12. Ping LS, Yat FSY, Kwok WY. Status capateicus leading to the obstetric complication of prolonged labour. *J Clin Sleep Med* 2007;**3**:56–7.
13. Dahaba AA, Xu GXX, Liu QH, Xue JX, Metzler H. Bispectral index monitoring of a narcolepsy–cataplexy episode during regional aesthesia. *Anesth Analg* 2009;**108**:613–5.
14. Pasteau F, Graftieaux JP, Scavarda D, Leon A. Problems posed by spinal anesthesia in a patient with Gelineau disease. *Ann Fr Reanm* 1996;**15**:669–72.
15. Doyle A, Wilkinson D. Day case general anaesthesia in a patient with narcolepsy. *Anaesthesia* 2008;**63**:880–2.
16. Burrow B, Burkle C, Warner DO, Chini EN. Postoperative outcome of patients with narcolepsy. A retrospective analysis. *J Clin Anesth* 2005;**17**:21–5.
17. Mesa A, Diaz AP, Frosth M. Narcolepsy and anesthesia. *Anesthesiology* 2000;**92**:1196–8.

The successful use of extra-corporeal membrane oxygenation in the management of a pregnant woman with severe H1N1 2009 influenza complicated by pneumonitis and adult respiratory distress syndrome

L.C. Robertson,[a] S.H. Allen,[b] S.P. Konamme,[c] J. Chestnut,[a] P. Wilson[a]

[a] *Department of Anaesthesia, Crosshouse Hospital, Kilmarnock, UK*
[b] *Department of Infectious Diseases, Crosshouse Hospital, Kilmarnock, UK*
[c] *Department of Obstetrics, Crosshouse Hospital, Kilmarnock, UK*

ABSTRACT

We report a case of H1N1 2009 influenza A, in a previously fit woman at 24 weeks of gestation, who presented atypically with abdominal pain. The infection was complicated by severe respiratory failure and acute respiratory distress syndrome, requiring ventilatory support, including extra-corporeal membrane oxygenation (ECMO). This was one of the first cases of severe H1N1 disease presenting in the UK. Use of extra-corporeal membrane oxygenation for the complications of H1N1 resulted in full maternal recovery and subsequent delivery of a healthy infant.
© 2010 Elsevier Ltd. All rights reserved.

Keywords: Pregnancy; H1N1; Intensive care; ECMO

Introduction

Pandemic H1N1 2009 influenza A, or 'swine flu', is an influenza type A virus. It differs from seasonal flu in that its distinct haemaglutinin (H1) and neuraminidase (N1) surface proteins contain elements derived from human, avian and pig influenza A viruses. H1N1 2009 influenza emerged in Mexico in March 2009 and by June 2009 the World Health Organization had declared a pandemic. Latest figures report in excess of 16,000 deaths worldwide.[1] We report a case of severe H1N1 disease in a previously healthy woman at 24 weeks of gestation.

Case report

A previously healthy 27-year-old white British woman (G3P1) was admitted to our maternity unit at 24 weeks of gestation with a 3-day history of fever, lower back and right-sided abdominal pain. Clinical examination revealed a gravid uterus consistent with gestational age and generalized abdominal discomfort. Except for slight tachypnoea, attributable to a pain response, she had neither respiratory symptoms nor signs and auscultatory findings were normal. Body mass index was 26 kg m^{-2}. Blood tests on admission revealed a normal white cell count (9.3×10^9 L^{-1}), with relative lymphopenia (1.2×10^9 L^{-1}) and mildly elevated C-reactive protein (46 mg L^{-1}). Alanine aminotransferase was slightly raised (63 U L^{-1}) but all other liver function tests and electrolytes were normal. Fetal ultrasound was unre-

markable and no obstetric cause for her pain was identified.

