Document facilitator: Infectious Diseases Registrar

Senior document owner: **Infectious Diseases Clinical Leader**

Document number: 1.104086 **Issue Date** 10 Sept 2019 .**Review Date** 10 Sept 2022

Type: Guideline

Name: Syphilis in pregnancy and congenital syphilis

Purpose

To provide guidance for screening, recognition, treatment and follow up of syphilis in pregnancy for those involved in antenatal and perinatal care to prevent vertical transmission from mother-to-baby.
To provide guidance for the prevention, evaluation and treatment of congenital syphilis.

Scope

- All Midwives
- All Obstetricians, Registrars and Senior House Officers
- All Neonatologists, General Paediatricians, Registrars and Senior House Officers
- All Infectious Diseases Physicians and Registrars
- All Sexual health Physicians and Registrars

Contents:

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Syphilis in Pregnancy Summary:

- Syphilis screening is recommended for all pregnant women in the 1st antenatal screen (first trimester).
- Repeat syphilis screening is recommended for women at risk for new infection at 28-32 weeks and at birth.
- **Any pregnant woman with a positive syphilis test should be discussed with an Infectious diseases specialist or Sexual health physician**.
- **Every effort should be made to identify and treat her sexual contacts**
- Treatment is required for all pregnant women with active syphilis to prevent mother-to-child transmission to the fetus. Treatment is as below:

Stage	Treatment
Early latent, primary or secondary syphilis *EIA +ve TPPA +ve RPR ≥ 1:2 with no history of treatment*	Single dose IM Benzathine penicillin 2.4 million units
Early latent, primary or secondary syphilis **in the third trimester** *EIA +ve TPPA +ve RPR ≥ 1:2 with no history of treatment*	2 doses of IM Benzathine penicillin 2.4 million units (1.8g) one week apart
Late latent syphilis *EIA+ve TPPA+ve RPR 1:1 or -ve with no history of treatment*	IM Benzathine penicillin 2.4 million units (1.8g) once weekly for 3 weeks *Note this is for maternal treatment, transmission to fetus unlikely*
Neuro-syphilis or ocular syphilis *(serum RPR is usually ≥ 1:8)*	IV Benzylpenicillin 1.8g IV Q4H for 10-14 days (may be given by continuous IV infusion 10.8g/24hours)

- If treatment is given after 20 weeks gestation, discussion with the MFM SMO around appropriate fetal monitoring is required.
- Following successful treatment of the woman and her partner, the major ongoing risk for congenital syphilis is maternal re-infection. Once treated, pregnant women with syphilis should have a follow up RPR performed at 28-32 weeks and at birth as a minimum, or monthly if high risk.
- All pregnant women with a new diagnosis of syphilis requires up to date HIV, chlamydia and gonorrhoea testing. A genital examination is always required.
- Contact tracing and treatment of contacts should be performed by infectious diseases or sexual health teams.

Background

Syphilis is caused by the spirochete *Treponema pallidum*. The disease is sexually transmitted and can be vertically transmitted through the placenta to baby resulting in congenital syphilis. The disease can manifest in 3 different stages – Primary, secondary and tertiary disease. Latent disease can also occur with asymptomatic patients detected on screening.

Primary syphilis presents with an ulcer or chancre at the site of infection. The ulcer is usually painless with a well-defined edge and indurated base. Presentation is on average 3 weeks after acquisition (incubation period 10-90 days).Secondary syphilis usually presents with constitutional symptoms such as fever, malaise, headache and lymphadenopathy. A rash often occurs typically involving the palms and soles but also may affect the trunk. There may be alopecia and condylomata lata (warty growths in the ano-genital area). There may also be neurological signs of cranial nerve palsies, ophthalmic signs and meningitis. Hepatitis may also be present. Presentation is on average 6 weeks after acquisition (range 2-24 weeks). Tertiary syphilis can occur after several months to years of untreated infection. This may involve the brain and spinal cord (neurosyphilis), cardiovascular system or cause skin lesions (gummas). Latent syphilis is when a person tests positive for syphilis infection without any symptoms. Early latent syphilis is defined as positive serology with no symptoms and infection acquired within the last 2 years. Late latent syphilis is defined as positive serology with no symptoms and acquisition >2 years. If there is any doubt about the time of acquisition, it should be treated as late latent syphilis.

