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Management of newborns at risk of neonatal and perinatal tuberculosis

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ABSTRACT

Tuberculosis (TB) is one of the commonest infectious diseases in the world with 10.4 million new cases estimated in 2015, of which one million are children. The prevalence of active TB in pregnant and postpartum women from high-prevalence countries is higher than 60 cases per 100 000 people per year. Here we presented three different cases of infants born to mothers with active TB and we reviewed the current recommendations on the prophylaxis of neonatal and perinatal tuberculosis. Currently there is a lack of concordance regarding the most appropriate time for TB reassessment and discontinuation of prophylaxis after birth. More reliable diagnostic tests are still needed to help physicians to decide the appropriate time to safely discontinue prophylaxis. An uniform consensus on management of infants born to TBC-infected mothers is highly necessary to improve the measures and interventions to limit the infection at birth.

1. Introduction

Tuberculosis (TB) continues to be a prevalent disease worldwide and a global public health problem in many countries, with more than 10 million new cases estimated in 2015, of which one million are children[1]. The prevalence of active TB in pregnant and postpartum women from high-prevalence countries is higher than 60 cases per 100 000 people per year and maternal TB is associated with an increased risk of fetal and perinatal mortality. Congenital and perinatal TB are still a challenge for physicians since they are often difficult to diagnose. Here we presented three different cases of newborns to mothers with active TB and we discussed current guidelines on prophylaxis of neonatal and perinatal TB.

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2. Case reports

2.1. Case 1

An Italian pregnant woman aged 31 years old with 36 weeks gestational age was admitted to the Emergency Department for persistent cough, mild fever (skin temperature 37.5 ℃) and pharyngitis started one month ago. She did not have any history of travels in the last year, neither contacts with people with persistent cough. Foetal heart rate showed initial signs of foetal distress, then the labour was induced. Neonatal weight was 2 550 g (50° percentile), length 44 cm (10°–25° percentile), head circumference 32.5 cm (50° percentile). APGAR score was 9-10-10. Clinical evaluation at birth and pulse oximetry were normal. The baby was breastfed and placed in the same room of the mother. Seven days after birth, the mother developed a worsening of cough. Chest X-ray (CXR), thoracic CT scan, molecular and microscopic research for *Mycobacterium tuberculosis* (*M. tuberculosis*) on sputum analysis were then performed and pulmonary tuberculosis of the mother was diagnosed. The baby was then isolated from the

mother and a complete screening for *M. tuberculosis* infection was performed.

2.2. Case 2

A Moroccan pregnant woman with 36+5 weeks gestational age was admitted at the Emergency Department for persistent cough and thoracic pain started 10 days ago. CXR showed cavitations compatible with pulmonary TB. Molecular, microscopic and cultural analyses of sputum showed positive results for TB infection. Therefore, she started treatment with oral isoniazid (INH), ethambutol (EMB), rifampicin (RIF) and pyrazinamide (PZA). Five days later, an urgent caesarean section was performed for preeclampsia. The newborn, a boy, showed APGAR score of 9-9-10, 2 600 g in weight, 47 cm in length, 33 cm in head circumference (50° percentile), normal outcome for physical examination and pulse oximetry. The microscopic and molecular analyses of mother's sputum for *M. tuberculosis* were repeated and gave negative result, thus rooming-in procedures and breastfeeding were allowed.

2.3. Case 3

The case 3 is a girl born to Arabian mother with active pulmonary TB diagnosed in the first trimester of pregnancy, and treated with INH, RIF and PZA during pregnancy. Because of scarce tolerability of INH (nausea and vomiting), INH was discontinued and the therapy was continued with RIF and PZA until the end of pregnancy. She gave birth to a girl at 40 weeks of gestational age with vaginal delivery. APGAR score was 10-10-10, weight 2 710 g (3° percentile), length 49 cm (10°–25° percentile), head circumference 33 cm (10° percentile); the results for physical examination and pulse oximetry were normal. Also in this case, rooming-in and breastfeeding were allowed, and microscopic and molecular research on mother's sputum for *M. tuberculosis* gave negative results.

In all three cases, CXR, three nasogastric aspirates for microscopic, molecular (DNA–PCR) and cultural identification of *M. tuberculosis*, blood and urine culture, interferon-γ release assay (IGRA) and tuberculin skin test (TST) were performed for the babies at birth and they were all negative for *M. tuberculosis* infection. For a complete clinical assessment, electrocardiogram, cerebral and abdominal ultrasound were also performed and showed normal outcomes. HIV screening was performed in all mothers and their babies, and they were all negative. Cerebral fluid analysis was not performed given the good clinical condition and normal blood analysis (C-reactive protein, blood count) and CXR. None of the babies showed any sign of disease during the observation. All babies were dismissed from the hospital with 10 mg/kg INH for prophylaxis and pyridoxine supplementation, then they were followed at our Infectious Disease Unit once a month for the first 6 months of life with complete clinical examination and blood assessment (C-reactive protein, blood count, liver function). CXR was repeated at two months of age, and TST and IGRA at 3 and 6 months of age, and all showed negative results. Then, INH was discontinued after 6 months. After the suspension of prophylaxis, patients continued to be re-followed at our unit every 3 months until 1 year of age.

