



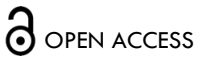
CASE REPORT

Pregnancy Outcome in Newly Diagnosed Tuberculosis in the Second Trimester: Case Report

Arnela Cerić Banićević¹, Amela Cerić², Zvezdana Ritan Mičić¹

¹ Clinic for Gynecology and Obstetrics¹

² Clinic for Hematology



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ABSTRACT

An estimated 1.7 billion people are infected with the tuberculosis bacillus and are therefore at risk of developing tuberculosis. Globally, until the SarsCo-V2 pandemic, tuberculosis was the most common cause of infectious disease-related death. For women infected with *Mycobacterium tuberculosis*, pregnancy is associated with an increased risk of developing or worsening tuberculosis. In some endemic areas, tuberculosis is an important cause of maternal mortality and morbidity and is associated with higher rates of preterm birth, low birth weight, and fetal death. In some studies, stillbirth and neonatal death were more common in patients with latent tuberculosis compared to uninfected patients, but no statistically significant difference was demonstrated. It has long been known that untreated tuberculosis poses a far greater danger to the pregnant woman and the fetus than the treatment of the disease, so early detection and treatment of tuberculosis in pregnancy is of key importance for reducing the aforementioned risks. The first case is a 37-year-old patient in the 24th week of pregnancy, achieved by in vitro fertilization. Due to the poor general condition and swelling of the amniotic fluid, the pregnancy was terminated by caesarean section. Further worsening of the clinical picture in the direction of an acute infection of the central nervous system, with the development of neurological symptoms. After radiological, microbiological and cytological processing, continuation of treatment of tuberculosis infection.

The second case is a 24-year-old pregnant woman in the 20th week of pregnancy, febrile with a dry cough and elevated inflammation parameters. On the 14th day of hospitalization, a wider diagnostic test was performed. Sputum on BK was negative, Quantiferon test was negative. Low-dose CT of the chest described bilateral lung infiltration and right-sided pleural effusion with subpleural nodules. On the 25th day of hospitalization due to the progression of the right-sided pleural effusion, the thoracic surgeon indicated VATS operative intervention. Pathohistological analysis confirmed that it was chronic granulomatous inflammation of the tuberculosis type.

In our two cases, the diagnostic and therapeutic approach and the outcome of the pregnancy are shown and the condition of the neonate. Both cases are in the second trimester of pregnancy, with difficult diagnosis due to negative tests for tuberculosis infection. The neonatal outcome of both pregnancies was poor.

Keywords: Pregnancy, Tuberculosis, Stillbirth

Introduction

Tuberculosis (TB) is one of the ten leading causes of death caused by a single infectious agent. Millions of people fall ill every year from this disease. According to WHO data, it is estimated that around 10 million people fall ill with TB in a year: 5.8 million men, 3.2 million women and 1 million children. In Europe, 6% of the population and 3% of the population in America are affected by tuberculosis. In the absence of systematically collected data, global modeling studies estimate 200,000 cases of tuberculosis during pregnancy each year. An estimated 900 million women worldwide have latent *Mycobacterium tuberculosis* (MTB). Pregnant women with MTB are more likely to develop active TB compared to men¹. Active TB disease during pregnancy remains associated with significantly increased risk for poor maternal and fetal outcomes, including a threefold increase in maternal morbidity (anemia, preeclampsia, and cesarean delivery), a ninefold increase in miscarriage, a twofold increase in preterm birth and low birth weight, and sixfold increase in fetal and neonatal death¹.

Pathogenesis and congenital infection

The pathogenesis of tuberculosis in the pregnant woman begins as in all other patients. After exposure, usually by inhalation, and local replication, there is dissemination of the organism by lymphatic spread, hematogenous spread, or both. If the organism affects the placenta or genital tract, the child may be congenitally infected. Congenital tuberculosis is a rare disease with a high mortality rate. The mycobacterium may be delivered to the infant directly via the umbilical vein, forming a primary complex in the liver of the infant with secondary hematogenous spread, or through aspiration or ingestion of infected amniotic fluid, leading to a primary focus in the lungs or gastrointestinal tract. The placenta should be examined histologically for granulomas, and acid-fast bacillus smear with mycobacterial culture should be obtained from a placental specimen when suspecting congenital tuberculosis in the infant. Congenital infection, or infection of the fetus, must be distinguished from disease in the newborn acquired postnatally.