Over the following 48 h she developed increasing pyrexia, vomiting and a non-productive cough. A chest X-ray was performed and revealed radiological changes consistent with right basal consolidation (Fig. 1). Intravenous antibiotics were changed, from 8-hourly cefuroxime 750 mg and metronidazole 500 mg, to 12-hourly clarithromycin 500 mg and 8-hourly meropenem 1 g to cover possible abdominal sepsis and/or community acquired pneumonia. Continuing abdominal pain associated with rebound tenderness and guarding in the right lower abdomen, prompted surgical review and emergency laparotomy. A macroscopically normal appendix was removed and no other intra-abdominal pathology was identified. General anaesthesia for surgery was induced with intravenous thiopental 350 mg and suxamethonium 100 mg, using a rapid sequence technique and cricoid pressure. Anaesthesia was maintained with oxygen, air and sevoflurane and analgesia provided with intravenous morphine. Rapid desaturation was noted at intubation despite thorough preoxygenation and a single successful intubation attempt. Her fraction of inspired oxygen (FiO_2) was 0.6–0.8 and positive end-expired pressure (PEEP) 5–8 cm H_2O was required to achieve peripheral oxygen saturations (SpO_2) >90%. An underlying diagnosis of H1N1 2009 influenza was considered but antiviral agents were not recommended because there was no exposure history, which was a requirement for diagnosis at that time.
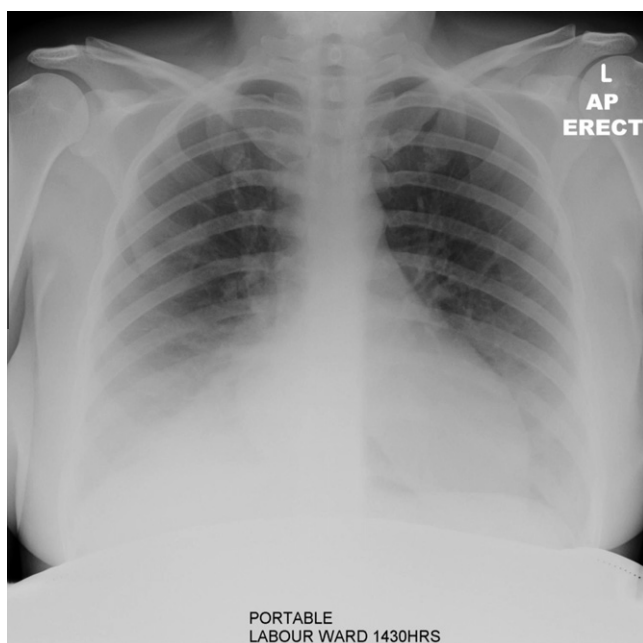
Fig. 1 Chest X-ray performed on day 2 showing right lower lobe collapse.

Post-operative recovery was managed on the surgical high dependency unit, with humidified oxygen and regular observations. Initial recovery was uneventful. However, over the next 36 h the patient deteriorated, displaying evidence of septic shock. Increasing oxygen requirements necessitated emergency admission to the intensive care unit (ICU) on admission day 6 and intubation and ventilation for type-1 respiratory failure. Urgent viral polymerase chain reaction returned positive for influenza A, H1N1 2009. Oseltamivir (Tamiflu) 150 mg 12-hourly by nasogastric tube was commenced and continued for 10 days.

Over the subsequent 5 days, acute respiratory distress syndrome (ARDS) developed. A progressive reduction in lung compliance and increasing requirements for ventilatory support prompted differing ventilation modes, consistent with recommendations for ARDS management.[2] Heavy sedation, with continuous intravenous infusions of propofol, midazalam and morphine, and muscle paralysis with atracurium infusion were required to enable ventilation. Despite this, she remained hypoxaemic with arterial blood gas results revealing SpO_2 83%, H^+ 41 nmol L^{-1}, PaO_2 6.2 kPa, $PaCO_2$ 6.6 kPa, HCO_3^- 29.2 mmol L^{-1}, base excess +3.5 mmol L^{-1}, with FiO_2 1.0. Airway pressures were high despite attempts at pressure reduction (peak inspiratory pressure 40 cm H_2O, PEEP 16 cm H_2O, inspiratory:expiratory ratio 1:1, inspiratory time 1.2 s). This resulted in barotrauma, with the development of surgical emphysema and bilateral pneumothoraces. A left-sided chest drain was inserted, while the right-sided pneumothorax was successfully managed conservatively.

