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Congenital Syphillis: On the Rise Again

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Abstract

Congenital syhllis (CS) is still a worldwide problem,although completely preventable.Suboptimal or absent prenatal care due to gaps in race, ethnicity and insurance play a major role. In some countries shortages and fragile delivery systems of penicillin G are also a contributing factor, as well as rising incidences of STDs among all adults. Antenatal screening and treatment of CS is difficult in low-resource countries and remote areas. People don't see syhillis as a serious disease like Zika or HIV. Therefore, awareness of CS and public health efforts should be enhanced further.

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Introduction

Congenital syphillis (CS) rises in a startling tempo in the U.S., according to a 2016 CDC alert n the bimonthly newsletter from the Association of Maternal & Child Health Programs [1]. The data are alarming.In 2015, women accounted for about one in 10 syphillis cases. National data show a 25 percent increase in syphillis among pregnant women from 2012-2014. In 2014, nearly one in five women with syphillis was pregnant. Paralleling the increase in syphyllis amonng women of reproductive age is a sharp increase in the number of babies born with congenital syphillis (CS). In fact, the number of CS cases is the highest since 2001. Each case is totally preventable.

Almost one quarter of cases are due to a lack of any prenatal care. Although the majority of pregnant women infected with syphilis received some prenatal care, maternal syphillis is often detected and treated too late. Of women who gave birth to an infant with CS, 42 percent were not tested in time to prevent CS. The U.S. is not unique in the rising incidence of CS.Australia has seen a dramatic increase of cases of CS too [2]. Also, in Brazil is CS on the rise. Syphillis infections among pregnant women in Brazil are reported 49 times higher than a decade ago [3]. Syphyllis is far deadlier than Zika, but people don't see syphillis as a serious disease like HIV and Zika. For this reason CS will be dicussed in this mini-review. Epidemiology, pathophysiology treatment and prevention are reviewed.

Epidemiology

In 2012, WHO estimated 930.000 maternal syhillis infections caused 350.000 adverse pregnancy outcomes including 143.000 early fetal death and stillbirths, 62.000 neonatal deaths, 44.000 preterm or low weight births and 102.000 infected infants with CS. Nearly 80% of adverse outcomes (274.000) occured in women who received anenatal care at least once. Comparing the updated 2008 estimates with the 2012 estimates, maternal syphllis decreased by 38% and congental syphillis decreased by 39%. The prevalence in all WHO countries

is 0, 66%. The distribution of maternal syphillis infections and adverse outcomes varies across regions. The burden of syphillis in pregnancy was greatest in Africa (prevalence 1,68%) and lowest in Europe (prevalence 0,15%)-[4].

Pathophysiology

Syphillis is caused by the gram-negative bacterium Treponema pallidum.It is further divided into the primary, secondary and tertiary stages based on the signs and symptoms of the disease. Infection of the fetus from the infected mother results n CS. In the first four years of acquiring syphillis, untreated women have a 70% chance of transmitting their infection to the fetus. If untreated for syphillis, 40% of these pregnancies result in perinatal death.

Even the live born neonates are infected and can develop acute systemic illness, bone deformities, developmental disabilities, blindness or deafness. Fifty percent of the infected neonates will manifest these problems immedately, whereas others will develop these later in life. There is strong evidence that syphillis, like other causes of genital ulcers, enhances human immunodefciency virus (HIV) transmission [5].

Symptoms and signs

Many patients are asymptomatic and the infection may remain clinnically silent throughout their life.

Early CS

This manifests during the first three months of life. Manifestations include characteristic vesicobullous eruptions or a macular copper=coloured rash on the palms and soles and papular lesions around the nose and mouth and in the diaper area, as well as petechial lesions. Generalized lymphadenopathy and hepatosplenomegaly often occur. The infant may fail to thrive and have a characteristic mucopurulent or blood-stained nasal discharge causing snuffles.