Risk factors for the progression of TB infection include previous TB infection, contact with infected persons, immigration, poor health and malnutrition, drug abuse, alcoholism, smoking, living conditions, and immunosuppression¹⁻³. In areas with a high incidence of the disease, universal screening for TB among pregnant women is recommended. For regions with low disease burden, screening should target selected at-risk pregnant women for early case detection. Tuberculous meningitis (TBM) is the most severe consequence of *Mycobacterium tuberculosis* infection⁴⁻⁹. The described clinical manifestations are often non-specific. Malaise, anorexia, fatigue, myalgia and headache are the most common non-specific symptoms. In the majority of patients with TBM, there is information that they felt bad for more than two weeks before the development of meningeal symptoms^{5,6}. In adult patients, the classic symptoms of meningitis often occur with fever, headache, stiff neck, focal neurological deficit, behavioral changes and altered state of consciousness⁶. The most common manifestation of tuberculosis in pregnancy is

pneumonia^{9,10}. Empyema is one of the complications of TB pneumonia in pregnancy¹⁰. Treatment of empyema depends on the stage of the disease. Video-assisted thoracoscopic surgery (VATS) is the preferred surgical treatment for stage II and stage III empyema¹¹⁻¹⁴. VATS in pregnant women is not that common, and only a few cases have been described in the literature^{12,13}.

The non-specific initial signs of this disease and the lack of quick and sensitive diagnostic tests are often the cause of late diagnosis. Many patients are initially treated empirically with broad-spectrum antibiotics, until worsening of the clinical picture leads to reconsideration of the differential diagnosis¹¹. In circumstances involving low resources, limited access to health care, limited diagnostic capacities and economic constraints, the initiation of treatment is impossible. In conditions of high resources, not recognizing the disease can lead to a delay in starting treatment.

The aim of the paper is to present two cases of tuberculosis infection in the second trimester of pregnancy, with a masked clinical picture in a short period of time. Both cases are extrapulmonary localization of TB infection, with difficult diagnosis, the impact of tuberculosis on pregnancy and vice versa, the impact of pregnancy on infection. In both cases, we had a poor neonatal outcome, which was influenced by early peramaturity. The increased incidence of TB infection, especially among healthcare workers, indicates the need to know the epidemiological situation and the social, professional and demographic risk groups.

First case report

The first presentation is the case of a 37-year-old pregnant woman who was in the 24th week of her first pregnancy achieved through in vitro fertilization. Hospitalized in our clinic due to spontaneous discharge of amniotic fluid and high temperature. In laboratory diagnostics, CRP 34, neutrophil granulocytes 6.6, lymphocytes 0.66. Antibiotic therapy was included according to the protocol of premature birth. On the fourth day of hospitalization, the pregnancy ended operatively by caesarean section. Neonatus 780 grams, Apgar score 6/7. On the first postoperative day, she was still febrile, with difficulty breathing and a headache. In the CT image, miliary micronodular shadows on both sides, excluded PTE. Change of antibiotic therapy by pulmonologist and infectious disease specialist. Blood culture negative, serological tests normal, Quantiferon negative, cervical smear E. Coli, sputum negative, Lowenstein in work. Among other tests, we performed serology for other possible causative agents (Brucellae, *Coxiella burneti*, *Chlamydia pneumoniae*, *Mycoplasma*, Herpes simplex virus, Cytomegalovirus and Epstein-Barr virus, *Toxoplasma gondii*, Rubella), as well as a CNS profile, none of which did not show the causative agent of acute infection, and the autoantibodies were all negative.

On the tenth postoperative day, the clinical picture worsened with neurological symptoms. Neurological findings: confused, disoriented, sleepy, pupils wide, Babinski positive on the left. CT urgently, and transfer to the clinic for infectious diseases such as

meningoencephalitis. Lumbar puncture was performed: mononuclear cells 82%, polymorphonuclear cells 17%, proteins, 1.87, glucose 1.7, CI 120. CSF clear, exuding without pressure. Lowenstein negative. Repeated lumbar puncture and bronchoscopy on the 15th day, sputum on Lowenstein positive. Therapy Ethambutol a 400 1x2, Isoniazid a 300x1, Rifampicin a 3001x2, Pyrazinamide a 500 2,0,2. From the discharge list of neonates: one month after the operation, due to the impossibility of establishing a diagnosis, deterioration of the general condition, thrombocytopenia, lymphadenopathy, increase in CRP and deterioration of radiological findings, the neonate is transferred to the Institute for Mother and Child in Belgrade. Mycobacterium tuberculosis isolated from gastric lavage and bronchoaspirate. Fatal outcome.

Continuous tuberculostatic (TS) therapy was continued intermittently after 12 months for a total of 18 months. After completing the treatment, the patient had a normal clinical and neurological status, normal cerebrospinal fluid and neuroradiological findings. After stabilization of the general condition, she achieves an orderly pregnancy and term birth.

