Congenital syphilis: still a serious, under-diagnosed threat for children in resource-poor countries

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Background: **With 700 000 to 1.5 million new cases annually, congenital syphilis remains a major infectious cause of morbidity and mortality in neonates, infants and children in resource-poor countries. We therefore analyzed the extent of congenital syphilis in the pediatric patient population at our rural hospital in Tanzania.**

Methods: **For this retrospective analysis, from January 1, 1998 to August 31, 2000, all cases of congenital syphilis were collected from the medical records of the neonatal and pediatric department at Haydom Lutheran Hospital in rural northern Tanzania. Age, sex, weight, clinical signs and symptoms, venereal disease research laboratory (VDRL) results of mother and/or child, hemoglobin concentration, treatment, and outcome were recorded and analyzed.**

Results: **Fourteen neonates and infants were included. The earlier the diagnosis, the more it rested on maternal data because the presentation of neonatal congenital syphilis resembled neonatal sepsis. Syphilitic skin lesions were only seen in the post-neonatal age group. VDRL results were positive in 11 of the 14 mothers, and in 4 of the infants. Anemia was common in older infants. No patient showed signs of central nervous system involvement. Two patients died, and the remaining were cured after standard treatment with procaine penicillin.**

Conclusions: **Highlighting the variable picture of congenital syphilis, this report demonstrates how difficult it is to make a correct diagnosis by solely history and clinical presentation in a resource-poor setting. Hence false-positive and false-negative diagnoses are common, and clinicians have to maintain a high index of suspicion in diagnosing congenital syphilis. Therefore, an important approach to control and finally eliminate congenital syphilis as a major public health problem will be universal on-site syphilis screening of all pregnant women at their first antenatal visit and immediate treatment for those who test positive.**

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Introduction

The spectrum of life-threatening diseases for children in developing countries is vast. The majority of young children suffer and die from infectious diseases, up to half in combination with malnutrition.[1,2] Commonly, pneumonia, diarrhoea, malaria, measles and HIV/AIDS are cited as the most frequent infectious causes.[1,2] In 2006, around 9.7 million children less than five years of age died in developing countries.[2] Among these deaths, almost four million were neonatal deaths.[2,3] In addition, about 3.2 million stillbirths occurred globally, more than 95% of them in developing countries.[4] In the neonatal period, sepsis, pneumonia, diarrhea, and tetanus are the most common infectious diseases.[3]

Neonatal tetanus claims around 180 000 lives per year and is being targeted by global control programs.[5] In contrast, congenital syphilis, another potentially fatal disease, is not high on the agenda but should not be forgotten in this list.[6,7] According to the most recent estimates, around two million pregnant women suffer from syphilis each year.[8,9] With an estimated 45% to 70% probability of vertical transmission, the World Health Organization (WHO) estimates the number of cases of congenital syphilis ranges between 700 000 and 1.5 million each year,[8,9] accounting for an estimated 420 000 to 600 000 perinatal deaths through stillbirth (up to 40% of affected pregnancies) and neonatal death (20%). An additional 20% of pregnancies will result in

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liveborn infants with congenital syphilis.[8,9] This figure is higher than the annual number of mother-to-child transmission of HIV, as well as the number of AIDS deaths in children,[7,10] yet congenital syphilis receives much less attention than the perinatal prevention and treatment of HIV/AIDS.[6-9]

There are still reports on congenital syphilis occurring in industrialized countries like the United States, Great Britain or Germany, and some figures even indicate a rising incidence of congenital syphilis in these countries despite a highly developed antenatal and postnatal health care system.[11-15] But the overwhelming proportion of cases of congenital syphilis (>90%) occurs in developing countries with scarce resources.[6-9] This tragedy continues despite the fact that congenital syphilis would be almost completely preventable by early diagnosis of maternal syphilis and adequate treatment during pregnancy.[9,16,17] In 2007, the WHO, with support of international partners around the world, launched a new initiative for the elimination of congenital syphilis as a public health problem. The new initiative promotes increased awareness of the global burden of congenital syphilis, that nations ensure that syphilis screening is provided to all pregnant women at their first antenatal visit, and that positive women are promptly treated with intra-muscular penicillin.[18] At present, many developing countries have not implemented this approach fully.[19]

