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Clinical Expert Series CME

Syphilis in Pregnancy

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Despite a national plan to eliminate syphilis by 2005, recent trends have reversed previously achieved progress in the United States. After a nadir between 2000 and 2013, rates of primary and secondary syphilis among women and congenital syphilis rose by 172% and 185% between 2014 and 2018, respectively. Screening early in pregnancy, repeat screening in the third trimester and at delivery among women at high risk, adherence to recommended treatment regimens, and prompt reporting of newly diagnosed syphilis cases to local public health authorities are strategies that obstetrician–gynecologists can employ to fight the current epidemic. In this report, clinical manifestations and management of syphilis in pregnancy are reviewed, and both traditional and reverse sequence screening algorithms are reviewed in detail in the context of clinical obstetrics.

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A PUBLIC HEALTH CRISIS

Syphilis is the clinical disease resulting from infection with the spirochete *Treponema pallidum* subspecies *pallidum*. Transmitted through sexual contact and across the placenta during pregnancy, the organism causing venereal and congenital syphilis has been around for more than 500 years.[1] Maternal syphilis is associated with a 21% increased risk for stillbirth, 6% increased risk for preterm delivery, and 9% increased risk for neonatal death.[2] Furthermore, syphilis is strongly associated with acquisition of human immunodeficiency virus (HIV) infection.[3,4] Despite near elimination of syphilis after the discovery of penicillin as a singularly effective therapy in the 1940s, the pathogen has remained a significant public health concern.[5]

In 1999, the Centers for Disease Control and Prevention (CDC) published a national plan to eliminate syphilis by 2005, citing the lowest rates ever reported.[6] After a nadir when rates of primary and secondary syphilis among women fluctuated between 0.8 and 1.7 cases per 100,000 females between 2000 and 2013, rates rose steadily after an initial increase seen in men beginning in 2000.[7] Between 2014 and 2018, primary and secondary syphilis in women increased by 172% (to 3.0 cases per 100,000 females) in the United States, and congenital syphilis rates have paralleled this rise, increasing by 185% (to 33.1 cases per 100,000 live births) in the same years.[7] In recent years, the rise has been seen primarily in the World Health Organization Region of the Americas, including North America, Central America and South America, although there is concern that worldwide penicillin shortages may herald a major global trend.[8,9] Significant racial disparities persist in the United States, with the rate of primary and secondary syphilis in black individuals almost five times the rate among white individuals in 2018.[7]

Proposed factors contributing to higher numbers of congenital syphilis in recent years include lack of access to prenatal care owing to untreated mental health and substance use disorders, recent immigration to the United States, or unstable housing.[10] More broadly, proposed reasons for general upward trends include limited access to early prenatal care, poor compliance with national screening guidelines among

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Table 1. Clinical Manifestations, Etiology, and Management of Primary, Secondary, Latent, Neurosyphilis, and Congenital Syphilis

	Symptomatic Infection		Latent Infection	
Stage	**Primary**	**Secondary**	**Early***	**Late†**
Timing of diagnosis	3 wk after infection	Usually 4–10 wk after chancre appearance or 2–4 mo after initial infection	Less than 1 y after initial infection	More than 1 y after initial infection
Clinical findings	Painless chancre Localized lymphadenopathy Atypical findings: multiple chancres, painful or pruritic lesions, coinfection with genital herpes or other STI	Skin rash (90%)—maculopapular, annular, palms and soles Mucosal lesions—oral mucous patches, genital condyloma lata (10–20%) Primary chancre may recur Generalized lymphadenopathy, alopecia Systemic symptoms—malaise, arthralgia, fever Rare: hepatitis, nephrotic syndrome	Asymptomatic Secondary lesions may recur in 25%	Asymptomatic
Etiology of clinical findings	Spirochetes replicate in chancre at site of inoculation	Hematogenous dissemination from chancre Replication of spirochetes at lower body surface temperatures Systemic immune response manifests internally	Intermittent seeding of bloodstream with spirochetes	Immune response ongoing, often not able to clear all organisms
Clinical course without treatment	Cell-mediated, delayed-type hypersensitivity reaction leads to resolution within 4–6 wk	Resolution of lesions within 1–6 mo Often incomplete clearance of organisms	Secondary lesions may recur in 25% Gradual progression to late infection	15–40% develop tertiary syphilis
Treatment	2.4 million units IM benzathine penicillin G Some recommend 2 weekly doses			2.4 million units IM benzathine penicillin G in 3 weekly doses
Follow-up after treatment	Repeat RPR if re-exposure suspected Repeat RPR at 28–32 wk of gestation and at delivery Arrange follow-up for repeat RPR in 6–12 mo after initial treatment			

RPR, rapid plasma reagin; HIV, human immunodeficiency virus; STI, sexually transmitted infection; CSF, cerebrospinal fluid; CNS, central nervous system; IM, intramuscular; IV, intravenous.

* Defined as syphilis, early nonprimary nonsecondary for surveillance purposes.

† Defined as unknown duration or late syphilis for surveillance purposes.

health care providers, reduced public awareness and public health funding for sexually transmitted infection (STI) prevention over the past decade, redirection of funding from comprehensive sexual education to abstinence-only programs for youth, and increased high-risk behaviors in populations with access to effective HIV preventive treatments.[11–13] Although risk factors such as multiple sexual partners or concomitant STI may be presumed, a recent examination of risk factors among pregnant women diagnosed with syphilis between 2012 and 2016 from the National Notifiable Disease Surveillance system demonstrated that almost half lacked traditional risk factors for the infection.[14] Addressing the current STI crisis will require a comprehensive approach with collaboration between the CDC, national political leaders, state and local public health authorities, and physicians on the front lines. As primary care providers for pregnant women, obstetrician–gynecologists (ob-gyns) should be familiar with the history of syphilis in this country,

