In normal situations, amniotic fluid is completely isolated from the maternal intravascular compartment. If an opening exists between the amniotic sac and uterine veins, amniotic fluid can be bolused into maternal circulation producing an embolism. Amniotic fluid emboli (AFE) may contain epithelial squamous cells, lanugo hair, vernix, mucin, and bile from meconium. Because of the accompanying anaphylaxis-like symptoms of shock, some researchers believe AFE should be more accurately termed “anaphylactoid syndrome of pregnancy.” AFE only occurs when there is a breach in the barrier between amniotic fluid and maternal circulation. There are 3 routes where this may occur. They are through endocervical veins, uterine trauma sites, and the placental attachment site.

In the 70 years since AFE was first reported, it still remains a syndrome whose etiology is not clearly understood. The clinical manifestations of AFE have been described in numerous accounts. It was believed for years that when an amniotic fluid bolus was pumped into the maternal circulation there was an intense showering of microscopic fetal debris particles that caused an acute occlusion of part of the mother’s pulmonary microvasculature. The sudden respiratory distress and cyanosis were thought to be related to right-sided heart failure or cor pulmonale. However, when pulmonary artery (PA) catheters were placed into patients with the syndrome, elevated pulmonary capillary wedge pressures, decreased left ventricular stroke work index, mild to moderate decreases in mean PA pressures and variable increases in central venous pressure, were revealed. These findings are indicative of left-sided heart failure.

It is postulated that the initial insult to the pulmonary system due to the exposure of the amniotic fluid debris may be because of a transient vasospasm, acute pulmonary hypertension, resulting in severe hypoxia. However, there is limited information, perhaps due to a lag between symptom onset and insertion of a PA catheter to confirm this postulation.

Of the patients who survive the initial hemodynamic collapse, 70% develop noncardiogenic pulmonary edema that resembles acute respiratory distress syndrome on chest radiograph. Forty-five percent develop a severe coagulopathy, disseminated intravascular coagulation (DIC), within 30 minutes to 4 hours. In the absence of laboratory confirmation of coagulopathy, spontaneous gingival bleeding, catheter site bleeding, and epistaxis strongly suggest DIC. There also may be the occurrence of neurological manifestations, such as seizures, confusion, or coma.

Amniotic fluid has procoagulant properties, as evidenced by an increase in Factor X activity when amniotic fluid is mixed with maternal blood. Increased thromboplastic activity also occurs. Amniotic fluid...
lacks plasmin and plasmin activator. Plasmin is generated from an inactive precursor called plasminogen. Plasmin forms as a response to tissue plasminogen activator (a plasmin proactivator), and thrombin (a plasmin proactivator), which leads to fibrin clot lysis and the formation of fibrin split products. It is speculated that thrombin generation in the pulmonary vasculature leads to plasmin and kinin production, which, in the absence of antiplasmin, perpetuates its own generation. If thrombin generation occurs in an environment with excess plasmin proactivator, a rapid coagulopathy develops. Fibrinogenolysis yields an increase in fibrin split products. The increase in fibrin split products is implicated in the development of severe uterine atony, which is found in the parturient with AFE. Thrombin is thought to stimulate the secretion of vascular endothelium, which in animal studies demonstrate myometrial and myocardial depression. This may contribute to the uterine atony and unstable hemodynamics seen in AFE syndrome.

The rarity of AFE or anaphylactoid syndrome of pregnancy, coupled with difficulty in diagnosing this syndrome, can result in fatal complications. The ability to recognize the signs and symptoms of AFE quickly and accurately and to begin treatment promptly remains a challenge for the anesthesia provider and the obstetrician. Even with aggressive resuscitation efforts and high-technology treatment, survival is rare. Reporting of suspected AFE cases to the National Registry for AFE, as well as the publication of case studies and potentially successful management protocols, help to further the understanding and treatment of this complex and life-threatening syndrome.

