AMNIOTIC FLUID EMBOLISM: AN EVIDENCE-BASED REVIEW

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Abstract

We conducted an evidence-based review of information bout amniotic fluid embolism (AFE). The estimated incidence of AFE is 1:15,200 and 1:53,800 deliveries in North America and Europe, respectively. The case fatality rate and perinatal mortality associated with AFE are 13–30% and 9–44%, respectively. Risk factors associated with an increased risk of AFE include advanced maternal age, placental abnormalities, operative deliveries, eclampsia, polyhydramnios, cervical lacerations, and uterine rupture. The hemodynamic response in AFE is biphasic, with initial pulmonary hypertension and right ventricular failure, followed by left ventricular failure. Promising therapies include selective pulmonary vasodilators and recombinant activated facto Vlla. Important topics for future research are presented.

Keywords

INTRODUCTION

Amniotic fluid embolism (AFE) is a rare and often fatal obstetric condition, characterized by sudden cardiovascular collapse, altered mental status, and disseminated intravascular coagulation (DIC). The presence of fetal debris in the pulmonary blood vessels of a mother who had died suddenly in labor was first described by Meyer[1] in 1926, but it was not until 1941 that death following sudden collapse during labor or in the immediate postpartum period was attributed to AFE.[2]

Understanding of the pathogenesis of AFE has increased substantially in the last two decades since this disorder was recognized as 1 of the main causes of maternal mortality in the United States.[3] Evidence on AFE, however, has been mainly based on individual case reports, autopsy series, or uncontrolled case series due to the low frequency of the condition. Moreover, several aspects on this condition remain a subject of controversy. This review critically examines, from the best available evidence, the current knowledge regarding the epidemiology, pathogenesis, pathophysiology, diagnosis, and treatment of AFE.

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MATERIALS AND METHODS

We searched several databases (all from inception to March 31, 2009) with the terms "amniotic embolism" and "amniotic embolus". We also searched references in retrieved articles, book chapters, review articles, and reports on maternal mortality from surveillance systems. Inclusion of individual articles was based on scientific merit and clinical relevance. The great majority of studies included were descriptive, mainly case reports and case series. We also included 2 population-based cohort studies and 6 case-control studies. Methodological quality was assessed using guidelines proposed for improving the reporting of these studies.[4,5] Details of methods used in the review are presented in the Appendix.

RESULTS

Incidence

In 1941, Steiner and Lushbaugh,[2] based on the occurrence of 3 cases of fatal AFE in the first 24,200 deliveries at the New Chicago Lying-In Hospital, estimated the incidence of AFE to be about 1 in 8000 deliveries (maternal mortality ratio of 12.4 deaths per 100,000 deliveries), but subsequently realized that this was an overestimation since no more cases were observed in the next 26,000 deliveries (corrected maternal mortality ratio of 6.0 deaths per 100,000 deliveries).[6] Forty studies[2,6–44] had data on the incidence of AFE and/or associated maternal and perinatal mortality around the world. Details of these studies are provided in the supplementary appendix (available online at www.ajog.org). According to recent large population-based studies,[24,36,38,40,42,43] the incidence of AFE, which includes both fatal and nonfatal cases, ranges between 1 in 12,953 deliveries in the United States,[40] to 1 in 56,500 in the United Kingdom.[43] Based on those studies, the pooled estimated incidence of AFE would be 1 in 15,200 deliveries (95% confidence interval [CI], 1 in 13,900 to 1 in 16,700 deliveries) in North America[24,36,40] and 1 in 53,800 deliveries (95% CI, 1 in 48,800 to 1 in 59,900 deliveries) in Europe.[38,42,43] There were no available data on incidence of AFE in other regions of the world. The true incidence of AFE, however, is difficult to determine because the diagnosis of this syndrome remains one of exclusion, with possible underreporting of nonfatal cases. On the other hand, it is possible that AFE is over-diagnosed for medicolegal reasons, since this complication is widely considered to be an unavoidable cause of maternal death. Additional research will be needed to evaluate why the incidence of AFE is over 3 times higher in North America than in Europe.

