

Neonatal Herpes Simplex Virus Infections

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KEYWORDS

• Neonatal herpes • Acyclovir • Polymerase chain reaction • Antiviral therapy

KEY POINTS

- Neonatal herpes simplex virus (HSV) infection can be difficult to differentiate from other causes of neonatal sepsis.
- The three major forms of neonatal HSV infection are disseminated disease (25% of cases); central nervous system (CNS) disease (30%); and skin, eye, and mouth disease (45%).
- The use of high-dose acyclovir for neonatal HSV disease has dramatically reduced mortality and morbidity from this disease.
- Disseminated HSV disease has a higher mortality rate (29%) than CNS disease (4%), but a lower frequency of disabilities 1 year after disease (disseminated, 17%; CNS, 69%).
- Neonates with HSV disease should receive oral acyclovir suppressive therapy for 6 months after completion of intravenous acyclovir treatment.
- New guidelines provide an evidence-based approach to evaluation and treatment of neonates born to women with active genital herpetic lesions.

VIRAL STRUCTURE

Herpes simplex viruses (HSV)-1 and -2 belong to alphaherpesviridae and are large, enveloped virions with an icosahedral nucleocapsid arranged around a linear, double-stranded DNA core. There is considerable cross-reactivity between HSV-1 and -2 glycoproteins, which mediate attachment to and penetration into cells and evoke host immune responses. Antigenic specificity is provided by glycoprotein gG, with the antibody response allowing for distinction between HSV-1 and -2.

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MATERNAL GENITAL HERPES

Terminology

Primary infection refers to acquisition of HSV-1 or -2 without prior exposure to either virus and hence no preformed antibodies. Nonprimary infection refers to acquisition of HSV-2 in an individual with prior HSV-1 antibodies and vice versa.

Reactivation is isolation of same type of virus from genital lesions as pre-existing type-specific antibodies. Symptomatic shedding refers to presence of lesions characteristic of genital herpes and detection of HSV-1 or -2 from the lesions by culture or polymerase chain reaction (PCR). Subclinical shedding refers to isolation of HSV-1 or -2 from genital mucosa by culture or PCR in the absence of lesions.

Epidemiology of Genital Infections During Pregnancy

Genital herpes infections are caused by HSV-1 or -2 and most infections are asymptomatic. HSV-2 seroprevalence among pregnant women is estimated to be 20% to 30% with approximately 10% of HSV-2 seronegative women living with a seropositive partner and hence at risk for acquisition of genital herpes during pregnancy.^{1,2} Among discordant couples, women seronegative for HSV-1 and -2 have an estimated 3.7% chance for seroconversion, whereas the risk for women already seropositive for HSV-1 to seroconvert to HSV-2 is estimated to be 1.7%.³ Similar to nonpregnant women, two-thirds of women who acquire genital HSV infection during pregnancy are either asymptomatic or have nonspecific symptoms. Among women with history of genital herpes acquired before pregnancy, 75% have at least one recurrence during pregnancy and 14% have prodromal symptoms or lesions at the time of delivery.^{4,5} For neonatal transmission, women must be shedding the virus symptomatically or asymptotically around the time of delivery. It has been shown that 0.2% to 0.39%⁶ of all pregnant women shed HSV in the genital tract around the time of delivery irrespective of prior history of HSV, and this incidence of shedding increases to 0.77% to 1.4% among women with prior history of recurrent genital herpes.^{7,8}

Distinguishing primary and nonprimary first-episode genital herpes episodes during pregnancy is based on information obtained from combination of genital culture or PCR data and serology. The risk of transmission of HSV to the neonate remains significantly higher with primary maternal infections acquired closer to the time of delivery compared with recurrent infections (50%–60% with primary infections vs <3% for recurrent infections), most likely caused by decreased transplacentally acquired antibody levels in the neonate and exposure in the birth canal to increased quantities of virus for longer duration.⁹ Fortunately, most genital herpes infections during pregnancy are recurrent and are associated with a lower risk of transmission to the neonate.