Second case report

The second presented is the case of a 24-year-old pregnant woman (primigravida) who, in the 20th week of pregnancy, was hospitalized at GAK due to a prolonged febrile condition and dry cough. Due to elevated inflammation parameters, the patient was initially treated with antibiotic therapy, and after consultation with an infectious disease specialist and a pulmonologist, the antibiotic therapy was corrected on two occasions. During hospitalization, pain occurs in the right half of the chest with a more pronounced dry irritating cough. On the 14th day of hospitalization, the patient was transferred to the Clinic for Infectious Diseases, where a wider diagnostic workup was performed along with consultative examinations. Sputum on BK was negative, Quantiferon test was negative, blood culture, urine culture, serological tests and smears were normal, PCR test for Covid-19 was negative, and sputum on Lowenstein was working. Subsequently, the patient stated that her sister was treated for tuberculosis five years ago. Low-dose CT of the chest described bilateral lung infiltration and right-sided pleural effusion with subpleural nodules. Corrected antibiotic therapy again, along with ulcer and thromboprophylaxis, and prescribed corticosteroid therapy and blood derivatives due to anemic syndrome. On the 25th day of hospitalization, due to the re-increase of inflammatory parameters and progression of the right-sided pleural effusion, the thoracic surgeon indicated operative intervention VATS debridement, and numerous adhesions and fine-grained changes on the right parietal pleura were verified intraoperatively. Parts of the pleura are sent for pathohistological analysis and definitive PH analysis confirms that it is chronic granulomatous inflammation of the tuberculosis type. Due to the aforementioned PH verification, treatment with antituberculosis drugs (Isoniazid 300 mg, Rifampicin 600 mg and Ethambutol 1200 mg) was started in the 24th week of pregnancy. Clinical, laboratory and radiological improvement resulted from the applied therapy, and the patient was discharged home on the 45th day, respiratory and hemodynamically stable, with a normal

sonographic finding of the fetus. In the 32nd week of pregnancy, the patient came for an examination because of the subjective feeling that she could feel the movements of the fetus less, and the intrauterine death of the fetus was verified by ultrasound. The pregnancy ended with induced labor and the birth of a dead female fetus weighing 1560 g. The patient continued further treatment with antituberculosis drugs and regular controls by a pulmonologist.

Discussion

Tuberculosis affects almost every organ in the body, but in 80% of cases it is the lungs^{11,12}. This disease significantly contributes to maternal mortality, as one of the three leading causes of death for women aged 15-45. In 2014, Sugarman points out that in the last two decades, there has been a big drop in maternal mortality. The estimated number of maternal deaths in 2013. worldwide was 289 000, a 45% decrease from 1990. Globally, the leading causes of maternal death include direct obstetric causes, such as hemorrhage and hypertensive disorders; however, other non-obstetric causes, including infectious diseases, are now responsible for 28% of maternal mortality worldwide Tuberculosis remains a significant global public health challenge. In 2013, an estimated 3.3 million cases of tuberculosis and 510 000 deaths from tuberculosis occurred in women worldwide¹³.

Tuberculosis in pregnancy represents two problems: one is the impact of tuberculosis on pregnancy and fetal development, and the other is the impact of pregnancy on the development of tuberculosis^{2,5}.

Rodriguez 2019. points that extrapulmonary TB remains a challenge to diagnose. Knowledge of the pathophysiology of TB in each organ and its imaging features can increase the detection rate in high-risk populations. The lymph nodes are the most frequently involved extrapulmonary organs. The presence of necrotic lymph nodes and other organ-specific imaging features increases the diagnostic probability of extrapulmonary infection. Extrapulmonary TB can occur regardless of a patient's immune status¹⁴.

Tuberculous meningitis is one of the most serious extrapulmonary manifestations of tuberculosis⁴. Women are at increased risk of tuberculosis during pregnancy. It is commonly assumed that immune changes associated with pregnancy represent an opportunity for mycobacterial infection and reactivation of tuberculosis¹². In the case of our patient, tuberculosis occurred during pregnancy and resulted in tuberculous meningitis, when, as a rule, the clinical forms are more serious. It was primarily tuberculosis in pregnancy that progressed slowly and manifested itself in the full clinical picture after cesarean delivery in the form of tuberculous meningitis. Tuberculosis symptoms were masked by symptoms that are common during pregnancy (such as weight loss masked by weight gain during pregnancy, sweating, anemia), as stated in the professional literature¹².

