Chapter

Amniotic Fluid Embolism

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Abstract

Amniotic fluid embolism (AFE) is a rare complication of pregnancy often resulting in catastrophic maternal and fetal outcomes. Given the rarity of this condition, there is a wide variation in reported incidence of amniotic fluid embolism. The pathophysiology of AFE is not completely understood. It is thought to be the result of a breach of the maternal-fetal barrier resulting in an abnormal maternal proinflammatory response. AFE presents as a sudden onset of hypoxia, hypotension, and coagulopathy during labor and delivery or in the immediate postpartum period. Abnormalities in the fetal heart tracing are almost always present. Risk factors often include advanced maternal age, induction of labor, cesarean delivery, operative vaginal delivery, placenta previa, and placental abruption. The diagnosis of amniotic fluid embolism is made based on clinical presentation. There are no laboratory tests that confirm the diagnosis of AFE; however, serum tryptase levels, complement levels, zinc coproporphyrin, and serum sialyl Tn (STn) may support the diagnosis. Management of women with AES is supportive and most often requires admission to an intensive care unit. Although maternal morbidity and mortality remain high, advances in medical technology and improvements in obstetrical critical care and early diagnosis of AFE have improved outcomes.

Keywords: amniotic fluid embolism, maternal mortality, DIC, pregnancy, hypoxia, shock, hypotension

1. Introduction

Amniotic fluid embolism (AFE) is a rare pregnancy complication often resulting in significant maternal and fetal/neonatal morbidity and mortality. AFE is one of the leading causes of maternal mortality in developed countries and is most often diagnosed at the time of delivery or in the immediate postpartum period. The term amniotic fluid embolism developed from a theory based on a small subset of patients who were deemed to have died as result of an embolic event associated with amniotic fluid. This theory has largely been discredited by a growing body of evidence that suggests AFE is most likely the result of an abnormal proinflammatory response in the host [1]. Given the rarity of this syndrome, the reported incidence varies greatly from 1.9 per 100,000 in the United Kingdom to as high as 6.1 per 100,000 in Australia [1, 2]. However, even with prompt diagnosis and timely treatment, maternal mortality rates remain high.

2. Pathophysiology

AFE was first described in the 1920s by J.R. Meyer. It was later recognized as a syndrome in 1941 when Steiner and Lushbaugh reported autopsy findings of 32 women who died suddenly during childbirth. The common histopathological finding among these women was the presence of amniotic fluid debris in the pulmonary vasculature [1]. Therefore, the historical hypothesis was based on an obstruction of the pulmonary arteries from amniotic fluid or fetal debris [1, 3]. Medical advancements in the 1980s allowed for more frequent use of the pulmonary artery catheter to obtain arterial histologic specimens from living patients [1]. There were several reports of pathologic findings that were previously thought to be diagnostic of AFE found in pregnant women that did not have AFE. These findings called into question previous cases diagnosed as AFE that were based solely on pathologic findings.

The second and more commonly accepted theory is that AFE results from a complex sequence of reactions involving an abnormal activation of proinflammatory mediators in the host leading to an immunologic response [1–7]. This response is similar to the systemic inflammatory response syndrome (SIRS). Amniotic fluid contains several procoagulant factors including platelet-activating factor, leukotrienes, bradykinin, cytokines, thromboxane, and arachidonic acid, which aids in the understanding of why disseminated intravascular coagulation (DIC) is observed in 80% or more of women diagnosed with AFE [1, 7, 8]. In conjunction with these responses, a profound hemodynamic change leads to the maternal collapse and death in patients with AFE. Thus, during the first minutes, a sudden increase in pulmonary vascular resistance as a result of an inflammatory/anaphylactoid vasoconstriction leads to a right ventricular dysfunction with dilation of the right ventricular chambers, with a left shift of the interventricular septum and a decrease of the left ventricular filling pressures, with hypotension and cardiovascular collapse [9]. This severe pulmonary vasoconstriction produces an oxygen shunt, with ventilation-perfusion mismatching and severe hypoxia. Finally, left ventricular failure may be present as a consequence of myocardial injury secondary to some inflammatory mediators or myocardial ischemia [10].

