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Serologic Screening for Genital Herpes Infection

US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

IMPORTANCE Genital herpes is a prevalent sexually transmitted infection in the United States, occurring in almost 1 in 6 persons aged 14 to 49 years. Infection is caused by 2 subtypes of the herpes simplex virus (HSV), HSV-1 and HSV-2. Antiviral medications may provide symptomatic relief from outbreaks but do not cure HSV infection. Neonatal herpes infection, while uncommon, can result in substantial morbidity and mortality.

OBJECTIVE To update the 2005 US Preventive Services Task Force (USPSTF) recommendation on screening for genital herpes.

EVIDENCE REVIEW The USPSTF reviewed the evidence on the accuracy, benefits, and harms of serologic screening for HSV-2 infection in asymptomatic persons, including those who are pregnant, as well as the effectiveness and harms of preventive medications and behavioral counseling interventions to reduce future symptomatic episodes and transmission to others.

FINDINGS Based on the natural history of HSV infection, its epidemiology, and the available evidence on the accuracy of serologic screening tests, the USPSTF concluded that the harms outweigh the benefits of serologic screening for genital HSV infection in asymptomatic adolescents and adults, including those who are pregnant.

CONCLUSIONS AND RECOMMENDATION The USPSTF recommends against routine serologic screening for genital HSV infection in asymptomatic adolescents and adults, including those who are pregnant. (D recommendation)

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Author/Group Information: The US Preventive Services Task Force (USPSTF) members are listed at the end of this article.

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The US Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without obvious related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

Summary of Recommendation and Evidence

The USPSTF recommends against routine serologic screening for genital herpes simplex virus (HSV) infection in asymptomatic

adolescents and adults, including those who are pregnant (D recommendation) (Figure 1).

Rationale

Importance

Genital herpes is a prevalent sexually transmitted infection (STI) in the United States; the Centers for Disease Control and Prevention (CDC) estimates that almost 1 in 6 persons aged 14 to 49 years have genital herpes.¹ Genital herpes infection is caused by 2 subtypes of HSV, HSV-1 and HSV-2. Unlike other infections for which screening is recommended, HSV infection may not have a long asymptomatic period during which screening, early identification, and treatment may alter its course. Antiviral medications may provide symptomatic relief from outbreaks; however, these medications do not cure HSV infection. Although vertical transmission of HSV can occur between an infected pregnant woman and her infant during vaginal delivery, interventions can help reduce transmission. Neonatal herpes infection, while uncommon, can result in substantial morbidity and mortality.

Figure 1. US Preventive Services Task Force Grades and Levels of Certainty

What the USPSTF Grades Mean and Suggestions for Practice		
Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

USPSTF Levels of Certainty Regarding Net Benefit	
Level of Certainty	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as the number, size, or quality of individual studies. inconsistency of findings across individual studies. limited generalizability of findings to routine primary care practice. lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of the limited number or size of studies. important flaws in study design or methods. inconsistency of findings across individual studies. gaps in the chain of evidence. findings not generalizable to routine primary care practice. lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.
The USPSTF defines certainty as “likelihood that the USPSTF assessment of the net benefit of a preventive service is correct.” The net benefit is defined as benefit minus harm of the preventive service as implemented in a general, primary care population. The USPSTF assigns a certainty level based on the nature of the overall evidence available to assess the net benefit of a preventive service.	

Detection

In the past, most cases of genital herpes in the United States have been caused by infection with HSV-2. Adequate evidence suggests that the most widely used, currently available serologic screening test for HSV-2 approved by the US Food and Drug Administration is not suitable for population-based screening, based on its low specificity, the lack of widely available confirmatory testing, and its high false-positive rate. Rates of genital herpes due to HSV-1 infection in the United States may be increasing. While HSV-1 infection can be identified by serologic tests, the tests cannot determine if the site of infection is oral or genital; thus, these serologic tests are not useful for screening for asymptomatic genital herpes resulting from HSV-1 infection.

Benefits of Early Detection and Intervention

Based on limited evidence from a small number of trials on the potential benefit of screening and interventions in asymptomatic populations and an understanding of the natural history and epidemiology of genital HSV infection, the USPSTF concluded that the evidence is adequate to bound the potential benefits of screening in asymptomatic adolescents and adults, including those who are pregnant, as no greater than small.