Neurosyphilis		Congenital	
Early	Late	Early	Late
May occur with any stage; more common with high RPR titer or HIV	Decades after initial infection	Younger than age 2 y	Older than age 2 y
Aseptic meningitis Cranial nerve palsies—blindness, vertigo, deafness Ocular involvement—retinitis, uveitis Meningovascular syphilis (years after infection): myelopathy, nerve palsies, stroke	General paresis—progressive dementia, psychiatric symptoms Tabes dorsalis—ataxia, impaired proprioception, areflexia, Argyll Robertson pupils May coexist with findings of tertiary syphilis	Growth restriction, hydrops fetalis, stillbirth Findings similar to secondary syphilis—rash, hepatomegaly, snuffles, nerve palsies, seizures Laboratory—anemia, thrombocytopenia, hepatitis Bone abnormalities Pneumonia	Abnormal teeth Interstitial keratitis, retinitis Cranial nerve palsies Bone or joint deformations—saddle nose, frontal bossing, saber shin, high palate
Acute immune reaction within CSF Vasculitis of small and medium-size arteries in CNS	Chronic immune reaction to spirochetes; destruction of neural tissue	Transplacental transmission; subacute systemic inflammatory response	Transplacental transmission; chronic immune reaction to spirochetes; destruction of tissue
Worsening meningitis or gradual progression of neurologic symptoms	Slow decline in neurologic function, poor prognosis	Progressive worsening with high mortality rate	Chronic, progressive lesions
Aqueous crystalline penicillin G 18–24 million units/d IV for 10–14 d in consultation with specialists		Aqueous crystalline penicillin G	Aqueous crystalline penicillin G
Arrange repeat CSF examination in 6 mo in consultation with specialists Arrange follow-up for repeat RPR in 6 mo		Follow-up examination and serologic testing in consultation with pediatric specialists	

and be prepared with up-to-date knowledge regarding screening, diagnosis, and treatment recommendations for pregnant women.

The aims of this report are to review the pathophysiology, diagnosis, and current management of syphilis in pregnancy in light of recent changes in staging and testing paradigms, to provide historical context to the current public health crisis, and to discuss future directions in syphilis research.

CLINICAL MANIFESTATIONS OF SYPHILIS

As a chronic infection, syphilis is known for its multiple stages, both symptomatic and asymptomatic. The myriad manifestations of this "Great Masquerader" are well-described, are not altered by pregnancy status, and may be best understood within the context of the human immune response to syphilis (Table 1). This extracellular spirochete is unique in its stimulation and evasion of the host immune system: although protective immunity does not develop after treatment, an untreated syphilis infection is generally protective against *T pallidum* superinfection for several decades.[15]

PRIMARY SYPHILIS

T pallidum efficiently traverses mucus membranes or breaks in intact skin to infect the host. Primary syphilis, which occurs at a median of 3 weeks after initial infection, is characterized by a painless chancre at the

site of inoculation with surrounding localized lymphadenopathy (Fig. 1). Within the chancre, densely packed extracellular spirochetes replicate, and lesions are highly infectious.[16] Because the site of the chancre may be located on the cervix or vagina, lesions may be missed without a thorough pelvic examination. Some lesions may mimic or coexist with other infections such as genital herpes, and clinicians should be attuned to possible atypical symptoms of pain or pruritis. In an immunocompetent host, primary infection induces a cell-mediated, delayed-type hypersensitivity reaction that results in local clearance of organisms and resolution of the chancre within 4–6 weeks, even if untreated.[17] Women with HIV infection may be more likely to experience multiple chancres, or chancres that persist after secondary lesions appear.[18] Without treatment, inadequate clearance results in systemic dissemination of organisms leading to secondary manifestations of disease approximately 6–8 weeks after resolution of the chancre.

SECONDARY SYPHILIS

Secondary syphilis occurs in approximately 25% of untreated women, and clinical symptoms usually manifest between 4 and 10 weeks after the initial appearance of the chancre. This clinical stage is characterized by the classic hallmarks of diffuse maculopapular skin rash, mucosal lesions (oral lesions including mucous patches[19] and genital condyloma lata) and generalized lymphadenopathy (Fig. 2). The cutaneous manifestations of secondary syphilis, occurring in up to 90% of women, result from disseminated spirochetes replicating at lower body surface temperatures (Fig. 3). A chancre may recur during secondary syphilis, and mucosal lesions (both oral and genital) are highly contagious, conferring an approximately 50–60% risk of transmission to sexual contacts. Some women may describe systemic symptoms such as malaise, arthralgias, and fevers. In rare cases, hepatitis and nephrotic syndrome may occur. Systemic symptoms are caused by a widespread–albeit ineffective–immune response.[20] Although both innate and adaptive host immune responses are able to resolve the lesions of secondary syphilis, they are unable to completely eradicate the bacteria, which employ several strategies for host immune evasion. These include maintenance of a smooth outer membrane with few exposed proteins, and a programmed genetic alteration of these outer membrane proteins to foil the host's antibody response.[21–23] Manifestations of secondary syphilis resolve in approximately 1–6 months regardless of treatment, and typically resolve within a few weeks after adequate syphilotherapy.

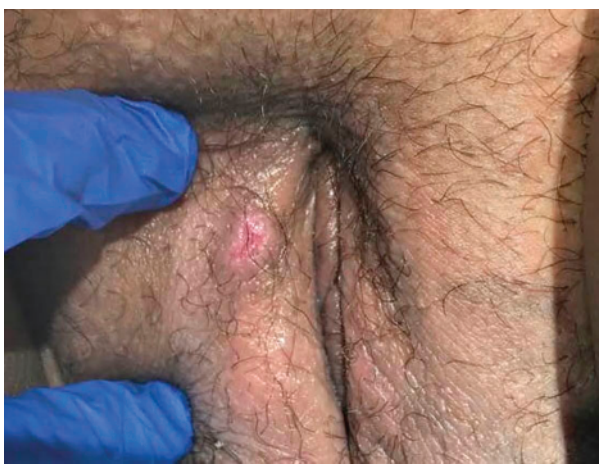

Fig. 1. Vulvar chancre of primary syphilis. Image courtesy of Dr. Alejandra Perez-Moore. Used with permission.
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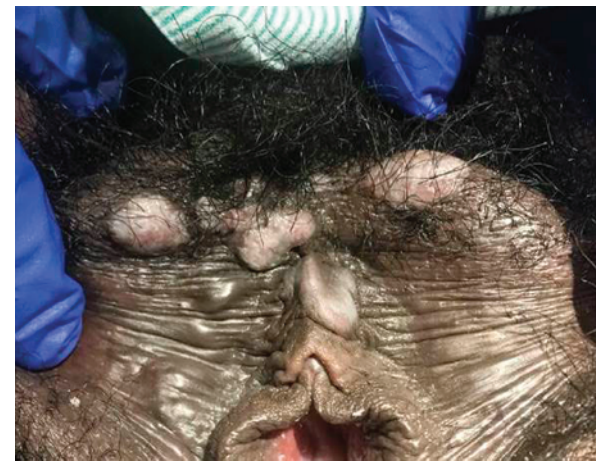

