



## Severe acute respiratory infection with influenza A (H1N1) during pregnancy

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**To the Editor:** Pregnant women are at high risk of severe acute respiratory infection if infected with the influenza A (H1N1) virus. On 14 August 2009 the first complicated H1N1 obstetric patient was admitted to the obstetric critical care unit (OCCU) at Tygerberg Hospital with respiratory distress. The clinical picture was that of bronchopneumonia, and she tested positive for H1N1. Subsequent pregnant patients admitted to the OCCU with respiratory compromise or flu symptoms were screened for the virus.

Eleven days later 13 cases were confirmed. Five patients had acute lung injury and required ventilation and inotropic support. Three of the patients with acute lung injury subsequently died. Three patients required continuous positive airway pressure (CPAP) support only, with no inotropics needed. The remaining 5 patients presented early, received oseltamivir within 48 hours and did not require critical care admission.

All the patients admitted to the OCCU and the medical intensive care unit (ICU) initially presented with flu symptoms, respiratory distress and changes on the chest radiograph indicating an active diffuse pulmonary parenchymal process. Six patients underwent uncomplicated caesarean sections for fetal distress after they were stabilised. Maternal and neonatal outcomes varied. The key factor appears to be early clinical diagnosis and oseltamivir within 48 hours of the onset of symptoms. The demographic data and maternal and fetal outcomes are set out in Table I.

### Comments on critical care management

1. Severe and relatively fast-onset acute lung injury with pulmonary shunts in excess of 50% and lung compliance in the region of 10 - 15 ml/cm H<sub>2</sub>O warranted high inspired oxygen

concentrations and positive end-expiratory pressure (PEEP) settings (in the order of 15 - 22 cm H<sub>2</sub>O).

2. Acute and severe pulmonary hypertension, as is commonly found in acute lung injury (mean pulmonary artery pressures in the region of 40 - 45 mmHg),<sup>1</sup> appeared not overtly due to spasm, as sildenafil (by mouth) did not decrease the pressure or improve the right heart output.

3. Acute (and predictable) right heart failure as measured by decreased stroke work despite raised effective pulmonary artery elastance often manifested with a raised central venous pressure.

4. Ineffective circulation as gauged by a mixed venous desaturation in the order of 50% was often exacerbated by a raised temperature, which resulted in a raised VO<sub>2</sub> and hence lowered the mixed venous saturation.

5. The partial arterial carbon dioxide level (PaCO<sub>2</sub>) was often raised. This hypercapnia, and the resultant respiratory acidosis, was accepted as part of the management strategy. The hypercapnia was unlikely only to have been due to lower tidal volumes (as part of the lung protective strategy), and may also have been caused by an increase in dead space (due to an increase in ventilatory frequency mandated by an attempt to maintain an acceptable minute ventilation) and possibly intrapulmonary arterial clots (which have been shown to occur in patients with acute lung injury).<sup>1</sup> The difference between the PeCO<sub>2</sub> and PaCO<sub>2</sub> (as a substitute for the proper Bohr equation which required average expired CO<sub>2</sub>) supports the contention that the patients suffered from excessive high ventilation perfusion (dead space) lung units. In this regard the high PEEP may have contributed to intra-alveolar vessel occlusion, although the effect of PEEP is to a large extent buffered by poor compliance of the lungs.

6. From a management point of view implementation of the protective lung ventilation strategy is suggested, and in particular the physician should not attempt to normalise the PaCO<sub>2</sub> by increasing the ventilation. By increasing the minute ventilation (whether with an increase in frequency or respiratory rate) one will only further load the right ventricle (and limit the cardiac output with the predicted effect on mixed venous saturation). If the raised carbon dioxide is partially the result of the dead space lung lesion, increasing the minute ventilation will not necessarily result in an improved PaCO<sub>2</sub>.

7. If and when the intrapulmonary shunt is severe, as was seen in our cases, optimisation of factors that could affect the mixed venous saturation becomes of prime importance. These can be deduced from the adapted Fick equation: CvO<sub>2</sub> = CaO<sub>2</sub>

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**Table I. Demographic details of patients and outcomes**

Age (yrs)	Gestation (wks)	Obstetrics	Oseltamivir <48 h	Organ dysfunction at admission	Respiratory support required	Outcome	Pregnancy
25	40	Low risk	Yes	Respiratory	CPAP	Home	Alive, well
34	31	Preterm labour	No	ALI	Invasive ventilation	Death	Neonatal ward, well
20	32	Eclampsia	Yes	Respiratory	CPAP	Home	Home, well
29	27	HIV pos., CD4 497	No	ALI, ARF	Invasive ventilation	Death	IUD
19	30	Low risk	No	ALI, ARF, DIC	Invasive ventilation	Death	ENND
35	28	Pre-eclampsia	Yes	Respiratory	CPAP	Home	Neonatal ward, well
41	40	Low risk	No	ALI	Invasive ventilation	ICU; MODS	Alive, well
19	38	Low risk	No	ALI	Invasive ventilation	ICU; MODS	Alive, well

ALI = acute lung injury; ARF = acute renal failure; DIC = diffuse intravascular coagulopathy; CPAP = continuous positive airway pressure; MODS = multiple organ dysfunction syndrome; IUD = intra-uterine death; ENND = early neonatal death.

–  $\text{VO}_2/\text{CO}$ , where  $\text{CvO}_2$  = mixed venous oxygen content,  $\text{CaO}_2$  = arterial oxygen content,  $\text{VO}_2$  = oxygen consumption and  $\text{CO}$  = cardiac output. Attempts to normalise a raised temperature will improve mixed venous saturation; maintenance of a 'higher' haemoglobin (perhaps 12 g/dl) and inotrope support of the right ventricle are essential adjuncts. We do not suggest that this approach will improve survival (there are no data to indicate this), but it did assist with the oxygenation problem experienced by our patients.