Maternal and perinatal mortality

The maternal mortality ratio associated with AFE ranged between 0.5–1.7 deaths per 100,000 live births or deliveries (0.5 for Sweden and the United Kingdom, 0.7 for Canada, 1.5 for Australia, and 1.0–1.7 for the United States). In developing countries, the reported maternal mortality ratios ranged between 1.8–5.9 per 100,000 deliveries. Overall, in the last 10 years, AFE accounted for 5.0–15.0% of all maternal deaths in developed countries (5.3% for the United Kingdom, 10.9% for Canada, 13.1% for Australia, and 13.7% for the United States), being the leading cause of maternal death in Australia, the second cause of maternal death in the United States, the third cause of maternal death in France and Poland, and the second cause of direct maternal death in the United Kingdom. In China, regional studies reported that AFE was the second cause of maternal death.

1n 1979, Morgan,[11] based on 272 cases of AFE published in the English literature, reported a maternal fatality rate of 86%. In Clark's national registry, the maternal fatality rate was 61% for the period 1988–1994.[19] More recent population-based studies have reported a decrease in case fatality rate from AFE (13.3% for Canada, 21.6% for the United States, 24.0% for the United Kingdom, and 44.0% for Sweden), justifying the view that this

condition should not be considered as uniformly lethal. This could be due to improved reporting, inconsistent case definitions, or improvements in treatment. Another possibility is publication bias in previous series, due to selective reporting of severe cases. The perinatal mortality associated to fatal AFE in the last decade ranged between 9 and 44%.[37,39]

Risk factors

Until recently, the understanding of the risk factors for the development of AFE derived from case reports, autopsy series, or cumulative reviews in which there was no control group for comparisons. As of 2009, only 2 large population-based retrospective cohort studies,[36,40] each using data from 3 million hospital deliveries, have examined the independent association between AFE and several potential risk factors after controlling for the effects of confounders (Table 1). Risk factors found in both studies to be significantly associated with an increased risk of AFE included maternal age of 35 years or older, cesarean delivery, forceps-assisted and vacuum-assisted vaginal deliveries, placenta previa, abruption placenta, eclampsia, and fetal distress. Unfortunately, the ability to make inferences about causality is limited, because temporal relationships cannot be determined when using these databases. Thus, although operative deliveries and fetal distress can precede the AFE, it is also possible that reverse causality explains these associations. Other significant risk factors associated with AFE were polyhydramnios and cervical laceration or uterine rupture in the Canadian study,[36] and African American race and other minority ethnic groups in the American study.[40] With regard to induction of labor, the 2 studies yielded conflicting results: the Canadian study[36] reported that medical induction of labor nearly doubled the risk of AFE compared with a spontaneous labor (adjusted odds ratio [OR], 1.8; 95% CI; 1.3–2.7), whereas the American study[40] did not find a significant association (adjusted OR, 1.5; 95% CI, 0.9–2.3). Preeclampsia was found to be a significant risk factor for AFE in the American study but not in the Canadian study. Maternal age below 20 years and dystocia were significant protective factors against the development of AFE in both studies. Advanced maternal age in first pregnancy, primigravidity, high parity, multiple gestations, premature rupture of membranes, chorioamniotis, and fetal macrosomia did not alter the risk of AFE.

The results of these studies, however, could have been influenced by the fact that identification of AFE was based on clinical diagnosis as recorded in the medical record, without other verifying evidence, and depended on correct coding of that diagnosis. Moreover, nonfatal AFE might have been over diagnosed in these studies. A prospective, national study of amniotic fluid embolism using the UK Obstetric Surveillance System (UKOSS) is currently in the process of assessing whether these risk factors are present in this population.[43]

Pathogenesis

The pathogenesis of AFE is not clearly understood. The entrance, by various proposed mechanisms and routes, of amniotic fluid into the systemic maternal circulation, which then triggers clinical manifestations of the condition, continues being the main mechanism involved in the pathogenesis of AFE. Traditionally, it has been assumed that in order for AFE to occur there must be a breach in the physical barriers between the maternal and fetal compartments, mainly at the level of endocervical veins,[45,46] uterine trauma sites,[47] and the placental attachment site.[47] A pressure gradient that favors the entry of amniotic fluid from the uterus into the maternal circulation is thought to be present.[48] Support for this hypothesis comes from the work of Talbert et al,[49] who found that significant amounts of ^{125}I-labeled albumin were transferred from amniotic fluid into the maternal circulation following intraamniotic injection of hypertonic saline. This mechanism probably explains the increased risk of AFE among women with placenta previa, placental abruption, operative deliveries, cervical laceration or uterine rupture, and polyhydramnios. With regard to the

mechanism for the late presentation of AFE, Courtney[50] proposed that amniotic fluid and fetal debris trapped in the uterine veins at the time of delivery may be released into the circulation later during uterine involution.

