Lesson 316: Management of the Patient With Amniotic Fluid Embolism

Written by: Andrey F. Bilko, BS, MD, Senior Medical Student, Penn State College of Medicine, Hershey, Pennsylvania; James J. Lamberg, DO, Resident, Department of Anesthesiology, Penn State Hershey Medical Center, Hershey, Pennsylvania

Reviewed by: Sonia J. Vaida, MD, Professor of Anesthesiology and Obstetrics and Gynecology, Department of Anesthesiology, Penn State Hershey Medical Center, Hershey, Pennsylvania

REVIEW DATE: April, 2015

Read this article, reflect on the information presented, then go online and complete the lesson post-test and course evaluation before the termination date below. (CME credit is not valid past this date.) You must achieve a score of 80% or better to earn CME credit.

TIME TO COMPLETE ACTIVITY: 2 hours
RELEASE DATE: June 1, 2015
TERMINATION DATE: May 31, 2016

COPYRIGHT: This material is subject to copyright ©2015 Icahn School of Medicine at Mount Sinai. All rights reserved.

Professional Gaps

Amniotic fluid embolism is one of the leading causes of maternal mortality (≤10%) in the United States and the Western world. It occurs rarely but is an unpredictable obstetrical emergency. Only with prompt perioperative recognition and management by an anesthesiologist can morbidity and mortality be reduced. Many anesthesiologists may not be aware of the essential steps to be taken for appropriate care.

Learning Objectives

At the completion of the activity, the reader will be able to:

1. Define amniotic fluid embolism
2. State the incidence and prevalence of amniotic fluid embolism
3. Describe the major clinical features of amniotic fluid embolism, including cardiogenic shock
4. List the differential diagnosis for suspected amniotic fluid embolism
5. Describe how to establish a diagnosis of amniotic fluid embolism
6. Describe the cardiovascular, pulmonary, neurologic, and hematologic consequences
7. Determine appropriate initial treatment for life-threatening symptoms
8. Review management options for the first phase of the syndrome
9. Review management options for the second phase of the syndrome
10. Formulate a plan for postoperative management

Case

A 33-year-old, gravida 3, para 2 woman at 36 weeks’ gestation was admitted to the labor and delivery floor for management of painless vaginal bleeding. Her antepartum obstetric history was significant for an anterior placenta previa and a prior cesarean delivery (CD). On admission, the patient was afebrile
and normotensive with stable vital signs and her laboratory results were within normal limits. A non-emergent CD was planned. Following the delivery of a viable infant, there was significant difficulty with placental delivery. A classical incision was required for removal of the tissue. During initial closure of the uterine incision, the patient became unresponsive with pulseless electrical activity.

Amniotic fluid embolism (AFE) is a rare, apparently unpreventable, and often catastrophic complication unique to pregnancy. It is caused by the introduction of fetal amniotic fluid into maternal circulation. First described in the literature almost 100 years ago, and recognized as a syndrome shortly thereafter, limited progress has been made in understanding the pathogenesis and pathophysiology of AFE due to its rarity and unclear definition. Additionally, most animal studies have shown a wide spectrum of physiologic changes, with the most reasonable conclusion being that the injection of amniotic fluid into the circulation may sometimes result in pathologic effects.\(^1\) Current thinking suggests a mechanism of a maternal immune response to fetal material.\(^1\)\(^-\)\(^6\)

In an effort at a more systematic and standardized data collection, Clark et al\(^7\) and Tuffnell\(^8\) in the United States and the United Kingdom, respectively, established national registries for suspected AFE with entry criteria that included the following:

1. acute hypotension or cardiac arrest;
2. acute hypoxia (dyspnea, cyanosis, or respiratory arrest);
3. coagulopathy or severe hemorrhage; with
4. onset during labor, CD, or within 30 minutes postpartum, with no other explanation for the findings.

These criteria have become the basis for recognition of AFE in clinical practice.