3. Discussion

Given that TB continues to be a prevalent disease in the world and a global public health issue in many countries, from 2006 there was an increased attention to the specific challenges of TB in children and an increased recognition of its importance as a global public health issue.

In particular, the prevalence of active TB in pregnant and postpartum women is at a rate higher than 60 cases per 100 in high-prevalence countries according to the report of WHO, and maternal TB has been associated with an increased risk of spontaneous abortion, perinatal mortality, small size for gestational age, and low birth weight[1]. Maternal TB has been associated with an increased risk of spontaneous abortion, perinatal mortality, small size for gestational age, and low birth weight. Any delay in diagnosis or treatment can unfavourably influence the outcome. Congenital TB is a rare complication of *in utero* infection due to maternal haematogenous spread. The diagnosis of congenital TB is often difficult and indistinguishable from other neonatal or congenital infections, because symptoms usually occur in the second or third week of age. Hepatosplenomegaly, respiratory distress and fever are common. Chest radiography is almost universally pathologic. Newborns with TB show high mortality rate (up to 60%) and high risk of disease progression (40%)[2,3]. Given these assumptions, early treatment is mandatory.

Perinatal TB is extremely rare especially if the mother with TB has completed antitubercular treatment (ATT) or if she has received ATT for more than 2–3 weeks during pregnancy. However, considering the lack of data regarding the epidemiology of vertical TB transmission and the high mortality rate of the disease, every patient born to mother with active TB should be carefully evaluated to rule out neonatal TB[4,5]. Clinical signs of perinatal TB are usually unspecific; they could mime the signs of other infections and could appear only after several days of life[6]. Definitive diagnosis requires the detection of *M. tuberculosis* from at least one culture obtained from different specimens (gastric aspirates, sputum, tracheal aspirates in case of mechanical ventilation, skin

Table 1
Comparison of recommendation on prophylaxis of newborns at high risk of perinatal TB.

Guidelines	Pre-prophylaxis assessment (assessment for tubercular disease)	Duration of prophylaxis	Post-prophylaxis assessment	
WHO [8]	Careful history, clinical examination (including growth assessment), TST, CXR, bacteriological confirmation, investigation relevant for suspected pulmonary TB and suspected extrapulmunary TB, HIV testing	6 months	Symptoms	If post-prophylaxis assessment negative, stop treatment.
AAP [6]	TST, CXR, lumbar puncture, appropriate cultures, placental histology	3–4 months	TST	If post-prophylaxis assessment positive, assess for active TB
NICE [9]	CXR, appropriate cultures for bacteriological confirmation (microscopy, culture, histology, nucleic acid amplification tests), IGRA and/or TST (with expert input)	6 weeks	TST and IGRA	

lesions, ear secretions, ascitic fluid, cerebrospinal fluid, urine, or other body fluids or a tissue biopsy). Gastric aspirate is the most used in the clinical practice, since neonates show higher gastric microbiological density compared to older infants (70%)[4].

TST and IGRA are important tools for TB diagnosis, but they show low sensibility in newborns due to low reactogenicity and poor helper T-cell responses. Therefore, a negative result should not rule out the diagnosis. Repetition of the tests after 3 months can increase the chances of a positive result[5]. Because of insufficient data about the use of IGRA test in children < 2 years old, TST is generally preferred in this age group. Anyway, in case of moderate-to-high suspicion of TB, the use of both tests is recommended[6]. CXR is frequently not diagnostic for neonatal TB because radiological signs (scattered infiltrates or unspecific hypodensity) are often not detected in newborns and may appear two weeks after birth[4]. Placenta histological and cultural analyses are helpful for the diagnosis of congenital TB; the detection of granulomas and alcohol-acid resistant bacilli or isolation of *M. tuberculosis* is diagnostic. However, in the clinical practice, maternal TB is rarely suspected at the time of delivery, and this analysis is not routinely performed.

If neonatal TB is excluded, prophylaxis with INH (10–15 mg/kg/day in single oral dose) is anyway recommended in all cases of infants born to mothers with TB, in particular if they received treatment for less than 2–3 weeks or if their sputum is positive for TB. Pyridoxine supplementation (25–50 mg daily) should be administered together with INH for infants exclusively breastfed[7]. Currently, there is a lack of concordance among the main medical societies recommendations regarding the most appropriate time for TB reassessment and discontinuation of prophylaxis in newborns. The World Health Organization (WHO) recommends to continue INH prophylaxis for 6 months[8]. On the other hand, the Committee on Infectious Disease of the American Academy of Pediatrics (AAP) suggests 3 or 4 months of INH prophylaxis before repetition of TST. Recently, National Institute for Care and Excellence (NICE) guidelines recommended INH prophylaxis only for 6 weeks if TST and IGRA results were negative (Table 1)[9].

To date, the diagnosis of TB in newborns is still a public health issue, since in this age the sensibility of available diagnostic tests is very low. There is a need of more reliable diagnostic tests, whose results could help physicians in deciding the appropriate time to safely discontinue prophylaxis. A uniform consensus on management of infants born to TBC-infected mothers is highly needed in order to improve and standardize the measures and interventions to limit the infection in newborns.

Conflict of interest statement

We declare that we have no conflict of interest.

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