Harms of Early Detection and Intervention

Based on evidence on potential harms from a small number of trials, the high false-positive rate of the screening tests, and the potential anxiety and disruption of personal relationships related to diagno-

Figure 2. Serologic Screening for Genital Herpes Infection: Clinical Summary

Population	Asymptomatic adolescents and adults, including those who are pregnant
Recommendation	Do not routinely screen for genital herpes simplex virus (HSV) infection. Grade: D
Screening Tests	The most widely used, currently available serologic screening test for HSV-2 is not suitable for population-based screening, based on its low specificity, the lack of widely available confirmatory testing, and its high false-positive rate. While serologic screening tests can detect HSV-1 infection, the tests cannot determine if the site of infection is oral or genital.
Treatment and Interventions	There is no cure for genital HSV infection. Antiviral medications are used for the management of symptomatic outbreaks and for prevention in patients with a history of frequent symptomatic outbreaks.
Balance of Benefits and Harms	The USPSTF concludes with moderate certainty that the harms outweigh the benefits for population-based screening for genital HSV infection in asymptomatic adolescents and adults, including those who are pregnant.
Other Relevant USPSTF Recommendations	The USPSTF recommends intensive behavioral counseling interventions to reduce the likelihood of acquiring a sexually transmitted infection for all sexually active adolescents and for adults at increased risk. The USPSTF has also issued recommendations on screening for other sexually transmitted infections, including chlamydia and gonorrhea, hepatitis B virus, HIV, and syphilis. These recommendations are available on the USPSTF website (https://www.uspreventiveservicestaskforce.org).

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to <https://www.uspreventiveservicestaskforce.org>.



HIV indicates human immunodeficiency virus; USPSTF, US Preventive Services Task Force.

sis, the USPSTF found that the evidence is adequate to bound the potential harms of screening in asymptomatic adolescents and adults, including those who are pregnant, as at least moderate.

USPSTF Assessment

The USPSTF concludes with moderate certainty that the harms outweigh the benefits for population-based screening for genital HSV infection in asymptomatic adolescents and adults, including those who are pregnant.

Clinical Considerations

Patient Population Under Consideration

This recommendation statement applies to asymptomatic adolescents and adults, including those who are pregnant, without a history of genital HSV infection (Figure 2).

Screening Tests

The USPSTF does not recommend serologic screening for genital HSV infection in asymptomatic persons.

Treatment

The CDC provides guidance for the diagnosis and management of genital HSV infection.²

Additional Approaches to Prevention

The USPSTF recommends intensive behavioral counseling interventions to reduce the likelihood of acquiring an STI for all sexually active adolescents and for adults at increased risk.³

Useful Resources

The USPSTF has issued recommendations on screening for other STIs, including chlamydia and gonorrhea,⁴ hepatitis B virus,⁵ human immunodeficiency virus (HIV),⁶ and syphilis.⁷

Other Considerations

Research Needs and Gaps

There are many areas in need of research to better understand the detection and management of asymptomatic genital HSV infection, including

- Improved epidemiologic data on the true prevalence and natural history of asymptomatic genital HSV infection in the United States
- Development of screening and diagnostic tests with higher specificity that detect both asymptomatic genital HSV-1 and HSV-2 infections
- Behavioral interventions to reduce the transmission of genital HSV infection, including interventions to reduce the risk of transmission to uninfected pregnant women
- Further interventions to prevent and treat neonatal herpes infection
- Potential effectiveness of antiretroviral medications, including topical gels, as preexposure or postexposure prophylaxis
- More data on the potential harms of screening in asymptomatic persons, including psychological distress and the disruption of personal relationships
- Increased understanding of the potential role of HSV infection in increasing the risk of HIV infection and the management of coinfection with HSV and HIV

Research to develop a cure for genital HSV infection and a vaccine to prevent genital HSV infection should continue.

Discussion

Burden of Disease

Genital herpes is an STI caused by 2 related viruses, HSV-1 and HSV-2. In adolescents and adults, genital infection often results in outbreaks of blisters (vesicles) in the area in and around the genitals and rectum. These blisters break and leave sores (ulcers) that are often painful. The first outbreak of genital herpes is usually the most painful and may be accompanied by flu-like symptoms, including fever, body aches, and swollen glands. Among persons who have a symptomatic first outbreak, 70% to 90% will have at least 1 more symptomatic outbreak within the first year, with an average of 4 outbreaks.^{8,9} Repeat outbreaks are usually shorter and less severe than the initial outbreak. Although the risk of transmission is higher during a symptomatic outbreak, persons with genital herpes can spread the infection to sexual partners even when they are asymptomatic. Studies suggest that up to 85% of persons who are found to be infected with HSV-2 and who report no prior symptoms of genital herpes have a symptomatic outbreak within 6 months of being tested. According to some experts, persons who receive education about genital herpes may be more likely to recognize and report its symptoms. If this is true, some persons who are considered "asymptomatic" may have actually experienced symptoms but not identified them as genital herpes.

