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CLINICAL PROBLEM-SOLVING

A severe community-acquired pneumonia during pregnancy

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A 39-year-old pregnant woman (G3P2, gestational age 28 weeks) visited her general practitioner with a three-day history of fever, malaise and flu-like symptoms. A common flu was suspected and a re-evaluation was planned for the next day. The next day the symptoms were rapidly progressive and she was seen by her obstetrician.

Physical examination at that time showed a blood pressure of 121/77 mmHg, heart rate 109 beats/min and a temperature of 39.5 °C. She complained about abdominal tenderness in her left and right upper quadrant.

Laboratory results: haemoglobin 7.1 mmol/I (normal range at 28 weeks of pregnancy 6.8-8.7 mmol/l); haematocrit 0.32 l/l (>0.32); MCV 90 fl; leukocytes 11.7 /nl; CRP 245 mg/l, lactate 0.7 mmol/l, bilirubin 9 µmol/l, troponin-I <0.0450 µg/l, NT-pro-BNP 67 pmol/l. Arterial blood gas analysis: pH 7.41 (7.35-7.45), pCO_2 3.2 kPa (4.5-6.0), $p0_2$ 12.7 kPa (9.5-13.0), HCO_3 15.1 mmol/l (22.0-26.0), base excess -7.9 mmol/l (-2.0-2.0), O_2 saturation 98% (92-99) *(Table 1)*. Urine analysis: Protein (quantitative) 2.0 g/l (0.0-0.15 g/l), leucocytes negative, erythrocytes negative, nitrite negative.

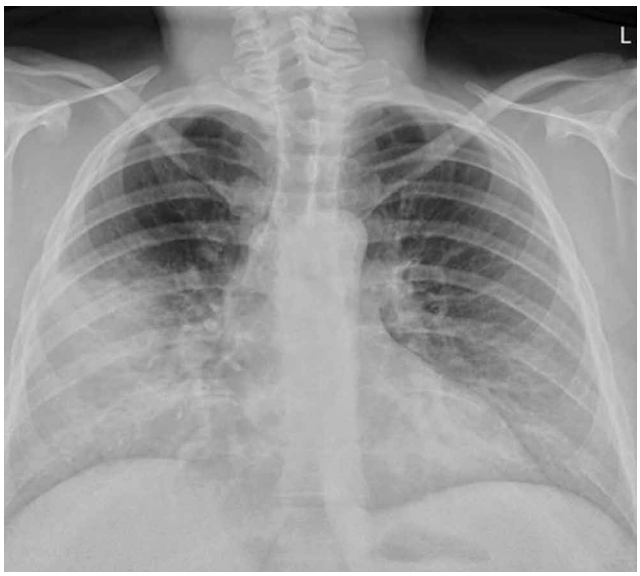

Figure 1. A chest X-ray at hospital admission shows a right middle lobe infiltrate

Table 1. Overview of arterial blood gas analysis prior to admission to the ICU

	Day 1 18:49	Day 2 7:10	Day 3 16:23	Day 4 17:20	Day 5 18:16
pH (7.35-7.45)	7.41	7.39	7.41	7.34	7.16
pCO_2 (4.5-6.0 kPa)	3.2 kPa	3.4 kPa	4.0 kPa	5.0 kPa	8.2 kPa
PO_2 (9.5-13.0 kPa)	12.7 kPa	12.5 kPa	13.3 kPa	9.0 kPa	8.6 kPa
HCO_3 (22.0-26.0 mmol/l)	15.1 mmol/l	14.8 mmol/l	18.5 mmol/	19.9 mmol/l	20.9 mmol/l
Base excess (-2.0-2.0 mmol/l)	-7.9 mmol/l	-8.5 mmol/l	-4.8 mmol/l	-4.8 mmol/l	-8.0 mmol/l
Saturation	98%	98%	98%	93	86%
Lactate (0.5-1.7 mmol/l)	0.7 mmol/l		0.8 mmol/l	0.7 mmol/l	0.6 mmol/l

Abdominal ultrasound showed no abnormalities. A chest X-ray showed a right middle lobe infiltrate *(figure 1)*. The patient was admitted to the obstetric ward with the diagnosis of community-acquired pneumonia (CAP) and she was started on amoxicillin/clavulanic acid. Initially her clinical condition briefly improved and her fever disappeared. However, one day after admission her symptoms worsened with progressive dyspnoea and hypoxaemia and internal medicine was consulted. She was then admitted to the internal medicine ward. In the following hours her respiratory rate increased to 32 breaths/min and her saturation measured by pulse oximetry dropped to 77%. A newly performed chest X-ray now showed bilateral infiltrates *(figure 2)*.