Fig. 2. Vulvar condyloma lata of secondary syphilis. Image courtesy of Dr. Edward Wells. Used with permission.
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LATENT SYPHILIS

Latent syphilis is characterized by positive diagnostic testing in a patient without objective findings consistent with clinical syphilis infection. Clinically, latent syphilis is divided into early and late (or unknown duration) latent stages, depending on the timing of initial infection based on a detailed history of exposure and reported symptoms. In 2018, the CDC revised the surveillance nomenclature for "early latent syphilis" to "syphilis, early nonprimary nonsecondary" to clarify that certain clinical manifestations such as neurosyphilis may occur during any stage.[24] From a clinical perspective, however, the name still represents infection which occurred within the

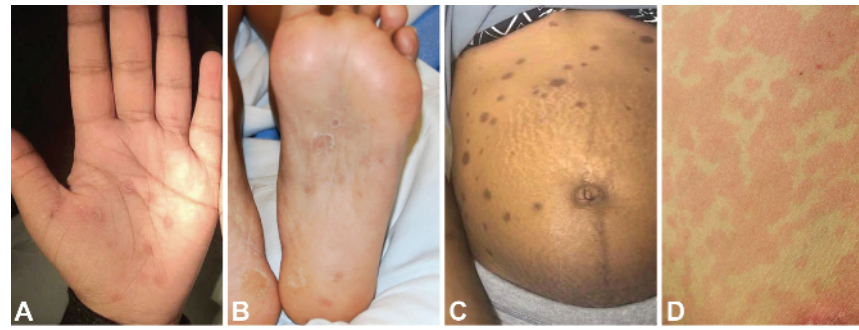

Fig. 3. Cutaneous rashes of secondary syphilis. These classically involve the palms (**A**) and soles (**B**) and may be more circumscribed (**C**) or diffusely maculopapular (**D**). Images courtesy of Drs. Amanda Zofkie, Sophia Cline, and Eddie McCord. Used with permission.

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previous 12 months, but without obvious primary or secondary lesions at the time of clinical diagnosis (Table 1). In a woman with early latent syphilis diagnosed within 12 months of initial infection, secondary lesions may recur in 25% of patients, and neurologic symptoms may occur any time during latent disease (see "Neurosyphilis"). In late latent syphilis, now known as "unknown duration or late syphilis" from a surveillance perspective, infection duration is either unknown or greater than 1 year. Late latent syphilis is characterized by intermittent bacteremia, which may seed the placenta, and carries an approximate 10% risk of fetal infection during pregnancy.[17] The absence of clinical manifestations represents a shift in the balance between treponemal replication and immune activation to hold the infection in check. If an appropriate cell-mediated immune response by the host is maintained, the infection may remain latent, or suppressed.[20] However, if immunity wanes, mechanisms to evade host immunity allow bacteria to persist in multiple sites and eventually result in the late manifestations of disease, known as *tertiary syphilis.*

TERTIARY SYPHILIS

Tertiary syphilis, which occurs in up to 40% of individuals with untreated syphilis, refers to benign gummas and cardiovascular syphilis, but not to neurosyphilis, and is rare in a reproductive-aged population. Coinfection with HIV, particularly in patients with significant immunosuppression, is associated with prolongation of symptoms in early infection and more rapid progression to tertiary syphilis. Symptoms such as cutaneous nodules, gummas, and vascular aneurysms are a result of a chronic inflammatory reaction by the immune system which attempts, unsuccessfully, to clear persistent spirochetes.

NEUROSYPHILIS

Neurologic manifestations of syphilis infection may occur at any time during the course of infection, and can be divided into either early or late neurosyphilis. Early neurologic involvement, which may include meningitis, uveitis or retinitis, or stroke-like symptoms, occurs in approximately 1% of patients with secondary syphilis, and is less frequent in primary or early latent disease.[25] Late neurosyphilis occurs a decade or more after initial diagnosis, and may occur along with other manifestations of tertiary syphilis.

CONGENITAL SYPHILIS IN THE NEONATE

Congenital syphilis may result from maternal syphilis infection before or during pregnancy. Risk of fetal infection is related to the stage of maternal infection: congenital syphilis occurs in approximately 50–80% of women with untreated primary, secondary, or early latent syphilis, compared with approximately 10% of women with late latent syphilis. Although transplacental transmission of *T pallidum* can occur at any time during gestation, it occurs with increasing frequency as gestation advances. The risk of transmission decreases with increasing time since primary or secondary infection and is reported to be only 2% after 4 years. Syphilitic stillbirths are included as cases of congenital syphilis for national reporting purposes.[7]

Clinical manifestations of congenital syphilis are divided into two characteristic syndromes, known as *early congenital syphilis* and *late congenital syphilis.* Early congenital syphilis is diagnosed in the first 2 years of life and may involve clinical symptoms similar to those in adult secondary syphilis. Classically, hepatosplenomegaly, desquamating skin rash, rhinitis ("snuffles"), anemia, thrombocytopenia, and osteochondritis may be observed (Fig. 4).[26] Children with infection may also be asymptomatic at birth, but years later develop sequelae of late congenital syphilis. Diagnosed after 2 years of life, late congenital syphilis may be characterized by notched teeth (Hutchinson's teeth), deafness, and interstitial keratitis of the eye; all three together are known as *Hutchinson's Triad.* Central nervous system involvement with developmental delay, hydrocephalus, seizures, and nerve palsies, as

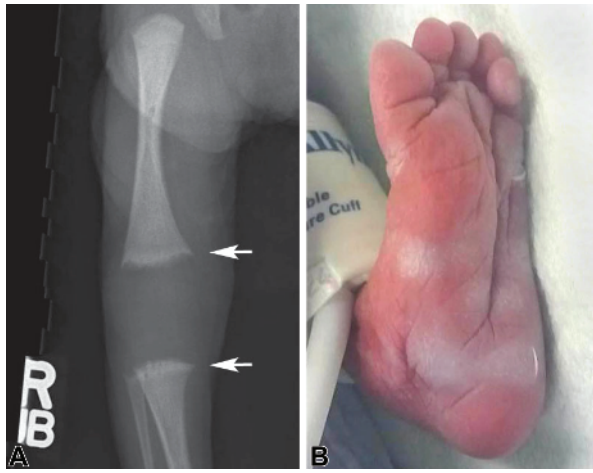

Fig. 4. Congenital syphilis in a neonate with radiographic evidence of osteochondritis (**A**) and desquamating skin rash (**B**).