In line with the initiative, this paper aims to remind clinicians who work in resource-poor health care settings, and elsewhere, of congenital syphilis in infants and children by presenting its diverse clinical features, the challenges in diagnosis and treatment, and the opportunities for large-scale prevention as seen in a rural area in northern Tanzania, a country with an estimated seven percent prevalence of syphilis in pregnant women.[20]

Methods

Setting

Our study setting was Haydom Lutheran Hospital (HLH), a rural hospital located in the northern part of the country and owned by the Mbulu diocese of the Evangelical Lutheran Church in Tanzania. The hospital is situated at the southern edge of Mbulu district, at the south-western border of Manyara region (380 km south-west of Mount Kilimanjaro).[21,22] In general, people in the area mainly live on subsistence farming and livestock keeping. The hospital has 350 beds officially and serves a population of more than 500 000 people. It contains surgical, internal, gynecological/obstetric, pediatric and tuberculosis wards.[21,22] The laboratory facilities were very basic at the time of the study and, in the context of the patient group concerned, provided only hemoglobin measurement, qualitative venereal disease research laboratory (VDRL) test, and microscopy of cerebrospinal fluid (CSF). Each year, more than 12 000 inpatients and 70 000 outpatients are treated.[22] Children represent about 30%-40% of total patient numbers.[22] Around 3000-3500 children are born each year at the hospital, but about 12 000 are born at home without skilled attendance in the total catchment area, thus reducing the chance of detecting congenital syphilis early.[21,22] At the time of this study, the hospital served 22 mobile maternal-and-child-health (MCH) clinics located up to 100 km away from HLH, on a monthly basis, and one permanent daily MCH clinic at HLH. More than 25 000 examinations in pregnant women (physical exam, weight, blood pressure, hemoglobin, VDRL testing and penicillin treatment (these latter two being available only at the Haydom site)) and more than 65 000 in children under five years (physical exam, weight, and immunizations) were performed.[21,22] Around 90% of pregnant women attended antenatal clinics in the catchment area, but only about 25% attended before 20 weeks of gestation.[21,22] About 25%-40% of pregnant women were seen at the clinic at Haydom where VDRL test and penicillin treatment were offered. Of these women, only 20%-30% were tested selectively with the VDRL test alone, based on their obstetric history (previous stillbirth) and/or clinical signs and symptoms, and 17% had a positive VDRL test result.[23] At that time, on-site test systems were not available. If diagnosed as having maternal syphilis, all of them received standard penicillin treatment. Barriers to testing and treatment were unavailability at the mobile clinics and non-universal VDRL screening guidelines at Haydom due to financial constraints on the side of the provider. Cost to patients was not an issue as all these services were provided free of charge.

Patients

All neonates, who were born at the hospital, and children up to 15 years of age who were admitted to the neonatal or pediatric wards at HLH from January 1, 1998 to August 31, 2000 were included in this retrospective analysis. On average, there were more than 6000 cases each year.[22] We restricted our investigation to inpatient records, and did not review pediatric outpatient records. All cases with the final diagnosis of congenital syphilis (based on maternal and neonatal history, presenting signs and symptoms, and laboratory results if available) were primarily collected from the admission books in the wards. Then the patient records were reviewed and analyzed. Age at diagnosis, sex, weight, clinical signs

and symptoms, VDRL results of mother and/or child (if available), hemoglobin concentration, mode and duration of treatment, and outcome (cure/death) were recorded.

