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Genital Herpes Complicating Pregnancy

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Abstract:

Approximately 22% of pregnant women are infected with herpes simplex virus (HSV)-2, and 2% of women will acquire HSV during pregnancy. Remarkably, up to 90% of these women are undiagnosed because they are asymptomatic or have subtle symptoms attributed to other vulvovaginal disorders. Diagnosis of genital herpes relies on laboratory confirmation with culture or polymerase chain reaction assay of genital lesions and type-specific glycoprotein G-based serologic testing. Neonatal herpes is the most severe complication of genital HSV infection and is caused by contact with infected genital secretions at the time of labor. Maternal acquisition of HSV in the third trimester of pregnancy carries the highest risk of neonatal transmission. Despite advances in the diagnosis and treatment of neonatal herpes, little change in the incidence or serious sequelae from this infection has occurred. As such, prevention of the initial neonatal infection is critically important. Obstetricians are in a unique position to prevent vertical HSV transmission by identifying women with genital lesions at the time of labor for cesarean delivery, prescribing antiviral suppressive therapy as appropriate, and avoiding unnecessary invasive intrapartum procedures in women with genital herpes. Enhanced prevention strategies include identification of women at risk for HSV acquisition during pregnancy by testing women and possibly their partners for HSV antibodies and providing counseling to prevent transmission to women in late pregnancy.

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The prevalence of genital and neonatal herpes continues to rise.¹ About 1.6 million new cases of genital herpes occur annually,² 22% of pregnant women are seropositive for herpes simplex virus (HSV)-2, and more than 2% of women acquire genital herpes during pregnancy.³ Given the high prevalence of HSV infection in women of reproductive age, obstetricians need to be able to diagnose and manage HSV in pregnancy and are in the unique position to prevent HSV transmission to the neonate.

The most devastating complication of genital HSV is infection of the neonate at the time of delivery. Neonatal HSV occurs in up to 1 in 3,200 live births,⁴ with an estimated incidence of 1,500 cases in the United States annually.⁵ Neonatal HSV causes disseminated or central nervous system (CNS) disease in approximately 50% of cases. Up to 30% of these infants will die, and up to 40% of survivors will have neurologic damage, despite antiviral therapy.⁵ The social and economic costs of the long-term care of infants with sequelae from neonatal herpes are substantial.⁶ Therefore, prevention of neonatal herpes infection remains critically important in decreasing the sequelae from this disease. This article will review genital HSV in pregnancy, emphasizing challenges in diagnosis and treatment of maternal infection in pregnancy, and prevention of vertical transmission.

EPIDEMIOLOGY OF GENITAL HERPES

A national survey conducted in the early 1990s showed that the seroprevalence of HSV-2 in the general U.S. population was 22%, an increase of 30% from 1978.^{1,7,8} Consistent with that estimate, a recent study of suburban primary care offices showed an HSV-2 seroprevalence rate of 25.5%.⁹ Seroprevalence studies of pregnant women observed HSV-2 seroprevalence rates of 20-30%.³ Ten percent of pregnant women are at risk of HSV-2 acquisition from their partners, and most of these women are at unsuspected risk.¹⁰ Overall, 2% of women in a general obstetrics practice acquire HSV during pregnancy.³ For HSV-2 seronegative women with HSV-2 seropositive partners, the risk of HSV-2 acquisition in pregnancy is up to 20%.¹⁰

Between 75% and 90% of HSV-2 infected persons are not aware of having the infection.^{1,11-13} Most sexual transmission of HSV occurs during episodes of subclinical reactivation among persons with unrecognized infection.^{11,14-17} Recent studies indicate that virtually all HSV-2 seropositive persons have virologically active infection with intermittent shedding from the genital mucosa, and most have mild (thus unrecognized and undiagnosed) disease.¹² Among women, including pregnant women, these mild genital symptoms are frequently attributed to other genital conditions, such as recurrent yeast or urinary tract infections, bacterial vaginitis, and allergies to condoms, semen, spermicides, and pantyhose.^{12,13,18,19}

Herpes simplex virus-2 seroprevalence data underestimates the actual prevalence of genital herpes because it does not include an increasing proportion of genital herpes due to HSV-1.^{20,21} Herpes simplex virus-1 has emerged as a major cause of genital herpes, particularly among college-age populations, in which up to 80% of new cases of genital HSV were caused by HSV-1.²¹⁻²³ Epidemiologic studies suggest that oral genital contact is a risk factor for genital HSV-1.²⁰ Although clinical presentation of initial genital herpes is the same for HSV-1 and HSV-2, the differences in prognosis dictate the need to identify the viral type. The frequency of genital reactivation is much less with HSV-1, which rarely recurs symptomatically or asymptotically after the first year of infection.^{24,25} In contrast, genital HSV-2 continues to recur, often frequently, for many years.²⁶