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well as bone deformities resulting from long-term inflammation and skeletal damage, may occur.

Most neonates with infection are born without overt clinical evidence of congenital syphilis and may develop stigmata of syphilis over time, when follow-up and treatment are more difficult. Additionally, definitive diagnosis of congenital syphilis is challenging for the same reasons that diagnosis in adults remains elusive. Public health surveillance case definitions of congenital syphilis are intentionally broad, and both confirmed and probable cases (neonates born to inadequately treated mothers or those with reactive serum nontreponemal tests and physical, radiographic, or cerebrospinal fluid [CSF] abnormalities consistent with syphilis) are reported to the CDC.[24]

PLACENTAL MANIFESTATIONS OF SYPHILIS INFECTION

In a woman with untreated syphilis, the placenta may have gross and histopathologic characteristics of *T pallidum* infection. On gross examination, the placenta appears large, pale, and hydropic. On microscopic examination, terminal villi appear enlarged and densely cellular, with evidence of chronic villitis.[27] Villi demonstrate an abundance of Hofbauer cells, placental macrophages which are thought to play a role in regulation of normal pregnancy as well as in the response to congenital infection.[28,29] Umbilical cord sections demonstrate necrotizing funisitis, characterized by perivascular rings of necrotic debris surrounding the large vessels (Fig. 5). *T pallidum* may be detected by immunohistochemistry in either placenta or umbilical cord specimens.

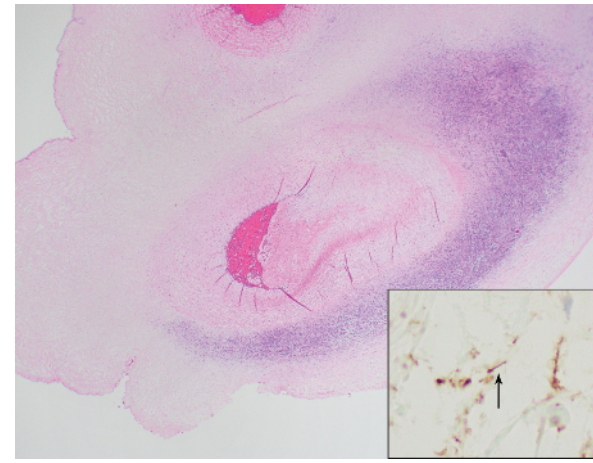

Fig. 5. Cross-section of an umbilical cord from a congenital syphilis case demonstrates necrotizing funisitis, which is characterized by rings of necrotic debris (*purple*) surrounding large vessels; *T pallidum* (*arrow, inset*) detected by immunohistochemistry staining of the umbilical cord. Photomicrographs courtesy of Dr. Rebecca Collins. Used with permission.

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PRENATAL SCREENING FOR SYPHILIS

All pregnant women should be screened for syphilis at the first prenatal visit or at first presentation to care.[30–32] Additionally, testing for syphilis is recommended as part of the evaluation for stillbirth.[33] Screening and treatment early in pregnancy is associated with decreased incidence of congenital syphilis, preterm birth, low birth weight, stillbirth, and neonatal death.[34,35] Repeat screening in the early third trimester, between 28 and 32 weeks of gestation, and again at delivery is recommended in women at high risk for syphilis or who live in areas with high syphilis prevalence.[30,31] State laws differ with regard to required timing and frequency of testing, but, overall, more than 80% of states require syphilis screening at the initial prenatal visit and some require additional testing in the third trimester and at delivery.[36] A list of prenatal syphilis screening requirements by state is available at https://www.cdc.gov/std/treatment/syphilis-screenings-2018.htm. In some states, providers who fail to abide by syphilis screening laws may be subject to civil or criminal liabilities.[36,37] In recent years, some states, including Texas, have added additional screening requirements to address the rise in congenital syphilis cases.[38] Clinicians should familiarize themselves with syphilis prevalence in their communities and with current local and state laws for screening and reporting STIs. Women who test positive for syphilis should be offered HIV testing if not performed simultaneously with the positive syphilis test.

DIAGNOSIS AND THE QUEST FOR A TEST: DIRECT DETECTION METHODS

Diagnosis of syphilis has challenged clinicians, particularly in the past century, owing to certain inherent properties of this "stealth pathogen."[22] In a laboratory, the organism is difficult to stain (hence the name *Treponema* "pallidum," or pale), replicates slowly, and is completely dependent on a mammalian host for sustained growth, making it difficult to cultivate in a laboratory setting.[17,39] Indeed, the gold standard for diagnosis has historically been rabbit infectivity testing, which requires live rabbits for cultivation and direct detection. This method is highly sensitive, but impractical outside of a research protocol. Unlike other microbes, the helical structure of *T pallidum* consists of an outer membrane, which displays few proteins that can be targeted for diagnostic purposes in the laboratory or by the immune system, and its narrow width prevents direct visualization with ordinary light microscopy, instead requiring darkfield microscopy, which is not readily available in many outpatient settings.[40,41] As a result, so-called direct detection methods (ie, darkfield microscopy, polymerase chain reaction, and direct fluorescent antibody for *T pallidum*) allow identification of *T pallidum* from a clinical lesion, but these methods have limitations that prevent widespread use in clinical settings (Box 1). Some pathology laboratories offer immunohistochemistry of pathologic specimens to directly detect spirochetes in pathologic samples such as placenta or autopsy tissues.

