Resurgence of congenital syphilis: A profile of symptomatic newborns with congenital syphilis requiring admission to the nursery at a peri-urban regional hospital in KwaZulu-Natal Province, South Africa

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Background. Congenital syphilis should by now be a medical rarity. However, there has been a recent global resurgence despite preventive measures and effective treatment. This has significant impact on the health system, with existing data on the burden of congenital syphilis and preventable factors coming mainly from developed countries.
Objectives. To describe maternal and newborn demographic characteristics of newborns admitted with symptomatic congenital syphilis, their spectrum of disease, as well as outline their clinical outcomes and identify modifiable factors that led to the development of the syphilis infection.
Methods. A retrospective chart review of 46 mothers and their 47 newborns admitted to the nursery at Prince Mshiyeni Memorial Hospital, eThekwini, South Africa between January 2018 and March 2021 with symptomatic congenital syphilis.
Results. Of the 47 symptomatic newborns, 12 (26%) died – 50% of them within 24 hours of birth. Factors associated with death were hydrops fetalis, seizures, low APGAR scores and the need for resuscitation at birth. Hepatosplenomegaly, the characteristic rash and pallor were the 3 most common presenting signs. The average length of stay was 19.7 days. Nineteen neonates required admission to ICU for invasive ventilation (40%). Thirteen babies (28%) required non-invasive ventilation. Fourteen newborns (30%) required inotropic support. Red cell transfusion was required in 26 newborns (55%) and platelet transfusion in 4 (9%). Most mothers accessed antenatal care (83%), with 71% testing negative for syphilis at booking. Inadequate treatment of the partner, untreated and inadequately treated maternal syphilis, lack of follow-up testing plans with absent repeat testing at 32 - 34 weeks' gestation were the main modifiable factors.
Conclusion. Despite good antenatal attendance and early maternal syphilis testing, 47 newborns were admitted to a regional nursery in KZN with congenital syphilis over a period of 39 months. This study highlighted the burden of disease in the neonatal population as reflected by the need for intensive care, a prolonged hospital stay and predictors of mortality. The health system failures are related to maternal testing, treatment and tracing. Strengthening of existing programmes together with novel measures such as extended re-testing protocols and mass treatment of sexually active adults need to be explored to curb the rise of congenital syphilis.

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Congenital syphilis should by now be a medical rarity. However, it remains a significant public health problem worldwide, with its incidence increasing in developed countries such as the USA.[1] There was a 261% increase in the number of reported congenital syphilis cases in the USA during 2013 - 2018. Among these reported cases in 2018, 94 were stillbirths/early infant deaths.[2] Likewise, in South Africa (SA), according to the National Institute of Communicable Diseases (NICD), for the period 1 July 2017 - 31 December 2020, there were 794 clinical notifications of congenital syphilis cases and 11 170 rapid plasma reagin (RPR)-positive results from infants/children <2 years. During this period there was an increase in both the number of clinical notifications and RPR-positive results from infants/children. Notably, 51% of all notifications were from KZN.[3] Syphilis is a well-known and important cause of adverse pregnancy outcomes. In 2016, the World Health Organization (WHO) estimated there were 988 000 maternal syphilis infections globally resulting in 355 000 adverse pregnancy outcomes, of which half were stillbirths/neonatal deaths.[4] Newborns with congenital syphilis are more likely to require admission to the neonatal intensive care unit (NICU) and have an increased length of stay and greater hospitalisation costs.[5] At one SA hospital, 68% of symptomatic babies with congenital syphilis required NICU admission, and 38% of these infants died.[6] Each case of congenital syphilis reflects a healthcare system failure to provide the best antenatal care to pregnant women and their babies, as congenital syphilis can be prevented by early, repeated testing of mothers and penicillin treatment of infected women and their sexual partners.[1] Given the rise in case numbers and association with significant morbidity and mortality, the present study highlights cases of congenital syphilis admitted to a regional neonatal unit, describes their clinical presentation and identifies gaps in care.

Methods

Data collection and statistical analysis

Between January 2018 and March 2021, maternal and newborn records of babies admitted to the nursery at Prince Mshiyeni Memorial Hospital (PMMH) with symptomatic congenital syphilis were reviewed. Patient details were sourced from the Nursery Congenital Syphilis Notification Register and the Infection Prevention and Control Department. Congenital syphilis mortality data were obtained from the Perinatal Problem Identification Program (PPIP). A standardised data collection tool was utilised to record details of antenatal care, maternal HIV, nutritional and syphilis status at booking and later in pregnancy, as well as treatment details of mothers, their partners and newborns. Additional information related to past obstetric outcomes were also recorded. Neonatal information included gestational age, growth parameters, need for resuscitation at birth, investigations and management, length of hospital stay and outcome.

