Syphilis in pregnancy and congenital syphilis
Meena Ramchandani, MD, MPH

Syphilis among women and congenital cases in South Dakota, 2021
Dr. Mary Carpenter

Disclosures

Stockholder: Gilead and Merck

Caveat: Language is evolving, and though our aim is to change accordingly, we acknowledge that CDC guidelines are written using binary language with respect to gender.

The increase in congenital cases is a result of the increase in syphilis among women
Provisional Data, January - December 2021

Cases of Syphilis (all stages), SD, 2016-2021.
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Total # of women with Syphilis in 2021: 459
Of those, 16 (3%) turned into a congenital case
69 (15%) were pregnant at time of investigation

Counties with the highest number of pregnant women with syphilis. SD, 2021.
Provisional Data, January – December 2021

Pennington 35%
Todd 23%
Minnehaha 12%
Oglala Lakota 12%

Age range of pregnant women with syphilis. SD, 2021.
Provisional Data, January – December 2021

American Indian 35%
Black 77%
White 4%

Race of pregnant women with syphilis. SD, 2021.
Provisional Data, January – December 2021
Risk factors of pregnant women with syphilis. SD, 2021.

- Heterosexual... 38%
- Previous history... 62%
- Sex while intoxicated... 41%
- Engaged in IDU... 40%
- History of... 38%
- Partner who used IDU... 38%
- Anonymous partner... 5%

Of those 16 mothers...

- One (6.3%) had her first prenatal appointment (and testing) in the 2nd trimester, while in jail.
- Six (37.5%) had their first prenatal appointment (and testing) in the 3rd trimester, of which four (25%) took place 30 days or less before delivery.
- Six (37.5%) did not have any prenatal care and only were tested during labor/delivery.
- Thirteen (81.3%) were adequately treated, but six (37.5%) were treated after delivery.
- Three (18.8%) gave birth to a premature stillborn.

Cases of congenital syphilis by county. SD, 2021.

- Buffalo: 1
- Hughes: 1
- Minnehaha: 1
- Oglala Lakota: 2
- Pennington: 4
- Todd: 6
- Tripp: 1

Of the 13 alive newborns...

- One (7.7%) was born prematurely; all other births were a term.
- Seven (53.8%) had a reactive syphilis test.
- All newborns received treatment.
- One baby died of cardiac arrest at 5 months of age.
Overview

Focus on pregnant people and congenital syphilis
- Epidemiology
- Clinical manifestations of syphilis in adults and newborns
- Syphilis diagnosis in adults and newborns
  - Serologic testing
  - Diagnostic pathways and neonate management
- Treatment and follow-up

Primary & Secondary Syphilis – Reported Cases by Sex and Sex Behavior*, 2015-2019

Congenital Syphilis — Reported and Projected Cases by Year of Birth, US, 2010–2020

* 31 states able to classify ≥ 70% of cases
* Reported and projected 2020 congenital syphilis data are preliminary as of July 29, 2021.

Department of STD Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention
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Congenital syphilis – reported stillbirths and infant deaths, US, 2010-2020*

* Reported 2020 congenital syphilis data are preliminary as of July 29, 2021.

Congenital syphilis – case counts and rates of reported cases by race/ethnicity, US, 2020*

* Reported 2020 congenital syphilis data are preliminary as of July 29, 2021.

Congenital Syphilis — spread across the US, 2010–2019

SYPHILIS IN SOUTH DAKOTA

2021 DATA

ADULT SYphilis

- 874 infections reported
- 627% increase from 2020
- 1,050% increase from 5-year median

CONGENITAL / SYPHILITIC STILLBIRTHS

- 16 congenital and 4 syphilitic stillbirths
- 300% increase from 2019
- 700% increase in 5-year median

RISK FACTORS:

- 95% heterosexual exposure
- 45% history of other STIs
- 45% history of incarceration
- 5% American Indian
- 59% reported age range of 25-39 years old

