CPHLN LABORATORY GUIDELINES Canadian Public Health Laboratory Network laboratory guidelines for congenital syphilis and syphilis screening in pregnant women in Canada

Ameeta E Singh BMBS MSc FRCPC^{1*}, Paul N Levett DSc (D)ABMM FCCM FAAM^{2*}, Kevin Fonseca PhD D(ABMM)³, Gayatri C Jayaraman MPH PhD⁴, Bonita E Lee MD FRCPC MSc⁵

AE Singh, PN Levett, K Fonseca, GC Jayaraman, BE Lee. Canadian Public Health Laboratory Network laboratory guidelines for congenital syphilis and syphilis screening in pregnant women in Canada. Can J Infect Dis Mid Microbiol 2015;26(Suppl A):23A-28A.

Despite universal access to screening for syphilis in all pregnant women in Canada, cases of congenital syphilis have been reported in recent years in areas experiencing a resurgence of infectious syphilis in heterosexual partnerships. Antenatal screening in the first trimester continues to be important and should be repeated at 28 to 32 weeks and again at delivery in women at high risk of acquiring syphilis. The diagnosis of congenital syphilis is complex and is based on a combination of maternal history and clinical and laboratory criteria in both mother and infant. Serologic tests for syphilis remain important in the diagnosis of congenital syphilis and are complicated by the passive transfer of maternal antibodies which can affect the interpretation of reactive serologic tests in the infant. All infants born to mothers with reactive syphilis tests should have nontreponemal tests (NTT) and treponemal tests (TT) performed in parallel with the mother's tests. A fourfold or higher titre in the NTT in the infant at delivery is strongly suggestive of congenital infection but the absence of a fourfold or greater NTT titre does not exclude congenital infection. IgM tests for syphilis are not currently available in Canada and are not recommended due to poor performance. Other evaluation in the newborn infant may include long bone radiographs and cerebrospinal fluid tests but all suspect cases should be managed in conjunction with sexually transmitted infection and/or pediatric experts.

Key Words: Canada; Congenital; Management; Pregnancy; Screening; Syphilis

CURRENT CANADIAN SURVEILLANCE CASE DEFINITION FOR CONGENITAL SYPHILIS

Classically, congenital syphilis is divided into two clinical syndromes: early (diagnosis during the first two years of life including stillbirths) and late (after two years of life with mainly teeth, bone and central nervous system manifestations). Only early congenital syphilis is nationally notifiable in Canada.

Confirmed case – Early Congenital Syphilis (within two years of birth):

http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/35s2/Syphilis-eng.php

Laboratory confirmation of infection:

 Identification of *Treponema pallidum* by dark-field microscopy, fluorescent antibody, polymerase chain reaction (PCR) or equivalent examination of material from nasal discharges, skin lesions,

Les directives du Réseau des laboratoires de santé publique du Canada sur le dépistage de la syphilis congénitale et de la syphilis chez les femmes enceintes du Canada

Même si toutes les femmes du Canada ont accès au test de dépistage de la syphilis, des cas de syphilis congénitale ont été déclarés ces dernières années dans des régions où l'on constate une résurgence de la syphilis infectieuse chez des partenaires hétérosexuels. Il est toujours important de procéder à un dépistage anténatal pendant le premier trimestre, de le reprendre entre 28 et 32 semaines de grossesse, puis à l'accouchement chez les femmes très vulnérables à la syphilis. Le diagnostic de syphilis congénitale est complexe. Il repose sur l'histoire de la mère ainsi que sur des critères cliniques et des critères de laboratoire à la fois chez la mère et le nourrisson. Les tests sérologiques de la syphilis s'imposent toujours pour diagnostiquer la syphilis congénitale, mais ils sont compliqués par le transfert passif des anticorps maternels qui peut nuire à l'interprétation des résultats réactifs chez le nourrisson. Tous les nourrissons nés d'une mère dont les tests de syphilis sont réactifs devraient subir des tests non tréponomiques (TNT) et des tests tréponomiques (TT) conjointement aux tests de la mère. Un titrage du TNT au moins quatre fois plus élevé que la normale chez le nourrisson à l'accouchement est fortement évocateur d'une infection congénitale, mais l'absence d'un tel résultat n'en exclut pas la possibilité. Les tests d'IgM pour déceler la syphilis ne sont pas offerts au Canada. Ils ne sont pas recommandés en raison de leurs piètres résultats. Parmi les autres évaluations du nouveau-né, soulignons les radiographies des os longs et les tests du liquide céphalorachidien, mais il faut prendre en charge tous les cas présumés conjointement avec des pédiatres ou des spécialistes des infections transmises sexuellement.

placenta, umbilical cord or autopsy material of a neonate (up to four weeks of age) OR

- Reactive serology (non-treponemal and treponemal) from venous blood (not cord blood) in an infant/child with clinical, laboratory or radiographic evidence of congenital syphilis whose mother is without documented evidence of adequate treatment OB
- Detection of *T. pallidum* DNA in an appropriate clinical specimen Consultations are currently underway to include a Canadian case definition for probable early congenital syphilis.

