

Cardiopulmonary distress during obstetrical anaesthesia: attempts to diagnose amniotic fluid embolism in a case series of suspected allergic anaphylaxis

T. HARBOE¹, M. D. BENSON², H. OI³, E. SOFTELAND^{4,5}, L. BJORGE⁶ and A. B. GUTTORMSEN¹

¹Department of Anaesthesia and Intensive Care and Center for Occupational and Environmental Allergy, Haukeland University Hospital, Bergen, Norway, ²Evanston Healthcare, Department of Obstetrics and Gynaecology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA, ³Department of Obstetrics and Gynaecology, Hamamatsu University School of Medicine, Hamamatsu, Japan, ⁴Department of Biomedicine, University of Bergen, Norway, ⁵Department of Anaesthesia and Intensive Care, Haukeland University Hospital, Bergen, Norway and ⁶Division of Obstetrics and Gynaecology, Haukeland University Hospital, Institute of Clinical and Molecular Medicine and The Gade Institute, Section for Microbiology and Immunology, University of Bergen, Bergen, Norway

Background: Cardiopulmonary distress during obstetrical anaesthesia may result from a drug-induced allergic reaction, but, in the obstetrical setting, allergic anaphylaxis may be inseparable from amniotic fluid embolism in terms of the clinical presentation. Further investigations, using allergy tests and other laboratory analyses, are then needed to pursue a diagnostic clarification. **Methods:** Twelve women suspected of having developed anaphylaxis during obstetrical anaesthesia underwent allergy follow-up investigations and further serological tests with the amniotic fluid embolism marker sialyl Tn and complement factors (C3 and C4) in an attempt to differentiate amniotic fluid embolism from drug-induced allergic anaphylaxis.

Results: The diagnostic programme revealed one case of probable amniotic fluid embolism and four cases of probable drug-induced allergic anaphylaxis. Of the remaining seven cases, there were two cases that, by diagnostic exclusion, could be

classified as possible cases of amniotic fluid embolism. The cause of the reactions remained unresolved in five cases.

Conclusions: It can be difficult to differentiate between anaphylaxis and amniotic fluid embolism, especially amongst survivors. Diagnostic markers that can be applied on peripheral blood samples are promising, but larger studies are needed to validate their use in the diagnosis of causes of cardiopulmonary distress during obstetrical anaesthesia.

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ANAESTHESIOLOGISTS generally have a high awareness of the risk of anaphylaxis related to anaesthesia. Many anaesthetic departments have established routines for blood sampling, referral and allergy follow-up in cases of suspected anaphylaxis. Serum tryptase (s-tryptase) is the single most useful diagnostic test to confirm anaphylaxis (1). The slow elimination of tryptase from the circulation means that the optimal sampling time is 1–4 h after the reaction (2). Diagnostic markers for amniotic fluid embolism based on peripheral blood samples have also been introduced. These include sialyl Tn (STN) (3), zinc coproporphyrin (4) and complement factor consumption (5).

Amniotic fluid embolism largely gives the same clinical manifestations as allergic anaphylaxis. In cases of cardiopulmonary distress during obstetrical

anaesthesia, the two entities cannot always be separated by the clinical presentation alone. Follow-up investigations after such events should therefore try to explore both diagnoses. The aim of this study was to investigate the possibility that some suspected anaphylactic reactions might in fact be cases of amniotic fluid embolism. Serum samples obtained for s-tryptase analysis were further analysed for levels of STN and the complement factors C3 and C4.

Materials and methods

During a 4-year period (2000–2003) 15 women were referred for allergy follow-up at the Centre for Occupational and Environmental Allergy, Haukeland University Hospital, Bergen, Norway after suspected anaphylaxis during obstetrical

anaesthesia. The patients were referred from six different hospitals in southern Norway. In three cases, there was no surplus serum after s-tryptase analysis, and further investigation using STN and C3/C4 was not possible. This case series presents the remaining 12 cases in which attempts were made to differentiate amniotic fluid embolism from allergic anaphylaxis by case history, allergy follow-up and peripheral blood analyses.