NEONATAL HERPES

Epidemiology

HSV infection of the neonate is an uncommon occurrence with an estimated rate of approximately 1 in 3200 deliveries.¹⁰ Neonatal HSV infections occur far less frequently compared with other serious neonatal infections overall. With approximately 4 million deliveries per year in the United States, an estimated 1500 cases of neonatal HSV disease occur annually in the United States.¹¹ When compared with other reportable congenital infections, such as syphilis, toxoplasmosis, and rubella, the overall incidence of neonatal HSV disease is higher yet the disease still does not require mandatory reporting.¹²

Factors Influencing Transmission of HSV to Neonate

Factors that influence transmission of HSV to neonate include the following:

1. Type of maternal infection (primary vs secondary)^{6,10,13}
2. Maternal antibody status^{10,14,15}
3. Mode of delivery (vaginal vs cesarean section)¹⁰
4. Duration of rupture of membranes^{10,13}
5. Integrity of cutaneous barrier (use of fetal scalp electrodes and other instrumentation)¹⁰
6. Type of HSV (HSV-1 vs -2)¹⁰

The risk of neonatal acquisition of HSV is significantly higher with first-episode primary and first-episode nonprimary maternal infections when compared with recurrent genital infections. Brown and colleagues¹⁰ evaluated approximately 40,000 pregnant women to assess the effect of maternal serologic status and cesarean section on transmission of HSV to the neonate. Of the approximately 40,000 women in the study who had cultures obtained from the external genitalia, approximately 31,000 women had serologic results available. Of these, 121 women were identified who were asymptotically shedding virus at the time of delivery and who had serologic analysis. The risk of neonatal transmission was identified as 57% with first-episode primary infection compared with 25% with first-episode nonprimary infection and 2% with recurrent genital HSV infections. This study, for the first time, also documented the protective effect of cesarean section in preventing neonatal HSV. Other statistically significant risk factors in this large study for transmission of HSV to neonate were isolation of HSV-1 from genital lesions when compared with HSV-2 and use of invasive monitoring techniques, such as fetal scalp electrodes.

In a smaller study of approximately 7000 women at risk of acquiring HSV during pregnancy, Brown and colleagues³ documented a maternal seroconversion rate of 3.2% and noted that HSV seroconversion completed before labor was not associated with increased neonatal morbidity but infections acquired close to labor were associated with increased incidence of neonatal HSV and worse morbidity.

Cesarean delivery has been proved to be effective in preventing the transmission of HSV to the neonate.¹⁶ It is important, however, to note that neonatal HSV cases have occurred despite cesarean delivery before rupture of membranes.^{2,17} Evidence also exists for prolonged rupture of membranes¹³ and disruption of mucocutaneous barrier by the use of fetal scalp electrodes and other instrumentation to affect the acquisition of neonatal HSV disease.^{10,18}

Prematurity as a risk factor for acquisition of neonatal HSV is not well studied. Although there is a larger proportion of premature infants with neonatal HSV compared with the general population and neonatal HSV infections in this population is associated with significant mortality and morbidity,¹⁹ it is not well known if genital herpes leads to prematurity or prematurity increases the risk of acquiring neonatal HSV.²⁰

Although it has been shown that the chances of acquisition of HSV-1 are decreased in women seropositive for HSV-2, transmission of HSV-1 to the neonate has been documented to be high irrespective of primary or recurrent infection when compared with HSV-2 transmission patterns.¹⁰

Neonatal HSV Disease Classification and Clinical Presentation

Neonatal HSV is acquired during one of three time periods: (1) in utero (5%); (2) peripartum (85%); or (3) postnatal (10%). HSV infection acquired in the intrauterine, peripartum, or postnatal period is classified into the following types and is predictive of

mortality and morbidity (**Table 1**)^{21–25}: disseminated disease; central nervous system (CNS) disease; and skin, eye, or mouth (SEM) disease.

Intrauterine infection

In utero infection with HSV is a rare entity but is unlikely to be missed because of presentation at birth and extent of involvement. It occurs in approximately 1 in 300,000 deliveries.²⁶ Affected infants present with a triad of clinical findings^{27–29}: cutaneous (scarring, rash, aplasia cutis, hyperpigmentation or hypopigmentation); ophthalmologic (microphthalmia, chorioretinitis, optic atrophy); and neurologic (intracranial calcifications, microcephaly, encephalomalacia).