Transplacental transmission to the fetus can occur at any stage of pregnancy and at any stage of disease. The risk is highest in the early stages of infection (primary or secondary syphilis). The risk of congenital syphilis in adequately treated women is between 1-2% with the highest risk in those with secondary syphilis or within 4 weeks of birth. Babies born to all women treated for syphilis in current pregnancy require evaluation at birth.

In the absence of effective treatment, the impact of syphilis infection include second trimester miscarriage or stillbirth (25%), neonatal death at term (11%), or preterm or low birth weight infant (13%). 27% of untreated babies who survive to 30 days are likely to develop symptoms of congenital syphilis. Prior to delivery, sonographic signs of congenital syphilis include hepatomegaly, ascites, hydrops, fetal anaemia or a thickened placenta. Longer term implications include multi-system manifestations such as deafness, neurologic impairment, developmental delay, and bone deformities.

Congenital syphilis can be prevented through early screening of all pregnant women and identification of high risk pregnancies with appropriate testing and treatment.

Diagnostics

Serology is the diagnostic test of choice in pregnancy. Approximately 50% of women will have no symptoms and will only be diagnosed by serological testing. An Enzyme immunoassay (EIA) is used as the initial screening treponemal test and all positive EIA tests will automatically have a second treponemal test (TPPA) and non-treponemal test (RPR). If the TPPA is positive then current or past treponemal infection is confirmed. The treponemal tests (TPPA/EIA) will stay positive for life.

The RPR provides a quantitative result that correlates with disease activity and can be used to monitor adequacy of treatment.

Successful treatment is associated with a fall in the RPR >4 fold (i.e. from 1:16 to 1:4) or reduction to non-reactive. This can be highly variable and if interpretation is unclear, please discuss with a Clinical microbiologist.

Biological false positives can occur (EIA or TPPA Negative, RPR positive) but there may be false negatives in early infection. If at risk of early infection or contact of syphilis, give treatment. If low risk, repeat at 4 weeks. See summary table for further interpretation of results.

Contact tracing

- Contact tracing should be actively performed by either Infectious diseases or Sexual health teams.
- Sexual contacts within 3 months of those with primary, secondary or early latent syphilis should be offered treatment, even if initial serology is negative, or abstain from unprotected sex.
- Long-term sex partners of those with latent syphilis should be evaluated and treated based on evaluation.
- Contact tracing period:

Stage of index case	Look-back period
Primary	Duration of symptoms plus 3 months
Secondary	Duration of symptoms plus 6 months
Early latent	12 months

Notification

- All cases of infectious syphilis cases are notifiable – this should be performed by the treating team.
    - Infectious diseases or sexual health teams will notify for the pregnant woman
    - Paediatrics or neonatologists will notify for cases of congenital syphilis
- The forms can be accessed on the ESR STI surveillance page - https://surv.esr.cri.nz/public_health_surveillance/sti_surveillance.php
- Case definitions for infectious syphilis and congenital syphilis for ESR area available on the Ministry of Health website.

Antenatal care

- All pregnant women should be offered screening of syphilis at their first antenatal appointment or at the time of confirmation of pregnancy.
- The aim is that all pregnant women receive their first antenatal blood test during the first trimester.
- All pregnant women, especially those with syphilis should have a sexual history taken in a manner that allows an assessment of risk of new infection with syphilis or other STI. Those at risk should be offered another test in the third trimester or at birth.