**Literature related to AFE etiology and morbidity**

In the 1920s, Ricardo Meyer of Brazil first reported the presence of fetal cellular debris in the maternal circulation as being associated with maternal complications, such as expiring suddenly during or immediately following delivery. In 1941, after examining autopsy reports of 8 maternal deaths, Steiner and Lushbaugh reported amniotic fluid debris in the maternal pulmonary vasculature. The entity they labeled as maternal pulmonary embolism by amniotic fluid emboli is known today as AFE.

Occurrence rates of AFE are said to vary from 1:8,000 to 1:83,000. A California study reports a 1:20,646 occurrence rate. The different rates can be explained by the increased awareness of the syndrome. AFE is attributed to 5% to 18% of all maternal deaths. Mortality rates reported from suspected AFE vary from 26% to 86%, with the wide variance being speculated as possible improvements in intensive care management and disparate case definitions. Among the survivors, thrombotic stroke occurs as the most frequent neurologic sequelae. Even with the evolution of scientific knowledge, the medical profession has remained largely unable to predict, prevent, or to decrease the occurrence of AFE.

A complicated pregnancy often precedes AFE. The complications range from amniocentesis, polyhydramnious, placenta accreta, fibroid uterus, the presence of a cervical suture, to fetal demise. AFE also may occur after abdominal trauma. Traumatic placement of an intrauterine pressure catheter has been reported as yet another risk factor for AFE. However, AFE has been reported in normal pregnancies. The majority of cases occur during or immediately after labor, therefore, immediate recognition and treatment are needed to improve outcomes.

Presently, the AFE diagnosis is not based on any clinical or laboratory finding. Disseminated intravascular coagulation develops in 40% of patients, while 10% to 15% have bleeding diathesis as the initial symptom. Seizures occur in 10% to 20% of patients. Profound hypoxia and right-sided heart failure follow PA spasm and may account for a 50% mortality rate within the first hour. In mothers with AFE, 24% to 93% show pulmonary edema that presents as acute respiratory distress syndrome on chest radiograph. Laboratory values reveal prolonged clotting times, increased fibrin-split products, and thrombocytopenia. There are currently no estimates of the mortality associated with left-sided heart failure.

There are 3 identified phases of AFE in humans. Phase 1 includes:

1. Respiratory – distress and cyanosis
2. Hemodynamic – pulmonary edema and hemorrhagic shock
3. Neurologic – confusion and coma

These manifestations can occur in combination, separately, and in different magnitudes. If patients survive the initial cardiorespiratory insult, 40% to 50% progress into phase 2, which is characterized by coagulopathy, hemorrhage, and shock. In phase 2, left-sided heart failure is evident and is the most reported sign in humans. Increases in pulmonary capillary wedge pressure, PA pressure, and central venous pressure are characteristic of pulmonary edema. For some patients this is their first and only clinical manifestation. By phase 3, acute symptoms have passed and injury to the brain, lung, and renal systems is already established. Phase 3 may last...
weeks, and patients may die as a result of severe brain and lung injury. Infection and multiorgan system failure also may cause death.1

The classical description of AFE is that strong uterine contractions occur simultaneously with an opening between the amniotic sac and uterine veins causing an amniotic fluid bolus to be “pumped” into maternal circulation. The accumulation of amniotic cellular debris becomes “trapped” in the maternal pulmonary circulation.2 There are many exceptions to the classical description.13 When intratracheal pressure is greater than maternal mean pressure, maternal-fetal exchange ceases. The mean pressure is believed to be 25 to 35 mm Hg.12 It is speculated that “trapped” amniotic fluid in the uterine vein is gradually released into maternal circulation if uterine tone decreases, thus explaining delayed AFE syndrome.14 With no identifiable risk factors, late onset of symptoms may be due to the passage of amniotic fluid debris by a transpulmonary route or through a maternal patent foramen ovale.15

It is a misconception that squamous cells in the lungs are a marker for AFE.13 Squamous cells are found in both pregnant and nonpregnant women who have had PA catheters inserted. This is a result of contamination from the skin. It also has been shown that in a normal peripartum there may be findings of amniotic fluid debris including squamous cells, lanugo hair, and mucin in maternal circulation in the absence of AFE.13 However, in mothers with clinical evidence of AFE, fetal debris, such as mucin, vernix, and lanugo in maternal circulation, are frequently found coated with leukocytes, suggesting a maternal reaction to the foreign material.13

