Tuberculosis in pregnancy resulting to congenital tuberculosis: A case report

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ABSTRACT

Tuberculosis (TB) has been known to be nearly as old as human history. In 2017 WHO Global TB report, in the Philippines the incidence rate was 554/100,000. Tuberculosis contributed to a significant proportion of the global burden of disease, and has significant effect on maternal and perinatal outcomes. Congenital tuberculosis is a rare complication in utero of tuberculosis infection[1,20] with reported incidence of only 358 cases in literature up to 1995 and another 110 cases reported between 1995 and 2009. This paper discusses the case of a 17-year-old young primigravida, diagnosed with tuberculosis few months before pregnancy and treated with first-line quadruple anti-TB regimen. However, she developed jaundice with elevated liver enzymes, hence, the medications were discontinued. Re-challenge of anti-TB drugs were done, however, the patient persistently showed signs and symptoms of adverse drug reactions to anti-TB drugs. At 29 weeks age of gestation, she was admitted for control of preterm labor. Congenital anomaly scanning showed hepatomegaly, intraabdominal abscess, and pseudocyst formation, suggestive of congenital TB. Because of this, the anti- TB drugs were re-introduced despite the elevated liver enzymes with closer monitoring of liver function tests. However, despite aggressive tocolysis, the patient eventually delivered preterm to a live baby boy with poor outcome. The baby expired on the 18th day of life.

Keywords: tuberculosis, pregnancy, congenital TB

INTRODUCTION

The history of tuberculosis (TB) can be trace back to about 7000 years ago when Hippocrates discovered it among the Egyptian mummies, described then as phthisis.[1,2] It was declared a public health emergency in the African Region in 2005[1,2] and has since continued to be a major cause of disability and death[1,2]. In 2017 WHO Global TB report, the incidence rate in the Philippine was 554/100,000, and the mortality rate was 21/100,000. Global report showed that TB is one of the three leading causes of death among women aged 15-45 years[1,3]. One South African study has shown that the sensitivity of clinical screening for TB among pregnant women is as low as 28%[4,5]. This shows that without active screening and case finding program among pregnant women, we can never hope to reach sufficient numbers of cases diagnosed and treated[4]. The incidence rate of tuberculosis in pregnancy is not readily available in many countries due to a lot of confounding factors[1]. It is, however, expected that the incidence of tuberculosis among pregnant women would be as high as in the general population, with possibly higher incidence in developing countries[1]. In a recent epidemiological modeling study, Sugarman et al. estimated that there may have been 216,500 (95% uncertainty range 192,000-247,000) active TB cases among pregnant women globally in 2011, with the highest case burden (41.3% of cases) in the WHO African region[4,6]. Earlier study by Schaefer reported a new case rate of 18-29/100,000 in pregnancy, which was similar to the 19-39/100,000 reported for the city of New York[1,8]. A recent United Kingdom study, however, quoted an incidence of 4.2 per 100,000 maternities[1,8], which may be a reflection of the current global fall in the incidence of the disease[1,3].

The result of TB in pregnancy may be affected by many factors, including the severity of the disease, how advanced the pregnancy at the time of diagnosis, the presence of extrapulmonary spread, and HIV coinfection and the treatment instituted[1]. Failure to comply with treatment also worsens the prognosis[1,9]. Other obstetric complications that have been reported in these women include a higher rate of spontaneous abortion, intrauterine growth restriction, and suboptimal weight gain in pregnancy[1,10,11]. Others include preterm labor, low birth weight, and increased neonatal mortality[1,12]. Late diagnosis is an independent factor, which may increase obstetric morbidity about 4-folds, while the risk of preterm labor may be increased in about 9-folds[1,11,13,14]. Congenital TB may occur as a result of maternal TB when it involves the

genital tract or placenta[15]. A review of Perspectives on Tuberculosis in Pregnancy, Bates M et al. reported that the prevalence of active TB among pregnant women ranges from 0.06% to 0.25% in low-burden countries. In high-burden countries, rates of between 0.07% and 0.5% were found among HIV-negative women, and between 0.7% and 11% among HIV-positive women[4,5]. Failure to comply with treatment also worsens the prognosis[1,9].

Congenital TB may occur as a result of maternal TB when it involves the genital tract or placenta[15]. Mothers of these infants frequently have tuberculous pleural effusions, meningitis, and disseminated disease, but a few of them were diagnosed at the time of delivery or afterward[15]. There are no specific signs and symptoms pathognomonic for congenital TB, and the devastating consequences in the absence of early therapy signify the importance of early diagnosis and treatment during the neonatal period[15]. Clinical manifestations are non-specific and include poor feeding, fever, irritability, failure to thrive, cough, and respiratory distress[15]. Examination reveals hepatosplenomegaly, splenomegaly, and abdominal distension[15]. The diagnosis of TB meningitis (TBM) is even more difficult[15]. Congenital tuberculosis is a rare complication in utero tuberculosis infection[1,16] while the risk of postnatal transmission is significantly higher[1,17]. It may be as a result of hematogenous spread through the umbilical vein to the fetal liver or by ingestion and aspiration of infected amniotic fluid[1,18]. A primary focus subsequently develops in the liver, with the involvement of the peri-portal lymph nodes. The tubercle bacilli infect the lungs secondarily, unlike in adults where over 80% of the primary infections occur in the lungs[1,19]. Congenital tuberculosis is feasibly difficult to distinguish from other neonatal or congenital infections from which similar symptoms may arise in the second to the third week of life. These symptoms include hepato-splenomegaly, respiratory distress, fever, and lymphadenopathy. Radiographic abnormalities may also be present but these generally appear later[1,12]. The diagnosis of neonatal tuberculosis may be facilitated by employing a set of diagnostic criteria developed by Cantwell et al.[1,16], including the demonstration of primary hepatic complex/caseating granuloma on percutaneous liver biopsy at birth, tuberculous infection of the placenta, or maternal genital tract tuberculosis, and the demonstration of lesions during the first week of life. The possibility of postnatal transmission must be excluded by a thorough investigation of all contacts, including hospital staff and attendants[1]. As much as half of the neonates delivered with congenital tuberculosis may eventually die, especially in the absence of treatment[1,7, 20-23].