The traditional view has been that entry of amniotic fluid into the maternal circulation resulted in obstruction of pulmonary capillaries by amniotic fluid emboli, leading to cardiovascular collapse. However, the usual absence of physical evidence of pulmonary vessel obstruction, the high degree in variability in clinical course, and the failure to consistently reproduce the disease in animal models[51,52] suggest that physical obstruction to the circulation is not the main mechanism of AFE. Some investigators have suggested that immunologic factors could be involved in the pathogenesis of this syndrome.[53–56] In 1984, Hammerschmidt et al[53] found that amniotic fluid could activate complement when incubated with normal plasma and postulated that complement and granulocyte activation by amniotic fluid could contribute to the pulmonary collapse of this syndrome. In 1993, Benson[55] suggested that AFE might actually result from anaphylaxis to fetal material leaking into the maternal circulation, which would stimulate a cascade of endogenous-immune mediators, resulting in a reaction similar to anaphylaxis. However, in a further study, this same investigator did not find evidence to support the role of mast cell degranulation (anaphylaxis) in the pathophysiology of the disease.[57] In contrast, all of the 8 women with AFE had abnormally low C3 and C4 complement concentrations, suggesting that complement activation could play a role in the pathogenesis of AFE. This hypothesis remains to be proved.[56]

Pathophysiology

The entrance into the circulation of amniotic fluid constituents will result in the release of various primary or secondary endogenous mediators, which cause the principal physiologic derangements that characterize this syndrome. The list of proposed mediators is extensive and includes histamine,[56] bradykinin,[58] endothelin,[59,60] leukotrienes,[61] and other arachidonic acid metabolites.[62]

Hemodynamic changes

Initial explanations for the hemodynamic changes associated with AFE were based on findings from animal experimentation.[63,64] In general, experimental AFE in animals produced severe pulmonary artery hypertension, leading to acute cor pulmonale without evidence of left ventricular compromise.[65] This was attributed to a vasoconstrictor response of the pulmonary vasculature to the presence of amniotic fluid or particulate matter in amniotic fluid.[11] In 1985, Clark et al[66] challenged this traditional view. Reanalyzing 5 published cases of AFE, which included hemodynamic data derived from pulmonary artery catheterization, as well as a report of a sixth case, these authors reported only mild to moderate increases in mean pulmonary artery pressure, a variable increase in central venous pressure, and a high pulmonary capillary wedge pressure with evidence of left ventricular failure. These findings were confirmed 3 years later by the same group[67] in 4 women suffering from AFE, with hemodynamic data derived from pulmonary artery catheterization performed within 2 hours of the acute cardiovascular collapse. In 1999, Shechtman et al[68] published the first report of transesophageal echocardiography findings during the hyperacute stage of AFE (within 30 minutes of the collapse). Transesophageal 4-chamber images showed severe pulmonary hypertension, acute right ventricular failure with a leftward deviation of the interatrial and interventricular septum, and severe tricuspid regurgitation. There were no signs of left ventricular dysfunction or of pulmonary edema. Similar findings were subsequently reported in 4 cases in which transesophageal echocardiography was performed during the early course of AFE.[69–72] In all of these cases, the transesophageal echocardiography showed that left ventricular filling, because of a

dilated right ventricle with deviation of the interventricular septum. These findings suggest that pulmonary vasoconstriction and increased pulmonary vascular resistance are the primary mechanisms responsible for the cardiovascular collapse in AFE. It is important to highlight that most studies demonstrating left ventricular failure as the main hemodynamic alteration associated with AFE were performed more than 1 hour after the onset of clinical signs. In conclusion, the current available evidence suggests hemodynamic response to AFE is biphasic, with initial increase pulmonary vascular resistance and right ventricular failure, followed by left ventricular failure.[54] Additional explanations for the left ventricular failure include ischemic injury to the myocardium[66] and/or a possible direct myocardial depressant effect of amniotic fluid or other mediators.[54] Hypoxemia could be explained by the severe ventilation-perfusion mismatching due to intense vasoconstriction of the pulmonary vasculature that occurs with the initial phase.