This data leads one to wonder why there is so much variability in different mother's responses. The incidence of AFE does not seem to be related to the delivery route.12 Although there is a high occurrence of AFE in cesarean sections, this probably reflects the high cesarean section rates seen today as opposed to 50 years ago.12 There is no relation between oxytocin and hyperstimulation leading to AFE; rather uterine hypoxia induces the myometrial hypertonus that has been observed in AFE.12

It has been reported that coagulation changes that accompany AFE were not appreciated until the 1950s.3 Clinically, hemorrhage may be the initial sign, but this is related to DIC. Of the parturients who survive the initial insult of AFE, 37% develop DIC. The etiology of DIC remains speculative, but if DIC is present, mortality soars.5

What is known is that in the presence of DIC, there are activated factors II, VII, and X in amniotic fluid. But, their concentrations are lower than those of any mother at term and probably do not contribute to the coagulopathy. Amniotic fluid does, however, have direct factor X activating properties, which have thromboplastic-like effects. This could stimulate or support clotting. These properties increase with gestational age.5

It is suggested that tissue factor, also known as factor III, which is found in amniotic fluid, may be the trigger for clotting.5 Other possible triggering agents are fetal epithelial cells from the respiratory, gastrointestinal, genitourinary tract, and sloughed skin. If tissue factor is the culprit, it activates the extrinsic pathway by binding with factor VII. This can then trigger clotting by activating either factor IX or X. It is speculated that when clotting is triggered in the microvasculature of the lungs, local thrombogenesis can cause vasoconstriction and microvascular thrombosis.7 Fifty percent of patients present with signs and symptoms of respiratory failure, 25% with cardiovascular signs, 15% with hemorrhage, and 10% with seizures as the initial sign. DIC is almost inevitable if the patient survives more than 1 hour with AFE.5

A literature review revealed no reported instances of recurrent AFE,15 but there have been 5 successful pregnancies reported following the syndrome.15 An example was a case report of a woman who, 2 years after an AFE, discussed her options with her obstetrical staff. The patient was told that there was limited information available regarding this decision, but she decided to continue with the pregnancy. After a 36-week uncomplicated gestation, an elective cesarean section was planned. The patient's past history of AFE dictated that delivery be in a setting where rapid access to cardiopulmonary resuscitation equipment and specially trained medical personnel were available. The patient underwent amniocentesis to test fetal lung maturity and received steroids for 1 week to increase the infant's lung production of surfactant. The patient had a cesarean section under regional anesthesia and suffered no complications.15

**Literature related to anaphylactoid syndrome of pregnancy**

Contemporary literature suggests that the term “amniotic fluid emboli” may not accurately describe the anaphylaxis-like manifestations encountered in the patient with suspected AFE.12 Anaphylactic shock and septic shock both involve the entrance of a foreign substance into the circulation. Bacterial endotoxins or specific antigens directly or indirectly result in the release of various primary and secondary endogenous mediators. The release of these mediators results in physiologic
changes, such as profound myocardial depression, decreased cardiac output, pulmonary collapse, and DIC. These findings also are present with AFE.

With an interest in AFE pathophysiology, Benson set out to test 2 hypotheses that involved maternal immune response to fetal antigen. In his first hypothesis, he proposed that maternal anaphylactoid symptoms resulted from mast cell degranulation and histamine release. Histamine release is the mechanism underlying anaphylactic reactions. The second hypothesis was that maternal illness resulted from massive activation of the complement pathway. As part of his research he also sought to measure a specific fetal antigen, sialyl Tn, which has been proposed as a diagnostic tool for AFE. Sialyl Tn is a glycoprotein, mucoid in nature, that originates in both adult and fetal intestinal and respiratory tracts. It is found in both meconium and in amniotic fluid. Seven out of 9 patients diagnosed with AFE had serum assays that suggested anaphylaxis. Five had elevated serum tryptase alone; 1 had tryptase and urinary histamine. However, 7 of 8 patients had assays for mast cell degranulation that were negative, whereas all 6 patients who died had elevated sialyl Tn. Seven out of 8 patients had abnormal complement 3 (C3) levels and 8 of 8 patients had abnormal complement 4 (C4) levels. Decreased complement levels in patients diagnosed with AFE suggest that complement activation has a significant role in AFE pathophysiology.