Case histories

The case histories were based on information provided by the referring anaesthesiologists and patient interviews. Maternal and gestational age, previous diseases, allergies, previous anaesthesia, prescription medication, method of delivery, obstetrical complications, bleeding volume, blood coagulation parameters (if obtained), anaesthetic drugs given prior to the adverse events, time intervals between the administration of substances and events, recorded clinical manifestations and acute management were recorded. Hypoxia was defined as pulse oximetry saturation of less than 90%, and hypotension was defined as a systolic blood pressure of less than 90 mmHg. Coagulopathy was diagnosed in cases in which two or more coagulation parameters could be deemed abnormal [blood platelet count $< 100 \times 10^9/l$; plasma D-dimer $> 2 \text{ mg/l}$; plasma fibrinogen $< 1.0 \text{ g/l}$; prothrombin time-international normalized ratio (PT-INR) > 1.2].

s-Tryptase

s-Tryptase was measured using the Pharmacia UniCAP FEIA system (Pharmacia Diagnostics AB, Uppsala, Sweden). Serum samples were obtained within the first hours after the reaction (45 min to 4 h), with control values obtained from routine pre-operative samples, post-operative samples (12–24 h after the reaction) and samples at the follow-up examinations (some months later). The s-tryptase analysis was regarded as positive if the level was above $24 \mu\text{g/l}$ (the upper 97.5% laboratory reference area limit) in the sample drawn within 4 h after the reaction. It was also regarded as positive if the within 4-h s-tryptase level was at least three times higher than the background level (the level found in the pre-operative, post-operative and/or follow-up samples).

Specific immunoglobulin E (IgE)

Specific IgE to latex, suxamethonium and pentothal was analysed at the Laboratory of Clinical Biochemistry, Haukeland University Hospital, Bergen, Norway, using

the Pharmacia CAP FEIA system (Pharmacia Diagnostics AB) on serum samples.

Skin tests

Skin prick tests were performed in duplicate according to the European Academy of Allergy and Clinical Immunology Guidelines (6, 7). A standardized skin prick test panel was used consisting of histamine chloride 10 mg/ml, negative control solution, suxamethonium, rocuronium, vecuronium, pancuronium, atracurium, fentanyl, pentothal, propofol, latex 100 HEP and chlorhexidine. The anaesthetic drugs were tested in undiluted concentrations. Other drugs, such as oxytocin, synthetic colloids and local anaesthetics, were added if indicated by the case history. Intradermal tests with neuromuscular blocking agents, opioids, local anaesthetics and oxytocin were performed in individual cases when the skin prick tests were negative. If regional anaesthesia had been applied, subcutaneous challenge tests were performed with the local anaesthetics used.

STN immunoassay with monoclonal antibody TKH-2

The concentration of STN antigen was determined by an immunoradiometric competitive inhibition assay using the monoclonal antibody TKH-2 in a one-step procedure at BML Inc. (Tokyo, Japan) (8). Briefly, beads coated with purified STN were incubated with 50 μl of sample and 200 μl of iodine-125-labelled TKH-2 antibody solution for 90 min. The radioactivity bound to the beads was measured by a gamma counter. All samples were assayed in duplicate.

C3 and C4

The serum levels of the complement factors C3 and C4 were determined using precipitating antisera in a Nephelometer Analyser (Behringwerke AG, Marburg, Germany) at the Department of Microbiology and Immunology, Haukeland University Hospital, Bergen, Norway.

Diagnostic criteria

Reactions were diagnosed as IgE-mediated anaphylaxis if the clinical manifestations were typical of a serious immediate hypersensitivity reaction and if the allergy tests detected IgE to a substance that had been administered with a plausible time relation to the reaction (9).

Reactions were diagnosed as probable amniotic fluid embolism if the clinical manifestations were typical and if STN was elevated in the first blood

sample obtained after the reaction. If both allergy tests and STN were negative, cases were diagnosed as 'possible' amniotic fluid embolism if the three cardinal clinical manifestations of hypotension, hypoxia and coagulopathy were present during the incident.

Results

The mean maternal age was 31 years (range, 25–38 years). All were at full term, except case 7 who was 36 weeks pregnant and case 12 who was 18 weeks pregnant (information on gestational age was lacking in two cases). Six patients had a history of atopic disease, such as allergic rhinoconjunctivitis, atopic eczema or asthma. One had a history of possible morphine allergy, and one had tested positive to suxamethonium after a previous anaphylactic reaction during general anaesthesia.