- Offer re-screening between 28-32 weeks (or at any time at the woman's request) for women with risk factors. These may include:
    - Women with previous syphilis
    - Women who have a new sexual partner since pregnancy registration
    - Women with more than one sexual partner during pregnancy
    - Women with an STI diagnosed during pregnancy or whose partner is diagnosed with an STI.
- Recommend testing or retesting for syphilis at any gestation if symptoms are present:
    - Symptoms of a primary infection include maternal ulcerative skin lesions (most common sites are vulva, vagina, anus, occasionally lips/mouth).
    - Secondary stage symptoms include skin rashes on hands, soles of feet or other parts of the body and/or flu like symptoms.
- Women should be tested at delivery if no tests have been performed earlier in pregnancy.(refer to GA CL-23 "Unbooked woman" policy)
- Any pregnant women who are sexual contacts of a known or suspected syphilis case should be presumptively treated with a single dose IM Benzathine penicillin 2.4 million units (1.8g) irrespective of their initial test result.
- Any woman who has a fetal death after 20 weeks gestation should be tested for syphilis.
- If there are abnormal fetal ultrasound findings – i.e. IUGR, fetal hydrops, ascites or hepatosplenomegaly, review maternal syphilis serology and/or repeat testing.

Management of the pregnant woman with positive syphilis test

All pregnant women with a positive syphilis test in pregnancy should be referred to a Sexual health physician or Infectious diseases specialist to assist with assessment, treatment guidance, and contact tracing.

- If patient seen in WHAS or women diagnosed after 20 weeks, refer to Infectious Diseases registrar or consultant (Contact details via Switchboard).
- If patient in community, refer to the Sexual health Service- on call consultant available on 0508 14441.

Treatment

Treatment should be given according to the stage of disease (Primary, Secondary, Early or late latent, Tertiary) and must be done only after discussion with Sexual health Physician or Infectious Diseases Team.

Stage	Treatment
Early latent, primary or secondary syphilis *EIA +ve TPPA +ve RPR ≥ 1:2 with no history of treatment*	Single dose IM Benzathine penicillin 2.4 million units
Early latent, primary or secondary syphilis **in the third trimester** *EIA +ve TPPA +ve RPR ≥ 1:2 with no history of treatment*	2 doses of IM Benzathine penicillin 2.4 million units (1.8g) one week apart

Late latent syphilis *EIA+ve TPPA+ve RPR 1:1 or -ve with no history of treatment and unknown acquisition*	IM Benzathine penicillin 2.4 million units (1.8g) once weekly for 3 weeks *Note this is for maternal treatment, transmission to fetus unlikely*
Neuro-syphilis or ocular syphilis *(serum RPR is usually ≥ 1:8)*	IV Benzylpenicillin 1.8g IV Q4H for 10-14 days (may be given by continuous IV infusion 10.8g/24hours)

Treatment:

- If there is any doubt about the time of acquisition in latent disease, it should be treated as late latent syphilis.
- Treatment must be administered as promptly as possible after the positive result. If there has been an unavoidable delay for over 2 weeks, repeat serology should be performed on the day of treatment.
- CDC guidelines recommend a single dose for Primary, Secondary and Early latent syphilis. There is some evidence for the use of 2 doses based on expert opinion and clinical practice, although no head to head trials have been performed.
- All women with a positive test should be offered repeat HIV and other STI screening.
- Women should avoid sexual contact until any genital lesions resolve or 2 weeks after treatment completed.
- All sexual partners should be contact traced and subsequently treated. This should be done by the same team (Infectious diseases or Sexual health) seeing the pregnant woman. See below for contact tracing.
- **Treatment and recommendations around birth should be clearly documented in clinical notes. A birth plan (appendix 1) should be filled out and included in the maternity care plan.**

Important notes:

- **Benzylpenicillin cannot be substituted for long acting Benzathine penicillin**
- Benzathine penicillin can be ordered from the hospital pharmacy in working hours, or if out of hours, contact the on call pharmacist. Benzathine penicillin must be kept in the fridge, but should be warmed in a hand before injection..
- Missed doses are not acceptable for pregnant women receiving treatment for late latent disease. If any are missed the full course should be repeated.
- Penicillin allergy should be discussed with the ID team to arrange desensitisation or advise about alternative treatment.
- Tetracycline and doxycycline are contraindicated in the second and third trimester of pregnancy.
- Macrolides, ceftriaxone and azithromycin are not recommended for treatment.