All data were analysed descriptively, including means and standard deviations (SDs). Chi square and Fischer's exact test were used to compare newborn factors associated with death. Stata version 17 (Stata Corp., USA) was used for data analysis.

Diagnosis and management of syphilis

Symptomatic congenital syphilis was defined as a positive RPR result (titre >1:1) in an infant with features of early congenital syphilis. Diagnostic testing for syphilis was performed on syphilis-exposed and unexposed babies for whom there was a clinical suspicion of congenital syphilis. Current recommendations advise three doses of benzathine benzylpenicillin (2.4 mu by intramuscular injection) 1 week apart for treatment of syphilis in pregnancy. A mother is regarded as fully treated if she received all three doses. Incomplete treatment is classified as receipt of a non-penicillin regimen, <3 doses of benzathine benzylpenicillin and if the last dose was given <4 weeks before delivery.

Ethics

Ethics approval for the present study was obtained from the University of KwaZulu-Natal Biomedical Research Ethics Committee (ref. no. BREC00002357/2021).

Results

Fifty-three newborns were identified with early congenital syphilis. Of these, three were excluded as they had no confirmatory RPR results (two died soon after admission and one had a fluorescent treponemal antibody (FTA) result only). Furthermore, three babies had incomplete maternal notes. The records of 46 mothers and 47 newborns (1 twin pregnancy delivery) born between January 2018 and March 2021 were included in our analysis.

Maternal characteristics

The mean (SD) maternal age was 24.8 (5.2) years. Seven (15%) syphilis-positive mothers were teenagers. The majority were multiparous (57%) and 8 (17%) had a history of a stillbirth and/or early neonatal losses. Twenty-nine mothers (63%) were HIV-infected. Twenty-three (79%) of the HIV infected mothers were on antiretroviral therapy (ART), one was not initiated and five defaulted ART. Only 19 (62%) HIV-infected mothers had documented viral load (VL) results – 9 (47%) were suppressed (VL <50) and 10 (53%) were unsuppressed (Table 1).

Table 1. Characteristics of maternal syphilis cases

Variable	Total; $N = 46$, n (%)	
Age		
<=19	7	(15)
20-25	17	(37)
26-30	15	(33)
31-35	6	(13)
>=36	1	(2)
Parity		
0	20	(43)
1	9	(20)
2	11	(24)
3	4	(9)
4	2	(4)
Previous pregnancy losses/neonatal deaths		
None	38	(83)
Miscarriage	4	(9)
IUD	2	(4)
Neonatal death	1	(2)
TOP	1	(2)
BMI		
Normal	13	(28)
Overweight	12	(26)
Obese	4	(9)
Unknown	17	(37)
Booked	38	(83)
Early	22	(58)
Late	16	(42)
Unbooked	8	(17)
HIV status		
Positive	29	(63)
Viral load > 50	10	(34)
Viral load < 50	9	(31)
Viral load not known	10	(34)
Negative	17	(37)

Booked mothers

Most mothers (n=38; 82.6%) accessed antenatal care, with 58% booking early (<20 weeks' gestation). Thirty-one (67.4%) mothers had complete booking data for syphilis testing – five had tests done with no recorded dates and two had testing done after their booking visits. Of the 31 mothers who tested at the antenatal booking visit, 22 (71%) had negative syphilis tests. Of the five mothers who had syphilis testing in pregnancy but no recorded dates, three were negative and two were positive. Of the two mothers that did not get a booking syphilis test but tested later in pregnancy, both had positive RPR tests but only one had her result followed up by medical staff. Of the 38 booked mothers who tested at booking/later in pregnancy, 13 (34.2%) had tested positive for syphilis: nine were not treated; three were incompletely treated (one mother had a repeat negative Rapid test in labour); and one mother received treatment for syphilis. However, there was a 5-week gap between the first and second dose of benzathine benzylpenicillin.

Unbooked mothers

Eight (17%) mothers were unbooked and only tested in labour/post-delivery. Seven tested positive and one tested negative (false negative Rapid test). Four had incomplete treatment, two completed treatment and two were not treated in hospital.

