Supplement Article

Mother-to-Child Transmission of Herpes Simplex Virus

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Received March 17, 2014; accepted May 7, 2014.

Infections with herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2), both alpha herpesviruses, are highly prevalent worldwide. Both HSV types commonly cause genital infection, which, when acquired or reactivated during pregnancy, carries with it the risk of transmission to the fetus or neonate. Women who acquire primary or first-episode genital herpes during pregnancy are at greater risk for transmitting the infection than are women with recurrent genital herpes. Because viral infection and reactivation are frequently asymptomatic, many affected women are unaware of their infection and risk of transmission to their infants. Neonatal HSV infection can have devastating long-term consequences, especially when the central nervous system (CNS) is involved. Treatment of affected neonates with intravenous acyclovir has improved outcomes but there is room for further improvement, especially in regard to CNS disease. Working with pregnant women to prevent mother-to-child transmission of HSV is an important component in reducing the overall disease burden of neonatal HSV infections.

Key words. herpes simplex virus type 1; herpes simplex virus type 2; perinatal transmission.

INTRODUCTION

Herpes simplex virus (HSV) infections are common worldwide. HSV infections that are transmitted from pregnant women to their neonates can cause significant disease and even death in the infants. Two distinct viral types of HSV exist, type 1 (HSV-1) and type 2 (HSV-2), and both can be responsible for neonatal disease. The era of antiviral therapy has led to improved clinical outcomes in affected neonates, but significant morbidity and mortality remain in infants with invasive HSV disease. This review offers an overview of the epidemiology and clinical features associated with mother-to-child transmission of HSV. Treatment recommendations are briefly discussed, as well as current strategies for preventing vertical transmission of HSV infections. Gaps in research are also highlighted.

DESCRIPTION OF THE PATHOGEN

HSV-1 and HSV-2 are members of the Herpesviridae family of DNA viruses, grouped along with varicella-zoster virus in the alphaherpesvirus subfamily. The alphaherpesviruses are characterized by short reproductive cycles, host cell destruction during active replication, and the ability to establish lifelong latency in sensory neural ganglia [1]. Both HSV-1 and HSV-2 are large virions with a lipid envelope surrounding an icosahedral nucleocapsid. Within the nucleocapsid is a core of linear, double-stranded DNA of approximately 152 kbp. A proteinaceous tegument separates the nucleocapsid and envelope. The HSV lipid bilayer envelope is embedded with surface glycoproteins that mediate attachment and entry into host cells and are responsible for evoking the host response. At least 4 envelope glycoproteins (gB, gD, gH, and gL) have been shown to be essential to cell entry [2]. The genomes of HSV-1 and HSV-2 are approximately 50% homologous, and as such there is considerable cross-reactivity between antigenically related glycoproteins of both HSV types [3]. Type-specific glycoproteins exist, such as glycoprotein G (gG-1 and gG-2 for HSV-1 and HSV-2, respectively), allowing for differentiation of the 2 virus types via the host's antigen-specific antibody response.

EPIDEMIOLOGY

HSV-1 and HSV-2 infections are common in both developed and less-developed countries and are associated

Journal of the Pediatric Infectious Diseases Society, Vol. 3, Suppl 1, pp. S19–S23, 2014. DOI:10.1093/jpids/piu050

with lifelong infection. Although either HSV-1 or HSV-2 can cause genital infection, HSV-1 has typically been more associated with orolabial lesions whereas HSV-2 has historically been the more common cause of genital lesions. In the United States, the seroprevalences of HSV-1 and HSV-2 were 57.7% and 17%, respectively, in persons 14–49 years old during the period spanning 1999–2004 [4]. A follow-up study from 2005 to 2010 showed that HSV-1 seroprevalence had decreased to 53.9%, whereas HSV-2 seroprevalence had not significantly changed (15.7%) [5]. Secondary analysis of this study population demonstrated that the largest decline in HSV-1 seroprevalence occurred in the 14–19-year-old age group, meaning that an increasing number of adolescents are without protective HSV-1 antibodies at the time of their sexual debut [6]. This finding comes at a time when HSV-1 has become the predominate virus causing genital herpes, responsible for 60%–80% of genital herpetic infections in certain populations of young women [7, 8]. Several risk factors for HSV genital infection have been identified, including female gender, longer duration of sexual activity, minority ethnic group, prior history of other genital infections, lower family income, and number of sex partners [9].