Jarisch-Herxheimer reaction

- Up to 40% of patients may develop a transient inflammatory reaction in the first 24hrs after treatment, especially in early syphilis. Symptoms include fever, chills, myalgias and headaches and is known as a Jarisch-herxheimer reaction. It typically begins within 1-2 hours, peaks at 8 hours and lasts about 24hrs.

- In pregnancy, the Jarisch-herxheimer reaction may trigger uterine contractions, preterm labour and/or non-reassuring fetal heart rate tracings.
- Women being treated for early syphilis after 20 weeks should be monitored during treatment due to the increased risk of pre-term labour. Women in this group should be referred to the obstetric team for inpatient treatment.
- There is no evidence that steroids reduce the Jarisch-herxheimer reaction in pregnant women, therefore they are usually not recommended for prevention.

Monitoring and follow up

- Repeat serology should be performed to ensure RPR levels drop appropriately and to check there has been no re-infection. At a minimum, this should be repeated at 28-32 weeks and at delivery, or monthly if at high risk of re-infection. This should be directed and chased by the Infectious diseases or Sexual health teams.
- If RPR levels increase or do not fall as expected, previous treatment should be reviewed if adequate and should be re-discussed with either the sexual health team or infectious diseases.
- Any woman treated for syphilis in pregnancy should be referred to obstetrics for ultrasound monitoring and follow up in the maternal foetal medicine clinic.
- Women with syphilis in pregnancy should have post-partum follow up with Sexual health or the Infectious diseases team.

Management around delivery

- Intrapartum care for women treated for syphilis in pregnancy is as per normal procedures
- Breastfeeding is not normally contraindicated unless there is an active syphilis lesion on the breast.
- The placenta should be sent for histology and PCR if the newborn is at high risk of congenital infection (See below for risk stratification). Fresh tissue is required for PCR testing.
- Ensure Neonatal staff are informed and present for the birth
- If there is inadequate treatment prior to delivery or a high suspicion for congenital syphilis, gloves should be worn for handling the newborn as they are potentially contagious until 24hrs of penicillin treatment has been completed.

Care of the newborn and congenital syphilis summary

- Babies with suspected congenital syphilis must be assessed by a neonatologist or paediatrician
- Notify Neonatal staff regarding the birth of any child from a mother treated for syphilis in pregnancy
- Paired serology from mother and baby is required for diagnosis – Cord blood cannot be used.
- Discuss diagnostic testing with Clinical microbiologist if there is suspicion for congenital syphilis.
- Treatment:

	Treatment
Newborn (0-7 days old) Proven, highly probable congenital syphilis. Asymptomatic, possible congenital syphilis. • If Maternal treatment was: ○ Inadequate ○ Unknown ○ Non-penicillin regimen	Benzylpenicillin 50mg/kg IV every 12 hrs during the first 7 days of life and every 8 hours thereafter for a total of 10 days OR Procaine Penicillin 50mg/kg IM daily for 10 days
Newborn (8-30 days of age)	Benzylpenicillin 50mg/kg IV every 8 hours for 10 days Alternative: Procaine penicillin 50mg/kg IM daily for 10 days
Greater than 30 days of age	Benzylpenicillin 50mg/kg IV every 4-6 hourly for 10 days Alternative: Procaine penicillin 50mg/kg IM daily for 10 days

- Babies with possible, proven or highly probable congenital syphilis should be followed up by the paediatrics team and have repeat serology at 3, 6 and 12 months or until RPR non-reactive on 2 occasions.

