Neonatal Cholestasis Secondary to Congenital Syphilis

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ABSTRACT

We report two infants with neonatal cholestasis and hepatosplenomegaly secondary to congenital syphilis. The onset of jaundice of the first infant was at six weeks of life and the second case on the 28th hour of life with associated neurologic and bone involvement. The diagnosis was suspected based on a maternal history of untreated syphilis, clinical findings, and a reactive rapid plasma reagin. Early recognition and treatment can lead to clinical improvement but prevention by mandatory testing and treatment of maternal syphilis is a more effective strategy.

Keywords: congenital syphilis, neonatal cholestasis, rapid plasma reagin

INTRODUCTION

Syphilis is a highly contagious disease that causes serious health problems if not treated. It is caused by *Treponema pallidum*, a gram-negative spirochete that is detected in Giemsa-stained smears of syphilitic lesions.[1,2] Most cases of syphilis are transmitted through sexual contact but they may also be transmitted vertically depending on the stage of syphilis in the pregnant woman. If the mother is in the primary or secondary stage of syphilis, the probability of transmission is > 80%.[2] Maternal-to-child transmission can be transplacental or through the exposure of the child to the birth canal during delivery, a condition known as congenital syphilis.[3]

In 2016, the estimated global burden of congenital syphilis was at 661,000 children, or around 473 cases per 100,000 live births. The number has decreased from 748,000 cases in 2012, reflecting increased access to antenatal care and syphilis screening worldwide.[4] In the Philippines, a search of the Philippine Pediatric Society's registry of diseases reported that out of 4.7 million cases from 2006 up to June 2021, 239 had congenital syphilis (A50.9), 185 of whom were reported in the last 5 years (2016 to 2020).[5] Review of records of the Division of Infectious Disease and Tropical Medicine of the UP PGH Department of Pediatrics showed that there were a total of 73 cases of early congenital syphilis who were referred from 2016-2020, with an estimated incidence of 1-1.5 per 1,000 admissions per year.

Congenital syphilis may present either as an early disease if diagnosed before two years of age, or as a late disease if it occurs after two years. Based on 310 cases of congenital syphilis, early disease manifestations included hepatomegaly in 100 cases (32%), skeletal deformities in 91 (29%), splenomegaly in 56 (18%), low birth weight (< 2.5 kg)

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in 51 (16%), anemia in 50 (16%), skin lesions in 45 (15%) and hyperbilirubinemia in 40 (13%). Other less common manifestations seen in less than 10% of cases included CSF pleocytosis, nephritis, chorioretinitis, and failure to thrive.[6,7]

Late manifestations result from scarring in early congenital syphilis and most commonly include frontal bossing (87%), short maxilla (84%), high palatal arch (76%), and Hutchinson triad (75%). The latter includes interstitial keratitis, eighth nerve deafness, and Hutchinson's teeth, which are abnormal permanent peg-shaped and notched upper central incisors.[6,7]

There have been very few local reports of early congenital syphilis both in the local and foreign literature and these present mainly with jaundice. In 1948, "congenital hepatoptosis" or displacement of the liver was reported in an autopsy of a six-week-old infant diagnosed with syphilis who also had intestinal stenosis and died of subdural hematoma.[8] Liver histology of this infant showed diffuse interstitial hepatitis. In 1954, the Department of Social Hygiene of the Manila Health Department reported 300 cases of congenital syphilis, 85% of whom were described to have a negative Kahn titer after one and half years.[9] No recent local studies were reported after these. In this report, we describe two infants with neonatal cholestasis secondary to early congenital syphilis, one with the onset of jaundice at six weeks of life and another on the 28th hour of life. Both mothers were informed and gave oral consent for the cases to be reported.

CASES

Case 1

The patient is a 2-month-old boy, born full term to a 32-year-old G3P2 (2-0-0-2) mother via spontaneous vaginal delivery at a local hospital. The mother had seven prenatal consults at a local health center, where she underwent ultrasound imaging but had no other laboratory tests such as screening for hepatitis B and syphilis. During pregnancy, she had intermittent bouts of headache and dizziness that were relieved with paracetamol. She also had an intake of ferrous sulfate and calcium supplements while pregnant. There were no other maternal illnesses. She has had three sexual partners, with unknown sexual practices.