Between 20% and 30% of pregnant women have antibody to HSV-2 [10, 11]. Women lacking antibody to both HSV-2 and HSV-1 have a nearly 4% chance of acquiring HSV-1 or HSV-2 during the course of pregnancy, while women seronegative for HSV-2 but seropositive for HSV-1 have a 2% chance of acquiring HSV-2 [12]. When a person with no prior HSV-1 or -2 antibody acquires either virus in the genital tract, a *first-episode primary infection* results. If a person with preexisting HSV-1 antibody acquires HSV-2 genital infection, a *first-episode nonprimary infection* ensues. Viral reactivation from latency and subsequent antegrade translocation of virus from sensory neural ganglia to skin and mucosal surfaces produces a *recurrent infection*. Identification of a primary or nonprimary first-episode genital HSV infection during pregnancy can be problematic in that, similar to nonpregnant women, a majority of these genital infections are asymptomatic or so clinically subtle that they are misdiagnosed. As such, it is not surprising that nearly 80% of women who deliver an HSV-infected infant have no known history of genital HSV lesions [13].

Neonatal acquisition of HSV infection occurs in an estimated 1 in 3200 deliveries in the United States (US) [14]. Mother-to-child transmission can occur *in utero* (5%), during the peripartum period (85%), or postnatally (10%) [15]. HSV is not transmitted through breast milk; rather, postnatal acquisition of HSV is due to direct contact with a person shedding the virus, usually via an orolabial or other cutaneous lesion. Because of the increasing incidence of HSV-1 genital infections, the majority of neonatal HSV infections in many parts of the world now are caused by HSV-1 [16, 17]. Recurrent genital lesions pose less of a risk for transmission to an exposed neonate than primary or nonprimary infections, likely due to the transplacental passage of protective antibodies. In a US study population, Brown et al. demonstrated an increased transmission risk of 57% in women with first-episode primary genital infections, versus a 2% risk increase in those with recurrent genital lesions [14]. Other factors associated with increased risk of mother-to-child HSV transmission include detection of HSV-1 or HSV-2 from the cervix or external genitalia via viral culture or polymerase chain reaction (PCR), duration of rupture of membranes, disruption of the neonate's cutaneous barrier by the use of a fetal scalp electrode or other invasive instrumentation, and vaginal delivery [18].

CLINICAL FEATURES OF MATERNAL HSV INFECTIONS

Primary or first-episode HSV genital infections in pregnant and nonpregnant women are commonly asymptomatic, but they can also present with lesions on the vulva, labia, vaginal introitus, or cervix. Symptomatic cutaneous lesions typically present as painful erythematous papules that quickly progress to the characteristic vesicular lesions filled with clear fluid, often appearing in a cluster. These fragile vesicles typically burst, but if they do not, an influx of inflammatory cells may cause the lesions to develop into pustules. After rupturing, each lesion will appear as a shallow ulcer on an erythematous base. Mucosal lesions typically have no vesicles and progress straight to ulcerations. These painful ulcers are usually gray/white, approximately 1–3 mm in diameter, and crust over as they begin to heal. The total process can last as little as 8–10 days or as long as 21 days. A more severe illness with systemic involvement can also occur during primary or first-episode HSV infections, but this is rare in immunocompetent hosts.

Viral reactivation from latency may be symptomatic or asymptomatic, both of which result in viral shedding. Regardless of the reported history of HSV infection, up to 0.4% of pregnant women will shed HSV from the genital tract during the time of delivery [19]. Among pregnant women with a history of recurrent genital HSV infections, the rate of shedding has been reported to be as high as 1.4% [20].

CLINICAL FEATURES OF NEONATAL HSV INFECTIONS

Peripartum neonatal transmission can occur when there is shedding of the virus from the genital tract around the time

of delivery. Postnatally acquired HSV infection can also occur as a result of direct contact with HSV-infected persons, usually from an orolabial or cutaneous source. Postnatal HSV infection causes the same range of neonatal disease as is seen in peripartum infections (categories described below), with no appreciable difference in the severity of disease on average.