Coagulopathy

Although the precise mechanism inducing DIC from AFE remains unclear, it is probably multifactorial. In vitro, amniotic fluid decreases whole blood clotting time, produces a "thromboplastin-like effect", induces platelet aggregation and activates the complement cascase.[73] The current hypothesis is that, in AFE, the presence of tissue factor in amniotic fluid activates the extrinsic pathway by binding with factor VII, and this triggers clotting by activating factor X, with the subsequent development of a consumptive coagulopathy.[74–76] The activation of the clotting cascade in the pulmonary vasculature may cause generation of microvascular thrombosis, which could then cause vasoconstriction.[74] Additional data report that high levels of a latent form of plasminogen activator inhibitor type 1 in amniotic fluid can be reactivated by a denaturing agent in maternal circulation, leading to DIC.[77] Recently, it has been proposed that DIC may be a secondary result of complement activation rather than the direct introduction of pro-coagulants into the maternal circulation.[56]

There is controversy about the extent to which bleeding is due to a consumption coagulopathy or to massive fibrinolysis. Harnett et al,[78] using thromboelastography analysis, have demonstrated that the addition of amniotic fluid to blood from pregnant women causes a hypercoagulable state related to the procoagulant activity of amniotic fluid and enhanced platelet activation, but there was no evidence of fibrinolysis, suggesting that the primary cause of bleeding in AFE is consumption coagulopathy. Similar results were reported by Liu et al,[79] using blood from non pregnant women.

Histopathology

The gross pathologic changes are usually non specific and can include pulmonary edema, atelectasis, pulmonary congestion, emphysema, and evidence of thrombosis. Usually, there are no visible thrombi in the main pulmonary arteries, heart or elsewhere.[2,80] The traditional view was that the diagnosis could be based on demonstrating the presence of fetal debris, presumable from the amniotic fluid, within the pulmonary vasculature. Amniotic fluid contains epithelial squamous cells from the fetal skin, mucin derived from meconium excreted by the fetal intestine, fat derived from the vernix caseosa, and hair.[2,78] These constituents can be specifically identified by using immunohistochemical markers for cytokeratin AE1/AE3, Alcian blue or mucicarmine staining, oil red O staining, and polarized light, respectively.[81–83] Kobayashi et al,[84] reported that immunohistochemical staining using monoclonal antibody TKH-2 is a more sensitive method to detect meconium and amniotic fluid-derived mucin in the lung sections of patients with AFE than conventional hematoxylin eosin or Alcian blue staining. Oi et al[85] reported positive TKH-2 staining within the pulmonary vasculature in 14 of 15 (93%) women with AFE. Recently, Fineschi et al[86] evaluated complement C3a expression as a histopathological test for diagnosing fatal AFE, the expression of complement C3a was lower than in the control group (6 women

dying of trauma during pregnancy). Fetal debris has also been detected in the capillaries of the cervix, lower uterine segment, kidneys, heart, liver, spleen, adrenal glands, pancreas, and brain.[2,45,46,80,87–89]

Clinical manifestations

AFE typically occurs during labor and delivery or in the immediate postpartum period, although it can occur as late as 48 hours postpartum. About a 70% of cases occur before delivery (range 63–76%).[13,19,25,35,40] AFE has also been reported to occur following induced abortion,[90,91] feticide,[92,93] intrapartum amnioinfusion,[94,95] transabdominal amniocentesis,[96,97] blunt abdominal trauma,[98,99] surgical trauma,[100] removal of a cervical suture,[101] and manual removal of placenta.[102] The classic presentation of AFE is characterized by sudden cardiovascular collapse, with profound systemic hypotension, cardiac dysrhythmia, cyanosis, dyspnea or respiratory arrest, pulmonary edema or the adult respiratory distress syndrome, altered mental status, and hemorrhage. These signs and symptoms of AFE can occur separately or in combination and in different degrees. The precise progression of signs and symptoms in the initial phase of AFE has been difficult to elucidate, because of the low frequency of the condition and lack of monitoring from the onset of the disorder.

Frequencies of the main presenting signs and symptoms of AFE reported in large case series are summarized in the supplementary appendix available online. It should be emphasized that this information could be affected by underreporting of signs and symptoms in clinical records. The most common presenting signs and symptoms included hypotension, respiratory distress, and cyanosis, which were detected in up to 100% of women, DIC in approximately 50% (range, 22–83%), and seizures in about 20% (range, 10–48%). The percentage of patients experiencing cardiac arrest and dyspnea varied between 30–87% and 48–72%, respectively. Fetal distress was diagnosed in 50–100% of cases. Cases of AFE with atypical presentations, in which coagulopathy[43,103–105] or severe fetal bradycardia[106,107] are the initial or even the only presenting feature have been reported in the literature. Maternal death due to AFE is typically caused by sudden cardiac arrest, hemorrhage from coagulopathy or the development of acute respiratory distress syndrome and/or multisystem organ failure after initial survival of the acute event.

