REVIEW ARTICLE

CURRENT CONCEPTS

Maternal and Neonatal Herpes Simplex Virus Infections

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An estimated 25 to 65% of pregnant women in the United States have genital infection with herpes simplex virus type 1 (HSV-1) or HSV type 2 (HSV-2).[1] Neonatal HSV infection, defined as infection in a newborn within 28 days after birth, is an especially devastating consequence of the epidemic of genital herpes. Untreated neonatal HSV infection is associated with only a 40% survival rate, and even with the early initiation of high-dose intravenous acyclovir therapy, it results in considerable disability among survivors.

On the basis of hospital discharge data, the frequency of neonatal HSV infection in the United States varies according to the patient population, with the rate of infection ranging from 1 case per 12,500 live births (8 per 100,000) to 1 per 1700 live births (60 per 100,000) (Table 1). In a retrospective study in California, the rate was 12.2 cases per 100,000 live births from 1995 to 2003.[6] Analysis of data from 30 U.S. health plans, which included 17 million enrollees, showed a rate of 60 cases per 100,000 live births.[8] Prospective, single-center studies in the United States have shown rates of neonatal HSV infection as high as 31.2 cases per 100,000 (1 in 3200) live births.[9] These incidence data for neonatal HSV infection are similar to those for perinatal human immunodeficiency virus (HIV) infection before the advent of the routine use of antiretroviral agents in pregnancy, and the incidence is higher than that of congenital syphilis, toxoplasmosis, and congenital rubella in years in which the virus was not epidemic (Table 1).[6,16-20]

PATHOPHYSIOLOGY

Most neonatal infections result from exposure to HSV in the genital tract during delivery, although in utero and postnatal infections occasionally occur.[21] Although most clinical-management guidelines for HSV infections are directed to the care of women with long-established disease, the risk of transmission is significantly higher among women who acquire genital infection with HSV-1 or HSV-2 during pregnancy than among women with long-standing HSV-2 infection in whom the virus is reactivated in the genital tract at term (25 to 50% vs. <1%) (Fig. 1 and Table 2). Thus, although the number of infants born to women with newly acquired HSV infection at the end of pregnancy is much smaller than the number of infants born to women with established HSV-2 infection, the much greater efficiency of HSV transmission during newly acquired genital HSV infection accounts for the fact that 50 to 80% of cases of neonatal HSV infection result from women who acquire genital HSV-1 or HSV-2 infection near term.[21,22] Most cases of genital HSV infection in women occur without signs or symptoms of disease and are associated with cervical viral shedding.

HSV-2 is detected in genital secretions at term by culture in approximately 2% of HSV-2–seropositive women and by polymerase-chain-reaction (PCR) assay in 8 to

15% of HSV-2–seropositive women.[24,25] Almost none of this viral shedding is accompanied by clinically detectable genital lesions. Despite the frequent exposure to HSV during birth, neonatal herpes develops in less than 1% of infants delivered vaginally to women with HSV-2 shedding at term.[21,22,26] The discrepancy between the high shedding rate among women with established HSV-2 infection and the low neonatal-transmission rate suggests a role of transplacental antibodies in abrogating the risk of infection. This difference between the risk of neonatal transmission associated with initial acquisition of HSV during pregnancy and the risk associated with reactivation of previous infection contributes to the divergent patient care and public health strategies that have been suggested to address neonatal HSV infection.

DIAGNOSIS

Genital HSV infections are often subclinical and, even if symptomatic, have nonspecific signs and symptoms. Case series have shown that most primary genital herpes infections in pregnant women are not diagnosed accurately by clinicians.[27] Pregnant women who present with HSV infection should undergo both a type-specific serologic assay and a test of the virus to identify and type the HSV infection.[24] This approach allows the clinician to objectively determine which infants are at highest risk for infection. Laboratory tests include viral isolation in culture or direct fluorescence antibody studies to detect viral protein in genital lesions, or PCR to test for the presence of viral DNA.[24] PCR assessment is the most sensitive and usually the most rapid measure.[28] Accurate type-specific serologic assays are based on the difference in epitope-specific immune responses to the HSV glycoprotein G molecule of HSV-1 and HSV-2; occasionally, tests based on whole-antigen response are reported inaccurately as being type-specific by diagnostic laboratories. Similarly, commercial assays of IgM antibodies against HSV-1 and HSV-2 are not validated in pregnant women or in infants. Antibodies against glycoprotein G type 1 or glycoprotein G type 2 tend to develop reasonably late in the course of infection — at 2 to 12 weeks; hence, detection of the virus in a seronegative woman or discordance between the type of viral isolate and antibody status (e.g., an HSV-2 isolate in a mother with only HSV-1 antibodies) indicates recently acquired infection.

