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Case report

Congenital syphilis: Missed opportunities and the case for rescreening during pregnancy and at delivery

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ABSTRACT

Two infants treated for syphilis born to at risk mothers who screened negative at their first prenatal visit but were not rescreened at delivery are described. The first presented with classic, but unrecognized, features of congenital syphilis. In the second case, possible early maternal syphilis was diagnosed soon after delivery using the treponemal first reverse-screening algorithm. Although the child's physical exam was normal and the maternal rapid plasma reagin (RPR) negative, the child was treated for syphilis because maternal confirmatory treponemal tests suggested recent seroconversion. Given the re-emergence of congenital syphilis, our report aims to demonstrate the importance of rescreening women at increased risk and improve awareness of common manifestations of the syphilis disease in the newborn. For women at increased risk, repeat syphilis testing early in the third trimester and again at delivery in communities and populations with a high prevalence of syphilis is recommended.
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Introduction

Between 2014 and 2018 the United States has recognized a 165 % increase in primary and secondary syphilis among women of reproductive age [1]. Concurrently, congenital syphilis has increased and now occurs at a rate of 33.1 cases per 100,000 live births [1,2]. If untreated during pregnancy, maternal syphilis may result in fetal demise, or congenital infection, which may lead to severe physical and neurological disability or newborn death [3–6]. Key to prevention is screening pregnant women for syphilis at the initial prenatal visit, and if at increased risk, again in the third-trimester and at delivery [1,7,8]. The State of Ohio where our cases originated, requires syphilis screening of all pregnant women at the first antenatal visit but does not require repeat testing later in pregnancy nor at delivery [9]. Highlighting the importance of rescreening, we report two infants born to mothers whose initial first trimester screens were negative and who were not rescreened at delivery despite having risk factors. One case demonstrates a classic presentation of congenital syphilis infection while the other was only recognized because of maternal serologic testing using the treponemal first reverse-screening algorithm. Together these cases illustrate the spectrum of presentation of syphilis in young infants, the lack of recognition among clinicians of the disease, the extremely imperfect strategy of using risk-based rescreening guidelines especially in communities and populations where the prevalence of syphilis is high, and highlights missed opportunities for identifying exposed infants.

Case 1

A 3 $^{1}/_{2}$ month old male infant presented on four occasions for persistent erythematous perianal papules, rhinorrhea and peeling of the lower and upper extremities. He was born at term via caesarean section to a 19-year-old primigravida mother with negative first-trimester screening results, including for human immunodeficiency virus (HIV) and syphilis, the latter by syphilis antibody screen (BioPlex^{TM} 2200 Syphilis IgG, Biorad Assay). At 38 weeks gestation, the mother developed genital lesions presumed by the obstetrical team to be primary herpes simplex virus (HSV). The HSV-1 IgG serology was positive but polymerase chain reaction (PCR) assays from the lesions were negative for both HSV-1 and HSV-2. She was not rescreened for syphilis. The mother

Abbreviations: CDC, Centers for Disease Control and Prevention; CSF, cerebrospinal fluid; HSV, Herpes Simplex Virus; HIV, Human Immunodeficiency Virus; PCR, Polymerase Chain Reaction; RPR, Rapid Plasma Reagin; STIs, sexually transmitted infections; VDRL, Venereal Disease Research Laboratory.

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was treated for presumed primary HSV infection with oral valacyclovir and with metronidazole for bacterial vaginosis. She also received cefazolin once as surgical prophylaxis for caesarean section at delivery. The child had a normal newborn examination. HSV skin surface cultures, blood PCR and cerebrospinal fluid (CSF) PCR from the infant were all negative. Given the presumed first-episode non-primary maternal HSV infection, the child received preemptive therapy with intravenous acyclovir per American Academy of Pediatrics guidance [10]. At one month of life, he developed a rash on the arms and feet that subsequently desquamated. He also had persistent rhinorrhea. At two months of life, two erythematous perianal papules developed and progressed to large plaques. At 3 $^{1}/_{2}$ months of life, he was seen in the Emergency Department for rhinorrhea and the perianal rash. A dermatology referral was made, where condyloma lata (Fig. 1) was suspected and testing for syphilis was performed in both the infant and the mother.