CLINICAL CHARACTERISTICS AND DIAGNOSIS OF HERPES SIMPLEX VIRUS IN PREGNANCY

The clinical manifestations of genital herpes cannot be relied upon to diagnose infection or to differentiate a newly acquired infection from a reactivated infection.²⁷ Approximately 70% of newly acquired HSV infections among pregnant women are asymptomatic or unrecognized.^{3,10} The remaining 30% of women with new infections have clinical presentations that range from minimal lesions and mild discomfort to widespread genital lesions associated with severe local pain, dysuria, sacral paresthesia, tender regional lymph node enlargement, fever, malaise, and headache. Aseptic meningitis occurs less frequently, and disseminated disease is rare. Similarly, reactivations of genital herpes are most commonly unrecognized. In a study of 201 consecutive pregnant women, 177 gave no history of genital herpes although 30.4% were HSV-2 seropositive.²⁸ The spectrum of clinically evident episodes varies from very mild episodes to severe symptoms that are clinically indistinguishable from a severe new infection.^{3,27}

As such, providers should consider HSV when caring for women with subtle genital symptoms or with clinically unusual severe illness in pregnancy because both ends of the disease spectrum are easiest to miss. In all cases, the diagnosis of genital HSV infection requires laboratory confirmation, although antiviral therapy can be initiated based on clinical presentation. Centers for Disease Control recommend that both virologic tests and type-specific serologic tests for HSV be available in clinical settings that provide care for patients at risk for sexually transmitted infections.²⁹ Isolation of HSV in cell culture is routinely done in patients who present with genital ulcers or other mucocutaneous lesions. However, the sensitivity of culture is relatively low, especially in recurrent lesions, and declines further as lesions begin to heal. Polymerase chain reaction (PCR) assays for HSV DNA are more sensitive, have become more widely commercially available, and can be used instead of viral culture.³⁰⁻³³ Both PCR and viral culture should be typed to determine whether HSV-1 or HSV-2 is the cause of the infection. As with culture, lack of HSV detection by PCR does not indicate lack of HSV infection because viral shedding is intermittent. Thus, type-specific HSV serology is an important diagnostic tool for women who lack lesions at the time of presentation or whose cultures or PCR assays are negative. If new infection is suspected and the HSV serology does not detect HSV antibodies and virus is not isolated from the lesion, repeat serologic testing in 6 weeks should be performed.

Rarely, new or recurrent HSV infection in pregnancy can cause disseminated disease, usually with prominent hepatitis or encephalitis, or it can cause postpartum endometritis. In such cases prompt diagnosis and initiation of therapy are critical to clinical outcome. Disseminated HSV should be considered in women who report a flu-like prodrome including fever that progresses to pneumonitis, hepatitis, and or encephalitis, with or without characteristic skin lesions after midpregnancy.^{34,35} Herpes simplex virus hepatitis typically presents in the third trimester of pregnancy with fever, anicteric hepatic dysfunction, highly elevated transaminases, and abdominal tenderness. Mucocutaneous lesions may appear late or not at all, and the diagnosis is made only at autopsy in 25% of reported cases.³⁶ Herpes simplex virus encephalitis should be considered in any pregnant woman with new onset seizures, change in mental status, or fever and headache.³⁷ The diagnosis is confirmed with PCR assay of the cerebral spinal fluid. For postpartum women with persistent puerperal fever, despite antibiotics and anticoagulants, HSV endometritis should be considered and confirmed with endometrial biopsy for HSV PCR or culture.^{38,39}

Based on serologic and viral detection test results, genital HSV is classified as primary, nonprimary first episode, or reactivation disease. Primary infection is characterized by isolation of HSV-1 or HSV-2 from genital secretions in the absence of HSV antibodies in serum. Nonprimary first episode disease is characterized by isolation of HSV-2 from genital secretions in the presence of HSV-1 antibodies in serum. Reactivation disease is characterized by isolation of HSV-1 or HSV-2 from the genital tract in the presence of HSV antibodies of the same serotype as the isolate. These categories are important in pregnancy because the risk of perinatal HSV transmission varies accordingly.

