Asthma in pregnancy complicated by iatrogenic pulmonary oedema

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Summary: We report a unique case of near fatal acute pulmonary oedema developing with intravenous ritodrine, given in an attempt to suppress premature labour. The novel aspect of the case is that the patient had also been treated in the previous week with high dose nebulized beta-agonists for an episode of acute severe asthma, demonstrating that this idiosyncratic reaction to beta-adrenergic agents only occurs with the intravenous route of administration. The management of acute severe asthma occurring in pregnancy is discussed with a review of previous literature regarding possible mechanisms of beta₂-agonist-induced pulmonary oedema.

Introduction

Breathlessness is a common symptom during pregnancy, but is not thought to be due to increased airways resistance.¹ Nevertheless, asthmatic patients do occasionally deteriorate² and can pose therapeutic problems. Intravenous beta₂-adrenoreceptor agonists including ritodrine,³ salbutamol,^{4,5} terbutaline,⁶ fenoterol,⁷ and isoxuprine⁸ have been found to cause acute pulmonary oedema, occasionally fatal, when used as tocolytic agents, particularly with concurrent administration of corticosteroids to accelerate fetal lung maturation.

We report a patient with severe asthma during pregnancy, ventilated and treated uneventfully with nebulized salbutamol and corticosteroids, who, upon receiving parenteral ritodrine for premature labour, developed near fatal pulmonary oedema.

Case report

A 23 year old woman, 26 weeks pregnant, was admitted with acute severe asthma. Despite regular inhaled salbutamol, beclomethasone, disodium cromoglycate and oral aminophylline, she had become increasingly symptomatic throughout pregnancy. In the past, she had required multiple admissions for her asthma, but had never required positive pressure ventilation. There was a previous history of episodic angioedema. She was pyrexial 38°C, with a tachycardia of 140 beats/min, and 25 mmHg of paradox, peak

expiratory flow rate (PEFR) was 70 litres/min and arterial blood gases (F_{iO_2} = 70%) showed pH = 7.23, P_{O_2} = 163 mmHg (21.7 kPa), P_{CO_2} = 45 mmHg (6 kPa) and HCO_3^- = 18 mmol/l. A chest radiograph showed only hyperinflation (Figure 1).

Despite intensive bronchodilator treatment she deteriorated, the P_{CO_2} rising to 55 mmHg (7.3 kPa), and within one hour of admission elective endotracheal intubation and ventilation was undertaken.

Figure 1 Chest X-ray taken on admission.

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In addition to positive pressure ventilation (Engstrom Erica, Sweden) at a minute volume of 9.6 litres, nebulized salbutamol (5 mg) and ipratropium bromide (0.25 mg) 4 hourly, hydrocortisone 200 mg 4 times a day and intravenous aminophylline achieving plasma levels of 11 mg/l were continued. The initial peak inspiratory pressure was 55 cm H₂O, falling to 30 cm H₂O after 24 hours.

The PCO_2 was maintained at 30 mmHg (4 kPa), approximating to 'normal' levels during pregnancy¹, the PO_2 averaging 100 mmHg ($FiO_2 = 40\%$). She was weaned off the ventilator after 8 days, and maintained on nebulized salbutamol 5 mg, 5 times daily and oral prednisolone.

At 10 days, uterine contractions were apparent, with a closed cervix for which intravenous ritodrine, 10 mg/h was instituted (50 mg/500 ml of alternating saline and dextrose). The following day the dose of ritodrine was increased to 20 mg/h resulting in an immediate increased heart rate from 100 to 144 beats/min. Forty hours after commencing ritodrine, she became acutely breathless, heart rate 170 beats/min, $PO_2 = 73$ mmHg (9.7 kPa), $PCO_2 = 68$ mmHg (9.1 kPa) ($FiO_2 = 60\%$), requiring emergency reintubation, when copious pulmonary oedema fluid was aspirated. A chest X-ray confirmed florid pulmonary oedema (Figure 2), and central venous pressure was 12 cm H₂O. Positive pressure ventilation and frusemide, with discontinuation of the ritodrine, produced a rapid clinical and radiographic improvement.

Figure 2 Chest X-ray on day 12 after emergency reintubation.

In the 48 hours prior to this episode there had not been any change in haematocrit, haemoglobin, or serum albumin with a positive fluid balance of 1.3 litres recorded, occurring within the previous 24 hours only. Electrocardiography demonstrated the evolution of T wave inversion in leads 1, 2, AVL, V3–V6, with echocardiographic evidence within 12 hours of onset of the pulmonary oedema of normal left ventricular function (ejection fraction 60%), and a small pericardial effusion. Cardiac enzymes were transiently elevated.

Within 12 hours, the membranes ruptured spontaneously to reveal meconium stained liquor, intravenous Syntocinon was commenced and 8 hours later a stillborn male child was delivered. The patient was extubated 12 hours post-delivery and discharged 1 week later, the electrocardiogram showing persistent T wave inversion; the echocardiograph was normal.

Discussion

Beta₂-agonists are effective in inhibiting premature labour, but may precipitate acute pulmonary oedema. The first case was published in 1977⁹ with over 70 subsequent reported cases, with 8 deaths. A particularly high incidence (5%) was reported in one series consequent upon the infusion of terbutaline.⁶ Only 3 previously reported cases have required positive pressure ventilation, the majority responding within 24 hours to withdrawal of the tocolytic agent and diuretic therapy.¹⁰

The underlying mechanism of the pulmonary oedema is not clear (for review see ref 10), reported cases having been associated with high and normal pulmonary capillary wedge pressure.¹¹ Beta₂-agonists stimulate anti-diuretic hormone, the renin-aldosterone axis, and may increase cardiac output by 40%, potentially causing fluid overload when cardiac output is already increased by up to 40% due to the pregnant state. Predisposition to pulmonary oedema in twin pregnancies (33% of reported cases⁶) with beta-agonist administration in saline¹² and with concomitant administration of corticosteroids (63% of reported cases) supports this mechanism.

No direct effect of beta-agonists on pulmonary vascular permeability has been reported, but direct cardiotoxicity is suggested.¹³ Up to 55% of patients treated with ritodrine develop transient T wave inversion, independently of induced hypokalaemia. Sub-endocardial myocardial infarction has also been reported.¹³

In our case the enzyme rise was probably secondary to insertion of a central line, although with a persistent electrocardiographic abnormality, a small infarct can-

not be excluded. The normal echocardiogram, however, militates against left ventricular dysfunction as the cause of the pulmonary oedema.

To our knowledge, pulmonary oedema complicating intravenous beta₂-agonist therapy is unique to pregnancy and the puerperium with no reported cases consequent upon their administration by either the nebulized or intravenous routes, in the treatment of acute asthma. Although larger intravenous doses are generally recommended for tocolytic therapy, the dosage schedules overlap, and pulmonary oedema has

been reported at doses commonly employed in the treatment of acute asthma.⁴⁻⁶

A severe deterioration of asthma during pregnancy is likely to be treated with corticosteroids, with the potential development of pulmonary oedema, if beta-agonists are administered intravenously. Since nebulized and intravenous beta-agonists are equally effective,¹⁴ it would seem preferable to use the inhaled route in the treatment of asthma during pregnancy, to circumvent this potentially fatal iatrogenic complication.

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