

# Amniotic Fluid Embolism with Late Respiratory Failure

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**A** mniotic fluid embolism (AFE) was first described by Meyer in 1926.<sup>1</sup> A rare clinical entity, AFE is an obstetric catastrophe, often leading to maternal death. It has been called the most unpredictable and, for the most part, unpreventable cause of maternal death, as well as “the most dangerous and untreatable condition in obstetrics.”<sup>2</sup> The disorder is uncommon, and the mortality rate is high.

Few physicians have experience in treating patients with an AFE, and there is no specific recommended therapy other than supportive care. The diagnosis of AFE is usually made on clinical grounds and is often certain, even without autopsy confirmation. The diagnosis should be considered in patients with complicated deliveries who develop mental confusion, fever, hypotension, profound hypoxia, bilateral alveolar infiltrates, an increased leukocyte count, or coagulopathy.

Since 1926, more than 300 case reports involving AFE have appeared in the literature. This report discusses the case of a woman who developed an AFE 36 hours after cesarean delivery and survived.

## CASE PRESENTATION

A 21-year-old woman (gravida 1, para 0) at 37 weeks' gestation was admitted to the hospital because of complete breech presentation. External cephalic version was attempted, without success. The patient subsequently developed abdominal pain, and fetal distress was detected. Because of suspected placental abruption, emergency cesarean delivery was performed, with the patient receiving epidural anesthesia; an epidural catheter was already in place from the attempted external cephalic version.

Thirty-six hours postpartum, the patient became febrile, tachycardic, tachypneic, and hypotensive. Temperature was 38.7°C (101.7°F), blood pressure was 86/51 mm Hg, heart rate was 160 bpm, and respirato-

ry rate was 35 breaths/min. Leukocyte count increased to  $22 \times 10^3/\text{mm}^3$  from a baseline of  $14 \times 10^3/\text{mm}^3$ , and platelet count was  $82 \times 10^3/\text{mm}^3$ . Prothrombin time and partial thromboplastin time were within normal limits (11.6 seconds and 32.9 seconds, respectively). Arterial blood gas analysis (**Table 1**) showed hypoxia. A chest radiograph revealed multiple patchy and nodular infiltrates, with a small left pleural effusion. Results of testing for disseminated intravascular coagulation (DIC) were negative.

The patient was transferred to the medical intensive care unit with a differential diagnosis of AFE, aspiration pneumonia, septic embolism, or septic shock. She received 100% oxygen via a nonrebreather mask and 1 L of saline to stabilize her blood pressure, which subsequently improved to 110/80 mm Hg. Furosemide was administered because of decreased urine output and radiographic findings of pulmonary vascular congestion; urine output subsequently improved. Additionally, ticarcillin/clavulanate and gentamicin were administered intravenously because of possible aspiration pneumonia.

Interpretation of a ventilation-perfusion scan obtained before the patient was transferred to the intensive care unit indicated an indeterminate probability of pulmonary embolism. Serial Doppler ultrasonography studies of the lower extremities showed no abnormalities. Heparinization was not indicated in this patient, given the indeterminate probability of pulmonary embolism suggested by the ventilation-perfusion scan and her low

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clinical probability of having a pulmonary embolism, according to criteria suggested by the Prospective Investigation of Pulmonary Embolism Diagnosis Investigators.<sup>3</sup> Echocardiography showed severe pulmonary hypertension and right ventricular dilatation, with a displaced interventricular septum pressing on the left ventricle. However, no vegetations were seen on echocardiography, and blood cultures were sterile. Placement of a Swan-Ganz catheter was considered but deemed unnecessary, in view of the improving clinical status of the patient.

A repeat radiograph obtained 24 hours after the first one revealed marked resolution of the patchy nodular infiltrates. Follow-up arterial blood gas analysis on hospital day 3 showed improvement of the hypoxia (pH, 7.48; PCO<sub>2</sub>, 28.5 mm Hg; PO<sub>2</sub>, 71.2 mm Hg; oxygen saturation [while breathing 2 L of oxygen via a nasal cannula], 95.6%); leukocyte count also decreased to 10 × 10<sup>3</sup>/mm<sup>3</sup>. The patient's continued clinical improvement was monitored, and she was discharged 13 days after hospital admission.