CASE REPORT

This is the case of a 17-year-old young primigravida, single, presently residing at Pandacan, Manila admitted for the first time at our institution due to hypogastric pain. She was diagnosed to have primary complex when she was seven years old and was treated for six months with unrecalled medications. She has no known allergies to food and drugs. Her mother was treated for pulmonary tuberculosis. She has family history of Hypertension and Diabetes Mellitus on both sides. She is single and currently a senior high school student with no known vices. She had her menarche at age 12, with succeeding menses occurring at irregular intervals (30-60 days) lasting for three to five days, using three moderately soaked pads per day, associated with dysmenorrhea, relieved by rest. She had her first coitus at the age of 16 to a 16-year-old non-promiscuous sexual partner. There was no history of dyspareunia, leucorrhea, or post-coital bleeding. This is her first pregnancy. Her last menstrual period was December 20-23, 2018.

Five months prior to admission, the patient experienced upper back pain on expiration, with no associated symptoms such as fever, cough nor dyspnea. She self-medicated with salbutamol nebulization which offered temporary relief. No consultation was done. One week after, she noticed that her back pain was already associated with non-productive cough and chest pain, easy fatigability, and difficulty of breathing. She consulted at a local health center and was prescribed with Salbutamol nebulization, Clarithromycin, and Prednisone, which offered temporary relief of symptoms. Chest x-ray was done which revealed hazy reticular densities on the left upper lung field. Direct sputum smear microscopy was negative for AFB. The patient was advised to complete Clarithromycin and was referred to TB DOTS. She was subsequently started on HRZE four tablets once a day. She noticed disappearance of symptoms except for occasional difficulty in breathing. However, after one month of taking HRZE, the patient noted jaundice. She was then referred to a tertiary hospital, wherein laboratory tests were done (Tables 1, 4, 5, 6). Significant results were elevation of liver function tests: AST 5.5x, ALT 6.5x, Total bilirubin 2x, Direct bilirubin 6x and indirect bilirubin 7x. Ultrasound of the hepatobiliary tract showed liver parenchymal disease. She was categorized as Pulmonary Tuberculosis, clinically diagnosed Pediatric Community Acquired Pneumonia-Benign. For the jaundice, the main consideration was drug-induced liver injury secondary to HRZE. She was advised to discontinue HRZE, for liver function tests every three days and sent sputum for gene Xpert.

Two months prior to admission, the liver enzymes decreased already to almost normal levels. The patient was for re-challenged with ethambutol, rifampicin,

Table 1. Imaging studies

HBT ultrasound (done outside) 05/09/19	The liver is not enlarged and has a slightly heterogenous parenchymal echo pattern. The intrahepatic ducts and CBD(2.7cm) are not dilated. The portal vein, inferior vena cava, and the hepatic veins are unremarkable. The gallbladder is adequately distended with unthickened walls. No intraluminal echoes are seen. IMPRESSION: Liver Parenchymal Disease considered
HBT ultrasound 07/02/19	Liver: not enlarged with regular external contour; there is normal parenchymal echogenicity; no focal hepatic mass is seen. Intrahepatic ducts/common bile: not dilated; common bile duct measure 0.39cm. Gallbladder: normal-sized; layering medium and low-level echoes are noted in the lumen. The wall is not thickened. There is incidental note of right hydronephrosis IMPRESSION: Gallbladder bile sludge Normal ultrasound of the liver No bile duct dilatation is seen. Incidental note of right hydronephrosis

Table 2. Fetal well-being studies

June 21, 2019	
Biometry	Single live, intrauterine pregnancy in breech presentation 22 2/7 weeks by fetal biometry Male fetus with good cardiac and somatic activity (133bpm) Posterior grade I high lying placenta Adequate amniotic fluid volume (4.22cm) Sonologic estimated fetal weight is Appropriate for gestational age 511g (-/+75g)
July 1, 2019	
Congenital Anomaly Scan	Pregnancy uterine 23 3/7 weeks AOG by fetal biometry, breech presentation, live, singleton Sonographic estimated fetal weight: 650g Good cardiac activity (fht:132bpm) Active fetal movements Adequate amniotic fluid volume (SDP=4.27cm) Placenta posterior, grade II, placental edge is 4.3cm away from the internal cervical os EDD: October 25, 2019 Consider echogenic bowel otherwise, no other obvious gross anomaly seen at the time of scan Suggest follow up scan

