Proposed diagnostic criteria for the case definition of amniotic fluid embolism in research studies

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Amniotic fluid embolism is a leading cause of maternal mortality in developed countries. Our understanding of risk factors, diagnosis, treatment, and prognosis is hampered by a lack of uniform clinical case definition; neither histologic nor laboratory findings have been identified unique to this condition. Amniotic fluid embolism is often overdiagnosed in critically ill peripartum women, particularly when an element of coagulopathy is involved. Previously proposed case definitions for amniotic fluid embolism are nonspecific, and when viewed through the eyes of individuals with experience in critical care obstetrics, would include women with a number of medical conditions much more common than amniotic fluid embolism. We convened a working group under the auspices of a committee of the Society for Maternal-Fetal Medicine and the Amniotic Fluid Embolism Foundation whose task was to develop uniform diagnostic criteria for the *research* reporting of amniotic fluid embolism. These criteria rely on the presence of the classic triad of hemodynamic and respiratory compromise accompanied by strictly defined disseminated intravascular coagulopathy. It is anticipated that limiting research reports involving amniotic fluid embolism to women who meet these criteria will enhance the validity of published data and assist in the identification of risk factors, effective treatments, and possibly useful biomarkers for this condition. A registry has been established in conjunction with the Perinatal Research Branch of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development to collect both clinical information and laboratory specimens of women with suspected amniotic fluid embolism in the hopes of identifying unique biomarkers of this condition.

Key words: amniotic fluid embolism, critical care

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Introduction

> *"Let us be careful not to make it (the diagnosis of amniotic fluid embolism) a waste-basket for all cases of unexplained death in labor."*
>
> N. J. Eastman,[1] 1948

Amniotic fluid embolism (AFE) is an uncommon, but often fatal condition unique to obstetrics.[2] Current concepts regarding pathophysiology and management of this condition have been summarized elsewhere.[2,3] Scientific understanding of this condition, its pathophysiology, and its management have all been historically hampered by a lack of uniform diagnostic criteria. Many reports prior to the mid-1980s were based upon the detection of squamous cells and occasionally other debris of presumed fetal or placental origin in the maternal pulmonary circulation at autopsy or from a distal port aspirate of a pulmonary artery catheter.[2,3] However, subsequent studies have documented that these findings are not specific to AFE.[4-8] In addition, such reports, by definition, only included women who died and underwent autopsy, or were critically ill and required invasive hemodynamic monitoring, thus potentially eliminating less severely affected women and skewing both estimates of frequency and mortality. Thus, reports based on histologic findings are biased.[2,4-7] In recent years, investigators have made attempts to identify serum markers for the diagnosis of AFE.[2] Many of these studies are difficult to interpret for 3 reasons. First, the detection of acute-phase reactants in critically ill women believed to have had AFE limited value when the control group is composed of healthy pregnant women, rather than critically ill pregnant women with conditions other than AFE. Second, many of these reports contain insufficient information regarding the clinical condition of study patients to convince the reader versed in critical care obstetrics that the patient actually had AFE. Finally, many studies report a numerator that suggests a disease incidence orders of magnitude greater than that generally accepted for AFE. Case series involving a critical review of individual medical records generally yield lower frequencies and higher mortality rates than those based on administrative data alone; such series suggest that 30-50% of cases coded as AFE have other far more likely diagnoses when examined carefully by maternal-fetal medicine and allied specialists with expertise in critical care.[2,8,9]

These published observations are in line with the clinical experience of the authors of this report, each of whom

TABLE 1
International criteria for diagnosis of amniotic fluid embolism

United Kingdom:
Clinical diagnosis of AFE (acute hypotension or cardiac arrest, acute hypoxia, or coagulopathy in absence of any other potential explanation for signs and symptoms observed) OR pathologic diagnosis of fetal squames or hair in lungs.[14]