Complement activation is thought by some to play a role in the pathophysiology of AFE. Virtually all patients diagnosed with AFE develop some degree of acute respiratory distress syndrome (ARDS). Various case series evaluating serum complement levels in patients with AFE have noted significantly decreased levels of C3 and C4 compared to a control group of normal laboring patients who all had complement levels within the normal range [7]. Decreased levels of C3 are thought to be consistent with complement activation.

3. Incidence and risk factors

3.1 Incidence

The true incidence of amniotic fluid embolism is unknown. Discrepancies in diagnosis as well as inconsistencies in reporting practices lead to a wide range of estimates. AFE incidence ranges between 1 in 8000 and 1 in 80,000 pregnancies [8, 11, 12]. In 2012, Knight et al. reviewed available data sources from Australia, Canada, the Netherlands, the United Kingdom, and the United States to investigate incidence rates and identify variations in methodology in diagnosis of AFE. Their analysis found a reported incidence of AFE ranging from 1.9 cases per 100,000 in the United Kingdom to 6.1 cases per 100,000 cases in Australia. Differences in the reported incidence were attributed to a lack of internationally accepted diagnostic criteria for nonfatal cases of AFE as well as variance in methodology.

3.2 Risk factors

Review of various data registries reveals a wide range of conflicting data regarding identifiable risk factors for AFE. Historically, risk factors associated with AFE included situations where there was an increased likelihood of exchange of maternal and fetal components [1, 2, 13]. Events such as cesarean delivery, operative vaginal delivery, cervical trauma, placenta previa, and abruption were frequently reported [9, 13–16].

Knight et al. in 2012 reviewed data sources on incidence of AFE in Australia, Canada, the Netherlands, the United Kingdom, and the United States. Where data was available, they also examined risk factors associated with AFE. There were only two associations that were consistent across all five countries: induction of labor and maternal age [2]. In the Netherlands the association with age was not statistically significant. This may be a result of the limited power of the study given that all reported cases occurred in women who were 29 years of age or older. The data from Canada showed an association between AFE and all methods of medical induction of labor, while in the United Kingdom, there was only a statistically significant association with induction of labor using vaginal prostaglandins [2]. In the United States, all methods of induction of labor showed an increased odds ratio; however, this was not statistically significant [2]. Increased odds of AFE associated with placental previa and placental abruption was also observed. In the United Kingdom there was a statistically significant association between cesarean section when the amniotic fluid embolism occurred after delivery. There was no association with forceps or vacuum delivery; however, only a small subset of women underwent an operative vaginal delivery, so there is limited power to detect this association [2].

Another group of researchers who conducted a population-based cohort study on 3 million birth records in the United States from 1999 to 2003 found AFE was associated with maternal age greater than 35 (OR 2.2, 95% CI 1.5–2.1). However, they did not find that AFE was significantly associated with induction of labor. They also reported an association of placenta previa (OR 30.4, 95% CI 15.4–60.1) and cesarean delivery (OR 5.7, 95% CI 3.7–8.7) [16].

Maternal risk factors [1, 3, 5, 6, 8, 9, 11, 13–16]:

- Advanced maternal age, >35
- Multiparity
- Diabetes
- Ethnic minority

Fetal risk factors [15, 16]:

- Male fetus
- Multifetal gestation
- Fetal distress
- Polyhydramnios
- Intrauterine death

Obstetrical factors [1, 3, 5, 6, 8, 9, 11, 13–16]:

- Induction or augmentation of labor
- Cesarean section
- Cervical or abdominal trauma
- Premature rupture of membranes
- Operative vaginal delivery
- Placenta previa/accreta
- Placental abruption
- Eclampsia