There is currently no cure for genital herpes; once infection has occurred, the virus remains in a person for life. For this reason, the prevalence of infection increases with age. Data from the 2005-2010 National Health and Nutrition Examination Survey indicate that the prevalence of HSV-2 infection ranged from 1.2% in adolescents aged 14 to 19 years to 25.6% in adults aged 40 to 49 years.¹⁰ Overall, 15.7% of persons aged 14 to 49 years in the United States tested positive for HSV-2 infection between 2005 and 2010.¹⁰ These estimates, however, should be interpreted with caution; because of a lack of confirmatory testing, these data may overestimate the prevalence of HSV-2 infection. These data also may underestimate the overall prevalence of genital herpes, as they do not account for herpes infection caused by HSV-1. In the National Health and Nutrition Examination Survey, women were almost twice as likely to be infected with HSV-2 as men (20.9% vs 11.5%), in part because of anatomical factors that predispose women to infection.¹¹ Rates of HSV-2 infection also vary by race/ethnicity and geographical region and are higher in men who have sex with men.¹⁰

The herpes simplex virus may be transmitted from mother to infant during vaginal delivery. Among women with a prior history of symptomatic genital herpes, nearly 75% will have at least 1 recurrence during pregnancy and about 14% will have symptoms or clinical recurrence at the time of delivery.^{12,13} Evidence shows, however, that vertical transmission and subsequent severe neonatal HSV infection are most likely in pregnant women who develop the initial genital infection during pregnancy.^{14,15} The overall incidence of neonatal herpes is low.^{14,16} Older data from a 2006 study using a multistate pediatric inpatient discharge database estimated the incidence of neonatal HSV infection as 9.6 cases per 100 000 births (95% CI, 4.3-12.0).¹⁶ The most recent estimate of neonatal herpes incidence

comes from a large study in New York City of cases reported between 2006 and 2010. Using a clinical laboratory system, that study found 76 cases of neonatal HSV infection among approximately 571 000 infants—an estimated incidence rate of 13.3 cases per 100 000 live births.¹⁷ The study also found that of the 72% of cases for which HSV typing was done, infections were almost equally caused by HSV-1 and HSV-2 (28 vs 27 cases).¹⁷ Incidence rates are thought to vary by geographic region and race/ethnicity. In the multistate study, incidence rates were substantially higher in infants born to women covered by Medicaid (15.1 cases per 100 000 live births) vs private insurance (5.4 cases per 100 000 live births).^{16,18}

Approximately 45% of infants with neonatal HSV infection develop relatively mild skin, eye, or mucous membrane infections; 30% develop a central nervous system infection; and 25% develop disseminated disease.¹⁹ Four percent of infants with a central nervous system infection and 30% of infants with disseminated disease may die as a result.²⁰

Scope of Review

The USPSTF commissioned a systematic evidence review to examine the evidence on the accuracy, benefits, and harms of serologic screening for HSV-2 infection in asymptomatic adolescents and adults, including those who are pregnant.^{21,22} The evidence review also considered the effectiveness and harms of preventive medications and behavioral counseling interventions in asymptomatic populations to reduce future symptomatic episodes and transmission to susceptible sexual partners and infants.

Accuracy of Screening Tests

HerpeSelect (Focus Diagnostics), the most widely available serologic test for genital HSV-2 infection approved by the US Food and Drug Administration, has a pooled estimate of sensitivity of 99% (95% CI, 97%-100%) and a pooled estimate of specificity of 83% (95% CI, 72%-91%).²² A second test, the biokit HSV-2 Rapid Test (Biokit USA), has a pooled estimate of sensitivity of 84% (95% CI, 73%-91%) and specificity of 95% (95% CI, 93%-97%).²² In the general US population, the positive predictive value may be as low as 75% for the biokit test and as low as 50% for HerpeSelect. Western blot is considered to be the gold standard for the serologic diagnosis of herpes. Western blot test results can be obtained by sending a blood sample to a single research laboratory (University of Washington Clinical Virology Laboratory); however, this test is not widely available as a screening or confirmatory test for persons who screen positive for HSV-2 on one of the less-specific, commercially available serologic tests. No studies have examined the screening accuracy of serologic HSV tests in pregnant women. Serologic HSV tests may be clinically useful for persons with persistent undiagnosed genital symptoms and in other diagnostic settings.

