Amniotic Fluid Embolism

Richard S. Gist, MD*
Irene P. Stafford, MD†
Andrew B. Leibowitz, MD*
Yaakov Beilin, MD*‡

Amniotic fluid embolism is one of the most catastrophic complications of pregnancy. First described in 1941, the condition is exceedingly rare and the exact pathophysiology is still unknown. The etiology was thought to be embolic in nature, but more recent evidence suggests an immunologic basis. Common presenting symptoms include dyspnea, nonreassuring fetal status, hypotension, seizures, and disseminated intravascular coagulation. Early recognition of amniotic fluid embolism is critical to a successful outcome. However, despite intensive resuscitation, outcomes are frequently poor for both infant and mother. Recently, aggressive and successful management of amniotic fluid embolism with recombinant factor VIIa and a ventricular assist device, inhaled nitric oxide, cardiopulmonary bypass and intraaortic balloon pump with extracorporeal membrane oxygenation have been reported and should be considered in select cases.
(Anesth Analg 2009;108:1599–602)

Amniotic fluid embolism (AFE) is one of the most catastrophic complications of pregnancy. Passage of amniotic fluid into the maternal circulation was first reported by Meyer[1] in 1926, and the syndrome was first described by Steiner and Lushbaugh[2] in 1941. However, the condition is exceedingly rare and the exact pathophysiology is still unknown. Common presenting symptoms include dyspnea, nonreassuring fetal status, hypotension, seizures and disseminated intravascular coagulation (DIC). Early recognition of AFE is critical to a successful outcome. However, despite intensive efforts at resuscitation, outcomes are frequently poor for both infant and mother. Aggressive management with the use of recombinant factor VIIa (rfVIIa) and a ventricular assist device,[3] inhaled nitric oxide,[4] cardiopulmonary bypass,[5] and intraaortic balloon pump with extracorporeal membrane oxygenation (ECMO)[6] have recently been reported with successful outcomes.

To better understand the risk factors and clinical presentation of women with AFE, two registries were developed, one by Clark et al.[7] in the United States and one by Tuffnell[8] in the United Kingdom (UK). Entry criteria were the same in both registries and included: 1) acute hypotension or cardiac arrest, 2) acute hypoxia, 3) coagulopathy, and 4) onset during labor, cesarean delivery or dilation and evacuation or within 30 min of evacuation of the uterus. Both of these registries have limitations since they depend on self-reporting and limited numbers of patients were entered, 46 in the United States registry published in 1995 and 44 in the UK registry published in 2005.

From the *Department of Anesthesiology, Mount Sinai School of Medicine of New York University, New York City, New York; †Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Dallas, Texas; and ‡Department of Obstetrics and Gynecology, Mount Sinai School of Medicine of New York University, New York City, New York.

Accepted for publication December 6, 2008.

There was no outside support for this review.

Address correspondence and reprint requests to Yaakov Beilin, MD, Department of Anesthesiology, The Mount Sinai Medical Center, Box 1010, One Gustave L. Levy Place, New York City, NY 10029-6574. Address e-mail toyaakov.beilin@mountsinai.org.

DOI: 10.1213/ane.0b013e31819e43a4

Incidence and Outcome

The true incidence of AFE is unknown but is estimated to occur between 1 in 8000 and 1 in 80,000 deliveries,[7–9] with reported mortality rates in older reports as high as 60% even with aggressive and immediate treatment.[7] Maternal morbidity is also high and only 15% of survivors may be neurologically intact. More recent data suggest a lower mortality rate can be achieved, 27% in a population-based study performed in 1999[10] and 37% in the UK registry from 2005.[8] It is unclear if the improved mortality rate is related to better critical care management or an artifact related to different reporting techniques yielding a larger denominator. Neonatal outcome is generally poor with a mortality rate of 20%–25% and, of the survivors, only 50% may be neurologically intact.[7,8] There are no proven risk factors to the development of AFE and its onset cannot be predicted.