The patient was meconium stained at birth, with an Apgar score of 8, 9 and birthweight of 2.62 kg, with no other feto-maternal complications. He was discharged with good suck and activity and without jaundice after two days in the hospital. He was exclusively breastfed for two months, after which he was given milk formula. He was well until the 6th day of life when jaundice was noted but no consult was done.

At 1 ½ month, the patient was brought to the local health center for routine vaccination. He was noted again to be jaundiced with increasing abdominal girth and tea-colored urine. He was advised to undergo sunlight exposure.

Due to the persistence of jaundice, the patient was brought to our institution. At this time, stools were pale-colored (stool color #2–3) based on a standard infant stool color card.[10] Physical examination revealed stable vital signs with no wasting (weight for length, 50th percentile) but with severe stunting (length for age < 3rd percentile) and microcephaly (head circumference < 3rd percentile). The patient was jaundiced with icteric sclerae. The liver was firm, palpable 5 cm below the right costal margin, and with smooth edges. The spleen was palpable 3 cm below the left costal margin. There were no gross bone deformities or skin lesions. The assessment was neonatal cholestasis probably neonatal hepatitis, etiology undetermined.

Laboratory investigations showed anemia [87 g/L (normal value: 105–140)], normal white cell count [WBC: 13 x10^9 cells/L (nv 6–14 x 10^9)] but with lymphocytic predominance (74%) and normal platelet count [222 x 10^9 cells/L (nv 150–450)]. Direct hyperbilirubinemia [Total 10.18 mg/dl (normal value: 0.2-1.3); direct bilirubin 7.67 mg/dL (nv: 0.0-0.4)] was noted with elevated liver enzymes [AST 454 U/L (nv: 17–59); ALT 169 IU/L (nv: <50); GGT of 150 U/L (nv: 15–73)]. Albumin (32 g/L nv: 19–49) and prothrombin time (1.16, nv: 1–1.2) levels were within normal. The HBsAg was non-reactive. Ultrasound of the liver showed hepatosplenomegaly with unremarkable bile ducts and gall bladder. Due to the maternal history of multiple sexual partners, a rapid plasma reagin (RPR) qualitative test was done on the patient which was noted to be reactive. A lumbar tap was subsequently performed to exclude CNS involvement and analysis showed a WBC count of 6 x 10^6/L (Polymorphonuclear cells 2, lymphocytes 4), which was not compatible with neurosyphilis. There was an insufficient amount of specimen to send for CSF protein and VDRL testing. The CSF culture was negative. The patient was managed as neonatal cholestasis secondary to congenital syphilis and was started on penicillin G treatment.

After four days of penicillin, the stool color was noted to improve. Jaundice gradually decreased in intensity with total bilirubin from 10.2 to 6.6 mg/dl on the 9th day of penicillin G treatment. The patient was sent home after completing 10 days of treatment and advised to take ursodeoxycholic acid as choleretic and multivitamin supplements. Unfortunately, the patient was lost to follow up during the COVID-19 pandemic.

During the patient's confinement, a qualitative rapid plasma reagin test was done on the mother and the test was also reactive. Quantitative RPR and treponemal tests were not done as these were unavailable in our institution. Maternal HIV was non-reactive. The mother was also advised to undergo penicillin G treatment.