Management of mothers with an initial negative test

Of the 25 mothers who tested negative during pregnancy, two had missing data regarding repeat testing. One of these patients had a negative Rapid test at booking but a high titre-positive RPR test at

the subsequent visit one month later. The results were not checked, and she was untreated. Only two of the 25 mothers whose initial test was negative, had repeat tests later in pregnancy as per National Department of Health (NDoH) guidelines. The first patient was tested at 32 weeks' gestation but was called back too late to check her results and subsequently presented in labour at term. She only received treatment then. The second patient tested at 34 weeks' gestation, delivered 3 weeks later but received inadequate treatment. Twenty-one mothers who initially tested negative did not have repeat testing. Six of these 21 mothers delivered at ≤32 weeks' gestation making repeat testing impossible. However, 15 mothers delivered at or after 33 weeks' gestation but were not re-tested. One of these mothers had a repeat HIV test on 5 occasions but no syphilis test and the baby was born at term following good antenatal attendance. In three mothers, no repeat testing was done during labour or post delivery despite features of congenital syphilis and positive serology in their babies. Subsequently, two of these mothers were untreated and one had inadequate treatment.

Maternal testing in labour or post-delivery

Seventeen mothers had repeat testing done either during labour or post delivery (12 mothers had repeat syphilis tests in labour and five had repeat tests post delivery). Four of the 12 mothers had a negative repeat Rapid test during labour. This may be due to false-negative tests occurring as part of a 'prozone' phenomenon, as the babies had positive serology and features of congenital syphilis. Two of these four mothers had a confirmatory positive RPR test result. Three of the four mothers with possible false-negative RPR results were HIV-positive – one was virologically suppressed, 1 one had an HIV VL >1 000 RNA copies/mL, and one had no HIV VL result.

In-hospital treatment of mothers with positive syphilis serology

While in a hospital setting, only three of the 12 mothers received complete treatment. Seven mothers received inadequate treatment and two were not treated. Post delivery, four mothers tested positive for syphilis, and one had a negative Rapid test despite the neonate being admitted with congenital syphilis. No RPR test was done for this mother, and she remained untreated. Two mothers had inadequate treatment, one was completely treated, and one mother's treatment status was unknown. Contact tracing was documented in 3 maternal records only.

Neonatal characteristics

Of the 47 babies admitted to the nursery with symptomatic congenital syphilis, 12 (26%) died – 50% within 24 hours of birth. Discharge data were available for 32 of 35 babies that survived (74%). The average length of stay was 19.7 days, with a median (interquartile range) length of stay of 16.5 (6 - 26) days. Of the babies who died, seven (58%) had low APGAR scores, which is associated with increased mortality (odds ratio (OR) 10.09; 95% confidence interval (CI) 1.82 - 67.89). Twenty-three babies required resuscitation at birth (49%), including 10 of the 12 (83%) babies that died. The need for resuscitation at birth was associated with an increased risk of death (OR 8.08; 95% CI 1.41 - 87.1). Hepatosplenomegaly, characteristic rash and pallor were the three most common presenting signs. Five babies were hydropic, of whom only one survived. Hydropic babies had an increased risk of death (OR 15.66; 95% CI 1.33 - 860.64). Seizures occurred in nine newborns (19%) – a clinical feature also associated with an increased risk of mortality (OR 5.28; 95% CI 0.89 - 34.63). A total of 19 (40%) neonates required ICU admission for invasive ventilation, 13 (28%) required non-invasive ventilation and 13 (30%) required inotropes. Red cell transfusion was required in 26 (55%) and platelet transfusion in 4 (9%). Thirty-three newborns were notified (70.2%). However, only two of the 12 babies who died (16.6%) were notified (Table 2).

Modifiable factors

Medical personnel-related factors were the main contributors to babies developing congenital syphilis, with poor contact tracing, inadequately treated maternal syphilis and transcription errors (mothers with positive syphilis results noted as negative in subsequent notes and discharge summaries) featuring as the top three factors.

Of the four cases where benzathine benzylpenicillin was not available, three were given an alternative regimen (incompletely prescribed) and one mother was not treated at all (only received treatment post delivery) (Table 3).

Discussion

Over a period of 39 months, we reviewed maternal records of 46 mothers and 47 babies with congenital syphilis admitted to the neonatal unit at PMMH. Poor antenatal care has previously been reported as an important factor responsible for the continued high incidence of congenital syphilis globally.[5] Similarly, in a recent study in Cape Town,[6] a large proportion of mothers whose babies had congenital syphilis were unbooked (56%). However, in our study, most mothers had initiated antenatal care (83%). Additionally, most booked early (58%) with many mothers testing negative at booking (71%). An initial negative test could indicate a false negative result owing to testing before seroconversion or the prozone phenomenon, or infection with *Treponema pallidum* during pregnancy but subsequent to the time of antenatal booking. Other explanations for the possible false negative results include a true false negative secondary to a substandard or expired rapid kit, user error (misinterpretation of results or reading result too early) or false documentation – recording a result as being negative when the test was not performed. Rapid tests, which are used in many primary healthcare settings, have a sensitivity of 93 - 98%.[6] Sexually transmitted diseases (STDs) have a profound impact on sexual and reproductive health.[7] Safe sex practices during pregnancy are, therefore, imperative as a preventive measure to combat maternal and congenital syphilis. Repeat testing later in pregnancy is essential to detect those women who acquire syphilis during pregnancy. In our study, repeat testing was poorly demonstrated, despite good antenatal attendance.