Australia:
Clinical diagnosis of AFE (acute hypotension or cardiac arrest, acute hypoxia, or coagulopathy in absence of any other potential explanation for signs and symptoms observed) OR pathologic/postmortem diagnosis (presence of fetal squames/debris in pulmonary circulation).[15]

Japan:
1. Symptoms appeared during pregnancy or within 12 h of delivery;
2. Intensive medical intervention was conducted to treat ≥1 of following symptoms/diseases: (a) cardiac arrest, (b) severe bleeding of unknown origin within 2 h of delivery (≥1500 mL), (c) DIC, or (d) respiratory failure; and
3. If findings or symptoms obtained could not be explained by other diseases. Consumptive coagulopathy/DIC due to evident etiologies such as abnormal placentation, trauma during labor, and severe preeclampsia/eclampsia should be excluded.

Uterine AFE was considered to have occurred when fetal debris and amniotic fluid components were found in uterus in pathological examination of cases of severe uterine hemorrhage after placental removal (eg, atonic bleeding) in absence of other obstetric hemorrhagic complications such as abnormal placentation, trauma during labor and delivery, and severe preeclampsia/eclampsia.[16]

AFE, amniotic fluid embolism; *DIC*, disseminated intravascular coagulation.

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has an extensive background in reviewing the medical records of women with presumptive AFE for individual, local, regional, and national reviews of maternal mortality. This confusion is also reflected in widely varying criteria for the diagnosis of AFE used in several recent international registry reports[8,10-17] (Table 1). These definitions are nonspecific, and when viewed through the eyes of individuals with experience in critical care obstetrics, would include a substantial number of women with medical conditions much more common than AFE. Thus, reports based on these criteria are likely to contain both patients with conditions other than AFE, and some patients who actually have the condition.

These considerations lead to a troubling conclusion: much of the available literature on AFE includes a heterogeneous population of critically ill pregnant women, only some of whom actually have the condition of interest. When the numerator is relatively small, inclusion of even a few cases with the incorrect diagnosis can invalidate even the most carefully collected data. The problem is further compounded by the belief of most investigators that there exist occasional atypical forme fruste cases of AFE in which the overlap between this syndrome and other types of critical illness is even less well demarcated. We believe such observations largely explain the current inability to consistently identify any risk factors for AFE, evaluate the efficacy of therapeutic maneuvers, or identify hypotheses of pathophysiology beyond the involvement of abnormal activation of proinflammatory mediator systems similar in nature, if not in degree, to other conditions involving the systemic inflammatory response syndrome (SIRS).[2,8,18] Since AFE remains one of the most common causes of maternal death in high-resource countries, these problems are more than academic.[10-21]

In an effort to remedy this situation, we convened a working group under the auspices of the "M in Maternal-Fetal Medicine Committee" of the Society for Maternal-Fetal Medicine and the Amniotic Fluid Embolism Foundation whose task was to develop uniform diagnostic criteria for the *research* reporting of AFE. Members were chosen for their recognized clinical and research expertise in critical care obstetrics, AFE, and related fields, and included representatives from maternal-fetal medicine, pulmonary/critical care medicine, hematology, and obstetric anesthesiology. The goals of this group may be summarized as follows:

1. Identify specific clinical criteria that, if present, could be explained by no known pathophysiologic process other than AFE.
2. Accept the likelihood that in doing so, some atypical cases of actual AFE will be excluded. An analysis of data

TABLE 2
Uniform diagnostic criteria for research reporting of amniotic fluid embolism

1. Sudden onset of cardiorespiratory arrest, or both hypotension (systolic blood pressure <90 mm Hg) and respiratory compromise (dyspnea, cyanosis, or peripheral capillary oxygen saturation [S_pO_2] <90%).
2. Documentation of overt DIC following appearance of these initial signs or symptoms, using scoring system of Scientific and Standardization Committee on DIC of the ISTH, modified for pregnancy.[19] Coagulopathy must be detected prior to loss of sufficient blood to itself account for dilutional or shock-related consumptive coagulopathy.
3. Clinical onset during labor or within 30 min of delivery of placenta.
4. No fever (≥38.0°C) during labor.