Table 3. Complete Blood Count as OPD basis

Complete Blood Count	Normal Values	06/16/19 (done outside)	07/04/19
Hemoglobin	12-16g/ dL	134	11
Hematocrit	37-45%	39	32
WBC	4.40-11 x 10^3/ uL	8.4	7.8
Segmenters Lymphocytes Monocytes Eosinophils	56-65% 25-35% 2-8 1-5	63 32 3 2	72 18 8 2
Platelet	150-450x 10^3/ uL		434
Blood typing			O "+"

and isoniazid. However, she complained of nausea and vomiting every time she takes the medication. Because of secondary amenorrhea of five months duration, a pregnancy test was done which revealed a positive result. She was then referred to OB service, wherein a biometry was done showing live pregnancy, 22 weeks and 2 days, with weight appropriate for gestational age and normal amniotic fluid. (Table 2)

Table 4. Liver Function Test (other institution)

Blood chemistry	Normal Values	May 10, 2019
SGPT/ALT	0-35 U/L	228
SGOT/AST	14-36 U/L	198
Total Bilirubin	0.20-1.30mg/dL	2.58
Direct Bilirubin	0.0-0.30mg/dL	1.87
Indirect Bilirubin	0-0.10mg/dL	0.71

Table 5. Liver Enzyme Test (other institution)

Blood chemistry	Normal Values	5/20/19	5/24/19	06/02/19	06/06/19 (hold HRZE)	06/16/19
SGPT/ALT	0-45 U/L	121	52	43	41.0	108
SGOT/AST	0-45 U/L	87	44.4	39	38	85
Total Bilirubin	<18.8umol/L				31.9	15.4
Direct Bilirubin	<4.3umol				5.70	6.45
Indirect Bilirubin	<17.1umol				26.2	8.95
Albumin	3.7-5.5 g/dL		3.95			

Table 6. Imaging studies(other institution)

5/2/19	
Chest x-ray	Hazy reticular densities seen on the left upper lung. The heart is not enlarged. Left costophrenic sulcus is blunted. The rest of the visualized structures are unremarkable. Impression: PTB, left upper lung, activity undetermined. Pleural effusion and thickening left.
May 2, 2019 Ultrasound	Scanning of the right hemithorax fails to show fluid collection in the pleural spaces and subdiaphragmatic areas. The visualized portions of the lung parenchyma are unremarkable. Scanning the left hemithorax fails to show fluid collection in the pleural spaces and subdiaphragmatic areas. The visualized portions of the lung parenchyma are unremarkable. Impression: unremarkable chest ultrasound negative for pleural effusion.
3/19/19	
Direct Sputum Smear Microscopy	Negative
Xpert MTB/RIF (sputum)	MTB not detected
Chest x-ray 7/10/19	Suspicious minimal opacities are noted in both upper lung fields Pulmonary vascular markings are within normal. The heart is not enlarged The diaphragm, costophrenic sulci, and chest bones are intact. Remark: Suggest apicolordotic and left spot oblique views if warranted.

At 23 weeks age of gestation, the patient consulted at another private tertiary hospital for first prenatal check-up. She complained of vaginal itchiness and irregular uterine contractions. On physical examination, the vital signs were normal. Abdominal exam showed normal fetal heart rates and appropriate estimated fetal weight. On speculum examination, the vaginal wall was coated with white curd-like discharge. On internal examination, the cervix was closed and uneffaced. Routine prenatal laboratories were done showing normal results. Repeat liver function tests showed elevated results: ALT 2.7x, total bilirubin 2x, direct bilirubin 6x, indirect bilirubin 5x. Repeat ultrasound of the hepatobiliary tract showed gallbladder bile sludge (Tables 3, 4, 7,8,9). She was referred to Gastroenterologist and she was started on Ursodeoxycholic acid 250mg/tab 2 tablets 2x a day.

Tocolysis was done in the form of Isoxsuprine 10mg/tab 1 tablet 3x a day and Micronized Progesterone was started. Miconazole 1200mg vaginal suppository single dose was given for the vaginal candidiasis. She was advised to follow-up every three days with repeat liver function tests.

At 29 weeks age of gestation, the patient complained of hypogastric pain for three days. She consulted in the out-patient department. She had stable vital signs, good fetal heart tones, and the estimated fetal weight was appropriate for age. The uterine contractions were occurring every 6-7 minutes, moderate to strong lasting for 50 seconds. Internal examination showed a close and uneffaced cervix. She was subsequently admitted for tocolysis. Magnesium sulfate drip was started for neuroprotection as well as tocolysis. Micronized progesterone was continued.

However, the contractions remained to be regular and strong; hence, isoxuprine drip was added with rescue doses of Terbutaline given subcutaneously. Sedation was also given round the clock. She was given Dexamethasone 6mg IM every 12 hours for four doses. Biometry with Congenital Anomaly Scan was done which showed polyhydramnios with AFI of 32, Category II intrapartal monitoring for areas of minimal variability, and the contractions were strong every two minutes. The cervix was shortened. The baby was large for gestational age (1, 757 +/- 264 grams). The fetus also had bilateral ventriculomegaly, brachycephaly, cardiomegaly with right atrial dilatation, echogenic stipplings on the left lung, encapsulated intraabdominal mass to consider abscess and echogenic liver borders. Congenital tuberculosis was the primary consideration for the fetus. Hence, the quadruple anti-TB drugs were re-introduced despite elevated liver function tests (AST 1.7x, ALT and total bilirubin 2x, direct bilirubin 6x, indirect bilirubin 4x). She was also referred to the Perinatologist for co-management. The plan was to do amnioreduction once the contractions are controlled. The result of sputum gene Xpert came in with no MTB detected. Rectovaginal swab for GBS was negative. Her liver function tests were monitored every three days.

