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Case Scenario: Amniotic Fluid Embolism

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AMNIOTIC fluid embolism (AFE) is a rare but potentially catastrophic obstetric emergency. Despite earlier recognition and aggressive treatment, morbidity and mortality rates remain high. An estimated 5–15% of all maternal deaths in Western countries are due to AFE.[1] Recent retrospective reviews of population-based hospital databases in Canada[2] and the United States[3] found AFE incidences of 6.1–7.7 cases per 100,000 births. The United States cohort used data from the Healthcare Cost and Utilization Project-Nationwide Inpatient Sample from 1998 to 2003, which included all hospital admissions in the United States. The Canadian database included three million hospital deliveries from 1991 to 2002. The only prospective study also included data from three million deliveries in the United Kingdom and reported an incidence of 2.0 per 100,000 births.[4] This cohort used the United Kingdom Obstetric Surveillance System to identify women with AFE from 2005 to 2009.

Early studies revealed mortality rates as high as 61–86%, but more recent estimates suggest a case fatality of 13–26%.[3–5] This decrease in risk for maternal mortality from AFE may be the result of previous diagnosis and better resuscitative care as well as changes to case inclusion criteria. Fetal outcome remains poor if AFE occurs before delivery, with a neonatal mortality rate approximately 10%.[6–8] First reported by Meyer in 1926,[9] and then later identified as a syndrome in 1941 by Steiner and Lushbaugh,[10] AFE has historically been a postmortem diagnosis; confirmed only at autopsy revealing epithelial squamous cells, lanugo hair, and fat from vernix or infantile mucin in the maternal pulmonary vasculature. More recent incidence data results from national registries in the United States and the United Kingdom, which used clinical entry criteria in laboring women or parturients undergoing cesarean section or dilation and evacuation of an intrauterine fetal demise. These criteria included acute maternal cardiovascular collapse with evidence of respiratory compromise and/or coagulopathy.[3,4,8]

The pathophysiology of AFE is not completely understood. AFE most commonly occurs during labor, delivery, or the immediate postpartum period. However, it has been reported to occur up to 48 h postpartum.[1] Once thought to be the result of an actual embolic obstruction of the pulmonary vasculature by components of amniotic fluid, AFE might result from immune activation and present as an anaphylactoid process. AFE likely involves a spectrum of severity from a subclinical process to a catastrophic event. Early recognition and prompt and aggressive resuscitative efforts enhance the probability of maternal and neonatal survival.

Case Report

A 42-yr-old woman, at 38 weeks gestation of her fourth pregnancy (gravida 4, para 3) and obese (110 kg), experienced spontaneous onset of contractions. Her pregnancy was complicated by diet-controlled gestational diabetes and mild preeclampsia. Her platelet count on admission was 220,000/ml. An epidural was requested for labor analgesia and was placed without incident. The initial dosing of the epidural included a 2-ml, 2% lidocaine subarachnoid test dose followed 5 min later by a 5-ml, 2% lidocaine intravenous test dose; both test doses were considered negative. An appropriate bilateral sensory and mild motor block developed and an infusion of 0.1% bupivacaine with fentanyl 2 mcg/ml was initiated at 10 ml/h, producing excellent labor analgesia. Approximately 1 h after epidural placement, thoracic dermatomal levels to cold were confirmed at the umbilicus and the