Due to severe hypoxic respiratory failure *(table 1)* she was then admitted to the intensive care unit (ICU) where she was intubated and mechanically ventilated. She was ventilated with pressure controlled ventilation (PCV) with PEEP at 18 cm H_2O, pressure control at 20 cm H_2O, FiO_2 of 100%, respiratory rate 22/min and tidal volume of 6 ml/kg of ideal body weight. Because

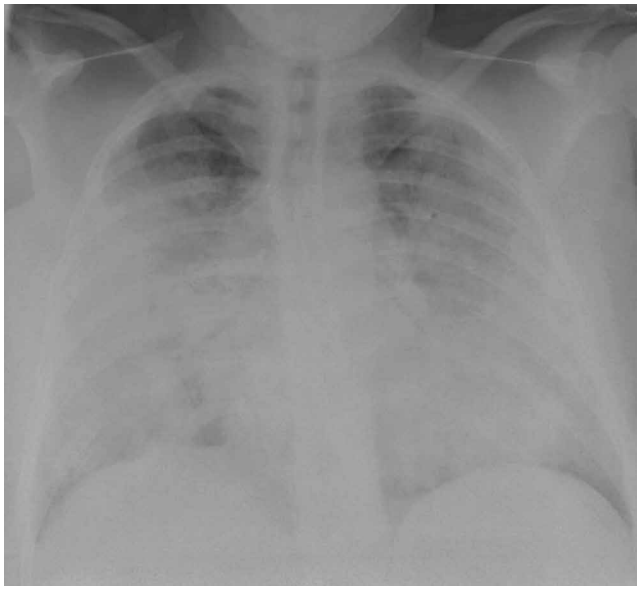

Figure 2. A chest X-ray repeated after clinical deterioration the following day shows bilateral infiltrates

of persistent hypoxaemia with a PaO_2/FiO_2 <100, ventilation in the prone position was started. The antimicrobial agents were switched from amoxicillin/clavulanic acid to cefotaxime, erythromycin and oseltamivir after taking new cultures, swabs for polymerase chain reaction (PCR) testing and urinary antigen tests (for *Legionella* type 1 and *pneumococci*).
Assessment by the obstetrician including foetal ultrasound showed no abnormalities concerning the condition of the foetus.

This 39-year-old pregnant woman was admitted to the obstetric ward because of community-acquired pneumonia (CAP). Two questions arise here. First, why did this young woman get CAP? The incidence of CAP is highest at a very young age and at old age (>65 years). Was this patient immunocompromised? The reported estimated prevalence of antepartum pneumonia is similar to that in the non-pregnant population at 0.78 to 2.7 per 1000.[1] Pregnancy is considered to be an important risk factor for severe complications following influenza virus infection.[2] During the H1N1 influenza pandemic of 2009-2010, pregnant women had an increased risk to be hospitalised or admitted to ICUs due to an influenza pneumonia, and were at higher risk of death compared with non-pregnant adults.[2] Some studies show that pregnant women respond differently to pathogens than non-pregnant women. One theory is that placental immune response and its tropism for specific viruses and pathogens affect the pregnant woman's susceptibility to and severity of certain infectious diseases. But up to now no real pathophysiological mechanism has been elucidated.[3]