## DISCUSSION

### Epidemiology and Etiology

The reported incidence of AFE ranges from 1 in 8000 births<sup>4</sup> to 1 in 80,000 births.<sup>5,6</sup> Peterson and Taylor<sup>7</sup> estimate that 10% of maternal deaths in the United States result from AFE.

The mechanism by which amniotic fluid suddenly enters the maternal circulation is unknown but most likely involves a tear or defect in the membranes adjacent to open maternal vessels. A possible entry site that has been proposed is the placental implantation site<sup>8</sup>; this theory necessitates the presence of tears in the membranes near the placental site, and such disruptions have indeed been demonstrated in some cases. Because endocervical veins are lacerated during labor, some authors contend that these lacerated veins or similar small, incomplete tears in the lower segment are the portals of entry of amniotic fluid.<sup>9</sup> Still other authors<sup>8</sup> link AFE to traumatic disruptions of the uterus, which can be associated with rupture, cesarean section, placenta accreta, excessive fetal size, difficult labor, intrauterine fetal death, high parity, and advanced maternal age. Although nearly all these proposed etiologic factors involve events occurring during labor or delivery, approximately 10% of cases of AFE occur prior to labor, and a very rare case has been reported in a woman at only 20 weeks' gestation.<sup>10</sup>

### Pathophysiology

The exact underlying pathophysiology of AFE remains controversial. Two separate life-threatening

**Table 1.** Results of Initial Arterial Blood Gas Analysis in the Case Patient

	Breathing Room Air	Breathing 100% Oxygen*
pH	7.49	7.51
PCO <sub>2</sub>	32 mm Hg	29.4 mm Hg
PO <sub>2</sub>	41 mm Hg	74 mm Hg
Oxygen saturation	80%	96%

\*Via a nonrebreather mask.

processes seem to occur either simultaneously or in sequence, namely, cardiorespiratory collapse and coagulation failure.

The primary cardiovascular event that follows development of an AFE is pulmonary hypertension—either caused by mechanical obstruction<sup>11</sup> or mediated by prostaglandins<sup>5,12,13</sup>—leading to decreased left atrial pressure, decreased cardiac output, and systemic hypotension. Acute cor pulmonale next develops, and ventilation-perfusion inequalities ensue, causing hypoxia, cyanosis, tachypnea, and sometimes seizures. Vagus-mediated bradycardia and constriction of coronary arteries can occur simultaneously.

Leukotrienes and other arachidonic acid metabolites, thought to be the mediators of immediate hypersensitivity reactions, are secreted by the human placenta; some authors have suggested that they also play a mediating role in AFE.<sup>4</sup> Platelet-activating factor, a bioactive lipid, can reproduce many of the pathophysiologic features of acute respiratory distress syndrome in animal models when given exogenously. Notably, there is a high concentration of platelet-activating factor found in amniotic fluid; its action on the lungs has been well documented<sup>14</sup> and includes bronchoconstriction, increased vascular permeability, edema formation, neutrophil recruitment, platelet aggregation, and stimulation and release of leukotrienes C<sub>4</sub> and D<sub>4</sub> and thromboxane A<sub>2</sub>. Arachidonic acid mobilization from the amniotic tissue also chemically characterizes the onset of labor. Release of arachidonic acid from its phosphoesterified form is regulated by a Ca<sup>2+</sup> homeostatic mechanism, which in turn is influenced by platelet-activating factor.<sup>15</sup>

The second major consequence of AFE is failure of coagulation. As many as 50% of patients who survive the first hour after onset of an AFE develop bleeding secondary to DIC, and most of these patients have laboratory evidence of coagulopathy. Although the case patient did not have a coagulopathy, her decreased platelet count might have been a forme fruste of DIC.

**Table 2.** Differential Diagnosis of an Amniotic Fluid Embolism

**Cardiovascular**

- Acute left ventricular failure of any cause
- Air embolism
- Cerebrovascular accident
- Myocardial infarction
- Thrombotic pulmonary embolism

**Obstetrical**

- Abruptio placentae
- Disseminated intravascular coagulation
- Eclampsia
- Hemorrhagic shock
- Inverted uterus
- Ruptured uterus

