

## 30. Screening for Genital Herpes Simplex

### RECOMMENDATION

Routine screening for genital herpes simplex virus (HSV) infection by viral culture or other tests is not recommended for asymptomatic persons, including asymptomatic pregnant women. There is insufficient evidence to recommend for or against the examination of pregnant women in labor for signs of active genital HSV lesions, although recommendations to do so may be made on other grounds (see *Clinical Intervention*). See Chapter 62 for recommendations on counseling to prevent sexually transmitted diseases.

### Burden of Suffering

Primary genital herpes simplex virus (HSV) infection occurs in approximately 200,000–500,000 Americans each year,<sup>1</sup> mostly in adolescents and young adults. Between 25 and 31 million individuals are chronically infected.<sup>1,2</sup> Both HSV types 1 (HSV-1) and 2 (HSV-2) can infect the genitalia, but HSV-2 causes the majority of primary and recurrent genital herpes infections.<sup>3</sup> Most HSV-2 infections are asymptomatic, detected only by seroconversion;<sup>4,5</sup> 16% of the adult population is HSV-2 seropositive.<sup>2</sup> In symptomatic genital herpes, the chief clinical morbidity is painful, pruritic vesicles that may coalesce into large ulcerative lesions.<sup>3</sup> Systemic symptoms, such as fever, headache, myalgia, and malaise, are reported by two thirds of patients with primary first-episode genital herpes, and serious complications such as meningitis (reported in 8%) may ensue.<sup>3</sup> After initial infection, the virus enters a latent state in spinal cord ganglia. Infected persons may periodically experience viral reactivations that can be asymptomatic, characterized by viral shedding alone, or symptomatic, marked by a recurrence of signs and symptoms that are less severe than those of primary genital herpes.<sup>3</sup> The sexual contacts of individuals with either symptomatic or asymptomatic disease are at risk of becoming infected.<sup>6</sup>

In pregnant women, the rate of genital herpes reported as a maternal risk factor on birth certificates is 8.0/1,000 live births.<sup>7</sup> Pregnant women with genital HSV infection can transmit the virus to their newborns. The

majority (82–87%) of neonatal infections occur during delivery, but some also occur in utero or postnatally.<sup>8–10</sup> In 1984 it was estimated that the minimum annual incidence of neonatal HSV infections in the United States, based on voluntary reporting, was 4/100,000 live births;<sup>11</sup> intensive local surveillance in one county in Washington found a rate of 12/100,000 live births.<sup>12</sup> One fourth of HSV-infected neonates develop disseminated disease and one third have encephalitis.<sup>13,14</sup> Even with antiviral treatment, the mortality rate is 57% among infants with disseminated disease and 15% among those with encephalitis.<sup>13</sup> Severe neurologic impairment occurs in about one third of those who survive encephalitis or disseminated disease.<sup>13,14</sup> Among infants with infection apparently limited to mucocutaneous involvement, death or severe impairment is rare but other complications such as visual impairment or seizures occur in about 5%.<sup>13,14</sup>

### Accuracy of Screening Tests

History and physical examination are not adequate screening tests for either active (i.e., transmissible) or latent genital HSV infection, because most infected persons are asymptomatic;<sup>4,3,15</sup> their clinical manifestations may resemble a number of other causes of genital ulcerations;<sup>16</sup> and viral shedding in association with recurrent disease may be asymptomatic.<sup>3,17</sup>

The most commonly used test for detecting active genital HSV infection is viral culture. The sensitivity of this test is variable, however, depending upon the viral titer present, ranging in one study from 93% for vesicles to 72% for ulcers and 27% for crusted lesions, and from 82% for ulcerative lesions in first episodes to 43% for ulcerative lesions in recurrent episodes.<sup>16,18</sup> Since the viral titer in asymptomatic shedding is 10–100 times less than that in symptomatic episodes,<sup>17</sup> the sensitivity of viral culture for detecting HSV infection in asymptomatic individuals is likely to be low. In addition, conventional viral culture is time-consuming and technically demanding, and only 40–48% of positive results are available within 24 hours.<sup>19–21</sup> Viral culture techniques may be modified to produce final test results within 16–24 hours, but sensitivity is then reduced by 5–20% compared with final conventional culture results in symptomatic patients;<sup>20–24</sup> sensitivity is likely to be reduced further in asymptomatic patients.