TYPE-SPECIFIC HERPES SIMPLEX VIRUS SEROLOGIC ASSAYS

Antibodies to HSV develop during the first several weeks after infection and persist indefinitely. Most of the immune response is type common for HSV-1 and HSV-2. However, the response to HSV-2 is distinguishable from HSV-1 because the surface glycoprotein G differs in size and epitope content between HSV-1 and HSV-2.⁴⁰ Serologic assays that detect antibodies to the HSV-1 glycoprotein G (gG1) and the HSV-2 glycoprotein G (gG2) and discriminate between HSV-1 and HSV-2 have been developed and are commercially available. These assays also permit the detection of HSV-2 infection occurring in the presence of HSV-1 antibodies or an HSV-1 infection occurring in the presence of HSV-2 antibodies.^{41,42}

The presence of type-specific HSV-2 antibody indicates genital infection because almost all HSV-2 infections are sexually transmitted. The presence of HSV-1 antibody alone is more difficult to interpret, especially in persons without a history of oral or genital herpes. Most people with HSV-1 antibody have oral HSV infection acquired in childhood, which may be asymptomatic. However, HSV-1 antibody may indicate genital HSV-1 infection because this may be asymptomatic also. Lack of symptoms in an HSV-1 seropositive person does not distinguish genital from orolabial or cutaneous infection.

Since 1999, several HSV glycoprotein G-based type-specific serologic tests have received U.S. Food and Drug Administration (FDA) approval and are currently marketed (Table 1). A finger-stick test for HSV-2 is marketed in the United States by Biokit USA (Lexington, MA) as "biokit HSV-2" and by Fisher Healthcare (Houston, TX) as "SureVue HSV-2." Focus Diagnostics (Cyprus, CA) markets worldwide "HerpeSelect HSV-1 ELISA," "HerpeSelect HSV-2 ELISA," and "HerpeSelect HSV-1 and HSV-2 Immunoblot." The immunoblot test can detect antibodies to HSV-1 and HSV-2 on a single strip, whereas the enzyme-linked immunosorbent assay (ELISA) format provides separate plates for HSV-1 and HSV-2. Recently, Trinity Biotech (Wicklow, Ireland) gained FDA approval for its "Captia HSV-1 ELISA" and "Captia HSV-2 ELISA." We believe that these assays should replace the non-glycoprotein G-based HSV assays (many of which are still marketed as "type-specific") that are in widespread use and provide inaccurate results.⁴³

Graphic

Table 1. Glycoprotein G-Based Type-Specific Tests for Herpes Simplex Virus Antibody

The assays described above differ in their operational characteristics. The finger-stick, point-of-care (office-based) diagnostic test can be done during the clinic visit.⁴⁴⁻⁴⁶ However, care must be taken in reading the color end point of these assays because variability in reading has been documented.⁴⁷ Focus Diagnostics' and Trinity Biotech's assays are designed for use in hospital or reference laboratories. The HerpeSelect Immunoblot can be performed in clinical laboratories that are approved for moderately complex work.⁴⁸ Choice of test should be driven by the availability of a high throughput laboratory and the volume of samples.

All of the type-specific assays are comparable in performance with the Western blot.^{41,45,47-51} The sensitivities of these tests for detection of HSV-2 antibody vary from 93-100%, and false-negative results may occur, especially at early stages of infection. The specificities of these assays are 96% or greater. Focus Diagnostics is developing a second-generation ELISA to increase the specificity of the HerpeSelect HSV-2 ELISA. False-positive results can occur, especially in patients with low likelihood of HSV infection. Repeat or confirmatory testing with a second glycoprotein G-based test may be indicated in some settings, especially if recent acquisition of genital herpes is suspected.

TREATMENT OF SYMPTOMATIC HERPES SIMPLEX VIRUS IN PREGNANCY

Primary or First-Episode Herpes Simplex Virus

Antiviral therapy is recommended for women with symptomatic primary or first-episode HSV infection during pregnancy.⁵² Oral antiviral medication for 7 days hastens lesion healing and reduces viral shedding, and we recommend it unless the episode is especially mild. For women with disseminated HSV, pneumonitis, hepatitis, or complications of the central nervous system, intravenous acyclovir at a dose of 5-10 mg/kg body weight, administered every 8 hours until clinical improvement is observed, followed by oral antiviral therapy for at least 10 days of total therapy, is recommended.²⁹ Antiviral therapy should be initiated as soon as the diagnosis is suspected rather than waiting for laboratory confirmation. Early consultation with an infectious diseases specialist also is recommended if disseminated HSV is suspected (Table 2). Clinicians should be aware that seroconversion may be delayed when first-episode HSV infection is treated with antiviral medications.⁵³

Graphic

Table 2. Recommended Doses of Antiviral Medication for Herpes in Pregnancy

Recurrent Herpes Simplex Virus

Before labor, recurrent HSV does not appear to have an adverse effect on pregnancy outcomes.⁵⁴ Therefore, treatment with antiviral medication is indicated only to relieve maternal symptoms. Generally, a 2- to 5-day course of oral antiviral medication will shorten the symptomatic period.²⁹ For women with frequent or severe recurrences, daily suppressive therapy with antiviral medication may be indicated, especially after the first trimester (Table 2).