Box 1. Direct and Indirect (Serologic) Diagnostic Tests for Syphilis

Direct-detection methods

- Animal inoculation (rabbit infectivity testing)
- Darkfield microscopy
- Polymerase chain reaction
- Direct fluorescent antibody
- Immunohistochemistry

Serologic tests

- Nontreponemal tests
  - Rapid plasma reagin
  - Venereal disease research laboratory
- Treponemal tests
  - Indirect fluorescent-antibody
  - Microhemagglutination assay
  - *Treponema pallidum* particle agglutination assay
  - Chemiluminescence immunoassay
  - Enzyme immunoassay

SEROLOGIC TESTING: TRADITIONAL AND REVERSE SCREENING ALGORITHMS

In most clinical settings, syphilis is diagnosed indirectly, using serologic tests along with clinical history and physical examination (Box 1). In a traditional screening algorithm, presumptive serologic diagnosis of syphilis requires two tests: an initial nontreponemal test (ie, rapid plasma reagin or venereal disease research laboratory) followed by a confirmatory treponemal-specific test (Fig. 6).[31] The rapid plasma reagin is the most commonly used nontreponemal antibody in the United States. This test measures antibody to cardiolipin, which is thought to be contained within *T pallidum,* as well as in the damaged host cell membrane.[42] A confirmatory test is required because false positive nontreponemal tests occur, and the false-positive rate for a rapid plasma reagin is about 1% in pregnant women.[43] When reactive, the nontreponemal test is quantified as a titer, which typically correlates with disease activity and is used to follow treatment response.

The traditional algorithm contrasts with newer reverse sequence algorithms that have been employed in some clinical laboratories (Fig. 6). The reverse sequence algorithm begins with a treponemal antibody test, typically an automated enzyme or chemiluminescence immunoassays. The advantage to this test is in the laboratory throughput: for high volume laboratories, the ability to perform automated testing has proposed cost advantages.[44] The sensitivity of available treponemal immunoassays ranges between 97% and 100%, depending on clinical stage and the specific assay used.[45] However, false positive rates are as high as 40–80%, and thus reflex testing is still required.[46] When reactive, a treponemal immunoassay is reflexed to a nontreponemal test such as rapid plasma reagin, and the following scenarios may result:

1. If both the treponemal and nontreponemal tests are reactive, the diagnosis of presumptive active syphilis is made, and the clinical history and physical examination provide evidence for timing of infection. In women with previously treated syphilis, a reactive treponemal antibody and low-level (less than 1:8), serofast nontreponemal titer may persist. If prior treatment is confirmed and there is no suspicion of reinfection, no further treatment is necessary. On rare occasions, both nontreponemal and treponemal tests can be falsely positive as a result of previous exposure to a nonvenereal endemic syphilis (ie, yaws or bejel) or other infection causing a reactive treponemal immunoassay in a woman with false positive rapid plasma reagin.

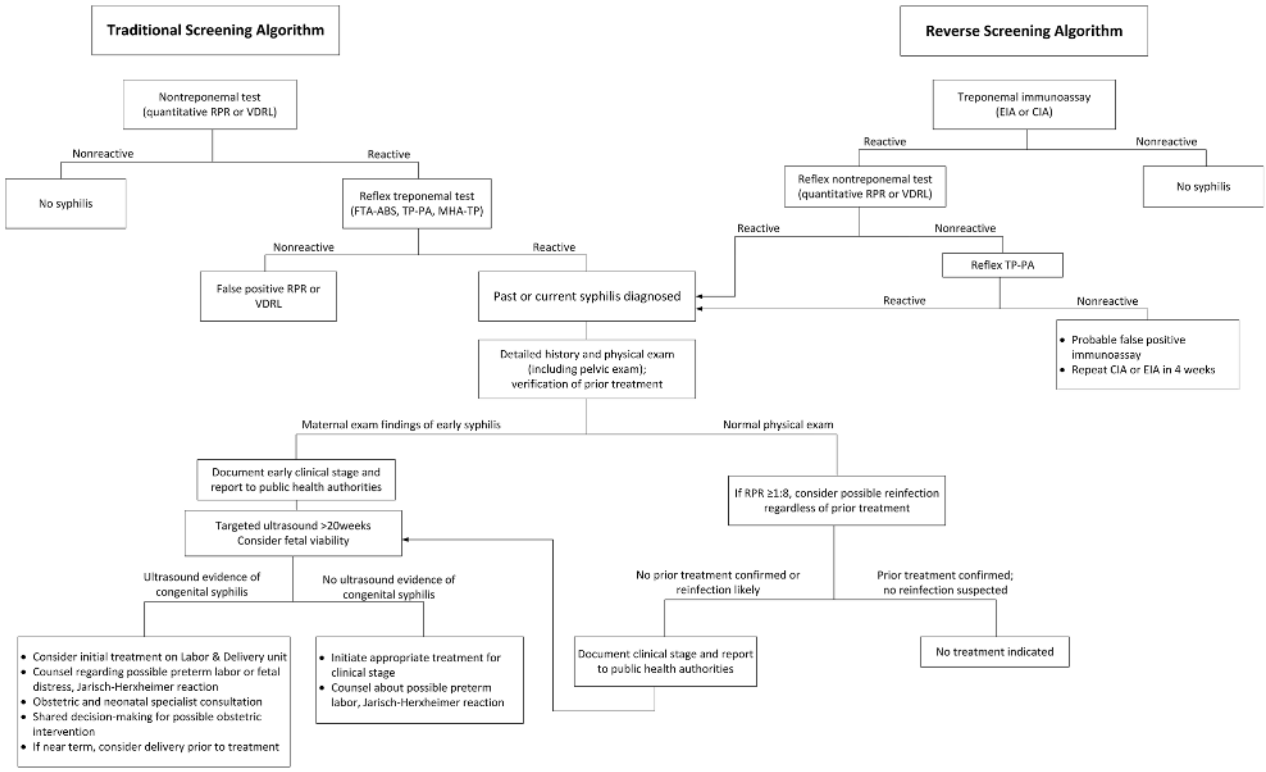

Fig. 6. Clinical evaluation for syphilis in pregnancy using the traditional or reverse sequence algorithms. RPR, rapid plasma reagin; VDRL, venereal disease research laboratory test; EIA, enzyme immunoassay; CIA, chemiluminescence immunoassay; FTA-ABS, indirect fluorescent-antibody; TP-PA, *Treponema pallidum* particle agglutination assay; MHA-TP, microhemagglutination assay.