8. Because of the poor lung volume, the patients were distressed and ventilation was difficult. Allowing for attempts at spontaneous respiration is useful, but sufficient support is required. Towards this end intermittent mandatory ventilation (IMV) with CPAP (the latter assisted by pressure-support ventilation (PSV)) worked in some and bilevel positive airway pressure (BIPAP) (again with PSV) gave reasonable results in others. The PSV on top of the CPAP (either for the IMV/CPAP or the  $\text{P}_2$  during BIPAP) was necessary because the patients could not sustain spontaneous breathing. When spontaneous breathing was allowed the patients seemed more comfortable, but the PSV needed to be carefully adjusted keeping in mind their inability to manage a compliance of 10 - 20 ml/cm  $\text{H}_2\text{O}$ .

9. In one of the critically ill patients on adrenaline, the paracetamol blood concentration (1 hour after nasogastric administration) was not detectable. We measured this in an attempt to (crudely) try to gauge the effectiveness of gut absorption, which may well be of significant importance for the absorption of oseltamivir. If gut absorption is poor (which will not be surprising given the severity of illness and use of adrenaline), it cannot be certain whether oseltamivir is absorbed at all. This question will require a much more detailed and expert study.

10. Autopsy confirmed what had been suspected clinically – solid, heavy lungs, with little (overt) pulmonary oedema. Generally speaking the lungs looked very much like lungs in the inflammatory (or past the initial oedema) stage of acute lung injury. The macroscopic impression was that of severe acute lung injury (which during life the Murray score

had shown that it indeed was).<sup>2</sup> The heart was enlarged, and although there is reason to suggest right ventricular enlargement, the impression of left heart enlargement is difficult to explain apart from a viral myocarditis or reversible global myopathy associated with severe inflammation (and sepsis) as possible cause.<sup>3</sup> At the time of writing the histological report was not yet available.

### Comments on obstetric critical care management

1. Screen all pregnant and newly delivered patients with respiratory compromise and SIRS (systemic inflammatory response syndrome) for the H1N1 virus.
2. Commence oseltamivir treatment immediately when an obstetric patient presents with flu symptoms, with or without respiratory compromise. If gut absorption is poor in the later stages of the disease, early administration of the drug is particularly important.
3. Admit stable patients with moderate and severe respiratory symptoms (dyspnoea, respiratory rate >24/min) to a dedicated observation area, as they may deteriorate rapidly.
4. Early transfer to high care and ICU is essential when respiratory distress develops.
5. Attempts should be made to stabilise the patient first, followed by a systemic evaluation.
6. Betamethasone must be administered if the fetus is viable and the gestational age under 34 weeks.
7. The patient should be evaluated by an anaesthetist.
8. Monitor the fetus only when the patient is stabilised and fit for anaesthetic if the fetus is considered to be viable.
9. Early delivery by caesarean section is advisable if the gestational age is  $\geq 34$  weeks and the patient is critically ill requiring ventilation. Consider postponing delivery by 24 - 48 hours after the first betamethasone dose if the fetus is viable and the gestational age less than 34 weeks, provided the mother is stable, the fetal condition is satisfactory, and the mixed venous saturation can be maintained around 70%.



10. Consider early use of steroids (hydrocortisone 200 mg daily in two divided doses) in severe H1N1 cases requiring intubation and ventilation.<sup>4</sup>

## Prevention strategies

### General and specific strategies recommended include:

1. Distribute H1N1 information to all community health care centres, antenatal clinics and midwife obstetric units.<sup>5</sup>
2. All pregnant women with flu symptoms should go to their community health facility and must be treated with oseltamivir 75 mg twice daily for 5 days. Paracetamol should be added for symptomatic relief.
3. If the patient is stable with no respiratory compromise she should stay at home for 7 days.
4. If there is any change in her condition she must seek medical help from her health care provider.
5. Refer women with moderate to severe respiratory symptoms (dyspnoea and/or a respiratory rate of >24/min) for evaluation to a level 2 hospital as a matter of urgency.
6. Hospitals must have H1N1 prevention and management plans and inform the Department of Health, via the Communicable Disease Control hotline (0861-364-232), of new H1N1 cases and complications.
7. Patients requiring respiratory support or with organ system dysfunction must be transferred to tertiary hospitals urgently. These patients deteriorate rapidly and are often difficult to transfer after intubation. In addition, the management of mechanical ventilation is difficult.
8. Infection control principles should be applied rigorously:<sup>5</sup>
  - Cohort patients.
  - The assessment area should be situated away from other pregnant women.
  - Admit, preferably to a medical high-care unit (HCU) or an ICU.
  - Pregnancy complications must be managed in an isolation room in the labour ward.

- Inform and counsel all staff members regarding patients, precautions and occupational risk.
- Prioritise access from rural referral hospitals.
- Assess need for reducing ICU-dependent elective surgical procedures.
- Increase ICU capacity.

9. Neonatal aspects:

- H1N1 does not cross the placenta and is not transmitted in breastmilk.
- A stable mother with mild disease and a healthy baby can stay at home. Droplet and contamination precautions need to be adhered to, and breastfeeding should continue. There is no need to prescribe oseltamivir to a healthy neonate. Medical help must be sought when the neonate appears unwell.
- Symptomatic neonates and neonates of mothers with severe disease must be assessed by health professionals trained in neonatal care. The neonatal dose for oseltamivir is 3 mg/kg.

In conclusion, novel influenza A (H1N1) should not be underestimated in pregnancy. Early oseltamivir, careful observation and early transfer to critical care facilities when indicated will decrease maternal and perinatal mortality.

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