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patient had a moderate lower extremity motor block. Ultrasound examination by the obstetrician revealed a transverse lie and a fetus that was not engaged in the pelvis. Several attempts at external cephalic version were unsuccessful, and a cesarean section was scheduled. The patient was given two incremental doses of 5-ml, 3% 2-chloroprocaine. Immediately after the second epidural dose of 3% 2-chloroprocaine was administered, the patient experienced sudden shortness of breath and an "odd sensation on her forehead." Within seconds, she proceeded to have a grand mal seizure. Her airway was supported with oxygen by facemask, and seizure activity ceased within 20–30 s without pharmacologic intervention. Initial vital signs revealed a maternal pulse of 130 beats/min, blood pressure of 90/60 mmHg, and peripheral oxygen saturation of 95%. Fetal heart rate precipitously declined from a baseline of 140 to 80 beats/min. Approximately 5 min after the seizure resolved, the patient rapidly deteriorated to complete cardiovascular collapse. Advanced cardiac life support was initiated with chest compressions on a backboard with the maximum uterine displacement that could be obtained, and the patient's airway was secured with tracheal intubation. The patient received 1 mg atropine and 1 mg epinephrine intravenously, without improvement in vital signs. External chest compressions did not produce recognizable waveforms on the peripheral pulse oximetry screen and were judged to be inadequate. The decision was quickly made to perform bedside cesarean section. A 3,200-g male infant was delivered 5 min after maternal cardiac arrest. The infant had Apgar scores of 3 at 1 min and 5 at 5 min. Immediately after delivery, a maternal radial pulse became palpable and a blood pressure of 75/58 mmHg was obtained. The patient was rapidly transported to the nearby operating room, and general anesthesia was initiated with midazolam and fentanyl alone due to the hemodynamic instability. Nitrous oxide and sevoflurane were added to deepen the anesthetic as hemodynamics stabilized. A radial arterial line and a central venous line were placed upon the patient's arrival in the operating room. An epinephrine infusion starting at 5 mcg/min was titrated to produce blood pressures of approximately 90/50 mmHg. The initial arterial blood gas in the operating room on a fractional inspired oxygen tension (F_{IO_2}) of 1.0 was pH 7.22, pCO_2 35 mmHg, HCO_3 16 mEq/l, and pO_2 80 mmHg. Uterine atony developed within minutes after delivery and was treated with multiple doses of intramuscular methergine and intramyometrial prostaglandin F2-α in addition to crystalloid infusion with 40 units/l of oxytocin. Initial coagulation studies were abnormal with a prothrombin time of 20 s, an activated partial thromboplastin time of 80 s, platelets 112,000/ml, and fibrinogen 150 mg/dl. Resuscitation with crystalloid, colloid, and blood products continued while surgeons performed an urgent hysterectomy. The estimated surgical blood loss was 3,000 ml. The patient received eight units of packed erythrocytes, four units of fresh frozen plasma, two units of platelets, and four units of cryoprecipitate in the operating room. The patient was maintained on vasopressors, transferred to the intensive care unit, and intubated on an F_{IO_2} of 1.0. She received an additional six units of packed erythrocytes, four units of fresh frozen plasma, two units of platelets, and four units of cryoprecipitate in the first 3 h in the intensive care unit, before her coagulation profile improved to near normal. The initial chest x-ray was compatible with pulmonary edema. Over the next 48 h, she was weaned from ventilator support, her coagulopathy resolved, and her cardiovascular status stabilized. The patient was discharged home 5 days after surgery with no apparent neurologic deficits.

Table 1. Differential Diagnosis for Seizure and/or Cardiovascular Collapse in the Obstetric Patient

• Local anesthetic toxicity	• Drug reaction
• High spinal anesthesia	• Pulmonary aspiration
• Eclampsia	• ARDS
• Thrombotic pulmonary embolus	• Uterine rupture
• Air embolus	• Bilateral pneumothorax
• Anaphylaxis	• Acute decompensation of valvular disease
• Acute myocardial infarction	• Peripartum cardiomyopathy
• Cerebral hemorrhage	• Sepsis
• Cerebral mass	• Amniotic fluid embolism

ARDS = acute respiratory distress syndrome.

Discussion

AFE remains a diagnosis of exclusion and should always be considered early in the course of clinical management of any obstetric emergency involving cardiovascular collapse. This patient developed new onset of seizure activity followed by almost immediate hemodynamic instability. Local anesthetic toxicity was our initial concern because of the temporal relationship of the injection and seizure activity. Intralipid therapy briefly was considered, but the total dose of chloroprocaine was thought to be well below maximum usage guidelines of 11 mg/kg and unlikely to cause sustained cardiovascular depression, particularly in the circumstance of a tested, well-functioning epidural. The self-limited nature of the seizure and the presumed rapid hydrolysis of chloroprocaine by plasma pseudocholinesterase further diminished the likelihood of local anesthetic toxicity. Several other diagnoses were considered in the differential (as shown in table 1).