In utero (congenital, antepartum) HSV transmission, on the other hand, presents as a distinct clinical entity characterized by the triad of cutaneous findings (active lesions, scarring, aplasia cutis, hyper- or hypopigmentation), neurologic manifestations (microcephaly, intracranial calcifications, hydranencephaly), and eye findings (chorioretinitis, microphthalmia, optic atrophy) present at birth. This triad describes the classic findings of congenital HSV infection, but more subtle presentations can also occur. Intrauterine HSV infection has been found to occur with both primary and recurrent maternal HSV infections [21], although the risk from a recurrent infection is less. *In utero* transmission is exceedingly rare, with an estimated transmission rate of 1 in 300,000 deliveries in the United States [22].

Neonatal HSV infection acquired in the peripartum or postpartum period can be categorized as skin, eye, and/or mouth (SEM) disease, central nervous system (CNS) disease, or disseminated disease. SEM disease accounts for approximately 45% of neonatal HSV infections and by definition does not involve the CNS or other organ systems. Infants with CNS disease make up about 30% of neonatal HSV infections. These infants may have mucocutaneous involvement, but lack evidence of other organ system involvement. Disseminated disease accounts for the remaining 25% of neonatal HSV infections and may involve the CNS along with multiple other organ systems including the liver, lungs, adrenals, gastrointestinal tract, and the skin, eyes, or mouth [23]. Approximately two thirds of infants with disseminated HSV infection will also have CNS involvement. The presentation of SEM and disseminated disease usually occurs earlier than that of CNS disease (on average, 9–11 days after birth versus 16–17 days) [24].

Disseminated neonatal HSV infections may present with a septic appearance, including respiratory failure, hepatic failure, and disseminated intravascular coagulopathy. When present, vesicular skin lesions are a key component in recognizing the clinical presentation of HSV disease, but clinicians should be aware that up to 40% of infants with disseminated disease never develop a vesicular rash during the course of their illness.

The clinical presentation of neonatal HSV CNS disease commonly involves nonspecific symptoms such as lethargy, irritability, poor oral intake, and temperature instability. Other symptoms more indicative of underlying encephalitis can also be present, including a bulging fontanelle and focal or generalized seizures. Cutaneous lesions can be a diagnostic clue, but as many as 35% of infants with HSV CNS disease will never have a vesicular rash identified; thus, as with disseminated HSV disease, the absence of a rash does not rule out neonatal HSV infection [23]. Focal CNS involvement can occur via retrograde axonal transport, whereas hematogenous spread to the CNS is more commonly associated with a diffuse pattern of brain involvement.

In the pre-antiviral era, most neonatal HSV infections resulted in significant morbidity or death. Infants with disseminated disease had 85% mortality by 1 year of age and only 50% of survivors had normal neurodevelopmental outcomes. Infants with CNS disease had a lower mortality rate of 50% by 1 year of age, but only 33% of survivors had normal neurodevelopmental outcomes [25]. Use of intravenous acyclovir at a dose of 60 mg/kg/day in 3 divided doses has improved 1-year mortality rates to 29% and 4% for disseminated and CNS diseases, respectively [26]. Furthermore, this 60 mg/kg/day dose of acyclovir was shown to improve neurodevelopmental outcomes in infants with disseminated disease (83% of survivors had normal neurodevelopmental outcomes), but not for infants with CNS disease (31% of survivors had normal neurodevelopmental outcomes). Further studies aimed at optimizing the efficacy of antiviral therapy, including the development of novel antiviral agents and the investigation of the potential benefit of combination therapies, are needed. Neurologic outcomes for infants with CNS disease recently have been improved upon with use of oral suppressive acyclovir therapy administered for 6 months following the completion of a standard acyclovir neonatal HSV treatment course. Infants with CNS disease who received suppressive acyclovir therapy at a dose of 300 mg/m^2/dose administered orally 3 times a day for 6 months had better neurodevelopmental outcomes compared to the placebo group, and infants with CNS and SEM disease had less frequent recurrences of skin lesions while receiving the suppressive therapy [27].