The infant's syphilis antibody screen (BioPlex™ 2200 Syphilis IgG, Biorad Assay), was positive with an antibody index >8.0 and the Rapid Plasma Reagin (BD Macro-Vue™ RPR, Becton Dickinson) was reactive at >1:512 dilution. A CSF Venereal Disease Research Laboratory (VDRL) test was also reactive (1:1), with 18 nucleated cells/μL in the CSF. CSF protein was 45 mg/dL (normal range 15−48 mg /dL) and CSF glucose was 47 mg /dL (normal range 60–80 mg /dL). Long bone radiographs revealed features of congenital syphilis, including periostitis (Fig. 2). The mother's antibody screen (BioPlex™ 2200 Syphilis IgG, Biorad Assay) was positive with an antibody index >8.0 and her RPR (BD Macro-Vue™ RPR, Becton Dickinson) was reactive at 1:64. He received intravenous crystalline penicillin G for 10 days. The condyloma lata resolved within 72 h of treatment. By 6 months the infant's RPR had decreased fourfold and the CSF VDRL was non-reactive. Reflecting the lack of awareness of the clinical features of syphilis, 3 outpatient caregivers were exposed to potentially infectious lesions or secretions while examining the child. All 3 tested negative for syphilis three months after exposure.

Case 2

An eight day old male infant was hospitalized for neonatal HSV, limited to the scalp. He was born at 38 2/7 weeks gestation via spontaneous vaginal delivery to an 18-year-old primigravida mother. At 7 weeks gestation, the mother tested positive for trichomoniasis, but negative for other sexually transmitted infections (STIs) including HIV and for syphilis by antibody screen (BioPlex™ 2200 Syphilis IgG, Biorad Assay). At the mother's request, she was again screened for syphilis at 16 and 30 weeks, testing negative by treponemal IgG antibody assay. Testing for syphilis was not repeated at delivery. During labor, the mother developed fever and received single doses of cefazolin and clindamycin. On day 8 of life the child was admitted with cutaneous HSV lesions without dissemination. Due to concern that the mother had had recent primary HSV, she was re-tested for STIs including syphilis. Using a reverse-sequence testing algorithm, her syphilis total antibodies treponemal screen was positive (BioPlex™ 2200 Syphilis Total (IgM/IgG), Biorad Assay) but the reflex non-treponemal RPR (Becton Dickinson technology) assay was non-reactive. A confirmatory treponemal antibody enzyme immunoassay was subsequently positive with an antibody index value of 2.5 (Trep-Sure™ Syphilis Total Antibody EIA, Trinity Biotech). A prozone phenomenon was excluded. The infant's

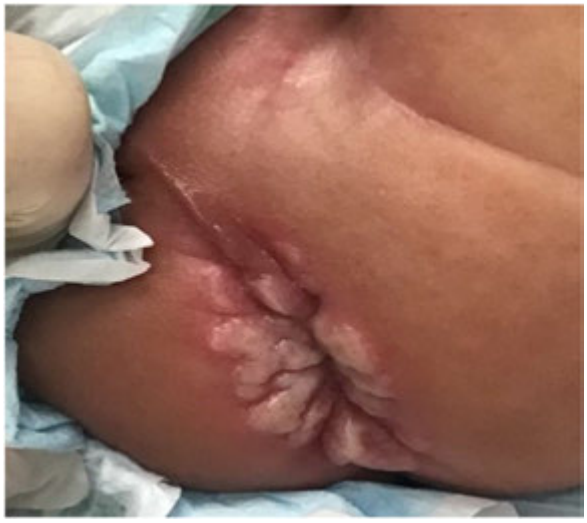

Fig. 1. Perianal condyloma lata at time of syphilis diagnosis.