Antiviral Drug Choice and Safety in Pregnancy

Acyclovir is a nucleoside analog that is highly specific for HSV-infected cells. Once inside the infected cell, acyclovir is selectively activated by the viral thymidine kinase and specifically inhibits viral replication. Acyclovir crosses the placenta, is concentrated and excreted by the fetal kidney, and is found in the amniotic fluid and fetal tissue. Although it is concentrated in amniotic fluid, it does not appear to accumulate in the fetus.⁵⁵ The bioavailability of oral acyclovir is only approximately 20%, and frequent dosing is required to achieve therapeutic levels. The limited available data suggest that the physiologic changes that occur in late pregnancy do not significantly alter maternal acyclovir pharmacokinetics, which were similar to those reported for nonpregnant patients.^{55,56}

Valacyclovir is a prodrug of acyclovir and requires hepatic metabolism to become active. It has the benefit of longer half-life, allowing for less frequent dosing, which may improve compliance. Further, the bioavailability of acyclovir after the administration of oral valacyclovir is 3-5 times greater than that of oral acyclovir.^{56,57} However, it is more expensive than acyclovir, and experience in pregnancy is limited because of its relatively recent introduction. Its mechanism of action is not different from that of acyclovir, but the consequences of higher levels of acyclovir in pregnancy are unknown. The efficacy of valacyclovir for episodic or suppressive

therapy or for the suppression of viral shedding is comparable with that of acyclovir.

Famciclovir also is a prodrug that undergoes rapid biotransformation to penciclovir, the active antiviral compound. Like valacyclovir, it has a greater bioavailability than acyclovir and can be dosed less frequently than acyclovir. No studies directly address the use of famciclovir in pregnancy, and therefore, at this time there is no recommended dose of famciclovir in pregnancy.

In our experience, antivirals frequently are used in pregnancy for the treatment or suppression of genital HSV. Acyclovir, valacyclovir, and famciclovir are Pregnancy Category B. A registry of neonates exposed to acyclovir in utero found no significant teratogenic effects to the fetus.⁵⁸ These data were sufficient to exclude a 7-fold increase in the risk of birth defects but could not address the risk of rare defects or those detected after the postnatal period.⁵⁸ Based on acyclovir toxicity data in neonates undergoing treatment for neonatal herpes, potential neonatal complications of in utero exposure include renal insufficiency and neutropenia.⁵⁹ Small studies of valacyclovir use in late pregnancy found no clinical or laboratory evidence of toxicity in participants or their infants over a 1-month (Sheffield JS, Hill J, Laibl V, Hollier LM, Sanchez P, Wendel GD. Valacyclovir suppression to prevent recurrent herpes at delivery: a randomized controlled trial [abstract]. *Obstet Gynecol* 2005;105:5S) or 6-month follow-up period.⁶⁰

Thus, limited data suggest the safety of antiviral medication in pregnancy. As with any medication used in pregnancy, consideration of the risk versus benefit in each clinical situation and open discussion with the patient should guide prescription. We believe that the maternal benefit from treating symptomatic HSV in pregnancy outweighs potential fetal risk, especially in the case of symptomatic primary infection occurring in the latter half of pregnancy or frequent or severe recurrent disease after the first trimester.

NEONATAL HERPES

Neonatal herpes is defined as the diagnosis of HSV infection in an infant within the first 28 days of life. It occurs in up to 1 in 3,200 live births in the Pacific Northwest,⁴ with an estimated incidence of 1,500 cases in the United States annually.⁵ Over 90% of cases are acquired intrapartum by contact with HSV in the maternal birth canal.^{4,61-63} The major sites of viral entry are the eye, nasopharynx, or site of scalp trauma. Rarely, neonatal herpes results from intrauterine exposure to HSV related to transplacental or ascending infection (most commonly in the setting of primary infection), or from postnatal acquisition of HSV-1 from close contact with persons with orolabial herpes, or HSV-1 infection at another nongenital site, such as the finger (eg, herpetic whitlow) or the breast.⁶⁴