Secondly, the severity of the pneumonia was underestimated. The obstetrician initially saw the patient and decided to admit her to the obstetric ward. A formal risk score was not quantified at that point. The attending physicians were misled by the initial clinical signs. Current guidelines suggest using a severity of illness model to evaluate the severity of pneumonia. Contemporary risk prediction models are the Pneumonia Severity Index (PSI) and the CURB-65.[4,5] Both models depend mainly on age, comorbidity and derangements of physiology. Especially young and otherwise healthy patients obtain few points for the age component and therefore only extremely severe illness is then recognised as severe CAP (PSI class 5 or CURB-65 >3).[6] This explains the overrepresentation of rather young patients who, despite a low PSI or CURB-65, still require treatment in the ICU.[7] In this particular instance, the initial PSI score was 44 points (Class I low risk, 0.1% 30-day mortality) and the CURB-65 was 0 points (0.6% 30-day mortality). Upon admission to the ICU the PSI score was 89 points (Class III, low risk, 0.9% 30-day mortality) and the CURB score was 1 point (low risk group: 2.7% 30-day mortality).
Another, rather pragmatic approach is that all patients who require ICU admission are considered to have a 'severe CAP'. Determination of the severity of the pneumonia is essential as the empirical antimicrobial coverage is broadened when a patient has 'severe CAP'. In such instances atypical pathogens also need to be covered. When the patient was transferred to the ICU the antimicrobial agents were switched from amoxicillin/clavulanic acid to cefotaxime and erythromycin.
In case of a severe CAP (requirement of ICU treatment) with an unknown pathogen, the current Dutch antibiotic guidelines (SWAB) advise to use the following first-line antimicrobial therapy: monotherapy with a quinolone (levofloxacin or moxifloxacin); or combination therapy with penicillin (or amoxicillin) and ciprofloxacin; or combination therapy with a second or third generation cephalosporin and a macrolide. [8] Fluoroquinolones, however, are contraindicated during pregnancy because they were associated with foetal harm in animal studies. We therefore chose for treatment with a combination of a cephalosporin and a macrolide, despite the higher risk of drug-drug-interactions (cytochrome P450 3A4 interactions) between macrolides and various other medications (with e.g. midazolam, fentanyl and more). Because the patient was admitted during the flu season, additional treatment with oseltamivir is also advised in order to cover for a possible influenza infection. PCR for viral and atypical pathogens is strongly advised.

Day 1 in the ICU

Despite aggressive treatment the patient's condition deteriorated rapidly. She was on pressure-controlled ventilation with PEEP at 20 cm H_2O, pressure control at 20 cm H_2O, FiO_2 100%, respiratory rare 26/min and tidal volume of 6 ml/kg of ideal body weight. With these settings she had a P/F ratio of 132 and hypercapnia (8.5 kPa) with concomitant acidosis

(pH 7.12). Echocardiography showed no signs of ischaemia, cardiomyopathy or right ventricular overload. There were no signs of hypervolaemia.

This patient had severe ARDS based upon the Berlin criteria.[9] There was a deterioration in her respiratory symptoms within one week of the initial clinical event, bilateral opacities on the chest X-ray, severe hypoxaemia and the respiratory failure was not due to cardiac failure or fluid overload. Anticipating that further treatment such as veno-venous extracorporeal membrane oxygenation (VV-ECMO) and complex neonatal care for the premature infant could be needed, the decision was made to transfer the patient to an academic centre the same day.

At what point should a caesarean section be considered?

This patient has severe ARDS on top of a restrictive pulmonary function (due to pregnancy) and sepsis. This is a life-threatening situation for both mother and child. Therefore caesarean section should be considered. At the moment the Dutch guidelines (NVOG richtlijn Perinataal Beleid bij Extreme Vroeggeboorte) advise to consider a caesarean section from the gestational age of 24 0/7 weeks.

Early delivery of a premature baby can lead to more neonatal complications such as respiratory distress syndrome. However, delaying delivery in an attempt to allow foetal maturation could place the mother at risk of multi-organ failure. Delaying caesarean section also prolongs the time that a foetus is in a potentially harmful environment in the uterus. This may result in an intrauterine death due to severe hypoxia or an acute event such as placental abruption.

The timing of performance of a caesarean section is a matter of ongoing controversy. Obviously, there is insufficient evidence about the effects of either approach on stillbirth or death after delivery in these cases. There is some circumstantial evidence from a 2013 Cochrane systematic review, however, to suggest that a policy of delaying delivery reduces the morbidity of neonates. Babies in the delayed delivery group were less likely to be admitted to the neonatal ICU and when admitted had a shorter length of stay. There were insufficient data to draw conclusions about the effect of expectant management on maternal outcome.[10]

Because of the risk of an emergency delivery of a premature child, corticosteroids (betamethasone 6 mg four times a day) were administered in order to stimulate foetal lung maturation.

Day 2 in the ICU

Upon arrival at the academic centre oxygenation initially worsened. The P/F ratio at that point was 80 with PEEP at 20 cm H_2O. She was put into the prone position in an air-fluidised bed and neuromuscular blocking agents were administered. Subsequently, in the following hours we saw significant improvement of oxygenation and ventilation and ventilator settings were reduced to PEEP at 18 cm H2O, pressure control at 15 cm H_2O, tidal volume of <4-5 ml/kg of ideal body weight and FiO_2 50%.

The *Pneumococcus* and *Legionella* urine antigen tests were reported to be negative.

