US Preventive Services Task Force | Recommendation Statement

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Screening for Syphilis Infection in Pregnant Women
US Preventive Services Task Force Reaffirmation Recommendation Statement

US Preventive Services Task Force

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Abstract

Importance Untreated syphilis infection in pregnant women can be transmitted to the fetus (congenital syphilis) at any time during pregnancy or at birth. Congenital syphilis is associated with stillbirth, neonatal death, and significant morbidity in infants (eg, bone deformities and neurologic impairment). After a steady decline from 2008 to 2012, cases of congenital syphilis markedly increased from 2012 to 2106, from 8.4 to 15.7 cases per 100 000 live births (an increase of 87%). At the same time, national rates of syphilis increased among women of reproductive age.

Objective To update the US Preventive Services Task Force (USPSTF) 2009 recommendation on screening for syphilis infection in pregnant women.

Evidence Review The USPSTF commissioned a reaffirmation evidence update to identify new and substantial evidence sufficient enough to change its prior recommendation. Given the established benefits and practice of screening for syphilis in pregnant women, the USPSTF targeted its evidence review on the direct benefits of screening on the prevention of congenital syphilis morbidity and mortality and the harms of screening for and treatment of syphilis infection in pregnant women.

Findings Using a reaffirmation process, the USPSTF found that accurate screening algorithms are available to identify syphilis infection. Effective treatment with antibiotics can prevent congenital syphilis and significantly decrease adverse pregnancy outcomes, with small associated harms, providing an overall substantial health benefit. Therefore, the USPSTF reaffirms its previous conclusion that there is convincing evidence that screening for syphilis infection in pregnant women provides substantial benefit.

Introduction

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 early screening for syphilis infection in all pregnant women (A recommendation) (**Figure 1**).

Figure 1. USPSTF Grades and Levels of Evidence

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USPSTF indicates US Preventive Services Task Force.

Rationale

Importance

Syphilis is an infection that is primarily sexually transmitted. Untreated syphilis infection in pregnant women can also be transmitted to the fetus (congenital syphilis) at any time during pregnancy or at birth. Congenital syphilis is associated with stillbirth, neonatal death, and significant morbidity in infants (eg, bone deformities and neurologic impairment).[1] After a steady decline from 2008 to 2012, cases of congenital syphilis markedly increased from 2012 to 2016, from 8.4 to 15.7 cases per 100 000 live births (an increase of 87%).[2] At the same time, national rates of syphilis increased among women of reproductive age.

Reaffirmation

In 2009, the USPSTF reviewed the evidence on screening for syphilis infection in pregnant women and issued an A recommendation.[3] The USPSTF has decided to use a reaffirmation deliberation process to update this recommendation. The USPSTF uses the reaffirmation process for well-established, evidence-based standards of practice in current primary care practice for which only a very high level of evidence would justify a change in the grade of the recommendation.[4] In its deliberation of the evidence, the USPSTF considers whether the new

The USPSTF found adequate evidence that screening tests can accurately detect syphilis infection in pregnant women.

Benefits of Detection and Early Treatment

The USPSTF found convincing evidence that early universal screening for syphilis infection in pregnant women reduces the incidence of congenital syphilis and the adverse outcomes of pregnancy associated with maternal infection.

Harms of Detection and Early Treatment

Screening for syphilis infection in pregnant women may result in potential harms, including false-positive results that require clinical evaluation, anxiety, and harms of treatment with antibiotic medications. However, the USPSTF concluded that these harms of screening are no greater than small.

USPSTF Assessment

Using a reaffirmation process,[4] the USPSTF concludes with high certainty that the net benefit of screening for syphilis infection in pregnant women is substantial.

Clinical Considerations

Patient Population Under Consideration

This recommendation applies to all pregnant women (**Figure 2**).

Figure 2. Clinical Summary: Screening for Syphilis Infection in Pregnant Women

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USPSTF indicates US Preventive Services Task Force.

Screening Intervals

All pregnant women should be tested for syphilis as early as possible when they first present to care. If a woman has not received prenatal care prior to delivery, she should be tested at the time she presents for delivery. In most cases of congenital syphilis, pregnant women received prenatal care but were not screened and treated for syphilis early enough during the pregnancy to prevent transmission to the fetus.

The USPSTF found no new studies that examined the effectiveness of repeated testing for syphilis during pregnancy. The Centers for Disease Control and Prevention (CDC)[5] and joint guidelines from the American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG)[6] endorse repeat screening. Specifically, these groups recommend that women at high risk for syphilis be rescreened early in the third trimester (at approximately 28 weeks of gestation) and again at delivery. Women at high risk for syphilis

repeat screening after exposure to an infected partner.[6] Clinicians should be aware of the prevalence of syphilis infection in the communities they serve.[7] Most states mandate screening for syphilis in all pregnant women at the first prenatal visit, and some mandate screening at the time of delivery.[8]