EPIDEMIOLOGY OF CONGENITAL SYPHILIS IN CANADA

Data from recent years suggest an increase in reported cases and corresponding rates of congenital syphilis and can be linked to jurisdictions

¹Division of Infectious Diseases, University of Alberta, Edmonton, Alberta; ²Saskatchewan Disease Control Laboratory, Regina, Saskatchewan; ³Alberta Provincial Laboratory for Public Health, Calgary, Alberta; ⁴Centre for Communicable Diseases and Infection Control, Public Health Agency of Canada, Ottawa, Ontario; ⁵Division of Pediatric Infectious Diseases, University of Alberta, Edmonton, Alberta *Denotes section lead

Correspondence: Dr Ameeta E Singh, Division of Infectious Diseases, University of Alberta, 3B20-11111 Jasper Avenue Northwest, Edmonton, Alberta T5K 0L4. Telephone 780-342-2300, fax 780-425-2194, e-mail ameeta@ualberta.ca

ACCESS This open-access article is distributed under the terms of the Creative Commons Attribution Non-Commercial License (CC BY-NC) (http:// creativecommons.org/licenses/by-nc/4.0/), which permits reuse, distribution and reproduction of the article, provided that the original work is properly cited and the reuse is restricted to noncommercial purposes. For commercial reuse, contact support@pulsus.com

TABLE 1
Reported cases and rates of confirmed early congenital syphilis*, 2000 to 2011, Canada

	Total reported	Rate (per 100,000	Number of reported cases*												
Year	cases	live births) [†]	BC	AB	SK	MB	ON	QC	NB	NS	PE	NL	ΥT	NT	NU
2000	2	0.6	1	0	0	0	0	1	0	0	0	0	0	0	0
2001	1	0.3	1	0	0	0	0	0	0	0	0	0	0	0	0
2002	3	0.9	0	1	1	0	1	0	0	0	0	0	0	0	0
2003	2	0.6	0	0	0	0	0	2	0	0	0	0	0	0	0
2004	0	0.0	0	0	0	0	0	0	0	0	0	0	0	0	0
2005	8	2.3	3	5	0	0	0	0	0	0	0	0	0	0	0
2006	7	2.0	2	4	0	0	1	0	0	0	0	0	0	0	0
2007	8	2.2	2	5	0	0	1	0	0	0	0	0	0	0	‡
2008	6	1.6	2	2	0	0	1	0	0	0	0	0	0	1	‡
2009	10	2.6	2	7	0	0	0	0	0	0	0	0	0	1	‡
2010	6	1.6	0	2	2	0	2	0	0	0	0	0	0	0	‡
2011	3	0.8	0	1	0	0	1	1	0	0	0	0	0	0	‡

*Refers to laboratory-confirmed cases of early congenital syphilis (within 2 years of birth); [†]Source: Statistics Canada, Canadian Vital Statistics, Birth Database; [‡]Data for Nunavut were not available from 2007 onwards; the population of Nunavut was thus excluded from the denominator when calculating national rates for these years.

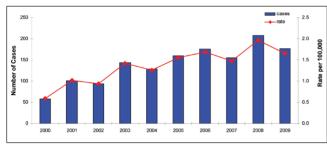


Figure 1) Reported cases and rates of infectious syphilis in females 15 to 59 years of age, 2000 to 2009. Rate per 100,000 population; population estimates provided by Statistics Canada. (Source: Statistics Canada, Demography Division, Demographic Estimates Section, July Population Estimates, 2000–2005 final intercensal estimates, 2006–2007 final post-censal estimates, 2008–2009 updated postcensal estimates). Infectious syphilis includes primary, secondary and early latent stages

that have reported outbreaks of syphilis in heterosexual partnerships (1,2) (Table 1, Figure 1).

APPROACH TO DIAGNOSTIC TESTS IN MOTHER AND INFANT

Figure 2 outlines the approach to investigations for syphilis in mothers and infants in suspect cases of congenital syphilis. It should be noted, however, that only a small proportion of cases of congenital syphilis are made based on specific laboratory tests while the majority are based on a combination of maternal history and other clinical criteria in both the mother and infant. Given the complexities of diagnosis, it is recommended that expert advice (eg, sexually transmitted infection specialist, infectious diseases specialist) be sought in the management of all cases of syphilis in pregnant women and infants.