Benson suggests that AFE may be an IgE-mediated anaphylactic reaction. Anaphylaxis is similar clinically to many descriptions of AFE including the sudden onset, collapse of the cardiovascular system, and the frequent occurrence of DIC. However, this is still controversial since AFE does not completely follow this path at all times.

Other pathways independent of IgE antibodies can liberate anaphylaxis mediators. They produce an identical clinical picture. The term “anaphylaxis” refers to a situation where an allergen enters the body and combines with IgE antibodies on the surface of basophils and mast cells. The mast cells and basophils become activated and produce the mediators that we know as histamine, leukotrienes, kinins, eosinophil chemotactic factor, and prostaglandins. These substances cause bronchospasm, pulmonary edema, vasodilatation, hypotension, dysrhythmias, and urticaria, but not always the cardiac failure associated with AFE.

Due to the striking similarities of anaphylactic reactions, the term “anaphylactoid” has come into use. Anaphylactoid refers to the reaction that occurs when an offensive agent enters the body and non-immunologically activates systems that cause degranulation of basophils and mast cells. Other systems that are activated include the complement system, the coagulation and fibrinolytic system, and the kinin generation system. Activation of these systems causes the release of the same mediators as anaphylaxis and causes a syndrome that is hard to distinguish from anaphylaxis. These mediators cause profound myocardial depression, decreased cardiac output, pulmonary hypertension, and DIC. It is well documented that all of these manifestations can occur in AFE; however, they do not necessarily do so.

Because of these discrepancies, it seems premature to change the term “amniotic fluid emboli” to “anaphylactoid syndrome of pregnancy.” Anaphylactic reactions involve dramatic cutaneous manifestations, and there is no evidence of this in the 1995 AFE National Registry analysis. Bronchospasm and upper airway swelling are typical hallmarks of anaphylaxis, and these findings are not present in patients with AFE. Anaphylactic reactions require prior sensitization, which is difficult to evoke even in patients reported with AFE following early pregnancy termination. There is no laboratory evidence to support that AFE patients have anaphylaxis or that there is mast cell involvement. Without mast cell involvement, the term “anaphylactoid,” which is interpreted as a “non–immune-mediated degranulation of mast cells” seems inappropriate.

The placenta and fetus would appear to serve as obvious potential foreign body antigens that could trigger a full-blown anaphylactic event. However, amniotic fluid has never elicited any toxic reactions in mothers unless there has been a lot of meconium present. In anaphylactoid reactions, antigens and antibodies are not involved, but in anaphylaxis and anaphylactoid syndrome, mast cells degranulate. An example of anaphylactoid syndrome in humans is the reaction that occurs when some patients receive intravenous contrast dye. This type of reaction can occur upon the patient’s first exposure, hence there is no antibody component. Serum tryptase levels 30 minutes to 4 hours after collapse have proven to be sensitive markers for mast cell degranulation. However, there has been no supporting data showing this type of IgE involvement with AFE.

It is evident that the controversy continues regarding AFE’s similarity to an anaphylactic response. It has been documented that the human placenta secretes leukotrienes and arachidonic metabolites, which are believed to be mediators of immediate hypersensitivity reactions. The sudden appearance of dyspnea and restlessness simulates an allergic reaction. The rapid resolution of pulmonary edema, despite nonspecific
and inconsistent treatment, supports the use of a term such as “anaphylactoid syndrome of pregnancy.”

**Literature related to management and outcomes**

Healthcare providers must be aggressive with initiation of supportive care immediately upon suspicion of AFE. Even if the provider is not immediately clear about what is occurring, it should be evident that whatever is occurring, is life threatening. Help must be summoned immediately and must include a team of individuals from obstetrics, anesthesia, and nursing who are familiar with emergency procedures.