Disseminated disease

In the preantiviral era, disseminated HSV infections accounted for one-half to two-thirds of all children with neonatal HSV disease. Since the development and use of antiviral therapy, disseminated disease has decreased to approximately 25% of all neonatal herpes² and usually presents around day 10 to 12 of life. Two-thirds of infants with disseminated disease also have concurrent encephalitis. Disseminated disease involves multiple organs, including CNS, lungs, liver, adrenal, and SEM. Although presence of a vesicular rash greatly facilitates identification of neonates with HSV disease, 20% of infants with disseminated disease never develop a vesicular rash.^{2,25,30} These patients usually present with viral sepsis, including respiratory failure, hepatic failure, and disseminated intravascular coagulation. Death from disseminated disease is usually caused by severe coagulopathy and extensive hepatic and pulmonary involvement.

CNS disease

Almost one-third of cases of neonatal herpes disease present as encephalitis and are categorized as CNS disease with or without skin involvement² and tend to present later than the other two entities at 16 to 19 days of life.²⁵ Clinical manifestations include

Clinical Characteristic	Disseminated Disease	CNS Disease	SEM Disease
Mode of acquisition	Peripartum/postpartum	Peripartum/ postpartum	Peripartum/ postpartum
Frequency	25%	30%	45%
Sites of involvement	CNS, liver, lung, adrenal, skin, eye, mucus membranes	Central nervous system with or without skin involvement	Skin, eye, mucus membranes
Presentation	Encephalitis, respiratory failure, hepatic failure, disseminated intravascular coagulation ± rash	Seizures, lethargy, irritability, poor feeding, temperature instability ± rash	± vesicular rash
Mortality	29%	4%	—
Normal development 1 y after treatment without subsequent antiviral suppressive therapy	83%	31%	100%

focal or generalized seizures, lethargy, irritability, poor feeding, temperature instability, and bulging fontanelle. A total of 60% to 70% of infants with CNS disease have skin lesions at some point during the course of the illness.²⁵ In the absence of skin lesions, the clinical presentation is indistinguishable from other causes of viral or bacterial sepsis. Mortality in these neonates is usually caused by devastating brain destruction with acute neurologic and autonomic dysfunction. Unlike herpes simplex encephalitis beyond the neonatal period, where there is a higher predilection for the temporal lobe to be involved, neonatal HSV often involves multiples areas of the brain.

SEM disease

Infection limited to SEM has historically accounted for 20% of cases of neonatal herpes disease but has increased to approximately 45% with the introduction of antiviral therapy.² Eighty percent of neonates with SEM disease have a vesicular rash on physical examination and usually present to medical attention around day 10 to 12 of life.²⁵

Differential Diagnosis

Several other infectious and non-infectious conditions mimic neonatal HSV disease. Bacterial pathogens include group B *Streptococcus*, *Listeria monocytogenes*, *Staphylococcus aureus*, *Escherichia coli*, and other gram-negative bacteria. Viral exanthematous infections that are confused for neonatal HSV include varicella-zoster virus infection, enteroviral sepsis, and symptomatic cytomegalovirus infection. Noninfectious cutaneous disorders should be considered and include erythema toxicum, incontinentia pigmenti, and Bednar's aphthae.

EVALUATION OF THE NEONATE WITH SUSPECTED HSV INFECTION

Viral Culture

Isolation of HSV by culture remains the definitive method of diagnosing neonatal HSV infection (**Box 1**). Conjunctivae, nasopharynx, mouth, and anus (surface cultures) are swabbed and transported in appropriate transport media on ice to a diagnostic virology laboratory for inoculation into cell culture systems that are monitored for cytopathic effects.³⁰ Typing of an isolate may be performed by one of several techniques for prognostic purposes. Other sites from which HSV can be cultured include cerebrospinal fluid (CSF) and blood. Of sites routinely cultured for HSV, skin and eye or conjunctival cultures provide the greatest yield.²⁵

