Anaphylaxis-induced hyperfibrinolysis in pregnancy

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ABSTRACT
Anaphylaxis during pregnancy is rare but life threatening to both mother and fetus. The anaesthetist may be unexpectedly faced with an obstructing airway, severe bronchospasm and cardiac arrest requiring perimortem caesarean delivery to relieve aortocaval compression. We present a case of anaphylaxis-induced hyperfibrinolysis, an infrequently discussed complication that could exacerbate postpartum haemorrhage and hamper resuscitative efforts.

Keywords: Anaesthesia; Pregnancy; Anaphylaxis; Hyperfibrinolysis; ROTEM; Thromboelastometry

Introduction

The diagnosis of hyperfibrinolysis in real time has become possible with the introduction of point-of-care viscoelastic coagulation testing. Guided antifibrinolytic therapy to minimise bleeding and avoid unnecessary blood product transfusion is now possible. This is particularly relevant in pregnancy when anaphylaxis may necessitate rapid delivery of the baby and surgical intervention as part of maternal resuscitation.

Case report

A 30-year-old nulliparous woman was booked for an emergency cervical cerclage for bulging membranes at 19 weeks of gestation. She had a body mass index of 34 kg/m^2 but no significant medical comorbidities. She had previously undergone three uncomplicated elective general anaesthetics for wisdom teeth extraction, laparoscopic cholecystectomy and dermoid cystectomy. She took no regular medications and reported no food or drug allergies.

Her baseline observations were heart rate 90 beats/min, non-invasive blood pressure 143/79 mmHg and oxygen saturation (SaO_2) 98% on air. Spinal anaesthesia was discussed but maternal preference was for general anaesthesia. Following pre-oxygenation, induction commenced with intravenous fentanyl 150 μg and propofol 200 mg mixed with lidocaine 30 mg. Without checking bag-mask ventilation, a size four laryngeal mask airway (LMA) Supreme™ was inserted but ventilation was suboptimal and a decision was made to intubate the trachea. A further dose of propofol 100 mg and suxamethonium 150 mg were given, and shortly thereafter ventilation through the LMA improved. Direct laryngoscopy showed a Grade 1 Cormack-Lehane view and intubation proceeded with a 7.5 mm tracheal tube.

Immediately thereafter it was noted that manual ventilation did not produce chest movement, the capnography trace was absent, oxygen saturation and blood pressure fell rapidly and the carotid pulse became impalpable. A pulseless electrical activity (PEA) arrest was declared and chest compressions commenced. Intravenous adrenaline 200 μg was given and the tracheal tube was reinserted to exclude oesophageal intubation. At this point, five minutes after induction of general anaesthesia, sinus rhythm of 86 beats/min was noted but with no measurable blood pressure, capnography or pulse oximetry traces. Based on the presence of severe bronchospasm and hypotension, anaphylaxis was suspected and additional adrenaline 200–400 μg boluses were administered. An adrenaline infusion was started at 0.75 μg/kg/min via a peripheral intravenous cannula. After four minutes of chest compressions, a capnograph trace and palpable carotid pulse returned. A radial arterial cannula was inserted under ultrasound guidance, which showed a flat pressure trace but blood was easily aspirated for blood gas analysis (Table 1). The rate of intravenous fluid administration was increased and an arterial pressure waveform became apparent following infusion of crystalloid 2000 mL. Ongoing haemodynamic instability necessitated two further episodes of chest compressions, each for 60 s, over the next 12 min due to loss of a palpable carotid pulse. Gradual stabilisation of cardiorespiratory parameters occurred, and serial blood gas analyses confirmed improving oxygenation. Total adrenaline administration was 1100 μg over the course of the acute events, which lasted 21 min.

Blood samples sent 25 min after induction included full blood count, electrolytes, coagulation screen, mast cell tryptase and rotational thromboelastometry (ROTEM). Notably, the ROTEM trace (Fig. 1) showed normal clot formation but evidence of hyperfibrinolysis with maximum lysis 100% (normal <15%); this was trea-

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Table 1 Serial blood gas samples from radial arterial line