Unfortunately, there is no specific treatment for AFE. Aggressive resuscitation followed by supportive treatment modalities provides the basis for care. The initial hypoxemia is usually so profound, that irreversible neurological injury may result despite tremendous resuscitative measures. If the patient has not delivered, she must be positioned on her left side to ensure good uterine blood flow. Shock develops quickly; therefore, a slight Trendelenberg position will help with central venous return and brain perfusion.

Tracheal intubation and mechanical ventilation with a high FiO₂ must be initiated to aid in the hypoxic event. Inotropic support should be guided by the use of a PA catheter. Therapy should be directed at improving contractility because of left ventricular failure. Drugs of choice for maintenance of blood pressure and cardiac output require higher than normal concentrations to obtain the desired effect, perhaps because of severe left ventricular failure or the higher volume of distribution: dopamine, 2 to 40 µg/kg per minute, dobutamine, 2 to 40 µg/kg per minute, and norepinephrine, 2 to 4 µg/min. Fluid resuscitation should be guided by measurement of cardiac chamber pressures with a PA catheter, being careful to avoid overhydration, since these patients are predisposed to pulmonary edema. The addition of positive end-expiratory pressure may improve oxygenation.

DIC must be treated aggressively with packed red blood cells, fresh frozen plasma, cryoprecipitate, and platelets. O Rh-negative or type-specific blood can be used if the patient is uncrossmatched. It should be noted that cryoprecipitate is rich in both fibrinogen and fibronectin. Fibronectin helps facilitate the uptake of cellular and other particulate matter from the blood via the reticuloendothelial system.

The use of heparin therapy to decrease clotting is controversial. Currently, it is not recommended to heparinize the patient; however, Bick administers heparin, 100 U/kg every 6 hours, or low molecular weight heparin, 100 to 150 U/kg every 12 to 24 hours. Some practitioners bolus heparin 3,000 to 5,000 U intravenously upon diagnosing AFE.

It is suggested that specific laboratory values be collected in all suspected AFE cases. They are complete blood cell count, plasma thromboplastin, activated partial thromboplastin time, fibrin degradation products, fibrinogen, arterial blood gases, chest radiograph, electrocardiogram, serum tryptase, serum sialyl Tn antigen, and zinc coproporphyrin. Blood samples must be collected from a wedged PA catheter. In order to limit the possibility of contamination, a more representative sample will be obtained from the pulmonary microvasculature if it is collected from the distal lumen of a wedged PA catheter. Discard the first 10 mL of blood as waste.

Corticosteroids and leukotriene inhibitors are recommended as part of supportive care. Corticosteroids, such as hydrocortisone, should be given at 500 mg every 6 hours. Many other types of interventions have been mentioned in the literature, such as open cardiac massage, aminocaproic acid, cardiopulmonary bypass, inhaled prostacyclin, inhaled nitric oxide, blood exchanges, prostaglandin inhibitors, and the use of 5-lypo-oxygenase, which is a leukotriene inhibitor, but none of these seemed particularly effective.

Treatment modalities for AFE from 1998 to the present were explicated in 2 case reports. Discussion of each case may shed some light on future therapies and diagnostics.