**Respiratory**

- Aspiration of gastric contents
- Bilateral pneumothorax

**Other**

- Reaction to local anesthetic
- Sepsis

Autopsy findings from patients who have died of AFE consistently include fetal squamae, lanugo hairs, mucin, and occasionally meconium in the small pulmonary vessels,<sup>4</sup> especially when these elements are searched for with special stains.<sup>16,17</sup> However, the detection of fetal squamae in central venous or pulmonary blood can no longer be considered pathognomonic, because small amounts can enter the maternal circulation in the absence of AFE.<sup>18,19</sup> Finally, it has recently been proposed that the associated pulmonary hypertension might be the result of amniotic fluid prostaglandins.<sup>5,12,13</sup>

**Clinical Manifestations**

The onset of symptoms in AFE is sudden and catastrophic. The patient is usually in labor or has recently delivered. There is no recognizable prodrome. In more than half of affected patients, the initial indication of AFE is respiratory distress, manifested as dyspnea, tachypnea, and cyanosis. Chest pain is rare. Another 25% of patients have shock,<sup>5,20</sup> which is out of proportion to the amount of blood lost, as the presenting sign. For another 10% of patients, seizure is the presenting sign.<sup>5,20</sup> Regardless of the presenting signs or symptoms, however, all affected patients experience

cardiovascular collapse marked by dyspnea, cyanosis, and hypotension within minutes of onset. There may be supraventricular or ventricular tachycardia, bradycardia, or asystole. Pulmonary edema develops in about 25% of cases.<sup>5,20</sup> Because DIC is often associated with this type of embolism, AFE should be seriously considered in the differential diagnosis of all pregnant patients with any evidence of coagulopathy.

The mortality rate in patients with AFE is exceedingly high; 25% of patients die within 1 hour of the onset of symptoms.<sup>5,20</sup> Overall, the reported mortality is 86%; the interval from onset of symptoms to death varies between 10 minutes and 32 hours.<sup>5,20</sup> However, it now seems increasingly possible that Steiner and Lushbaugh<sup>4</sup> were indeed correct in concluding that undiagnosed, nonfatal cases of AFE outnumber the fatal cases, because cardiopulmonary collapse is not an invariable accompanying finding. Signs and symptoms might be delayed for many hours postpartum, and many patients might survive, even if undiagnosed.<sup>4</sup>

**Diagnosis**

In the case patient, the acute onset of symptoms (ie, profound hypoxia, respiratory alkalosis, tachypnea, tachycardia) was highly suggestive of an embolic phenomenon. The rapid resolution of symptoms, the improvement in radiographic findings within 24 to 48 hours, and the lack of an identifiable source of infection or isolation of an organism made septic shock an unlikely diagnosis.

The provisional clinical diagnosis of AFE can usually be made with confidence, considering the timing, suddenness, and severity of the major signs and symptoms and the absence of predisposing factors for other conditions in the differential diagnosis (Table 2).<sup>21</sup> However, diagnostic tests involving detection of fetal debris in the maternal circulation is not a feasible approach, given the speedy destructive nature of this entity.

**SUMMARY**

AFE is a rare condition associated with a mortality rate of 80% to 90%. The condition mostly occurs during or immediately after labor, although it has been reported to occur as early as the 20th week of gestation<sup>9</sup> and as late as 48 hours postpartum. It usually occurs in multigravid women and patients who have had a difficult delivery. Cesarean section, placenta accreta, excessive fetal size, intrauterine death, and advanced maternal age increase the risk for AFE. Affected patients typically have mental confusion, agitation, seizures, respiratory distress, hypotension, coagulopathy, and bilateral alveolar infiltrates. The diagnosis is made clinically and can be

confirmed by retrieval of amniotic debris from the pulmonary artery via a Swan-Ganz catheter. Because of the catastrophic nature of the disease, most patients do not survive long enough for the diagnosis to be made. Postmortem diagnosis is made by detection of fetal squamae, lanugo hair, and mucin in the pulmonary vessels of patients dying of AFE.

Treatment is supportive, including cardiorespiratory support, heparinization, and administration of diuretics. Swan-Ganz catheterization usually is needed to manage shock in affected, critically ill patients. Heparinization is indicated if a pulmonary embolism is strongly suspected; the case patient was not heparinized because of her low clinical probability of having a pulmonary embolism and the indeterminate probability suggested by ventilation-perfusion scanning. Finally, there is no evidence of the therapeutic efficacy of administering digitalis, antihistamines, or spasmolytics. **HP**

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