When it became clear that conventional ventilation strategies were ineffective, and on calculation of a Murray Score of 3.5, referral was made for extra-corporeal membrane oxygenation (ECMO). Due to a lack of beds at the UK National Adult ECMO Centre, Glenfield Hospital, Leicester, the patient was referred to the Karolinska Institute in Sweden. A retrieval team was dispatched from Sweden comprising an intensivist, surgeon, perfusionist and ICU scrub nurse. ECMO was established in our ICU using a portable ECMO circuit primed with packed red cells. Access points for veno–venous ECMO were obtained by the retrieval team via cannulation of the right internal jugular and right femoral vein. The institution of ECMO allowed rapid reduction in FiO_2 and tolerance of a low volume, lung protection ventilatory strategy. Following a brief period of stabilization, she was air-lifted to the Karolinska Institute ECMO unit. A tracheostomy was performed the day after arrival in Sweden following which she was allowed to wake. She communicated with her family throughout ECMO treatment. After 17 days of continuous ECMO, her respiratory performance improved enough to allow conventional ventilation. On day 32 she was repatriated to our ICU on pressure sup-

port ventilation (FiO$_2$ 0.4, Pressure assist 12 cm H$_2$O, PEEP 5 cm H$_2$O) resulting in PaO$_2$ 16 kPa and PaCO$_2$ 4.6 kPa. She continued to improve and was successfully weaned from ventilation over the following days. The tracheostomy was decannulated on day 36 and she was discharged from ICU on day 37 and from hospital on day 45, when she was at 32 weeks of gestation.

Throughout the hospital admission daily fetal monitoring, initially with Doppler ultrasound and subsequently cardiotocography, revealed normal fetal heart rate, movement and growth, despite periods of prolonged and significant maternal hypoxia. Emergency delivery, either vaginally or by caesarean section, was considered several times to improve maternal oxygen delivery. However, on each occasion the delivery process was felt to be associated with unacceptable maternal risk. On day 16, a 700-mL vaginal haemorrhage occurred while she was receiving heparin to enable ECMO. Preparations were made for emergency caesarean section, including administration of maternal steroids to promote fetal lung maturation. Fortunately, the bleeding settled spontaneously and emergency delivery was not required.

Following hospital discharge, weekly antenatal review was performed. An elective caesarean section was performed at 38 weeks under spinal anaesthesia, resulting in delivery of a healthy infant.

Discussion

This case was one of the first presentations of severe H1N1 2009 influenza in the UK. It raised a number of issues regarding management and generated considerable media and professional interest. It is the only case we know of involving prolonged intensive care and use of ECMO for the complications of H1N1 infection in pregnancy, which has resulted in full maternal recovery and subsequent delivery of a healthy infant at term.

H1N1 2009 influenza A attaches itself to a receptor binding domain of a sialic acid moiety expressed on respiratory epithelial cells via its haemaglutinin (H1) surface protein. Following opsonisation, the virus replicates rapidly within the host cell. Neuraminidase (N1) enables release of new virions and in doing so causes lytic destruction of the host cell and induction of tumour necrosis factor and interferon cytokines. This renders the respiratory epithelial lining ineffective for functional gas exchange and may explain the reported success of ECMO treatment for H1N1 2009 as a salvage therapy during epithelial lining regeneration.

Disease severity is highly variable. In most people, H1N1 2009 is a mild 'flu-like' illness.[3] Gastrointestinal symptoms may occur and are indicators for hospital admission.[4–6] A minority of patients develop rapidly progressive respiratory failure approximately 4 days after symptom onset. As in this case, laboratory tests typically show a normal white cell count with mild lymphopenia.[5–7] Air-space shadowing on chest x-ray indicates H1N1 pneumonitis and is associated with a worse prognosis. Death may result from respiratory failure, multi-organ failure or septic shock. A third of fatal cases show evidence of secondary bacterial infection,[8] *Streptococcus pneumoniae* and *Staphylococcus aureus*, including methicillin-resistant strains have been most commonly isolated.