Neonatal HSV presents with a spectrum of disease that is classified based on clinical manifestations. Neonates with skin, eye, and mouth disease have limited viral dissemination without visceral involvement and account for 45% of cases since the advent of early antiviral therapy.^{65,66} Almost one third of neonates with HSV are classified with CNS disease, characterized by seizures, lethargy, irritability, tremors, poor feeding, temperature instability, and bulging fontanelle. The remaining 25% of cases have disseminated infection that involves multiorgan systems and may result in death from severe coagulopathy, liver dysfunction, and pulmonary failure.⁵

Factors that affect the severity of neonatal disease include prompt diagnosis and initiation of antiviral therapy. Polymerase chain reaction assay to detect HSV DNA in neonates has improved early diagnosis of disease. Although intravenous acyclovir has clearly reduced mortality and morbidity among neonates with skin, eye, and mouth disease, little improvement has been made to reduce morbidity associated with disseminated or CNS disease. Despite early intervention with high-dose antiviral therapy, 30% of infants with disseminated disease die, and 40% of survivors of CNS disease have severe neurologic damage.⁵ Therefore, prevention of neonatal infection is critical.

RISK FACTORS FOR NEONATAL HERPES

Herpes Simplex Virus in the Genital Tract at the Time of Labor

The main mode of transmission to the neonate is exposure to infected maternal secretions at the time of passage through the birth canal. Isolation of HSV from the maternal genital tract at the time of labor is the primary risk factor for neonatal HSV, with an estimated relative risk for infection of more than 300.⁴

Stage of Maternal Infection

The second most-important risk factor for neonatal herpes is the stage of maternal infection. Overall, 60-80% of the cases of neonatal HSV occur from women who acquire genital herpes (approximately 75% of the time without symptoms) in the third trimester of pregnancy.³ The risk of neonatal herpes is 30-50% among women subclinically shedding virus at the time of labor as a result of

having acquired genital herpes in the third trimester, compared with 3% among infants exposed to HSV from maternal symptomatic reactivation of genital herpes at the time of labor.^{4,62,63} The acquisition of genital HSV infection is associated with a high efficiency of transmission to the neonate because women with newly acquired infection in the third trimester of pregnancy do not have the 6-12 weeks necessary to develop type-specific homologous HSV antibody with which to transplacentally protect their neonate after intrapartum exposure. In addition, they also are likely to have high titers of virus in their genital secretions for many months after the initial infection.⁶⁷ Therefore, the infant of a mother with acquisition of genital herpes in the third trimester of pregnancy is at double jeopardy; the infant lacks the protection of transplacental type-specific antibodies and is likely to be exposed to significantly greater amounts of virus in the genital secretions during parturition.

Type of Herpes Simplex Virus Isolated from the Genital Tract

Neonates exposed to genital HSV-1 at the time of delivery are more likely to become infected than those exposed to HSV-2, regardless of stage of maternal infection.⁴ Thirty-one percent of neonates exposed to genital HSV-1 at the time of delivery became infected, compared with 3% of those exposed to HSV-2 (odds ratio 34.8, 95% confidence interval 3.6-335, adjusted for first-episode versus reactivation HSV).⁴ The mechanism of this observation is unclear, but it may explain, along with the increasing prevalence of genital HSV-1, the rising incidence of neonatal HSV-1 infection. However, infants exposed to HSV-1, in contrast to those exposed to HSV-2, are more likely to develop skin, eye, and mouth infection and less likely to develop central nervous system involvement.⁶⁸

Invasive Obstetrical Procedures

The major sites of intrapartum viral entry include the neonatal eyes, nasopharynx, and break in the integument. Thus, any procedure that damages the neonatal skin in labor can facilitate transmission of HSV. Among neonates exposed to HSV at delivery, 10% of those delivered with the use of fetal scalp electrode, vacuum, or forceps were infected, compared with 2% of those who did not have invasive obstetric procedures.⁴

METHODS FOR PREVENTING NEONATAL HERPES SIMPLEX VIRUS

Cesarean Delivery For Women With Herpes Simplex Virus in the Birth Canal at the Time of Labor

For women with genital lesions or prodromal symptoms suggestive of genital herpes, cesarean delivery is recommended to prevent neonatal infection.⁵² Although this has been recommended by The American College of Obstetricians and Gynecologists (ACOG) for decades, evidence for a benefit of cesarean delivery in preventing neonatal herpes is recent. Cesarean delivery significantly decreased, but did not completely eliminate, the risk of neonatal HSV among women with HSV detected in genital secretions at the time of labor.⁴ Cesarean delivery is likely to be more effective if done before rupture of membranes.