Results

Our record review identified 14 cases meeting our case definition of congenital syphilis, including 7 neonates (less than 28 complete days of life) and 7 infants (less than one year of age) (Table 1). In the latter group, 2 infants were reported to have been small for date (born at home), 3 did not gain weight properly, and 3 had recurrent fever episodes. Age at diagnosis ranged from the day of birth until 10 months. The earlier the diagnosis was suspected, the more it rested on maternal data (six of seven mothers with positive VDRL results, one with condylomata lata) because the presentation of neonatal congenital syphilis resembled more the clinical picture of neonatal sepsis (Tables 1 and 2).[13,24,25] None of the mothers had been screened for syphilis antenatally as they only attended the mobile MCH clinics which did not provide VDRL test. Their test was done during the diagnostic work-up of their sick children. The mother with condylomata lata had not been treated during pregnancy. Four neonates and 3 infants were underweight. Typical syphilitic skin lesions were only seen in the infant group (71%), representing the second stage of syphilis (Table 1, Fig. 1). In contrast, snuffles and mouth rhagades were found in one neonate (Fig. 2), and periostitis of the wrist in another one (Fig. 3) which was visible by X-ray as well (picture not shown). VDRL was positive in 11 of 14 mothers and in all 4 infants who were tested. Anemia and visible jaundice (no data on bilirubin levels available as they could not be measured at HLH) were not presenting features in the neonates, whereas anemia was common in the older infants (Table 1). No neonate or infant showed signs of central nervous system involvement, and lumbar punctures were not performed.

One preterm neonate died from concurrent respiratory distress syndrome due to prematurity, perhaps also due to a syphilitic involvement of the lungs (pneumonitis alba),[25] and another infant died from marasmus and presumed tuberculosis. The remaining 12 patients were all cured after standard treatment with procaine penicillin (PPF) (Table 1).[13,25]

The record review did not identify any children with syphilis older than ten months of age or with late congenital syphilis (Table 2).

Table 1. Characteristics of neonates and infants with congenital syphilis at Haydom Lutheran Hospital, 1998-2000

Basic data	Neonates (*n*=7)	Infants (*n*=7)
Age (mean, median, range)	4.4 (1.0) (0-21) days	3.6 (3.0) (1-10) months
Weight (mean, median, range)	2.35 (2.35) (1.35-4.0) kg	4.57 (5.0) (2.5-6.0) kg
Male:Female	3:4	4:3
Clinical signs and symptoms (*n*)		
Condylomata lata (mother)	1	0
Skin lesions (mother)	0	1
Prematurity/low birth weight/small for gestational age	4	2
Hepatomegaly	2	0
Splenomegaly	0	1
Fever	2	3
Poor feeding	1	0
Poor weight gain/malnutrition	0	3
Skin lesions (macular, papular, bullous, pustular, ulcerations, desquamation, esp. palms and soles)	0	5
Snuffles	1	0
Mouth rhagades	1	0
Osteochondritis/periostitis	1	0
Laboratory data (*n*)		
VDRL positive (qualitative)		
Mother (11 tested)	6	5
Child (4 tested)	1 (the mother not tested)	3 (2 of the mothers not tested)
Hemoglobin* (mean, median, range)	13.5 (13.1) (12.8-14.5) g/dL	8.1 (7.7) (6.4-11.2) g/dL
Treatment	All procaine penicillin fortified 50 000 IU/kg i.m. per day for 10 days	
Outcome (*n*)		
Cure	6	6
Death	1 (respiratory distress syndrome)	1 (marasmus + tuberculosis)

*: measured in 3 of the 7 neonates. VDRL: venereal disease research laboratory.