Premonitory symptoms

The seventh report of the confidential enquiry into maternal deaths in the United Kingdom[39] has highlighted that 11 of 17 women who suffered AFE reported some or all of the following symptoms: breathlessness, chest pain, feeling cold, lightheadedness, distress, panic, a feeling of pins and needles in the fingers, nausea, and vomiting. The interval between the onset of these symptoms and the collapse varied (from almost immediately to over 4 hours later). These symptoms might indicate hypoxia and might give the first clue to diagnosis of amniotic-fluid embolism in progress before collapse and hemorrhage occur. Tuffnell[35] suggested that monitoring maternal oxygenation by pulse oximetry in these circumstances should be considered in the peripartum period to detect at an early stage women who may develop AFE.

DIAGNOSIS

The diagnosis of AFE is based on the patient's clinical presentation and is essentially one of exclusion. Although wide consensus based on objective criteria is still to be achieved, the diagnosis is suspected in a woman experiencing several of the following features: hypotension (and/or cardiac arrest), respiratory distress, DIC, or coma and /or seizures during pregnancy or within 48 hours of delivery, in the absence of other medical condition

or potential explanation for the symptoms and signs observed.[56] Since some women with AFE may have secondary conditions, the emphasis is on whether these other medical problems seem to be the most likely cause of the women's illness.

Laboratory tests are nonspecific (a complete blood count, coagulation profile, arterial blood gases, cardiac enzymes, and electrolytes). The white blood cell count may be elevated and, depending on the presence of DIC, the hemoglobin and hematocrit values will be low. The laboratory manifestations of DIC include prolonged prothrombin and partial thromboplastin times, with decreased fibrinogen levels. Thrombocytopenia is a rare finding. Cardiac enzymes may be elevated, and arterial blood gases may show hypoxemia. The electrocardiogram may show tachycardia, with a right ventricular strain pattern in the early stage and ST and T wave abnormalities. Cardiac arrhythmias or asystole can be seen with severe cardiovascular collapse. Pulse oximetry may reveal a sudden drop in oxygen saturation. The chief radiographic abnormalities in AFE are diffuse bilateral heterogeneous and homogeneous areas of increased opacity, which are indistinguishable from acute pulmonary edema from other causes.[102] Transesophageal echocardiography may demonstrate severe pulmonary hypertension, acute right ventricular failure with a leftward deviation of the interatrial and interventricular septum, and a cavity-obliterated left ventricle during the early phase of AFE.[68–72] Occasionally, transient intracardiac thrombi[109] or embolus[110] can be seen.

No specific laboratory tests are available for making a diagnosis of AFE, yet several tests have been proposed to increase the index of suspicion for this diagnosis (Table 2). In 1976, Resnik et al,[111] first reported the identification of amniotic fluid debris in central venous blood aspirated from the distal lumen of a pulmonary arterial catheter of a survivor woman with AFE. This finding has been reported several times.[112–115] However, in the Clark et al's national registry[19] only 4 of 8 women (50%) had this finding. In addition, the detection of squamous cells in the pulmonary arterial circulation is not pathognomonic for AFE since they have been identified in 21–100% of pregnant women without AFE[116–119] and in non pregnant women.[118,120] Unfortunately, reliable differentiation between maternal and fetal squamous cells is still difficult in the clinical setting. Thus, the detection of squamous cells in the maternal pulmonary arterial circulation is not sufficient for the diagnosis of AFE. The identification of such findings in the maternal pulmonary arterial circulation is supportive of the diagnosis when they are found in large numbers, are coated with neutrophils, and/or they are accompanied by other fetal debris.[115,119]