SCREENING FOR SYPHILIS IN PREGNANT WOMEN AND INFANTS

Effective prevention and identification of congenital syphilis depends primarily on the identification of syphilis in pregnant women and, therefore, on the routine screening of all pregnant women for syphilis. With the resurgence of syphilis in Canada, universal screening of all pregnant women continues to be important and remains the standard of care in most jurisdictions (2). Antenatal screening for syphilis has been shown to be cost beneficial even in developed countries with a relatively low prevalence of syphilis (3). Initial screening should ideally be performed in the first trimester and should be repeated at 28 to 32 weeks and again at delivery in women at high risk for acquiring syphilis. More frequent screening

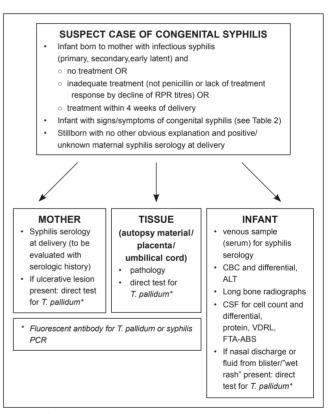


Figure 2) Algorithm of investigations in mother and infant in suspected cases of congenital syphilis. ALT Alanine aminotransferase; CBC Complete blood count; CSF Cerebrospinal fluid; FTA-ABS Fluorescent treponemal antibody absorption; RPR Rapid plasma reagin; VDRL Venereal Disease Research Laboratory

may be indicated in women at particularly high risk for acquisition (or re-infection) with syphilis in pregnancy (eg, sex-trade workers). In addition, consideration should be given to re-screening all pregnant women in areas experiencing heterosexual outbreaks of syphilis, regardless of the woman's risk profile (2). This is especially important in areas where congenital syphilis cases have been reported in women with no personal risk factors for syphilis. Screening in the first trimester and at 28 to 32 weeks' gestation seeks to prevent the transmission of syphilis to the fetus by maternal treatment in pregnancy while screening near term/delivery serves primarily to detect congenital cases and allow for early treatment. Any woman delivering a hydropic or stillborn infant at ≥ 20 weeks gestation should be screened for syphilis. No newborn should be discharged from hospital before confirmation that either the mother or newborn infant has had syphilis serology undertaken during pregnancy or at the time of labour or delivery and that the results will be followed up.

Screening of the mother's serum is preferred (rather than testing cord blood or the infant's serum) because of the ease of obtaining good-quality blood samples and the ability to provide maternal disease staging. Moreover, serological tests performed on infant serum can be non-reactive if the mother's non-treponemal serological test is of low titre or the mother was infected in late pregnancy (4). There have been case reports of 'missed' congenital syphilis with a negative maternal screen at delivery that likely represented mothers with early acute syphilis infection and non-reactive non-treponemal screening tests at the time of delivery (5,6). In areas experiencing a resurgence of infectious syphilis, it is important for health providers to include syphilis in the differential diagnosis of suspicious genital lesions and consult with local laboratories for appropriate sample collection for direct detection of syphilis and other pathogens such as herpes simplex virus.

TRANSMISSION AND OUTCOMES OF SYPHILIS IN PREGNANCY

Approximately 40% of pregnancies in women with infectious syphilis (primary, secondary or early latent) result in fetal demise (7). Untreated infants or infants with severe *in utero* infection may have blindness, deafness, and neurological, dental or orthopedic sequelae (8).

Transmission to the fetus occurs through transplacental transfer (most common) or contact with lesions during vaginal delivery (9). The majority of infants are infected in utero after the fourth month of gestation but infection can occur as early as nine weeks' gestation (10).

The longer the interval between infection and pregnancy, the more benign the outcome in the infant (Kassowitz's Law) (8). Earlier data on syphilis in pregnancy reported a risk of transmission of 70% to 100% with untreated primary or secondary syphilis and 40% with untreated early latent syphilis (9). In the same study, Fiumara (9) quoted a transmission rate of up to 10% with untreated late latent syphilis, but it is unclear whether transmission in this stage is due to unrecognized reinfection or relapse back into secondary-stage syphilis because one would not expect maternal spirochetemia in the late latent stage.

In the era of reverse-sequence algorithms, some experts have questioned the significance on transmission of results showing persistently positive screening treponemal tests and negative non-treponemal tests. A retrospective review of a large number of such cases in the United States found no convincing evidence of syphilis transmission from mothers with persistently negative nontreponemal test results. Only one case suggested that transmission may have occurred and, in this case, records were incomplete (11).