AFE has a variable presentation, ranging from subtle clinical changes to sudden and fatal cardiopulmonary collapse.\(^1\)\(^-\)\(^6\) The incidence of AFE varies widely, from 1 in 8,000 to 1 in 80,000 deliveries.\(^9\) The latest data suggest an incidence of 1 in 40,000.\(^1\) Given that AFE remains a diagnosis of exclusion, with potential underreporting of nonfatal cases and over-diagnosis of fatal cases in obstetrics, the true incidence remains elusive.\(^3\)

Most cases of AFE occur during labor and delivery or immediately postpartum.\(^1\)\(^-\)\(^6\) Rare cases occur in the late postpartum period following CD, amniocentesis, placenta removal, or therapeutic dilatation and evacuation, as well as following blunt abdominal trauma, cervical cerclage removal, and ruptured uterus.\(^1\)\(^-\)\(^6\) Many risk factors have been identified, including maternal age over 35 years, multiple pregnancies, CD, assisted delivery, placenta previa, placental abruption, eclampsia, fetal distress, polyhydramnios, uterine rupture, and ethnic minority status.\(^1\)\(^-\)\(^3\) Associations have also been made with male sex of the fetus, placement of intrauterine monitoring devices, and artificial rupture of membranes. However, the literature reveals conflicting conclusions, with none of the risk factors proven to have a direct causative link.\(^1\) These risk factors are also mostly nonmodifiable and random, making their identification of limited use in reducing or predicting AFE incidence.
Pathogenesis and Pathophysiology

The pathogenesis and pathophysiology of AFE are complex and poorly understood, with several proposed hypotheses. It is well accepted that the transfer of amniotic fluid into maternal circulation is the trigger leading to clinical manifestations. Some of the entry routes include endocervical veins, uterine trauma, and placental attachment sites.\(^\text{10}\) The notion of a pressure gradient favoring transfer into the maternal circulation also has been entertained by some but refuted by others.\(^\text{9}\)

Once present in the maternal circulation, amniotic fluid precipitates a reaction, the specifics of which remain unclear.\(^\text{1}\) Classically, it was thought that amniotic fluid emboli physically obstructed maternal pulmonary capillaries causing cardiovascular collapse.\(^\text{1}\) The lack of physical evidence showing pulmonary vessel obstruction and an inability to reproduce the syndrome in animal models, even with direct intravascular injection of amniotic fluid, suggests a different mechanism.\(^\text{1-6}\) The clinical events characterized by AFE, such as coagulopathy, acute respiratory distress syndrome (ARDS), and neurologic symptoms, are not typically seen with pulmonary embolism. More recent studies agree on a maternal immune reaction due to a multitude of vasoactive and procoagulant mediators contained within amniotic fluid.\(^\text{1-6}\) Platelet-activating factor, cytokines, histamine, bradykinin, thromboxane, endothelin, leukotrienes, arachidonic acid, and arachidonic acid metabolites can all be found in amniotic fluid and may cause immunologic and proinflammatory responses leading to symptoms associated with AFE.\(^\text{2,3}\) Clark compared the manifestations of AFE to systemic inflammatory response syndrome and proposed renaming the syndrome “anaphylactoid syndrome of pregnancy.”\(^\text{1}\)

Two specific hypotheses for the immune reaction responsible for AFE include anaphylaxis and complement activation.\(^\text{11}\)

To support the anaphylaxis mechanism, several studies looked at serum tryptase levels.\(^\text{11}\) During anaphylaxis, mast cells degranulate in response to immunoglobulin E binding to an antigen, and release inflammatory mediators such as tryptase and histamine, both used as markers for anaphylaxis. Tryptase has a half-life of several hours, making it easier to measure; histamine has a half-life of minutes.\(^\text{12}\) Results showed either no detectable or slightly elevated tryptase levels in patients with AFE, suggesting that anaphylaxis may not explain the primary mechanism.\(^\text{11}\) The evidence did support mast cell degranulation taking place only in the lungs of fatal AFE cases, with a possibility of pulmonary mast cell involvement as a secondary process.\(^\text{11}\) Another theory involves complement activation, which can also result in mast cell degranulation.\(^\text{2,3,11}\) Several studies showed decreased C3 and C4 levels in women with AFE, suggesting complement activation as a primary immune response followed by mast cell degranulation as a secondary response.\(^\text{11}\) It is important to note that some extent of complement activation has been shown to be a part of normal labor, with peaks during delivery.\(^\text{11}\) Complement activation plays an important role in the pathogenesis of ARDS, which is a frequent sequela of AFE, further suggesting the involvement of complement activation.\(^\text{12}\) Overall, involvement of the complement pathway appears to be a more promising theory, but still only a hypothesis requiring more substantial data.

