Sexually Transmitted Diseases, March 2006, Vol. 33, No. 3, p.170–174
DOI: 10.1097/01.olq.0000187203.27918.45

The Public Health Imperative for a Neonatal Herpes Simplex Virus Infection Surveillance System

BETTY A. DONOVAL, BS,* DOUGLAS J. PASSARO, MD, MPH,* AND JEFFREY D. KLAUSNER, MD, MPH†

About 1 in 5 sexually active adults in the United States has serologic evidence of genital herpes caused by herpes simplex virus type-2. Neonatal herpes simplex virus infection is a serious consequence of genital herpes infection. Herpes infection in neonates causes significant morbidity and neurologic damage and generally has a case-fatality ratio untreated of 60%. It is estimated that 440 to 1320 cases of neonatal herpes infections occur in the United States per year (11–33 cases occur per 100,000 live births). Given the challenges in surveillance for genital herpes due to the large number of asymptomatic infections and infrequent laboratory-based diagnosis, we recommend that to begin an effective national control program for herpes infections, a mandatory national surveillance system for neonatal herpes be implemented. Such a system would help assure appropriate therapy, help monitor trends and understand the burden of disease, identify risk determinants, and evaluate prevention efforts.

GENITAL HERPES IS A common sexually transmitted disease affecting 1 out of 5 sexually active adults in the United States.[1] It is caused primarily by the herpes simplex virus type 2 (HSV-2), as well as type 1 (HSV-1). HSV-2 is usually spread through sexual contact and is associated with genital infections. HSV-1, which is normally associated with recurrent oral herpes labialis, "cold sores," is increasingly recognized in genital infections.[2] HSV infections are lifelong viral infections with long periods of clinical latency and short periods of active disease. Although HSV infections can be associated with recurring painful blisters, most affected individuals show no or minimal symptoms. Maternal to child transmission of HSV may result in neonatal HSV infection, clinically manifesting as disease of the skin, eye, or mucosal membranes; encephalitis; or disseminated disease involving multiple organs.

Neonatal HSV infection is a serious consequence of genital HSV infection. Untreated neonatal HSV infection carries a mortality rate as high as 60%.[3] However, 60% to 80% of children with neonatal HSV infection are born to women with no history of genital HSV infection.[4] Therefore, screening mothers at risk for transmitting HSV infection by taking a medical history from the mother is not sufficiently sensitive for this lethal disease. While recent type-specific serologic assays for HSV-infection have become available, there are no clinical studies demonstrating their efficacy in reducing neonatal HSV transmission.

We would like to sincerely thank our collaborator Dr. Douglas Passaro for his insight and contributions. He is remembered not only as a respected colleague and teacher but a friend as well.

Correspondence: Betty Donoval, BS, University of Illinois Chicago, School of Public Health, 1603 W Taylor, Chicago, IL 60612. E-mail: bdonov2@uic.edu.

Received for publication April 12, 2005, and accepted July 27, 2005.

*From the *Division of Epidemiology, School of Public Health, University of Illinois, Chicago, Illinois; and the †STD Prevention and Control Services, San Francisco Department of Public Health, San Francisco, California*

Over the past 30 years, improvements in the diagnosis and management of neonatal HSV infection have reduced mortality and morbidity.[5] Since neonatal HSV infection is a rare disease, pediatricians may not be familiar with up-to-date treatment recommendations. Making neonatal HSV infection a reportable disease will help public health programs assure physicians are familiar with optimal patient care. Educating physicians on signs and symptoms of neonatal herpes can lead to more timely diagnosis and treatment. Of equal importance, it would allow public health professionals to conduct essential disease-control activities such as epidemiologic investigations, public health research, and evaluation of prevention efforts.