A few infants develop meningitis, choroiditis, hydrocephalus, or seizures, and others may be intellectually disabled. Within the first 8 months of life, osteochondritis (chondroepiphysitis), especially on the long bones and ribs, may cause pseudoparalysis of the limbs with characteristic radiologic changes in the bones.

Late CS

This manifests typically after 2 years of life and causes gummatous ulcers that lead to involve the nose, septum and hard palate and periosteal lesions that result in saber shins and bossing of the frontal and parietal bones. Neurosyphillis is usually asymptomatic, but juvenile paresis and tabes may develop. Optic atrophy, sometimes leading to blindness may occur.

Interstitial keratitis, the most common eye lesion, frequently recurs, often resulting in corneal scarring. Sensorineural deafness, which is often progressive, may appear at any age. Hutchinson incisors, mulberry molars, perioral fissures (rhagades) and maldevekopment of the maxilla resulting in “bulldog” facies are characteristic, if infrequent sequelae.

Diagnosis

This is based in early CS on clinical evaluation, darkfield microscopy of lesions, placenta or umbillical cord and serologic testing of mother and neonate and if possible a cerobrospinal (CSF) analysis. The diagnosis of late CS rests on clinical evaluation, and serologic testing of mother and child.

Diagnosis of early CS is usually suspected on maternal serologic testng, which routinely should be done in early pregnancy, and often repeated in the third trimester and at delivery. Neonates of mothers with serologic evidence of syphillis should have a thorough examination, darkfield microscopy or immunofluorescent staining of any skin or mucosal lesions and a quantitative nontreponemal serum test (e. g. rapid plasma reagin (RPR), Venereal Disease Research Laboratory VDRL). Cord blood is not used for serologic testing because results are less sensitive and specific. The placenta or umbillical cord should be analyzed using darkfield microscopy or fluorescent antibody staining if available.

Infants and young children with clinical signs of illness or suggestive serologic test results also should have a lumbar puncture with CSF analysis for cell cont, VDRL and protein, CBC with platele count, liver function tests as clinically indicaed (opthalmologic evaluation, chest X- rays, neuroimaging and auditory brain stem response. Syphillis can cause many different abnormalities on long bone X-rays, including periosteal reaction, diffuse or localized osteitis and metaphysitis.

The osteitis is someimes described as "diffuse moth-eaten changes" of the shaft. Metaphysitis commonly appears as lucent or dense bands that can alternate to give a sandwich or celery stalk appearance. The Wimberger sign is symmetric erosions of the upper tibia but there can also be erosions in the metaphysis of other long bones. Excessive callus formation at the ends of long bones has been described. Many affected infants have more than one of these findings.

Diagnosis is confirmed by microscopic visualization of spirochetes in samples from the neonate or placenta. Diagnosis is based on neonatal serologic testing. This is complicated by the transplacental transfer of maternal IgG antibodies, which can cause a positive test in the absence of infection. However, a neonatal nontreponemal antiody titer > 4 times the maternal titer would not generally result from passive transfer, and diagnosis is considered confirmed or highly probable. Maternal disease acquired late in pregnancy may be transmitted before development of antibodies. Thus in neonates with low titers but typically clinical manifestations syphillis is considered possible.

The utility of fluorescent assays for antitreponemal IgM, which is not transferred across the placenta is controversial, but such assays have been used to detect neonatal infection (FTA-ABS). Any positive nontreponemal test should be confirmed with a specific treponemal test to exclude false positive results, but confirmative testing should not delay treatment in a symptomatic infant at high risk of infection.

Diagnosis of late CS is by clinical history, distinctive physical signs and positive serologic tests. The Hutchinson triad of interstitial keratitis, Hutchinson incisors and 8th cranial nerve deafness is diagnostic. Sometimes the nontreponemal serologic tests for syhillis are negative, but the fluorescent treponemal antibody absorption test (FTA-ABS) is positive. The diagnosis should be considered in cases of unexplained deafness, progressive intellectual detoriation or keratitis.

