A pregnant woman with severe dyspnoea

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Preterm delivery is a feasible option in the third trimester of pregnancy in the treatment of pregnant women with acute respiratory distress syndrome due to miliary tuberculosis with respiratory failure https://bit.ly/3stKOzj

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Determining the treatment strategies for pregnant women with respiratory failure is difficult. To save the lives of both mothers and children, it is necessary to determine the timing of fetal delivery with the cooperation of not only respiratory physicians but also obstetricians and paediatricians.

Case presentation
During the coronavirus disease 2019 (COVID-19) pandemic in Japan, a 27-year-old Filipino woman in her 35th week of pregnancy became aware that the cough and dyspnoea which she developed a month earlier had worsened; hence, she urgently consulted her family doctor. She had no medical history or allergies, and her previous occupation was in hospitality. There was nothing remarkable about her housing environment. She experienced respiratory failure and was immediately transferred to our hospital and admitted to the intensive care unit. At the time of admission, she had a body temperature of 37.2°C, pulse rate of 110 beats·min⁻¹, blood pressure of 104/64 mmHg, and respiratory rate of 30 breaths·min⁻¹ or more. She was conscious with no abnormal neurological findings. She was administered 5 L·min⁻¹ of oxygen with a face mask; however, her respiratory condition worsened, and she was ventilated on the first day of hospitalisation. Figure 1 shows the chest radiography and computed tomography (CT) findings at the time of admission.

On admission, the COVID-19 antigen and antibody test results were negative. Mycoplasma antibody, Aspergillus antigen and β-D-glucan test results were negative. Notably, her HIV antibody test was negative. As the sputum tested positive for Mycobacterium tuberculosis using PCR, with an acid-fast bacillus smear of 1+, a diagnosis of pulmonary tuberculosis was made. Radiological images showed infiltrative shadows in the upper lobe of the right lung and diffuse miliary tuberculosis in both lungs. Respiratory failure worsened rapidly after admission to our hospital, with a ratio of arterial oxygen tension
to inspiratory oxygen fraction of 290. Her Acute Physiologic Assessment and Chronic Health Evaluation II score was 8 and Sequential Organ Failure Assessment score was 2. She developed acute respiratory distress syndrome (ARDS) associated with miliary tuberculosis. Blood test findings and arterial blood gas analyses are shown in table 1. Fetal ultrasonography and fetal heart rate waveform monitoring showed a Biophysical Profile Score of 10 points, confirming the health of the fetus.

**Task 2**

In this case, what measures should be taken to save the lives of the mother and fetus?

Obstetrician records prior to admission to our hospital showed no problem in fetal growth. The Centers for Disease Control and Prevention (CDC) treatment guidelines for pregnant women with tuberculosis suggest that treatment should be started immediately if the likelihood of tuberculosis is moderate or higher, and recommend the administration of the anti-tuberculosis drugs isoniazid (INH), rifampicin (RFP) and ethambutol (EB); however, pyrazinamide (PZA) is not recommended because of its unknown effects on the fetus [1]. In this case, consideration was given to the start of anti-tuberculosis drug administration at an early stage, but the rapid deterioration of the respiratory condition of the mother increased the possibility that both the mother and fetus would have difficulty in surviving. In general, since pulmonary surfactant secretion is completed in the 34th week of embryonic development, it can be presumed that the respiratory function of the fetus is mature. As there were no convulsions or increase in blood pressure, eclampsia was ruled out. Additionally, as no haemolysis, elevated liver enzyme or thrombocytopenia was observed in the blood test results, HELLP syndrome (Haemolysis, Elevated Liver enzymes and Low Platelets) was excluded. Therefore, before the start of tuberculosis treatment, fetal delivery via caesarean section was performed under ventilator control.

**Task 3**

Of the following specimens from the mother submitted for acid-fast bacillus testing at delivery, which is less important?

- a) Placenta
- b) Amniotic fluid
- c) Blood
- d) Vaginal discharge
- e) Urine

Although congenital tuberculosis is rare, high-risk tuberculosis conditions include miliary, genital or untreated tuberculosis, co-infection with HIV, and a positive sputum smear in mothers [2]. In miliary tuberculosis, the presence or absence of infection in the placenta and amniotic fluid, which are the sources of exposure for the neonates, is important for the diagnosis of congenital tuberculosis [2, 3].