Effectiveness of Early Detection and Treatment

Currently, there is no cure for genital HSV infection. Antiviral medications are generally used for the management of symptomatic outbreaks and for prevention in patients with a history of frequent symptomatic outbreaks. In studies, many persons identified with asymptomatic genital herpes (ie, they have been infected with HSV-2 and have never experienced symptoms) have a symptomatic outbreak within 6 months of testing. The increasing percentage of

genital herpes cases caused by HSV-1 also limits the potential benefit of serologic screening in asymptomatic persons. While HSV-1 infection can be detected through serologic tests, these tests cannot determine the site of HSV infection. Since HSV-1 can cause both oral and genital herpes infections, and oral herpes infection is very common, serologic tests for HSV-1 cannot be used to screen for asymptomatic genital herpes infection. The evidence is inadequate to determine if suppressive antiviral therapy reduces transmission of genital HSV infection between serodiscordant couples with an asymptomatic partner.

Pregnant adolescents and women with new or known history of genital HSV infection should be carefully observed during pregnancy. To reduce the chance of HSV transmission to the infant during delivery, women with active genital HSV lesions at the time of birth are usually offered the option of cesarean delivery. No studies have examined the effectiveness of antiviral therapy to decrease the risk for HSV transmission to pregnant women by an infected partner.

Potential Harms of Screening and Treatment

Serologic screening in asymptomatic persons will likely result in a large number of false-positive results. Given the limitations of currently available tests, 1 of 2 positive results may be false. Given the test characteristics of the most widely used serologic screening test for HSV-2 and a population infection prevalence of 15%, screening 10 000 persons would result in approximately 1485 true-positive and 1445 false-positive results. Confirmatory testing is not currently widely available and is only performed at a single research laboratory. There are social and emotional harms of receiving a false-positive result, in addition to the potential harms of unnecessary treatment with preventive antiviral medications.^{23,24} However, antiviral medications are generally considered to have few harms in nonpregnant adults.²¹

Estimate of Magnitude of Net Benefit

Based on the natural history of HSV infection, its epidemiology, and the available evidence on the accuracy of serologic screening tests, the USPSTF found adequate evidence to bound the potential benefits and harms and conclude with moderate certainty that the harms outweigh the benefits of serologic screening for genital HSV infection in asymptomatic adolescents and adults, including those who are pregnant.

Response to Public Comment

A draft version of this recommendation statement was posted for public comment on the USPSTF website from August 2 to August

29, 2016. The USPSTF reviewed and considered all comments received during this period. Several comments supported the USPSTF's analysis and conclusions; some comments noted that the recommendation is consistent with current clinical practice and advice from other organizations, including the CDC and the American College of Obstetricians and Gynecologists (ACOG). A few comments expressed concern that persons with asymptomatic genital herpes infection can (unknowingly) transmit the infection to sexual partners. While the USPSTF understands this concern, given the current lack of accurate, widely available serologic screening tests and the expected high rate of false-positive results that would occur with widespread screening in asymptomatic persons, the USPSTF continues to recommend against routine serologic screening in asymptomatic adolescents and adults. In addition, the USPSTF clarified its language about HSV-1 infection, noting that while HSV-1 infection can be identified by serologic tests, the tests cannot determine if the site of infection is oral or genital.

Update of Previous USPSTF Recommendation

This recommendation is consistent with and updates the 2005 USPSTF recommendation.²⁵ The current recommendation is based on substantial new evidence on the limited accuracy of serologic screening tests for genital HSV-2 infection and a small amount of new evidence on the benefits and harms of screening.

Recommendations of Others

The American Academy of Family Physicians,²⁶ ACOG,²⁷ and the CDC² do not recommend routine serologic screening for genital HSV infection in asymptomatic adolescents or adults. Diagnostic testing, however, in persons with recurrent atypical genital symptoms may be helpful. The CDC recommends consideration of serologic testing for HSV-2 in persons presenting for STI evaluation and for persons living with HIV infection.² The CDC also recommends consideration of screening for HSV infection in men who have sex with men and who are at high risk for HIV infection.²

The American Academy of Family Physicians,²⁶ ACOG,²⁸ and the CDC² do not recommend routine serologic screening for genital HSV infection in pregnant adolescents and women. The CDC² and ACOG²⁸ recommend asking pregnant women about history of genital HSV infection and consideration of cesarean delivery for women with prodromal symptoms or active genital lesions during labor to reduce the risk of neonatal HSV infection. The CDC recommends that women with recurrent genital herpes during pregnancy be offered suppressive therapy at 36 weeks of gestation.²

ARTICLE INFORMATION

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