Case 2

The patient is a newborn girl, born preterm (34 weeks by pediatric aging) to a 16- year-old G2P0 (0-0-1-0) woman via low segment cesarean section due to bleeding placenta

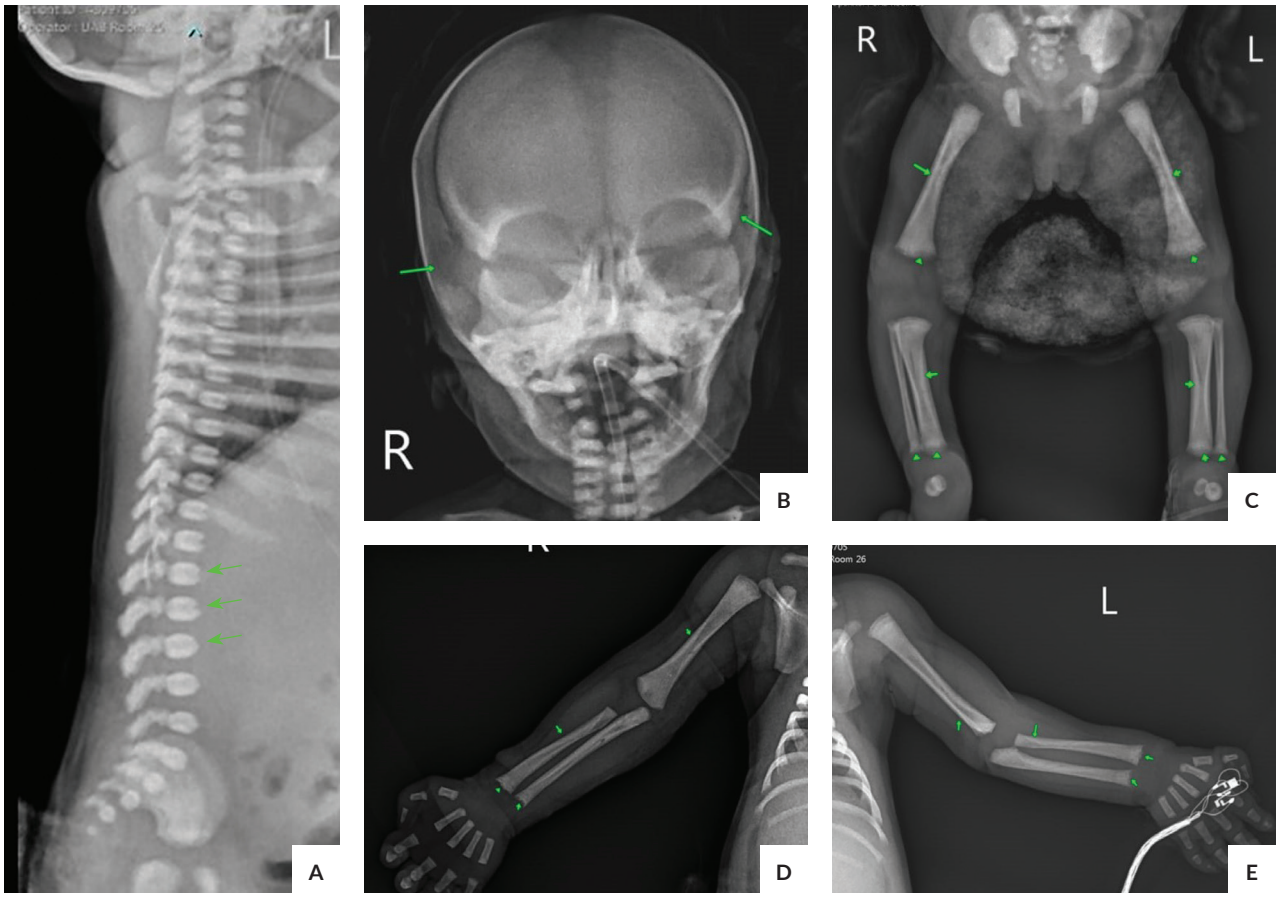

Figure 1. Skeletal survey showed findings consistent with congenital syphilis *(see arrows)*. **(A)** Rugger jersey spine with characteristic prominent endplate densities at multiple contiguous vertebral levels, producing an alternating sclerotic-lucent-sclerotic appearance. **(B)** Demineralized calvarium and signs of subtle molding consistent with craniotabes. **(C to E)** Bilateral periostitis of the bony pelvis, bilateral diaphyseal, and metaphyseal periostitis of the long bones with transverse metaphyseal hypodense bands.

