3,000 to 20,000 live births.¹ A woman who experiences a primary episode of genital HSV during the third trimester and who has not completed seroconversion by the onset of labor has a 33 percent chance of transmitting the virus to her infant.² In contrast, a woman experiencing a secondary reactivation of HSV during the intrapartum period has approximately a 3 percent chance of transmitting the virus to her infant.² Of known infected infants, only 30 percent have mothers who had symptomatic HSV or a sexual partner with clinical infection.³ Many neonatal infections occur because of asymptomatic cervical shedding of virus, usually after a primary episode of HSV infection.³

The prevalence worldwide of herpes simplex virus type 2 (HSV-2) seropositivity is alarmingly high (25 percent

seropositivity in the United States).³ Antibodies to HSV-2 have been detected in approximately 20 percent of pregnant women; however, only 5 percent report a history of symptomatic infection.⁴ Primary genital HSV infections during pregnancy occur at rates similar to those in nonpregnant women, and often these infections are asymptomatic. There is a 2 to 3 percent seroconversion rate in pregnant women.⁵ Transmission occurs from an HSV-2-positive partner and is often traced to asymptomatic shedding of virus. Symptomatic and asymptomatic primary genital HSV infections are associated with preterm labor and low-birth-weight infants.^{6,7} Because of the high prevalence of HSV among adults, physicians should be aware of the risk of a primary HSV infection in a pregnant woman and its potential consequences to the fetus.

Clinical Presentation

A neonatal HSV infection can be devastating to an infant.⁸ Most of these infections are caused by HSV-2, but 15 to 30 percent are found to be caused by herpes simplex virus type 1 (HSV-1). Most cases occur in the intrapartum period, but they may occur in utero and postnatally through contact with oral or skin lesions. Many infants infected with HSV are born prematurely and subsequently have a low birth weight. Congenital HSV infection (approximately 4 percent of all neonatal HSV infections) can result in an infant born with microcephaly, hydrocephalus, chorioretinitis and vesicular skin lesions.⁹ Three subtypes of

A woman experiencing a primary episode of genital herpes simplex virus infection in the third trimester who has not completed seroconversion by the onset of labor has a 33 percent chance of transmitting the virus to her infant.

TABLE 1

Clinical Presentations of Neonatal Herpes Simplex Virus Infections

Skin, eye and mouth disease
 Localized central nervous system disease
 Disseminated state involving multiple organs
 Nonspecific symptoms such as irritability, fever, poor feeding or lethargy

naturally acquired or postnatally acquired infection have been identified: (1) disease localized to the skin, eye or mouth; (2) encephalitis, with or without skin, eye or mouth involvement; (3) disseminated infection that involves multiple sites, including the central nervous system, lung, liver, adrenals, skin, eye or mouth.

The diagnosis of neonatal HSV can be difficult initially. The presentation is nonspecific, with signs and symptoms such as irritability, lethargy, fever or failure to feed at about one week of age (*Table 1*). Infants often do not have skin lesions (less than 50 percent of infants with encephalitis or disseminated disease). By the time diagnosis is made, many infants have severe disease and have developed complications. When diagnosis is delayed, mortality is high despite antiviral therapy. There is virtually no mortality among infants with disease limited to the skin, eyes and mouth, but mortality increases to 15 percent among infants with encephalitis and 57 percent among infants with disseminated disease, even with antiviral therapy. Long-term morbidity is common in infants who survive with encephalitis or disseminated disease, and may include seizures, psychomotor retardation, spasticity, blindness or learning disabilities (*Table 2*).⁸

Illustrative Case

A male infant was born vaginally at 39 weeks of gestation with a birth weight of 7 lb, 3 oz to a 35-year-old gravida 1 para 1 woman. The mother had an uncomplicated pregnancy and no known history of HSV infection. Rupture of membranes was spontaneous and labor was augmented. Delivery occurred approximately 20 hours after rupture of membranes. There was no intrapartum fever. The infant developed mild respiratory distress at delivery that resolved with bulb and orogastric suction and administration of free-flow oxygen. Apgar scores were 8 at

Most of the neonatal herpes simplex virus infections are caused by HSV-2 but 15 to 30 percent are caused by HSV-1.

one minute and 9 at five minutes. The newborn had a normal physical examination and an uncomplicated stay in the newborn nursery and was discharged home on the second day of life.