MANIFESTATIONS OF NEONATAL HSV INFECTION

Congenital HSV infection is rare; it shares clinical features such as microcephaly, hydrocephalus, and chorioretinitis with other congenital infections and is usually manifested by clinical abnormalities at birth. Postnatal acquisition of HSV is almost always due to HSV-1 and is associated with contact with hospital personnel or family members who are shedding HSV-1.[29] Ritual circumcision that involves suctioning of the wound with the mouth also has been associated with neonatal HSV-1 infection.[30]

Most neonatal infections result from exposure to HSV during delivery. The clinical presentation of these infections has been divided into three categories, each of which is associated with different outcomes and clinical manifestations. Neonates with infections that are confined to the skin, eyes, and mucosa, which account for about 45% of most case series, often have vesicular lesions on the skin, eye, or mouth and, by definition, have no central nervous system (CNS) or visceral-organ involvement (i.e., normal results of cerebrospinal fluid analysis and normal neurologic and computed tomographic [CT] findings, with no evidence of conditions such as pneumonitis, hepatitis, and coagulation problems). Systemic therapy is required; otherwise, further progression of the infection may occur. However, with high-dose intravenous acyclovir, the long-term developmental outcome of this form of neonatal herpes is good. Children with herpes infection that is confined to the skin, eyes, and mucosa often have recurrent outbreaks of cutaneous herpes during early childhood. Suppressive antiviral therapy reduces the frequency of these recurrences, but breakthrough infections may still occur.

CNS-associated infections, which account for 30% of most large case series, are associated with lethargy, poor feeding, and seizures; cutaneous lesions may or may not be present. Pleocytosis is usually present, HSV DNA in the cerebrospinal fluid is the most sensitive laboratory test for confirming the diagnosis, and analysis of samples obtained early in the course of the disease may have false negative results. Among infants with CNS HSV infection, the morbidity is higher among infants with HSV-2 infection than among those with HSV-1 infection and may include developmental delay, epilepsy, blindness, and cognitive disabilities. Prompt initiation of therapy influences

Table 1. Incidence of Neonatal HSV Infection and Other Congenital Infections in North America.*

Infection and Type of Data	Dates	Rate (no. per 100,000 live births)	Reference
Neonatal HSV infection			
National or state surveillance system			
Canada	2000–2003	5.9	Kropp et al.[2]
Washington State	2000–2004	11.5	Hofmann J, Stenger M: personal communication
Ohio	1999–2003	5.8†	Ohio Department of Health[3]
Hospital discharge data			
Washington State	1987–2002	8.4	Mark et al.[4]
New York City	1994–2003	13.4	Schillinger et al.[5]
California	1995–2003	12.2	Morris et al.[6]
California	1985–1995	11.5	Gutierrez et al.[7]
Integrated Health Care Information Services National Managed Care Benchmark Database	1997–2002	60.0	Whitley et al.[8]
Prospective cohort study of pregnant women — Washington State	1982–1999	31.2	Brown et al.[9]
Congenital syphilis‡			
Washington State	1996–2004	0.8	Hofmann J, Stenger M: personal communication
United States	2002	11.2	CDC[10]
Toxoplasmosis — Ohio§	1999–2003	<1.0†	Ohio Department of Health[3]
Group B streptococcal disease			
Selected counties in 10 states	2006	40.0	CDC[11]
Ohio	1999–2003	44.6	Ohio Department of Health[3]
Rubella¶			
United States	1970	2.1	Cochi et al.[12]
United States	1995–2005	<0.1	CDC[13]
HIV infection			
Washington State	2001–2008	0.4‖	Washington State Department of Health[14]
Michigan	1993–2000	5.4	CDC[15]
United States	2002	4.5	CDC[16]