Treatment

The CDC released treatment guidelines for sexually transmitted diseases n 2015, including the treatment of CS [6].

Evaluation and treatment of neonates

The diagnosis of CS can be difficult as maternal nontreponemal and treponemal IgG antibodies can be transferred through the placenta to the fetus, complicating the interpretation of reactive serologic tests for syphills in neonates, as mentoned above. Therefore, treatment decisons frequently must be made on the basis of:

1. Identification of syphillis in the mother.
2. Adequacy of maternal treatment.
3. Presence of clinical, laboratory, or radiographic evidence of syphillis n the neonate (infants aged < 30 days).
4. Comparison of maternal (at delivery) and neonatal nontreponemal serologic titers using the same test, preferably conducted by the same laboratory. Any neonate at risk for CS should receive a full evaluation and testing for HIV infection.

All neonates born to mothers who have reactive nontreponemal and treponemal test results should be evaluated with a quantitative nontreponemal serologic test (RPR or VDRL)performed on the neonate's serum, because umbillical cord blood can be contaminated with maternal blood and yield a false positive result and Wharton's gelly within the umbillical cord can yield a false-negative result.

Conducting a treponmal test (i.e. TP-PA, FTA-ABS.EiA or CIA) on neonatal serum is not recommended because it is difficult to interpret. No commercially available (IgM) test can be recommended. All neonates born to women that have reactive serologic tsts for syphillis should be examined thoroughly for evidence and clinical signs of CS, as discussed above.

The following scenarios describe CS evaluation and treatment of neonates born to women who have reactive serologic tests for syphillis during pregnancy. Maternal history of infection with T.pallidum and treatment for syphillis must be considered when evaluating the neonate for CS, in most scenarios except when CS is proven or highly probable (Scenario 1).

Scenario 1; Proven or highly probable CS.

Any neonate with

1. An abnormal physical examination that is consistent with CS. OR,
2. A serum quantitative nontreponemal serologic titer that is fourfold higher than the mother's titer. OR,
3. A positive darkfield test or PCR (polymerase chain reaction) of lesions or body fluids.
4. The absence of a fourfold or greater titer for a neonate does not exclude CS.

Recommended evaluation

- CSF analysis for VDRL, cell count and protein.
- Complete blood count (CBC) and differential and platelet count.
- As mentioned before and as clinically indicated. (e.g. long bone radiographs, liver function tests, neuroimaging, opthalmologic examination and auditory brain stem response).

Recommended regimens

Aquous crystalline pencillin 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. Or, Procaine penicillin G 50.000 units/kg/dose I.M. in a single dose for 10 days.

Scenario 2; Possible CS.

Any neonate who has a normal physical examination and a serum quantitative nontreponemal serologic titer equal or less than fourfold the maternal titer and one of the following

1. Mother was not treated, inadequately treated, or has no documentation of having received treatment, OR,
2. Mother was treated with erythromycin or a regimen other than recommended in these guidelines i.e., a nonpenicillin G regimen). OR,
3. Mother received recommended treatment < 4 weeks before delivery.
4. Women treated with a regimen other than recommended in these guidelines should be considered untreated.

Recommended evaluation

- CSF analysis for VDRL, cell count and protein.
- CBC, differential and platelet count.
- Long bone radiographs.

A complete evaluation is not necessary if 10 days of parenteral therapy is administered, although such evaluations might be useful. For instance, a lumbar puncture might document CSF abnormalities that would prompt close follow-up. Other tests (e.g. CBC, platelet count and bone radiographs) can be performed to further support a diagnosis of CS.

CSF test results obtained during the neonatal period can be difficult to interpret.Normal values differ by gestational age and are higher n preterm infants.Values as high as 25 white blood cells/cubic mm and/or protein of 150 mg/dl might occur among normal neonates. Lower values i.e 5 WBCs/cubic mm and protein of 40 mg/dl might be considered the upper limits of normal. Other causes of elevated values should be considered when an infant is being evaluated for CS.