The infant was brought to the emergency department the following day with a one-day history of poor breastfeeding, lethargy and an axillary temperature of 38.7°C (101.6°F). The examination was significant for mild lethargy, mild jaundice and a few scattered petechiae on the chest. Sepsis work-up was done and the cerebrospinal fluid (CSF) showed a white blood cell count of 2 per mm³ (2 × 10⁶ per L) and a red blood cell count of 17 per mm³ (17 × 10⁶ per L). The white blood count differential was 1 percent lymphocytes, 3 percent segmented neutrophils and 96 percent mononuclear cells. The cerebrospinal fluid glucose level was normal at 62 mg per dL (3.4 mmol per L) and the protein level was elevated at 62 mg per dL (0.62 g per L). After two days of negative bacterial cultures, intravenous antibiotics (ampicillin and cefotaxime [Claforan]), and clinical improvement, he was discharged home. On the seventh day of life, the infant experienced a seizure. He was admitted to the hospital with rapid decline and multiorgan failure. He died the following day. He was found to have positive cultures for HSV-1 from multiple sites (nasopharyngeal swab, liver biopsy). His mother also had a positive culture for HSV-1 from a breast lesion. This case illustrates the nonspecificity of the

TABLE 2

Complications of Neonatal Herpes Simplex Virus Infections

Seizures	Blindness
Psychomotor retardation	Learning disabilities
Spasticity	Death

Information from Jacobs RF. Neonatal herpes simplex virus infections. Semin Perinatol 1998;22:64-71.

Herpes simplex virus infections should be considered in all neonates who present with nonspecific symptoms such as fever, poor feeding, lethargy or seizures in the first month of life.

signs and symptoms of an HSV infection in a neonate, the lack of a history of HSV in the mother and the often tragic outcome of this disease.

Diagnosis of HSV Infections

The hallmark of primary episode genital HSV infections in adults is multiple painful vesicles in clusters on an inflamed surface. Associated symptoms may include pruritus, dysuria, vaginal discharge and tender regional lymphadenopathy. There is often a systemic prodrome of fever, malaise and myalgias one to two days before the appearance of lesions.

Secondary episodes of genital herpes are similar, but they often are associated with fewer lesions and are unilateral on the genitals. The symptoms of secondary episodes are usually less severe with few systemic symptoms. A suspected genital HSV infection should be confirmed with a diagnostic test. Traditionally, this has been viral culture of vesicular fluid. Typically, it may take two to three days to receive a report. More rapid diagnosis may be obtained by direct immunofluorescent staining using fluorescein-conjugated monoclonal antibodies to HSV.¹⁰ The sensitivity of this test is 80 to 90 percent compared with viral culture.

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The polymerase chain reaction (PCR) is a more sensitive assay. An additional 9 percent of culture-negative women were PCR positive for HSV-2.¹¹

Diagnosis of an HSV infection in an infant requires a high index of suspicion because the history of an active infection, primary or secondary, in a mother is often not given. HSV infections should be considered in all neonates who present in the first month of life with nonspecific symptoms such as fever, poor feeding, lethargy or seizure. Any vesicular rash in an infant up to eight weeks of age should be cultured and the infant immediately started on antiviral therapy with acyclovir (Zovirax) pending culture results. Cultures of blood, CSF, urine and fluid obtained from the eyes, nose and mucous membranes should also be obtained. CSF should be tested for HSV by PCR assay.

Antiviral Therapy for HSV Infections

All primary episodes of genital HSV infections should be treated with antiviral medications, including primary episodes occurring in pregnant women. This recommendation is supported by a recent statement of the American College of Obstetricians and Gynecologists (ACOG).¹² Currently available antiviral medications are acyclovir, famciclovir (Famvir) and valacyclovir (Valtrex). They are nucleoside analogs that selectively inhibit viral replication. They reduce the duration of active painful vesicular lesions and the duration of symptomatic and asymptomatic shedding of virus.^{13,14} Acyclovir was the first drug developed in this class and has a high safety profile. It is selective against HSV-infected cells. The two newer medications, famciclovir and valacyclovir, have a higher bioavailability with greater absorption resulting in higher plasma levels. They require less frequent daily dosing. Acyclovir is not teratogenic when given to women during the first trimester of pregnancy.¹⁵

Studies are underway to determine the efficacy of using antiviral therapy in pregnant women who develop HSV infections or as a prophylactic measure in high-risk pregnant women during the third trimester to prevent symptomatic infections or asymptomatic viral shedding.¹⁶⁻¹⁸ Currently, the data suggest prophylactic acyclovir will lower the recurrence rate of HSV infection in women who experience their first episode of HSV during pregnancy. In one study¹⁶ of 46 women who experienced their first episode of genital herpes during pregnancy, the cesarean section rate was significantly decreased in the women prophylactically treated with acyclovir from 36 weeks of gestation up to delivery to prevent a secondary recurrence of infection.