**FIGURE 1** Pre-treatment a) chest radiograph, showing infiltration shadows in the upper right lobe and miliary shadows in both lungs; and b) CT scan, showing diffuse miliary shadows in both lungs.
Tuberculosis can spread from the placenta to the umbilical vein, infect the placenta or genitals, and be transmitted to the fetus via inhalation or ingestion of contaminated amniotic fluid [3]. In this case, *M. tuberculosis* was not detected in the amniotic fluid or blood but was detected in an acid-fast bacillus culture of placental tissue, which, along with the chest radiographs, led to the diagnosis of miliary tuberculosis. Additionally, no tubercle bacilli were detected in the fetal gastric juice. Many children with congenital tuberculosis show abnormal findings on chest radiographs and are most often reported to have miliary tuberculosis [4]. Although the neonate in this case had normal chest radiography findings with negative tuberculin reaction, a dosage of INH with pyridoxine was prescribed by a paediatrician as a treatment for latent tuberculosis.

### TABLE 1  Blood analyses

| Parameter                                      | Value   | Normal range          |
|------------------------------------------------|---------|-----------------------|
| Haematocrit, %                                 | 32.2    | 35–45                 |
| Haemoglobin, g·dL⁻¹                            | 10.1    | 11.9–15.1             |
| White blood cells, ×10⁹ per L                  | 7.4     | 4.0–9.5               |
| Neutrophils, %                                 | 91.8    | 42.2–73.2             |
| Eosinophils, %                                 | 0.5     | 0.5–7.3               |
| Basophils, %                                   | 0.1     | 0.0–1.8               |
| Monocytes, %                                   | 2.2     | 2.2–8.4               |
| Lymphocytes, %                                 | 5.4     | 20.1–47.3             |
| Platelets, ×10⁹ per L                          | 275     | 160–350               |
| Fibrinogen, mg·dL⁻¹                           | 435     | 150–330               |
| Prothrombin time/international normalised ratio| 0.97    | 0.85–1.23             |
| Fibrin/fibrinogen degradation products, µg·mL⁻¹| 19.4    | 0.0–4.0               |
| D-dimer, µg·mL⁻¹                               | 8.9     | 0.0–1.0               |
| Total protein, g·dL⁻¹                          | 4.7     | 6.3–7.9               |
| Serum albumin, g·dL⁻¹                          | 1.7     | 3.9–5.0               |
| Immunoglobulin G, mg·dL⁻¹                      | 648     | 870–1700              |
| Total bilirubin, mg·dL⁻¹                       | 0.6     | 0.3–1.2               |
| Alanine transaminase, U·L⁻¹                    | 11      | 6–27                  |
| Aspartate transaminase, U·L⁻¹                  | 22      | 13–33                 |
| Alkaline phosphatase, U·L⁻¹                    | 213     | 38–113                |
| Lactate dehydrogenase, U·L⁻¹                   | 325     | 124–222               |
| Creatine kinase, U·L⁻¹                         | 32      | 45–163                |
| Amylase, U·L⁻¹                                 | 34      | 37–125                |
| Serum sodium, mEq·L⁻¹                          | 132     | 136–147               |
| Serum potassium, mEq·L⁻¹                       | 3.6     | 3.6–5.0               |
| Serum chloride, mEq·L⁻¹                        | 100     | 98–109                |
| Blood urea nitrogen, mg·dL⁻¹                   | 4       | 8–20                  |
| Creatinine, mg·dL⁻¹                            | 0.45    | 0.46–0.79             |
| Brain natriuretic peptide, pg·mL⁻¹             | 4.3     | ≤18.4                 |
| C-reactive protein, mg·dL⁻¹                    | 10.46   | ≤0.14                 |
| Sialylated carbohydrate antigen KL-6, U·mL⁻¹   | 838     | <500                  |
| β-D-glucan, pg·mL⁻¹                            | <2.6    | ≤20                   |
| *Aspergillus* antigen                          | Negative | Negative               |
| *Mycoplasma pneumonieae* antibody              | <40-fold | <40-fold               |
| Cytomegalovirus antigenaemia test              | Negative | Negative               |
| Hepatitis B surface antibody                   | Negative | Negative               |
| Hepatitis C antibody                           | Negative | Negative               |
| HIV antibody                                   | Negative | Negative               |
| COVID-19 antigen test                          | Negative | Negative               |
| COVID-19 antibody test                         | Negative | Negative               |
| T-SPOT.TB test                                 | Positive | Negative               |
| Arterial blood gas analysis¹                   |         |                       |
| pH                                             | 7.354   |                       |
| *P*<sub>o₂</sub>, mmHg                         | 116     |                       |
| *P*<sub>CO₂</sub>, mmHg                        | 39.8    |                       |
| Base excess, mEq·L⁻¹                           | −3.0    |                       |