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2. In women with reactive treponemal immunoassay and nonreactive nontreponemal antibody, this may represent a false positive immunoassay, which is common in pregnant women.[47] In this case, the laboratory should reflexively perform a second treponemal antibody (different from the first) for confirmation. Often, the second treponema antibody test is the *T pallidum* particle agglutination test.
   a. If the *T pallidum* particle agglutination test is nonreactive, the probability of false positive treponemal immunoassay is high. Repeat testing with a treponemal immunoassay (enzyme or chemiluminescence immunoassay) is recommended in 4 weeks. The repeat screen may be nonreactive in subsequent screening, confirming the initial false positive.[47]
   b. If the *T pallidum* particle agglutination test is reactive, this establishes the presumptive diagnosis of past or current syphilis. Three scenarios are possible: early syphilis (before rapid plasma reagin seroconversion, or with high titer and "prozone" reaction, in which high antibody titers interfere with rapid plasma reagin test reactivity in the laboratory), previously treated syphilis, or latent syphilis without prior treatment and gradual decline of rapid plasma reagin to nonreactive. A detailed clinical history and physical examination are paramount to establish risk factors for syphilis, confirm previous treatment regimens, and document any physical evidence of early-stage infection. If no previous treatment can be confirmed in an asymptomatic patient, initiation of a full course of treatment for latent syphilis is recommended. For counseling purposes, there is low probability of vertical transmission of syphilis when the maternal nontreponemal titer is nonreactive and her risk of untreated syphilis is low.[48]

Further evaluation for neurosyphilis with lumbar puncture and CSF analysis is currently recommended only for patients with clinical symptoms suggestive of central nervous system involvement, such as cranial nerve dysfunction, acute meningitis, or altered mental

status.[31] Recommendations are similar for women living with HIV. Currently, the initial recommended test for evaluation of CSF is the venereal disease research laboratory test.[31]

FUTURE DIRECTIONS IN SYPHILIS DIAGNOSIS

As described, the diagnosis of syphilis is still currently made based clinical history, physical examination, and indirect (serologic) testing. The recent evolution in syphilis serologic tests (with accompanying reverse sequence algorithm) resulted from major advances in the field over the past 20 years. The complete genome of *T pallidum* was sequenced in 1998.[49] This achievement spurred the development of new diagnostic techniques using recombinant treponemal antigens, such as the previously described treponemal-specific immunoassays. Admittedly, diagnostic quandaries are common, and lead to patient (and physician) distress. As our ability to study syphilis is made easier using new technologies, DNA and polymerase chain reaction–based molecular tests will likely play a role in the evolution of syphilis diagnosis over the next 20 years.[50–52]

DIAGNOSIS OF CONGENITAL SYPHILIS INFECTION IN THE FETUS

Definitive diagnosis of congenital syphilis in a fetus may be made by direct detection of *T pallidum* in amniotic fluid, but this method requires invasive testing and has poor sensitivity.[53] In clinical settings, congenital infection is presumed in all cases of maternal syphilis infection during pregnancy. When present, ultrasonographic findings consistent with congenital infection represent fetuses with severe infection. Ultrasound findings of congenital infection typically are not manifest until after approximately 18–20 weeks of gestation owing to relative immaturity of the fetal immune response. Findings may include placentomegaly, hepatomegaly, polyhydramnios, ascites, and nonimmune hydrops (Fig. 7).[54] Placentomegaly is defined as placental thickness exceeding 4 cm.[55] Fetal anemia may be detected by performance of middle cerebral artery Doppler studies.[56] Detailed ultrasonography to evaluate for evidence of congenital syphilis is considered when maternal syphilis is diagnosed (Fig. 6). In particular, targeted ultrasonography is considered before initial treatment when maternal infection is diagnosed near the threshold of fetal viability. When ultrasound findings of congenital syphilis are identified after fetal viability, initial treatment in an inpatient setting with monitoring of the mother and fetus are recommended to detect possible fetal distress or preterm labor (see "Clinical response to treatment and the Jarisch-Herxheimer reaction").

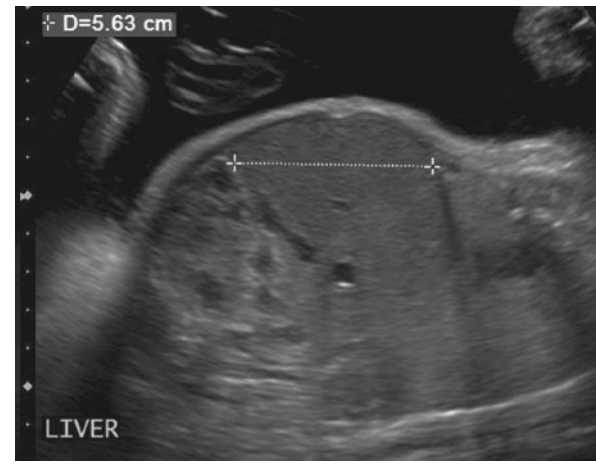

Fig. 7. Hepatomegaly seen on ultrasonogram of a fetus with congenital syphilis infection.
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TREATMENT IN PREGNANCY

Optimal treatment of syphilis during pregnancy is estimated to reduce the risk of congenital syphilis by 97%, stillbirth by 82%, preterm birth by 64%, and neonatal mortality by 80%.[57] Long-acting parenteral penicillin G is the only currently recommended treatment for syphilis in pregnancy, although efforts are underway to develop alternative treatment options given the potential for antimicrobial resistance to emerge.[58] The CDC recommends that pregnant women should be treated with the penicillin regimen appropriate for their stage of infection.[31] Dosing recommendations for the commonly used intramuscular benzathine penicillin G preparation are based primarily on decades of clinical experience, pharmacokinetic studies, and observational studies in nonpregnant patients rather than randomized clinical trials.[31,59] Penicillin crosses the placenta, although its distribution through the amniotic fluid and fetus is poorly understood.[60] Furthermore, current evidence is not sufficient to determine the optimal maternal penicillin dose or regimen required to treat congenital infection.[61] That said, a single intramuscular injection of benzathine penicillin G 2.4 million units has an overall efficacy of 98% in preventing congenital infection.[62] Congenital syphilis in the neonate despite maternal treatment is more common among women treated for early-stage syphilis, high nontreponemal titers, ultrasonographic evidence of congenital syphilis, or those who deliver soon (defined as within 30 days) after initiating treatment.[54,63] For these reasons,

some experts recommend a second intramuscular dose of 2.4 million units of benzathine penicillin G for women diagnosed with early clinical stage infection. Our practice is to routinely administer two doses of 2.4 million units intramuscular benzathine penicillin G over 2 consecutive weeks to all women with early-stage syphilis, with an interval of no more than 10 days between injections.