Time from induction (min)	13	31	69	120	453
Location	OR	OR	OR	OR	ICU
pH	7.18	7.09	7.14	7.20	7.31
pCO_2 (mmHg)	41.6	48.3	41.4	35.2	31
pO_2 (mmHg)	53.1	97.4	73.1	105	118
HCO_3 (mmol/L)	15.0	14.1	13.4	13.2	15
cBE (mmol/L)	−11.7	−13.8	−13.9	−13.3	−10
SaO_2 (%)	75.8	93.9	88.0	96.9	99.0
Haemoglobin (g/dL)	15.6	13.2	14.9	12.7	11.9
Na (mmol/L)	135	136	136	135	139
K (mmol/L)	5.0	3.1	3.2	3.2	2.9
Glucose (mmol/L)	6.7	12.0	15.3	17.2	11.2
Lactate (mmol/L)	6.3	8.6	7.3	6.8	5.4

OR: operating room; ICU: intensive care unit.

ted with tranexamic acid 1 g. Other coagulation results were within normal limits: platelets 448×10^9/L, international normalised ratio 1.1, activated partial thromboplastin time 29.4 s, thrombin clotting time 15.5 s and fibrinogen 2.9 g/L. A central venous cannula was inserted for adrenaline infusion.

Sixty-eight minutes after induction of general anaesthesia, the cervix was 3 cm dilated but obstetric ultrasound revealed the fetus to be terminally bradycardic. The uterus was evacuated over the next 24 min; estimated blood loss was 100 mL with no need for blood product transfusion. At this stage the patient's clinical observations showed a heart rate of 120 beats/min, invasive blood pressure 118/79 mmHg on 0.06 μg/kg/min adrenaline and SaO_2 96% on 50% inspired oxygen. A total of 4000 μg adrenaline and 5500 mL crystalloid fluid had been given. The patient was transferred to an offsite intensive care unit (ICU).

Tracheal extubation took place the following morning. There was no evidence of neurological injury. Serial blood samples for tryptase taken at 25 min, 6 h and four weeks post-induction were 36.7, 12.8 and 2.6 μg/L respectively (normal <14 μg/L). Suxamethonium specific IgE was elevated at 5.9 KU/L (titres 3.5–17.5 KU/L are considered high). Intradermal skin testing conducted four weeks after the event showed a positive wheal and flare reaction to a 1/1000 dilution of suxamethonium 50 mg/mL and 1/1000 dilution of mivacurium 2 mg/mL with negative responses to fentanyl, propofol, lignocaine and other muscle relaxants.

Discussion

The incidence of anaphylaxis during pregnancy has been estimated at 3–8 per 100 000 deliveries but this is likely to be an underestimate as data have tended to focus on severe cases and those occurring in late pregnancy.[1–3] Antibiotics are the likeliest drug to cause anaphylaxis in this group,[1,3] unless in association with general anaesthesia when suxamethonium is more likely to be responsible.[4–6] The elevated tryptase and specific IgE level in our patient supported the skin testing results indicating an allergy to suxamethonium with cross reactivity to the non-depolarising muscle relaxant mivacurium.

Hyperfibrinolysis is a coagulopathy that has traditionally been diagnosed using indirect measures of clot breakdown, such as elevated amounts of d-dimer and fibrin degradation products.[7–9] With the development of viscoelastic tests of coagulation, such as ROTEM and thromboelastography (TEG), it is now possible to recognise hyperfibrinolysis in real time providing clinically useful information to guide management. Hyperfibrinolysis diagnosed using point-of-care viscoelastic tests has been well described in major trauma, liver and cardiac surgery.[10–12] In obstetrics, pregnancy-specific reference ranges have been defined for ROTEM.[13,14] Viscoelastic testing has been used to guide blood product replacement in major obstetric haemorrhage[9,15–19] and to assist decision making for neuraxial blockade.[20,21]

There are several case reports of anaphylaxis-induced hyperfibrinolysis where activation of the fibrinolytic system has been hypothesised to occur as a consequence of mast cell degranulation.[7,8,22–25] Tryptase released by mast cells has been shown to activate both tissue type (tPA)[26,27] and urinary type (scu-PA)[28] plasminogen activators leading to increased production of plasmin, a serine protease that degrades fibrin to dissolve formed blood clots. In patients undergoing general anaesthesia, most reports of anaphylaxis-induced hyperfibrinolysis have resolved spontaneously over 20–120 min without antifibrinolytic treatment. When surgery can be postponed or there is time to monitor if bleeding starts, a conservative approach may be warranted. However, we believe that early antifibrinolytic therapy should be considered when anaphylaxis is diagnosed in pregnancy because urgent delivery may be required due to fetal distress from placental hypoperfusion, or maternal cardiac arrest necessitating perimortem caesarean delivery. The risk of bleeding is high and a proactive approach to minimising blood loss seems prudent. Spontaneous resolution of hyperfibrinolysis cannot be relied upon in