All infants suspected to have or who are diagnosed with an HSV infection should be treated with parenteral antiviral therapy. The duration of disease before antiviral therapy is initiated is significantly correlated with morbidity and mortality. Currently, suggested therapy is acyclovir 60 mg per kg per day in three divided doses intravenously for 14 days for disease limited to skin, eyes and mucous membranes, and 21 days for central nervous system or disseminated disease.^{1,19}

Reduction of Risk for Neonatal HSV Infections

A history of HSV in a pregnant woman and her partner should be obtained at the first prenatal visit (*Table 3*).^{1,12,17,20} Women with a negative personal history of HSV (especially those with a positive history in the male partner) should be counseled on ways to avoid infection, especially during the third trimester. Use of condoms or abstinence must be emphasized in this high-risk set of patients, even if the male partner has no active lesions. Women who have multiple sexual partners should be counseled on reducing the risk of sexually transmitted diseases. Weekly cervical cultures in

late pregnancy for women with a history of genital HSV infection are no longer recommended. Type-specific serologic testing of pregnant women at high risk of primary HSV infection has been suggested.⁴ At the present time, type-specific serologic tests are not widely available and their reliability is questionable.

Prophylactic acyclovir should be considered in the third trimester for women at especially high risk of having an active HSV infection at the time of labor. This would include women who have frequent outbreaks of genital herpes.^{17,20}

Antiviral therapy with acyclovir should be given to pregnant women who have a primary episode of genital HSV. It should also be given to women with an active genital herpes infection, primary or secondary, near term or at the time of delivery. A recent statement by ACOG supports the use of antiviral therapy in pregnant women with outbreaks of genital herpes.¹² Acyclovir has proved safety and efficacy and may prevent neonatal HSV infection. All use of acyclovir during pregnancy should be reported to the Acyclovir in Pregnancy Registry.²¹

Women should be asked carefully about symptoms of herpes infections at the onset of labor. To look for any further signs of infection, a vaginal speculum examination should be performed on any woman who has any signs or symptoms suggesting HSV infection at the onset of labor. Any patient who has a suspected active genital HSV infection or prodromal symptoms of HSV infection should undergo cesarean section, regardless of whether the membranes have ruptured. There is no difference in the management of a primary or secondary episode of HSV at the time of delivery. The current standard of care is that any woman with an active HSV lesion is delivered by cesarean section. Although the risk of vertical transmission from a secondary reactivation is low (approximately 3 percent), it is still present and most importantly, it is often difficult to differentiate between primary and secondary herpes infections.

Cesarean section alone does not completely remove the risk of transmission of HSV to the infant, and such potentially exposed infants should be handled with caution. Rupture of membranes for more than four to six hours before delivery increases the risk of transmission of HSV to the infant.²² The use of fetal scalp electrode monitoring during labor also provides a potential port of entry for the virus into the infant.¹² Nongenital herpes lesions do not necessitate a cesarean delivery, but the lesions should be covered with an occlusive dressing before vaginal delivery.¹²

TABLE 3
Methods to Reduce Risk of Neonatal HSV Infection

A history of HSV infection in the woman and her sexual partner should be obtained at the first prenatal visit.
Pregnant women with no known history of HSV should be counseled about methods to avoid infection.
Condom use by the sexual partner with history of HSV should be encouraged if the woman has no known history of HSV infection.
Prophylactic use of acyclovir in the third trimester should be considered in women with frequent HSV infection outbreaks.
Acyclovir should be given to all pregnant women with active genital HSV infection near term or at the time of delivery.
All women presenting in labor should be asked about symptoms of HSV infections.
All laboring women with active genital HSV infections should be delivered by cesarean section.
All HSV-exposed neonates should be monitored closely for any signs of infection, and cultures for HSV-1 and HSV-2 should be obtained.

HSV = herpes simplex virus.

Information from references 1, 12, 17 and 18.

Weekly cervical cultures for herpes simplex virus in women with a history of genital herpes are no longer recommended in late pregnancy.

The HSV-exposed neonate should be monitored closely for any signs of infection. Initial cultures should be performed at 24 to 48 hours, then weekly cultures of conjunctiva, nose, mouth, urine and rectum for HSV-1 or HSV-2 have been suggested.¹ Empiric acyclovir may be instituted in infants born to mothers with suspected primary HSV infection because the risk of infection in the infant is 33 to 50 percent.¹ Any exposed infant with clinical signs of HSV should be cultured (conjunctiva, nose, mouth, urine, rectum, CSF, blood buffy coat), CSF should be sent for PCR analysis, and the infant should be immediately started on intravenous acyclovir therapy. There have been no studies to date assessing benefits of prophylactic antiviral medications given to a clinically well exposed neonate, because the duration of effective prophylaxis is not known. The use of acyclovir may suppress the virus but may not eradicate it in an exposed infant. Infants born to women with active genital HSV lesions should be managed with contact precautions and be kept in a private room.¹

Postpartum women, family members and nursery personnel with active herpetic lesions of the mouth or skin should be instructed to use contact precautions with the infant. Nursery personnel with an active herpetic whitlow should not have direct care of neonates.¹

The authors would like to acknowledge Terry Seaton, Pharm.D., James Deckert, M.D., and Jae Lee, M.D., for critical evaluation of the manuscript.