Table 2. Signs and symptoms of congenital syphilis (modified from references 13, 24, 25)

Disease stage	Signs and symptoms
Early congenital syphilis	
In neonates (resembles more neonatal sepsis)	Prematurity, low birth weight, small for gestational age Bullous rash Hepatomegaly, splenomegaly Jaundice Anemia Fever, septicemia
In infants (resembles more secondary syphilis)	Failure to thrive Skin and mucous membrane lesions (usually involving palms and soles) Persistent nasal discharge (snuffles, sometimes bloody) Osteitis, osteochondritis, periostitis (pseudoparalysis) Nephrosis, nephritis Hemolytic anemia Condylomata lata Central nervous system infection (and virtually all other organs)
Late congenital syphilis* (after 2 years of age; resembles more tertiary syphilis)	Skull bossing, saber shins Clutton joints Saddle nose Hutchinson teeth, mulberry molars Perioral rhagades Interstitial keratitis 8th nerve deafness Symptomatic neurosyphilis

*: rare in Africa.

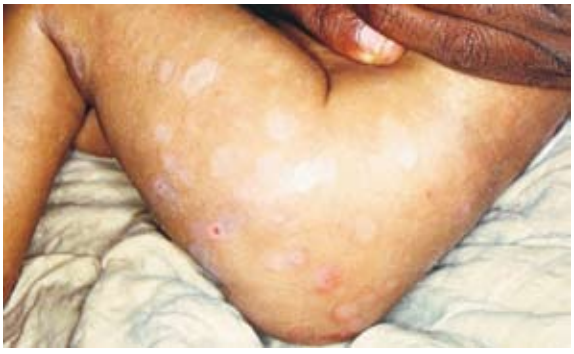

Fig. 1. Syphilitic maculo-papular skin lesions in a 3-month-old infant.

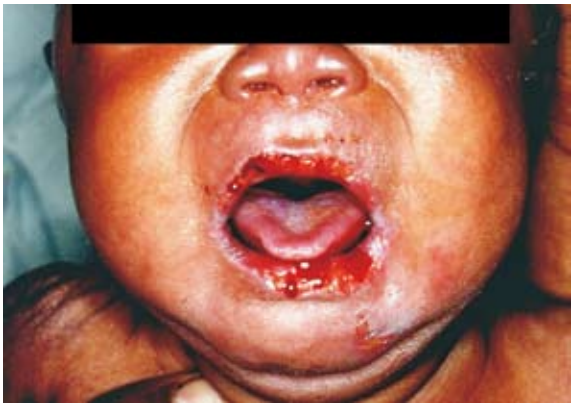

Fig. 2. Syphilitic mouth rhagades in a 3-week-old neonate.

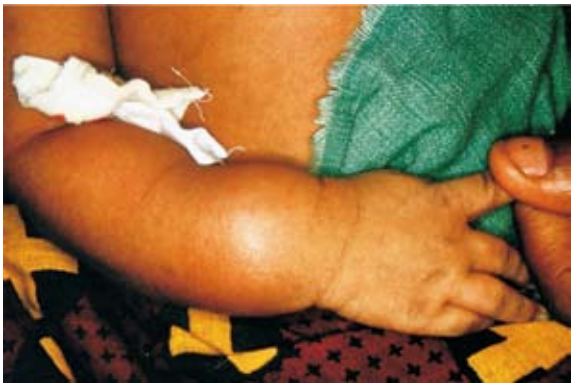

Fig. 3. Syphilitic wrist periostitis (painful on touch) with pseudo-paralysis in a 3-week-old neonate, disappearing already after 3 days of treatment.

Discussion

From a clinician's point of view, this report highlights the variable picture of congenital syphilis, and serves as an example of how difficult it can be to reach the correct diagnosis based almost solely on history and clinical presentation in a resource-poor setting. Because of the small number of patients, the distribution of presenting signs and symptoms in our group is not completely comparable to that of other reports from developing countries like Kenya,[26] Papua New Guinea[27] and Zambia,[28] but still demonstrates the whole spectrum of congenital syphilis fairly well. Many other presenting signs and symptoms of congenital syphilis have been reported in the literature, but most of the reports are from medical centers of excellence like universities in developed and developing countries, which have the laboratory means to diagnose congenital syphilis even in case of atypical presentation.