All patients had systemic respiratory and/or circulatory manifestations. Nine patients developed hypoxia, six of whom were also reported to have bronchospasm. Two patients had dyspnoea without hypoxia and one patient had no respiratory involvement. Hypotension was reported in 10 cases. Cutaneous reactions were reported in six cases (urticaria, generalized rash or angio-oedema). Six patients had abnormally large blood loss (1 litre or more), and laboratory evidence of coagulopathy was found in three cases. Fetal bradycardia was detected in three cases immediately prior to or during the reaction. Fetal death was diagnosed prior to the event in two other cases. We judged seven events to be life threatening. Short case histories are summarized in Appendix 1 and clinical features are displayed in Table 1.

The diagnostic results are summarized in Table 2. s-Tryptase was elevated in four cases, and IgE-mediated allergy was detected in three of these. Four patients had skin prick tests positive to suxamethonium, and two of these patients also had elevated serum levels of specific IgE to suxamethonium. All four reacted within a few minutes after the induction of general anaesthesia and probably developed IgE-mediated allergic anaphylaxis to suxamethonium. One patient (case 12) had an intradermal test positive with oxytocin (1 : 100 dilution). Allergic reactions to oxytocin-containing drugs are rare. Our experience using intradermal tests with oxytocin is limited. Case 12 was therefore judged to be possible allergic anaphylaxis as the intradermal result could be false positive.

One patient (case 1) had a highly elevated STN in the post-event sample, and further testing did not detect any relevant allergy. She developed manifestations during epidural anaesthesia with bupivacaine and sufentanil, which would be a very rare cause of anaphylaxis. This was judged as a probable case of amniotic fluid embolism. Another patient (case 11) had elevated STN in the post-event sample as well as in a pre-operative sample (taken 22 h before the reaction). This patient also had a skin prick test positive to suxamethonium. When considering these results, together with the fact that her manifestations developed a few minutes after exposure to suxamethonium, this was judged as a probable IgE-mediated allergic drug reaction despite the finding of an elevated STN.

Amongst the cases with negative allergy tests and negative STN, case 2 was diagnosed as 'possible' amniotic fluid embolism based on a history of hypoxia, hypotension and coagulopathy during labour. Case 12, with an uncertain oxytocin intradermal test, otherwise met the criteria for 'possible' amniotic fluid embolism.

Five patients had decreased levels of C4, one also with a decreased level of C3, in the post-event sample. All patients had base level s-tryptase, C3 and C4 within the normal range.

Discussion

With this case series we applied a novel approach to the evaluation of cardiopulmonary distress during obstetrical anaesthesia using diagnostic tests to detect both IgE-mediated allergy and amniotic fluid embolism. Amongst the 12 cases drug-induced allergic anaphylaxis was well established in only four. Two cases were probably amniotic fluid embolism, and one additional case had positive indicators for both diagnoses. This series illustrates the need to consider both amniotic fluid embolism and anaphylaxis when cardiopulmonary distress occurs during obstetrical anaesthesia, but a definite differential diagnostic approach cannot be proposed. However, several interesting diagnostic aspects were revealed.

STN analysis was only positive in two of the 12 cases, and this low rate could have several explanations. Firstly, the patient population was primarily selected by anaesthesiologists on the basis of a clinical suspicion of drug-related anaphylaxis. Not surprisingly, relevant drug allergy was found in about one-third of cases. STN has been found to be a sensitive marker of amniotic fluid embolism in fatal cases (10). In our series all patients survived,