Diagnostic markers for AFE based on peripheral blood sample have also been suggested. These include zinc coproporphyrin, sialyl Tn, tryptase, and complement factors. Kanayama et al[121] found that plasma concentrations of zinc coproporphyrin (a characteristic component of meconium) were increased in all of the 4 women with AFE but in only 1 of 50 control cases with no diagnosis of AFE. Three studies[57,85,122] have evaluated the diagnostic accuracy of serum sialyl Tn, a fetal antigen present in meconium and amniotic fluid, detected through the use of the TKH-2 monoclonal antibody. Serum concentrations greater than 50 U/mL yielded sensitivities between 78–100% and the specificities between 97–99%. Increased serum levels of tryptase, a marker of mast cell degranulation, in women with AFE have been reported by some authors[123,124] but not by others.[83,125] Benson et al[57] reported that serum tryptase was negative in all of the 6 women with AFE. However, they found that decreased serum levels of C3 and C4 complement had sensitivities between 88–100% and a specificity of 100% for the diagnosis of AFE. It should be noted that all of these laboratory tests are not currently available in the majority of hospitals. In conclusion, at the present time there is no test that can reliably confirm the diagnosis of AFE in suspected cases. Serum diagnostic markers, such as zinc coproporphyrin, sialyl Tn antigen, and C3 and C4 complement, are promising, but larger studies are needed.

Differential diagnosis

Several other obstetric and nonobstetric life-threatening emergencies may present similar to AFE. The differential diagnosis of AFE is extensive and includes disorders of embolic, cardiac, respiratory, infectious, and immunologic nature (Table 3).

TREATMENT

The management of AFE is supportive and directed towards the maintenance of oxygenation, cardiac output and blood pressure, and correction of the coagulopathy. Treatment should take place in an intensive care unit, if possible. In the event of maternal cardiac arrest, cardiopulmonary resuscitation should be initiated immediately and, if the gestational age of the undelivered alive fetus is viable, cesarean section could be considered.[126] Uterine evacuation after unsuccessful resuscitation may be therapeutic for the mother, because the weight of the gravid uterus on the inferior vena cava impedes blood return to the heart and decreases systemic blood pressure.[127,128]

Monitoring of the patient with suspected AFE should include continuous cardiac telemetry monitoring to detect and treat arrhythmias, continuous respiratory monitoring with pulse oximetry or with an end-tidal CO_2 monitor, continuous blood pressure monitoring, and pulmonary artery catheter for monitoring cardiac output, central venous pressure, pulmonary capillary wedge pressure, systemic vascular resistance, and pulmonary artery pressures.[129,130] In addition, pulmonary artery catheter guides hemodynamic management and provides direct access for blood samples for monitoring of arterial gases. Transesophageal echocardiography has also been reported to be useful in evaluating cardiac function and guiding fluid therapy. Initial laboratory data generally includes a complete blood count with platelets; type and cross-matching; arterial blood gases; electrolytes; and coagulation studies, including prothrombin time, partial thromboplastin time, fibrin degradation products, D-dimer, and antithrombin III levels.

The initial goal is the rapid correction of maternal hemodynamic instability, which includes correction of hypoxia and hypotension, for preventing additional hypoxia and subsequent end-organ failure. Oxygen should be administered immediately by whatever means necessary, including face mask, bag-valve mask, or endotracheal intubation, in concentrations adequate to keep oxygen saturation at 90% or higher.[129,130] Treatment of hypotension includes optimization of preload, with rapid volume infusion of isotonic crystalloid solutions. Fluid therapy should be based on pulmonary artery catheter or transesophageal echocardiography monitoring. In cases of refractory hypotension, vasopressors such as dopamine or norepinephrine may be necessary. Inotropes, such as dobutamine, dopamine, and milrinone can be added because β-adrenergic agonists improve myocardial contractility in addition to the α-adrenergic vasoconstrictor effects. It is desirable to maintain systolic blood pressure at or higher than 90 mmHg, an arterial PaO_2 of at least 60 mmHg, with acceptable organ perfusion, asindicated by a urinary output of at least 0.5 mL/kg/h or greater than 25 mL/h.[129,130]

Administration of blood components is considered the first line of treatment for correcting coagulopathy associated with AFE. Since DIC is frequently associated with severe hemorrhage, transfusion of packed red blood cells is a priority in order to maintain oxygen delivery to the tissues. Specific laboratory coagulation abnormalities are treated with transfusion of fresh frozen plasma, platelets, and/or cryoprecipitate. Cryoprecipitate is particularly useful, because it can be used administered to replenish clotting factors in lieu of fresh frozen plasma. In addition, since cryoprecipitate contains fibronectin, it could facilitate the removal of cellular and particulate matter, such as amniotic fluid debris, from the blood via the monocyte/macrophage system.[46,131] Recently, recombinant activated factor VIIa has

been used to manage severe DIC resistant to conventional blood product replacement in women with AFE.[132,133] Uterine bleeding in a woman already delivered can be controlled by massage and use of intravenous oxytocin. If uterine bleeding is unresponsive to these methods, manual exploration to look for fragments of retained placenta or membranes or a search for cervical or uterine lacerations needs to be considered. If bleeding is profuse and pharmacological intervention is unsuccessful, a hysterectomy may be necessary.