These facilities are usually not available in resource-poor settings where the majority of cases of congenital syphilis occur. The only other relevant diagnostic laboratory tool at hand was a qualitative VDRL test which would not allow to differentiate between passive transfer of antibodies, or true congenital infection.[13,25,29] X-ray examination of bones was only performed in the patient with clinical signs of bone involvement.[30] Although lumbar puncture in congenital syphilis is recommended in all cases in current guidelines,[13,18,25,31-33] it was not performed in our series due to lack of resources (material and financial), and due to no realistic chance for additional meaningful information in view of the meagre laboratory facilities available.[16] Therefore all patients were treated for 10 days as if CSF infection would have been present although no infant had clinical signs of meningitis.[13,18,24,25,32,33] The outcome, with a survival rate of 86%, was at least as good as in other hospital-based case series from developing countries.[26-28] The two deaths were due to other concurrent diseases,

but one might consider that at least in the premature neonate, syphilitic involvement of the lung (pneumonitis alba)[25] may have played a major causal role.

Because of the weaknesses of a solely clinical diagnosis, a false-positive diagnosis is always possible in health systems like the Tanzanian one. This is quite likely to occur if one has to rely on non-treponemal VDRL or rapid plasma reagin (RPR) results (which are cheap and widely available tests in these countries).[34] They can be misleading because there may be some biological false-positive results, and the antibody can be passively transferred to the infant during pregnancy.[29] Our hospital laboratory, which is most likely representative of the majority of laboratories in rural health facilities in developing countries, has not provided the opportunity for quantitative VDRL test and confirmatory test combined with more specific treponemal test.[13,25,29] As the sera could not be sent to reference laboratories due to financial and logistic constraints, there was no alternative but to use these results as an additional hint in our clinical diagnosis.

A maternal history of diagnosis and treatment for syphilis during pregnancy should be considered as a strong predictor for congenital syphilis and should initiate a thorough examination of the infant. Even in case of an asymptomatic infant, the WHO suggests to consider the use of a single dose of penicillin in a resource-poor setting.[16,18]

Probably many patients are not diagnosed at all. If one calculated the annual incidence of congenital syphilis from these 14 cases in our community catchment area with roughly 15 000 births each year, then it was about 1 in 3000 infants. But this must have been a serious underestimate because there should have been more than 600 cases each year in the community and several of them in hospital, if we assume a prevalence of 7% in the population of pregnant women when taking other seroprevalence studies from Tanzania as a baseline,[20] and a stillbirth rate of 40% in these affected women.[8,9] Even if one took a maternal syphilis prevalence of only 2%, which was found in an antenatal study in the Haydom area recently,[35] more than 150 cases should have been diagnosed each year. Whatever the exact incidence of congenital syphilis might be in the area, as in the catchment area no other health institutions were equipped to treat children with congenital syphilis, an enormous number of missed diagnoses must have occurred, possibly as stillbirths or early neonatal and infant deaths.

Cases of late congenital syphilis (Table 2) have never been diagnosed at the hospital according to the medical staff, and also have never been reported in resource-poor settings in Africa.[28] Whether the death of these patients is due to complications of early congenital syphilis or whether they are simply not diagnosed correctly in later life remains unknown at present, but both options seem equally possible.

The treatment of congenital syphilis is usually straightforward, as Treponema pallidum is still fully susceptible to penicillin.[13,16,18,24,25,32,33] Therefore, we administered the recommended full 10-day course of PPF to all patients also because of the missing CSF results. Whether new treatment approaches like the one-dose azithromycin treatment for syphilis in adults[36] will ever be used for congenital syphilis on a large scale in settings of developing countries remains questionable at present, mainly due to financial and logistic constraints and doubts about its efficacy on congenital syphilis.[37]