PREVENTION OF VERTICAL HSV TRANSMISSION

Since the majority of mother-to-child transmission of HSV infection occurs as a result of exposure to virus shed from the genital tract as a neonate passes through the birth canal, the most common strategies for preventing transmission seek to reduce neonatal exposure to active genital lesions. In women with active recurrent genital HSV lesions, antiviral suppressive therapy with oral acyclovir or valacyclovir can be started at 36 weeks of gestation, a practice

that has been associated with decreased genital lesions at the time of delivery, decreased viral detection by viral culture or PCR, and subsequently a reduced need for cesarean delivery for the indication of genital HSV [28]. Despite these benefits, antiviral suppressive therapy has not yet been studied well enough to definitively show that this practice prevents neonatal HSV disease.

The American College of Obstetricians and Gynecologists (ACOG) currently recommends that women with active recurrent genital herpes should be offered suppressive antiviral therapy beginning at 36 weeks of gestation [9]. Clinicians should recognize that suppressive therapy does not completely obviate the risk of perinatal transmission, as demonstrated by a recent report of 8 cases of neonatal HSV infection in infants whose mothers had been receiving antiviral suppressive therapy in the weeks leading up to delivery [29]. Further studies are needed to determine whether or not the reduction in incidence of genital lesions at the time of delivery observed on suppressive antiviral therapy actually translates into prevention of neonatal acquisition of infection.

Another prevention strategy recommended by ACOG is that cesarean delivery should be performed in women with active genital lesions (whether primary or recurrent) or with prodromal symptoms that may indicate an impending genital outbreak [9]. This practice has been shown to reduce the neonate's risk of acquiring HSV, although it does not completely eliminate it [14]. For maximum effect on risk reduction, cesarean delivery should be performed prior to rupture of membranes. If rupture has already occurred and genital lesions are present, cesarean delivery is still recommended. In women with a history of recurrent genital herpes but with no active lesions or prodromal symptoms at the time of delivery, cesarean delivery is not currently advised. Routine antepartum screening for HSV, whether by history, physical exam, or virologic testing, does not predict those women who are shedding HSV at delivery [30]. Testing of asymptomatic women at the time of delivery via culture or PCR also is not recommended at this time, although a multicenter clinical trial evaluating the feasibility of screening asymptomatic women at delivery with a new rapid-turnaround PCR kit is currently under way (ClinicalTrials.gov Identifier: NCT01878383). If such screening could be routinely performed at the time of delivery, it is possible that preemptive antiviral therapy administered to the neonate could play a role in disrupting mother-to-child transmission of HSV in women who are found to be asymptomatically shedding.

For asymptomatic neonates born either vaginally or by cesarean delivery to women with active herpetic genital lesions, guidance has been proposed to help determine the risk of HSV transmission and to optimize intervention for the baby [31]. This algorithm, developed jointly by the American Academy of Pediatrics' Committee on Infectious Diseases and the Committee on Fetus and Newborn, gives guidance concerning risk stratification, diagnostic work-up, and appropriate antiviral therapy, including the use of preemptive antiviral therapy in asymptomatic neonates in certain high-risk situations.

Table 1. Research Needs in Maternal and Neonatal Herpes Simplex Virus (HSV) Infections

- The effect of maternal suppressive antiviral therapy on the incidence of neonatal HSV infection
- Research and development of optimal treatment strategies for the management of HSV discordant couples to prevent acquisition of HSV infection during pregnancy
- Vaccine strategies aimed at preventing maternal transmission of HSV
- The feasibility of rapid-turnaround peripartum screening of asymptomatic women with HSV polymerase chain reaction
- The efficacy of preemptive antiviral therapy in neonates born to women asymptomatically shedding HSV at the time of delivery
- Development of safe novel antiviral agents with increased efficacy, including penetration across the blood-brain barrier, for neonates with HSV infection
- Investigation of the potential benefit of combination antiviral therapies for neonates with HSV infection

CONCLUSION

Due to the high prevalence of genital HSV infections and the potentially devastating consequences of neonatal HSV disease, it is important that clinicians understand how to recognize and treat neonatal HSV infections in a timely manner, and how best to reduce mother-to-child transmission. Outcomes for neonatal HSV infections have improved in the past 30 years, but there is continued need for further studies to help maximize the prevention and treatment of this disease (Table 1).

Acknowledgments

Financial support. This work was supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development—National Institutes of Health.

Potential conflicts of interest. Both authors: No reported conflicts.

Both authors have submitted the ICMJE Form for Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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