* CDC denotes Centers for Disease Control and Prevention, HIV human immunodeficiency virus, and HSV herpes simplex virus.
† Vital statistics used to calculate the rate were obtained from www.odh.ohio.gov/healthStats/vitalstats/birthstat.aspx.
‡ Congenital syphilis is reportable at both state and national levels and varies greatly according to region.
§ Toxoplasmosis is reportable in 13 states; however, most of these states do not differentiate between congenital and noncongenital cases. Congenital toxoplasmosis is reported in Ohio. Between 1999 and 2003, there was only 1 case of congenital toxoplasmosis, resulting in an annual incidence of less than 1.0 case per 100,000 live births.
¶ Congenital rubella syndrome is reportable in most states. In 1970, before widespread rubella immunization, there were 77 cases of congenital rubella syndrome, with an incidence of 2.1 cases per 100,000 live births. Since vaccination has become routine, the rate has decreased to less than 0.1 cases per 100,000 live births.
‖ Vital statistics used to calculate the rate for 2001–2007 were obtained from www.doh.wa.gove/EHSPHL/CHS/CHS-Data/Overview.htm, and vital statistics used to calculate the rate for 2008 were obtained from www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57_19.htm#table1.

the outcome; unfortunately, nonspecific manifestations may delay the diagnosis. Acyclovir therapy has substantially improved survival (Table 3); however, neonates with CNS HSV-2 infection still have high rates of developmental problems at 1 year, and more than 50% of these children have moderate-to-severe neurologic abnormalities.[32,33] Moreover, relapses of CNS infection may occur, further increasing morbidity.