Polymerase Chain Reaction

The application of PCR to CSF samples has revolutionized the diagnosis of CNS neonatal herpes disease.^{31–35} However, performance of PCR is highly dependent on the manner the CSF sample is collected, stored, and transported to the laboratory.³⁶ The overall sensitivities of CSF PCR in neonatal HSV disease have ranged from 75% to 100%, with overall specificities ranging from 71% to 100%.^{33,34,37} The results of the PCR should always be interpreted, taking into consideration the clinical presentation of the neonate. A negative PCR result from the CSF does not rule out neonatal HSV disease, because the test may be negative in very early stages of the infection as a result of low viral load or the sensitivity of the test being used. In comparison, blood PCR in neonatal HSV has been evaluated to a lesser extent and in smaller cohorts.^{34,35,38}

Serologic Testing

Serologic diagnosis of neonatal HSV is not very helpful and is not usually recommended because of transplacentally acquired maternal IgG, which confounds the assessment of neonatal antibody levels during acute infection. Serial antibody assessment

Box 1**Evaluation and treatment of neonatal HSV disease**

1. Specimens to obtain before initiating anti-viral therapy
 - a. CSF – Indices, bacterial culture, HSV DNA PCR
 - b. Surface cultures ± PCR
 - c. Base of vesicle or suspicious lesions culture ± PCR
 - d. Whole Blood – PCR
 - e. Whole Blood – Alanine aminotransferase (ALT)
2. Treatment of Neonatal HSV
 - a. Intravenous Acyclovir
 - b. Dose – 60 mg/kg/day divided in 3 doses
3. Duration of Treatment:
 - a. SEM Disease – 14 days
 - b. CNS Disease – Minimum 21 days^a
 - c. Disseminated Disease – 21 days
4. Antiviral Suppressive Therapy after Treatment (SEM, CNS and Disseminated Disease):
 - a. Oral acyclovir 300 mg/m²/dose, three times a day for 6 months
 - b. Monitor absolute neutrophil count while on therapy

^a In neonates with positive CSF HSV PCR at the end of therapy, antiviral therapy should be continued until PCR negativity is achieved.

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may be useful in specific circumstances where a mother with primary genital HSV late in gestation transfers very little antibody to the neonate. Overall, serologic studies play no role in the diagnosis of neonatal HSV infection and are not currently recommended for diagnostic purposes.

Specimens to Obtain Before Starting Antiviral Therapy

Before initiation of empiric parenteral antiviral therapy, the following specimens should be collected to aid in the diagnosis of neonatal HSV disease or to determine if antiviral therapy may be discontinued if HSV has been excluded³⁰:

1. CSF for indices, bacterial culture, and HSV DNA PCR
2. Swab for viral culture from the base of vesicles, suspicious areas, and mucous membrane lesions for viral culture; PCR may be performed in addition to cultures, if desired
3. Swab from mouth, conjunctiva, nasopharynx, and rectum (surface cultures) for viral culture; PCR may be performed in addition to cultures, if desired
4. Whole blood for HSV DNA PCR
5. Blood to determine alanine aminotransferase (ALT)

TREATMENT OF NEONATAL HSV

The earliest antiviral agents effective against HSV included 5-iodo-2'-doxyuridine and 1-β-D-arabinofuranosylcytosine, but were found to be too toxic for human use.

Vidarabine, licensed for use in the United States in 1977, was the first antiviral for which the therapeutic efficacy outweighed toxicity for use in cases of life-threatening HSV disease. Because of toxicity associated with administration of intravenous vidarabine, its use was restricted by the Food and Drug Administration to life-threatening HSV and varicella-zoster virus infections.²¹ In the 1980s, a landmark study comparing the efficacy of intravenous vidarabine with lower-dose acyclovir (30 mg/kg/d administered three times a day for 10 days) for neonatal herpes disease²² found a lack of therapeutic superiority of the lower-dose acyclovir over vidarabine. Acyclovir was soon the treatment of choice because of its safety profile and ease of administration. Subsequently, a higher dose of acyclovir (60 mg/kg/d divided in three doses for 14–21 days) has been shown to remarkably improve mortality associated with neonatal HSV disease.²⁴