On the first hospital day, the patient complained of occasional difficulty of breathing. There was note of blood pressure elevation, the highest was 140/90 mmHg. Urine albumin was negative. She was started on Methyldopa 250mg/tab 1 tab every 8 hours for the Gestational Hypertension. She continued to experience uterine contractions occurring every 9-12 minutes, mild to moderate, lasting for 50-55 seconds. Tocolytic agents were continued, but Magnesium sulfate was discontinued after 24 hours.

Table 7. Diagnostic tests(done as OPD at our institution)

Diagnostics	Normal value	07/01/19	07/05/19
HbsAg	1.00	0.21 (nonreactive)	
Syphilis		nonreactive	
LDH	120-246	180	
Rubella IgG	>10		54.89 positive
Anti-HIV Ag/Ab	0.90		0.20

Table 8. Papsmear (done at our institution)

	06/27/19
Pap smear	Specimen is satisfactory for evaluation Negative for intraepithelial lesion or malignancy Reactive cellular changes associated with moderate inflammation

Table 9. Liver Function Test (done at our institution)

Blood chemistry (done at our institution)	Normal values	07/01/19	07/10/19
SGPT/ALT	0-34 U/L	93	121
SGOT/AST	14-59 U/L	56	77
Total bilirubin	0.20-1.30 mg/dL	2.80	
Direct bilirubin	0-0.40	2.40	
Indirect bilirubin	0-0.10	0.50	

Table 10. C&S(done at our institution-as OPD)

Urine culture and sensitivity	
07/04/19	No growth after 48 hours of incubation

Table 11. Diagnostic Tests (in-patient)

Complete Blood Count	Normal Values	8/13/19	8/16/19	8/19/19 (postop)
Hemoglobin	12-16g/ dL	11.6		
Hematocrit	37-45%	33.4		
WBC	4.40-11 x 10^3/ uL	10.4		
Segmenters Lymphocytes Monocytes Eosinophils	56-65% 25-35% 2-8 1-5	77 15 7 1		
Platelet	150-450x 10^3/ uL	405		
SGPT/ALT	0-34 U/L	130	155	72
SGOT/AST	14-59 U/L	104	101	44
Total bilirubin	0.20-1.30 mg/dL	2.80		
Direct bilirubin	0-0.40	2.40		
Indirect bilirubin	0-0.10	0.40		
Creatinine	0.52-1.25	0.60		
Magnesium	1.60-2.30	1.76		

On the second hospital day, still with persistence of uterine contractions, Indomethacin 100mg/tab 1 tab per rectum was given and proceeded with amnioreduction, draining 1 liter of yellow, clear fluid. The amniotic fluid was submitted for TB culture and drug sensitivity testing, AFB smear, gram stain, and Gene Xpert testing. Indomethacin was continued for 48 hours at a dose of 50mg per orem every 6 hours. Repeat AST and ALT on the third day of re-introduction of anti-TB drug showed no significant interval change.

On 4th hospital day, the patient's preterm labor progressed with cervical dilatation of 6 cm and fully effaced. The presentation was footling breech; hence, an emergency low transverse cesarean section was performed. The outcome was a live baby boy, 32 weeks by pediatric aging, 1620 grams which was appropriate for gestational age, APGAR score of 5 becoming 9. Anthropometric measurements are within normal limits. The amniotic fluid was clear yellow amounting to 800cc. The placenta was grossly normal and was sent for histopathologic examination. Random peritoneal and omental biopsies were done. Peritoneal fluid and amniotic fluid were submitted for AFB and GS/CS (Table 12). Stool AFB microscopy was also done. The results of all AFB smears and GG/CS were all negative.

The baby developed tachypnea with desaturation; hence, he was hooked to mechanical ventilator. Baby gram revealed respiratory distress syndrome, soft tissue mass (2.7x3.2cm) with calcified borders on the right hemiabdomen, peritoneal lining calcification, to consider meconium peritonitis. Abdominal x-ray showed fecal retention and noted the same soft tissue mass in the right hemiabdomen. 2D echo revealed Patent Ductus

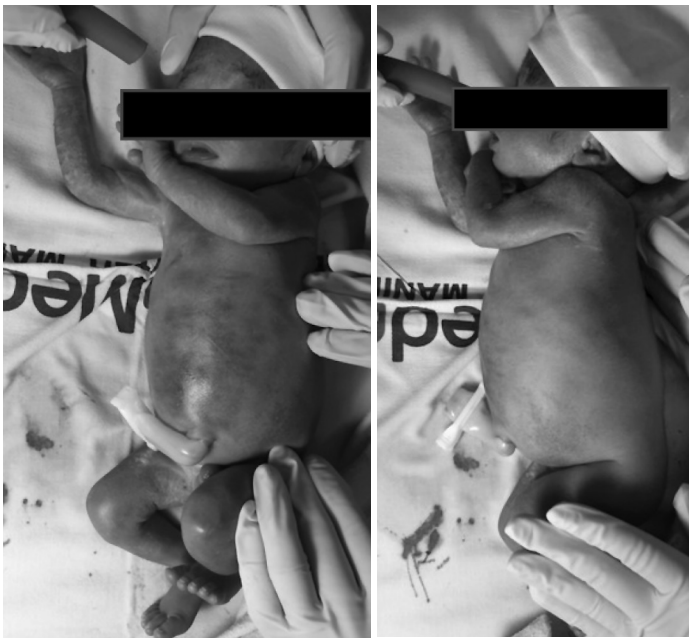

Figure 1. Livebirth baby boy preterm, birthweight: 1620grams birth length: 38cm; head circumference: 27cm; abdominal circumference: 29cc, chest circumference: 26cm APGAR Score 5, 9 Ballard Score 32 weeks AGA