Clinical Course of AFE

The presenting signs and symptoms of AFE involve many organ systems. Acute dyspnea or sudden agitation and anxiety are common premonitory symptoms. It is estimated that approximately 10–50% of patients with AFE present with seizures.[1,4] Rapid decline in pulse oximetry values or sudden absence or decrease in end-tidal carbon dioxide may be apparent. Hemodynamic compromise quickly follows these

Table 2. Possible Presenting Signs and Symptoms of AFE

- Acute dyspnea and/or cyanosis
- Sudden tachycardia
- Hypotension
- Acute agitation, anxiety, or mental status changes
- Seizure
- Diffuse coagulopathy
- Sudden desaturation on pulse oximetry
- Loss of end tidal carbon dioxide in the intubated patient
- ST segment changes and right heart strain on ECG
- Fetal distress

AFE = amniotic fluid embolism; ECG = electrocardiogram.

prodromal signs. The first sign of AFE may be acute fetal distress. Table 2 shows possible signs/symptoms of AFE.

Three phases in the clinical course of AFE have been described. The first or immediate phase is often characterized by altered mental status, respiratory distress, peripheral oxygen desaturation, and hemodynamic collapse. The second phase involves coagulopathy and hemorrhage and occurs in an estimated 4–50% of patients with presumed AFE. Although older studies of AFE required either sudden, unresuscitatable maternal death or the subsequent development of disseminated intravascular coagulation (DIC) for inclusion in the AFE database, it is now recognized that DIC does not develop in all cases of AFE. Tissue injury and end-organ system failure comprise the last phase of AFE. Clinical findings will vary depending on the organ system(s) predominantly affected. Ventilation-perfusion mismatching as a result of pulmonary vascular constriction at the onset of AFE may explain sudden hypoxia and respiratory arrest.[7] Pulmonary hypertension and right-heart strain/failure may be the result of physical amniotic fluid debris in the pulmonary vasculature or, perhaps more likely, result from circulating pulmonary vasoconstrictive mediators. The mechanisms for myocardial dysfunction that lead to early hypotension are multifactorial. Proposed explanations include myocardial failure in response to sudden pulmonary hypertension, a direct myocardial depressant effect of humoral mediators in amniotic fluid, deviation of the intraventricular septum due to right ventricular dilation, and/or ischemic myocardial injury from hypoxemia.[11–13]

The etiology of coagulopathy is also thought to be multifactorial. Although there are many cases where no coagulopathy develops, there are also reports of coagulopathy and hemorrhage being the initial and only presenting sign of AFE. Patients with severe AFE will often develop abnormal coagulation within the first few hours of the inciting event. Whether the coagulopathy is primarily a consumptive process or due to massive fibrinolysis is controversial.[1,14] The intravascular entry of procoagulant and anticoagulant factors of amniotic fluid may disrupt the coagulation balance of pregnancy. Encephalopathy associated with AFE is thought to be secondary to hypoxia and includes a spectrum of symptoms ranging from altered mental state to seizures. As many as 85% of AFE survivors have been reported to have residual neurologic deficits, which account for much of the morbidity seen with these events.[7]

Table 3. Clinical Associations with Amniotic Fluid Embolism (AFE)

Maternal risk factors
- Advanced maternal age
- Preeclampsia/eclampsia
- Trauma
- Diabetes mellitus

Neonatal risk factors
- Intrauterine fetal demise
- Fetal distress
- Fetal macrosomia

Complications of pregnancy that have been linked to AFE
- Placenta previa
- Placental abruption
- Operative delivery
- Recent amniocentesis
- Meconium-stained amniotic fluid
- Uterine overdistension
- Chorioamnionitis
- Induction of labor
- Rupture of amniotic membranes
- Uterine rupture
- Cervical laceration
- Saline amnioinfusion
- Cell-salvaged blood transfusion

Multiple risk factors and clinical diagnoses have been associated with AFE but no clinical predictors have been clearly identified.