*P*<sub>o₂</sub>: arterial oxygen tension; *P*<sub>CO₂</sub>: arterial carbon dioxide tension. ¹: with oxygen 5 L·min⁻¹ by face mask.

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Task 4
Which haematological parameter is related to mortality in tuberculosis?

a) White blood cell count
b) Haemoglobin
c) Albumin
d) C-reactive protein
e) D-dimer

The clinical course of the patient at our hospital is shown in figure 2. Figure 3 shows the progress in chest radiography findings. The radiological image on the third day shows the non-cardiogenic pulmonary oedema that indicated ARDS. For the mother, administration of methylprednisolone (mPSL) was initiated for ARDS on the first day of illness, before delivery. From the second day of illness, after delivery, besides pyridoxine, administration of four anti-tuberculosis drugs was started (INH 200 mg·day\(^{-1}\), RFP 450 mg·day\(^{-1}\), EB 500 mg·day\(^{-1}\) and PZA 900 mg·day\(^{-1}\)). In addition, considering that the effect of the action of mPSL would be reduced when used in combination with RFP, mPSL was administered at 2 mg·kg\(^{-1}\), which was twice the usual dose for treatment. On the fifth day, a fever of \(\geq 39^\circ\text{C}\) appeared, the respiratory condition deteriorated, and post-operative infection and the onset of ventilator-related pneumonia were suspected. The antibacterial agents vancomycin (VCM) and meropenem (MEPM) were administered based on the assumption of infection with staphylococci, streptococci and \(\text{Pseudomonas aeruginosa}\). Subsequently, thrombocytopenia gradually progressed and platelet count decreased to 90 000 per \(\mu\text{L}\) on the sixth day, and the pregnancy-modified International Society on Thrombosis and Haemostasis disseminated intravascular coagulation (DIC) score was 20 points. Furthermore, levels of fibrin/fibrinogen degradation products (FDP) and D-dimer were 25.9 \(\mu\text{g·mL}^{-1}\) and 19.8 \(\mu\text{g·mL}^{-1}\), respectively, which were higher than those at the time of admission; moreover, DIC signs were observed.

![Image of a clinical course diagram](https://doi.org/10.1183/20734735.0012-2022)

**FIGURE 2** Clinical course of the mother in our hospital. Day 1 was the day of admission. The mother’s general condition improved at discharge as a result of continued administration of anti-tuberculosis drugs and methylprednisolone. C-reactive protein (CRP) decreased and albumin recovered. Drug eruptions appeared twice, both of which were caused by antibiotics.
Therefore, thrombomodulin alpha was immediately administered for 7 days. Subsequently, the platelet count started to increase, and FDP and D-dimer levels tended to decrease.

On the sixth day, erythema, as shown in figure 4, appeared on her right arm and showed a growing trend. Upon consultation with a dermatologist, a drug eruption was suspected.

**Task 5**

Which drug should be considered first for discontinuation?