Other rapid screening methods, such as cytology and direct fluorescent antibody staining, are widely available but are substantially less sensitive than is conventional viral culture.<sup>6</sup> Newer methods, not yet licensed for clinical diagnostic testing for HSV, include enzyme immunoassay (EIA), polymerase chain reaction (PCR), and DNA hybridization. EIA and PCR show concordance of >93% with the results of conventional viral culture in symptomatic women.<sup>25–28</sup> In one study in asymptomatic pregnant women, PCR had a reported concordance of 100% with conventional culture.<sup>27</sup> EIA, however, had a concordance of only 59% with conventional viral culture in a large study of samples taken primarily from “presumed asymptomatic” women.

matic” pregnant women.<sup>25</sup> EIA can provide results within several hours, whereas even with automated techniques PCR currently requires more than a day to process and is extremely labor intensive. Both EIA and PCR may react with nonviable virus or viral particles,<sup>25–28</sup> thus overestimating the risk of infectivity. Results from studies of DNA hybridization appear less promising, with a sensitivity of 25% and specificity of 88% compared to conventional culture,<sup>22</sup> and 43% and 71%, respectively, compared to cytology,<sup>29</sup> on samples from symptomatic patients.

An estimated 35–80% of infants with neonatal herpes are born to women with no known history of genital herpes or physical signs of infection at delivery.<sup>10,12,13</sup> Therefore, screening asymptomatic pregnant women has the potential of identifying unrecognized active HSV infections. In order for routine screening at the onset of labor to be useful for clinical decision making regarding surgical or medical intervention to prevent neonatal herpes, rapid and accurate methods of detecting asymptomatic HSV infections likely to be transmitted would be needed. The yield of routine screening by viral culture in asymptomatic pregnant women is quite low; large-scale screening studies have isolated HSV by culture from only 0.20–0.35% at the time of delivery.<sup>30–32</sup> A positive viral culture does not necessarily mean an infant will become infected during delivery. The risk of acquiring neonatal herpes infection from an asymptomatic pregnant woman with active viral shedding from reactivated disease is less than 5%, whereas from a woman with first-episode genital disease the risk is 33%.<sup>31</sup> A negative culture, however, does not eliminate an infant’s risk of infection. In one large cohort study, the mothers of 30% (3 of 10) of the infected newborns were culture negative at the time of delivery,<sup>31</sup> and in a case series of infants with neonatal herpes, 61% (54 of 89) of the pregnant women had negative cultures within the 2 weeks before delivery.<sup>33</sup> In asymptomatic women with a history of recurrent herpes, surveillance cultures during the 4 weeks before delivery did not correlate with viral shedding at delivery.<sup>34</sup> Thus, screening near term is not adequate to predict accurately the likelihood of HSV transmission from asymptomatic pregnant women to their offspring.

Antibody testing can accurately distinguish HSV-seropositive from HSV-seronegative persons and therefore may be useful to detect asymptomatic carriers at potential risk for transmitting disease, as well as persons susceptible to primary infection. Commercial assays are insensitive to recent infections, however, and they are unreliable for distinguishing HSV-2 from HSV-1 antibodies.<sup>35,36</sup> Antibody test results do not indicate whether the virus is currently capable of being transmitted.