- 36% sex while intoxicated
- 29% used IV drugs
- 21% cases reported among a institutionalized population

This is a preventable disease: awareness, aggressive screening, appropriate and timely treatment is key to prevention

Talk to public health if suspected case and call early!
Congenital Syphilis — Missed Prevention Opportunities among Mothers of Infants with Congenital Syphilis, United States, 2015–2019

Clinical manifestations and Staging

Patient Case

- Your patient is a 37 year old pregnant woman who presents to your clinic for routine testing.
- She has no symptoms, but has a positive RPR titer of 1:8 found on routine screening.
- Her confirmative TPPA is also reactive.
- She tests on occasion, and her last test was negative 2 years ago.
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Natural history and clinical staging of syphilis

Exposure
- 10-90 days
- Primary Syphilis: chancre(s)
- 4-10 weeks after chancre(s) disappear(s)
- Secondary Syphilis
- Latent Syphilis
  - Early (<1 year)
  - Late (>1 year)
- Late Complications
  - Up to 25%

Neurosyphilis can occur at any stage

Congenital syphilis

- Transplacental infection can occur during any stage of syphilis and at any time during gestation
- Results in spontaneous abortion, stillbirth, infant with active or latent syphilis
  - High morbidity and mortality
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Congenital syphilis

- Early Disease: detected before 2 years of age
  - 60% of infected infants symptomatic at birth
  - Symptoms: Stillbirth, HSM and liver dysfunction, Skeletal involvement, rash, CNS infection, nephrotic syndrome, rhinorrhea (snuffles), others
  - Leads to great morbidity/mortality
- Late Disease: detected after 2 years of age
  - Bony and/or teeth malformations, deafness, keratitis, neurosyphilis
- Get help from Pediatric ID if questions and call early!

Syphilis testing in pregnant adults

- Syphilis screening should occur 3 times during pregnancy!
  - First prenatal visit (or at time of pregnancy confirmation)
  - Third trimester (~28 weeks)
  - Delivery (and post-partum visit, if ongoing risk)
- Risk factors for syphilis acquisition in pregnancy
  - Sex with multiple partners
  - Transactional sex or sex + drug use
  - Late entry into prenatal care (first visit in 2nd trimester or later)
  - No prenatal care
  - Meth or heroin use
  - Incarceration of pregnant individual or their partner
  - Unstable housing or homelessness

Workowski et al. Sexually Transmitted Infections: Treatment Guidelines. MMWR Recomm Rep 2021;70(4)
Syphilis testing in pregnant adults, cont.

- Either algorithm is permitted. Use same quantitative NTT (and same lab, if possible) for adult/baby pair
- Serofastness is not uncommon. Higher titers (>1:8) might raise suspicion for re-infection and/or treatment failure
- If syphilis diagnosed in 2nd half of pregnancy, fetal sono recommended to evaluate for congenital abnormalities
- Testing recommended for any fetal death >20 wks EGA
- Neonates should not be dc’d unless syphilis status of mother has been determined

Syphilis testing in Pregnancy

- For evaluating pregnant persons/baby pairs near delivery:
  - Traditional Strategy might be more useful
  - Rapid comparison of maternal/infant RPR/VDRL (use only one test for comparison)
  - Implement management quickly
  - When access to prenatal care is not optimal→do RPR at time pregnancy is confirmed and treat if positive
- Can then follow testing with a treponemal specific test afterwards
- Second half of pregnancy: sonographic fetal evaluation for congenital syphilis.
  - This evaluation should not delay therapy
  - Sonographic signs: hepatomegaly, ascites, hydrops, fetal anemia, or a thickened placenta indicate a greater risk for fetal treatment failure
  - Consultation with obstetric specialists and peds ID
  - Call public health→they can help you!