Day 3 in the ICU

The microbiology lab revoked the negative result of the *Legionella* urine antigen test. Repeat *Legionella* urine antigen test was positive and the PCR on nasal lavage fluid also turned out to be positive for *Legionella pneumophila*. The antimicrobial chemotherapy was switched to macrolide monotherapy. Further investigation revealed that she had been working in the cleaning service and that she may have been exposed to *Legionella pneumophila* while cleaning air-conditioned office buildings. Hence she was diagnosed with Legionnaires' disease with concomitant ARDS.

In the following days oxygenation improved significantly in response to the treatment. Because she responded so well to treatment, it was concluded that VV-ECMO would not be necessary.

Is the management of the pregnant patient with ARDS the same as for the non-pregnant patient?

Optimal treatment consists of 'protective ventilation', small tidal volumes (<6 ml/kg of ideal body weight), ventilation in the prone position,[11] high PEEP[12] and the use of neuromuscular blocking agents during the first 48-72 hours.[13] Placing a pregnant patient in the prone position can be done safely.[14]

In the treatment of severe ARDS permissive hypoxaemia and permissive hypercapnia are accepted strategies to reduce the risk of ventilator-induced lung injury. However, during pregnancy these strategies can be harmful to the foetus. Foetal gas exchange is dependent on diffusion across the surface between the maternal sinuses and the foetal capillaries. Maintaining an adequate gradient of pCO2 and pO_2 is crucial. In normal physiology during pregnancy, maternal hyperventilation results in a mild respiratory alkalosis with maternal pCO_2 around 3.8-4.3 kPa, which increases the gradient favouring CO_2 transfer. Adequate buffering is achieved by compensatory renal excretion of bicarbonate. The decrease in pCO_2 on the foetal side of the circulation assists oxygen loading. The increase in pCO_2 in the maternal intervillous sinuses assists oxygen unloading. This is referred to as the Bohr effect, and facilitates the reciprocal exchange of O_2 for CO_2.[15,16]

Furthermore, maternal acidosis is associated with lower foetal pH and foetal acidosis in turn is associated with foetal distress, poor Apgar scores and adverse neonatal outcome.[16]

Therefore permissive hypoxaemia and permissive hypercapnia can lead to foetal hypoxaemia and acidosis, which consequently can lead to an increased risk of preterm delivery and foetal morbidity or mortality. Our strategy in this case was that the

occurrence of hypercapnia and acidosis with pH <7.3 would be the point that VV-ECMO would be started.
Our recommendation is as follows: aim for the maintenance of normal pH levels (7.3-7.4) and normocapnia (4.6-6.0 kPa), on the condition that protective ventilation is preserved. This, obviously, is a matter of opinion based on the physiological principles previously explained and comparative studies are lacking.

Foetal monitoring in the prone position was challenging because of frequent loss of signal and artefacts. We recommend using an air-fluidised bed when placing a pregnant patient in the prone position as this will better distribute the pressure that is put on the abdomen. Regular assessment of foetal well-being and maternal monitoring with multidisciplinary consultations are essential. Intermittent cardiotocography and assessment by the obstetrician is the best alternative to continuous foetal monitoring.

While sedated with propofol and remifentanil the patient developed high blood pressure with a systolic pressure ≥160 mmHg), which did not react to appropriate levels of analgosedation. She had no history of hypertension and had been normotensive since admission. We started magnesium sulphate and labetalol to manage her hypertension. Urine protein showed proteinuria 1.06 g/l and protein/creatinine ratio of 119.2 mg/mmol. Protein in a 24-hour specimen was 0.8 grams. The platelet count was 332 x 10^9/l (150-450 x 10^9/l), ASAT 53 U/l (0-30 U/l), and ALAT 30 U/l (0-35 U/l). There were no signs of acute kidney injury and the urinary analysis showed no casts.

The hypertension did not respond to analgosedation, and therefore could possibly be caused by preeclampsia. Preeclampsia refers to the new onset of hypertension and proteinuria *(table 2)* or hypertension and end-organ dysfunction with or without proteinuria after 20 weeks of gestation in a previously normotensive woman.