#### Effectiveness of Early Detection

The detection of HSV infection in asymptomatic, nonpregnant individuals would be useful if treatment were available to either eradicate latent HSV

infection or to prevent transmission to sex partners by eliminating or reducing viral shedding. There is currently no effective treatment for eradicating latent herpes infection. Both episodic and continuous oral acyclovir reduce viral shedding, lesion healing time, and local and systemic symptoms during symptomatic primary first-episode and recurrent genital HSV infections.<sup>37-42</sup> When used continuously for up to 4 years, oral acyclovir produces only minor side effects and minimal emergence of resistant strains in immunologically normal individuals.<sup>41-43</sup> The beneficial effects of acyclovir on lesion healing and viral shedding in symptomatic individuals have not been documented to prevent or reduce transmission to sex partners, however. Based on a single, small before-after study, oral acyclovir does not appear to prevent asymptomatic viral shedding,<sup>44</sup> and no studies have evaluated its ability to decrease infectivity and disease transmission during episodes of asymptomatic shedding.

Routine screening for HSV-2 antibodies may be useful to identify persons with previously unrecognized infection,<sup>4</sup> who could then be instructed in the recognition of recurrent episodes. Such instruction results in recognition of clinically symptomatic genital herpes on follow-up in 50% of seropositive persons with previously unrecognized infection.<sup>45</sup> Counseling seropositive persons to avoid sexual activity or to use condoms during symptomatic episodes may reduce transmission of herpes to their sex partners.<sup>45,46</sup> Among a series of 144 couples with one partner with recurrent herpes and one without antibody, all of whom were advised to abstain from skin-to-skin contact during active episodes and about the risks of transmission during asymptomatic periods, acquisition of genital herpes occurred in 6% who used barrier contraception and 14% who did not ( $p = 0.19$ ), but only 15% of couples used condoms routinely.<sup>47</sup> Although not specifically designed to evaluate counseling, this study suggests a limited benefit from knowledge of susceptibility. The effectiveness of this strategy in preventing HSV-2 transmission has not been evaluated adequately; it may not provide any incremental benefit over routine counseling of all sexually active adults regarding prevention of sexually transmitted diseases.<sup>48</sup>

The early detection of active HSV infection may be of greater importance during pregnancy because cesarean delivery can be performed. This has the potential to reduce the exposure of the neonate to virus in the birth canal that occurs during vaginal delivery, although the evidence for the effectiveness of this intervention is limited. Small, uncontrolled case series of symptomatic women with positive genital cultures during the 1-2 weeks before delivery<sup>49,50</sup> or with positive cervical cultures at the time of delivery<sup>51</sup> suggest a protective effect of cesarean deliveries; no controlled trials have evaluated this intervention. None of these studies differentiated primary from recurrent infections, which have different rates of HSV transmission. Cesarean delivery is clearly not completely effective, since large

case series of newborns infected with HSV reveal that 19–33% of them were delivered by cesarean delivery.<sup>11,33,52</sup> Information concerning the effectiveness of cesarean delivery in preventing neonatal herpes transmission by asymptomatic pregnant women comes from a large cohort study that screened such women by viral culture during early labor.<sup>31</sup> In this study, 8% (1 of 13) of infants delivered by cesarean delivery to culture-positive women became infected, compared to 14% (6 of 43) of infants delivered vaginally to culture-positive women. Drawing conclusions from this study is difficult, however, because sample size was insufficient to establish statistical significance; reasons for selection of vaginal delivery are not given; and differences between the two groups in the proportions of primary versus recurrent infections, site of positive culture (i.e., cervical vs. other), and duration of rupture of membranes are not delineated. Thus, the benefit of cesarean delivery in either symptomatic or asymptomatic culture-positive women is not established.