Treatment with three weekly doses of 2.4 million units intramuscular benzathine penicillin G is recommended for late latent (ie, unknown duration or late syphilis) in pregnancy. Similar to treatment for early syphilis, the optimal dosing interval has not been established. Currently the CDC acknowledges that an interval of 7–9 days between doses may be optimal based on pharmacokinetic studies, but clinical experience suggests that an interval of 10–14 days between doses may be acceptable.[31] A conservative practice is to allow an interval of up to 10 days between intramuscular injections for treatment of late latent syphilis in pregnancy. If a patient misses a scheduled dose, the treatment course is restarted.

TREATMENT AFTER EXPOSURE

Treatment for presumed early syphilis is recommended for women with sexual contact with a partner diagnosed with primary, secondary, or early latent syphilis with the preceding 90 days.[31] If the exposure occurred more than 90 days before the patient's diagnosis, initial serologic testing for syphilis is recommended; if testing is not available, treatment for presumed early syphilis should be administered. If serologic results are negative, no treatment is indicated. For positive serologic results, clinical staging is performed, and treatment appropriate to the clinical stage of infection is initiated.

ALTERNATIVES TO PENICILLIN IN PREGNANCY

In pregnancy, there are currently no recommended alternative therapies to penicillin that reliably cross the placenta to treat the fetus as well as the mother. Although considered an alternative in nonpregnant individuals, doxycycline is generally avoided in pregnancy because other tetracyclines have been associated with staining of developing teeth and transient suppression of bone marrow growth.[64] Despite initially promising research, azithromycin resistance is frequently reported and does not reliably treat the fetus with infection.[65,66] Finally, parenteral ceftriaxone has been used successfully to treat maternal syphilis, but there are limited data supporting an optimal regimen.[67]

For pregnant women reporting a penicillin allergy, a thorough clinical history should be taken to determine whether the reported reaction is moderate to high risk for anaphylaxis or other life-threatening drug reaction.[68] In women with a clinical history consistent with a moderate to high risk allergic reaction, formal evaluation for possible penicillin allergy testing in a setting with clinicians trained in recognition and treatment of hypersensitivity reactions is recommended. For women with verified IgE-mediated hypersensitivity reactions, penicillin desensitization is indicated.[69]

CLINICAL RESPONSE TO TREATMENT AND THE JARISCH-HERXHEIMER REACTION

Symptoms of primary or secondary syphilis should resolve within a few weeks after treatment is initiated. Clinical response to syphilotherapy may include a Jarisch-Herxheimer reaction, an acute febrile reaction characterized by myalgia, fever, headache, and potentially preterm labor and fetal heart rate tracing abnormalities in pregnant women. A systemic response involving increased circulating proinflammatory cytokines resulting from release of massive amounts of lipopolysaccharide by dying spirochetes after treatment, the Jarisch-Herxheimer reaction typically occurs within the first 24 hours after treatment, and is more frequent among patients with early syphilis or high nontreponemal titers.[70] Jarisch-Herxheimer reaction has also been reported after intrapartum maternal group B streptococcal prophylaxis.[71] Before treatment, women should be counseled about the potential for these symptoms, as well as on appropriate management with antipyretics. Symptoms of preterm labor or decreased fetal movement warrant additional evaluation with fetal heart rate monitoring. Because fetal heart rate tracing abnormalities may occur in a severely affected fetus, initial treatment at a center with the capability for emergent delivery and neonatal stabilization is recommended for women with ultrasound evidence of congenital infection in a potentially viable fetus. Pretreatment counseling by obstetric and neonatal specialists is warranted to ensure shared decision-making about any potential emergent intervention. Our practice for women with ultrasound evidence of congenital syphilis in a potentially viable fetus is to administer the first dose of intramuscular penicillin G on the labor and delivery unit with fetal monitoring and neonatology consultation. Subsequent doses are administered in the outpatient setting as appropriate for the clinical stage of infection.

Treatment of women with high nontreponemal titer, early clinical stage, or severely affected fetuses

should not be delayed for concern about a possible Jarisch-Herxheimer reaction. However, for maternal syphilis with high nontreponemal titer or ultrasound evidence of congenital infection diagnosed late in the third trimester, initial delivery followed by neonatal stabilization and transfer to an intensive care unit for treatment may be considered in select cases in coordination with obstetric and neonatal specialists. In contrast, in the case of hydrops fetalis secondary to congenital syphilis diagnosed in the second trimester, maternal counseling should include a coordinated discussion of the potentially poor prognosis regardless of whether emergent delivery is considered.[56] Antepartum corticosteroid administration may be considered for a woman with preterm labor symptoms or whose fetus shows signs of compromise such that emergent delivery may be indicated. There is little evidence that corticosteroid administration prevents or mitigates the Jarisch-Herxheimer reaction.