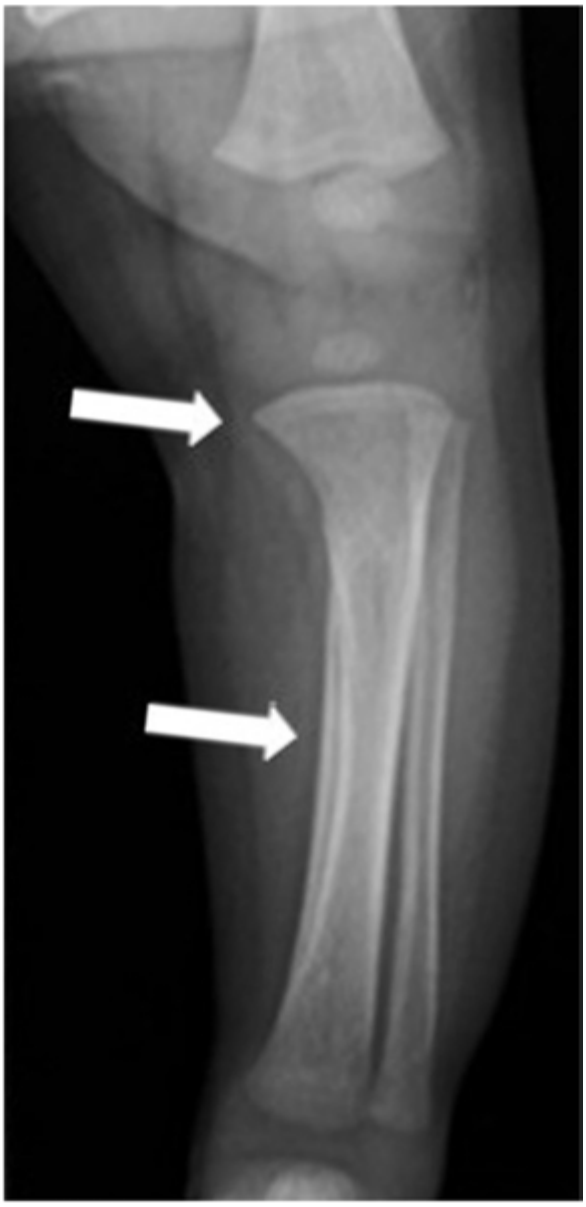

Fig. 2. Radiograph of the left tibia and fibula showing sandwich-shaped metaphysitis (lower arrow), seen as an alternation of hyperdense and hypodense layers. The upper arrow shows the formation of a medial tibial beak with osteochondondritis.

evaluation demonstrated a normal exam, negative syphilis total antibodies screen and RPR, non-reactive CSF VDRL, and normal radiographs of the long bones. As the mother had not received treatment for syphilis during pregnancy, the child was in hospital already, and follow-up could not be assured for the infant, he was treated as a high risk exposure/possible congenital syphilis and received empiric intravenous crystalline penicillin G for 10 days, in addition to intravenous acyclovir.

Discussion

Screening for syphilis during pregnancy is an important public health practice aimed at preventing congenital infections. The Centers for Disease Control (CDC) recommends that all pregnant women be screened for syphilis at the first prenatal visit [11]. Women at increased risk of infection are recommended to be rescreened at 28–32 weeks gestation to allow time for treatment and resolution of infection to occur prior to delivery. A third screening may be performed at delivery to detect any late term acquisition of infection. In the United States, the laws regulating syphilis screening during pregnancy vary by state. Forty-six states require testing of all pregnant women at the first prenatal visit [12,13]. Twenty-one states require some form of repeat screening for syphilis during the third-trimester and or at delivery, in some cases only if the mother is at increased risk.

These two cases illustrate a need for heightened clinical awareness of syphilis by providers and emphasize the importance of rescreening pregnant woman at risk for syphilis infection early during the third-trimester and again at delivery. In the first case, there were multiple failures to recognize clinical findings of syphilis, both in the mother and the infant. The second case emphasizes the importance of rescreening at delivery women from populations at high risk for syphilis, even in asymptomatic mothers, and the potential benefit of using a reverse-screening approach to detect early disease. The syphilis total antibodies assay used as the treponemal screening test typically becomes positive 2–3 weeks after exposure whereas non-treponemal assays such as the RPR do not become reactive until several weeks after the treponemal assays [14,15]. Reverse-sequence testing algorithms offer a potential advantage over traditional screening in detecting very recent infections because of the shorter window period and may be particularly useful when testing women who are at increased risk, whether due to personal or epidemiological factors.

As a result of the recent increase in syphilis among women and the concomitant rise in congenital syphilis among infants, several states have legislated that all pregnant women be screened at three time points: the first prenatal visit, early third-trimester and at delivery [12]. Louisiana and Florida have mandated universal third-trimester rescreening and have effectively prevented most cases of congenital syphilis [16]. Minnesota mandated universal rescreening at 3 time points in 2016 [13]. During the following two years, 69 cases of syphilis were identified among pregnant women including 18 acute infections. Five infants (28 %) would not have been identified with screening at the first prenatal visit only. Their report found no documented case in which a negative screening test during the early third-trimester was followed by a positive test at delivery.