Some centers suggested that it is justifiably safe to allow an HSV-2 seropositive woman to deliver her infant vaginally despite the presence of a genital herpetic lesion.⁶⁹ This is based upon the low risk of transmission to the neonate from a woman with established genital herpes.⁴ However, this low observed rate may reflect the practice of delivering women with lesions or symptoms at the time of labor by cesarean as well as the fetal protective effect of transplacental transmission of homologous antibody. Currently, the standard of care in the United States is to deliver women with symptomatic reactivation of genital herpes at the time of labor by cesarean. Based upon our experience and available data, we feel that this standard of care should persist. In women with established genital HSV but without active genital lesions or prodromal symptoms at the time of labor, cesarean delivery is not indicated.

Currently, physical examination is the main method to infer the presence of HSV in the genital tract at the time of labor. All women with known genital herpes should be questioned about genital symptoms and have a thorough examination of the cervix, vagina, and vulva at the time of admission in labor.

Physical examination to detect HSV in the genital tract has significant limitations. First, clinical diagnosis of genital herpes lacks sensitivity and specificity. Among women who underwent cesarean delivery for active genital herpes at the University of Washington, the positive predictive value of genital lesions for viral detection was 28% by culture and 47% by PCR.⁷⁰ Thus, a significant portion of women with cesarean delivery for active genital HSV did not have HSV detected in the genital tract by our current methods. Second, and perhaps more importantly, physical examination does not identify the majority of women who transmit HSV to their infants because these women lack genital lesions.^{3,4}

A clinically useful laboratory-based means of detecting HSV in the birth canal to inform the safest mode of delivery is not available currently. In the past, viral cultures of genital swabs collected in the late third trimester of pregnancy were used to predict women at risk of HSV transmission. However, results from prenatal specimens rarely correlated with culture results of swabs collected at the time of delivery.⁷¹ Therefore, this practice was abandoned in the late 1980s.⁵² Viral cultures or traditional HSV PCR to detect

HSV from genital swabs collected at the time of labor are not clinically practical because results are not available before delivery. Until a valid rapid test to detect HSV in the genital tract at the time of labor becomes available, we continue to perform cesarean deliveries for women with genital lesions at the time of labor based on physical examination findings to prevent neonatal herpes.

Some specialists recommend cesarean delivery for women with newly acquired HSV in the third trimester of pregnancy to reduce the risk of neonatal HSV, regardless of symptoms or signs at the time of labor. Others recommend treatment with acyclovir, followed by suppressive therapy for the remainder of the pregnancy. Then, if type-specific antibodies are present by the time of delivery and the woman is without lesions, vaginal delivery is allowed. We believe that the latter approach is potentially risky because suppressive therapy may not completely eliminate viral shedding, and although type-specific antibodies are detectable, they may not provide sufficient passive immunity if quantities are low.

Antiviral Suppressive Therapy

In women with symptomatic genital herpes, antiviral suppressive medication initiated at 36 weeks of gestational age reduces the need for cesarean delivery for lesions and viral detection from the genital tract by both culture and PCR at the time of delivery (Sheffield et al [abstract] (Table 2).⁷²⁻⁷⁷ Although a study to prove that suppressive therapy prevents neonatal herpes is unlikely to be feasible, it is reasonable to prescribe suppressive therapy to women with symptomatic recurrent HSV to reduce the need for cesarean delivery for HSV lesions and to decrease neonatal viral exposure at the time of vaginal delivery.⁵² At this time, data are insufficient to recommend antiviral suppressive therapy to all asymptomatic HSV-2 seropositive pregnant women. However, after discussion of the potential risks and benefits, antiviral suppressive therapy in the last trimester of pregnancy may be a reasonable option for these patients.

The recommended doses of acyclovir and valacyclovir for HSV suppression in the third trimester of pregnancy are based on those used in the clinical trials published to date and are treatment doses in nonpregnant women. It is possible that lower doses of these medications in pregnancy may be equally effective given the similar pharmacokinetics of these drugs in pregnant and nonpregnant women. However, the pharmacokinetics data in pregnancy is limited, and to date, suppression trials have not been performed using the lower doses. Thus, the higher doses are recommended at this time (Table 2). Currently, there is no recommended dose of famciclovir in pregnancy.

Prevent the Acquisition of Herpes Simplex Virus by Pregnant Women

Although the current recommendations of ACOG do not include universal testing,⁵² we recommend universal HSV serologic screening in pregnancy when feasible. Given our current understanding of the risk of neonatal herpes, we believe that prevention of neonatal HSV will depend in large part upon prevention of maternal acquisition of genital HSV in the third trimester of pregnancy.