AFE can present with any combination of cardiovascular, pulmonary, neurologic, and hemorrhagic symptoms, with hypotension and nonreassuring fetal status being the most common. These signs and symptoms are followed by pulmonary edema or ARDS, cardiac arrest, and coagulopathy.

The hemodynamic changes associated with AFE are complex and not fully understood. Findings from experimental animal studies show AFE is associated with severe pulmonary artery hypertension and right ventricular (RV) failure, caused by either occlusion or vasospasm of the maternal pulmonary vasculature.
Acute cor pulmonale and systemic hypotension result.¹ Human data do not support sustained periods of pulmonary hypertension, but suggest left ventricular (LV) failure as a precursor to hypotension.¹

A biphasic model of cardiogenic shock has been proposed, with acute pulmonary hypertension and RV failure, followed by LV failure to reconcile animal and clinical findings. During cardiogenic shock, systemic vascular resistance (SVR) increases as a compensatory mechanism, although initially SVR may be decreased due to the normal physiologic change in pregnancy and systemic vasodilation during the first stages of AFE.⁴,¹² Transesophageal echocardiography has shown LV failure due to impaired LV filling secondary to a dilated right ventricle, with deviation of the interventricular septum into the left atrium and ventricle.²,³ Additional mechanisms for LV failure include myocardial ischemic injury and a direct depressant effect of amniotic fluid on the myocardium.

Hypoxia is the most common manifestation of respiratory failure, explained by severe hypoventilation and perfusion mismatch caused by acute pulmonary hypertension and pulmonary edema. Noncardiogenic pulmonary edema occurs in patients in whom LV function improves, suggesting the development of a pulmonary capillary leak syndrome. This theory is supported by the presence of high protein concentrations and amniotic fluid debris in the exudative edema fluid.³,⁵,¹⁰ Although noncardiogenic pulmonary edema seems to result from widespread damage to the alveolar-capillary membrane, similar to the mechanism of ARDS, lung function recovers much quicker than the typically prolonged course of ARDS.

The mechanism behind coagulopathy in AFE is unclear and likely multifactorial. It is thought to result from both procoagulant and anticoagulant factors present in amniotic fluid. The current hypothesis suggests that tissue factor contained in amniotic fluid activates the extrinsic coagulation pathway by binding with factor VII, which in turn activates factor X, leading to a consumptive coagulopathy.³,⁵ Once the clotting cascade is activated in the pulmonary vasculature, local thrombin generation leads to vasoconstriction and microvascular thrombosis. Amniotic fluid also contains activated clotting factors II, VII, and X, but the concentrations are much lower than that found in maternal serum at term.⁵ Several studies used thromboelastography and showed that addition of amniotic fluid to blood from pregnant women accelerated clot formation with no evidence of fibrinolysis, further suggesting consumptive coagulopathy as the primary cause for hemorrhage.³,⁵,⁶

### Differential Diagnosis

The clinical presentation of AFE is variable, with all of the characteristic symptoms not evident on the initial patient presentation, making the differential diagnosis broad (Table 1).
It is useful to recognize the sometimes subtle differences in the presentation of pulmonary, venous air, and amniotic fluid embolism. Several signs are shared between these three disorders, including hypotension, dyspnea, cyanosis, and cardiovascular collapse. Table 2 lists other signs for each of the disorders that are not typically shared.