Table 1

Case	Anaesthesia indication	Anaesthesia	Time from anaesthetic to reaction (min)	Delivery	Severity	Symptoms and signs	Blood loss (ml)	Coagulopathy	Other diseases	History of allergy
1	Fetal death	Epidural	30	VD	Severe	Dyspnoea, hypotension, rash	2000	Yes	Urticaria	Suxa
2	Fetal distress	Epidural	5	Caesarean	Severe	Hypoxia, hypotension, rash	5400	Yes	Angio-oedema	Atopy
3	Slow progress	Epidural	30	Caesarean	Moderate	Hypotension, shivering, agitation	1200	No	None	Atopy
4	Breech presentation	Epidural	75	Caesarean	Moderate	Dyspnoea, hypotension, rash	500	No	SLE	Atopy
5	Fetal distress	General	10	Caesarean	Severe	Hypoxia, bronchospasm, hypotension, rash	400	No	None	None
6	Breech presentation	General	13	Caesarean	Moderate	Hypoxia, bronchospasm, hypotension, rash	800	No	None	Morphine
7	Twin gestation	General	<5	Caesarean	Moderate	Hypoxia	1500	No	Anti-cardiolipin antibodies	Atopy
8	Vaginal tear repair	General	<5	VD	Severe	Hypoxia, bronchospasm, hypotension	350	No	Pericarditis	Diabetes
9	Fetal distress	General	<5	Caesarean	Moderate	Hypoxia, bronchospasm, hypotension, rash	1000	No	None	None
10	NI	General, failed spinal	5	Caesarean	Severe	Hypoxia, bronchospasm, hypotension, rash	NI	NI	None	Atopy
11	Breech presentation	General, failed spinal	<5	Caesarean	Severe	Hypoxia, bronchospasm, hypotension	NI	NI	Diabetes	Atopy
12	Fetal death	General	10	Evacuation	Severe	Hypoxia, hypotension	1000	Yes	Leiden mutation	None

Severe, life-threatening; moderate, not life-threatening; NI, no information; SLE, systemic lupus erythematosus; Suxa, suxamethonium; VD, vaginal delivery.

Table 2

Diagnostic results for 12 cases of cardiopulmonary distress during obstetrical anaesthesia.

Case	Time interval*	s-Tryptase	STN	C3	C4	Detected drug allergy	Diagnosis
1	02:30	7.2	656.7	1.240	0.130	Suxamethonium†	Amniotic fluid embolism
2	03:25	6.6	16.3	0.713	0.033	None	Amniotic fluid embolism
3	01:15	3.7	27.3	1.130	1.139	None	Unknown
4	01:35	3.5	24.3	1.150	0.058	None	Unknown
5	01:30	146.0	14.4	0.984	0.151	None	Unknown
6	04:00	3.1	16.9	1.340	0.206	None	Unknown
7	01:15	2.2	14.0	1.020	0.093	None	Unknown
8	01:10	34.5	17.4	0.900	0.156	Suxamethonium	Drug allergy
9	02:30	3.7	10.0	1.100	0.096	Suxamethonium	Drug allergy
10	01:30	28.5	13.4	Not done	Not done	Suxamethonium	Drug allergy
11	01:05	28.8	60.8	Not done	Not done	Suxamethonium	Drug allergy
12	00:45	4.3	16.2	0.907	0.132	Oxytocin	Amniotic fluid embolism or drug allergy?

s-Tryptase upper reference limit, 24 µg/l; sialyl Tn (STN) upper reference limit, 47 U/ml; C3 lower reference limit, 0.830 g/l; C4 lower reference limit, 0.130 g/l.

*Time interval from start of the event to blood sampling for tryptase, STN, C3 and C4 analysis (h:min).

†Patient was not administered suxamethonium or other neuromuscular blocking agents prior to the reaction in question.

and close to one-half of the reactions were judged not to be life-threatening. Knowledge about STN levels in survivors is scarce. Larger series on such patients have not been published. There is a possibility that STN is less sensitive in survivors (5). Mild events must also be judged as more diagnostically open than severe cases, and could be explained by several more trivial factors, such as the pharmacodynamic effects of anaesthesia, non-allergic drug reactions, responses to painful stimuli under light anaesthesia, unrecognized bacterial infection or uncompensated blood loss. There are also other possible diagnoses for severe reactions, such as thromboembolic embolism, air embolism, primary heart disease and blood transfusion reaction (11). The patient records did not reveal any such serious diagnoses, with the exception of case 8 who went into labour with an unrecognized obstructing pericarditis.