Care of the newborn

- Low risk- If the mother is treated appropriately >4 weeks before birth with dropping RPR, the risk is low.
    - Follow up involves a clinical examination and paired serology (neonate and mothers serology) taken at birth.
    - Repeat serology should be performed 3 monthly in infant until negative.
    - If infant serology is negative at birth and at 3 months, no further testing is required.
- All others are considered high risk. Clinical examination, paired serology, CSF examination and placental evaluation should be performed and treatment consideration as below.
- A precautionary single dose Benzathine penicillin 50mg/kg IM may be considered if there is concern about serological follow-up for a baby in whom congenital syphilis is considered unlikely but cannot be completed excluded. This must only be done on discussion with a specialist.
- Do NOT use cord blood for serological testing. Serum from the neonate is required for serology.

Congenital syphilis

60-90% of newborns with congenital disease will have no clinical signs at the time of birth. Early signs and symptoms are often subtle and non-specific. Suspect congenital syphilis in: babies born to women who had syphilis requiring treatment in pregnancy irrespective of adequacy of treatment, limited or no antenatal care, are diagnosed as having syphilis (any stage) within three months postpartum.

Babies with suspected congenital syphilis must be assessed by a neonatologist or paediatrician. The maternal serology and treatment history should be available.

- Early signs:
    - Fever
    - Hepatosplenomegaly, Hepatitis, Jaundice
    - Skin or mouth lesions
    - Rhinitis, ulceration of nasal mucosa - “snuffles”: usually during the first week of life and rarely after the third month. Nasal discharge contains spirochaetes and is contagious via direct contact.
    - Inflammation of long bones (osteochondritis, perichondritis)
    - Haematologic disturbances (anaemia, thrombocytopenia, leukopenia or leucocytosis)
    - Low birth weight, failure to thrive
    - Necrotising funisitis – inflammation of the umbilical cord
    - Rash: usually appears 1-2 weeks after rhinitis and commonly presents with pealing of the hands and feet and a maculopapular rash
    - Generalised lymphadenopathy: palpable epitrochlear lymphadenopathy is highly suggestive of syphilis infection
- Investigations:
    - RPR serology paired with mother (do not use umbilical cord blood due to risk of false positive)
    - Placental histology

- PCR swab of lesions, secretions or placenta – please discuss with clinical microbiology
- CSF examination
- FBC
- Long bone X-rays
- CXR
- LFTs
- Ophthalmologic exam
- Audiologic examination (auditory brain stem response)
- Neuroimaging

Diagnosis:

- Proven, highly probable congenital syphilis:
  - Abnormal physical examination consistent with congenital syphilis OR
  - A serum RPR titre fourfold high than the mother's titre OR
  - PCR of lesions or body fluids
- Possible congenital syphilis
  - Normal clinical examination, serum RPR equal to or less than fourfold the maternal titre AND
  - Mother not treated, inadequately treated or no documentation of treatment OR
  - Mother treated with non-penicillin regimen OR
  - Mother received recommended treatment <4 weeks before delivery OR
  - Placental investigations are positive

Treatment

	Treatment
Newborn (0-7 days old) Proven, highly probable congenital syphilis. OR Asymptomatic, possible congenital syphilis. • If Maternal treatment was: o Inadequate o Unknown o Non-penicillin regimen	Benzylpenicillin 50mg/kg IV every 12 hrs during the first 7 days of life and every 8 hours thereafter for a total of 10 days OR Procaine Penicillin 50mg/kg IM daily for 10 days
Newborn (8-30 days of age)	Benzylpenicillin 50mg/kg IV every 8 hours for 10 days Alternative: Procaine penicillin 50mg/kg IM daily for 10 days
Greater than 30 days of age	Benzylpenicillin 50mg/kg IV every 4-6 hourly for 10 days Alternative: Procaine penicillin 50mg/kg IM daily for 10 days