Recommended regimens

- Aqueous crystalline pencillin G 100.000-150.000 units/kg/day, admnistered as 50.000 units/kg/dos IV every 12 hours during the first 7 days of life and 8 hours thereafter for a total of 10 days. OR,
- Procaine penicillin G 50.000 units/kg/dose I.M. in a single dose for 10 days. OR,
- Benzathine pencillin G 50.000 units/kg/dose I.M. in a single dose.

Before using the single-dose benzathine penicilln G regimen the complete evaluatin must be normal and follow-up must be certain. Neonates born to mothers with untreated early syphillis at the time of delivery are at increased risk for CS and the 10 day course of pencillin G may be considered even if the complete evaluation is normal.

Scenario 3: CS less likely.

Any neonate who has a normal physical examination and a serum quantitative nontreponemal serologic titer equal to or less than fourfold the maternal titer and both of the following are true:

1. Mother was treated during pregnancy;treatment was appropriate for the stage of infection and treatment was administered > 4 weeks before delivery and,
2. Mother has no evidence of reinfection or relapse.

Recommended evaluation

No evaluation is recommended.

Recommended regimen

Benzathine penicillin G 50.000 units/kg/dose I.M. in a single dose. Another approach involves not treating the infant, but rather providing close serologic follow-up every 2-3 months for 6 months for infants whose mother's nontreponemal titers decreased at least fourfold after appropriate therapy for early syphillis or remained stable for low titer, latent syphillis (e.g. VDRL< 1:2;RPR<1:4).

Scenario 4: CS unlikely.

Any neonate who has a normal physical examination and a serum quantitative nontreponemal serologic titer equal to or less than fourfold the maternal titer and both of the following are true:

1. Mother's treatment was adequate before pregnancy and,
2. Mother's nontreponemal serologic titer remained low and stable (i.e serofast) before and during pregnancy and at delivery (VDRL< 1:2;RPR< 1:4).

Recommended evaluation

No evaluation is recommended.

Recommended regimen

No treatment is required, but infants with reactive nontreponemal tests should be followed serologically to ensure the nontreponemal test returns to negative.Benzathine penicillin G 50.000 units/kg as a single I.M. injection might be considered, particularly if follow-up is uncertain and the neonate has a reactive nontreponemal test.

Special Considerations

Penicillin Allergy

Infants and children who require treatment for CS but who have a history of penicillin allergy or developed an allergic reaction presumed secondary to penicillin shoul be desensitized and then treated with penicillin.Skin testing remains unavailable for infants and children because the procedure has not been standardized for this age group. Data are insufficient regarding the use of other antimicrobial agents (e.g. ceftriaxone) for CS in infants and children.If a nonpencillin G agent is used, close clinical, serologic and CSF follow-up is required in consultation with an expert.

Penicilln Shortage

During periods when the availability of aqueous crystalline penicillin G is compromised the following is recommended:

1. For neonates with clinical evidence of CS (Scenario 1) check local sources for aqueous crystalline penicillin G (potassium or sodium). If IV pencillin G is limited, substitute some or all daily doses with procaine penicillin G (50.000 IU/kg/dose I.M. a day in a single daily dose for 10 days). If aqueous or procaine pencillin G is not available ceftriaxone (in doses appropriate for birth weight) can be considered with careful clncal and serologic follow-up, and in consultation with an expert, as evidence is insufficient to support the use of ceftriaxone for the treatment of CS.Management might include a repeat CSF examination at age 6 months if the initial examination was abnormal. Ceftriaxone must be used with caution in infants with jaundice.
2. For neonates without any clinical evidence of CS use:
   - Procaine penicillin G 50.000 IU/kg/dose i.m. a day in a single dose for 10 days.
   - Benzathine penicillin G, 50.000 IU/kg i.m. as a single dose.If any part of the evaluation of CS is abnormal or was not performed, CSF examination is not interpretable, or follow-up is uncertain procaine penicillin G is recommnded. A single dose of ceftriaxone is inadequate therapy.
3. For premature infants who have no clinical evidence of CS (Scenario 2 and 3) and might not tolerate i.m. injections because of decreased muscle mass, IV ceftriaxone can be considered under close supervision.