It has been suggested that amniotic fluid embolism might actually result from anaphylaxis to fetal material leaking into the maternal circulation (12). If amniotic fluid embolism is a type I hypersensitivity reaction, one would expect mast cell degranulation and tryptase release (13). Mast cell degranulation and elevated s-tryptase have been reported in cases of amniotic fluid embolism (14–16), but cases have also been described where s-tryptase has remained normal (5, 17). We did not use statistical tests on the results in our case series, but there was no suggestion of a correlation between elevated s-tryptase and elevated STN. In contrast, there seemed to be a correlation between elevated s-tryptase and the detection of relevant IgE-

mediated allergy, similar to findings in larger studies on anaphylaxis during anaesthesia (2, 18).

The clinical similarities between amniotic fluid embolism and anaphylaxis imply the need for additional diagnostic methods. However, when the additional diagnostic tests fail to yield a positive clarification, one may attempt to reach a tentative diagnosis on the basis of the clinical presentation and the information provided by the negative test results. When the probability of drug-induced allergic anaphylaxis is decreased by a thorough allergy investigation, possible amniotic fluid embolism could be diagnosed by exclusion. Such a diagnosis would necessarily be rendered with a degree of uncertainty.

There may also be clinical differences between amniotic fluid embolism and anaphylaxis that may be diagnostically indicative. Of the 12 cases in this series, all patients with elevated s-tryptase and all patients with suxamethonium allergy were reported to have bronchospasm. Only one patient with bronchospasm did not have elevated s-tryptase and/or suxamethonium allergy. Moreover, only one of the six patients with large blood loss and none of the three patients with coagulopathy were reported to have bronchospasm. Thus, the occurrence of bronchospasm and large blood loss roughly divides this small case series into two separate groups. In the medical literature, bronchospasm is a central manifestation of anaphylaxis (~40%) (19), but is less commonly reported in cases of amniotic fluid embolism (15%) (20). Excessive bleeding with coagulopathy is common in amniotic fluid embolism, but is hardly ever reported in cases of

anaphylaxis during anaesthesia. One would also expect cutaneous signs, such as urticaria, angio-oedema and flushing, to be indicators of anaphylaxis. Such signs have not been associated with amniotic fluid embolism (21). In our series, both cases diagnosed as probable or possible amniotic fluid embolism had cutaneous manifestations. Interestingly, they both had a previous history of episodic urticaria or angio-oedema. In addition, both cases were suspected as possible anaphylaxis and not amniotic fluid embolism. Several explanations are possible: the observations may have been influenced by expectations or may be a coincidence; the amniotic fluid embolism diagnosis may be erroneous; or cutaneous manifestations could possibly occur in some cases of amniotic fluid embolism. Larger studies must be conducted to evaluate the differential diagnostic importance of these clinical manifestations.

The transitory decreases in serum complement levels seen in this study cannot be used diagnostically *per se*. Sequential changes in serum complement levels during anaphylactic reactions may reflect redistribution as a result of dynamic shifts in plasma volume rather than consumption by activation (22). Interestingly, of the five patients with a fall in complement levels, four had a blood loss of 1 litre or more and received volume substitution accordingly. The complement analyses used are rather insensitive for the detection of complement activation. The measurement of the terminal complement complex (TCC; SC5b-9) is a more sensitive technique for this (23). This analysis should preferentially be performed on plasma, but, as such samples were not available, we could not include this method in the analysis panel in our study.

Conclusion

The number of women receiving analgesia and/or anaesthesia during labour and delivery is increasing. At Haukeland University Hospital, Bergen, Norway, the rate of regional anaesthesia for vaginal delivery is ~35% and the Caesarean section rate is ~12%. Cardiopulmonary distress in these patients is a diagnostic challenge, in which amniotic fluid embolism and drug allergy can be equal possibilities. The differential diagnosis is important for several reasons. The patient may require anaesthesia in the future, and avoiding the allergen is then crucial. Both the patient and medical staff may benefit psychologically from having a more definite explanation for the incident, which may have led to permanent sequelae or loss. Moreover, patient injuries often result in

medico-legal questions, and a reliable diagnosis is a key element in resolving these issues.

When amniotic fluid embolism is diagnosed by exclusion, some uncertainty will remain. Further studies should be conducted to develop diagnostic tests that can be applied to survivors of possible amniotic fluid embolism.