- Babies with possible, proven or highly probable congenital syphilis should be followed up by the paediatrics team and have repeat serology at 3, 6 and 12 months or until RPR non-reactive on 2 occasions.
- The treatment duration of 10 days does not change for neurosyphilis (VRDL positive on CSF testing). If positive at birth then repeat CSF at 6 months for VRDL, cell count and protein. Retreatment indicated if repeat CSF is abnormal.
- Decline in antibody titres is usually seen by 3 months in the uninfected baby. If initial baby's serology and testing was negative and the mother was adequately treated, follow-up at 3 and 6 months. If serology remains negative at 6 months then no further testing is required.
- Serum RPR (non-treponemal test) should be negative by 12 months, if not, seek expert advice.

References

1. *CDC syphilis guidelines - https://www.cdc.gov/std/tg2015/syphilis-pregnancy.htm*
2. *ASHM STI management guidelines -http://www.sti.guidelines.org.au/sexually-transmissible-infections/syphilis#management*
3. *WHO guidelines for the treatment of Treponema pallidum (syphilis). 2016*
4. *ASID Management of Perinatal infections 2014*
5. *South Australian Perinatal Practice Guideline - Syphilis in Pregnancy*
6. *Syphilis in pregnancy and congenital syphilis birth plan -Waikato DHB guidelines*
7. *Rac MW, Revell PA, Eppes CS. Syphilis during pregnancy: a preventable threat to maternal-fetal health. Am J Obstet Gynecol 2017; 216:352.*
8. *SR Arnold, EL Ford-Jones. Congenital syphilis: A guide to diagnosis and management. Paediatr Child Health 2000;5(8):463-469.*
9. *Alexander J. M., Sheffield J. S., Sanchez P. J., Mayfield J., Wendel G. D., Jr. Efficacy of treatment for syphilis in pregnancy. Obstetrics & Gynecology. 1999;93(1):5–8.*

Appendix

Appendix 1: Example birth plan

Appendix 1. Example birth plan

Mother's Details	
Name	
Address	
DOB	
NHI	
Phone number(s)	
Estimated Date of Delivery	
❑ Mother's consent to record SHC code in hospital records ❑ SHC Lab Code (to search for maternal RPR in LIS)	
Delivery Team Actions	
❑ No need to contact on-call paediatric team from syphilis viewpoint	
❑ Contact on-call paediatric team when baby is delivered	
❑ Send placenta for histology and treponemal PCR if syphils treatment indicated for infant	

Congenital Syphilis Risk

Congenital syphilis unlikely	Higher risk of congenital syphilis
❑ Maternal treatment completed	❑ **Maternal infection: partial or no treatment***
❑ Treated with penicillin	❑ **Treated with non-penicillin***
❑ Treatment completed >30 days pre-delivery	❑ **Treatment <30 days before delivery***
❑ 4x drop in RPR achieved	❑ 4x drop in RPR not achieved
❑ Final RPR titre ≤1:4 (VDRL 1:2)	❑ Final RPR titre >1 in 4 (VDRL >1 in 2)

*The presence of any of the 'bold asterisk' factors above means inadequate maternal treatment & requires neonatal treatment at birth. Also, congenital syphilis can still occur despite the absence of the three 'bold' factors.

Maternal Syphilis Care

[Include stage, treatment & treatment dates, most recent RPR, whether coded or under NHI, & any concerns e.g. re-infection risk from partner, treatment late in pregnancy, etc]

❑ Low risk: assess infant clinically; if no physical signs of syphilis check 'initial blood tests' (page 6)
OR
❑ High risk: treat infant at birth after clinical assessment, 'initial blood tests' and 'further tests' (page 6)

Please discuss all infant blood test results with Paediatric Team

Sexual Health Physician:
Signed: Date:

Birth Plan Form to be given to the patient with copies to: Paediatric SMO, LMC +/- Obstetric SMO if high risk, and GP