The current recommendations are to treat all neonates with HSV disease parenterally with acyclovir given at 60 mg/kg/d divided every 8 hours.^{24,30} The dosing interval may need to be increased in premature infants depending on their renal clearance.³⁹ Duration of treatment is 14 days for infants with SEM disease and 21 days for neonates with CNS and disseminated disease presentations.³⁰ All neonates with CNS involvement should have repeat CSF PCR performed on CSF at the end of therapy to document a negative CSF PCR result and for CSF indices. HSV DNA detected in CSF after completion of acyclovir therapy has been associated with poorer outcomes.³³ In those rare neonates with positive CSF PCR at the end of therapy, antiviral therapy should be continued until PCR negativity is achieved.^{25,30,33} Because the significance of blood DNA PCR positivity remains largely unknown, serial measurement of blood DNA PCR for assessing response to therapy is not recommended at this time.³⁰ Although a retrospective study that compared the prevalence of neonatal HSV disease with bacterial meningitis among infants admitted through the emergency department for sepsis evaluation revealed that the incidence for both entities was similar, the number of infants with neonatal herpes included in the study was too small to draw any definite conclusions about empiric antiviral coverage for all infants undergoing sepsis evaluation in the first month.⁴⁰ Experts in the field differ regarding opinion about empiric coverage for such infants.^{41,42}

Prognosis

Mortality

In the preantiviral era, 85% of neonates with disseminated disease and 50% of neonates with CNS disease died by 1 year of age.²¹ Currently, with the use of the higher dose of acyclovir (60 mg/kg/d divided in three doses for 21 days), 1-year mortality has been reduced to 29% for disseminated disease and 4% for CNS disease.²⁴ Risk factors associated with higher mortality include lethargy and severe hepatitis in neonates with disseminated disease and lethargy and seizures in infants with CNS disease.²⁵

Morbidity

In the preantiviral era, 50% of survivors with disseminated disease and 33% of neonates with CNS disease developed normally at 12 months of age.²¹ After the initiation of high-dose acyclovir, 83% of neonates with disseminated disease and 31% with CNS disease develop normally at 12 months of age.^{21,24} Seizures before or at the time of initiation of antiviral therapy has been associated with increased risk of morbidity in neonates with disseminated and CNS disease.²⁴

Morbidity after SEM disease has dramatically improved after initiation of antiviral therapy. In the preantiviral era, 38% of the infants with SEM disease developed developmental disabilities at the age of 12 months, and after introduction of vidarabine and

lower-dose acyclovir the percentages dropped to 12% and 2%, respectively.²² None of the infants with SEM disease in the high-dose acyclovir study developed developmental disabilities at 12 months age.²⁴

Antiviral Suppressive Therapy After Treatment

The outcome of neonatal herpes depends on the extent of disease. Approximately 20% of survivors with disseminated disease have neurologic sequelae compared with 70% of neonates with CNS disease.²⁴ A phase III, placebo-controlled trial performed by the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group showed good evidence for use of acyclovir-suppressive therapy for 6 months after completion of standard therapy for neonatal HSV disease. Infants with CNS disease stratified to the treatment arm were found to have better neurodevelopmental outcomes compared with the placebo group, and infants with SEM disease were found to have less frequent recurrence of skin lesions while receiving suppressive therapy.⁴³ Although almost half of infants enrolled in an earlier small phase I/II trial were found to have increased incidence of neutropenia,⁴⁴ the phase III trial of acyclovir-suppressive therapy found similar rates of neutropenia in the treatment and placebo arms of the study,⁴³ although the *p*-value approached statistical significance. The current recommendation for antiviral-suppressive therapy after completion of treatment of neonatal herpes disease is to treat with oral acyclovir at 300 mg/m²/dose, three times a day for 6 months. Absolute neutrophil counts should be monitored at 2 and 4 weeks and monthly thereafter after initiation of suppressive therapy.³⁰ Orally administered acyclovir, however, has low bioavailability and requires frequent dosing. Recently, pharmacokinetic and safety profile of an extemporaneously compounded valacyclovir oral suspension in pediatric patients 1 month to 11 years was assessed. Clearance of acyclovir after administration of valacyclovir was found to be prolonged in infants younger than 3 months compared with older age groups,⁴⁵ and at this time valacyclovir should not be used for prolonged antiviral suppression after neonatal HSV disease.