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Address:
Dr Torkel Harboe
Department of Anaesthesia and Intensive Care
Haukeland University Hospital
N-5021 Bergen
Norway
e-mail: torkel.harboe@helse-bergen.no

Appendix 1: short case histories for 12 cases of cardiorespiratory distress during obstetrical anaesthesia

Case 1

Age: 35 years. Verified intrauterine death in the 38th week of pregnancy. Vaginal delivery with epidural anaesthesia. Reaction 30 min after start of epidural: urticaria, angio-oedema, tachycardia, hypotension, lowered level of consciousness not related to hypotension. Excessive bleeding post-partum. Platelet count, $122 \times 10^9/l$; D-dimer, $> 20 \text{ mg/l}$; fibrinogen, $< 0.1 \text{ g/l}$.

Case 2

Age: 29 years. Planned Caesarean section because of breech presentation. Contractions in the 38th week of pregnancy. Epidural anaesthesia established while awaiting capacity in the operating theatre. Acute dyspnoea, flushing, urticaria, hypotension, hypoxia, fetal bradycardia 5 min after start of epidural. Caesarean section under general anaesthesia. Excessive bleeding. Platelet count, $97 \times 10^9/l$; D-dimer, $> 20 \text{ mg/l}$; fibrinogen, 0.2 g/l ; PT-INR, 1.1.

Case 3

Age: 28 years. Caesarean section because of protracted delivery. Epidural anaesthesia. Shortly after delivery: hypotension, shivering, feeling cold, agitated. Large blood loss. Platelet count, $126 \times 10^9/l$; D-dimer, 6.0 mg/l ; fibrinogen, 4.1 g/l ; PT-INR, 1.1.

Case 4

Age: 28 years. Systemic lupus erythematosus. Caesarean section because of breech presentation. Epidural anaesthesia. Shortly after delivery: hypotension, dyspnoea and chest pain, itch and rash on upper body. Normal bleeding. Platelet count, $238 \times 10^9/l$; D-dimer, 3.0 mg/l ; fibrinogen, 3.8 g/l .

Case 5

Age: 36 years. Fetal distress. Emergency Caesarean section under general anaesthesia. Shortly after delivery: hypotension, hypoxia, elevated airway pressure, urticaria. Normal bleeding.

Case 6

Age: 33 years. Emergency Caesarean section under general anaesthesia because of unexpected breech presentation. Shortly after delivery: bronchospasm and hypoxia. Normal blood loss.

Case 7

Age: 38 years. Anti-cardiolipin antibodies. Delivery of twins under general anaesthesia because of threatening HELLP syndrome (haemolysis, elevated liver enzymes, low platelets). Difficult intubation. Refractory hypoxia after intubation despite easy ventilation with 100% oxygen. Excessive blood loss. Platelet count, $141 \times 10^9/l$; D-dimer, $> 4 \text{ mg/l}$.

Case 8

Age: 32 years. Diabetes mellitus. Post-partum suture of vagina under general anaesthesia. Shortly after induction: bronchial obstruction, severe hypotension, ventricular bradycardia. Cardiac ultrasound: pericardial fluid; 400 ml slightly blood-tinted fluid removed. Normal blood loss.

Case 9

Age: 25 years. Emergency Caesarean section under general anaesthesia because of fetal distress. Immediately after induction: bronchospasm, hypoxia, hypotension, subcutaneous oedema. Large blood loss, but no information on coagulopathy.

Case 10

Age: 29 years. Caesarean section under general anaesthesia after failed regional anaesthesia. Five minutes after induction: bronchospasm, flushing, severe hypotension. No information on blood loss.

Case 11

Age: 33 years. Caesarean section because of breech position. General anaesthesia because of failed spinal anaesthesia. Immediately after induction: severe hypotension, bronchospasm, hypoxia. No information on blood loss.

Case 12

Age: 31 years. Dilatation and evacuation because of intrauterine death in 18th week of pregnancy. Induction with fentanyl and propofol uncomplicated. Surgery uncomplicated until shortly after Syntocinon 5 IU intravenously. Circulatory collapse and cyanosis without apparent bronchospasm. Post-operative large blood loss. Platelet count, $122 \times 10^9/l$; D-dimer, 3.5 mg/l ; fibrinogen, 0.2 g/l ; PT-INR, 1.5.