Pathophysiology

The pathophysiology of AFE is poorly understood as human study is obviously limited. Experimental animal studies into the pathogenesis and treatment of AFE have produced mixed results. Some models have failed to reproduce the syndrome even with direct intravascular injection of amniotic fluid,[11,12] and some have only been able to do so when the injected amniotic fluid was stained with meconium.[13,14]

AFE, as a clinical syndrome, was first characterized by the presence of amniotic fluid debris in the maternal pulmonary circulation, and the amniotic fluid was thought to cause an embolic phenomenon.[2,15] Steiner and Lushbaugh,[2] in their original description of AFE, reported the presence of mucin, amorphous eosinophilic material and squamous cells in women with AFE, consistent with the presence of amniotic fluid. They hypothesized that amniotic fluid was forced into the maternal circulation during contractions leading to the embolic event. The theory was supported by analyzing the women in their series who developed AFE. Most cases of AFE occurred in multiparous women who delivered vaginally during a tumultuous or hyperstimulated labor. However, knowledge of uterine physiology and results of other studies have called this theory into question. During contractions, especially forceful ones, when uterine pressure increases above maternal venous pressure, maternal-placental exchange decreases or ceases, but certainly does not increase. Therefore, Clark et al.[7] speculated that the least likely time for transfer of amniotic fluid is during tumultuous labor or during uterine tachysystole. Furthermore, Lee et al.[16] demonstrated that fetal squamous cells can be found in the pulmonary circulation of women without clinical evidence of AFE, and other investigators could not reproduce the syndrome in two separate animal models, mini-pigs and monkeys, by injecting amniotic fluid directly into their circulation.[11,12] Finally, Clark et al.[7] found that 19% of women in their registry first manifested symptoms during cesarean delivery when there is no tumultuous labor.

Clark et al.[7] recognized that the clinical course and hemodynamic changes of AFE were similar to patients with anaphylactic shock and proposed that AFE was more of an immunologic than embolic phenomena. Amniotic fluid contains many vasoactive and procoagulant substances, such as platelet activating factor, cytokines, bradykinin, thromboxane, leukotrienes and arachidonic acid, and entrance of even minute amounts of these substances into the maternal circulation could cause the syndrome.[17] This would explain why fetal cells were not always found in women who suffered AFE. They further recommended changing the name of the syndrome from AFE "to the anaphylactoid syndrome of pregnancy." In support of this "immunologic" theory is the finding that AFE seems to be more common in women carrying male fetuses, and these women are also at increased risk for Rh isoimmunization, another immunologic-based condition.[18] Some have suggested that plasma tryptase levels, a mast cell enzyme, may be helpful in the diagnosis of AFE.[19,20] Further support for an immune basis is that complement activation, another component of the immune response, may play a role in the pathogenesis of AFE. Specifically, C3 and C4 levels are markedly decreased in women with AFE.[21]

Table 1. Signs and Symptoms of Amniotic Fluid Embolism[7]

Signs or symptoms	Frequency
Hypotension	100%
Fetal distress	100%
Pulmonary edema or ARDS	93%
Cardiopulmonary arrest	87%
Cyanosis	83%
Coagulopathy	83%
Dyspnea	49%
Seizure	48%
Uterine atony	23%
Bronchospasm	15%
Transient hypertension	11%
Cough	7%
Headache	7%
Chest pain	2%

ARDS = adult respiratory distress syndrome.

Adapted from Clark SL, Hankins GD, Dudley DA, Dildy GA, Porter TF. Amniotic fluid embolism: analysis of the national registry. Am J Obstet Gynecol 1995;172:1158–67.

Clinical Presentation

AFE usually occurs intrapartum or in the immediate postpartum period. The symptoms are often sudden and protean. Clark et al.[7] found the most common presenting signs and symptoms were hypotension and signs of nonreassuring fetal status (100%), pulmonary edema or respiratory symptoms (93%), cardiac arrest (87%), cyanosis (83%), and coagulopathy (83%) (Table 1). Tuffnell[8] found that the most common presentation was a sudden change in either the maternal or fetal condition, but he did not specify the exact symptom.

Clark et al.[22] proposed a biphasic model of the hemodynamic consequences of AFE. The initial response is acute pulmonary hypertension and vasospasm leading to right ventricular failure, hypoxia, and cardiac arrest. If one survives this initial insult, then the pulmonary hypertension is generally not sustained and may be replaced with left ventricular failure and pulmonary edema. Increased pulmonary artery pressure has not been consistently reported probably because this finding may be short-lived.[23] When cardiac pressures are measured early in the process, pulmonary and right ventricular pressures have been found to be elevated.[5] Hankins et al.[14] demonstrated in a goat model that injecting 2.5 mL/kg of homologous amniotic fluid IV increased right heart and systemic vascular resistance. They also demonstrated that the presence of meconium was needed to produce left heart failure and hypoxia. These findings were confirmed by Petroianu et al.[13] and might explain a role for meconium as the putative cause for mast cell degranulation and inflammatory response. This would explain why in Clark et al.'s[7] series the worst maternal outcomes were in those with meconium-stained amniotic fluid. It is also possible that meconium does not cause the syndrome, but is simply present because it is a nonspecific marker of either maternal or fetal stress.