As a novel virus, all population groups are susceptible to H1N1 2009 influenza A. WHO has identified three groups at increased risk: pregnant women (particularly in the second and third trimesters), children less than 2 years of age and people with pre-existing lung disease.[3] Obesity is a risk factor for severe disease and mortality. Health care workers are at increased risk of contracting the virus as a result of occupational exposure. Due to the atypical presentation of this case, multiple health care professionals were exposed before diagnosis and institution of protective measures and isolation. Despite this we are not aware of any cases of H1N1 infection occurring as a result of this exposure.

Pregnancy is an independent risk factor for developing severe influenza.[9] During previous influenza A pandemics, before antibiotic use, mortality rates for pregnant women exceeded 50%.[10] In the current H1N1 pandemic, pregnant women are recognized to be at increased risk of hospitalization, ICU admission, severe disease and complications.[6,11,12] The full impact on fetal outcome has yet to be established.

Guidelines on H1N1 2009 influenza A management in pregnancy have been published.[4] These emphasize the need for early recognition of H1N1 in pregnancy and treatment strategies aimed at improving fetal and maternal outcome. In most cases of H1N1 in pregnancy, maternal care will take precedence. Delivery may be required for fetal or maternal indications. Early delivery may reduce the physiological burden of pregnancy and improve maternal condition. However, the benefits of reduction in oxygen demand must be weighed against risks to maternal health associated with fetal delivery. In the case presented, emergency delivery was considered several times to improve maternal clinical condition and oxygen delivery. However, the patient's respiratory condition was so precarious that it was felt unlikely that she would survive the additional cardio-respiratory stress associated with delivery.

Management of H1N1 2009 influenza involves supportive care, coupled with early antiviral use and targeted antibiotic therapy. Approximately 1% of cases are severe enough to require hospitalization[4]; of these 20–30% may need ICU support.[12,13] ICU stays are typically of moderate duration (2–3 weeks)[14] and it was feared that critical care facilities would be stretched in a pandemic situation.[15] The antiviral agents oseltamivir (Tamiflu) and zanamivir (Relenza) are indicated for

treatment. They act against the neuraminidase receptor preventing release of new virus particles into the airway. Normally treatment is for 5 days, although for severe disease a minimum of 10 days high-dose treatment (oseltamiver 150 mg 12 hourly) is recommended due to prolonged viral shedding in ventilated patients.

There are limited data on the use of oseltamivir and zanamivir in pregnancy. It is recommended that use be based on an individual case risk/benefit analysis. Zanamivir is administered by powder inhalation resulting in lower systemic concentrations and less fetal exposure compared with enterally administered oseltamivir. In the absence of respiratory co-morbidity, inhaled zanamivir should therefore be used as first line antiviral treatment in pregnancy.[4] However, zanamivir may induce bronchospasm and the potential for this in a patient whose respiratory function was already critically impaired precluded its use in this case. Successful use of intravenous zanamivir (unlicensed) for H1N1 2009 disease in a non-pregnant patient has been reported.[16] Solubilisation of zanamivir powder to allow nebulisation (unlicensed) is contraindicated in ventilated patients following a fatal episode thought to result from crystalline precipitation of the lactulose base causing obstruction of the ventilator.[17]

Respiratory support strategies in severe H1N1 pneumonitis include conventional invasive ventilation, airway pressure release ventilation (APRV), high-flow oxygenation (HFO) and ECMO, which provides external blood oxygenation and carbon dioxide removal thus reducing the burden of pulmonary gas exchange. ECMO use in neonatal respiratory failure is well documented,[18] however, application in adults has been less successful. The recently published CESAR trial compared ECMO with conventional lung ventilation strategies in adults with severe but potentially reversible respiratory failure.[19] An improvement in 6-month survival of 63% in the ECMO randomized group compared to 47% in the control arm was reported. ECMO use in 2009 H1N1-associated respiratory failure has been reported to produce survival rates of 71%.[10]

Use of ECMO in pregnancy is less well documented. A small number of case reports exist, with variable outcomes.[20–25] In this limited subset, maternal and fetal survival appears to be associated with shorter durations of mechanical ventilation prior to ECMO. The main problems reported are technical, relating to low flow rates at femoral access points as a result of the gravid uterus. This has been overcome by emergency delivery,[24] or placement of additional venous access points.[25] These complications were not encountered in this case. The risk of obstetric haemorrhage in a patient who is systemically anticoagulated to allow ECMO is a concern and requires vigilance and prompt treatment. It was fortunate in this case that an episode of vaginal bleeding settled spontaneously.