Of the booked mothers with positive syphilis test results at booking/during pregnancy, treatment rates were extremely poor (92% were incompletely/not treated). Pillay *et al.*,[6] also found an overall poor maternal treatment rate in their cohort. Similarly, in a Ugandan study, only 51.7% mothers were reported to have received treatment for syphilis.[8] Furthermore, this study demonstrated very poor contact tracing documentation and partner treatment. An evaluation of routine syphilis screening in antenatal care clients at KZN primary healthcare clinics showed that healthcare providers gave minimal information and/or counselling on syphilis, and the importance of treatment of positive clients and their partners was not emphasised. There is no formal strategy to track positive clients/their partners who had not been treated. Providers were unclear on whether partners should be tested before treatment.[9] Pillay *et al.*[6] also highlighted a deficiency in partner tracing and treatment in their study. A renewed focus is needed to prevent and manage STDs in sexually active men.

Previous pregnancy loss has been identified as a risk factor for congenital syphilis.[10,11] In our study, 17% of mothers had a

Table 2. Characteristics of newborns with congenital syphilis: comparison between deaths and survivors

Variable	Deaths (*N*=12), *n* (%)		Survivors (*N*=35), *n* (%)		*p*-value
Gender					0.55
Male	6	(50)	14	(40)	
Female	6	(50)	21	(60)	
Gestation					0.41
Preterm	11	(92)	27	(77)	
Term	1	(8)	8	(23)	
Birthweight					0.19
<1 000	1	(8)	0		
1 001 - 1 500	1	(8)	4	(11)	
1 501 - 2 500	9	(75)	22	(63)	
>2 500	1	(8)	9	(26)	
Growth parameters					0.74
AGA	9	(75)	23	(66)	
SGA	3	(25)	11	(31)	
LGA	0		0		
Unknown	0		1	(3)	
Mode of delivery					0.78
NVD	5	(42)	13	(37)	
C/S	7	(58)	22	(63)	
Place of delivery					0.31
Inborn	12	(100)	30	(86)	
Outborn	0		5	(14)	
APGARs					0.006
Low (5 minute <7)	7	(58)	4	(11.4)	
Normal	5	(42)	26	(74.3)	
N/A (BBA)	0		5	(14.3)	
Need for resuscitation					0.008
Yes	10	(83)	13	(37)	
No	2	(17)	22	(63)	
Type of resuscitation					
Advanced (intubation and/CPR/adrenaline)	4	(40)	2	(15)	0.15
Basic	4	(40)	11	(85)	
Unknown	2	(20)	0		
Laboratory derangements					
Anaemia	10	(83)	25	(71)	
Thrombocytopenia	8	(67)	16	(46)	
Elevated transaminases	6	(50)	21	(60)	
Conjugated hyperbilirubinaemia	2	(17)	12	(34)	
Hypoalbuminaemia	6	(50)	25	(71)	
Nephrotic range proteinuria	2	(17)	7	(20)	
Neurosyphilis	1	(8)	3	(9)	
Long-bone changes	0		8	(23)	

Table 3. Summary of modifiable factors.

Patient related	Medical personnel related	Administrative
Late booking (16/46 – 35%)	Poor contact tracing and partner treatment (43/46 – 93%)	False negative Rapid results (8/46 – 17%)
Unbooked (8/46 – 17%)	Untreated/inadequately treated maternal syphilis at clinic and hospital level (30/46 - 65%)	Benzathine penicillin stock out (4/46 – 9%)
Defaulted ART (5/29 – 17%)	Transcription errors – results in notes and discharge summaries (17/46 – 37%)	
Teenage pregnancy (7/46 – 15%)	No plan by clinic for repeat testing at 32 - 34 weeks' gestation/ repeat testing not done (14/46 – 30%)	
Substance use (3/46 – 7%)	Poor notification of babies who died with congenital syphilis (2/12 - 17%)	
Failed to return to clinic on prescribed date (2/46 – 4%)	RPR results not checked timeously and therefore not acted upon (3/46 – 7%)	
	Failure to call mothers back timeously for review of RPR results (2/46 – 4%)	
	Not tested at booking (2/46 – 4%)	

previous pregnancy loss. In the event of an unexplained stillbirth, maternal syphilis testing should be done or repeated. If a rapid test is not available, treating the mother for syphilis prior to discharge should be considered in areas with high syphilis prevalence. While there was poor availability of HIV VL results, not all HIV-positive mothers were virally suppressed or on ART. The high prevalence of HIV co-infection in adults further impacts on the global burden and challenges of eliminating congenital syphilis.[1]