Epidemiology of Genital Herpes Simplex Virus Infection

Since there is no reporting system in place for genital HSV infections in most states and infection is often unrecognized, population-level assessments of disease are limited and rely on research studies. The impact of genital herpes in the US population has been studied indirectly through serologic data gathered through the National Health and Nutrition Examination Surveys (NHANES). Population-based serologic studies, such as NHANES, are the best estimates we have for HSV infection rates and are considered adequate to measure rates of infection but fail to measure important burdens of HSV-associated disease such as neonatal infection, genital ulcer disease, or aseptic meningitis. Those surveys are population-based surveys of the noninstitutionalized civilian population of the United States aged 12 to 74 years conducted by the Centers for Disease Control and Prevention. According to NHANES III (1988–1994), the seroprevalence of HSV-2 infection was 21.9% among study participants.[1] That prevalence corresponds to 45 million people being infected with HSV-2 in the United States. Those researchers estimated that 1 million new infections occurred each year, based on changes in age-specific prevalence. The age-adjusted seroprevalence increased from 16% in NHANES II (1976–1980) to 21% in NHANES III; that increase was most dramatic in younger age groups. The prevalence was also higher in women (25.6%) than men (17.8%). A 2002 serosurvey in suburban primary care physicians' offices nationwide showed a similar seroprevalence of 25.6%.[6]

Economic Issues in Genital and Neonatal Herpes

The economic burden of genital HSV infection in the United States is substantial. In a cost assessment based on 2 approaches—(1) a survey of physicians analyzing healthcare resource utilization and (2) a large administrative claims data set—it was estimated that the total direct costs ranged from $283 to 984 million in 1996. Indirect costs were calculated using the human capital approach, which calculates time consumed by hospitalization, time lost from work, and travel/waiting room time, and bases its costs on an average hourly wage of $14. Indirect costs measured up to $214 million from production losses.[7] Among the American youth aged 15 to 24, it was estimated that in the year 2000 the total direct medical costs were $292.7 million. That ranks third in cost among the 8 major sexually transmitted diseases in the United States in 2000, following HIV and HPV.[8] The average cost of neonatal herpes has been approximated using acute hospital care costs and various long-term services. In 1999, the average cost of neonatal HSV-1 infection was estimated to be $14,561 and $45, 478 for neonatal HSV-2 infection.[9]

Epidemiology of Neonatal Herpes Simplex Virus Infection

Neonatal HSV infection is a serious consequence of genital HSV infection. If left untreated, its case-fatality ratio of up to 60% makes it as dangerous as any neonatal infection.[10] It is estimated that 11 to 33 cases occur per 100,000 live births per year in the United States,[11,12] or approximately 440 to 1320 cases for the 4 million births occurring in the United States each year.[13] In a more recent study of neonatal HSV infection rates in Washington State, women with all HSV serologic classifications were at risk for transmitting HSV to their infants. HSV-seronegative mothers had the highest rate of neonatal HSV infection, 54 per 100,000 live births, while women that were HSV-1 and HSV-2 positive had infection rates of 26 per 100,000 and 22 per 100,000 live births, respectively.[14] Of those infants that do survive, there are often serious lifelong debilitating consequences, with over 50% of infants having moderate or more severe neurologic impairment.[15]

Neonatal HSV infection is acquired 3 ways. Most transmission (90%) results from exposure to infected cervicovaginal secretions from an active maternal genital infection at delivery.[3] Newly acquired maternal HSV infections before the development of maternal antibody, particularly those acquired during the third trimester, are responsible for approximately half of the cases of neonatal HSV infection; the remainder is acquired from mothers experiencing a reactivation of HSV infection at delivery. Of the remaining 10%, 5% of neonatal HSV infections are acquired in utero and the other 5% occur from contact from a nonmaternal source.[16,17] Maternal transmission to the infant is greatly influenced by the mother's serologic status. If HSV-1 or HSV-2 infection was acquired by the mother late in pregnancy and she has not yet seroconverted before delivery, then 15%–50% of vaginally delivered infants become infected. However, the risk of an infant being infected falls to less than 1% among women with prior or long-standing infection.[18]