Consideration of steroid use in H1N1 disease is important for several reasons. These include the potential use of steroids as a primary treatment to improve outcome in severe H1N1 disease and their use in promoting fetal lung maturation in pregnant patients with concurrent H1N1 infection. Use of corticosteroids in sepsis and ARDS has a rational basis in attenuating inflammatory response. Initially promising results[26] have, however, been overshadowed by studies that have failed to show improvement in outcome with steroid use, and have highlighted their potential for significant adverse effects.[27,28] Steroid use in ICU is therefore reserved for refractory cases. Corticosteroids are most likely to be used in patients with 2009 H1N1 who meet criteria for administration due to severe septic shock. Of greater concern is the possible temptation to use steroids as a primary adjuvant therapy for cases of severe H1N1. Steroids were widely used in this capacity during the global Severe Acute Respiratory Syndrome (SARS) outbreak. Retrospective data analysis from the outbreak failed to show any benefit with steroid treatment and indicate possible harm as a result of their use.[29] Despite this there is already one report of 2009 H1N1 pneumonitis treated successfully with zanamivir and high-dose corticosteroids.[16] WHO guidelines do not recommend high-dose steroids in the treatment of H1N1 2009 influenza.[30]

Corticosteroid use may also be considered in pregnant patients with H1N1 disease when premature delivery is contemplated, in order to promote fetal lung maturity and improve fetal outcome. The potential benefits for the fetus must be weighed against any potential detriment to maternal health. Current evidence suggests that low-dose steroids (betamethasone 12 mg given in two doses 12–24 h apart) to promote lung maturity are unlikely to cause significant maternal harm.[31,32] This finding has not, however, been validated for H1N1 disease. In our case, maternal steroids were administered on day 16 to promote fetal lung maturation when emergency delivery seemed inevitable. Although delivery did not occur, the use of steroids under these circumstances did not appear to have any detrimental effect on maternal state or outcome.

This was one of the first cases of severe H1N1 2009 influenza A occurring in the UK and highlights the susceptibility of pregnant women to this disease and its complications. Despite atypical presentation and development of severe disease and complications, outcome was excellent for both mother and infant. Effective multidisciplinary care and prompt involvement of specialist services undoubtedly helped. It is hoped that presentation of this case may raise awareness of the risks of H1N1 2009 infection in pregnancy and provide evidence that good outcomes, for both mother and infant, are possible.

Acknowledgements

We would like to thank all staff involved with the care of this patient. In particular we are grateful to Dr. Palmer and the ECMO team at the Karolinska Institute, Sweden, for their clinical assistance.