4. Diagnosis

There should be a high level of suspicion of AFE for a pregnant or postpartum woman with an acute onset of cardiopulmonary compromise, DIC, and altered mental status. The diagnosis of AFE is one of exclusion and is based upon clinical findings of sudden onset of hypoxia, cardiovascular compromise, and/or coagulopathy. The differential diagnosis of AFE includes, but is not limited to, pulmonary embolism, anaphylaxis, placental abruption, myocardial infarction, eclampsia, aspiration, and septic shock [1, 4, 5]. To date there are no specific laboratory tests available to diagnosis AFE. Some recent publications have suggested an insulin-like growth factor binding protein-1 as a useful biomarker for AFE diagnosis, with high sensitivity and specificity; however, this is not extensively used [6].

The Society of Maternal-Fetal Medicine (SMFM) and the Amniotic Fluid Embolism Foundation proposed a definition of AFE based on four diagnostic criteria, which are all required to be present. This definition was specifically developed for research purposes.

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 < 90%)

2. Documentation of overt DIC after appearance of these initial signs or symptoms, using this scoring system of the Scientific and Standardization Committee on DIC of the International Society on Thrombosis and Hemostasis (ISTH), modified for pregnancy. Coagulopathy must be detected before loss of sufficient blood to itself account for *dilutional* or shock-related consumptive coagulopathy

3. Clinical onset during labor or within 30 minutes of delivery of placenta

4. Absence of fever (≥38°C) during labor" [6, 14].

Although there are no specific tests that are currently recommended to confirm the diagnosis of amniotic fluid embolism, there are test that may help to support the

diagnosis. Initial evaluation should always include assessment of arterial blood gas to determine the degree of hypoxemia. In addition to arterial blood gas measurements, serial complete blood counts and coagulation studies should be trended in order to detect early coagulopathy [9]. These studies can aid in the early identification of DIC. Abnormalities often include a prolonged prothrombin time (PT) which is due to consumption of clotting factors as well as a decreased fibrinogen. Intervention is often indicated if the PT is 1.5 times the normal limit. Activated partial thromboplastin time may not be as helpful as values may be within normal reference range.

Additional laboratory tests proposed include various markers of C3 and C4 complement activation, serum tryptase, insulin-like growth factor binding protein-1, urinary histamine, and arachidonic acid metabolites [1, 4, 9]. Tryptase is a serine protease that has a half-life of several hours and has been useful in the diagnosis of anaphylaxis. Given the similarities of the reported pathophysiology of AEF and anaphylaxis, elevated levels of serum tryptase may aid in diagnosis. There have been reports of the use of immunostaining techniques of the monoclonal TKH-2 antibodies in maternal serum and lung tissue. Although data is limited, there are a few studies that have evaluated the use of serum sialyl Tn (STn) which is a fetal antigen in meconium as well as amniotic fluid that can be detected with TKH-2 monoclonal antibodies. TKH-2 reacts with fetal components (meconium and mucin) which stain the lung tissue of women with AFE [4, 5, 9]. Researchers found that serum levels of sialyl Tn greater than 50 U/ml had a sensitivity between 78 and 100% and a specificity between 97 and 99% [9]. Another biomarker of interest is zinc coproporphyrin, which is also a component of amniotic fluid found in maternal serum and can be elevated in women with AFE [1, 4, 9].

Radiographic findings are nonspecific and not diagnostic. The most common radiographic abnormalities in AFE are bilateral interstitial and alveolar infiltrates with areas of increased opacity which is indistinguishable from pulmonary edema [4, 9]. The use of bedside transesophageal echocardiography may aid in early identification of acute pulmonary vasoconstriction or left heart failure precipitating earlier intervention [4, 9].