Our study showed a case fatality rate of 26% among infants with congenital syphilis. Reported case fatality rates for symptomatic congenital syphilis in Africa vary between 15% in Mozambique to 38% in SA.[5] Disease notification was higher than previously reported[6,12] but extremely poor in babies who died. Congenital syphilis hospitalisations are increasing and contribute significantly to the healthcare utilisation burden.[13] The average length of stay for newborns in our unit was 19.7 days, with 40% requiring NICU admission for ventilation. Umapathi *et al.*[13] showed that the mean length of stay and mean hospitalisation charges were significantly higher in congenital syphilis compared with other hospitalised infants without congenital syphilis. They noted that prevention would be cost-saving (estimated USD345 million from 2009 to 2016 - the equivalent of ZAR 6 295 077 000.00) in the USA.[13] In a report published by the Centres for Disease Control and Prevention in 2018, contributors to missed opportunities for prevention of congenital syphilis in the USA included lack of adequate maternal treatment despite timely antenatal diagnosis of syphilis, lack of timely antenatal care, and late identification of seroconversions[2] (similar to our study findings). Similarly, Srinivas *et al.*[14] noted a lack of routine antenatal testing, shortage of penicillin, and lack of training among healthcare providers as contributors to the congenital syphilis resurgence.

Benzathine benzylpenicillin is the only recommended antibiotic to prevent mother-to-child transmission of syphilis during pregnancy. Recently, there has been a shortage of penicillin worldwide. This is attributed to a perceived lack of profit for manufacturers.[15] Alternative drug regimens have been identified by the NDoH[16] for the management of syphilis in pregnancy. One such alternative regimen is a 28-day course of amoxicillin and probenecid for 28 days, which has implications for drug compliance, side-effects and reluctance of partners to be treated.

Locally, Pillay *et al.*[6] identified poor maternal treatment rates with failure to access antenatal care and late booking as possible factors contributing to congenital syphilis in the Western Cape Province. This was contrary to our study, where most mothers were booked and treatment failure was mostly related to non-compliance by medical personnel with treatment protocols. Additional modifiable factors identified by Pillay *et al.*[6] included poor notification and partner tracing as well as failure to recheck syphilis serology after 32 weeks of gestation in mothers who initially tested negative. These factors were similar to our study findings.

The cornerstone of eliminating congenital syphilis is antenatal screening and treatment of mothers with penicillin. These simple interventions need to be strengthened, as evidenced by the health system failures identified in our study. Syphilis management protocols need to be regularly reviewed by all cadres of staff. In addition, novel and innovative policies and practices should be considered. Given the inconsistency with which rescreening guidelines are followed, a strong argument can be made for implementing revised rescreening protocols.[17] The mean gestational age in our study was 34 weeks, similar to that described by Pillay *et al.*[6] Therefore, these mothers would have missed repeat antenatal testing and adequate treatment prior to delivery. Extended and more frequent retesting protocols during the first and second trimesters of pregnancy may be warranted in areas of high prevalence to detect and treat maternal syphilis timeously. The cost-effectiveness of such an intervention would have to be evaluated in our setting. Additionally, in areas where syphilis prevalence is high and healthcare system failures dominate, alternative strategies such as mass epidemiological treatment could be considered. Mass treatment of adults aged 15 - 49 years with 1g azithromycin in an area of Uganda resulted in a significant reduction in syphilis prevalence.[18]

Study limitations

Owing to the retrospective design of the study, mothers and babies with missing records had to be excluded. Furthermore, stillbirths and babies who were not notified, as well as those admitted to the paediatric wards, were not included. Therefore, our results reflect a minimum estimate of the burden of congenital syphilis in our setting.

Conclusion

Despite good antenatal attendance and early maternal syphilis testing, 47 newborns were admitted to a regional nursery in KZN with congenital syphilis over a period of 39 months. Our study highlights the neonatal burden of this disease as reflected in the need for intensive care, prolonged hospital stays and predictors of mortality. Health system failures are predominantly due to healthcare personnel and relate to inadequate maternal testing, treatment and tracing. Strengthening of existing programmes, together with novel measures, such as extended and more frequent re-testing protocols and mass treatment of sexually active adults, need to be explored to curb the rise of congenital syphilis.

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