- a) INH
- b) RFP
- c) EB
- d) PZA
- e) VCM
- f) MEPM

In general, when a drug eruption develops, as in this case, anti-tuberculosis drugs are the first to be suspected. RFP is the drug most often associated with drug eruption, followed by INH, PZA and EB [9]. However, clinically, all anti-tuberculosis drugs can cause eruptions. If an anti-tuberculosis drug eruption is suspected, the administration of all anti-tuberculosis drugs should be discontinued and desensitisation therapy selected after drug eruption has improved. If anti-tuberculosis drugs were discontinued, miliary tuberculosis and the mother’s general condition may have worsened. Therefore, in this case, the possibility of drug eruption due to antibacterial drugs was considered first. Localisation of erythema spreading from the insertion site of the antibacterial drip needle was also suggestive of red man syndrome. On the seventh day, rapid improvement of erythema was observed after discontinuation of VCM. Subsequently,
administration of anti-tuberculosis drugs and MEPM was continued. Since *Klebsiella pneumoniae* was detected at level 3+ bacterial mass from the aspirated sputum collected on the fifth hospital day, MEPM was changed to sulbactam/ampicillin (SBT/ABPC) on the 10th hospital day. However, on the 12th day, erythema appeared in the lower abdomen and gradually expanded; therefore, a drug eruption was suspected. SBT/ABPC was discontinued on the 15th day of hospitalisation and changed to MEPM. Subsequently, the erythema improved rapidly, and MEPM was continued until the 20th day of illness. On the 15th day, the mother was withdrawn from mechanical ventilation, C-reactive protein level decreased significantly, serum albumin level recovered, and her general condition gradually improved. On the 21st day, she was transferred to our intensive care unit and subsequently to another hospital for tuberculosis treatment. No tubercle bacilli were detected in the aspirated sputum collected on the 21st day, the day of discharge.

Her transfer was followed by continued anti-tuberculosis treatment and rehabilitation, which went smoothly, and she was discharged approximately 2 months later. Figure 5 shows the CT scans at the time of admission to our hospital, transfer to another hospital, and discharge from the other hospital. The CT findings at discharge in the other hospital were markedly improved compared to those in our hospital.

Furthermore, after the patient was transferred, a drug susceptibility test for cultured *M. tuberculosis* revealed its sensitivity to INH, RFP and EB, and resistance to PZA. On reporting this result to the other hospital, the treatment was changed to INH, RFP and EB and continued for a total treatment period of 12 months.

**Discussion**

Miliary tuberculosis accounts for about 1–2% of all tuberculosis infections and about 20% of all extrapulmonary tuberculosis infections. Mortality due to miliary tuberculosis is high, the rate being 20–30% [10]. Pregnancy is an important risk factor for the development of miliary tuberculosis, which significantly increases the mortality rate of pregnant and postpartum patients, especially those infected with HIV [11], accounting for 25% of HIV-negative maternal mortality and 32% of HIV-positive maternal mortality [12].

In this case, a difficult decision had to be made on how to save the lives of a 35-week pregnant woman with miliary tuberculosis, ARDS and severe respiratory failure, and her fetus. Miliary tuberculosis is fatal, and the best timing of delivery for pregnant women with respiratory failure is unclear. The CDC’s treatment guidelines for pregnant women with tuberculosis state that anti-tuberculosis treatment should be started early; however, there is no mention of the timing of fetal delivery [1].

When treating a pregnant woman with miliary tuberculosis, a treatment method in which tuberculosis treatment precedes delivery wherein the mother’s condition tends to improve is generally considered. Regarding the administration of anti-tuberculosis drugs to pregnant women, there are no drugs that are classified as Pregnancy Category Rating X (contraindicated in the US Food and Drug Administration Pregnancy Category), but the recommendation level of PZA is low, and there are three drugs, namely INH, RFP and EB, which are routinely administered. The combination of these three drugs is likely to be a treatment option for tuberculosis [13]. However, even if tuberculosis treatment is initiated in advance of delivery, the condition of the pregnant woman may worsen and, eventually, the lives of both the mother