The highest fatality rate among neonates with

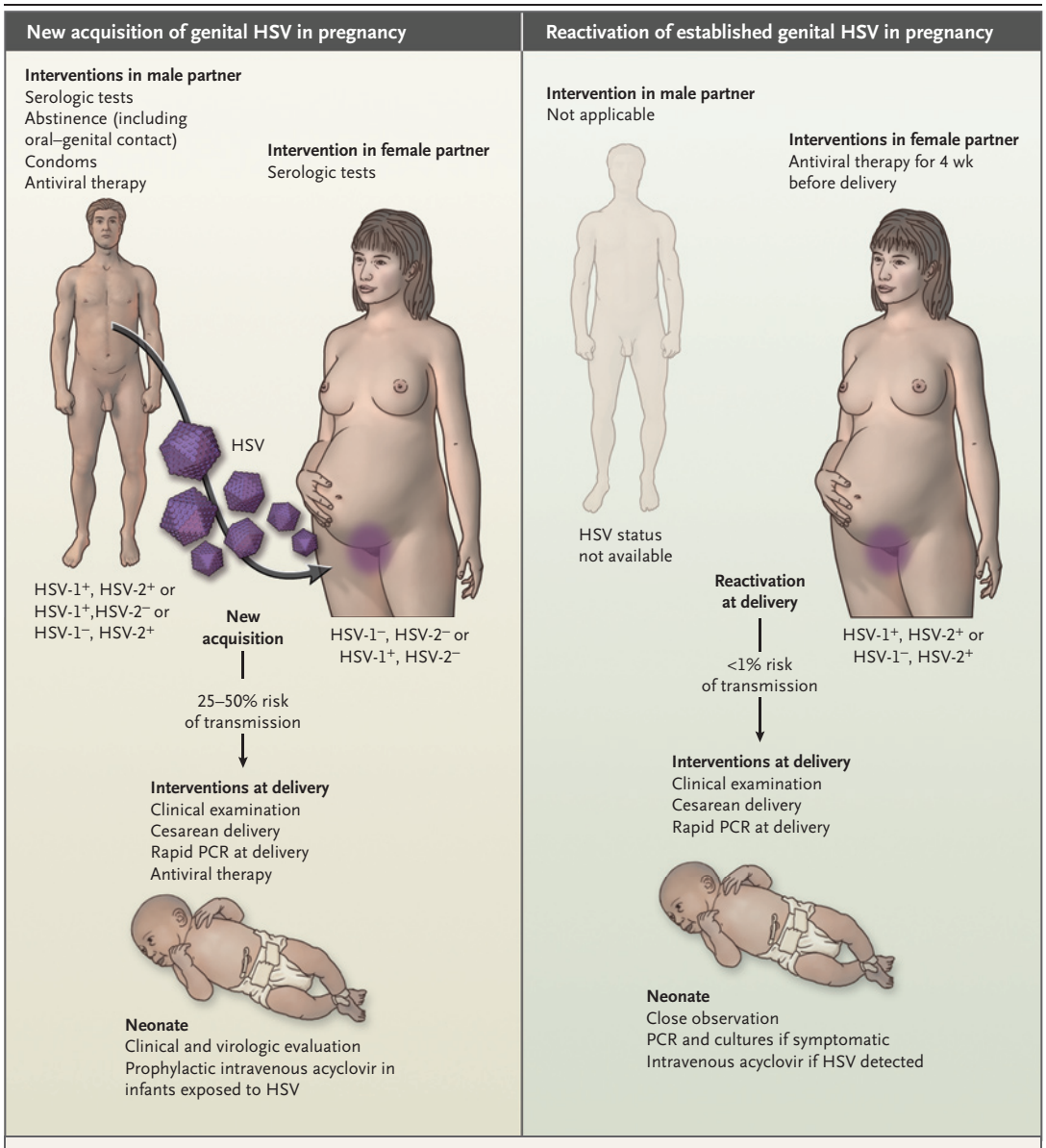

Figure 1. Pathogenesis of Neonatal Herpes Simplex Virus (HSV) Infection.

HSV-1 and HSV-2 denote herpes simplex virus type 1 and type 2, respectively, and PCR polymerase chain reaction. Because of the high risk of neonatal HSV associated with new acquisition of genital HSV in pregnancy, most experts recommend the initiation of intravenous acyclovir even in children in whom HSV is not detected.

HSV infection is associated with disseminated infection; these infections, which account for 25% of case series, involve multiple organs (e.g., the lungs, liver, and brain) and are clinically indistinguishable from bacterial sepsis.[29,32,33] The risk of death from disseminated neonatal HSV infection is high (30%), even with antiviral therapy.[32,33] Any vesicular rash in a neonate should be evaluated for HSV infection. Since a rash is absent in up to 50% of cases of neonatal HSV infection, all infants younger than 4 weeks with CNS infection or sepsis syndromes should undergo a laboratory evaluation, preferably with a PCR assay for HSV; the assessment should also include assessment of plasma and blood samples for HSV DNA.[23,34] A PCR assay of cerebrospinal fluid for HSV is considered to be cost-effective in febrile newborns with pleocytosis.[35]

Table 2. Common Misperceptions about Neonatal Herpes.*

Misperception	Evidence
Most infants with neonatal HSV infection are born to women with a history of genital herpes.	Most cases of maternal–fetal transmission involve women with undiagnosed genital herpes, many of whom have acquired HSV-1 or HSV-2 for the first time near term.
HSV-1 infection usually is acquired from nonmaternal sources.	Neonatal HSV-1 infection accounts for 30–50% of all reported cases of HSV-1 infection; more than three fourths of cases are from recently acquired genital HSV-1 in the mother, with subsequent transmission to the infant during delivery.
Suppressive antiviral therapy at the end of pregnancy eliminates the risk of neonatal HSV infection.	Suppressive acyclovir reduces the frequency of genital lesions near term and the frequency of cesarean delivery; there are no data to suggest it reduces the risk of neonatal herpes.
Most infants with neonatal herpes have vesicular lesions.	Neonatal HSV infection often presents with a sepsislike syndrome or with a new onset of seizures. Skin or mucosal lesions may appear only late in the disease course, or not at all.
Cutaneous HSV infection in the infant can be treated with topical or oral antiviral agents.	All cases of presumptive neonatal HSV infection should be treated with intravenous acyclovir. Infants with confirmed disease of the skin, eyes, and mucosa should be treated with 60 mg/kg/day for 14 days, and infants with CNS or disseminated disease should be treated for 21 days.
IgM antibodies are useful for the diagnosis of neonatal herpes.	IgM assays are not reliable. HSV DNA detection is the optimal method for diagnosis.†

* CNS denotes central nervous system, HSV herpes simplex virus, HSV-1 HSV type 1, and HSV-2 HSV type 2.
† Data are from Sullender et al.[22] and the American Academy of Pediatrics.[23]