References

1. WHO. Pandemic H1N1 – update 89 (online). <http://www.who.int/csr/don/2010_02_26/en/index.html>; 2009 accessed 27.02.10.
2. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301–8.
3. WHO. Clinical features of severe cases of pandemic influenza: pandemic H1N1 briefing note 13. <http://www.who.int/csr/disease/swineflu/notes/h1n1_clinical_features_20091016/en/index.html>; 2009 accessed 27.02.10.
4. Department of Health and the Royal College of Obstetricians and Gynaecologists. Pandemic H1N1 2009 influenza: clinical management guidelines for pregnancy. 30 October. <http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_107770>; 2009 accessed 27.02.10.
5. Patel M, Dennis A, Flutter C, Thornton S, D'Mello O, Sherwood N. Pandemic (H1N1) 2009 influenza: experience from the critical care unit. Anaesthesia 2009;64:1241–5.
6. Jain S, Kamimoto L, Bramley AM et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April–June 2009. N Engl J Med 2009;361:1935–44.
7. Perez-Padilla R, de La Rosa-Zambezi D, Ponce de Leon S, Hernandez M, Quinones-Falconi F, Bautista E et al. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. N Engl J Med 2009;362:680–9.
8. Centers for Disease Control and Prevention. Bacterial coinfections in lung tissue specimens from fatal cases of 2009 pandemic influenza A (H1N1) – United States, May–August 2009. Morb Mortal Wkly Rep 2009;58:1071–4.
9. Dodds L, McNeil SA, Fell DB et al. Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. CMAJ 2007;176:463–8.
10. Harris JW. Influenza occurring in pregnant women. JAMA 1919;14:978–80.
11. Jamieson DJ, Honein MA, Rasmussen SA, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet on line July 29 2009. doi:10.1016/S0140-6736(09)6134-0.
12. Kumar A, Zarychanski R, Pinto R, et al. Critically ill patients with 2009 influenza A (H1N1) infection in Canada. JAMA online October 12 2009. (doi:10.1001/jama2009.1496).
13. The Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators. Extracorporeal membrane oxygenation for 2009 influenza A (H1N1) acute respiratory distress syndrome. JAMA 2009;302. doi:10.1001/jama.2009.1535.
14. The ANZIC Influenza Investigators. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. N Engl J Med 2009;362:1925–34.
15. Nayanah Siva. BMJ news: number of swine flu patients going into intensive care is rising. BMJ 2009;339:b4528.
16. Kidd JM, Down J, Nastouli E, Shulman R, Grant PR, Howell DCJ et al. H1N1 pneumonitis treated with intravenous zanamivir. Lancet 2009;374:1036.
17. GlaxoSmithKline, October 2009. Important drug warning – Relenza (zanamivir) inhalation powder must not be nebulized (letter). <http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM186224.pdf>; 2009 accessed 27.02.10.
18. Tracey Jr TF, DeLosh T, Bartlett RH. Extracorporeal Life Support Organisation 1994 report. ASAIO J 1994;40:1017–9.
19. Peek GJ, Mugford M, Tiruvoipati R et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomized controlled trial. Lancet 2009;374:1352–63.
20. King PT, Rosalion A, McMillan J, Buist M, Holmes PW. Extracorporeal membrane oxygenation in pregnancy. Lancet 2000;356:45–6.
21. Cunningham JA, Devine PC, Jelic S. Extracorporeal membrane oxygenation in pregnancy. Obstet Gynecol 2006;103:792–5.
22. Greenberg LR, Moore TR. Staphylococcal septicemia and adult respiratory distress syndrome in pregnancy treated with extracorporeal carbon dioxide removal. Obstet Gynecol 1995;86:657–60.
23. Lee WA, Kolla S, Schreiner Jr RJ, Hirschl RB, Bartlett RH. Prolonged extracorporeal life support for varicella pneumonia. Crit Care Med 1997;25:977–82.
24. Parkins MD, Fonseca K, Peets AD, Laupland KB, Shamseddin MJ, Gill MJ. A potentially preventable case of serious influenza infection in a pregnant patient. CMAJ 2007;177:851–3.
25. Clark GPM, Dobson PM, Thickett A, Turner NM. Chicken pox pneumonia, its complications and management. A report of three cases, including the use of extracorporeal membrane oxygenation. Anaesthesia 1991;46:376–80.
26. Dellinger RP, Levy MM, Carlet JM et al. Surviving sepsis campaign guidelines for the management of severe sepsis and septic shock. Crit Care Med 2004;32:858–73.
27. Sprung CL, Annane D, Keh D et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008;358:111–24.
28. Edwards P, Arango M, Balica L et al. Final results of MRC CRASH, a randomized placebo-controlled trial of intravenous corticosteroid in adults with head injury-outcomes at 6 months. Lancet 2005;365(9475):1957–9.
29. Stockman LJ, Bellamy R, Garner P. SARS: a systemic review of treatment effects. Public Libr Sci Med 2006;3(9):e343.
30. WHO, November 2009. Clinical management of human infection with pandemic (H1N1) 2009: revised guidance. <http://www.who.int/csr/resources/publications/swineflu/clinical_management_h1n1.pdf>; 2009 accessed 27.02.10.
31. Crowley PA. Antenatal corticosteroid therapy: a meta-analysis of the randomized trials, 1972 to 1994. Am J Obstet Gynecol 1995;173:322–5.
32. Roberts D, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2006;(3). Art. No.: CD004454. doi:10.1002/14651858.CD004454.pub2.