previa. The mother's first pregnancy was a spontaneous abortion at 20 weeks age of gestation for which she underwent dilatation and curettage 10 months before her admission. For this pregnancy, the mother had three prenatal consults at their local health center but did not undergo any prenatal screening tests. She was admitted to our institution due to preterm labor and on examination, she was found to have two discrete, non-tender, hypopigmented ulcerations, approximately 1 x 1 cm around the perianal region with no associated inguinal lymphadenopathy. Sexual history revealed that she was sexually abused at 13 years old and has one sexual partner who denied promiscuity. Work-up revealed a reactive RPR quantitative test (1:64), moderately positive fluorescent treponemal antibody absorption (FTA-ABS) test (1:10), and fetal hepatomegaly on congenital anomaly scan. Work-up for hepatitis B, HIV, and TORCH (Toxoplasma IgM, rubella IgM, and cytomegalovirus IgM) showed negative results. She was assessed to have primary syphilis and was started on intramuscular benzathine penicillin G 2.4 million IU, given approximately 4 hours before emergency cesarean section due to the occurrence of profuse vaginal bleeding. Upon delivery, the placenta was noted to be abnormally enlarged and weighed 600 grams.

The patient was born with good cry and activity, with an Apgar score of 8,9. Her weight of 2.5 kg was appropriate for gestational age but the length of 42 cm and head circumference of 30 cm was less than the 10th and the 25th percentile, respectively. The fontanels were soft and flat. There was no jaundice. The abdomen was distended with the liver palpable 2 cm below the right costal margin and the spleen 3.5 cm below the left costal margin. There were no skin lesions.

The patient had respiratory distress (respiratory rate of 60 breaths per minute) and desaturation (oxygen saturation of 90–92%) on her 4th minute of life, hence she was placed on continuous positive airway pressure and was eventually shifted to non-invasive positive pressure ventilation due to persistent respiratory distress. A babygram confirmed the presence of reticular opacities in both inner lung zones consistent with neonatal pneumonia.

Table 1. Comparison of clinical and diagnostic features of two patients diagnosed with congenital syphilis

	Case 1	Case 2
Demographic characteristics		
Age/Sex	2 months/M	Newborn/F
Clinical presentation	Jaundice	Respiratory distress
Onset of symptom	6 weeks old	4th minute of life
Onset of jaundice	6 weeks	28th hour of life
Maternal history	Multiple sexual partners; Seven prenatal consults	Sexual abuse at 13 years old; Three prenatal consults
Birth weight < 2500 g	Absent	Absent
Physical examination		
Length	< 3rd percentile	< 10th percentile
Head circumference	< 3rd percentile	25th percentile
Skin lesions	Absent	Absent
Jaundice	Present	Present
Hepato- and/or splenomegaly	Present	Present
Hematologic Investigations		
Anemia	Present	Present
Leucopenia/Leucocytosis	Absent	Absent
Lymphocytic predominance	Present	Present
Thrombocytopenia	Absent	Present
CSF study		
Protein	Not done*	Elevated
WBC	Normal	Normal
Ultrasound of Liver	Hepatosplenomegaly	Normal liver size; splenomegaly
Skeletal survey	Not done	Craniotabes, rugger jersey spine, and periostitis of the bony pelvis and long bones

** Inadequate specimen*

On the patient's 28th hour of life, she was noted to have jaundice up to the chest and bilirubin levels showed cholestasis [Total bilirubin 7.83 mg/dL (nv 1–10.5), Direct bilirubin 4.94 mg/dL (nv 0–0.6)]. The transaminase [ALT 9 IU/L (nv 6–40)] and the prothrombin time (INR 0.91) levels were normal. Further laboratory work-ups revealed anemia (Hemoglobin 120 g/L, nv 150–240) and thrombocytopenia (platelet count 50 x 10^9/L, nv 84–478) with normal WBC count (WBC 29.70 x 10^9/L, nv 9.1–34) but with lymphocytic predominance (65%) The quantitative serum RPR was positive at 1:256 and titers were 4-fold higher than the mother at 1:64. The CSF analysis showed elevated protein for age (164 mg/dL, nv <150), a normal white cell count [WBC 6 x10^6/L (PMN 2, lymphocytes 4)]. CSF VDRL test was not available at the time of testing. The blood and CSF cultures were sterile. The whole abdominal ultrasound showed a normal liver size and echogenicity, splenomegaly, and small-for-age but morphologically intact kidneys. The skeletal survey demonstrated craniotabes, rugger jersey spine, and periostitis of the bony pelvis and long bones suggestive of congenital syphilis (Figure 1). There was also an incidental finding of basioccipital fracture on the skeletal survey but was not confirmed on craniocervical CT scan.