TREATMENT OF NEONATAL HSV INFECTION

Antiviral therapy with intravenous acyclovir reduces mortality from 85% to 31% among infants with disseminated disease and from 50% to 6% among infants with CNS disease (Table 3). Acyclovir at a dose of 20 mg per kilogram of body weight given intravenously every 8 hours for 21 days is recommended for disseminated and CNS disease,[23] and the same dose for 14 days is recommended for disease limited to the skin and mucous membranes. Many experts also recommend the 14-day regimen for asymptomatic infants born to women who acquired HSV infection near term.[23] Acyclovir is superior to vidarabine, the only other antiviral agent that has been systematically evaluated for neonatal HSV infection. Transient neutropenia has been detected in about 20% of infants treated with these high doses of acyclovir, but it has not been reported to result in clinically significant adverse outcomes.[33] Rare cases of acyclovir-resistant neonatal HSV infection have been reported.

PREVENTION OF NEONATAL HSV INFECTION

Neonatal HSV infection is as severe as other neonatal infections for which preventive strategies have been implemented, and it remains one of the most serious neonatal infections (Table 3). The medical literature and popular press report an ongoing controversy about the best strategies for the prevention of neonatal HSV infection, with diverse and sometimes conflicting conclusions.[36-40] Since this is an area of common misunderstanding, we review these issues.

REDUCING ACQUISITION OF HSV-1 AND HSV-2 IN LATE PREGNANCY

Development of a vaccine that prevents the acquisition of HSV-1 and HSV-2 would be the most effective strategy for reducing cases of neonatal herpes. However, at present, such a vaccine is not available. Protective immunity against HSV is incompletely understood, and the commonly used animal models — mice and guinea pigs — share only certain aspects of human HSV infections; this

Table 3. Outcome of Neonatal Herpes.*

Site of Disease	Death		Normal Outcome†	
	No Therapy	IV Antiviral Therapy	No Therapy	IV Antiviral Therapy
	percent			
Disseminated	85	31	Rare	83
Central nervous system	50	6	Rare	31
Skin, eyes, and mucosa	0‡	0	62	100

* Data on patients who did not receive therapy are from Whitley et al.,[31] and data on patients who received intravenous (IV) antiviral therapy are from Kimberlin et al.[32]
† A normal outcome is defined as the achievement of developmental milestones within 24 months after infection.
‡ Skin, eye, and mucosal infection will progress to encephalitis or disseminated disease in the absence of antiviral therapy in a high proportion of infants.

has limited the development of candidate vaccines against HSV. Previous investigational vaccines have lacked efficacy against HSV-2 infection in clinical trials; a single-antigen recombinant vaccine was shown to have partial efficacy against HSV-2 disease but only marginal efficacy in reducing the rate of acquisition of HSV-2 among seronegative women. A phase 3 trial of this product is under way. An effective HSV-2 vaccine for pregnant women would need to prevent subclinical reactivation of HSV at the time of delivery in order to prevent neonatal herpes.

Other proposed strategies for reducing the rate of acquisition of HSV during pregnancy include counseling of all women to avoid unprotected sexual intercourse and unprotected oral–genital contact in late pregnancy, serologic testing of pregnant women to identify those at risk for HSV acquisition, and serologic testing of pregnant women and their partners to identify those with discordant serologic status. These strategies rely on a change in sexual behavior by pregnant women at risk. Advocates of abstinence in late pregnancy emphasize its universal applicability and low cost. However, this approach does not apply to pregnant women with previous HSV-2 infection, who account for 30 to 60% of women in most obstetrical practices. Moreover, abstinence alone is an approach that is untested, and studies of abstinence in other situations cast doubt on its effectiveness.[41,42]

The use of demographic and clinical characteristics to identify women at high risk for transmission of HSV to neonates is a potentially cost-effective strategy; this approach was initially adopted for testing for hepatitis B virus (HBV) infection, HIV infection, and group B streptococcal disease in pregnancy. A recent population-based case–control study of neonatal HSV infection in Washington State showed that demographic or clinical characteristics could not be used to identify women at high risk for transmitting HSV to their infants; these findings suggest that such a selective approach is not likely to be effective.[4] Universal testing is now recommended for HBV infection, HIV infection, and group B streptococcal disease in pregnancy.