There are 3 potential approaches to preventing maternal acquisition of HSV in late pregnancy. The first is to obtain a glycoprotein G-based (type-specific) HSV serologic assay at a prenatal visit between 24 and 28 weeks of gestation when blood is routinely drawn for diabetes screening (Fig. 1). Screening at 24-28 weeks of gestation places the counseling and interventions in the third trimester of pregnancy, which is the time of greatest risk for subsequent neonatal HSV transmission if the mother should acquire genital herpes. For women who are identified as HSV-2 seropositive but unaware of their infection, this would provide adequate time to educate them about the significance of this finding and how to identify recurrences, particularly at the time of labor.¹⁹ It would also allow the patient and her provider time to formulate an appropriate labor and delivery plan.

Graphic

Fig. 1. Algorithm for testing and counseling women without involvement of the male partner. *Brown. Genital Herpes Complicating Pregnancy. Obstet Gynecol 2005.*

Women who are seronegative (ie, without antibodies to either HSV-1 or HSV-2) or those who are HSV-1 seropositive but have no antibodies to HSV-2 should be counseled to avoid unprotected genital-to-genital contact during the third trimester. In addition, the women who are HSV-seronegative should also be counseled to avoid oral-genital contact during this same time period because about 30% of cases of neonatal HSV are caused by genital HSV-1 acquired by the mother in the last trimester of pregnancy.⁴

The disadvantage to HSV serotesting only women to determine HSV susceptibility is that it does not account for exposure status. That is, it does not determine whether the sexual partner has HSV. Without partner testing, a larger number of women will require

counseling based on susceptibility to HSV alone, including those who are not at risk of acquisition because their partner is not infected. Women may be less likely to adhere to counseling messages because they believe that their partner is not infected with HSV. Those women who learn that they have HSV-2 infection may worry about transmitting to their partners, if the partner's status is unknown.

The second approach provides HSV serologic screening of pregnant couples to identify HSV susceptible women with serologically discordant partners. (Fig. 2) Published studies indicate that only 15-25% of couples in early pregnancy are discordant in their HSV serologic status with the pregnant woman at risk (Gardella C, Brown Z, Wald A, Selke S, Zeh J, Morrow R, et al. Risk factors for herpes simplex virus transmission to pregnant women. *Am J Obstet Gynecol* 2005, in press). Therefore, this approach targets counseling toward those at highest risk for acquiring genital HSV. If the woman is HSV-2 susceptible and the partner has an HSV-2 infection, the couple should be advised to avoid genital contact during the third trimester. If this is not possible, then condoms should be used.⁷⁸ Additionally, the HSV-2 seropositive partner can be treated with suppressive antivirals in conjunction with condom use during the third trimester of her pregnancy.⁷⁹ If the woman is HSV seronegative and the partner has only HSV-1 antibody, then oral-genital contact should be avoided in the third trimester. Because some HSV-1 seropositive men will have a genital rather than an oral HSV-1 infection, such HSV-1 discordant couples should also be counseled to either use condoms or avoid genital contact in the third trimester. The efficacy of these measures has not been determined in pregnancy.

Graphic

Fig. 2. Algorithm for testing and counseling women with involvement of the male partner. *Brown. Genital Herpes Complicating Pregnancy. Obstet Gynecol* 2005.

If screening both partners is the preferred method, it may be most efficient to screen for HSV antibodies at 14-18 weeks of gestation, a time when maternal blood is drawn for the detection of fetal neural tube defects and chromosomal disorders. This would allow ample time to approach the partners of susceptible women and to initiate appropriate interventions. There are some disadvantages to this "couples approach." The partner may refuse to participate in the screening or counseling process. It may also be difficult to identify a single sexual partner, or the partner may change during the course of the pregnancy.

The third approach is appropriate where serologic testing is either not available or economically not feasible. In these circumstances, it may be appropriate to advise all women to abstain from all forms of sexual contact in the third trimester of pregnancy. Because the frequency of sexual activity declines significantly with advancing gestation and particularly in the third trimester, this may not pose a hardship to many women and will obviate, in part, the need for serologic testing.^{80,81} However, it lacks the objective certainty and credibility of a counseling recommendation built upon a serologic test result. It will also fail to identify and thereby fail to permit interventions for HSV-2 seropositive women with unrecognized genital herpes.