Approach to an Infant Exposed to HSV During Maternal Primary or Recurrent Genital HSV Infection

Recommendations for the management of infants exposed to HSV in the intrapartum period until recently were based on expert opinion and did not take into consideration the change in epidemiology of genital HSV (primary vs recurrent infections and HSV-1 vs -2 infections in women). The most recent Clinical Report endorsed by the American Academy of Pediatrics provides evidence-based guidance on the management of neonates born to women with active genital herpetic lesions (**Box 2**).⁴⁶

The recommendations take into consideration maternal serologic status, presence of genital lesions at the time of delivery, and route of delivery. The recommendations are applicable only to institutions that have access to PCR facilities and require neonatal and obstetric clinicians involved to work very closely with laboratory personnel for timely access to laboratory results. Moreover, the guidelines are only applicable to care of infants exposed to HSV from maternal genital lesions present at the time of delivery and not to situations of asymptomatic shedding.

Testing of women in labor

All women with genital lesions characteristic of HSV at the time of delivery should have viral culture and PCR sent off from the lesions. Further characterization of type as HSV-1 or -2 is required for correlation with serology to determine status of maternal infection (primary vs recurrent).

Box 2**Management of infants born to women with genital lesions at delivery**

1. Determine maternal serologic and virologic status
 - a. Send viral culture and PCR for HSV from genital lesions at delivery
 - b. Characterize type of HSV (HSV-1 vs -2)
 - c. Determine maternal HSV serology
 - d. Determine status of maternal infection at delivery (primary vs recurrent infection)
2. Infants born to women with lesions at delivery with genital herpes before pregnancy
 - a. Determine status of maternal infection at delivery (primary vs recurrent infection)
 - b. Obtain surface cultures and blood DNA PCR from neonate for viral culture \pm PCR at 24 hours
 - c. Obtain CSF for HSV PCR and serum ALT level if previously mentioned tests positive
 - d. Neonatal HSV infection: treat pre-emptively with intravenous acyclovir for 10 days
 - e. Neonatal HSV disease: treat with intravenous acyclovir for 21 days (CNS/disseminated disease) or 14 days (SEM disease)
3. Infants born to women with genital lesions at delivery without genital herpes before pregnancy
 - a. Determine status of maternal infection at delivery (primary vs recurrent infection)
 - b. Obtain surface cultures, blood DNA PCR, serum ALT, and CSF for HSV PCR from neonate for viral culture \pm PCR at 24 hours
 - c. Initiate treatment with intravenous acyclovir
 - d. Maternal recurrent infection and neonate asymptomatic: discontinue acyclovir
 - e. Maternal first episode primary or nonprimary maternal infection and neonate asymptomatic: treat pre-emptively with acyclovir for 10 days
 - f. Neonatal HSV infection: treat pre-emptively with acyclovir for 10 days
 - g. Neonatal HSV disease: treat with intravenous acyclovir for 21 days (CNS/disseminated disease) or 14 days (SEM disease)

Management of newborns born to women with lesions at delivery and a history of genital herpes before pregnancy

For women with a history of genital herpes before pregnancy, the likelihood of lesions present at delivery being recurrent is high and the risk of transmission to the infant is low (<3%). At approximately 24 hours after delivery, surface cultures (conjunctiva, mouth, nasopharynx, rectum, and scalp electrode site when present) and blood DNA PCR should be obtained for viral culture and PCR. It is not required to start acyclovir therapy in these neonates because of lesser risk for acquisition of neonatal HSV. Waiting for 24 hours after delivery before collection of samples is recommended to differentiate contamination of neonatal skin by maternal secretions during the birth process versus true HSV infection of the baby. It is acceptable to discharge these infants who continue to be clinically well at 48 hours with instructions to caregivers for very close monitoring and immediate medical attention with development of any findings concerning for neonatal HSV.