Type-specific serologic testing for HSV to identify women at risk for acquiring genital herpes near term also has been advocated as a potential preventive strategy. Knowledge of HSV status in women who are at special risk for acquiring infection near term may allow more effective counseling on behaviors to reduce risk, such as abstinence or protected coitus in the last trimester in combination with avoidance of oral–genital contact (cunnilingus). Surveys show that women are interested in testing for HSV during pregnancy and that the psychosocial distress resulting from an unexpectedly positive result of an HSV-2 serologic test is minimal and transient.[43,44] Serologic identification of infection status is widely advocated and has been successful in the prevention of HIV infection in the United States and Africa.[45,46] Critical to the knowledge of serologic status is the effectiveness of strategies that target pregnant women identified as being HSV-2–seronegative. Condoms appear to have a 50% rate of efficacy in reducing the risk of HSV transmission from men to women and from women to men.[47] Valacyclovir therapy in patients with HSV-2 infection also reduces the risk of sexual transmission to the susceptible partner, by 48%.[48] However, pregnancy may increase susceptibility to the

acquisition of HSV; it is not known whether the use of condoms or antiviral therapy in the HSV-2–positive sexual partners of seronegative pregnant women will have protective effects in the women.[49]

Serologic testing of both the pregnant woman and her partner has also been suggested — a strategy that identifies 12 to 20% of cases in which the partner is HSV-seropositive and the pregnant woman is HSV-seronegative (and at risk for infection).[50,51] This approach may be expensive and may not be applicable when a woman has multiple partners during pregnancy. However, the advantage of such an approach is that it targets high-risk couples for intensive behavioral strategies, including consistent condom use. This approach also is most amenable to the use of antiviral therapy in the HSV-2–infected male partner. There have been no clinical trials to determine whether the identification of couples with discordant results of serologic testing will reduce incident maternal HSV infection, and such trials are needed.

The aforementioned approaches address the reduction of incident HSV-2 infections. Since neonatal HSV-1 infection accounts for 30 to 50% of cases of neonatal herpes,[2] attention to the role that genital HSV-1 infection plays in neonatal infection seems prudent, especially since commercial assays for determining antibody status are available for both HSV-1 and HSV-2. We are unaware of any studies that have examined strategies to prevent genital HSV-1 infection.

REDUCING NEONATAL HERPES IN HSV-2–SEROPOSITIVE WOMEN

Type-specific HSV-2 serologic testing during pregnancy can identify women who are HSV-2–seropositive but who have unrecognized genital herpes. On the basis of this information, obstetrical strategies can be instituted to reduce the risk of transmission of infection, such as minimizing the use of invasive monitoring devices (Fig. 2). The public health advantage of such testing is less clear. The diagnosis of newly recognized genital herpes and explanation of the attendant risks during pregnancy (as well as the risk of transmission to sexual partners) require considerable effort. Approximately 20 to 25% of patients would require counseling about a new disease. For a practitioner who sees neonatal HSV infection rarely (in 1 in 5000 to 1 in 10,000 deliveries), this approach may be viewed as impractical. Moreover, the optimal strategy for treating women with newly identified, established genital HSV-2 infection in pregnancy is unclear.

Current guidelines recommend cesarean deliveries in women with clinical evidence of recurrent genital herpes at term (Fig. 2).[24] Several small studies have shown that the use of antiviral agents daily at the end of pregnancy can reduce recurrences of genital HSV infection and shedding at term, as well as the need for subsequent cesarean deliveries,[52] but these studies have not addressed the question of whether such treatment can reduce the risk of neonatal HSV infection. Neonatal transmission of the virus from women who are HSV-2–seropositive is rare; thus, a large number of mothers and neonates would need to receive antiviral therapy to prevent a single case of neonatal HSV infection. The levels of acyclovir in amniotic fluid can be similar to those seen in infants treated with systemic acyclovir, and neutropenia develops in up to 20% of such infants.[33] Although a pharmacologic approach may offer a potential benefit in reducing morbidity from cesarean deliveries due to HSV infection, the widespread exposure of neonates to acyclovir has not been tested and could have unnecessary toxic effects. Thus, the routine use of antiviral agents in HSV-2–seropositive women in late pregnancy, especially in the majority of women without a history of genital herpes, should be based on evidence of efficacy in reducing the incidence of neonatal HSV infection and minimal toxic effects in the infant.