Case

- 29 yo pregnant woman seen for first pregnancy visit. Her syphilis screening comes back with a reactive RPR (1:2) and a syphilis IgG that is positive.
- She recalls that she was treated for secondary syphilis 2 years ago. You obtain records and see that her initial titer was 1:256.
- After treatment, the RPR had fallen to 1:16 at six months, then to 1:2 at 1 year.
- The titer remained at 1:2 two years later.

Polling Question 2
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Syphilis in pregnancy: management tree

**REVERSE-SEQUENCE ALGORITHM**

- EIA, CMI, or other T pallidum immunoassay
- No further action needed in most cases (does not rule out incubating or early primary infection)

- No serologic evidence of syphilis
- No further action needed in most cases (does not rule out incubating or early primary infection)

- False-positive EIA/CMIA (Syphilis infection unlikely)
- OR New infection with early seroconversion

**TRADITIONAL ALGORITHM**

- Non-Treponemal Testing (RPR, VDRL)
- Treponemal Testing (FTA-ABS, TPPA, EIA)
- PTA-SSB, TP-PA, or EIA
- EIA pos, RPR neg, TP-PA neg

- Prior syphilis, abnormal exam, high prevalence community, partner is infected?
- No and able to f/u

- If e/o primary syphilis, treat
- Yes or unable to f/u
- If unable to confirm prior history, treat
- Repeat testing in 4 weeks. If RPR and TP-PA pos, treat

- Prior syphilis, abnormal exam, high prevalence community, partner is infected?
- No h/o adequately treated infection?
- No h/o treatment
- Stage infection and treat accordingly

- H/o adequately treated infection?
- No further work-up or treatment needed

- EIA pos
- RPR neg
- TP-PA pos

- EIA pos
- RPR neg
- TP-PA neg

- Chancre?
- Normal exam

- If e/o primary syphilis, treat
- Repeat testing in 4 weeks. If RPR and/or TP-PA pos, treat

- If unable to confirm prior history, treat
- Repeat testing in 4 weeks. If RPR and TP-PA neg, stop

- Prior syphilis, abnormal exam, high prevalence community, partner is infected?
- No and able to f/u

- Prior syphilis, abnormal exam, high prevalence community, partner is infected?
- No h/o adequately treated infection?
- No h/o treatment
- Stage infection and treat accordingly

- H/o adequately treated infection?
- No further work-up or treatment needed

- EIA pos
- RPR neg
- TP-PA pos

- EIA pos
- RPR neg
- TP-PA neg
### Neonatal syphilis testing

- Transplacental antibodies may persist for days to >15 months: use quantitative NTT, not treponemal!
- Serum specimen is preferred over cord blood or Wharton’s jelly
- Key elements for neonatal diagnosis
  - Serology and CSF evaluations
  - Detailed physical examination, including radiology
  - Placental or cord histopathology, including PCR testing
- Darkfield microscopy of skin lesions or body fluids (nasal discharge, etc.)

Call pediatric ID for help!

### Neonatal evaluation and treatment scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Exam</th>
<th>Titer relative to mother</th>
<th>Other considerations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven/Probable</td>
<td>Abnl*</td>
<td>≥4x</td>
<td>Positive darkfield, PCR, silver stain from placenta, cord, lesions, body fluid</td>
<td>Aqueous crystalline PCN G IV x10 days or procaine PCN G IM daily x10 days</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>≤4x</td>
<td>Mother inadequately treated (non-PCN bx) or within 30 days of delivery</td>
<td>May treat as above or with benzathine PCN G IM x1</td>
</tr>
<tr>
<td>Possible</td>
<td>Normal</td>
<td>≤4x</td>
<td>Mother appropriately treated &gt;30 days prior, no relapse/reinfection</td>
<td>Benzathine penicillin G IM x1 or monitor for RPR decline</td>
</tr>
<tr>
<td>Less likely</td>
<td>Normal</td>
<td>≤4x</td>
<td>Mother appropriately treated and titer low/stable</td>
<td>No treatment, follow serologically</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Normal</td>
<td>≤4x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Further eval with CSF, CBC w/ diff, long bone XR, other clinically indicated tests