SEROLOGIC RESPONSE TO TREATMENT

Treponemal antibodies typically remain positive for life when syphilis is diagnosed. To assess response to treatment, a nontreponemal antibody titer is performed at the time of initial treatment, and this same test is used to follow treatment response. Commonly, a fourfold or two-dilution change in titer is needed to demonstrate a clinically significant change in serial nontreponemal tests.[31] Adequate treatment response is defined in nonpregnant populations as a fourfold decline in nontreponemal titer within 6–12 months after therapy; in pregnancy, this decline depends primarily on when during pregnancy treatment is initiated. Women treated for primary or secondary syphilis and with initially high nontreponemal titers are more likely than women with latent infection or low titers to experience a fourfold decline before delivery. Women treated later in pregnancy have less time to achieve a fourfold decline in nontreponemal titer before delivery, but this does not necessarily reflect treatment failure.[72] Importantly, achievement of a fourfold decline in maternal nontreponemal serologic titers after treatment does not guarantee that fetal treatment has been adequate. For this reason, all exposed neonates should be evaluated for congenital syphilis after delivery. The interval at which to repeat a nontreponemal titer after adequate maternal treatment is not clear, because most women will deliver before a serologic response to treatment can be definitively assessed.[31] In general, a nontreponemal titer may be repeated if maternal re-exposure to an untreated partner is suspected, although the decision to retreat is a clinical one. There is little evidence supporting the benefit of repeating monthly nontreponemal titers after adequate therapy. In all women, we inquire about partner treatment and potential for re-exposure at each prenatal visit after maternal diagnosis, and repeat a rapid plasma reagin test at 28–32 weeks or sooner if the clinical history suggests re-exposure or reinfection. If clinical symptoms persist or recur, or when nontreponemal titer increases by fourfold (two-dilution) or greater for more than 2 weeks, reinfection should be considered and retreatment initiated.[31] Data are weak regarding the added utility of CSF examination for asymptomatic women who do not experience fourfold decline in nontreponemal titer after appropriate penicillin therapy, and this is not our routine practice unless neurologic symptoms occur.[73]

With appropriate treatment, the nontreponemal antibody titer usually declines and may become nonreactive with time, although this response may take 1–2 years. Some patients may have a persistent, low nontreponemal titer known as "serofast" despite complete treatment (typically less than 1:8). A serofast rapid plasma reagin is more common with lower initial rapid plasma reagin titers and latent syphilis at the time of diagnosis.[74,75] When past treatment has been confirmed and there is no suspicion of re-exposure in a patient with serofast rapid plasma reagin or venereal disease research laboratory test, no additional treatment is indicated. In our obstetric practice, located in an area with relatively high prevalence of syphilis, reinfection is suspected and treatment is administered for a rapid plasma reagin titer of 1:8 or higher, even when past treatment has been confirmed.

REPORTING NEW CASES OF SYPHILIS

In addition to adhering to recommended best practices for screening and treatment of syphilis in pregnant women, clinicians should ensure that newly diagnosed cases, including clinical exam findings, diagnostic tests, and treatments administered, are promptly reported to local health authorities. Smaller practices may not have the resources to arrange immediate posttest counseling and treatment during pregnancy. When existing infrastructure does not support a comprehensive strategy, obstetricians should establish relationships with referral maternity centers and local health authorities to whom pregnant women can be referred for immediate counseling and treatment. By promptly reporting new cases of syphilis–particularly early clinical stage disease–the local health department can deploy trained disease intervention specialists who conduct formal interviews, establish surveillance plans, and track potentially exposed or infected partners.

ADDED COMPLEXITY: REVERSING THE EPIDEMIC IN UNDERSERVED POPULATIONS

In addition to socioeconomic barriers that prevent access to early prenatal care among underserved and minority women, there are barriers to trust between a patient and physician, specifically with regard to diagnosis and treatment of syphilis in this country. Much of our understanding about the clinical manifestations and natural history of syphilis infection is informed by observational and experimental studies performed by physicians on human subjects who were not able to give informed consent. In the early twentieth century, facing a seemingly insurmountable public health crisis of syphilis before the use of penicillin, the U.S. Public Health Service led investigational efforts to better understand the transmission and natural course of syphilis infection. The Tuskegee Syphilis Study, ongoing from 1932 to 1972, involved the U.S. Public Health Service–sponsored observation of untreated syphilis in more than 400 black men who were not offered treatment, even after penicillin was recognized to be highly effective.[76] Revelations of the unethical conduct of this study paved the way for passage of the National Research Act in 1974 and led to publication of the landmark Belmont Report in 1979.[77] In 2010, just a decade ago, a second "Tuskegee-like" series of studies came to light, known as the Guatemalan STD Studies.[78] From 1946 to 1948, the National Institutes of Health–funded U.S. Public Health Service conducted a study of syphilis and other pathogens in which more than 1,300 children, sex workers, prisoners, and others were deliberately infected in Guatemala to avoid oversight by U.S. authorities. Clinicians and public health authorities have since struggled to reestablish trust in underserved communities at highest risk for both syphilis and HIV infection. A nuanced appreciation of this troubled past will aid clinicians in overcoming potential barriers that could prevent vulnerable women from accessing care and adhering to prescribed treatments. Uniquely situated on the "front lines" of women's health care, ob-gyns have an opportunity to play a major role in reducing maternal and neonatal morbidity caused by syphilis.

FUTURE DIRECTIONS: A VACCINE FOR SYPHILIS PREVENTION

Unlike pathogens such as rubella and varicella viruses, for which vaccines elicit protective immunity for both mother and fetus, there is no such vaccine to prevent syphilis infection. A vaccine candidate targeting a specific adhesin protein Tp0751, believed to play a key role in dissemination of organisms from the primary chancre, has been described.[79] Challenges to successful syphilis vaccine development include the need to ensure safety and efficacy during pregnancy and with HIV coinfection, and the need to protect both the individual from disseminated disease after primary infection, as well as partners after exposure to primary chancres.[80] In May 2019, the National Institutes of Health announced new funding for the development of vaccines targeting STIs. Though well-timed and much needed during the current syphilis crisis, the fruits of this effort may not be realized for decades.

CONCLUSIONS

Despite near elimination of syphilis in the United States only two decades ago, venereal *Treponema pallium* has made an unwelcome return, and a spotlight is again focused on increasing rates of maternal and congenital syphilis. Simultaneously, new technologies have improved our understanding of the inner workings of this stealth pathogen, added new tools for diagnosis, and stimulated research on potential alternatives to penicillin.[22] Ob-gyns should be well-informed about current guidelines for syphilis screening and treatment in pregnancy, and understand strengths and limitations of new testing algorithms in the context of recent advances in syphilis science. Ultimately, collaboration among physicians, scientists, public health facilities and political leaders will be needed to increase public awareness, facilitate access to early prenatal care in underserved communities, and reverse the current epidemic.

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