DIAGNOSIS OF CONGENITAL SYPHILIS

i) Overview

The assessment and management of infants with reactive syphilis serology or born to mothers with reactive syphilis serology is complex. The stage of maternal syphilis, gestational age of the fetus at the time of acquisition and treatment of infection, adequacy and timing of maternal treatment and immunological response of the fetus can cause varied manifestations of congenital syphilis. The diagnosis of congenital syphilis is based on both a clinical evaluation and on laboratory investigations. Diagnosis is further complicated because up to 60% of infected infants are asymptomatic at birth or have subtle, non-specific findings (12,13).

ii) Clinical findings

Table 2 outlines the more common early and late (>2 years) manifestations of congenital syphilis. None of these signs are pathognomonic, however, and can be seen in other congenital infections. After fetal infection occurs, any organ system can be affected because of widespread spirochetal dissemination.

iii) Radiographic findings

Bone involvement occurs in 60% to 80% of untreated congenital syphilis cases and is usually multiple and symmetric. Long-bone radiographs may show deep soft-tissue swelling, periosteal reactions and metaphyseal demineralization of the long bones (14,15). When demineralization or destruction of the upper medial tibial metaphysis is evident radiographically, this is called Wimberger's sign. The epiphysis is rarely involved in congenital syphilis. Bony involvement usually resolves spontaneously during the first six months of life. Long bone x-rays are one of the most sensitive clinical studies for the detection of physical evidence of congenital syphilis and abnormalities have been reported in up to 20% of asymptomatic infected infants (16,17). However, there are no specific data on radiographic findings in premature neonates.

Pneumonia alba, a fibrosing pneumonitis, occurs in a minority of cases. Chest radiographs may show a slowly resolving diffuse pulmonic infiltrate.

iv) Cerebrospinal fluid (CSF)

Current guidelines recommend that CSF evaluation be performed in all neonates/infants with suspected congenital syphilis because positive CSF may provide the only evidence of congenital syphilis in asymptomatic infants born to treated mothers and to permit abnormalities to be monitored (2,18,19).

CSF should be sent for cell count and differential, protein, VDRL and FTA-ABS. CSF test results obtained during the neonatal period can be difficult to interpret, with normal values differing by gestational age and being higher in preterm infants. CSF white blood cell counts ranging from $5 \times 10/L$ to $20 \times 10/L$ and CSF protein ranging from 0.45 g/L to 1.0 g/L are considered to be normal by different experts (20). Beeram et al (21) reported in a retrospective case series that CSF leukocyte and protein values were similar in infants diagnosed with or without syphilis.

In adults with neurosyphilis, CSF-VDRL lacks sensitivity but a reactive VDRL is diagnostic of neurosyphilis. CSF FTA-ABS is highly sensitive but non-specific for neurosyphilis; a negative CSF FTA-ABS helps to exclude a diagnosis of neurosyphilis (22-25). The low sensitivity of CSF VDRL is similar in neonates based on published data in congenital syphilis comparing VDRL with rabbit infectivity test and immunoglobulin M (IgM) immunoblot (26,27). Of note, however, Michelow et al (27) reported three infants with positive rabbit-infectivity test of CSF but normal cerebrospinal fluid indexes and non-reactive cerebrospinal fluid VDRL tests. Rabbit infectivity tests and IgM immunoblot are not readily accessible diagnostics tests in Canada. CSF molecular diagnostic tests may have some utility in this setting but more data are needed to understand the clinical sensitivity and specificity of these diagnostic tests in neurosyphilis.

Current guidelines recommend repeat lumbar punctures approximately every six months in infants with abnormal CSF indexes until the abnormalities normalize but the natural history of abnormal CSF parameters in infants is yet to be defined.

v) Other laboratory tests

Hepatitis is an early manifestation detected by elevated transaminase and alkaline phosphatase levels in blood (14,15). Direct hyperbilirubinemia and prolonged prothrombin time can also occur. Anemia (Coombs negative hemolytic anemia) tends to occur later and is reported in 58% of cases of symptomatic infants with early congenital syphilis. Whereas mild anemia is often mistaken for physiologic anemia of the newborn or iron deficiency, severe anemia may mimic disseminated malignancy or leukemia. Leukocytosis occurs in up to 72% and thrombocytopenia in up to 40%. Renal manifestations such as proteinuria and hematuria occur in up to 16%.

vi) Serological tests for syphilis

Serological tests for syphilis remain the mainstay of diagnostic tests for syphilis. The diagnosis of congenital syphilis is complicated by the passive transfer of maternal antibodies (treponemal and non-treponemal) to the fetus, which can complicate the interpretation or reactive serological tests in the infant. All infants born to mothers who have