Clinical Presentation of Neonatal Herpes Simplex Virus Infection

Neonatal HSV infection acquired at delivery presents itself in 3 forms. Disease localized to skin, eye, or mucosal membranes represents about 40% of all neonatal HSV infections and presents within 3 weeks of delivery.[3] Central nervous system (CNS) disease represents about 35% of cases of neonatal HSV infection and also presents within 3 weeks of delivery.[3] However, nonspecific symptoms and signs make CNS disease difficult to diagnose, and it should be considered as a diagnostic possibility in any infant with altered mental status less than 6 weeks of age. Disseminated disease constitutes about 25% of cases and usually presents within the first week of life. Disseminated disease may be present as neonatal sepsis or jaundice; it is difficult to diagnose and has the worst prognosis for the infant.[3] The prognosis for neonates with HSV infection is dependent on the form of HSV infection. Before the use of antiviral therapy, 85% of neonates with disseminated disease died, while 50% of neonates with CNS disease died. With the use of antiviral therapy, mortality rates decreased to 54% (disseminated) and 14% (CNS disease).[5] The rapid diagnosis and treatment of neonatal HSV infection has great medical benefit. Antiviral therapy for HSV infection has reduced the mortality of neonatal HSV infection from 60% to about 10%, although neurologic sequelae may remain.[19,20]

However, when the mean time between the onset of disease symptoms and initiation of therapy was compared from the early 1980s to the late 1990s, no progress has been made in decreasing the time from symptoms to treatment.[21] Improvement in disease outcome can only occur if this interval is decreased.[21] Raising the awareness of this condition among primary care providers, through a surveillance program, can facilitate quicker initiation of therapy.

Surveillance for Genital and Neonatal Herpes Simplex Virus Infection

Because there is no comprehensive national surveillance program for neonatal HSV infection, trends in incidence, complications, and clinical outcomes are gross estimates. This complicates the development and evaluation of effective prevention strategies. An awareness of that problem led expert consultants at a meeting convened by Centers for Disease Control and Prevention in May 1998 to recommend that the Centers for Disease Control and Prevention "support surveillance demonstration projects for genital and neonatal herpes in a variety of populations and geographic areas" and use those projects to "explore the efficacy and feasibility of various approaches to surveillance and their abilities to assess trends and the efficacy of prevention efforts."[22] However, to date those recommendations have not been translated to public policy.

Sixteen states list genital herpes as a reportable disease, but there is variability in both the methods and quality of reporting. Often, there are few cases reported, and quality assessment of reporting is infrequent.[23] The asymptomatic and recurrent nature of genital HSV infection makes it a difficult disease to monitor: often, it is not clear if clinical manifestations such as vesicles or ulcers represent newly acquired HSV infection or recurrent symptoms, making disease reporting based on symptoms in adults both insensitive and nonspecific. Unreliable ICD-9 coding for diagnosed cases, a lack of provider familiarity with HSV diagnostic tests, and the variable use of those HSV diagnostic tests are also barriers to effective surveillance. Those and other barriers were found in a study trying to determine the incidence of neonatal HSV infections from past discharge and death records in California.[24] That study found potential problems with possible missed diagnoses and diagnostic codes that did not differentiate between primary or recurrent genital HSV infections at the time of delivery, or merely a history of lesions.

Although there are potential problems with neonatal HSV infection surveillance as well, focusing on that subset of HSV infection as a surveillance measure may be more practical and feasible. Currently there are 4 states (Connecticut, Massachusetts, South Dakota, and Washington) that have neonatal HSV infection on their list of reportable diseases. A recent evaluation of the state of Washington's provider-based neonatal herpes surveillance sys-

tem was examined for completeness of reporting. The results of that evaluation indicated that the sensitivity of case reporting was extremely low (1.8%) (Dr. Fujie Xu, personal communication, April 12, 2004). Although the disease is rare in neonates, laboratory tests that are routinely used to confirm infection are available. Australia has been able to run a successful active national neonatal herpes surveillance system since 1997. Through December 2003, the reported rate of neonatal herpes is 3.38 per 100,000 live births.[25]

Implementing a mandatory national surveillance system for neonatal herpes would have many useful outcomes to public health (see Table 1). Neonatal herpes reporting would give a better epidemiologic understanding of the infection. It would enable public health professionals and researchers identify maternal risk determinants, monitor trends in infection, and estimate the burden of disease. It would identify cases that may have been prevented or inappropriately treated, resulting in opportunities for direct clinical education. That information could be used to promote prevention and disease control strategies by identifying populations at risk or geographical areas for interventions. Through provider education, the correct and consistent use of HSV diagnostic tests can be achieved.