DIC, disseminated intravascular coagulation; *ISTH*, International Society on Thrombosis and Hemostasis.

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TABLE 3
Modified International Society on Thrombosis and Hemostasis scoring system for overt disseminated intravascular coagulation in pregnancy

- Platelet count: >100,000/mL = 0, <100,000/mL = 1, <50,000/mL = 2
- Prolonged prothrombin time or international normalized ratio: <25% increase = 0, 25-50% increase = 1, >50% increase = 2
- Fibrinogen level: >200 mg/L = 0, <200 mg/L = 1

Score ≥3 is compatible with overt disseminated intravascular coagulation in pregnancy

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from an ongoing registry suggests that 8-10% of actual AFE cases will be excluded as atypical utilizing these criteria.[9]

3. Recommend that, in any *research* setting, reported cases should fulfill a case definition of AFE, to promote uniformity in data sets composed of women who are likely to have this condition.
4. From a study of these patients, identify risk factors, management principles, and possible biomarkers that are actually specific to AFE.
5. Once such markers have been identified by analyses confined to the uniform case definition group, utilize them to identify other women with AFE whose presentation may be atypical, thus further expanding our understanding of this condition.

The committee recommends that the criteria outlined in Table 2 be met in any woman reported for research purposes as having AFE. Rationale for these criteria are discussed below.

1. Sudden onset of cardiorespiratory arrest, or both hypotension (systolic blood pressure <90 mm Hg) and respiratory compromise (dyspnea, cyanosis, or peripheral capillary oxygen saturation (S_pO_2) <90%). Women with AFE will classically experience almost simultaneous hemodynamic collapse and respiratory compromise reflecting primary cardiovascular and pulmonary insults as well as additional compromise of oxygenation secondary to the initial cardiovascular insult.[2,8]
2. Documentation of overt disseminated intravascular coagulation (DIC) using the scoring system of the Scientific and Standardization Committee on Disseminated Intravascular Coagulation of the International Society on Thrombosis and Hemostasis (ISTH), modified for pregnancy[22] (Table 3). Coagulopathy must be detected prior to the loss of sufficient blood to itself account for dilutional or shock-related consumptive coagulopathy. The literature contains reports of women with apparent AFE who did not have DIC.[2,8] However, this is uncommon; the presence of significant coagulopathy is one of the hallmarks that typically distinguish AFE from conditions such as myocardial infarction, anaphylaxis or drug reaction, anesthetic accident, and pulmonary thromboembolism. Thus the inclusion of DIC as a necessary diagnostic criterion serves to keep reported research data sets clean while eliminating very few women who actually have this condition. The DIC scoring system of the ISTH is widely recognized and validated.[22] We have modified this system based upon well-documented coagulation changes that occur in normal pregnancy, most prominently involving moderate to marked elevation of fibrin markers in third trimester and postpartum women and the physiologic substantial elevation of plasma fibrinogen seen in term pregnancy[23,24] (Table 3). Thus the presence of elevated levels of fibrin split products, d-dimer, or other tests indicative of thrombin activation would not be considered evidence of overt DIC in pregnancy, and a fibrinogen level <200 mg/L rather than the standard ISTH cutoff of 100 mg/L has been used. In addition, because of the more frequent use of the international normalized ratio rather than prothrombin time in US obstetrics, the original use of prothrombin time by the ISTH has been modified to reflect comparable relative changes in international normalized ratio.