TABLE 2

Common clinical features of congenital syphilis

Feature	Usual timing	Details						
Early congenital								
Spontaneous abortion/stillbirth/fetal hydrops	Any gestation	Occurs in approximately 40% of cases if syphilis acquired during pregnancy, with risk being highest for first trimester infection						
Low birth weight/prematurity		Up to 50% of cases depending on maternal stage of infection						
Necrotizing funisitis	At birth	Umbilical cord looks like a 'barber-shop pole' – rare but pathognomonic finding if present						
Rhinitis and/or snuffles	Often first manifestation	Occurs in approximately 4%-40% of cases in first two weeks of life						
Rash	Onset in first 8 weeks	Occurs in approximately 50% cases – usually diffuse maculopapular rash but can also have desquamation alone, vesicular, bullous, papulosquamous or muscosal lesions						
Hepatomegaly/splenomegaly	Onset in first 8 weeks	Occurs in approximately 20% to 50% of cases and may persist for years						
Lymphadenopathy		Occurs in approximately 5% of cases						
Nonsuppurative, including epitrochlear sites								
Early or late congenital								
Neurosyphilis	Can be present at birth or can be delayed	Occurs in approximately 50% cases - usually asymptomatic						
Musculoskeletal involvement	Onset in first week with permanent boney changes eventually developing	Osteochondritis or perichondirits, seen initially radiographically (25% of cases) and later as pseudoparalysis, which can be confused with child abuse as there are both boney and soft tissue limb changes – later develop frontal bossing, poorly developed maxillas, saddle nose, winged scapulas and sabre shins						
Recurrent arthropathy and painless knee effusions (Clutton's joints) occur between 8–15 years of age								
Enlargement of sternoclavicular part of the clavicle (Higoumenakis' sign)								
Mulberry molars	Age 13–19 months	First molars have dwarfing of the cusps and hypertrophy of the enamel surrounding the cusp giving it the appearance of a berry						
Late congenital								
Interstitial keratitis*	Age 4–20 years							
Hutchinson's teeth* When perman dentition eru		Note that permanent dentition starts to develop at approximately 20 weeks gestation.						
Upper central and lateral incisors widely spaced and shaped like screwdrivers with notches								
Eighth nerve deafness*	Age 10–40 years	Hearing loss at 8–10 years of age						

reactive non-treponemal (NTT) and/or treponemal tests (TT) should have both NTT and TT performed.

Parallel testing of both the mother's and the infant's serum at delivery with the same non-treponemal test and preferably by the same laboratory will help to determine the significance of the serological findings in the infant. A fourfold or higher titre in the infant's serum at delivery over the mother's titre is strongly suggestive of congenital infection (12). However, the absence of an infant's titre that is fourfold or greater than the mother's titre does not exclude congenital infection as studies of serum pairs from infected mothers and infants show that <30% of infants have higher titres than their mothers (28).

IgM antibodies may be detected in >80% of symptomatic infants but data on its sensitivity in asymptomatic infants are limited (29,30). Moreover, the traditional FTA-ABS IgM test is technically difficult to perform and steps to remove IgG and interference by rheumatoid factor (19S FTA-ABS IgM test) have resulted in increased specificity but loss of sensitivity with this assay (31). One assay with IgM capture format and labelled treponemal antigens was more sensitive than the 19S FTA-ABS IgM test but the number of patients included in the study was small (29). Another study reported a immunoblot for IgM that was more sensitive and specific than the 19S FTA-ABS IgM test, but it was an in-house assay that required special reagents and expertise (32).

Due to the poor performance of currently available IgM tests for syphilis including a commercially available immunoglobulin (IgM)

licensed for use by the United States Food and Drug Administration (Captia Syphilis-M EIA, Trinity BioTech, Ireland), they are not currently recommended by the CDC (4) and are not currently available in Canada other than for research purposes. One other Health Canadaapproved test for syphilis IgM testing is available: BioPlex 2200 Syphilis (Bio-Rad Laboratories, USA), but there are no published data on the utility of this test in the diagnosis of congenital syphilis.

For serological tests in the newborn, venous blood should be used in preference to cord blood as the latter is frequently contaminated with maternal blood (33).

NTT titres should decline by three months of age and should be non-reactive by six months of age if the infant was not infected (ie, if the reactive test was due to passively transferred antibodies) or was infected but adequately treated (4). The serological response to treatment is expected to be slower for infants treated after the neonatal period. Stable or rising titres might indicate persistent infection and is an indication for repeat evaluation and treatment. The diagnosis of congenital syphilis can be excluded if the NTT becomes non-reactive before six months of age in an infant who has not received treatment (34). Similarly, negative TT can be used to exclude congenital syphilis if the tests are non-reactive before the age of one year in an infant who has not received treatment.

TT can remain positive despite effective treatment. Passively transferred antibodies can persist in an infant up to 15 months of age and, as such, a reactive TT after 18 months of age is diagnostic of congenital syphilis; such infants require full evaluation and treatment for congenital syphilis if treatment was not provided or deemed inadequate by history (35). Sero-reversion to nonreactive treponemal tests has been observed after two to three years in 15% to 25% of adults treated during the primary stage of syphilis (36). Similarly, a study using fluorescent treponemal antibody absorption (FTA-ABS) test showed that only approximately one-half of the infants with clinical or laboratory evidence of congenital syphilis at birth had reactive FTA-ABS at 12 months of age (28). A recent Canadian case series of infants with congenital syphilis reported that 69% infants sero-reverted their treponemal tests by 18 months and cases that did not sero-revert their TT were statistically more likely to have had delayed treatment and to have higher maternal RPR titres at birth (37).