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**FIGURE 5** Changes in computed tomography findings. a) Miliary tuberculosis observed in both lungs at the time of admission. b) Persistence of infiltration shadow due to pneumonia developed during hospitalisation, noted before discharge from our hospital. c) Improved miliary and infiltration shadows compared to previous images.
and fetus may not be saved. Furthermore, if side-effects of anti-tuberculosis drugs appear, it may be difficult to carry out tuberculosis treatment. Conversely, if the fetus can be delivered first, there is the advantage that the mother can be given stronger intensive care thereafter. In addition, delivery can avoid the effects of maternal miliary tuberculosis and hypoxia for the neonate. For this reason, we proposed performance of caesarean delivery under mechanical ventilation prior to administration of intensive care for the mother and discussed it with the obstetrics team. From an obstetric perspective, fetal lung function is considered to be almost complete at 35 weeks of gestation, and the neonate can survive outside the womb with a low probability of complications, while if the mother is in the first or second trimester of pregnancy, delivery is challenging. Furthermore, in this case, miliary tuberculosis was severe, and the compression of the thoracic cavity by the uterus due to the continuation of pregnancy was likely to further exacerbate the respiratory condition of the mother. Therefore, we decided to deliver the fetus before tuberculosis treatment. Delivery was performed via caesarean section while taking sufficient measures against air infection under ventilator control. After delivery, intensive care was provided for miliary tuberculosis to save the mother. The neonate was not diagnosed with congenital tuberculosis but was treated for latent tuberculosis. Even now, more than a year after birth, the infant is healthy without developing tuberculosis. Thus, in order to deliver soon after hospitalisation, satisfactory functioning of the mother’s organs, being in the third trimester of pregnancy, and normal growth of the fetus are considered as optimal factors, warranting a careful assessment of the possible outcomes for both the mother and neonate.

In the intensive care unit, four anti-tuberculosis drugs and a high dose of mPSL and thrombomodulin alpha (causing an increased risk of bleeding) could be actively administered to the mother after fetal delivery for miliary tuberculosis, later found to be PZA-resistant. In addition, early administration of mPSL may have been effective in the prevention of not only ARDS but also immune reconstitution inflammatory syndrome (IRIS) after the initiation of anti-tuberculosis drugs. It has been reported that the serum albumin level of HIV-negative patients with pulmonary tuberculosis and IRIS was significantly lower than the population mean of 2.4 g·dL\(^{-1}\) [14]. The serum albumin concentration in the pregnant woman in our case was 1.7 g·dL\(^{-1}\) at the time of admission, suggesting a high risk of developing IRIS. Furthermore, it was important to determine the suspected drug eruption that appeared after the start of tuberculosis treatment. Because the erythema that appeared in this case was suspected of being a drug eruption due to an anti-tuberculosis drug, temporary discontinuation of the anti-tuberculosis drugs was also considered. However, in the case of drug eruption, it is occasionally very difficult to identify the causative drug, and thus the decision on the adjustment of treatment is delayed [15]. The range of appearance of the eruption was the point of diagnosis, and the spreading of erythema locally around the infusion needle insertion site in the upper arm, in the first drug eruption, led to the diagnosis of red man syndrome. During the second drug eruption, a tendency of the erythema to gradually spread from the abdomen was observed, and the suspected drug was SBT/ABPC. Thus, it was considered that the discontinuation of treatment with SBT/ABPC without discontinuing the anti-tuberculosis drugs also contributed to the improvement in the mother’s condition.

In conclusion, we delivered the fetus of a 35-week pregnant woman who presented with respiratory failure due to miliary tuberculosis and ARDS via caesarean section; subsequent intensive care was able to save the lives of both. In particular, for saving the mother’s life, it may be important to continue the administration of mPSL and anti-tuberculosis drugs without interruption. In addition, to treat pregnant women with miliary tuberculosis, medical facilities and equipment must be in place to prevent further tuberculosis infections.

If a pregnant woman with miliary tuberculosis in the third trimester experiences respiratory failure, consultation with an obstetrician or paediatrician to assess the condition of the fetus for the possibility of an early delivery may be a life-saving treatment strategy.
### Answer 3

| e. |
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<< Go to Task 3

### Answer 4

| c. Serum albumin has been reported to be more valuable than C-reactive protein for predicting and monitoring the severity and course of ARDS [5]. In addition, low albumin at the time of admission in patients with tuberculosis is associated with mortality; thus, serum albumin was used as an index of this condition in our case [6]. |

<< Go to Task 4

### Answer 5

| e. Erythema appeared on the upper arm around the infusion needle insertion site and tended to expand, suggesting red man syndrome, an allergic reaction to VCM, the incidence of which varies between 3.7% and 47% [7]. Studies on VCM have also reported that the most severe reactions occur in patients aged <40 years, especially in children [8]. |

<< Go to Task 5

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