Table 13. Fetal well being (in-patient)

Biophysical Profile 08/13/19	Single live intrauterine pregnancy, in breech presentation, with good cardiac and somatic activities, 31 1/7 weeks by composite sonar aging (HC, FL, AC) Placenta is posterior, high lying, grade II Biophysical profile score is 8/8 with polyhydramnios (32.45cm) IPM is category II for areas of minimal variability, with strong contractions every 2 minutes Short cervix Sonographic estimated fetal weight is 1757=/- 264grams; above the 90th percentile for gestational age Incidental findings: bilateral ventriculomegaly Brachycephaly Cardiomegaly with right atrial dilatation Echogenic stipplings, left lung Encapsulated intraabdominal mass Echogenic liver borders

Table 14. Baby diagnostic tests

Baby gram	revealed consider respiratory distress syndrome: clinical and laboratory correlation is suggested, soft tissue mass with calcified borders, right hemiabdomen. Ultrasound correlation is suggested for further, left peritoneal lining calcification, consider meconium peritonitis.
Abdominal x-ray	consider fecal retention, soft tissue mass in the right hemiabdomen with no significant change in size.
2d echo	Patent ductus arteriosus
Whole abdominal ultrasound	Encapsulated complex mass (3.0x4.4x1.1cm)with echogenic rim in the right lower hemiabdomen, cannot totally rule out hepatic in origin. Pseudocyst formation from an infectious process is also a possibility. Calcified hepatic borders. May be infectious in origin. Hepatosplenomegaly with left lobe calcification. Obscured pancreas and aorta. Normal Spleen and renal ultrasound. Underfilled urinary bladder.

Table 12. Culture, histopathologic test (in-patient)

Tests:	**Results:**
GBS Screening 8/14/19	Negative for GBS Specimen: rectovaginal swab
AFB (post-amnioreduction) 8/14/19	No acid-fast bacilli seen Specimen: urine
Peritoneal fluid C&S (post-amnioreduction) 8/16/19	No growth after 72 hours of incubation Specimen: amniotic fluid
Acid-fast bacilli (intraop) 8/18/19	No acid-fast bacilli seen Specimen: amniotic fluid
Acid fast bacilli (intraop) 8/18/19	No acid-fast bacilli seen Specimen: peritoneal fluid
Gram stain (intraop) 8/18/19	PMN: +1 No microorganism seen Specimen: amniotic fluid
Histopath result 8/18/19 HP-2019-2214	A. Mature singleton placenta 500grams with unremarkable 3 vessel umbilical cord; Chorioamnionitis, moderate B. Specimen: peritoneum Fibroadipose tissue with congestion and mild chronic inflammation C. Specimen: omentum Adipose tissue with congestion Negative for granuloma, all specimens

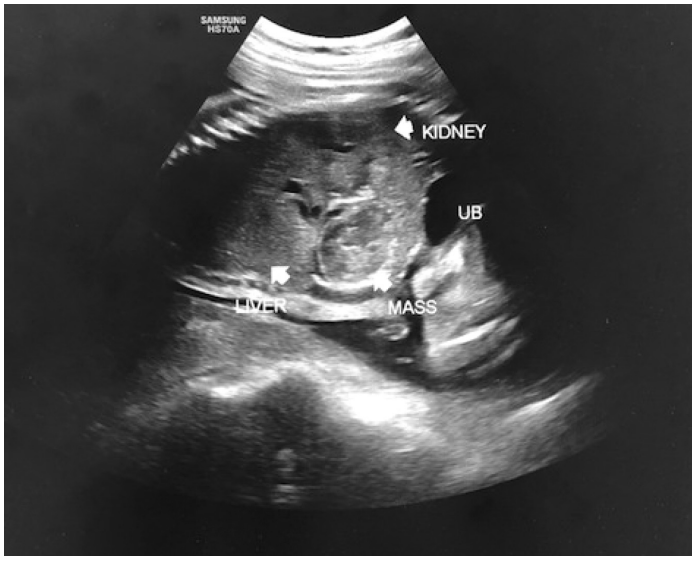

Figure 2. Biometry with Biophysical profile, showing the kidney, liver with intraabdominal mass

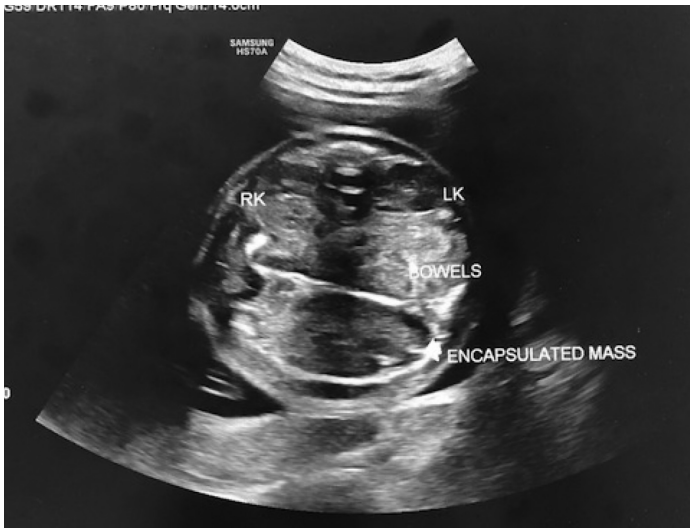

Figure 3. Biometry with Biophysical profile, showing the kidneys, bowels and encapsulated intraabdominal mass