In our practice, since 1984, we have routinely screened all pregnant women early in pregnancy for HSV antibodies using the Western blot assay. Women with HSV-2 are counseled regarding the signs of recurrence. For women without HSV-2 antibody, we inquire about the HSV status of the partner if this is known. If the partner has no history of genital herpes, we recommend serologic testing by his primary care provider or at the public health clinic. If this is not acceptable or feasible, we counsel the patient according to the algorithm in [Figure 1](#). If the partner has previously diagnosed genital HSV, the woman is counseled as outlined in [Figure 2](#). Because neonatal HSV is relatively rare, studies to directly measure the benefit of such an approach in preventing neonatal HSV are difficult, if not impossible, to perform. However, we see little risk in this approach, and our experience with counseling women about their serologic test results has been positive, in accordance with published studies in pregnancy and in other settings.⁸²⁻⁸⁴

Basic costs of these approaches can be measured indirectly and information about cost-effectiveness relies on modeling the cost of various outcomes and expenditures. Two recently published cost-benefit analyses generated remarkably different results, with the estimated cost per quality-adjusted neonatal life-year gained ranging from \$18,680 to \$155,988.^{85,86} Further research is required to understand the differences between the models.

Avoid Unnecessary Invasive Procedures in Labor

Women with genital herpes but without lesions or symptoms at the time of labor may proceed with vaginal delivery. However, we recommend avoiding artificial rupture of membranes, fetal scalp electrodes, and vacuum or forceps delivery in these women, except

when critical to obstetric care, because these practices appear to increase the risk of HSV transmission.⁴

POSTPARTUM RECOMMENDATIONS

For women with known genital herpes or documented HSV-2 infection, the pediatricians who care for the neonate postpartum should be informed of the potential risk of neonatal herpes for enhanced observation of the neonate. The parents should be educated regarding the early signs of neonatal herpes and advised to set a low threshold for seeking medical care for the newborn after hospital discharge.

Women with active genital herpes at the time of delivery are not restricted from contact with the neonate, but should wash their hands before contact. Women with active orolabial herpes should refrain from kissing the newborn at the face or site of skin break, such as a scalp electrode insertion site, and also should wash their hands before contact with the neonate. In women with frequent symptomatic disease, antiviral suppressive therapy to decrease symptomatic lesions can be considered, or episodic therapy can be used. Antiviral suppressive therapy is not routinely recommended in women with asymptomatic oral HSV-1 infection. The risk of transmission by these women is likely to be low in these circumstances because asymptomatic viral shedding tends to occur at the oral mucosa rather than the lips.⁸⁷ However, all women with orolabial HSV should be instructed to avoid biting their infants' nails because there have been case reports of herpetic whitlow resulting from this practice.^{88,89}

Women with HSV of the breast should avoid nursing from the affected side. Antiviral suppressive therapy can be considered for these women.

The American Academy of Pediatrics considers acyclovir to be compatible with breastfeeding.⁹⁰ Acyclovir is concentrated in breast milk, reaching peak levels approximately 3 hours after the initial maternal dose, with a half-life of 2-3 hours. The total dose received by infants of nursing mothers treated with acyclovir or valacyclovir reaches approximately 1 mg/d, which is about 1% of the effective neonatal dose.⁹¹⁻⁹⁴ Because the dose is so low, we use suppressive antiviral therapy for breastfeeding women if this is indicated for genital herpes or other mucocutaneous infection.

SUMMARY

Pregnant women are routinely tested for many medical problems, including a number of sexually transmitted diseases. However, genital herpes, a prevalent sexually transmitted disease with significant consequences for pregnancy, is not routinely evaluated. Acquisition of HSV near term has been documented to be the most common cause of neonatal herpes infection, which can have devastating sequelae. Now that commercially available, reliable glycoprotein G-based serologic assays are available, these assays may be included in prenatal testing. For the prevention of neonatal HSV, testing would identify women at risk for acquiring genital HSV so that they may be counseled against unprotected coitus or oral-genital contact in the third trimester. Serologic testing would also identify HSV-2 seropositive women who are unaware they have previously acquired HSV-2 infection. Examination of these women for genital lesions at the time of admission in labor and avoidance of scalp electrodes, early artificial rupture of membranes, and instrumented deliveries may reduce the risk of fetal intrapartum HSV exposure. In addition, identifying HSV-2 seropositive, asymptomatic women who are unaware of their disease would result in education about their infection, the recognition of recurrences, and methods of avoiding transmission to sexual partners.

There is still much to be learned about the optimal strategies for management of genital herpes in the pregnant woman. Nevertheless, there is, at the present time, also much that can be done to initiate programs to reduce this potentially preventable cause of a devastating neonatal infection.

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