Coagulation disorders are a prominent feature of the amniotic fluid syndrome. DIC is present in more

Table 2. Differential Diagnosis of Amniotic Fluid Embolism

Obstetric causes
Acute hemorrhage
Placental abruption
Uterine rupture
Uterine atony
Eclampsia
Peripartum cardiomyopathy
Anesthetic causes
High spinal anesthesia
Aspiration
Local anesthetic toxicity
Nonobstetric causes
Pulmonary embolism
Air embolism
Anaphylaxis
Sepsis/septic shock

than 83% of patients with AFE. The onset can occur as quickly as 10–30 min from onset of symptoms or may be delayed by as many as 4 h.[24] Amniotic fluid contains tissue factor that acts as a procoagulant and may account for the coagulopathy.[25] Tissue factor binds with Factor VII and activates the extrinsic coagulation pathway. Alternatively, the coagulopathy may be related to fibrinolysis due to increased levels of plasminogen activation inhibitor 1 in amniotic fluid.[26]

The differential diagnoses of AFE include obstetric, nonobstetric and anesthetic etiologies (Table 2).[27] Although each of the disorders listed has symptoms consistent with AFE, sudden onset of dyspnea in the face of cardiovascular collapse and DIC should lead the clinician to suspect AFE and initiate treatment. Since squamous cells have been found in the circulation of patients with and without the AFE syndrome, the diagnosis is one of exclusion based on presenting symptoms and clinical course, not based on laboratory or pathology findings.

Management

Early recognition of AFE is critical to a successful outcome. Management is primarily resuscitative and should be directed toward controlling the airway, maintaining vital signs and correcting coagulopathy. AFE is always associated with hypoxia. Therefore, control of the airway with tracheal intubation and administration of 100% O_2 with positive pressure ventilation should be performed as soon as possible. Venous access with large bore IV catheters should be accomplished without delay. Arterial catheterization should also be considered for accurate arterial blood pressure monitoring and frequent blood sampling.

If the presentation is before delivery, providers should consider expeditious delivery of the fetus. Early delivery of the fetus in the resuscitation process may increase the chances of perinatal survival without neurologic sequelae.[7] Also, delivery of the fetus aids in the maternal resuscitation efforts by improving venous return to the right heart.

Echocardiography is a sensitive tool to evaluate cardiac function and intravascular volume status. Both transthoracic and transesophageal modalities have been used by some clinicians in the diagnosis and management of AFE.[5,28] Verroust et al.[28] documented the presence of amniotic fluid in the right heart by echocardiography, which had a different appearance on echocardiography than blood. Care must be taken when inserting the transesophageal echocardiography probe in the coagulopathic patient.

Vasopressors and inotropic support are generally needed to varying degrees in AFE. Central venous access should be established for vasopressor infusion and monitoring. Choice of vasopressor drug depends on the clinical scenario. Phenylephrine, a pure α 1 agonist, is often an excellent choice early in the treatment of AFE because at that time point systemic vasodilation is the most prominent circulatory abnormality. Later in the course of the process, inotropic support is commonly needed, and drugs, such as norepinephrine, epinephrine, and dopamine, should be considered. Vasopressin may be used as primary therapy or as an adjunct to other inotropic therapies and has the benefit of sparing the pulmonary vasculature from vasoconstriction, especially at low doses.[29] In the face of right heart failure, milrinone or other phosphodiesterase inhibitors should be considered.

Blood and blood products, including fresh frozen plasma, platelets and cryoprecipitate, must be available and administered early in the resuscitation phase of AFE.[30] The successful use of rfVIIa has been reported,[3,31,32] although it has also been associated with massive intravascular thrombosis.[33] Aprotinin has also been effective in reducing hemorrhage with AFE.[34] However, after the results of the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) study of patients undergoing coronary artery bypass surgery that demonstrated an increased mortality with aprotinin as compared with lysine analogues, the drug is no longer available.[35] Other antifibrinolytic drugs, such as aminocaproic acid and tranexamic acid, have been described in the management of obstetric hemorrhage[36] and menorrhagia[37] and might also be considered during AFE. However, the authors are unaware of published reports in which these drugs were used specifically for treatment of the AFE-associated coagulopathy.