In view of the difficulties of a correct and early diagnosis of congenital syphilis in these settings, prevention is of major importance. Control strategies to prevent congenital syphilis have been proposed for several times.[6,8,9,16,18] Primary prevention, i.e., the prevention of infection with syphilis in women of child-bearing age, probably is and will not be successful as the unchanging numbers of new infections and the spread of the HIV epidemic demonstrate.[8-10] Thus, secondary prevention, i.e., early diagnosis and prompt treatment of pregnant women and their partners, has to be the cornerstone of control in the foreseeable future.[8,9,16,18] But this approach requires high coverage rates within functioning antenatal care services to be effective. In Tanzania, antenatal care coverage is above 90%, but more than 75% of pregnant women present after 20 weeks of gestation to the clinics.[38] The coverage rates are lower (<70%) in several countries in Sub-Saharan Africa and South Asia, than in Tanzania, and even fewer pregnant women present early during pregnancy.[2] Thus intrauterine infection with consecutive fetal demise may have occurred already.[8,9] Because re-infection after successful treatment during earlier stages of pregnancy[16,39] or primary infection in late pregnancy[16,40] is possible and not infrequent, repeat examinations must be available in late pregnancy as well.[8,9,16,18]

As part of the prevention strategy, the MCH staff have to screen maternal syphilis in women, as well as other sexually transmitted infections (STIs), considering that most of the women with syphilis are asymptomatic. But to accomplish universal screening and prompt treatment of syphilis in pregnant women, the MCH staff must have access to appropriate screening modalities feasible for use in their settings.[16,18] Some sites with access to sufficient laboratory capacity for RPR or VDRL test (with results quickly available) may be able to rely on existing laboratory capacity. However, if a large proportion of pregnant women are either not being screened, or if those positive do not receive treatment in 7 days or less, the existing program is inadequate. In these

cases or in settings without sufficient laboratory capacity, rapid treponemal point-of-care test[41] can be made at a clinical visit with immediate results and (if positive) treatment on site.[16,18] Hence, penicillin must be available at the site for immediate treatment of women and their partners.[8,9,16,18] The use of rapid treponemal point-of-care test may result in some overdiagnosis and overtreatment, but it is probably justifiable in high prevalence settings, even when considering costs and possible risks. Recent studies in Bolivia,[42] Mozambique[43] and South Africa[44] have demonstrated the feasibility and efficacy of on-site testing, and the WHO has recommended these tests in all countries.[16-18] The cost-effectiveness of this approach has been convincingly demonstrated in Haiti.[45] Tanzania has adopted this approach and formulated a national policy on universal syphilis screening of pregnant women at their first antenatal visit, but implementation is still lacking.[19]

Universal screening for syphilis was not available in the antenatal clinics at the HLH as a routine procedure during the period of study. Because of the difficulties in diagnosing clinical syphilis in pregnant women and congenital syphilis, as well as the low syphilis prevalence in pregnant women in the most recent study,[35] the hospital is now working on a strategy to implement universal on-site syphilis screening and prompt treatment in all its MCH clinics. Preferably these antenatal services are to be closely linked with other STI/HIV/AIDS prevention programs.[16,18,46] Therefore universal antenatal syphilis screening is planned to be incorporated at present in the local MCH and HIV/AIDS prevention program which is run by the hospital in the community.[35]

In conclusion, maternal and congenital syphilis present a continuing threat to the well-being of pregnant women, infants and children. Therefore, clinicians have to maintain a high index of suspicion in diagnosing congenital syphilis in ill neonates and infants. But secondary prevention of maternal syphilis, i.e., universal on-site screening of all pregnant women at their first antenatal visit and immediate treatment for those who test positive, will be the most important way to control and finally eliminate congenital syphilis as a major public health problem.[18] The means (testing and treatment) and policies are available, but what is lacking is national and local commitment to overcoming the barriers to implementation. Therefore, clinicians and public health specialists have to work together to advocate for the control and elimination of congenital syphilis more vigorously now.

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