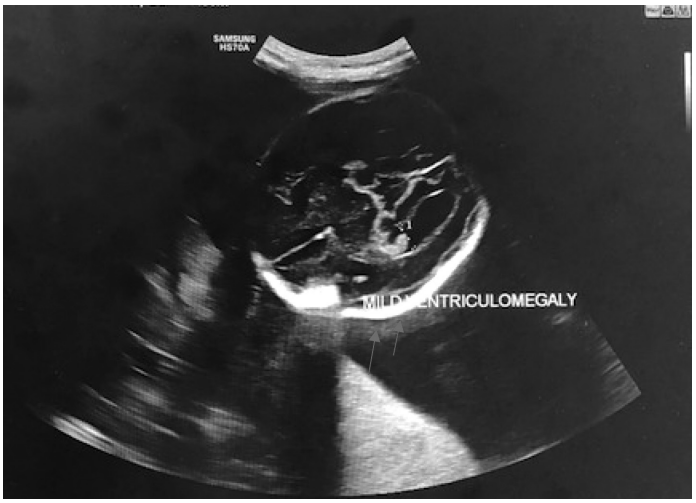

Figure 4. Biometry with Biophysical profile, showing mild ventriculomegaly

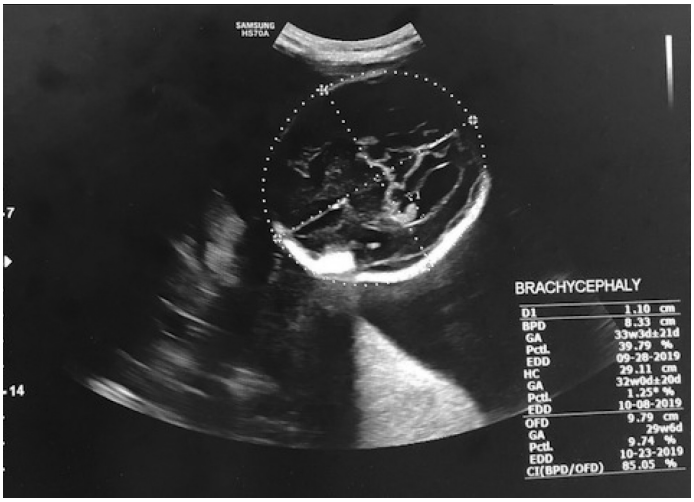

Figure 5. Biometry with Biophysical profile, showing brachycephaly

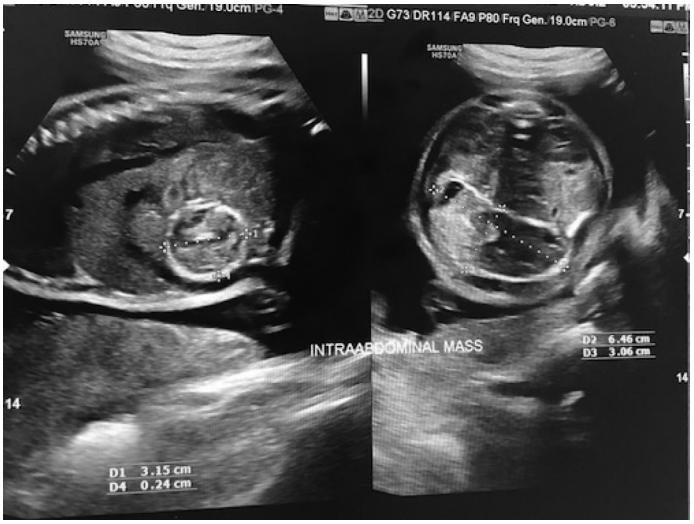

Figure 6. Biometry with Biophysical profile, showing the encapsulated intraabdominal mass