Interestingly, in the second case the diagnosis of maternal syphilis was made only through the use of the reverse-screening algorithm (Fig. 3); screening by the traditional approach (initial screening with a non-treponemal test) would not have detected the infection as the maternal RPR was non-reactive. An explanation for the non-reactive RPR in the setting of recent treponemal seroconversions would be early syphilis infection. The risks and benefits for treatment were considered given that congenital syphilis may cause significant morbidity to infants. As follow up for this infant was uncertain, the decision was made to treat the infant with a 10 day course of crystalline penicillin G rather than a single dose of benzathine penicillin G.

The optimal approach to screening pregnant women for syphilis has not been established. Advantages and disadvantages to both the traditional and reverse-screening approach exist with regard to cost, laboratory throughput, false-positive rates, ability to discern previous or latent infection, and improved sensitivity for diagnosis of acute infection [7,15,17]. In addition, where syphilis PCR is available, lesions should be swabbed and tested for confirmatory diagnosis.

Whether and how to rescreen women at increased risk for syphilis both early in the third-trimester and again at delivery are important questions. Although cost effectiveness analyses have not favored universal third-trimester rescreening of all pregnant women, this calculation may require adjustment especially for

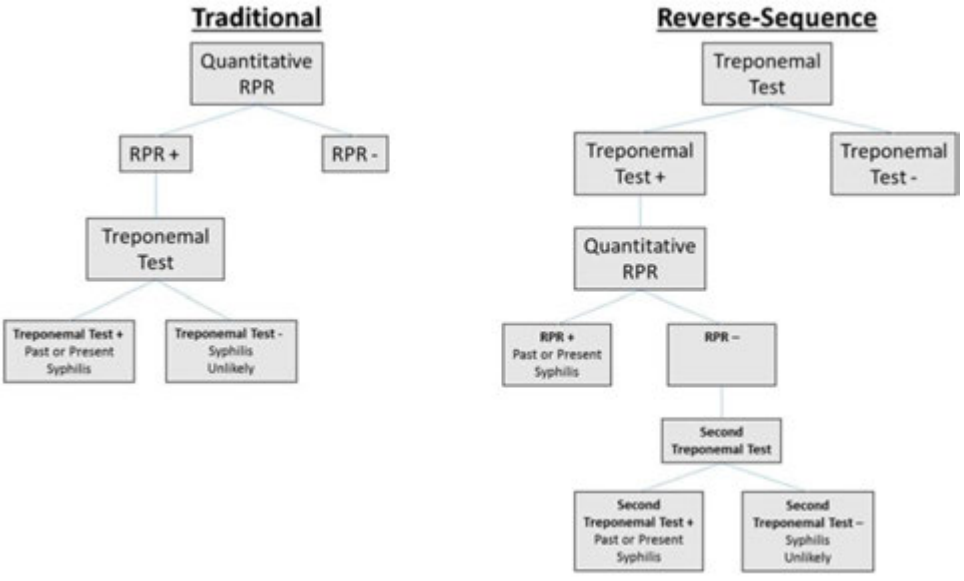

Fig. 3. Algorithms for traditional and reverse-sequence screening for syphilis.

communities with a high-prevalence of syphilis [18,19]. While the mothers of the infants described in these case reports both screened negative for syphilis initially, neither was rescreened at delivery despite residing in communities with a high-prevalence of syphilis and having histories of STIs.

Conclusion

Screening for syphilis at the first prenatal visit is the standard of care and currently required in most states but may fail to detect late term acquisition of maternal infection. The case reports presented highlight the importance of rescreening women at increased risk for syphilis both early in the third-trimester and again at delivery. Given the reemergence of syphilis and the inconsistency with which risk-based rescreening guidelines are followed, a strong argument can be made for adopting universal rescreening protocols to stem the rise of congenital syphilis.

Consent

Written informed consent was obtained from the guardian of the patient in Case 1 for publication of this case report and the accompanying clinical images.

Contributors' Statement Page: Dr. O'Connor drafted the initial manuscript. Drs. Foster, Gonzalez, Tamburro, Esper and Khadkoda revised and edited the manuscript. The clinical images were provided by Dr. Tamburro. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

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