vii) Direct tests for syphilis and histology of placenta

Direct tests such as darkfield microscopy, direct fluorescent antibody test and PCR can be used to identify T. pallidum from syphilis lesions (35,38). With dark-field or immunofluorescence microscopy, false negatives may be high due to poor sample collection or quality, reading techniques, the age or condition of the skin lesions and whether the patient has been treated (38,39). Thus, while a positive microscopy test confirms the diagnosis of syphilis for an infant, a negative microscopy result does not rule out infection. Molecular diagnostic tests, such as PCR, likely have higher sensitivity but the utility of syphilis PCR on swabs of suspected lesions, body fluids including nasal discharge, amniotic fluid, blood or CSF needs to be further evaluated (40,41). Examination of the placenta or umbilical cord using a direct test or PCR is especially helpful in identifying the presence of transplacental infection in the setting of stillborn investigation and maternal infectious syphilis. In addition, histological examination of the placenta should be performed. In comparison to serological tests, histologic examination improves the detection of congenital syphilis from 67% to 89% in liveborn infants and from 91% to 97% in stillborn infants (42).

viii) HIV testing

Given the similar modes of transmission of syphilis and HIV, all infants with reactive syphilis tests should also undergo concurrent HIV testing (43). Concurrent syphilis infection has been shown to be associated with vertical transmission of HIV (44).

DIAGNOSTIC AND MANAGEMENT CONSIDERATIONS

Detailed guidelines on the assessment, management and follow-up of pregnant women and neonates with syphilis are outlined in the Canadian STI Guidelines Syphilis chapter as well as the Canadian Pediatric Society guideline for congenital syphilis (2,18). The following provides an overview of the diagnostic and management considerations.

i) Pregnant women

The staging of maternal syphilis is complex and includes a combination of history, physical examination, epidemiological features, direct tests from lesions and serological tests (2). The effectiveness of treatment regimens for syphilis in pregnancy is dependent on a number of variables including stage of maternal syphilis, timing of therapy (maternal gestational age), severity of fetal infection at the time of therapy, type and mode of administration of antibiotics and fetal tissue penicillin levels (45). Given the complexity of syphilis in pregnancy, all cases should ideally be managed in conjunction with a STI expert.

Pregnancy may cause false positive treponemal as well as non-treponemal tests and therefore, similar to non pregnant patients, it is important that confirmatory tests be conducted before making a diagnosis of syphilis (46,47). Seropositive pregnant women should be considered infected unless an adequate treatment history is clearly documented and sequential serological antibody titres have declined. Serofast antibody titres may not require re-treatment if previous treatment was adequate, but persistent higher titres (eg, $\geq 1:8$ dilutions) might indicate reinfection and re-treatment may be required.

ii) Neonates

Management and treatment decisions in the neonate must be made based on a combination of factors:

- diagnosis and stage of maternal syphilis, treatment history, adequacy of maternal treatment (based on maternal serological follow-up) and ongoing risk factors for syphilis in mother and
- clinical, laboratory or radiographic evidence of syphilis in the infant An infant should be fully evaluated (including lumbar puncture and long bone radiographs) if born to a seropositive mother who was

untreated, treated with suboptimal regimens or treated within one month of delivery and also if the expected decline in maternal NTT titre did not occur or if maternal follow-up is inadequate or not long enough to assess for adequate treatment response.

iii) Older infants/children

Children (>2 years) who are identified as having reactive serological tests for syphilis should have maternal serology and records reviewed to assess if they have congenital or acquired syphilis. In addition, all children with suspect congenital syphilis should have CSF analysis, CBC and differential and other tests as clinically indicated (eg, long bone and chest radiographs, liver function tests, ophthalmologic examination).

FOLLOW-UP OF INFANTS WITH REACTIVE SYPHILIS TESTS

All infants born to mothers with reactive syphilis serology should be followed as per recommendations in the Canadian Guidelines for STI Syphilis chapter and the Canadian Pediatric guidelines for congenital syphilis (2,18). In general, infants suspected of congenital syphilis, especially those who did not receive adequate treatment, should have syphilis serology repeated every two to three months to confirm seroreversion of maternally transferred TT/NTT antibodies (uninfected infants) or stable/rise in NTT titres with persistently positive TT (confirming congenital infection).

SUMMARY

With the resurgence of infectious syphilis in Canada, universal screening of all pregnant women continues to be important and remains the standard of care in most jurisdictions. Women at risk of acquiring or becoming re-infected with syphilis during pregnancy should be screened at regular intervals during the pregnancy and at the time of delivery. In areas experiencing heterosexual outbreaks of infectious syphilis, consideration should be given to re-screening all pregnant women at delivery. In addition, no newborn should be discharged from hospital prior to confirmation that either the mother or infant had syphilis serology collected during pregnancy or delivery and that the results can be followed up.