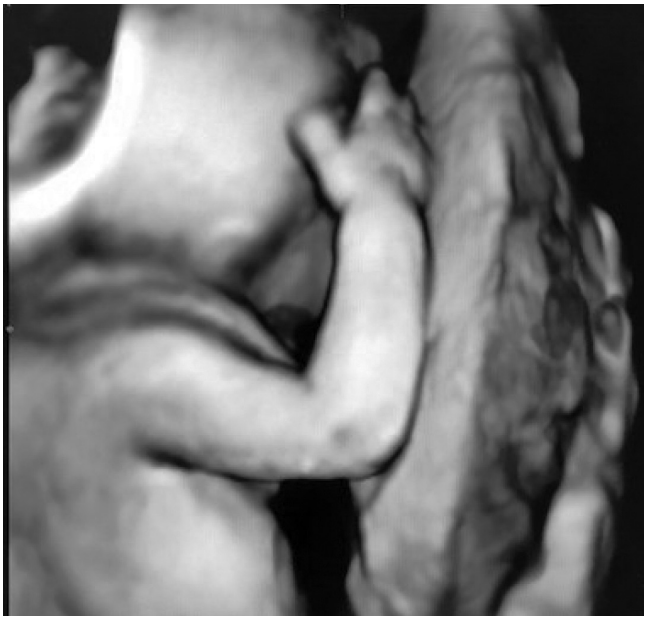

Figure 7. 4D Ultrasound of the Baby

Arteriosus. Whole abdominal ultrasound revealed encapsulated complex mass with echogenic rim in the right lower hemiabdomen measuring 4.52x3.99x2.67cm. The considerations for this mass were either primary hepatic mass versus pseudocyst formation from an infectious process. There was also note of calcified hepatic borders probably infectious in nature and hepatosplenomegaly with left lobe calcification (Table 4). 2D echo revealed Patent Ductus Arteriosus. The baby was started on Amikacin + Ampicillin. He was referred to Surgery and the plan was for exploration for the abdominal mass, cannot rule out bowel perforations. He was then transferred to another institution due to financial constraints. At the other institution, the baby underwent Exploratory Laparotomy. Intraoperative findings revealed a ruptured gallbladder, inflammation of the liver, gallbladder and bowels. Colostomy insertion was done, Baby expired 3 hours postop due to cardiopulmonary arrest secondary to multiple organ failure from sepsis.

The mother had unremarkable post-operative course with declining AST and ALT levels. Histopathologic studies of placenta showed moderate chorioamnionitis. Peritoneal and omental biopsies showed only mild chronic inflammation negative for granuloma. On 7th hospital day, the patient was discharged improve. The final diagnoses were: Pregnancy uterine, delivered term, breech, livebirth, appropriate for gestational age; Disseminated Tuberculosis; Jaundice in pregnancy, considerations are pregnancy-induced cholestasis vs adverse drug reaction to anti-TB drugs, resolving; Poor obstetric history for early preterm neonatal death secondary to congenital tuberculosis; Gestational Hypertension; Young primipara.

CASE DISCUSSION

The index patient was diagnosed with tuberculosis few months prior to pregnancy. She also had history of primary complex when she was seven years old and was treated for six months with unrecalled medications. There are several factors to identify to predispose recurrence of tuberculosis. These include immunosuppressive state, re-exposure, and drug resistance. Pregnancy alone is associated with immune suppression making one susceptible to infectious disease. The patient experienced upper back pain, non-productive cough, chest pain, easy fatigability and difficulty of breathing. She had stable vital signs, no co-morbidities, and was diagnosed with Pediatric Community Acquired Pneumonia-B (low risk). According to guidelines, antibiotic treatment as out-patient is the management of choice. But persistence of symptoms despite compliance with antibiotic should prompt the clinician to work-up the patient for tuberculosis. A chest x-ray was done which revealed hazy reticular densities on the left upper lung field. Direct sputum smear microscopy was negative for AFB. A sputum AFB has a sensitivity of 67.5% and specificity of 97.5, while chest x-ray has a sensitivity of 78% and specificity of 51%, a gene Xpert sensitivity of 88% and specificity of 98%. Therefore, despite the negative results of AFB smear and gene Xpert, tuberculosis was still the main consideration because of the clinical presentation of the patient.

The patient developed jaundice after 1 month of anti-TB treatment. While most patients complete the treatment without any significant adverse effect, there are few patients who experience adverse drug reaction. According to DOH, a data from Philippine plan of action to control tuberculosis from year 2010-2016. A total of 19,500 MDR-TB cases have been detected and provided with quality-assured second line anti-TB drugs. At least 75% of MDR TB patients are successfully treated. At least 730,00 children are initiated into anti TB treatment or given INH preventive therapy. The management is discontinuation of drugs and monitoring of liver enzymes, and subsequent re-challenge. In this case, she failed in the re-challenge. However, the quadruple anti-TB drugs were re-introduced despite elevated liver enzymes because of the need to halt the effects of congenital tuberculosis. In addition, adverse drug reaction was not the main consideration at this time because the medicines were discontinued for almost three months already. Tuberculosis itself may cause inflammation of the liver which may lead to elevated liver enzymes. Hepatic TB is encountered more frequently in Asian countries and hepatobiliary TB is seen commonly in the Philippines and among Filipino patients abroad. They theorized that this observation is probably due to racial vulnerability of Filipinos to the tubercle bacilli. Some of the case reports in the world literature of localized hepatic TB, especially causing obstructive jaundice, involved Filipino patients[24]. In this patient, subsequent monitorings of AST and ALT actually showed decreasing trend and improvement in total well-being was observed.

The first-line tocolytic agent is Nifedipine. However, this can not be given to patients taking Rifampicin, because of significant drug interaction. Rifampicin may substantially decrease the oral bioavailability of different types of prototype calcium channel antagonists (e.g. Verapamil and Nifedipine) to the extent that the therapeutic effects of these drugs are attenuated or almost abolished. Previous studies have revealed that these drug interactions can be attributable to induction of hepatic and intestinal CYP3A4 activity by Rifampicin. Rifampicin can also attenuate the hypotensive effects of the newer dihydropyridine calcium channel antagonists

(i.e. Nisoldipine, Nifedipine). These drugs undergo extensive pre-systemic elimination, leading to very low oral bioavailability, ranging from 14 to 19%. The finding that the treatment with Rifampicin elicited a 5-fold increase in the urinary 6β-hydroxycortisol/cortisol ratio, an index of hepatic CYP3A activity indicates that there was a substantial induction of this enzyme in the liver[25]. The baby of the index patient developed congenital anomalies compatible with congenital tuberculosis.