Because of the risk of morbidity in the mother, many authorities recommend that recently acquired genital HSV infections in pregnant women should be treated with antiviral medications.[24] Acyclovir is not teratogenic and may be administered either orally in pregnant women with a first episode of genital herpes or intravenously in pregnant women with severe HSV infection. A common regimen in pregnant women with a first episode of genital herpes is acyclovir at a dose of 400 mg given orally three times a day or valacyclovir at a dose of 500 mg given orally twice daily for 7 to 10 days. No data are available to assess whether such therapy reduces the rate of infection among infants.

IDENTIFYING INFANTS AT RISK

The isolation of HSV from the maternal genital tract at delivery is associated with a risk of neo-

natal HSV infection that is more than 300 times as high as the risk among infants with mothers in whom the virus has not been isolated.[9] Other risk factors associated with acquisition of the virus include the use of fetal-scalp monitors and the presence of cervical HSV infection (Fig. 2). The identification of infants who have been exposed to HSV allows resources to be directed to infants at highest risk. This strategy could be applied to infants born to mothers with first or recurrent episodes of HSV infection, with antiviral prophylaxis (or early expectant therapy) initiated in exposed infants. This approach requires a rapid, accurate assay to detect HSV shedding at delivery, initiation of early antiviral therapy in infants at risk, and determination of the effectiveness of the therapy in reducing acquisition of HSV and in improving the outcome for infected infants (Table 3).

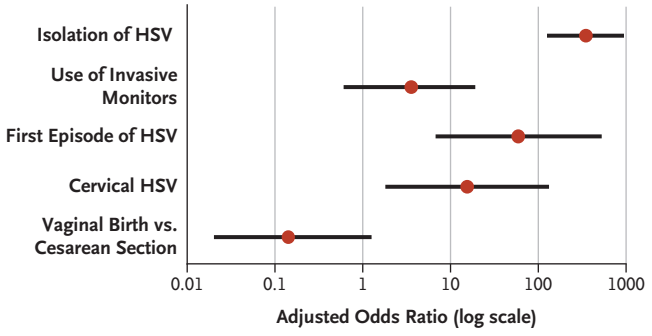

Figure 2. Risk of Transmission of Herpes Simplex Virus (HSV) Infection to the Neonate.

Data are based on a study of 202 pregnant women in whom HSV was isolated.[9]

Rapid PCR assays have been developed for many diseases, implemented in field hospitals, and used for testing samples obtained from women in labor.[53,54] In addition, point-of-care tests to identify HSV-2–specific antibodies have been developed and are commercially available, allowing clinicians to determine whether the risk of neonatal infection is high (in a seronegative mother) or low (in a seropositive mother); many authorities use these tests to determine whether systemic acyclovir prophylaxis should be administered.[55] At present, data on the optimal treatment of infants exposed to HSV at birth are scarce. The use of antiviral prophylaxis has been quite effective in preventing HSV-1 or HSV-2 infection in neonatal animal models.[56] One recommendation is to follow infants born to mothers who have HSV-2 shedding at term, with sequential sampling to detect the virus in urine and in the mucosa, in conjunction with close clinical follow-up to assess the infant for signs of illness and to initiate systemic therapy if HSV infection is present.[23] This approach could result in the early initiation of therapy in infants with neonatal HSV infection; early treatment is strongly associated with a favorable outcome.[32,33,57] Thus, the identification and observation of infants exposed to HSV would at least provide "best practices" monitoring. Alternatively, antiviral therapy could be initiated at birth in infants whose mothers did not have HSV antibodies, since their risk of invasive disease would be high. Infants born to women with antibodies to the viral type detected could be closely followed. These approaches, although potentially attractive, need to be empirically evaluated.

In summary, whether it is caused by HSV-1 or HSV-2, neonatal HSV infection is severe and persistent in the United States, with an incidence exceeding that of other infectious diseases for which nationwide preventive strategies have been established. The tools to devise better preventive strategies have been developed, and several strategies for reducing rates of infection have been outlined. Current guidelines issued by the American College of Obstetrics and Gynecology provide useful treatment tools but are not directed at the prevention of neonatal HSV infection, and they appear not to have altered the epidemiologic patterns of neonatal HSV infection in the United States in the past decade.[24] A concentrated effort to conduct studies that may provide guidance for effectively reducing the incidence of neonatal HSV infection is needed and will require an alliance between practitioners and academicians.

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