Even if cesarean delivery does offer some benefit in preventing the transmission of HSV to newborns, more definitive studies would be needed to determine the proper indications for abdominal delivery. For example, it is not clear whether cesarean delivery would be indicated when the risk of herpes transmission is low, e.g., in the setting of asymptomatic viral shedding, recurrent symptomatic disease, or when labial but not cervical cultures are positive.<sup>31,34,51,53</sup> In these relatively low-risk situations, the potential benefit to the fetus of averting HSV infection may not outweigh the known risk of complications in the mother and infant due to cesarean delivery. In cohort studies, cesarean delivery has been associated with increases in both maternal morbidity and mortality compared to vaginal delivery,<sup>54–56</sup> even when stratified by maternal diagnosis. A 1993 decision analysis model calculated that cesarean delivery for herpes lesions at delivery in women with recurrent genital HSV leads to 1,580 excess (i.e., performed solely to prevent HSV transmission) cesarean deliveries for every neonate saved from death or neurologic sequelae, and 0.57 maternal deaths for every neonatal death prevented; total costs were \$2.5 million per case of HSV averted, and \$203,000 per quality adjusted life-year (QALY) gained.<sup>57</sup> These estimates are sensitive to risk of vertical transmission (estimated to be 1%) and to the efficacy of cesarean delivery (estimated to be 80%); reductions in either of these could result in maternal deaths exceeding neonatal mortality. The decision analysis results change dramatically if only women with primary HSV infections are entered. In women with herpes lesions at delivery but no previous history of genital HSV, nine excess cesarean deliveries would be performed for every neonate saved, with 0.004 maternal deaths per neonatal death prevented, at a total savings of more than \$38,000, saving \$2600 per QALY gained. Net benefits persisted across all likely ranges of values entered into the model.

Serologic screening may prove useful for the prevention of primary HSV-2 infections in pregnancy. One study screened pregnant women and their partners for type-specific antibodies to herpes, and found that 10% (18 of 190) of the women were seronegative with seropositive partners, and therefore were at risk of contracting a primary HSV-2 infection during pregnancy; 7 of 18 couples continued to have unprotected intercourse after being informed of their serologic status, and 1 of the 7 seroconverted during pregnancy.<sup>5</sup> Studies evaluating the effectiveness of counseling such couples to abstain from sexual intercourse or to use condoms regularly during pregnancy to prevent neonatal herpes transmission have not been performed.

Another potential strategy for preventing the transmission of HSV to newborns is offering prophylactic acyclovir to pregnant women with recurrent herpes. A case series of 15 pregnant women with recurrent genital herpes demonstrated that suppressive treatment with acyclovir after 38 weeks of gestation was well tolerated with no toxicity to the mothers or infants.<sup>58</sup> None of the women experienced new symptomatic recurrences or asymptomatic viral shedding after beginning treatment and none of their infants developed neonatal infection. In a pilot randomized controlled trial, women with recurrent herpes who received acyclovir continuously at least 1 week before expected term had significantly fewer HSV recurrences/positive cultures and a significantly lower rate of cesarean delivery for herpes.<sup>59</sup> Four randomized controlled studies are currently being conducted, in the United States, Norway, and England, to determine the effectiveness and safety of prophylactic acyclovir in reducing the risks of asymptomatic shedding, cesarean delivery, and neonatal transmission when given in late pregnancy to women with histories of recurrent herpes (H. Watts, personal communication, July 1995; L. Scott, personal communication, July 1995).<sup>60,61</sup> Although acyclovir has not been found to be teratogenic in standard animal testing, and no recognizable pattern of birth defects has been detected among 601 reported cases of exposure during pregnancy, current data are only sufficient to exclude a teratogenic risk of at least 2-fold over the 3% baseline risk of birth defects.<sup>62,63</sup>

### Recommendations of Other Groups

The American College of Obstetricians and Gynecologists,<sup>64</sup> the American Academy of Pediatrics,<sup>65</sup> the Canadian Task Force on the Periodic Health Examination,<sup>66</sup> and the Infectious Disease Society of America<sup>67</sup> recommend against surveillance cultures for herpes infections in asymptomatic pregnant women. All four groups suggest careful examination of all women at the time of delivery and culture of active lesions, with cesarean delivery for women with positive findings on clinical examination.<sup>64-67</sup> No

organizations currently recommend screening for genital herpes simplex virus or antibody in the asymptomatic general population.