The first case described a patient known to have been diagnosed with AFE whose life was saved by extracorporeal membrane oxygenation (ECMO) and intra-aortic balloon pump (IABP) counterpulsation. The 34-year-old, gravida 7, para 3, aborted 3, patient was admitted at full-term. Within 4 hours, she developed sudden thoracic pain, dyspnea, cyanosis, and disorientation. These symptoms were associated with fetal bradycardia. An emergency cesarean section was performed under local anesthesia. During delivery, the mother had tachycardia, no palpable blood pressure, and DIC. Pulseless electrical activity was apparent; therefore cardiopulmonary resuscitation, catecholamine administration, ephedrine, phenylephrine infusion, electroshock, and massive blood transfusions were carried out. Unable to maintain hemodynamic stability and confirming right-sided heart failure with PA dilation and left cardiac compression, an IABP was inserted. Heparin was administered, and arteriovenous ECMO was started. Vital signs stabilized. The patient was weaned from ECMO and the IABP 40 hours after delivery. The patient was discharged 24 days after hospitalization without any deficits.
Traditionally, ECMO has been used as a treatment modality for the management of adults or infants in severe respiratory failure. This is the first mentioned report of ECMO being used for AFE. ECMO’s main role was as a substitute for a dysfunctional cardiopulmonary system in the above-mentioned patient. There is, of course, increased risk of coagulopathy with the heparinization that ECMO requires. Therefore, heparin and ECMO weaning should be considered within 24 hours. Cardiopulmonary bypass may play an important role in saving lives of these patients during the critical hours following the initial insult.20

In the second case, a 26-year-old gravida 3, para 1 patient presented at 40 weeks’ gestation. Due to irregular contractions, oxytocin was administered per protocol from 0.001 to 0.0075 U/min. Eighty minutes after oxytocin was administered, the patient developed dyspnea, palpitations, and blindness. She became severely anxious and cyanotic. Due to fetal bradycardia, the patient underwent an emergency cesarean section within 4 minutes of symptoms. Upon arrival at the delivery room, she was unconscious, cyanotic, had a heart rate of 90, and agonal respirations. There were no palpable pulses; therefore, pulseless electrical activity was diagnosed. The patient was intubated, oxygenated, and ventilated on 100% FiO2, and cardiopulmonary resuscitation was started. The baby was delivered with an Apgar score of 1 at 1 minute. Epinephrine and sodium bicarbonate were given. Central vein access was established. Arterial blood gases revealed metabolic acidosis, and severe hypoxemia. Because there was no uterine bleeding, the uterus was sutured and the abdomen was closed. It was only then that the pulse became palpable with a blood pressure of 90/60 mm Hg. A transesophageal echocardiogram was performed at that time showing a failing right ventricle, suprasystemic right-sided pressures, bulging of the interatrial and interventricular septums from right to left, severe tricuspid regurgitation, and a small effusion. Her PA systolic pressure was 45 mm Hg, and the left ventricle was small and compressed. Left ventricular failure was not treated, as opposed to the first patient. There were no arterial pulses, and within 10 minutes DIC developed. A subtotal hysterectomy was performed, followed by massive blood product administration, and open cardiac massage. Despite these resuscitative measures, the patient was pronounced dead after 1 hour and 55 minutes.21

This was the first report of the use of a transesophageal echocardiogram as a diagnostic tool during the acute phase of AFE.21 It revealed severe pulmonary hypertension and right ventricular failure. Increased central venous pressure was diagnosed immediately upon arrival to the delivery room. The PaO2/FiO2 ratio was 430. With these findings, pulmonary vasoconstriction and increased pulmonary vascular resistance were clearly suggested as the primary mechanisms responsible for the cardiovascular collapse.21 Recognition that AFE was in progress, and successful resuscitation of the left heart failure may have meant survival of this particular patient.

Summary

The incidence of AFE, although extremely rare, can occur during the care given by any anesthetist or anesthesiologist. Recognition of symptoms indicative of AFE is imperative because of the rapid deterioration that occurs. The mother experiencing an AFE must be treated as a critically ill patient. She is suffering from an acute life-threatening insult that affects the heart, lungs, and brain. Severe shock and coagulopathy are clinically evident. Treatment must begin immediately to give the patient a fighting chance for survival.

This literature search found that the medical community has not given up on the fight for knowledge and understanding of this complex phenomenon. Research continues into the acute management of AFE, through interpretation of the cardiac manifestations, through transesophageal echocardiogram, and through support for the failing heart and lungs with ECMO and IABP. Although mortality remains high, there are reports of healthy survivors. It is through published literature reviews and case studies of clinical experiences that fellow professionals are able to save lives. The information presented in this review can help anesthesia providers maintain vigilance for AFE, as well as initiate the latest known immediate care for the AFE victim during delivery.

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