Gould 2016. points that pregnancy itself, however, may mimic and thus mask the symptoms of early tuberculosis,

such as tachypnea and fatigue; this, in turn, may delay diagnosis and treatment. Of pregnant women screened for and diagnosed with tuberculosis, the majority have been shown to be asymptomatic and unaware of their disease. Failure to recognize and treat the infection in the pregnant woman may lead to congenital infection in the infant. As evidence of this, in some series of congenital tuberculosis, the mother was evaluated and tuberculosis was diagnosed only after the disease was diagnosed in the infant¹⁵.

Lewis 2021. was done a prospective observational study in a tertiary care center over a period of 1 year from January 2019 to January 2020. Pregnant women in the age-group of 18–42 years diagnosed with TB in the antenatal period were included in that study for evaluating maternal and fetal outcomes. : Five-thousand and two hundred patients delivered during the study period; among those, 70 diagnosed with TB in the antenatal period were included, making a prevalence rate of 1.34/1,000 per pregnant woman. There was a significant increase in the incidence of preterm delivery, anemia, and intrauterine growth restriction in TB. In that study, they found that maternal and perinatal outcomes in pregnant women with TB depend on site, the severity of disease, gestation at diagnosis, and complication of TB. The prevalence of TB in antenatal women at that institute was 1.34/1,000 per pregnant woman. A high suspicion is required to acknowledge the varying disease spectrum and thus complications of TB in antenatal women and initiate treatment early for better outcomes¹⁶.

Sobhy et al 2017. conducted a systematic review and meta-analysis to evaluate pregnancy outcomes associated with TB. Thirteen studies, including 3384 pregnancies with active TB and 119 448 without TB were included. Compared with pregnant women without TB, pregnant women with active TB was associated with increased odds of maternal morbidity. They concluded that active TB in pregnancy is associated with adverse maternal and fetal outcomes. Early diagnosis of TB is important to prevent significant maternal and perinatal complications¹⁷.

Wang et al. 2022. concluded that miliary tuberculosis occurs more often in pregnant women after extracorporeal procedures, as well as in the second trimester, which is also the case with our first report. The influence of miliary tuberculosis on the outcome of pregnancy with 34% of spontaneous abortions. Many patients develop a serious respiratory infection and possible ARDS, as well as elevated laboratory markers of inflammation, low lymphocytes, and anemia¹⁸. Nguyen et al. 2022. emphasize the need for family planning and preconception testing¹⁹.

Valles et al retrospectively followed the outcome of pregnancy, with the conclusion of more frequent development of preeclampsia, stillbirth, emergency termination of pregnancy and the birth of neonates with low birth weight, leaving the task of trying to find the exact mechanisms for the occurrence of the same in new research²⁰. Diagnosing tuberculosis in pregnancy can be difficult. Non-specific symptoms and very often negative tests for detecting MTB and TB can lead to delayed

diagnosis and late initiation of therapy. This can lead to serious complications for the mother and fetus. Tuberculosis is recognized as one of the most common infectious diseases causing morbidity and mortality during pregnancy. Although TB is associated with adverse pregnancy outcomes, the pathogenesis is not fully understood. Various mechanisms have been described, such as direct effects of microorganisms on the fetus or placenta or effects mediated by pathogen-induced immune responses. Placental vascularization may be affected by the maternal immune response, which in turn may have adverse effects on pregnancy outcome.

A review by Kothari et al. shows that the median diagnostic delay for TB in pregnancy is 32 days²¹. The diagnosis of TB pneumonia is usually delayed because chest X-rays are delayed in pregnant women. Recommended diagnostic tests for TB are smear microscopy, culture, and molecular DNA detection methods, such as XpertMTB/RIF. Microscopy has a low sensitivity and cannot distinguish MTB from other mycobacterial organisms. A culture may take more than four weeks to produce a result. WHO has recommended replacing microscopy with molecular rapid diagnostic tests³.

Minimally invasive surgery, such as VATS, allows for a quick recovery while minimizing complications. There are several published cases of performing VATS in pregnancy. Oshodi et al. show a pregnant woman who underwent VATS for the treatment of empyema at 25 weeks¹¹. The operation was successful, without complications for the mother and fetus. In another case report, Kim et al performed VATS on a 38-year-old female patient at 24 weeks of gestation for the treatment of lung cancer. In this patient, pulmonary lobectomy was performed without complications¹².