The assessment and management of syphilis in a pregnant women and newborn infant is complex and includes the need to determine the maternal stage of infection, gestational age of the fetus at the time of acquisition of maternal infection and treatment, adequacy of maternal treatment and maternal response to treatment. Infant evaluation includes a combination of laboratory tests including syphilis serological tests, radiographic tests and in some cases examination of cerebrospinal fluid. It is recommended that all pregnant women with syphilis and infants born to pregnant women with syphilis be managed in consultation with adult and pediatric experts.

DISCLOSURES: The authors have no conflicts of interest to declare.

REFERENCES

- 1. Public Health Agency of Canada. Report on Sexually Transmitted Infectious in Canada: 2011. http://www.catie.ca/sites/default/files/64-02-14-1200-STI-Report-2011_EN-FINAL.pdf (Accessed November 21, 2014).
- Public Health Agency of Canada. Canadian Guidelines on Sexually Transmitted Infections, Syphilis chapter, 2010. <www.phac-aspc.gc.ca/ std-mts/sti-its/pdf/510syphilis-eng.pdf> (Accessed December 8, 2010).

Singh et al

- 3. Walker DG, Walker GJ. Forgotten but not gone: The continuing scourge of congenital syphilis. Lancet Infect Dis 2002;2:432-6.
- Centers for Disease Control and Prevention. Sexually Transmitted Disease Treatment Guidelines, 2010. MMWR 2010;59:RR-12.
- 5. Dorfman DH, Glaser JH. Congenital syphilis presenting in infants after the newborn period. N Engl J Med 1990;323:1299-302.
- Jonna S, Collins M, Abedin M, Young M, Milteer R, Beeram M. Postneonatal screening for congenital syphilis. J Fam Pract 1995;41:286-8.
- Finelli L, Berman SM, Koumans EH, Levine WC. Congenital syphilis. Bull World Health Organ 1998;76(Suppl 2):126-8.
- Evans HE, Frenkel LD. Congenital syphilis. Clin Perinatol 1994;21:149-55.
- 9. Fiumara NJ. Syphilis in newborn children. Clin Obstet Gynecol 1975;18:183-9.
- Harter C, Benirschke K. Fetal syphilis in the first trimester. Am J Obstet Gynecol 1976;124:705-11.
- 11. Peterman TA, Newman DR, Davis D, Su JR. Do women with persistently negative nontreponemal test results transmit syphilis during pregnancy? Sex Transm Dis 2013;40:311-5.
- Stoll BJ. Congenital syphilis: Evaluation and management of neonates born to mothers with reactive serologic tests for syphilis Pediatr Infect Dis J 1994;13:845-52.
- Genc M, Ledger WJ. Syphilis in pregnancy. Sex Transm Infect 2000;76: 73-9.
- Berry MC, Dajani AS. Resurgence of congenital syphilis. Infect Dis Clin North Am 1992;6:19-29.
- Woods CR. Syphilis in children: Congenital and acquired. Semin Pediatr Infect Dis 2005;16:245-57.
- Brion LP, Manuli M, Rai B, Kresch MJ, Pavlov H, Glaser J. Long-bone radiographic abnormalities as a sign of active congenital syphilis in asymptomatic newborns. Pediatrics 1991;88:1037-40.
- Moyer VA, Schneider V, Yetman R, et al. Contribution of longbone radiographs to the management of congenital syphilis in the newborn infant. Arch Pediatr Adolesc Med 1998;152:353.
- Canadian Pediatric Society. Congenital syphilis: No longer just of historical interest. Paediatr Child Health 2009;14:1-5.
- Thorley JD, Holmes RK, Kaplan JM, et al. Passive transfer of antibodies of maternal origin from blood to cerebrospinal fluid in infants. Lancet 1975;1:651-53.
- Risser WL, Hwang LY. Problems in the current case definitions of congenital syphilis. J Pediatr 1996;129:499-505.
- Beeram MR, Chopde N, Dawood Y, Siriboe S, Abedin M. Lumbar puncture in the evaluation of possible asymptomatic congenital syphilis in neonates. J Pediatr 1996;128:125-9.
- 22. Golden MR, Marra CM, Holmes KK. Update on syphilis: Resurgence of an old problem. JAMA 2003;290:1510-4.
- Hooshmand H, Escobar MR, Kopf SW. Neurosyphilis. A study of 241 patients. JAMA 1972;219:726-9.
- 24. Davis LE, Schmitt JW. Clinical significance of cerebrospinal fluid tests for neurosyphilis. Ann Neurol 1990;27:211-2.
- Marra CM, Critchlow CW, Hook EW 3rd, Collier AC, Lukehart SA. Cerebrospinal fluid treponemal antibodies in untreated early syphilis. Arch Neurol 1995;52:68-72.
- 26. Sanchez PJ, Wendel GD Jr, Grimprel E, et al. Evaluation of molecular methodologies and rabbit infectivity testing for the diagnosis of congenital syphilis and neonatal central nervous system invasion by *Treponema pallidum*. J Infect Dis 1993;167:148-57.
- Michelow IC, Wendel GD Jr, Norgard MV, et al. Central nervous system infection in congenital syphilis. N Engl J Med 2002;346:1792-8.
- Rawstron SA, Mehta S, Marcellino L, Rempel J, Chery F, Bromberg K. Congenital syphilis and fluorescent treponemal antibody test reactivity after the age of 1 year. Sex Transm Dis 2001;28:412-6.