**Diagnosis**

AFE is a clinical diagnosis of a woman in labor or immediately postpartum who acutely experiences a cardiopulmonary collapse with concomitant neurologic and/or hematologic symptoms. Sudden onset of hypoxia, hypotension, and coagulopathy has been described as a classic triad of AFE, recognizing that many cases do not exhibit all of these symptoms. More subtle cases depend on exclusion of other alternative diagnoses. Signs of fetal distress can be presenting or accompanying signs of AFE due to hypoxia and fetal hypoperfusion.

Many laboratory findings have been proposed as diagnostic of AFE, including levels of tryptase, arachidonic acid metabolites, and other inflammatory or immunologic markers. Measurement of serum sialyl Tn antigen levels and concentrations of zinc coproporphyrin are other experimental tests. Specific postmortem findings such as immunohistologic staining for evidence of pulmonary mast cell degranulation are inconclusive, whereas the presence of fetal material in the pulmonary circulation is accepted by some as indicative of AFE, although it has been shown to be also present in healthy women.

Several laboratory and diagnostic tests may support the diagnosis of AFE but are nonspecific (Table 3).

The diagnosis of AFE does not have to be immediate because the treatment is supportive based on observed symptoms. However, it is extremely important to react promptly to any such symptoms, and be prepared for rapid deterioration.

**Treatment**

The overall management of AFE is symptomatic and based on maintaining oxygenation, cardiac output, blood pressure, and correcting coagulopathy (Table 4). The treatment of these life-threatening symptoms can be divided into 2 phases. The first phase focuses on cardiopulmonary collapse and the second addresses coagulopathy and hemorrhage.
Rapid maternal cardiopulmonary stabilization is the key to preventing mortality and morbidity. If the fetus has not been delivered at the time of cardiac arrest and is of viable gestational age, an immediate CD should be considered.\(^\text{15}\) If fetal viability is unknown or questionable, the decision to perform emergency CD depends on whether or not the gravid uterus is thought to interfere with maternal hemodynamics. Fundal measurements are inconsistent in estimating gestational age and should not be used for evaluation of fetal viability.\(^\text{15}\)

Delivery of the fetus reduces the weight of the uterus onto the inferior vena cava, increases blood return to the heart thus increasing systemic blood pressure, and reduces fetal exposure to hypoxia in utero. Left uterine displacement may improve venous return and cardiac output at 30 rather than 15 degrees.\(^\text{16}\) Although it may make chest compressions more difficult, left uterine displacement should be attempted.

With the onset of hypoxia, delivery of 100% oxygen should not be delayed in order to prevent irreversible neurologic injury and should be initiated by any available means including face mask, bag-valve mask, or preferably endotracheal intubation with mechanical ventilation. Oxygen saturation should be maintained at 90% or higher.\(^\text{3}\)

The advanced cardiovascular life support (ACLS) algorithm should be followed with certain modifications for pregnant patients in the case of asystole or pulseless electrical activity (Table 5).

Hypotension management is aimed to optimize preload by rapid volume infusion using isotonic crystalloid solutions. In cases of refractory hypotension with suspicion of low SVR, direct-acting vasopressors such as phenylephrine or norepinephrine should be used temporarily to restore aortic perfusion pressure.\(^\text{3-5}\) Inotropes such as dopamine, dobutamine, and/or milrinone may be used to improve myocardial contractility secondary to ventricular dysfunction due to their additional \(\beta\)-adrenergic agonist activity.\(^\text{3,4,19}\) Vasopressin spares the pulmonary vasculature from vasoconstriction,
especially at low doses, and can be used as a primary or adjunct agent. Systolic blood pressure should be maintained at $\geq 90$ mm Hg, with an arterial $\text{PaO}_2$ of $\geq 60$ mm Hg, and urine output of $\geq 0.5$ mL/kg/h. The use of diuretics may be necessary to mobilize pulmonary edema fluid.