Several other less common therapeutic approaches have been reported anecdotally, including aprotinin[134,135] and serine proteinase inhibitor FOY[136] to manage DIC, uterine artery embolization for controlling severe postpartum hemorrhage,[125,137] cardiopulmonary bypass for the treatment of catastrophic pulmonary vasoconstriction,[69] cardiopulmonary bypass and pulmonary artery thromboembolectomy,[138] inhaled aerosolized prostacyclin as a selective pulmonary vasodilator for the treatment of severe hypoxemia,[139] thrombolysis with tissue-plasminogen activator,[140] continuous hemodiafiltration for presumably eliminating amniotic fluid from the maternal blood stream, removal of cytokines, and treatment of metabolic acidosis,[141] arteriovenous hemofiltration,[142] exchange transfusion,[143] and extracorporeal membrane oxygenation and intraaortic balloon counterpulsation for treating left ventricular failure unresponsive to medical therapy.[144] The use of heparin therapy to treat DIC and corticosteroids is controversial.

Recently, McDonnell et al[72] reported the successful use of inhaled nitric oxide, a selective pulmonary vasodilator, in the treatment of acute right ventricular failure and pulmonary hypertension in a case of AFE presenting as cardiovascular collapse during labor. Other selective pulmonary vasodilators that might be beneficial for the treatment of severe pulmonary hypertension of AFE include prostacyclin and sildenafil.

Prognosis

The prognosis of a woman experiencing AFE has improved significantly with early diagnosis and prompt and aggressive treatment by a multidisciplinary team.[145] Although case fatality rates for AFE have fallen, there is still significant morbidity among survivors. In the Clark et al's national registry,[19] among the survivors, persisting neurological impairment was reported in 61% of women and 50% of infants. In the United Kingdom registry,[35] of the 31 women who survived, 6% had persisting neurological impairment whereas of the 33 infants who survived, 18% developed hypoxic ischemic encephalopathy and 6% developed cerebral palsy.

RECURRENCE

A total of 9 cases of successful pregnancy following AFE, with no instances of recurrent AFE, have been reported in the literature.[21,146–151] Therefore, although the available information is limited, the current evidence suggests that AFE is not a recurrent disease.

COMMENT AND CONCLUSIONS

With the exception of research on risk factors and some diagnostic tests, the available literature on AFE is mainly based on case reports or case series. Thus, there is a need for future research to generate information based on a higher level of evidence, and observational studies are needed. For reliable evidence on rare entities such as AFE, we need systematic review of case reports and case series rather than a haphazard selection of them. Therefore, a worldwide registry of patients with this complication in which uniform diagnostic criteria be used is urgently needed to address comprehensively unanswered questions. Clinicians should be encouraged to report cases uniformly for facilitating direct comparisons of individual reports and the performance of systematic reviews.

Although the understanding of AFE has improved in the last decade, this entity continues being associated with a high rate of maternal and perinatal morbidity and mortality. The possible association between AFE and both cesarean section and induction of labor deserves secular monitoring, given the increasing use of these interventions. More research on promising serum diagnostic tests, such as zinc coproporphyrin, sialyl Tn antigen, and C3 and C4 complement is needed. In addition, it is a priority to develop reliable histological or immunological methods for differentiate adult from fetal squamous cells in pulmonary arterial blood from surviving women. The routine use of transesophageal echocardiography in patients with AFE for evaluating hemodynamic changes to guide treatment more precisely should be encouraged. Selective pulmonary vasodilators, such as nitric oxide for the treatment of severe pulmonary hypertension during the acute phase of AFE, and recombinant activated factor VIIa for managing severe DIC resistant to conventional treatments deserve further study. Finally, future research regarding pathophysiology, early diagnosis, and management can focus on the role of inflammatory mediators, such as histamine, prostaglandins, and leukotrienes, whose biologic activity can explain many of the events that occur with AFE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Risk factors for amniotic fluid embolism in large population-based cohort studies