Risk Factors for AFE

AFE has been linked to multiple clinical associations. Underlying maternal and fetal conditions as well as factors related to complications of pregnancy have been associated with AFE, as shown in table 3. It should be noted that there are no clinical factors that are consistent predictors of AFE. However, there may be a strong association of AFE with cesarean section. In a recent prospective report from the United Kingdom, a 62% attributable risk associated with cesarean delivery and AFE is reported.[4] In addition, for patients with AFE presenting after delivery, there is an eightfold increased risk during cesarean section compared with vaginal delivery. The fact that the rate of cesarean section in the United States is approximately twice that in the United Kingdom may partially explain the lower reported incidence of AFE in the United Kingdom study. Historically a contraindication in obstetrics due to the risk of AFE, cell-salvaged blood *via* modern filtration devices is now considered safe in patients at risk for hemorrhage or in whom allogeneic blood transfusion is contraindicated.[15]

Pathophysiology

There are two theories regarding the pathogenesis of AFE. The first historic idea is that a tumultuous labor, abnormal placentation, surgical trauma, or any other breach of the

barrier between maternal blood and amniotic fluid allows the forced entry of amniotic fluid into the systemic circulation and results in a physical obstruction of the pulmonary circulation. There must be a pressure gradient that favors transfer of fluid from the uterus into the systemic circulation. There is, however, evidence refuting this theory. Radiologic studies have not shown amniotic debris obstructing pulmonary vessels. In addition, fetal squamous cells are not consistently found on autopsy in patients with presumed AFE, and animal models of AFE have not shown pulmonary vascular obstruction by amniotic debris.[1,11,16]

The second and increasingly favored hypothesis suggests that entry of amniotic fluid into the maternal circulation activates inflammatory mediators, causing a humoral or immunologic response.[17] AFE has even been labeled the "anaphylactoid syndrome of pregnancy."[7,16,18,19] This theory is supported by the fact that amniotic fluid contains vasoactive and procoagulant products including platelet-activating factor, cytokines, bradykinin, thromboxane, leukotrienes, and arachidonic acid. Concentrations of tissue factor and tissue factor pathway inhibitor, which trigger intravascular coagulation, are higher in amniotic fluid than in maternal serum.[20] It is speculated that maternal plasma endothelin concentrations are increased by entry of amniotic fluid into the systemic vasculature. Endothelin acts as a bronchoconstrictor as well as a pulmonary and coronary vasoconstrictor, which may contribute to respiratory and cardiovascular collapse.[19]

The direct procoagulant property of amniotic fluid may explain the prevalence of DIC in AFE. An alternative explanation for DIC is an immune-mediated response producing complement activation. Interestingly, an allergic history is common in women with AFE. As many as 41% of AFE patients in the national registry had a history of atopy or drug allergy.[7] Complement activation with markedly decreased C3 and C4 concentrations has been convincingly shown in patients with AFE compared with postpartum control patients.[17,21] Fetal antigens may react with membrane-bound immunoglobulin E on mast cells, causing release of histamine and tryptase. Both complement activation and mast cell degranulation support an immunologic mechanism.

Diagnosis of AFE

The diagnosis of amniotic fluid embolism continues to be one of exclusion in women who present with suggestive clinical criteria. The criteria used for inclusion in the national registries in the United Kingdom and the United States guide diagnosis. In the absence of other medical explanations, the peripartum patient who has any combination of acute hemodynamic collapse, respiratory distress/hypoxia, DIC, and/or mental status changes should be considered to possibly have AFE.

Initial diagnostic evaluation should include continuous pulse oximetry and arterial blood gas measurements to determine degree of hypoxemia. Serial complete blood counts and coagulations studies should be sent to follow trends and detect early coagulopathy. Increased serum tryptase and urinary histamine concentrations as well as significantly lower complement concentrations suggest an anaphylactoid process, but it has not yet been clearly shown that these are clinically relevant diagnostic markers during an acute event.[7,17,22] More studies are also needed to determine the utility of both monoclonal TKH-2 antibodies and zinc coproporphryin as rapid diagnostic markers.[23,24] Current studies of biochemical markers are thought to be flawed when the diagnosis of AFE is not based on strict clinical criteria.[16] Bedside transesophageal echocardiography may aid early diagnosis by showing acute pulmonary vasoconstriction, right ventricular dilation, and a collapsed left ventricle with leftward deviation of the intraventricular septum.[12,13,25,26] However, rapid access to transesophageal echocardiography is probably not available in many obstetric units. Supportive therapy as indicated by clinical circumstance is always the most important intervention and should supersede diagnostic studies. Attempts at obtaining blood or fluid samples for unvalidated diagnostic purposes should never interfere with resuscitation. Unfortunately, we do not currently have a good tool for reliable diagnosis of AFE. We must rely on severe clinical symptoms and exclusion of other clinical explanations and as a result, many subclinical presentations of AFE may be unappreciated. However, in cases of maternal death after suspected AFE, postmortem histopathologic and histochemical analysis may further support the clinical diagnosis of AFE.