* No missed doses permitted. Ceftriaxone IV may be ok if aqueous crystalline PCN shortage, no significant bilirubinemia, infant unable to tolerate IM – consult pediatrician/ID

### Other management considerations

- **Always ok to err on side of treatment** if any concern for undertreatment or re-exposure in parent
- Ampicillin ≠ benzathine/aqueous/procaine PCN
- Scenario 2 (possible): single dose benzathine PCN only if other testing is nl, CSF non-bloody and f/u is certain
- If neonate’s RPR is NR + parent is “low risk” – may consider benzathine PCN x1 w/o addl. eval for “incubating” syphilis
Syphilis treatment in pregnant adults

<table>
<thead>
<tr>
<th>Table. Treatment recommendations for syphilis during pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
</tr>
<tr>
<td>Early non-primary, non-secondary</td>
</tr>
<tr>
<td>Late syphilis (&gt;1 year or unknown duration)</td>
</tr>
<tr>
<td>Neuro or ocular syphilis</td>
</tr>
</tbody>
</table>

- Avoid tetracyclines in 2nd and 3rd trimester
- Optimal timing between doses is 7 days; up to 9 days may be permitted, otherwise restart course
- If PCN-allergic: urgent skin testing to confirm desensitization
- Engage OHA or local HD for partner services to get contacts tested and treated!

Jarisch-Herxheimer reaction

- **Pregnancy:** >20 weeks are at risk for premature labor and/or fetal distress (stillbirths are rare)
- Acute febrile reaction after initiation of antibiotics for the treatment of spirochetal infections, due to release of endotoxins and lipoproteins
- May cause malaise, nausea, vomiting, chills, exacerbation of rash.
- Seek obstetric attention if fever, contractions, or decreased fetal movement
- Typically resolves within 24 hours with supportive care; steroids not beneficial
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### Partners Needing Evaluation

- **Primary, secondary, early latent syphilis** - 3 months plus the duration of symptoms

### Partner Testing and Treatment

- **Contacts** – sex in 90 days preceding onset of case’s symptoms
  - Test and treat with 1st dose Benzathine PCN without waiting for test results
- **Contacts** – >90 days since last sex
  - Test – Treatment based on results and staging
  - Treat if testing not available or follow-up uncertain
- **Late latent syphilis**
  - Test partners

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### Follow up for the pregnant adult

- **If syphilis, always test for HIV!**
- **Monitoring is based on stage of pregnancy at diagnosis**
  - **Before/at 24 weeks EGA:** soonest to repeat titers is 8 weeks after tx
    (unless new signs/sx of 1ˢᵗ or 2ⁿᵈ syphilis)
  - **After 24 weeks EGA:** repeat titers at delivery
- **Consider monthly titer checks for those with ongoing risk factors**
- **Many may not achieve fourfold decrease before delivery**
- **Concern for re-infection or tx failure:** if sustained (>2 wks) fourfold titer increase after tx

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### Follow up for the neonate

- **If syphilis, always test for HIV!**
- **Physical exam and NTT titers every 2-3 mos. until neg**
- **Scenarios 3 & 4:** NTT titers should decrease by 3 mos. and be neg by 6 mos. If still positive → treat infant
- **If persistent NTT titers ≥6 months despite tx, consult OHA/pediatric ID and consider CSF eval**
- **If concern about “incubating” syphilis (initial NTT was neg), retest at 3 mos.**

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### Late congenital syphilis

- **Children >1 month with positive serologies**
  - Evaluation including CSF VDRL, cell count, protein, CBC
  - Other tests as clinically indicated
- **Parent’s serologies and records to differentiate congenital vs acquired syphilis**
- **Child should be tested for HIV**
- **Consider endemic treponematoses in adoptees, immigrants, refugee children from endemic countries**
- **Assess for sexual assault and child abuse – report!**
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Summary and conclusions