Conclusion

Over the past 10 years, there has been an increase in the number of people suffering from tuberculosis. Epidemiological data show an increase in the number of pregnant women with tuberculosis infection. The incidence of tuberculosis in pregnant women depends on its prevalence in the population and in the region. The disease affects about 0.3% of pregnant women. The clinical picture is variable and depends on several factors, immunostatus, comorbidities. Pregnant women are at increased risk of tuberculosis during pregnancy due to immune changes associated with pregnancy. Diagnosis of tuberculosis in pregnancy is difficult due to non-specific symptoms, increased incidence of extrapulmonary form of the disease, delay in performing radiological diagnostic tests and high rate of tuberculin-negative tests. In our two cases, the neonatal outcome was poor, which agrees with the latest data from the literature. Establishing the diagnosis in both cases took the most time in the therapeutic approach. Amnestic epidemiological information about an active tuberculosis infection in a family member is extremely important.

Conflict of interest:

The authors have no conflicts of interest to declare

Literature

1. World Health Organization. Global Tuberculosis Report 2023.
2. Centers for Disease Control and Prevention Basic TB facts: TB Risk Factors. 2016
3. World Health Organization. WHO consolidated guidelines on tuberculosis: module 3: diagnosis: rapid diagnostics for tuberculosis detection, 2021
4. Shuk Y, Hui A Tuberculosis in pregnancy. *Best Pract Res Clin Obstet Gynaecol.* 2022;85:34–44.
5. Miele K, Bamrah Morris S, Tepper NK. Tuberculosis in pregnancy. *Obstet Gynecol.* 2020;135:1444–1453.
6. Bates M, Ahmed Y, Kapata N, Maeurer M, Mwaba P, Zumla A. Perspectives on tuberculosis in pregnancy. *Int J Infect Dis.* 2015;32:124–127.
7. Thwaites GE. Advances in the diagnosis and treatment of tuberculous meningitis. *Curr. Opin. Neurol.* 2013;26:295–300. 6.
8. Zhang L, Feng G, Zhao G. Tuberculous meningitis in Asia. *Neurology Asia.* 2015;20(1):1-6. 7.
9. Jongeling AC, Pisapia D. Pearls and oysters: tuberculous meningitis. Not a diagnosis of exclusion. *Neurology.* 2013;80:e36 – e39
10. Kundu S, Mitra S, Mukherjee S, Das S. Lung India. Adult thoracic empyema: a comparative analysis of tuberculous and nontuberculous etiology in 75 patients. 2010;27:196–201.
11. Chan DT, Sihoe AD, Chan S, Tsang DS, Fang B, Lee TW, Cheng LC. Surgical treatment for empyema thoracis: is video-assisted thoracic surgery "better" than thoracotomy? *Ann Thorac Surg.* 2007;84:225–231
12. Oshodi T, Carlan SJ, Busowski M, Sand ME. Video assisted thoracic surgery in a second trimester pregnant woman with thoracic empyema: a case report. *J Reprod Med.* 2015;60:172–174.
13. Kim JW, Kim JS, Cho JY, Lee DH. Successful video-assisted thoracoscopic lobectomy in a pregnant woman with lung cancer. *Lung Cancer.* 2014;85:331–334.
14. Sugarman J, Calvin C, Moran A, Oxlade O. Tuberculosis in pregnancy: an estimate of the global burden of disease. *The Lancet Global Health.* 2014;12:710-716
15. Rodriguez S.Y., Renjifo M, Medina F. Extrapulmonary tuberculosis: Pathophysiology and imaging findings. *Radiographics.* 2019;7:2023-2037.
16. Gould J, Aronoff SC. Tuberculosis and pregnancy-maternal, fetal and neonatal considerations. *Am Soc Microbiol* 2016.
17. Lewis P, Budhewar A, Bavdekar N. Fetomaternal Outcome of Pregnant Women Infected with Tuberculosis. An Analytical study. *Journal of South Asian Federation of Obstetrics and Gynecology.* 2021;4:197-201.
18. Sobhy S, Babiker Z, Zamara J, Khan K, Kunst H. Maternal and perinatal mortality and morbidity associated with tuberculosis during pregnancy and the postpartum period: a systematic review and meta analysis. *BJOG: An international Journal of Obstetrics and Gynecology.* 2017;5:727-733
19. Wang K, Donghua R, Zhixin Q, Weimwn L. Clinical analysis of pregnancy complicated with miliary tuberculosis. *Ann Med.* 2022.54:71-79
20. Ngyien I, et al. Examining family planning and adverse pregnancy outcomes for women with active tuberculosis disease: a systematic review. *BMJ Open.* 2022
21. Walles J et al. Pregnancy Outcomes in Women Screened for Tuberculosis Infection in Swedish Antenatal Care. *Clin Infect Dis.* 2024.
22. Kothari A, Mahadevan N, Girling J. Tuberculosis and pregnancy--results of a study in a high prevalence area in London. *Eur J Obstet Gynecol Reprod Biol.* 2006;126:48–55