Screening Tests

Syphilis infection is caused by the *Treponema pallidum* bacteria. Current screening tests for syphilis rely on detection of antibodies to the infection rather than direct detection of the bacteria. Screening for syphilis infection is a 2-step process. Traditionally, screening involved an initial "nontreponemal" antibody test (ie, Venereal Disease Research Laboratory test or rapid plasma reagin [RPR] test) to detect biomarkers released from damage caused by syphilis infection, followed by a confirmatory "treponemal" antibody detection test (ie, fluorescent treponemal antibody absorption or *T pallidum* particle agglutination test). Because nontreponemal tests are complex, a reverse sequence screening algorithm has been developed in which an automated treponemal test (such as an enzyme-linked, chemiluminescence, or multiplex flow immunoassay) is performed first, followed by a nontreponemal test. If the test results of the reverse sequence algorithm are discordant, a second treponemal test (preferably using a different treponemal antibody) is performed. The USPSTF found no studies comparing the false-positive rate of the traditional screening algorithm with that of the reverse sequence screening algorithm among pregnant women. The CDC has provided more detailed guidance on testing for and treatment of sexually transmitted diseases, including syphilis.[9]

Treatment

In 2015, the CDC recommended parenteral benzathine penicillin G for the treatment of syphilis in pregnant women.[5] Evidence on the efficacy or safety of alternative antibiotic medications for pregnant women and the fetus is very limited; therefore, women who report a penicillin allergy should be evaluated and, if found allergic, desensitized and treated with penicillin. Because the CDC updates its recommendations regularly, clinicians are encouraged to consult the CDC website for the most up-to-date information.[9]

Additional Approaches to Prevention

Trends in congenital syphilis incidence rates are closely related to trends in primary and secondary syphilis infection rates among all women. Screening for syphilis in nonpregnant populations is an important public health approach to preventing the sexual transmission of syphilis and subsequent vertical transmission of congenital syphilis. The USPSTF recommends screening for syphilis in nonpregnant adolescents and adults at increased risk for infection.[10]

Useful Resources

The USPSTF has made recommendations on screening for other sexually transmitted infections, including chlamydia and gonorrhea,[11] hepatitis B virus,[12] genital herpes,[13] and HIV.[14] National-, state-, and county-level data on syphilis infection rates are also available from the CDC.[2]

Other Considerations

Research Needs and Gaps

Although the benefits of screening for syphilis infection in pregnant women to prevent congenital syphilis are well

to help identify optimal rescreening intervals and populations to rescreen during pregnancy, could help inform implementation of screening programs. Studies on treatment options besides penicillin could also be helpful.

Discussion

Burden of Disease

Although national rates of syphilis infection among pregnant women are not currently available, the incidence rates of primary and secondary syphilis infection among women and congenital syphilis among infants have been increasing, despite consistent recommendations and legal mandates to screen for syphilis in pregnant women.[2] In 2012, there were 0.9 cases of primary and secondary syphilis infection per 100 000 women and 8.4 cases of congenital syphilis per 100 000 live births. In 2016, the case rate had increased to 1.9 cases of primary and secondary syphilis infection per 100 000 women and 15.7 cases of congenital syphilis per 100 000 live births.[15]

Late or limited prenatal care has been associated with congenital syphilis.[2] Although nearly 70% of infants with congenital syphilis are born to mothers who received prenatal care, detection and treatment of maternal syphilis often occurs too late to treat the fetus and prevent congenital syphilis.[15] Recent data suggest that while screening rates for syphilis infection are generally high, the proportion of women screened earlier in pregnancy remains low (eg, 20% of women are screened only at the time of delivery).

Primary, secondary, and congenital syphilis rates differ by race/ethnicity. Case rates of primary, secondary, and congenital syphilis are higher in black, American Indian/Alaska Native, and Hispanic populations than in white populations.[2] Syphilis rates also differ by geography, with generally higher rates of primary, secondary, and congenital syphilis in the Western and Southern states and lower rates in the Northeastern and Midwest states. However, clinicians should be aware of the prevalence of syphilis infection in their community, as rates can vary.[2]

Syphilis can be transmitted to the fetus during all stages of maternal infection, although the risk is highest with primary and secondary maternal syphilis infection, which is why detection early in pregnancy is important.[5,16,17] Untreated syphilis infection during pregnancy greatly increases the risk of adverse pregnancy outcomes. A 2013 systematic review of 6 case-control studies found that compared with pregnancies that did not have maternal syphilis infection, untreated maternal syphilis infection during pregnancy was associated with an absolute difference of 21% for stillbirth or fetal loss, 9% for neonatal death, and 5% for prematurity or low birth weight.[18] Although infants born with congenital syphilis are often asymptomatic at birth, some may develop signs within the first several weeks of life, including rash, hemorrhagic rhinitis, lymphadenopathy, hepatosplenomegaly, and skeletal abnormalities.[19] Additional sequelae include anemia, neurologic impairment such as blindness or deafness, and meningitis.

Scope of Review

To reaffirm its 2009 recommendation on screening for syphilis in pregnant women, the USPSTF commissioned a reaffirmation evidence update. The aim of this update is to identify substantial new evidence that is sufficient enough to change the prior recommendation. Given the established benefits and practice of screening for syphilis in pregnant women, the USPSTF targeted its evidence review to the direct benefits of screening on the prevention of congenital syphilis morbidity and mortality and the harms of screening for and treatment of syphilis infection in pregnant women.