On untreated mother, a congenital transmission of tuberculosis may occur due to the hematogenous spread of the tuberculosis bacilli via the umbilical vein from the infected placenta to the fetal liver and lungs.[26] A less common cause of congenital tuberculosis is aspiration or ingestion of infected amniotic fluid in utero or before passage through the birth canal.[26] which may lead to primary complexes in the lungs and gastrointestinal tract. Generally, the bacilli in the lungs of the fetus remain dormant until after birth, when the considerable increase in oxygenation and pulmonary circulation may lead to activation of tuberculosis. Dissemination then occurs via the fetal circulation into the other organ systems, which may cause manifestations such as seen in this baby[24].

There are no specific signs and symptoms pathognomonic for congenital TB, and the devastating consequences in the absence of early therapy signify the importance of early diagnosis and treatment during the neonatal period[15]. Diagnostic tests confirming congenital TB are hepatosplenomegaly in 100% of cases, splenomegaly in 77.8% of cases, and abdominal distension 77.8% of cases, which are all present in the baby. Congenital tuberculosis is feasibly difficult to distinguish from other neonatal or congenital infections from which similar symptoms may arise in the second to the third week of life. When a pregnant woman with tuberculosis gives birth, the aim is to ensure TB free survival of her newborn infant. It involves diagnosing active tubercular lesion including congenital tuberculosis, and treatment of the neonate or prevention of transmission of tubercular infection to the neonate from the mother. There is no uniformity as is evident from the recommendations of the eminent societies of different countries across the globe. The decision to start isoniazid (INH) prophylaxis to the neonate depends on a number of factors including the history of detection and duration of maternal disease (before or during or after pregnancy), type of tuberculosis (pulmonary or extrapulmonary), and maternal compliance of treatment (regular or irregular). INH prophylaxis is recommended in the neonate if the mother has received treatment for <2 wk, or those who are on therapy for >2 wk but are sputum smear positive. American Academy of Pediatrics (AAP) recommends INH prophylaxis to all neonates of mothers who are diagnosed with tuberculosis in the postpartum period and/or after the commencement of breastfeeding has started as these newborns are considered potentially infected. Breastfeeding is crucial for the survival of the newborn. Human milk provides better nutrition, has immunological benefits and all efforts to continue breastfeeding in newborns with mothers having tuberculosis should be made. In case of maternal sickness or if mother is smear positive at the time of delivery or mothers with MDR TB, when breastfeeding may not be possible, expressed breast milk feeding is an alternative, with personal hygiene. AAP recommends continued feeding with expressed milk in mothers with pulmonary TB who are contagious, untreated or treated (< 3 wk) with isolation. WHO recommends feeding under all circumstances, however, close contact with the baby should be reduced.

Treatment regimens for congenital tuberculosis include isoniazid, rifampicin, ethambutol and kanamycin or amikacin for the first two months followed by isoniazid and rifampicin for 6-12 months. Bacillus Calmettee Guerin (BCG) vaccination protects against the dissemination of tuberculosis and severe disease. In neonates with congenital tuberculosis there is no utility of BCG vaccine. WHO recommends BCG vaccine after completion of INH therapy. As much as 50% of them will die in the absence of treatment[1,7, 20-23].

SUMMARY

In summary, we are presented with a 17-year-old primipara, diagnosed with tuberculosis, and treated with HRZE. However, she developed jaundice and elevated liver enzymes, thus the medications were discontinued. She had preterm labor at 29 weeks age of gestation, and eventually delivered to a preterm live baby boy with anomalies consistent with congenital TB.

Tuberculosis in pregnancy may affect many factors. Failure to comply with treatment also worsens the prognosis. Complications include preterm labor, low birth weight and increased neonatal mortality. Most patients complete the treatment without any significant adverse effect. There are few patients who experience adverse drug reaction. In managing adverse drug reaction, the treatment is a symptom-based approach.

The index patient developed jaundice. Anti-TB drug was discontinued but despite discontinuation there is still persistence of elevated liver function. Hepatic TB is encountered more frequently in Asian countries. In a study, it has been observed that hepatobiliary TB is seen commonly in the Philippines and among Filipino patients abroad and there is no explanation for this kind of occurrence but it has been suggested that Filipinos may have racial vulnerability to the tubercle bacilli. Some of the case reports in the world literature of localized

hepatic TB, especially causing obstructive jaundice, involved Filipino patients[24]. On untreated mother, a congenital transmission of tuberculosis may occur due to the hematogenous spread of the tuberculosis bacilli via the umbilical vein from the infected placenta to the fetal liver and lungs.[26] A less common cause of congenital tuberculosis is aspiration or ingestion of infected amniotic fluid in utero or before passage through the birth canal.[26] which may lead to primary complexes in the lungs and gastrointestinal tract. There are no specific signs and symptoms pathognomonic for congenital TB, and the devastating consequences in the absence of early therapy signify the importance of early diagnosis and treatment during the neonatal period[15]. Diagnostic test confirming congenital TB are hepatosplenomegaly, splenomegaly, and abdominal distension, which are all present in the baby. Congenital tuberculosis is feasibly difficult to distinguish from other neonatal or congenital infections from which similar symptoms may arise in the second to the third week of life. When a pregnant woman with tuberculosis gives birth, the aim is to ensure TB free survival of her newborn infant.

Tuberculosis in pregnancy is challenging. It is important for clinicians to remain vigilant when managing pregnant women from at-risk groups in the hope of minimizing the harm to both the mother and the baby. Treatment with first-line drugs is generally safe and improves maternal and neonatal outcome.

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