Follow-Up

Careful follow-up examinations and serologic testing should be performed every 3 months until the test becomes nonreactive or the titer has decreased fourfold. The seologic response after therapy might be slower for infants and children than neonates. If these titers increase at any point for more than 2 weeks or do not decrease fourfold after 12-18 months, the infant or child should be evaluated (e.g. through CSF examination), treated with a 10-day course of parenteral penicillin G and managed in consultation with an expert. Treponemal tests should not be used to evaluate treatment response, because the results are qualitative and persist after treatment.Furthermore, passive transfer of maternal IgG treponemal antibody might persist for at least 15 months after delivery.

Infants or children whose initial CSF evaluations are abnormal should undergo a repeat lumbar puncture every 6 months until the results are normal.After 2 years of follow-up, a reactive CSF VDRL test or abnormal CSF indices that persist and cannot be attributed to other ongoing illness requires retreatment for possible neurosyphllis and should be managed in consultation with an expert.

HIV infection

Evidence is insufficient to determine whether infants and children who have CS and HIV or whose mothers have HIV infection require different therapy or clinical management than is recommended for all infants and children.

Prevention

CS is a totally preventable disease but CS remains a significant problem worldwide.Plötzker., et al. analysed 119 articles published in 2017 relevant to CS prevention.They concluded that CS is a preventable disease, effectively avoided with appropriate antenatal care and benzathine penicillin G use. However, increasing syphillis rates among all adults, accompanied by gaps in the provision of prenatal care

to women at high risk of infection, are major contributers to CS persistence [7]. Sometimes, a penicillin G shortage plays a role, as is the case in Brazil [3].

Most pregnant women in the U.S. are on point with prenatal care now but gaps still persist by age, race, and ethncity and source of payment for delivery. According to 2016 data analysis by the National Center of Health Statistics (NCHS) 77, 1% of women began prenatal care in the first trimester. But women were less likely to receive care this early f they were younger, if they were non-Hispanic Native Hawain or other Pacific Islander women or if they were self-paid for their delivery [8].

There is no doubt STD (sexually transmitted diseases) programs have done their job in demonstrating the effectiveness of screening and treatment for maternal syphillis but once identified public health care should engage more in active case management [9]. Prenatal care can be very difficult in remote areas as was shown by the death of 6 infants in a cluster of 13 infants with CS in Northern Queensland, Australia [2,10]. In countries like Zambia and other resource-limited energy settings, same day cheap point-of-care commercial tests (ICS or RST;immnochromatographc strip, rapid syphillis test) are used [2].

These tests are not recommended by the CDC guidelines, as mentioned above but following the guidelnes strictly supposes a rich and well structured health care infrastructure.Same day treatment with a single i.m dose of benzathine G penicillin is prioritized to achieve the goal of eliminating CS under these circumstances, because they fear losing the mother out of sight after the first contact [11].

Conclusion

Congenital syphillis (CS) is still a worldwide problem that is completely preventable.Although the global prevalence is decreasing CS is on he rise again in e.g. the U.S, Australia and Brazil. Among the reasons are increasing incidences of STDs in adults, suboptimal or absent prenatal care due to gaps in race, ethnicity and insurances or shortages of penicillin G.Prenatal care and antenatal sceening for syphillis is the most cost-effective, feasible and practical solution to the ongoing problem of CS. In resource-imited countries and in remote areas, CDC guidelines cannot be followed strictly.Cheap point-of-care treponemal tests have to be used and treatment consists for practical reasons of a single dose of benzathine penicillin G 50.000 IU/kg i.m.People don't see syphillis as a serious disease making more deadly and disabled victims than Zika or Ebola. Awareness and public health efforts should be strongly enhanced. therefore.

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