Table 2. Definition of proteinuria in preeclampsia

Proteinuria in preeclampsia can be defined as any of the following [17]:
• Persistent ≥1+ (0.3 g/l) on a paper test strip dipped into a fresh, clean voided midstream urine specimen
• Random protein: creatinine ratio >0.3 mg protein/mg creatinine
• ≥0.3 grams protein in a 24-hour urine specimen

Nonetheless, proteinuria may also be explained as the result of infection. Especially for patients with streptococcal disease, a post-streptococcal glomerulonephritis can be encountered. In such patients proteinuria usually develops after 1-2 weeks. This patient, however, had not been ill for that long. Moreover, the diagnosis of Legionnaires' disease had already been confirmed, which made a streptococcal glomerulonephritis highly unlikely. Sepsis or septic shock are associated with kidney damage and subsequent proteinuria, but the amount of proteinuria in such patients is not well established.[18]

Day 4 in the ICU

The patient has Legionnaires' disease, severe ARDS superimposed on restrictive pulmonary function (due to pregnancy) and possible preeclampsia. Despite finally achieving adequate oxygenation, ventilation and pH, this was at the cost of relatively high ventilator pressure levels, possibly required for an extended period of time due to the severity of her illness. Regarding preeclampsia, the only cure is to deliver the baby. Occasionally, performance of a caesarean section can be postponed while closely monitoring the condition of the mother and foetus. In this case, however, the combination of pathologies had the potential for serious adverse outcome.
Taking this into consideration, the decision was made to perform a caesarean section in the ICU. The procedure was uncomplicated. She gave birth to a daughter (gestational age 28 weeks and 5 days). The APGAR score (10 points maximal) was 5 after 1 minute and 6 after 5 minutes. Because of respiratory insufficiency, the baby was intubated and ventilated.
Immediately after the caesarean section we continued mechanical ventilation in the prone position and applied the usual permissive hypoxaemia and hypercapnia strategies. Strikingly, we were able to reduce the ventilator support levels. The blood pressure normalised within hours and she no longer needed antihypertensive medication. Antimicrobial therapy was switched from erythromycin to levofloxacin with the intent to optimise the treatment of the *Legionella* infection. The patient was extubated one day after the caesarean section and she was discharged to the obstetric ward the following day. She received antibiotic treatment for a total duration of 14 days.
The PCR on *Legionella pneumophila* DNA on placenta, amniotic fluid and cord blood was negative. The baby was not treated for *Legionella*. The baby was ventilated for a couple of days and spent almost three months on the neonatal ward with a seemingly full recovery. There were no signs of neurological damage to the child.

Although there are some reports in the medical literature on horizontal nosocomial spread of *Legionella*,[19] there are no reports on vertical transmission of *Legionella* from the mother to the baby. The PCRs on placenta, amniotic fluid and cord blood are in concordance with previous findings that Legionella is not a blood transmissible disease.[20] Treatment of the baby is, therefore, not necessary. The mother was treated with the usual protective ventilation strategies and usual antimicrobial chemotherapy after delivery of the baby. Fluoroquinolones are thought to carry little risk from breast feeding to the baby. The

calcium in the milk is thought to bind the quinolones, reducing their bioavailability to the baby. Currently, there is insufficient evidence to approve or disapprove this assertion.[21]

Discussion

Is there an association between pneumonia and the subsequent development of preeclampsia?

Current theories for the pathophysiological basis for preeclampsia include a number of potential causes, including abnormal placentation, cardiovascular maladaptation to pregnancy, genetic and immune mechanisms, an enhanced systemic inflammatory response, and nutritional, hormonal, and angiogenic factors. There are hypotheses that infection in pregnancy may be involved in the aetiology of preeclampsia. Some studies have shown that urinary tract infection and periodontal disease during pregnancy are associated with an increased risk of preeclampsia.[18] Causality has not yet been proven and the mechanism remains unknown. Currently, to our knowledge, there are no studies that show a clear association between other maternal infections and preeclampsia. Therefore the question remains whether Legionnaires' disease was the trigger for preeclampsia.

Managing critically ill obstetric patients in the ICU can be challenging because of their altered physiology, different normal ranges for laboratory and clinical parameters during pregnancy, and potentially harmful effects of medications and interventions to the foetus. This is illustrated by the various treatment challenges encountered in this patient, such as 1) whether or not to perform a caesarean section, 2) treatment of *Legionella* infection during pregnancy, 3) management of preeclampsia and 4) the management of ARDS during pregnancy. What is also noteworthy is the emotional impact this all has on the whole team.

It is important to consider that emergency delivery is not routine for most ICUs. The ICU needs to prepare for an emergency caesarean section (e.g. instrumentation), keep an incubator in standby mode, and be equipped with appropriate material for the airway management of a premature infant. A multidisciplinary approach with a team consisting of the intensivist, obstetrician, anaesthesiologist, neonatologist, and nurse is key to optimise outcome;[19] and, as always, 'hope for the best but prepare for the worst.'

Disclosures

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