We propose that a surveillance system for neonatal HSV infection use the following case definition:

Herpes Simplex Virus Neonatal, Clinical Description

Infection with herpes simplex virus in utero or perinatally, resulting in clinical manifestations including vesicular lesions of the skin, eye, and/or mucosal membranes; CNS involvement with meningoencephalitis and/or disseminated disease in a newborn less than 6 weeks of age.

Laboratory Criteria for Diagnosis

Isolation or detection of herpes simplex virus by culture, antigen detection, and/or nucleic acid amplification from a clinical specimen. Histologic evidence of HSV infection from an autopsy in the case of death.

Case Classification

Probable: a case of clinically compatible illness in a newborn without other known causes of congenital infection.

Confirmed: a case that is laboratory confirmed.

Laboratories and medical providers would be required to report cases, with information including the infant's name, gender, age or date of birth, race/ethnicity, address of residence, specimen type, anatomical site of specimen, date of specimen collection, test performed, date of test result, test result, and type of delivery, as well as physician name, office address, phone number, facsimile number, and e-mail in each case of probable or confirmed neonatal HSV infection in newborns less than or equal to 6 weeks old to the local health department by mail, fax, or electronically within 1 calendar day. Although this time frame may be viewed as demanding by some laboratories, we still suggest that reporting be done within 1 day of establishing the diagnosis in order to assure proper treatment for affected neonates. Assurance of appropriate and timely treatment is an important public health responsibility, particularly for rare diseases, like NHSV.

TABLE 1. Potential Activities to Be Undertaken With Neonatal Herpes Reporting

1	Assure appropriate and timely therapy
2	Monitor trends and understand burden of disease
3	Identify risk determinants, populations at risk, and geographical areas at risk for potential interventions
4	Evaluate prevention interventions

By implementing a reporting system that is laboratory based, rather than one relying on providers, the previous inadequacies that were observed with neonatal HSV infection surveillance can be overcome. Case reporting is more likely to be timely, which ensures accurate data and cases that are amenable to intervention and evaluation. When a laboratory generates a positive HSV test, it can be matched to the subject's date of birth and then reported if it meets the case definition. Neonatal HSV infection typically presents itself within the first weeks of life. Since diagnoses are sometimes delayed, extending the case definition to the first 6 weeks or 42 days of life would be more sensitive and assure the identification of cases. Confirmed cases would include a positive HSV test, including viral culture, direct immunofluorescent antibody, direct enzyme-lined immunosorbent assay, polymerase chain reaction, or histologic diagnosis. Any isolation or detection of HSV in a newborn has a high specificity for infection, with most tests having specificity greater than 99%. Probable cases without a laboratory confirmation would be reported by medical providers. This system is simple, which can increase the amount of cases reported and will likely result in reliable data.

Optimizing Prevention Strategies

Cesarean deliveries are serious, costly procedures that often result in substantial maternal and child morbidity.[26] In an attempt to prevent cases of neonatal HSV infection, cesarean deliveries were routinely performed in women with a history of genital HSV infection. More recently, there have been some changes in practice, and cesarean delivery is currently recommended only for women with genital herpetic lesions at the time of delivery. With this recommendation, the number of caesarean deliveries in California has decreased from 1985 to 1995 without a change in the number of infants discharged with a diagnosis of HSV infection.[24] However, the current recommendation may still lead to an excessive and unnecessary number of cesarean deliveries.