Treatment of coagulopathy and hemorrhage associated with AFE requires blood component therapy, most often with activation of a massive transfusion protocol. Massive hemorrhage requires replacement with packed red blood cells and platelets, if thrombocytopenia is present. Specific coagulation laboratory abnormalities should guide administration of fresh frozen plasma, cryoprecipitate, and/or factor replacement. Cryoprecipitate is especially useful when fibrinogen is low or when volume overload is a concern. Cryoprecipitate also contains fibronectin, an opsonic $\alpha_2$ surface-binding glycoprotein that facilitates filtering of cellular and toxic particulate matter, such as amniotic fluid debris, through the reticuloendothelial system. The use of recombinant activated factor VIIa may be considered as a last resort in patients refractory to massive blood component therapy. However, it should be avoided for routine use because it can combine with circulating tissue factor, thus enhancing intravascular clot and worsening outcomes.

Disseminated intravascular coagulation is often associated with uterine atony, which may require treatment with uterotonic medications, such as oxytocin, and even necessitating a hysterectomy if hemorrhage cannot be controlled with aggressive blood product transfusion.

There are a number of newer treatment strategies that remain anecdotal and experimental (Table 6).

### Anesthetic Management

Standard monitoring, as defined by the American Society of Anesthesiologists (ASA), applies throughout the perioperative period. Monitoring of the patient should include continuous cardiac telemetry and respiratory monitoring with a pulse oximeter and capnography.

Establishing IV access is vital during resuscitation. Large-bore peripheral IV catheters, 18-gauge or larger, are preferred due to a high flow rate and their ease of placement. Placement of catheters above the diaphragm may be advantageous as aortocaval compression can prevent venous return to the heart. Most peripheral IV catheters have greater flow rates when compared with central venous catheters. A central venous catheter may be used for vasopressor infusion, but placement should not delay resuscitation efforts. Intraosseous cannulation is an option if IV access cannot be obtained.

Intra-arterial catheterization is especially useful for continuous and accurate arterial blood pressure monitoring and direct access to blood samples for arterial gas evaluation. With the progression of AFE, right-sided ventricular failure leads to left-sided failure, making a pulmonary artery catheter a consideration during fluid management. Transesophageal or transthoracic echocardiography is useful in guiding volume therapy and assessing cardiac function by evaluating LV filling. Current literature has not reviewed the use of stroke volume variation, pulse pressure variation, or esophageal Doppler in...
patients with AFE. These newer therapies have many theoretical advantages over pulmonary artery
catheterization, but more studies are needed in this patient population.

Most patients with AFE require transfer to the ICU. Mechanical ventilation, vasopressor support, and
inotropic support are often continued. Maternal mortality varies greatly, between 20% and 90%, with
worst outcomes following cardiac arrests despite appropriate treatment. Recently, mortality seems to
be declining, which is mostly attributed to early diagnosis and better intensive care. Morbidity, however,
remains high, with frequent devastating sequelae such as neurologic impairment.

Management of the Case Presented

Following endotracheal intubation and 2 rounds of ACLS resuscitation, spontaneous circulation returned.
With 2 large-bore IV lines available, an epinephrine infusion at 0.3 mcg/kg/min was started. Central
venous and intra-arterial catheters were placed. Significant bleeding suggested coagulopathy following
closure of the abdominal fascia. A massive transfusion protocol was initiated. Hemostasis and surgical
site closure were achieved after transfusion of 10 units of packed red blood cells, 7 units of fresh frozen
plasma, and 1 dose pack of platelets. The initial arterial blood gas results showed metabolic and
respiratory acidosis with pH 7.11, PCO₂ 53 mm Hg, and base deficit 11. The coagulation panel revealed
elevated prothrombin and thromboplastin with low fibrinogen.

Once transferred to the ICU, the patient continued to display worsening oxygenation despite increased
positive end expiratory pressure. Cardiac arrest requiring ACLS resuscitation and cardioversion again
occurred. With diffuse intrauterine hemorrhage she was taken back to the operating room for an
emergent hysterectomy during which a third cardiac arrest took place. Resuscitation was successful
following ACLS protocol and massive transfusion of 29 units of packed red blood cells, 32 units of fresh
frozen plasma, 9 units of cryoprecipitate, and 8 dose packs of platelets. Angiographic uterine artery
embolization was considered but the patient was not hemodynamically stable to allow safe transport to
the interventional radiology suite.