- Stoll BJ, Lee FK, Larsen S, et al. Clinical and serologic evaluation of neonates for congenital syphilis: A continuing diagnostic dilemma. J Infect Dis 1993;167:1093-9.
- Hollier LM, Harstad TW, Sanchez PJ, Twickler DM, Wendel GD. Fetal syphilis: Clinical and laboratory characteristics. Obstet Gynecol 2001;97:947-53.
- Meyer MP, Roditi D, Louw S. IgM rheumatoid factor removal and performance of the FTA-ABS (IgM) test in congenital syphilis. Genitourin Med 1992;68:249-53.
- 32. Herremans M, Notermans DW, Mommers M, Kortbeek LM. Comparison of a *Treponema pallidum* IgM immunoblot with a 19S fluorescent treponemal antibody absorption test for the diagnosis of congenital syphilis. Diagn Microbiol Infect Dis 2007;59:61-6.
- Schmitz JL, Gertis KS, Mauney C, Stamm LV, Folds JD. Laboratory diagnosis of congenital syphilis by immunoglobulin M (IgM) and IgA immunoblotting. Clin Diagn Lab Immunol 1994;1:32-7.
- Sanchez PJ, Wendel GD, Norgard MV. Congenital syphilis associated with negative results of maternal serologic tests at delivery. Am J Dis Child 1991;145:967-9.
- Herremans T, Kortbeek L, Notermans DW. A review of diagnostic tests for congenital syphilis in newborns. Eur J Clin Microbiol Infect Dis 2010;29:495-501.
- Romanowski B, Sutherland R, Fick GH, Mooney D, Love EJ. Serologic response to treatment of infectious syphilis. Ann Intern Med 1991;114:1005-9.
- Singh AE, Guenette T, Gratrix J, et al. Seroreversion of treponemal tests in infants meeting Canadian surveillance criteria for confirmed early congenital syphilis. Pediatr Infect Dis J 2013;32:199-202.
- Peeling RW, Ye H. Diagnostic tools for preventing and managing maternal and congenital syphilis: An overview. Bull WHO 2004;82:439-45.
- Cummings MC, Lukehart SA, Marra C, et al. Comparison of methods for detection of *Treponema pallidum* in lesions of early syphilis. Sex Transm Dis 1996;23:366-9.
- 40. Grimprel E, Sanchez PJ, Wendel GD, et al. Use of polymerase chain reaction and rabbit infectivity testing to detect *Treponema pallidum* in amniotic fluid, fetal and neonatal sera, and cerebrospinal fluid. J Clin Microbiol 1991;29:1711-8.
- 41. Martin IE, Tsang RSW, Sutherland K, et al. Molecular characterization of syphilis infection in Canada: Azithromycin resistance and detection of *Treponema pallidum* DNA in whole blood versus ulcers. J Clin Micro 2009;47:1668-73.
- Sheffield JS, Sanchezz PJ, Morris G, et al. Congenital syphilis after maternal treatment for syphilis during pregnancy. Am J Obstet Gynecol 2002;186:569-73.
- Schulte JM, Burkham S, Hamaker D, et al. Syphilis among HIV-infected mothers and their infants in Texas from 1988 to 1994. Sex Transm Dis 2001;28:315-20.
- 44. Lee MJ, Hallmark RJ, Frenkel LM, Del Priore G. Maternal syphilis and vertical perinatal transmission of human immunodeficiency virus type-1 infection. Int J Gynaecol Obstet 1998;63:247-52.
- Rolfs RT. Treatment of syphilis. Clin Infect Dis 1995;20:S23-38.
 Larsen SA, Steiner BM, Rudolph AH. Laboratory diagnosis and
- interpretation of tests for syphilis. Clin Microbiol Rev 1995;8:1-21. 47. Seña AC, White BL, Sparling PF. Novel *Treponema pallidum* complexies tests: A pagediam shift in symbilis acrosping for the 21st
- serologic tests: A paradigm shift in syphilis screening for the 21st century. Clin Infect Dis 2010;51:700-8.
- Parish JL. Treponemal infections in the pediatric population. Clin Dermatol 2000;18:687-700.
- 49. Hargrove A, Curtis N. Syphilis returns to the suburbs. Eur J Pediatr 2006;165:290-2.
- Chakraborty R, Luck S. Managing congenital syphilis again? The more things change. Curr Opin Infect Dis 2007;20:247-52.