- Rates of syphilis are increasing – both congenital syphilis and in adults of childbearing potential
- Be aware of your local epidemiology and risk factors in pregnancy. If in doubt, always ok to treat (and test)!
- Screening for syphilis and appropriate treatment are imperative in pregnancy
- PCN is drug of choice
- Treat index patients and all contacts
- Congenital syphilis can be prevented! Public health can provide support for diagnosis and treatment

CONGENITAL SYphilis (CS)
Evaluation and treatment of infants (<30 days old) born to women with syphilis during pregnancy*

Start
ALL INFANTS AND MOTHERS SHOULD HAVE SERUM RPR OR VDRL TITER DRAWN AT DELIVERY

Infant and Maternal Criteria

Infant Criteria:
- CS findings on physical exam
- Positive darkfield or PCR of lesion/body fluid

Maternal Criteria:
- Not treated
- Inadequately treated†
- Treatment undocumented
- Treated with a non-benzathine penicillin G regimen

No to all

Scenario 1:
Proven or Highly Probable CS
- CSF analysis
  - VDRL, cell count, and protein
- Complete blood count (CBC), differential, and platelet count
- Long-bone radiographs
- Tests as clinically indicated by signs on physical exam.

Aqueous crystalline penicillin G‡
100,000–150,000 units/kg/day, administered as 50,000 units/kg/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days

Scenario 2:
Possible CS
- CSF analysis
  - VDRL, cell count, and protein
- CBC, differential, and platelet count
- Long-bone radiographs

Any abnormalities, results not available,
OR follow-up uncertain

No abnormalities
AND follow-up certain

Benzathine penicillin G
50,000 units/kg/dose IM in a single dose

Scenario 3:
Less Likely CS
No additional infant evaluation
Review Maternal Titers & Stage:
- Treatment for early syphilis
OR
- Stable titer for low-titer, latent

No to both
OR follow-up uncertain

Yes to either
AND follow-up certain

No treatment indicated
with close serologic follow-up of infant every 2-3 months for 6 months


South Dakota Recommendations

PRENATAL CARE PROVIDERS
- All pregnant women should be screened for syphilis three times during pregnancy during this outbreak setting:
  - At first prenatal appointment or at time of initial pregnancy diagnosis if concerned for poor follow up
  - At 28 weeks
  - At delivery
- All pregnant women delivering a stillbirth (gestational age ≥20 weeks)

In an effort to stop congenital syphilis: SD-DPH recommends enhancing syphilis screening to emergency room departments and urgent care. In 2021 South Dakota mothers associated with congenital syphilis stillbirths had insufficient, late, or no prenatal care; however, some of these women and/or their partners were seen in emergency rooms and urgent care for reasons other than prenatal care. Screening women of reproductive age (15-45 years) and sex partners (women of reproductive age or another woman or person with whom they engage in sexual activity) can reduce congenital syphilis.

ADJUDICATE TREATMENT FOR INFECTED CASES DURING PREGNANCY
- Completion of a penicillin-based regimen, appropriate for stage of infection, initiated 30 or more days before delivery
- Pregnant women MUST be treated with penicillin. If allergic, she must be desensitized and treated to stage of illness.

No infant should leave the hospital without the mother’s serological status documented at delivery

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No infant should leave the hospital without the mother’s serological status documented at delivery
Additional resources

University of WA STD Prevention Training Center
  • [www.uwptc.org](http://www.uwptc.org)

National Network of STD/HIV Prevention Training Centers
  • [www.nnptc.org](http://www.nnptc.org)

CDC Treatment Guidelines
  • [www.cdc.gov/std/treatment-guidelines](http://www.cdc.gov/std/treatment-guidelines)

American Social Health Association (ASHA) booklets, books, handouts, the Helper
  • [www.ashastd.org](http://www.ashastd.org)
  • (800) 230-6039