   The requirement that coagulopathy be detected prior to the loss of sufficient blood to itself account for dilutional or shock-related consumptive coagulopathy will distinguish AFE from simple hypovolemic shock.
3. Clinical onset during labor or within 30 minutes of delivery of the placenta. This requirement is consistent with any condition involving acute inflammatory mediator release, and would apply to typical as well as most atypical cases. Although the literature contains occasional reports of presumed delayed-onset AFE, many of these diagnoses were based primarily on the finding of squamous cells in the maternal circulation in cases in which alternative diagnoses were, from a clinical standpoint, more likely. Most cases will occur well before the 30-minute window has elapsed, but clinical recognition may be delayed, especially during cesarean delivery under general anesthesia due to ongoing routine respiratory and hemodynamic support.
4. No fever (38.0°C) during labor. The current International Consensus Definitions for Sepsis and Septic Shock rely principally on the presence of elements of the SIRS coupled with organ failure.[25] A critical examination of these definitions

TABLE 4
Differential diagnosis of amniotic fluid embolism

	Amniotic fluid embolism	Hemorrhage	Sepsis	Anesthetic accident	Pulmonary thromboembolism	Systemic anaphylaxis
Hypotension	+++	+++	+++	+++	++	+++
Hypoxia	+++	+/−	+	+++	+++	+++
Coagulopathy	+++	+	+	No	No	No
Sudden onset	Yes	No	No	Yes	Yes	Yes
Prior fever	No	No	Yes	No	No	No
Recognized antecedent event	No	Hemorrhage	Chorioamnionitis	Anesthetic administration	No	Medication administration

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suggests that virtually all women with classic AFE would meet International Consensus Definitions for Sepsis and Septic Shock criteria for sepsis. There may be an important lesson in this observation regarding the ultimate nature of the pathophysiology involved in AFE.[19] However, from the standpoint of diagnosis of AFE syndrome, this potential confusion may be clarified by the observation that while fever is not a mandatory component of the SIRS in general medicine, its presence in young women with clinical chorioamnionitis or other sepsis-related conditions associated with cardiovascular collapse is virtually universal.[26,27] In contrast, fever is not a recognized component of the AFE syndrome. Thus this criterion, as well as the need for sudden, as opposed to gradual, hemodynamic deterioration and lung injury serve to distinguish AFE from straightforward sepsis.

The most common conditions diagnosed and coded in error as AFE are hypovolemic shock secondary to postpartum hemorrhage, anesthetic accident (eg, high spinal or inadvertent intravascular injection of a local anesthetic agent), pulmonary thromboembolism, septic shock, and anaphylactic shock.[4] Each of these conditions has clinical similarities to AFE (Table 4). The above uniform diagnostic criteria were largely developed to avoid inclusion of these patients in AFE data sets.

This approach is intended to apply only to patients included in research reports, and does not imply that, in clinical practice, women may not be occasionally diagnosed with atypical variants of AFE in which ≥1 of these required elements may be missing. However, exclusion of such patients from research consideration will, we believe, be an important first step in making progress in the diagnosis, management, and potential prevention of AFE.

Several investigators, including the authors of this study and the Amniotic Fluid Embolism Foundation, have established a protocol to collect clinical data as well as biological material (maternal blood, umbilical cord blood, paternal blood, saliva, human placentas, and other related specimens) of patients suspected to have AFE. The protocol for this has been approved by the Institutional Review Board of Baylor College of Medicine. The investigators are working with patient advocates through the Amniotic Fluid Embolism Foundation. Clinical records are reviewed to determine whether the cases meet the proposed diagnostic criteria reported in this article, or fit a different category (eg, atypical AFE, other diagnosis), and biological samples will be used to identify biomarkers for the diagnosis and prognosis of this condition. This project is being conducted in collaboration with the Perinatology Research Branch of *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. The investigators are particularly interested in samples of plasma and/or serum obtained at the time of admission *before* the patient has developed cardiovascular collapse and DIC leading to the diagnosis of AFE in the specified manner.[15] Individuals interested in submitting such samples are requested to save all laboratory specimens collected since admission, and contact one of these authors—gadildy@bcm.edu, slclark@bcm.edu, belfort@bcm.edu—for specifics regarding sample and records submission. ■

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