Postmortem Pathology

Histopathologic evidence of fetal cells and/or amniotic fluid elements aspirated from a pulmonary artery catheter was historically thought to be pathognomonic of AFE. However, the mere presence of fetal squamous cells in the pulmonary circulation is not necessarily diagnostic for AFE, as some squamous cells have been found in the pulmonary circulation of pregnant women without the diagnosis of AFE.[27–29] The clinical presentation in combination with a lack of other explanations for the maternal cardiovascular collapse is always of paramount importance for diagnosing AFE. Nonetheless, postmortem findings may support the clinical diagnosis of AFE.

In AFE, the lungs at autopsy often show pulmonary edema with foci of atelectasis and hyperinflation. Thrombi and amniotic debris are not grossly visible. Microscopically, pulmonary edema ranges from minimal to severe, and resuscitative efforts may artificially accentuate the edema. Alveolitis is apparent with evidence of alveolar damage including interstitial edema, swelling of endothelium, congestion of capillaries, and a small influx of alveolar macrophages. Neutrophilic alveolitis can be impressive, reminiscent of sepsis or antigen-antibody complex disease. Unlike these entities, alveolar hemorrhage is not generally a feature. Naked megakaryocytic nuclei may be found in capillaries, and platelet thrombi as well as looser collections of platelets may be found in small vessels. The elements of amniotic fluid (squamous

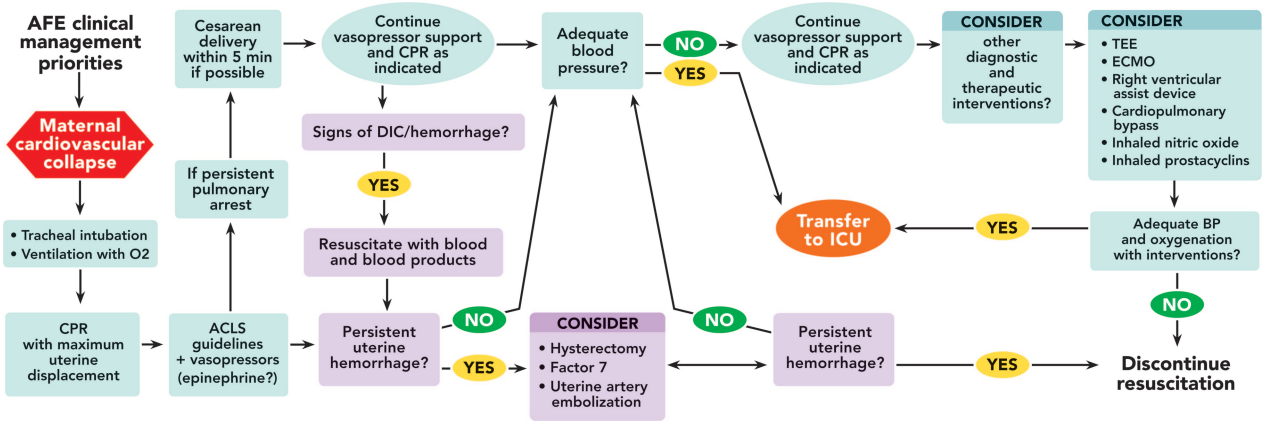

Fig. 1. Flow chart depicting clinical management priorities for amniotic fluid embolism. ACLS = advanced cardiac life support; AFE = amniotic fluid embolism; BP = blood pressure; CPR = cardiopulmonary resuscitation; DIC = disseminated intravascular coagulation; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; TEE = transesophageal echocardiography.