She was treated with a meningitic dose of aqueous crystalline penicillin G at 75,000IU/kg/dose every 12 hours for the first 7 days, then every 8 hours until day 14. During the hospital stay, no improvement in the bilirubin levels was noted as other factors aggravated the cholestasis including nosocomial sepsis and necrotizing enterocolitis. The latter required prolonged nothing-per-orem and the use of total parenteral nutrition. She eventually succumbed on the 45th day of life to multiple organ dysfunction syndrome (cardiovascular, respiratory, hematologic, renal, and hepatic) secondary to multi-drug resistant *Acinetobacter baumanii* sepsis.

DISCUSSION

We presented two infants with neonatal cholestasis secondary to congenital syphilis, one of whom had onset of jaundice at six weeks of life and another on the 28th hour of life associated with neurologic and bone involvement. Neonatal cholestasis secondary to congenital syphilis in our institution has not been reported in the last 15 years.[11] A comparison of the patients' clinical and diagnostic features is presented in Table 1.

The first case had jaundice and hepatosplenomegaly, anemia, with no skin, bone, or neurologic manifestations of syphilis. The second case had jaundice and splenomegaly with anemia, thrombocytopenia, elevated CSF protein suggestive of CNS involvement, and presence of microcephaly, sclerotic vertebrae, and periostitis of the long bones on the skeletal survey. The diagnosis of congenital syphilis was suspected based on the sexual history of their mothers and by a positive RPR test. For the first case, the two-month-old boy had a therapeutic response to penicillin G administration with a decrease in intensity of jaundice and improvement in stool color. However, for the second case, the presence

of jaundice and pneumonia in the premature infant was confounded by the development of necrotizing enterocolitis and nosocomial sepsis.

Our diagnosis of a highly probable congenital syphilis was based on the Center for Disease Control guidelines,[12] which define any neonate with the disease if there is: (1) a mother who has untreated syphilis at delivery; (2) a reactive non-treponemal test such as the rapid plasma reagin test; and (3) abnormal physical examination findings consistent with congenital syphilis. Both our patients had jaundice during their early neonatal period. Despite several prenatal consultations, their mothers did not undergo screening with RPR test, hence, failed to receive adequate treatment for syphilis at least four weeks before delivery. In centers with quantitative RPR capacity, a patient's RPR serologic titer that is fourfold higher than the mother is confirmatory as we have seen in our second case. Since RPR measures IgG antibody, the test does not distinguish between disease in the infant and maternally-derived antibody; hence, it is ideal to determine the RPR ratio between the infant and mother. However, the absence of a fourfold titer does not exclude the disease because the RPR titer ratio has low sensitivity (22%), but is highly specific (99%) in diagnosing congenital syphilis.[13] A treponemal test such as fluorescent treponemal antibody absorption test (FTA-ABS) or treponemal pallidum hemagglutination assay (TPHA) on those with congenital syphilis is not recommended as it is difficult to interpret.[12]

Initially, the minimum required investigations for an infant with cholestasis were done on both patients. These included a fractionated bilirubin, liver enzymes, and both serum albumin and prothrombin time, which are measures of the liver synthetic function. The results of their newborn screening were also expedited as this would exclude metabolic disorders presenting with jaundice including galactosemia, hypothyroidism, and tyrosinemia. A fasting ultrasound was also performed to identify the character of the bile duct, to visualize the presence of the gall bladder, and to assess the location of the liver and spleen. In both our patients, the ultrasound showed unremarkable bile ducts and gall bladder. It is also mandatory that the stool color is examined using a stool color chart as the presence of pale or acholic stools will suggest an obstruction of bile ducts. In our first patient, the stool color was initially pale; hence, we could not exclude an obstructive cause at the onset.