Since most women with recurrent genital lesions of HSV infection are not at great risk for transmitting HSV to their child, performing cesarean deliveries based on the presence of genital lesions might lead to excess procedures with minimal clinical benefit. When the efficacy, risks, and costs of cesarean delivery were examined in women with genital HSV lesions, it was concluded that women with primary infections at delivery should have a cesarean section. However, cesarean sections for women with recurrent infection result in unnecessary high maternal morbidity and mortality, as well as high financial expense.[27] However, changing clinical practice may raise issues of liability until professional guidelines are changed. A neonatal HSV infection surveillance system would permit a closer examination of the link between delivery type and neonatal HSV infection and provide better data on the morbidity of cesarean delivery, which can contribute to changes in recommendations.

Recent research demonstrates that there may be an effective HSV vaccine in the near future. The potential public health impact of a vaccine is great, especially for women.[28] Establishing a neonatal HSV surveillance system before an HSV vaccine is implemented would provide a baseline rate of disease to evaluate the impact of a vaccine once it became available. It would also help document the burden of neonatal HSV infection, likely increase public acceptance of the vaccine, and help in the evaluation the effectiveness of a vaccine in preventing an important and costly outcome at the population level and among high-risk subgroups.

In HSV-infected women with recurrent clinical HSV disease, acyclovir prophylaxis at 36 weeks' gestation has been found to have many clinical benefits at delivery. That antiviral therapy has been found to reduce clinical HSV recurrence at delivery, reduce the frequency of cesarean delivery for recurrent outbreaks, and reduce both total and asymptomatic HSV detection at delivery.[29] The current Canadian guidelines have been revised to recommend the use of suppressive acyclovir for the last 4 to 6 weeks of pregnancy in pregnant women with a history of genital HSV infection (Dr. Barbara Romanowski, personal communication, October 8, 2004). The American College of Obstetricians and Gynecologists also recommends antiviral therapy for women with primary and recurrent HSV episodes.[30] When adverse pregnancy outcomes were examined in women that were exposed to acyclovir during pregnancy in a case-control study, both the systemic and topical use of acyclovir did not pose a reproductive hazard, specifically with malformations at birth or preterm delivery. However, since there were limited data for spontaneous abortions, low birth weight, and stillborns, the results for those outcomes remain inconclusive.[31]

When the cost-effectiveness of prenatal acyclovir suppression in pregnant women with a history of genital herpes was analyzed, it was found to decrease the direct average cost for obstetrical care and delivery in women. In all women with a history of genital HSV infection, acyclovir use resulted in an estimated savings of $183 per patient, which nationally translates to $36,600,000 per year. The savings were even more substantial in women with their first episode of HSV infection and women with frequent recurrences of HSV infection, $455.00 and $391.00 per patient, respectively.[32] In addition, small studies suggest that acyclovir taken by the mother in the last 4 weeks of pregnancy can potentially help reduce the frequency of recurrent herpes and therefore the need for cesarean deliveries.[33] A neonatal HSV infection surveillance system would further help to evaluate this potentially dramatic effect.

Another type of proposed prevention strategy is the use of type-specific serologic screening tests for HSV infection in pregnant women.[10] Type-specific screening in pregnant women and their partners could also help prevent neonatal HSV transmission through use of appropriate antiviral therapy, route of delivery, and prevention counseling. Women at highest risk for transmitting HSV infection to their infants are those with newly acquired HSV infections, while the risk of transmission is estimated to be less than 1% in women with recurrent HSV infection.[3] If pregnant women were identified as being susceptible to HSV infection (i.e., HSV- antibody negative with a HSV-seropositive partner), those women could be advised to practice abstinence or consistent and correct condom use in their third trimester to prevent newly acquired HSV infection. Effective risk reduction could avoid cesarean sections and neonatal HSV infection. In addition, potentially infectious sex partners could use suppressive therapy for HSV infection to decrease the likelihood of transmission.[34]

In one study in which pregnant black teens were screened for HSV-2 infection during their first prenatal visit, 21.3% were HSV-2-seropositive; only 1 out of 127 knew she was infected.[35] The remaining 79% of those teens were at risk for HSV-2 acquisition during their pregnancy. Many of those teens reported having unprotected vaginal sex within the last 30 days, 14% reported having multiple partners after suspecting pregnancy, and 29% believed their boyfriend was having sex with other partners. With those high-risk behaviors and the high prevalence of HSV-2 in the population, HSV screening can provide the opportunity for counseling and education to decrease the risk of acquiring HSV-2 infection during the remainder of the pregnancy.