cells, mucin, lipid from vernix caseosa, and lanugo hairs) may be seen individually or admixed, usually in small arteries. The neutrophilic response appears focused on the foreign material to a degree, but not entirely. Lanugo hairs are birefringent and can be brought out by examination with polarized light. Microscopically, amniotic fluid debris may be found in other organs.[30–32] Hankins *et al.* showed that much of observable histopathology in experimental AFE depends on the amount of embolic solid material rather than fluid.[33] Because consumptive coagulopathy is common in advanced stages of AFE, fibrin microthrombi can often be found in a number of organs, including renal glomeruli. Frozen section immunofluorescence of lung, heart, kidney, and brain for immunoglobulins, fibrin, and complement could improve our understanding of AFE. This has not been done in the past but should be considered in future autopsies.

Management of AFE

The initial management of amniotic fluid embolism relies on early suspicion and early aggressive hemodynamic support. Oxygenation, circulatory support, and correction of coagulopathy continue to be the mainstays of therapy. Left uterine displacement is crucial in resuscitation efforts if the fetus remains *in utero*. As demonstrated in this case, cardiopulmonary resuscitation may be ineffective despite uterine displacement. It has been reported that immediate cesarean section will improve neonatal neurologic recovery and overall maternal outcome if performed within 5 min of maternal cardiovascular arrest.[34] Maternal resuscitative efforts are also enhanced by relief of aortocaval compression at delivery. Central venous access for fluid and blood product resuscitation is warranted if coagulopathy does not preclude this intervention. Transesophageal echocardiography may guide volume resuscitation and vasopressor therapy and aid in the diagnosis and treatment of cardiovascular pathology.[13] More invasive approaches to resuscitation have been reported, including exchange transfusion, extracorporeal membrane oxygenation, cardiopulmonary bypass, a right ventricular assist device, and uterine artery embolization.[35–37] The practicality of these interventions may very well depend on the resources available in individual institutions. Hysterectomy may be required in patients with persistent uterine hemorrhage to control blood loss. Recombinant factor VII has also been described as a treatment for hemorrhage occurring with AFE, but should be used with caution because a recent review of case reports has suggested worsened outcomes.[22] Both aerosolized prostacyclin and inhaled NO act as direct pulmonary vasodilators, and have been successfully used to treat the acute pulmonary vasoconstriction of AFE.[38,39] Figure 1 provides a schematic flow diagram for possible AFE management.

Conclusion/Knowledge Gap

Our understanding of the pathogenesis and diagnosis of AFE is rudimentary. The pathophysiologic mechanisms responsible for this catastrophic process require further elucidation. The clinical diagnosis remains one of exclusion in combination with management of the presenting clinical symptoms.

Two probable pathophysiologic mechanisms are likely and not necessarily mutually exclusive. There is a possible role of classic immunoglobulin E-mediated anaphylaxis. Further investigation with immunofluorescence for immunoglobulin E in the lung might support this mechanism. If the immune system is a primary factor in AFE, then complement-mediated, non-immunoglobulin E release of histamine and other mediators would be involved. Acute serum markers for an immunologic response in suspected AFE are being investigated. Possible serum markers include complement, tryptase, histamine, and fetal antigen concentrations. Until case report-based markers are validated, these tools are primarily of academic interest in the pursuit of understanding the pathogenesis of AFE. Without a reliable diagnostic tool, some subclinical AFE events are undoubtedly missed.

Assuming AFE is an immunologic response to the fetus, why is the development of AFE rare in parturients? And how should a survivor of AFE be counseled with respect to her

AFE risk with subsequent pregnancies? Interestingly, there have been multiple case reports of uncomplicated deliveries in women who had previous AFE,[40,41] suggesting that each fetus may be antigenically different, leading to varied qualitatively abnormal amniotic fluid and engendering different maternal immunologic responses. To our knowledge, there has not been a case report of recurrent AFE in a subsequent pregnancy.

Despite our lack of understanding of the pathophysiologic processes of AFE, it is very clear that early and aggressive management (including immediate cesarean section) of patients with clinically suspected AFE enhances both fetal and maternal resuscitation and improves survival. It is important to always consider AFE in the differential diagnosis of sudden maternal cardiopulmonary instability and remember that the lack of development of DIC and hemorrhage does not exclude the diagnosis of AFE.

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