Other novel approaches for the treatment of AFE have been successfully used. Inhaled nitric oxide has been used in the treatment of right-sided heart failure and pulmonary hypertension.[4] The use of cardiopulmonary bypass[5] and placement of an intraaortic balloon pump counter pulsation with ECMO have also been described in the management of severe hypoxia and left heart failure associated with AFE.[6] We recently reported the successful management of AFE with a right ventricular assist device and rfVIIa.[3]

CONCLUSION

AFE is a rare but often fatal complication of pregnancy and its onset can neither be predicted nor prevented. Early recognition of AFE with prompt intervention is paramount to a successful outcome. Management is resuscitative, geared toward maintaining vital signs and treating hemodynamic and coagulopathic derangements as they occur. A team approach among obstetrician, anesthesiologist and intensivist is necessary for a successful outcome. Despite early intervention, maternal and fetal mortality remain high. Aggressive management with novel products and devices, such as rfVIIa, cardiopulmonary bypass, ventricular assist device and ECMO, has been reported and should be considered.

REFERENCES

1. Meyer JR. Embolia pulmonary amino caseosa. Bras Med 1926;2:301–3
2. Steiner PE, Lushbaugh C. Maternal pulmonary embolism by amniotic fluid as a cause of obstetric shock and unexplained death in obstetrics. JAMA 1941;117:1245–54
3. Nagarsheth NP, Pinney S, Bassily-Marcus A, Anyanwu A, Friedman L, Beilin Y. Successful placement of a right ventricular assist device for treatment of a presumed amniotic fluid embolism. Anesth Analg 2008;107:962–4
4. McDonnell NJ, Chan BO, Frengley RW. Rapid reversal of critical haemodynamic compromise with nitric oxide in a patient with amniotic fluid embolism. Int J Obstet Anesth 2007;16:269–73
5. Stanten RD, Iverson LI, Daugherty TM, Lovett SM, Terry C, Blumenstrock E. Amniotic fluid embolism causing catastrophic pulmonary vasoconstriction: diagnosis by trans-esophageal echocardiogram and treatment by cardiopulmonary bypass. Obstet Gynecol 2003;102:496–8
6. Hsieh YY, Chang CC, Li PC, Tsai HD, Tsai CH. Successful application of extracorporeal membrane oxygenation and intra-aortic counterpulsation as lifesaving therapy for a patient with amniotic fluid embolism. Am J Obstet Gynecol 2000;183:496–7
7. Clark SL, Hankins GD, Dudley DA, Dildy GA, Porter TF. Amniotic fluid embolism: analysis of the national registry. Am J Obstet Gynecol 1995;172:1158–67
8. Tuffnell DJ. United Kingdom amniotic fluid embolism register. BJOG 2005;112:1625–9
9. Morgan M. Amniotic fluid embolism. Anesthesia 1979;34:20–32
10. Gilbert WM, Danielsen B. Amniotic fluid embolism: decreased mortality in a population-based study. Obstet Gynecol 1999;93:973–7
11. Spence MR, Mason KG. Experimental amniotic fluid embolism in rabbits. Am J Obstet Gynecol 1974;119:1073–8
12. Stolte L, van Kessel H, Seelen J, Eskes T, Wagatsuma T. Failure to produce the syndrome of amniotic fluid embolism by infusion of amniotic fluid and meconium into monkeys. Am J Obstet Gynecol 1967;98:694–7
13. Petroianu GA, Altmannsberger SH, Maleck WH, Assmus HP, Friedberg C, Bergler WF, Rüfer R. Meconium and amniotic fluid embolism: effects on coagulation in pregnant mini-pigs. Crit Care Med 1999;27:348–55
14. Hankins GD, Snyder RR, Clark SL, Schwartz L, Patterson WR, Butzin CA. Acute hemodynamic and respiratory effects of amniotic fluid embolism in the pregnant goat model. Am J Obstet Gynecol 1993;168:1113–29
15. Clark SL, Pavlova Z, Greenspoon J, Horenstein J, Phelan JP. Squamous cells in the maternal pulmonary circulation. Am J Obst Gynecol 1986;154:104–6