After the initial investigation, a targeted evaluation was done based on the maternal and family history and the physical examination of the infant. Due to the mothers' high-risk sexual history, both infants were screened for syphilis, which turned out positive. Other treatable disorders that should be excluded, if indicated, include TORCH, malaria, tuberculosis, and syphilis.

Jaundice with hepatosplenomegaly, as the only presentation of our first patient, is similar to the description of a two-week-old premature Japanese girl who presented solely with jaundice with no external malformation.[14] Autopsy done on this patient revealed non-syndromic paucity of intrahepatic bile ducts, which may explain the findings of pale- colored stool initially, similar to our first case. In other reports on congenital syphilis, the development of jaundice was noted in patients while already admitted for respiratory distress, with either concomitant maculopapular rash, pleural effusion, and ascites or purulent eye discharge and petechial rash.[15,16] Our second patient developed jaundice on the 28th hour of life when the patient was already on ventilatory support secondary to neonatal pneumonia. Approximately 50% of infants with congenital syphilis may present with pneumonia and the classic radiographic appearance is complete opacification of both lung fields known as *pneumonia alba* or fluffy, diffuse infiltrate involving all lung areas.[6] In our patient, what was only seen on baby gram was reticular opacities in the inner lung field.

Recognition and treatment of congenital syphilis are important as penicillin G treatment will lead to improvement of the patient. In our first patient, jaundice decreased and the stool color improved during treatment and he was eventually sent home. Our second patient was also treated for syphilis but jaundice did not resolve due to the presence of other problems related to prematurity. Ideally, infants with reactive nontreponemal tests should be thoroughly examined for late manifestations of congenital syphilis during follow up (e.g., teeth abnormalities, interstitial keratitis, cranial nerve palsy, deafness, bone, and joint changes) and serologic testing (i.e., RPR or VDRL) repeated every 2–3 months until the test becomes nonreactive. If tests remain reactive at 6–12 months, repeat CSF evaluation and co-management with an infectious disease specialist are indicated.[12]

Congenital syphilis is a preventable disease. The value of syphilis screening during antenatal check-ups should be emphasized as a mother who is positive for the disease should already be treated during pregnancy; thus, preventing transmission to the newborn. Among 355,000 estimated cases of congenital syphilis, adverse birth outcomes were noted in 57% of mothers who had prenatal check-ups but were not screened, like our cases; 21% had no prenatal check-ups, 16% had screening but were not treated, and only 6% were screened and treated.[4] A 10-year study in China showed that with the screening of pregnant women and treatment of those infected, the incidence of congenital syphilis declined from 109.3 to 9.4 cases per 100 000 live births.[17] In a meta-analysis with some studies with a high risk of bias, the performance of the rapid immunochromatographic syphilis point-of-care for the antenatal clinic was assessed using as reference standard the non-treponemal and treponemal tests for active syphilis in pregnant women. The immunochromatographic syphilis test was shown to have a pooled sensitivity and specificity for ICS of 0.85 (95% CrI: 0.73 to 0.92) and 0.98 (95% CrI: 0.95 to 0.99), respectively.[18]

In summary, we described two infants who had neonatal cholestasis secondary to congenital syphilis whose mothers had significant sexual histories, one who was sexually abused

and another with multiple sexual partners. The disease should be included in the differential diagnosis of an infant presenting with jaundice if maternal history is suggestive of high-risk sexual behaviors and after exclusion of other treatable causes of cholestasis. Continued maternal screening for syphilis among pregnant patients is recommended and should be emphasized during prenatal visits.

Acknowledgment

We would like to acknowledge the Division of Infectious and Tropical Medicine of the UP PGH Department of Pediatrics for the data on the number of early congenital syphilis cases referred to the department.