The USPSTF found no new evidence inconsistent with the benefits of screening for syphilis infection in pregnant women. Evidence from observational studies demonstrates fewer adverse pregnancy outcomes among pregnant women screened and treated for syphilis infection compared with pregnant women not treated. In particular, treatment appears to be more beneficial when provided earlier rather than later in pregnancy.[16] A 2014 systematic review of 54 observational studies found that incidence of congenital syphilis, preterm birth, low birth weight, stillbirth, and neonatal death was dramatically reduced in women treated for syphilis during pregnancy compared with women who had untreated syphilis.[20] However, only a slight reduction in stillbirth or fetal loss was observed in women who were only treated in the third trimester, compared with women who had untreated syphilis. Extended follow-up of a study previously considered by the USPSTF for its 2009 recommendation[3] reported on the effects of implementing a free syphilis screening and treatment program for all pregnant women living in Shenzhen, China, from 2002 to 2012 (n = 2 441 237).[21] During follow-up, screening uptake increased from 89.8% to 97.2%, and the congenital syphilis case rate decreased from 109.3 to 9.4 cases per 100 000 live births. During the same time, the incidence of adverse pregnancy outcomes decreased from 42.7% to 19.2%, and the incidence of stillbirth or fetal loss decreased from 19.0% to 3.3%. The USPSTF found this evidence to be consistent with findings from its previous evidence review.[22]

Potential Harms of Screening and Treatment

Potential harms of screening for and treatment of syphilis infection include false-positive results that require clinical evaluation, unnecessary anxiety to the patient, and harms of antibiotic medication use.[16] Consistent with previous reviews, the current, targeted review identified 5 studies that reported on false-positive rates of various screening tests[23-27] and 1 study that reported on false-negative RPR test results.[28] Overall, these studies demonstrate that false-positive results with chemiluminescence or enzyme-linked immunoassay in pregnant women are common (false-positive rates ranged from 0% to 88.2%)[23-27] and that false-negative RPR test results can result from undiluted serum with high titers (known as the prozone effect).[28] Because of the high potential for false-positive results with individual tests, a 2-step screening algorithm is recommended. The USPSTF found no studies that reported on the false-positive rate of the traditional or reverse sequence screening algorithm in pregnant women. Harms of treatment include rare adverse drug-related effects, such as anaphylaxis attributable to penicillin allergy and the Jarisch-Herxheimer reaction (febrile reaction with headache, myalgia, and other symptoms), which may occur within the first 24 hours after any type of syphilis therapy. The USPSTF found no studies that reported on harms to the fetus from treatment of syphilis infection.

Estimate of Magnitude of Net Benefit

The USPSTF considered the evidence using a reaffirmation process and found that accurate screening algorithms are available to identify syphilis infection. Effective treatment with antibiotics can prevent congenital syphilis and significantly decrease adverse pregnancy outcomes, with small associated harms, providing an overall substantial health benefit. Therefore, the USPSTF reaffirms its previous conclusion that there is convincing evidence that screening for syphilis infection in pregnant women provides substantial net benefit.

Response to Public Comment

A draft version of this recommendation statement was posted for public comment on the USPSTF website from February 6, 2018, to March 5, 2018. Most comments supported the recommendation statement. Several comments requested clearer guidance about the timing of initial syphilis screening (as early as possible after the

concerns. Several comments requested changes that are outside the scope of the USPSTF or not consistent with its methods and processes, and so no changes were made in response. These suggested changes included endorsement of guidelines from other organizations and discussion of evidence not considered in the USPSTF's deliberation on this recommendation. Some comments suggested additional citations; these were reviewed by the USPSTF but none met inclusion criteria.

Reaffirmation of Previous USPSTF Recommendation

This recommendation is a reaffirmation of the USPSTF 2009 recommendation statement.[3] In 2009, the USPSTF reviewed the evidence on screening for syphilis infection in pregnant women and found that the benefits of screening substantially outweighed the harms.[22] For the current recommendation, the USPSTF commissioned a targeted review[16] to look for substantial new evidence on the benefits and harms of screening and determined that the net benefit of screening for syphilis infection in pregnant women continues to be well established. The USPSTF found no new substantial evidence that could change its recommendation and, therefore, reaffirms its recommendation to screen for syphilis infection in all pregnant women.

Recommendations of Others

This recommendation statement is consistent with those of other professional and public health organizations. The CDC recommends screening for syphilis infection in all pregnant women at their first prenatal visit.[5] Joint guidelines from AAP and ACOG recommend screening for syphilis infection in pregnant women as early as possible in pregnancy.[6] The CDC, AAP, and ACOG also recommend repeat screening at 28 weeks of gestation and again at delivery in high-risk women. Women at high risk for syphilis infection include those living in high-prevalence communities, those living with HIV, and those with a history of incarceration or commercial sex work.[10] AAP and ACOG also recommend repeat screening after exposure to an infected partner.[6] The American Academy of Family Physicians recommends screening for syphilis infection in all pregnant women.[29]

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