### Discussion

There are currently no commercially available tests that are adequate to detect latent HSV-2 infections in asymptomatic patients. Even if accurate type-specific serology becomes widely available, there is no proven treatment to eradicate latent infection or to eliminate viral shedding in order to prevent disease transmission. Similarly, there is limited evidence that counseling persons known to have HSV offers any benefit over routine counseling of all sexually active adults to prevent sexually transmitted diseases. Evidence does not therefore support screening the asymptomatic general population for HSV infection.

For pregnant women (and those planning conception), the potential benefit of detecting asymptomatic and unrecognized HSV infection is the prevention of neonatal HSV transmission. The risk of transmitting HSV to their infants is slightly increased in pregnant women with asymptomatic shedding of HSV due to reactivated disease at delivery, and it is substantially increased in women with primary HSV infection at delivery. Culture results at the onset of labor are rarely available in time to affect clinical decision making, and there is good evidence that positive viral cultures in the weeks prior to delivery do not accurately predict the risk of neonatal HSV transmission. More rapid tests that could be performed at the onset of labor are either substantially less sensitive than culture or not yet widely available. Women with primary first-episode HSV infection at delivery are more likely to present with symptoms and signs detectable by physical examination, but such examinations have not been shown to be sensitive or specific. Even if the diagnosis of HSV is made by physical examination during labor, the evidence supporting the effectiveness of cesarean delivery in preventing neonatal HSV transmission is of poor quality, while there is fair evidence that cesarean delivery increases risk to the mother and fetus compared to vaginal delivery. A recent decision analysis predicts that if cesarean delivery prevents 85% of neonatal HSV infections that occur following vaginal delivery, a physical examination at labor for symptoms or signs of genital herpes would minimize the ratio of excess cesarean deliveries to cases of neonatal HSV infection averted, compared to other screening methods or no screening.<sup>68</sup> Another model that evaluated performing a physical examination at delivery, followed by cesarean delivery for women with genital herpes lesions, found clear evidence of benefit only for women with no history of genital herpes.<sup>57</sup> For women with recurrent herpes, the risk to the mother may outweigh that to the neonate, depending on assumptions made about the efficacy of cesarean delivery and the likely HSV transmission rate.



The use of acyclovir in pregnancy to reduce neonatal HSV has not been adequately evaluated, but trials are ongoing.

Although a history of genital herpes does not accurately predict HSV seropositivity, if the pregnant woman who lacks such a history has a partner known to have genital herpes, counseling to prevent HSV transmission to the woman could prevent primary HSV infection, thereby preventing neonatal HSV at little cost or risk to the patient. When commercially available, HSV serotyping at the first prenatal visit with serotesting of the partners of those who are HSV-2 seronegative would allow more accurate detection of pregnant women at risk for primary HSV infection. The effectiveness of counseling such women regarding primary prevention has not been demonstrated, however.

#### CLINICAL INTERVENTION

Routine screening for genital herpes simplex in asymptomatic persons, using culture, serology, or other tests, is not recommended (“D” recommendation). See Chapter 62 for recommendations on counseling to prevent sexually transmitted diseases.

Routine screening for genital herpes simplex infection in asymptomatic pregnant women, by surveillance cultures or serology, is also not recommended (“D” recommendation). Clinicians should take a complete sexual history on all adolescent and adult patients (see Chapter 62).

As part of the sexual history, clinicians should consider asking all pregnant women at the first prenatal visit whether they or their sex partner(s) have had genital herpetic lesions. There is insufficient evidence to recommend for or against routine counseling of women who have no history of genital herpes, but whose partners do have a positive history, to use condoms or abstain from intercourse during pregnancy (“C” recommendation); such counseling may be recommended, however, on other grounds, such as the lack of health risk and potential benefits of such behavior.

There is also insufficient evidence to recommend for or against the examination of all pregnant women for signs of active genital HSV lesions during labor and the performance of cesarean delivery on those with lesions (“C” recommendation); recommendations to do so may be made on other grounds, such as the results of decision analyses and expert opinion. There is not yet sufficient evidence to recommend for or against routine use of systemic acyclovir in pregnant women with recurrent herpes to prevent reactivations near term (“C” recommendation).

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