If the surface and blood virologic studies are negative at 5 days, further evaluation of the infant is recommended only with the development of any signs suggestive of neonatal HSV in the subsequent 6 weeks. If the surface and blood virologic studies

are positive, suggesting HSV infection, a full evaluation (CSF for indices and HSV PCR, serum ALT level) is recommended to determine presence and extent of HSV disease. Under these circumstances, therapy with intravenous acyclovir should be initiated in these infants as soon as possible.

If the results of the evaluation are negative (normal CSF indices and negative CSF HSV PCR, normal ALT measurement), suggestive of neonatal HSV infection, preemptive treatment for 10 days with parenteral acyclovir should be administered to prevent the progression of HSV infection to HSV disease. If the evaluation is suggestive of neonatal HSV disease (abnormal CSF indices with HSV CSF PCR positive or elevated serum ALT), treatment with acyclovir should be continued for 21 days for CNS or disseminated neonatal HSV disease as discussed previously, followed by oral suppressive therapy with acyclovir for 6 months.

Management of newborns born to women with lesions at delivery and no history of genital herpes before pregnancy

In women without a history of genital herpes before pregnancy, the presence of genital lesions at labor could represent primary infection (>50% risk of transmission to neonate); nonprimary infection (25% risk of transmission to neonate); or recurrent infection (<3% risk of transmission). The information obtained from viral culture and PCR of these lesions and maternal serologic status obtained at delivery should guide the clinician in determining the type of maternal infection and risk for transmission to the neonate and guide approach to management of neonate.

At approximately 24 hours after birth, surface cultures (eye, mouth, nasopharynx, and rectum) and blood for HSV DNA PCR should be obtained from the neonate. Because of the higher risk of transmission of HSV to neonates in these circumstances, CSF for determination of indices and HSV PCR and serum for ALT level should be obtained simultaneously, as should initiation of treatment with intravenous acyclovir.

If the maternal serology and virologic studies are more suggestive of a recurrent infection and the infant remains asymptomatic with no evidence of HSV infection or disease (negative result on surface cultures, blood DNA PCR, CSF PCR, and normal ALT level), discontinuation of parenteral acyclovir with instructions for close monitoring and re-evaluation with the development of any new signs is recommended.

If the maternal studies are suggestive of a primary or nonprimary genital infection and the neonate remains asymptomatic and lacks evidence of HSV infection or disease, treatment with 10 days of parenteral acyclovir is recommended (preemptive therapy).

With maternal recurrent or nonprimary infections involving infants with evidence of HSV infection or HSV disease, the guidelines are similar to those outlined in the approach to an infant born to a mother with history of genital herpes before pregnancy: 10 days of parenteral acyclovir for HSV infection (preemptive therapy), 14 days of parenteral acyclovir for neonatal SEM disease, and 21 days of parenteral acyclovir therapy for CNS or disseminated disease with documentation of negative CSF HSV PCR before stopping parenteral acyclovir therapy followed by 6 months of oral acyclovir-suppressive therapy as discussed previously.

STRATEGIES FOR PREVENTION OF NEONATAL HERPES

Cesarean Delivery

Delivery of the infant by cesarean section in women with active genital lesions can reduce the infant's risk of acquiring HSV^{10,13} and is recommended when genital lesions or prodromal symptoms are present at the time of delivery,¹⁶ although it does not completely eliminate the risk of neonatal HSV. Cesarean delivery is more likely to be

effective if performed before rupture of membranes, but in situations where rupture of membranes has occurred and genital lesions are observed on physical examination cesarean delivery is recommended to minimize exposure of the neonate to HSV.¹⁶ Physicians involved in the care of neonates should be aware that delivery by cesarean section does not entirely prevent transmission of HSV to the neonate. Transmission of HSV has been documented in circumstances where cesarean section was performed before rupture of membranes.^{2,17} Cesarean section is not currently recommended for women with a prior history of genital herpes and no active lesions or prodromal symptoms at the time of delivery.^{16,47} Protocols as outlined previously should be followed for care of neonates exposed to maternal genital lesions suggestive of HSV infection.