Following hysterectomy, the patient was transferred back to the ICU intubated, on vasopressor and
ionotropic support with epinephrine, norepinephrine, milrinone, and furosemide. She improved, was
extubated on the third postoperative day and discharged on postoperative day 10 without any
neurologic deficits.

Conclusion

Despite the rarity of the syndrome, recognition and management of AFE are essential and require
vigilance and immediate action. Prompt response to maternal cardiopulmonary collapse and anticipation
of consumptive coagulopathy reduces the chances of maternal and fetal mortality and morbidity. The
current understanding of AFE is still limited requiring a need for further research with a higher level of
evidence.

Dr. Elizabeth A.M. Frost, who is the editor of this continuing medical education series, is clinical professor of anesthesiology
at The Mount Sinai School of Medicine in New York City. She is the author of Clinical Anesthesia in Neurosurgery
(Butterworth-Heinemann, Boston) and numerous articles. Dr. Frost is past president of the Anesthesia History Association
and former editor of the journal of the New York State Society of Anesthesiologists, Sphere. She is also editor of the book
series based on this CME program, Preanaesthetic Assessment, Volumes 1 through 3 (Birkhäuser, Boston) and 4 through 6
(McMahon Publishing, New York City).
ABBREVIATED REFERENCES

Post-test

1. The shock state seen with amniotic fluid embolism (AFE) most resembles which of the following?
   a. Cardiogenic shock
   b. Distributive shock
   c. Hypovolemic shock
   d. Obstructive shock

2. The least appropriate product in the management of coagulopathy secondary to AFE is _____.
   a. cryoprecipitate
   b. fresh frozen plasma
   c. recombinant factor VIIa
   d. tranexamic acid

3. Of the following, the most likely risk factor for AFE is _____.
   a. fetal growth restriction
   b. nulliparity
   c. oligohydramnios
   d. placenta previa

4. Which of the following signs or symptoms is commonly seen with AFE but not typically seen with either venous air embolism or pulmonary embolism?
   a. Consumptive coagulopathy
   b. Cyanosis
   c. Dyspnea
   d. Systemic hypotension

5. Which of the following best describes the current understanding of the pathophysiology of AFE?
   a. Embolism of fetal material within the maternal pulmonary circulation
   b. Extensive mast cell degranulation with massive histamine release
   c. Maternal immune response to fetal material in the circulation
   d. Widespread activation of the clotting cascade with fibrinolysis
6. The classical triad of AFE is most likely to include_____.
   a. coagulopathy, hypotension, hypoxia
   b. cyanosis, coagulopathy, hemoptysis
   c. gasping, mill-wheel murmur, hypotension
   d. hypotension, dyspnea, cyanosis

7. Which of the following is most appropriate for the management of maternal cardiac arrest during pregnancy?
   a. Avoidance of epinephrine due to high risk for fetal acidosis from uteroplacental insufficiency
   b. Maintenance of supine position to direct cardiac output toward the brain
   c. Measurement of fundal size to determine fetal viability and need for emergent cesarean delivery
   d. Removal of internal and external fetal monitors

8. AFE occurs_____.
   a. intrapartum
   b. prepartum
   c. postpartum
   d. potentially during any of the above periods

9. Which of the following would be the most appropriate for management during the first phase of AFE?
   a. Cryoprecipitate
   b. Norepinephrine
   c. Supine positioning
   d. Uterine artery embolization

10. Intraoperative transesophageal echocardiography for a patient with AFE would most likely show which of the following?
    a. Diminished left ventricular contractility with significant pulmonary hypertension
    b. Hyperdynamic function, low afterload, and inadequate preload
    c. Obliteration of left ventricle at end systole and collapse of the vena cava with respirations
    d. Right ventricular collapse with marked respiratory variation of pulse pressure