16. Lee W, Ginsburg KA, Cotton DB, Kaufman RH. Squamous and throphoblastic cells in the maternal pulmonary circulation indentified by invasive hemodynamic monitoring during the peripartum period. Am J Obstet Gynecol 1986;155:999–1001
17. Walsh SW, Wang Y. Secretion of lipid peroxides by the human placenta. Am J Obstet Gynecol 1993;169:1462–66
18. Scott JR, Beer AE, Guy LR, Liesch M, Elbert G. Pathogenesis of Rh immunization in primigravidas. Fetomaternal versus maternofetal bleeding. Obstet Gynecol 1977;49:9–14
19. Fineschi V, Gambassi R, Gherardi M, Turillazzi E. The diagnosis of amniotic fluid embolism: an immunohistochemical study for the quantification of pulmonary mast cell tryptase. Int J Legal Med 1998;111:238–43
20. Nishio H, Matsui K, Miyazaki T, Tamura A, Iwata M, Suzuki K. A fatal case of amniotic fluid embolism with elevation of serum mast cell tryptase. Forensic Sci Int 2002;126:53–6
21. Benson MD. A hypothesis regarding complement activation and amniotic fluid embolism. Med Hypotheses 2007;68:1019–25
22. Clark SL. New concepts of amniotic fluid embolism: a review. Obstet Gynecol Surv 1990;45:360–8
23. Clark SL, Montz FJ, Phelan JP. Hemodynamic alterations associated with amniotic fluid embolism: a reappraisal. Am J Obstet Gynecol 1985;151:617–21
24. Malhotra P, Agarwal R, Awasthi A, DAS A, Behera D. Delayed presentation of amniotic fluid embolism: lessons from a case diagnosed at autopsy. Respirology 2007;12:148–50
25. Lockwood CJ, Bach R, Guha A, Zhou XD, Miller WA, Nemerson Y. Amniotic fluid contains tissue factor, a potent initiator of coagulation. Am J Obstet Gynecol 1991;165:1335–41
26. Estelles A, Gilabert J, Andres C, Espana F, Aznar J. Plasminogen activator inhibitor type 1 and type 2 in amniotic fluid during pregnancy. Thromb Haemost 1990;64:281–5
27. Karetsky M, Ramirez M. Acute respiratory failure in pregnancy: an analysis of 19 cases. Medicine (Baltimore) 1998;77:41–9
28. Verroust N, Zegdi R, Ciobotaru V, Tsatsaris V, Goffinet F, Fabiani JN, Mignon A. Ventricular fibrillation during termination of pregnancy. Lancet 2007;369:1900
29. Malay MB, Ashton JL, Dahl K, Savage EB, Burchell SA, Ashton RC Jr, Sciacca RR, Oliver JA, Landry DW. Heterogeneity of the vasoconstrictor effect of vasopressin in septic shock. Crit Care Med 2004;32:1327–31
30. Burtelow M, Riley E, Druzin M, Fontaine M, Viele M, Goodnough LT. How we treat: management of life-threatening primary postpartum hemorrhage with a standardized massive transfusion protocol. Transfusion 2007;47:1564–72
31. Franchini M, Franchi M, Bergamini V, Salvagno GL, Montagnana M, Lippi G. A critical review on the use of recombinant factor VIIa in life-threatening obstetric postpartum hemorrhage. Semin Thromb Hemost 2008;34:104–12
32. Prosper SC, Goudge CS, Lupo VR. Recombinant factor VIIa to successfully manage disseminated intravascular coagulation from amniotic fluid embolism. Obstet Gynecol 2007;109:524–5
33. Thomas GO, Dutton RP, Hemlock B, Stein DM, Hyder M, Shere-Wolfe R, Hess JR, Scalea TM. Thromboembolic complications associated with factor VIIa administration. J Trauma 2007:62:564–9
34. Stroup J, Haraway D, Beal JM. Aprotinin in the management of coagulopathy associated with amniotic fluid embolism. Pharmacotherapy 2006;26:689–93
35. Fergusson DA, Hébert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, Teoh K, Duke PC, Arellano R, Blajchman MA, Bussières JS, Côté D, Karski J, Martineau R, Robblee JA, Rodger M, Wells G, Clinch J, Pretorius R; BART Investigators. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med 2008;358:2319–31
36. Peng TC, Kickler TS, Bell WR, Haller E. Obstetric complications in a patient with Bernard-Soulier syndrome. Am J Obstet Gynecol 1991;165:425–6
37. Kriplani A, Kulshrestha V, Agarwal N, Diwakar S. Role of tranexamic acid in management of dysfunctional uterine bleeding in comparison with medroxyprogesterone acetate. J Obstet Gynaecol 2006;26:673–8