Antiviral Suppressive Therapy

In women with active recurrent genital herpes, antiviral suppressive therapy with acyclovir/valacyclovir initiated at 36 weeks of gestation has been associated with decreased genital lesions at the time of delivery and decreased viral detection by culture or PCR with a reduced need for cesarean section. Use of such suppressive therapy is an increasing practice among obstetricians and is recommended by the American College of Obstetricians and Gynecologists,¹⁶ even though subclinical viral shedding is not entirely suppressed. The use of such a practice in preventing neonatal HSV disease is not well studied. The Acyclovir in Pregnancy Registry, which recorded the outcomes of pregnancy in which in utero exposure to acyclovir or valacyclovir occurred, observed no adverse fetal outcomes or birth defects in fetuses exposed to these drugs.⁴⁸ The number of neonates in the registry was too small to draw any conclusions regarding efficacy or safety to the neonate from the use of such suppressive therapy during pregnancy.

A recent multicenter case series reported eight cases of infants with neonatal HSV disease acquired from mothers despite receiving antiviral suppressive therapies beyond 36 weeks of gestation.²⁹ Overall, although maternal antiviral suppressive therapy decreases the incidence of genital recurrences at labor, the extent to which these drugs prevent neonatal acquisition remains unknown and requires further research.

HSV Vaccine

Several attempts to develop a vaccine for genital herpes have been futile. An earlier HSV-2 gD subunit vaccine adjuvanted with alum was found to be effective in preventing HSV-1 or -2 genital herpes (~75% vaccine efficacy) and HSV-2 infection. However, efficacy was limited only to women who were HSV-1 and -2 seronegative before vaccination. There was no reported efficacy in men or women who were HSV-1 seropositive before vaccination.⁴⁹ Most recently, the results of a randomized, double-blind trial testing the efficacy of the same HSV-2 gD subunit vaccine involving women seronegative for HSV-1 and -2 were reported. The vaccine was found to have an efficacy of 58% for preventing HSV-1 genital herpes but lacked efficacy for preventing HSV-2 genital herpes.⁵⁰ Currently, no vaccine has proved to be effective for preventing acquisition of HSV-1 or -2.

Prevention of Maternal HSV Acquisition During Pregnancy

Various strategies have been recommended to prevent maternal acquisition during pregnancy but none have been tested in large-scale trials.^{12,51} The first approach is to screen all women with an IgG-based assay at 24 to 28 weeks of gestation. Women identified to be seropositive but unaware of a prior infection would benefit from education regarding significance of this finding and identification of recurrent lesions and

prodromal symptoms, particularly at the time of labor. Women found to be seronegative or seropositive to either HSV-1 or -2 should be counseled to avoid oral-genital and genital-genital contact, respectively. This strategy does not take into account the serostatus or exposure risk to the sexual partner.

The second approach recommends screening all couples for HSV serology at 14 to 18 weeks and appropriate counseling based on serology results for both partners. This approach might not be applicable in situations where a single partner cannot be identified or the partner changes during the course of pregnancy.

The third approach is to advise all pregnant women to abstain from all forms of sexual contact during the third trimester of pregnancy. The final approach might particularly be applicable in situations where serologic testing is either unavailable or is economically not feasible.

The feasibility of these approaches has not been tested in any studies and the applicability and cost-effectiveness of such interventions requires further study. The American College of Obstetricians and Gynecologists currently does not recommend routine screening of asymptomatic women for HSV during pregnancy.¹⁶

Prevention of Postnatal Acquisition

Although most neonatal HSV infections are acquired in the peripartum period, 10% of cases are acquired in the postpartum period by exposure to the virus from open lesions of caretakers. There have also been reports of neonatal HSV infections after Jewish ritual circumcision involving orogenital contact⁵² and it is important for physicians involved in the care of children to educate parents about the risks involved in such practices. Although it is recommended that infected household contacts and family members avoid contact with a newborn, it is prudent for infected healthcare personnel with active herpetic whitlow lesions to not be responsible for direct care of neonates.³⁰

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