Screening for asymptomatic infection in adults is safe and without significant psychological harm.[36] Adults that tested positive for HSV-2 antibodies had no significant change in mental health score from baseline or difference in mental health scores from adults that tested negative. HSV-2-seropositive adults did have a decline in positive sexual attitude at first, but the difference was temporary and no longer remained after 3 months.

Conclusion

Neonatal herpes is a serious consequence of genital herpes infection. With the increased prevalence of genital HSV infection in the US population, newborns are at continued risk for neonatal HSV infection. Without a neonatal HSV surveillance system, we are unable to perform essential public health activities. Instituting a mandatory laboratory-based national neonatal HSV infection reporting system would permit enhanced opportunities and measurable outcomes for disease control, prevention, and monitoring.

References

1. Fleming DT, McQuillan GM, Johnson RE, et al. Herpes simplex virus type 2 in the United States, 1976–1994. N Engl J Med 1997; 337:1105–1111.
2. Langenberg AGM, Corey L, Ashley RL, et al. A prospective study of new infection with HSV-1 and HSV-2. N Engl J Med 1999; 341: 1532–1538.
3. Prober C. Herpes simplex virus infections in pregnant women and neonates: an on-line continuing medical education publication of the American Herpes Foundation. 2003; 1:1–12.
4. Whitley RJ. Herpes simplex infection. In: Remington JS, Klein JO, eds. Infectious Diseases of the Fetus and Newborn Infant. 3rd ed. Philadelphia: WB Saunders; 1990:282–305.
5. Kimberlin DW. Neonatal herpes simplex infection. Clin Microbiol Rev 2004; 17:1–13.
6. Leone P, Fleming DT, Gilsenan AW, et al. Seroprevalence of herpes simplex virus-2 in suburban primary care offices in the United States. Sex Transm Dis 2004; 31:311–316.
7. Szucs TD, Berger K, Fisman DN, Harbarth S. The estimated economic burden of genital herpes in the United States: an analysis using two cost approaches. BMC Infect Dis 2001; 1:5.
8. Chesson HW, Blandford JM, Gift TL, et al. The estimated direct medical cost of sexually transmitted diseases among American youth, 2000. Perspect Sex Reprod Health 2004; 36:11–19.
9. Rouse DJ, Stringer JSA. An appraisal of screening for maternal type-specific herpes simplex virus antibodies to prevent neonatal herpes. Am J Obstet Gynecol 2000; 183:400–406.
10. Corey L, Handsfield HH. Genital herpes and public health addressing a global problem. JAMA 2000; 283:791–794.
11. Sullivan-Bolyai J, Hull HF, Wilson C, Corey L. Neonatal herpes simplex virus infection in King County, Washington: increasing incidence and epidemiologic correlates. JAMA 1983; 250:3059–3062.
12. Whitley RJ. Neonatal herpes simplex virus infections. J Med Virol 1993; 1(suppl):13–21.
13. Martin JA, Hamilton BE, Sutton PD, et al. Births: Final Data for 2002: National Vital Statistics Reports. Hyattsville, MD: National Center for Health Statistics; 2003:52.
14. Brown ZA, Wald A, Morrow RA, et al. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. JAMA 2003; 289:203–209.
15. Riley LE. Herpes simplex virus. Semin Perinatol 1998; 22:284–292.
16. Hutto C, Arvin A, Jacobs R, et al. Intrauterine herpes simplex virus infection. J Pediatr 1987; 110:97–101.
17. Whitley RJ. Herpes simplex virus infections. In: Remington JS, Klein JO, eds. Infectious diseases of the Fetus and Newborn Infant. 3rd ed. Philadelphia: WB Saunders; 1990:282–305.