Characteristic	Adjusted odds ratio (95% confidence interval)	
	Kramer et al[36]	Abenhaim et al[40]
Maternal age <20 years	0.2 (0.1–0.96)	0.4 (0.2 – 0.9)
Maternal age ≥35 years	1.9 (1.4 – 2.7)	2.2 (1.5 – 2.1)
Elderly primigravidity	0.6 (0.2 – 1.9)	1.0 (0.3 – 3.3)
Grand multiparity	1.8 (0.3 – 13.0)	----
Black race	----	2.4 (1.5 – 3.6)
Other minority ethnic groups	----	2.3 (1.5 – 3.6)
Previous cesarean section	0.8 (0.5 – 1.2)	0.9 (0.6 – 1.3)
Medical induction of labor	1.8 (1.3 – 2.7)	----
Induction of labor	----	1.5 (0.9 – 2.3)
Cesarean delivery	12.5 (7.9 – 19.9)[a]	5.7 (3.7 – 8.7)
	8.6 (4.3 – 17.4)[b]	
Forceps delivery	5.9 (3.4 – 10.3)	4.3 (1.9 – 6.6)
Vacuum delivery	2.9 (1.6 – 5.3)	1.9 (1.0 – 3.7)
Multiple pregnancy	2.5 (0.9 – 6.2)	1.5 (0.6 – 4.1)
Placenta previa	----	30.4 (15.4 – 60.1)
Abruptio placenta	----	8.0 (4.0 – 15.9)
Placenta previa or abruptio placenta	3.5 (2.3 – 5.5)	----
Preeclampsia	1.4 (0.8 – 2.5)	7.3 (4.3 – 12.5)
Eclampsia	11.5 (2.8 – 46.9)	29.1 (7.1 – 119.3)
Diabetes	1.5 (0.6 – 3.8)	2.3 (0.6 – 9.2)
Premature rupture of membranes	1.1 (0.6 – 2.0)	0.7 (0.4 – 1.5)
Chorioamnionitis	1.4 (0.6 – 3.2)	1.6 (0.7 – 3.4)
Fetal distress	1.7 (1.2 – 2.5)	1.5 (1.0 – 2.2)
Dystocia	0.6 (0.4 – 0.8)	0.4 (0.2 – 0.7)
Polyhydramnios	3.0 (1.2 – 7.3)	----
Fetal macrosomia	1.6 (0.9 – 3.0)	----
Cervical laceration or uterine rupture	3.8 (1.2 – 12.0)	----

[a] For cephalic presentation

[b] For non-cephalic presentation

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Table 2

Performance of tests proposed for diagnosing amniotic fluid embolism in suspected cases

Author, year	Test	Abnormal test result	AFE cases (n)	Non-AFE cases (n)	Sensitivity (%)	Specificity (%)
DiMarzo,[116] 1984	Squamous cells in central venous blood	Presence of squamous cells	0	11 (before delivery) 16 (after delivery)	----	9 0
Kuhlman,[117] 1985	Squamous cells in central venous blood	Presence of squamous cells	1	5	100	40
Clark,[118] 1986	Squamous cells in pulmonary arterial blood	Presence of squamous cells	1	15	100	0
Lee,[119] 1986	Squamous cells in pulmonary arterial blood	Presence of squamous cells	0	14	----	79
Clark,[19] 1995	Amniotic fluid debris in pulmonary arterial blood	Presence of amniotic fluid debris	8	0	50	----
Kanayama,[121] 1992	Zinc coproporphyrin	Serum levels >35nmol/L	4	50	100	98
Kobayashi,[122] 1993	Sialyl Tn antigen	Serum levels >50 U/ml	4	32	100	96
Oi,[85] 1998	Sialyl Tn antigen	Serum levels >50 U/ml	19	120	90	99
Benson,[57] 2001	Sialyl Tn antigen	Serum levels >50 U/ml	9	22	78	NR
	Serum tryptase	Increased levels in serum; cutoff point NR	6	22	0	NR
	C3 complement	Serum levels <70 mg/dl			88	100
	C4 complement	Serum levels <16 mg/dl	8	22	100	100

AFE, amniotic fluid embolism; *NR*, not reported

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Table 3

Differential diagnosis of amniotic fluid embolism

Pulmonary thromboembolism
Air embolism
Anesthetic complications (total spinal or high epidural block)
Drug-induced allergic anaphylaxis
Myocardial infarction
Cardiac arrhythmia
Peripartum cardiomyopathy
Aortic dissection
Aspiration of gastric contents
Reaction to local anesthetic drugs
Blood transfusion reaction
Sepsis
Postpartum hemorrhage
Uterine rupture
Placental abruption
Eclampsia

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