Statement of Authorship

All authors contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising, and approved the final version to be published.

Author Disclosure

All authors declared no conflicts of interest.

Funding Source

The study has no funding support.

REFERENCES

1. Woods CR. Syphilis in children: congenital and acquired. Semin Pediatr Infect Dis. 2005 Oct;16(4):245-57.
2. Peeling RW, Mabey D, Kamb ML, Chen X-S, Radolf JD, Benzaken AS. Syphilis. Nat Rev Dis Primers. 2017 Oct 12; 3:17073.
3. Stoltey JE, Cohen SE. Syphilis transmission: a review of the current evidence. Sex Health. 2015 Apr; 12(2):103-9.
4. Korenromp EL, Rowley J, Alonso M, Mello MB, Wijesooriya NS, Mahiané SG, et al. Global burden of maternal and congenital syphilis and associated adverse birth outcomes-Estimates for 2016 and progress since 2012. PLoS One. 2019; 14(2):e0211720.
5. Philippine Pediatric Society, Inc. ICD 10 Registry. [Internet]. [cited 2021 Mar 1]. Available from: https://pps.org.ph/icd-10-registry/
6. Dobson S, Sanchez P. Syphilis. In: Feigin and Cherry's Textbook of Pediatric Infectious Diseases. 8th ed. Philadelphia, PA: Elsevier; 2019.
7. Darville T. Syphilis. Pediatr Rev. 1999 May; 20(5):160-4, quiz 165.
8. Menes S, Ramos A, Guerrero R. Congenital hepatoptosis and subdural hematoma. Sto Tomas J Med. 1948 Sep;
9. Roda A, Pilapil Z, Laqui E, Ibarra L. Kahn reaction of syphilitics after a certain routine treatment. J Philipp Federation Private Med Practitioners. 1954 Dec;
10. Perinatal Services BC. BC Infant Stool Colour Card [Internet]. [cited 2021 Jun 1]. Available from: https://med.ubc.ca/files/2013/07/BCInfantStoolColourCard.pdf
11. Vitug JLD, Avila JMC, Gregorio GV. Histological pattern and outcome of Filipino children with liver disease who underwent percutaneous liver biopsy: a five-year survey. Acta Med Philipp. 2015 Dec 31; 49(4):12-7.
12. Congenital Syphilis - 2015 STD Treatment Guidelines [Internet]. [cited 2020 Apr 8]. Available from: https://www.cdc.gov/std/tg2015/congenital.htm
13. Gong X, Wu M, Zhao L. P760 Sensitivity and specificity of the quantitative test for TPPA and RPR for diagnosis of congenital syphilis in neonates. Sex Transm Infect. 2019 Jul 1; 95(Suppl 1):A326-7.
14. Sugiura H, Hayashi M, Koshida R, Watanabe R, Nakanuma Y, Ohta G. Nonsyndromatic paucity of intrahepatic bile ducts in congenital syphilis. A case report. Acta Pathol Jpn. 1988 Aug; 38(8):1061-8.
15. Filippi L, Serafini L, Dani C, Bertini G, Pezzati M, Tronchin M. Congenital syphilis: unique clinical presentation in three preterm newborns. J Perinat Med. 2004 Jun; 32(1):90-4.
16. Sood V, Cheilani H, Arya S. Congenital syphilis as neonatal cholestasis syndrome - an extinct entity? Journal of Pediatric Sciences. 2014; 6:e216
17. Lin JS, Eder ML, Bean SI. Screening for syphilis infection in pregnant women: updated evidence report and systematic review for the US Preventive Services Task Force. Obstetrical & Gynecological Survey. 2019 Feb; 74(2):75-6.
18. Phang Romero Casas C, Martyn-St James M, Hamilton J, Marinho DS, Rodolfo Castro, Harnan S. Rapid diagnostic test for antenatal syphilis screening in low-income and middle-income countries: a systematic review and meta-analysis. BMJ Open. 2018 Feb; 8(2):e018132.