18. Brown ZA, Benedetti J, Ashely R, et al. Neonatal herpes simplex infection in relation to asymptomatic maternal infection at the time of labor. N Engl J Med 1991; 324:1247–1252.
19. Whitley R, Arvin A, Prober C, et al. A controlled trial comparing vidarabine with acyclovir in neonatal herpes infection. N Engl J Med 1991; 324:444–449.
20. Whitley R, Nahmias A, Soong SJ, et al. Vidarabine therapy of neonatal herpes infections. Pediatrics 1980; 66:495–501.
21. Kimberlin DW, Chin-Yu L, Jocobs RF, et al. Natural history of neonatal herpes simplex virus infections in the acyclovir era. Pediatrics 2001; 108:223–229.
22. Handsfield HH, Stone KM, Wasserheit JN. Prevention agenda for genital herpes. Sex Transm Dis 1999; 26:228–231.
23. Bauer H. NCSD HSV/HPV program survey results: NCSD national meeting, October 2003. Available at: http://www.ncsddc.org/meetings/2003/NCSDViralSTDSurveyFinal.pdf. Accessed April 4, 2004.
24. Gutierrez KM, Halpern MSF, Maldonado Y, Arvin AM. The epidemiology of neonatal herpes simplex virus infections in California from 1985 to 1995. J Infect Dis 1999; 180:199–202.
25. Elliott E, Rose D. Reporting of communicable disease conditions under surveillance by the APSU, 1 January to 30 June 2003. Commun Dis Intell 2004; 28:4.
26. Marazzo JM, John GC, Krohn MA, Corey L. Cesarean delivery in women with genital herpes in Washington State, 1989–1991. Infect Dis Obstet Gynecol 1997; 5:29–35.
27. Randolph AG, Washington AE, Prober CG. Cesarean delivery for women presenting with genital herpes lesions: efficacy, risks, and costs. JAMA 1993; 270:77–82.
28. Garnett GP, Dubin G, Slaoui M, Darcis T. The potential epidemiological impact of a genital herpes vaccine for women. Sex Transm Infect 2004; 80:24–29.
29. Sheffield JS, Hollier LM, Hill JB, Stuart GS, Wendel GD. Acyclovir prophylaxis to prevent herpes simplex virus recurrence at delivery: a systematic review. Obstet Gynecol 2003; 102:1396–1403.
30. American College of Obstetricians and Gynecologists. ACOG practice bulletin: management of herpes in pregnancy. Int J Gynecol Obstet 2000; 68:165–174.
31. Ratanajamit C, Skriver MV, Jepsen P, et al. Adverse pregnancy outcome in women exposed to acyclovir during pregnancy: a population-based observational study. Scand J Infect Dis 2003; 35:255–259.
32. Scott LL, Alexander J. Cost-effectiveness of acyclovir suppression to prevent recurrent genital herpes in term pregnancy. Am J Perinatol 1998; 15:57–62.
33. Scott LL, Sanchez PJ, Jackson GL, et al. Acyclovir suppression to prevent cesarean delivery after first-episode genital herpes. Obstet Gynecol 1996; 87:69–73.
34. Corey L, Wald A, Patel R, et al. Valacyclovir HSV Transmission Study Group: once-daily valacyclovir to reduce the risk of transmission of genital herpes. N Engl J Med 2004; 350:11–20.
35. Crosby RA, DiClemente RJ, Wingood GM, Rose E. Testing for HSV-2 infection among pregnant teens: implications for clinical practice. J Pediatr Adolesc Gynecol 2003; 16:39–41.
36. Miyai T, Turner KR, Kent CK, Klausner J. The psychosocial impact of testing individuals with no history of genital herpes for herpes simplex virus type 2. Sex Transm Dis 2004; 31:517–521.