The authors indicate that they do not have any conflicts of interest. Sources of funding: none reported.

REFERENCES

- American Academy of Pediatrics. Committee on Infectious Diseases. In: Pickering LK, ed. 2000 Red book: report of the committee on infectious diseases. 25th ed. Elk Grove Village, Ill.: American Academy of Pediatrics, 2000:309-18.
- Brown ZA, Benedetti J, Ashley R, Burchett S, Selke S, Berry S, et al. Neonatal herpes simplex virus infection in relation to asymptomatic maternal infection at the time of labor. *N Engl J Med* 1991;324:1247-52.
- Fleming DT, McQuillan GM, Johnson RE, Nahmias AJ, Aral SO, Lee FK, et al. Herpes simplex virus type 2 in the United States, 1976 to 1994. *N Engl J Med* 1997;337:1105-11.
- Brown ZA. Genital herpes complicating pregnancy. *Dermatol Clin* 1998;16:805-10, xiv.
- Brown ZA, Selke S, Zeh J, Kopelman J, Maslow A, Ashley RL, et al. The acquisition of herpes simplex virus during pregnancy. *N Engl J Med* 1997;337: 509-15.
- Brown ZA, Vontver LA, Benedetti J, Critchlow CW, Sells CJ, Berry S, et al. Effects on infants of a first episode of genital herpes during pregnancy. *N Engl J Med* 1987;317:1246-51.
- Brown ZA, Benedetti J, Selke S, Ashley R, Watts DH, Corey L. Asymptomatic maternal shedding of herpes simplex virus at the onset of labor: relationship to preterm labor. *Obstet Gynecol* 1996;87:483-8.
- Jacobs RF. Neonatal herpes simplex virus infections. *Semin Perinatol* 1998;22:64-71.
- Jones CL. Herpes simplex virus infection in the neonate: clinical presentation and management. *Neonatal Netw* 1996;15:11-5.
- Pouletty P, Chomel JJ, Thouvenot D, Catalan F, Rabillon V, Kadouche J. Detection of herpes simplex virus in direct specimens by immunofluorescence assay using a monoclonal antibody. *J Clin Microbiol* 1987;25:958-9.
- Cone RW, Hobson AC, Brown Z, Ashley R, Berry S, Winter C, et al. Frequent detection of genital herpes simplex virus DNA by polymerase chain reaction among pregnant women. *JAMA* 1994;272:792-6.
- ACOG practice bulletin. Management of herpes in pregnancy. No. 8. October 1999. Clinical management guidelines for obstetrician-gynecologists. *Int J Gynaecol Obstet* 2000;68:165-73.
- Baker DA. Antiviral therapy for genital herpes in nonpregnant and pregnant women. *Int J Fertil Womens Med* 1998;43:243-8.
- Wald A, Zeh J, Barnum G, Davis LG, Corey L. Suppression of subclinical shedding of herpes simplex virus type 2 with acyclovir. *Ann Intern Med* 1996;124(1 pt 1):8-15.
- Centers for Disease Control and Prevention. Pregnancy outcomes following systemic acyclovir exposure—June 1, 1984-June 30, 1993. *MMWR Morb Mortal Wkly Rep* 1993;42:806-9.
- Scott LL, Sanchez PJ, Jackson GL, Zeray F, Wendel GD. Acyclovir suppression to prevent cesarean delivery after first-episode genital herpes. *Obstet Gynecol* 1996;87:69-73.
- Stray-Pedersen B. Acyclovir in late pregnancy to prevent neonatal herpes simplex [Letter]. *Lancet* 1990;336:756.
- Scott LL, Hollier LM, McIntire D, Sanchez PJ, Jackson GL, Wendel GD Jr. Acyclovir suppression to prevent clinical recurrences at delivery after first episode genital herpes in pregnancy: an open-label trial. *Infect Dis Obstet Gynecol* 2001;9:75-80.
- Kimberlin DW, Lin CY, Jacobs RF, Powell DA, Corey L, Gruber WC, et al. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. *Pediatrics* 2001;108:230-8.
- Prober CG, Corey L, Brown ZA, Hensleigh PA, Frenkel LM, Bryson YJ, et al. The management of pregnancies complicated by genital infections with herpes simplex virus. *Clin Infect Dis* 1992;15: 1031-8.
- Andrews EB, Yankaskas BC, Cordero JF, Schoeffler K, Hampp S. Acyclovir in pregnancy registry: six years' experience. The Acyclovir in Pregnancy Registry Advisory Committee. *Obstet Gynecol* 1992;79:7-13.
- Nahmias AJ, Josey WE, Naib ZN, Freeman MG, Fernandez RJ, Wheeler JH. Perinatal risk associated with maternal genital herpes simplex infection. *Am J Obstet Gynecol* 1971;110:825-37.