5. Clinical presentation

The classic presentation of AFE is often described as an acute onset of respiratory distress, hypoxia, hypotension (including cardiac arrest), seizures, and DIC either during labor, during delivery, or in the immediate postpartum period. If AFE occurs during labor, electronic fetal heart tracings frequently demonstrate acute changes characteristic of fetal hypoxia. There is often a rapid progression from the time of onset of the initial signs and symptoms to end organ damage and death. Severe consumptive coagulopathy is seen in only two obstetric conditions, AFE and massive placental abruption [4]. DIC is present in approximately 80% of patients with AFE and may develop at any time; however, half of affected patients develop coagulopathy within 4 hours of initial symptoms [2].

6. Management

The management of women diagnosed with AFE is centered on supportive care. Unfortunately, even with prompt recognition and appropriate treatment, maternal morbidity and mortality remain high. The Society for Maternal-Fetal Medicine (SMFM) recommends a multidisciplinary team approach consisting of anesthesiology, critical care medicine, respiratory therapy, and maternal-fetal

medicine [6]. Treatment is initially focused on maternal cardiopulmonary stabilization with a goal to limit end organ damage [2]. Intravenous access with two large bore IVs should be obtained in anticipation of the need for aggressive fluid resuscitation. Hypotension is corrected with optimization of preload via rapid infusion of isotonic crystalloid and colloid solutions [4, 8, 9]. Transthoracic or transesophageal echocardiography is helpful to guide fluid therapy [4–6, 9]. Placement of an arterial line and pulmonary catheter if feasible is also useful. In addition to IVF resuscitation, transfusions of packed red blood cells are necessary to aid in hypotension as well as restoration of oxygen carrying capacity. The use of vasopressors and or inotropic support is often necessary. A central line should be placed for infusion of vasopressors as well as monitoring. Following stabilization of the patient, admission to an intensive care unit is recommended for close monitoring. Initial laboratory testing should include a CBC, arterial blood gas, electrolytes, and a coagulation panel.

6.1 Hypoxia

Acute hypoxia is frequently the first sign of AFE and has been reported to be present in >90% of patients according to the AFE National Registry [2]. Maternal oxygenation should be monitored by pulse oximetry. The degree of respiratory compromise will determine the approach for oxygen delivery. Regardless of the route of delivery, oxygen should be administered immediately and judiciously. Intubation is often necessary but may not be required in all cases.

6.2 Cardiac arrest

The early phase of AFE often consists of right ventricular failure which can be identified with the use of transthoracic or transesophageal echocardiography [9, 13]. Findings of echocardiography may include a dilated right ventricle and a collapsed left ventricle with leftward deviation of the interventricular septum [9, 13]. Cardiopulmonary resuscitation (CPR) should be initiated immediately with priority given to high-quality chest compressions before rescue breaths [6]. Standard basic life support (BLS) and advanced cardiac life support (ACLS) protocols should also be initiated [1, 6]. If the fetus is undelivered and has reached a gestational age of potential viability (≥23 weeks), immediate delivery is indicated [1, 2, 6]. Preparation for a perimortem cesarean section should occur simultaneously with the initiation of CPR [1, 10]. The undelivered patient should be placed in a left lateral tilt that displaces the uterus to avoid compression of the aorta and IVC [2, 6]. Patients that progress to cardiac arrest have a dismal prognosis compared to their counterparts with AFE that do not develop cardiac arrest.

6.3 Coagulopathy

Hemorrhage with DIC requires initiation of a massive transfusion protocol. Correcting the coagulopathy may require aggressive repletion of red blood cells and blood products, fresh frozen plasma, platelets, and/or cryoprecipitate. Consideration should be given to arterial catheterization if possible, which allows for accurate blood pressure monitoring as well as blood sampling [5]. The use of recombinant factor VIIa has been reported in the literature, though data on its use is limited and conflicting. Research suggests that the use of recombinant factor VIIa most likely should be reserved for cases where conventional resuscitative measures fail [1]. Increasing evidence suggests the use of thrombelastometry for early identification of patients with AFE but also to guide management, providing a point of care for monitoring during the hemorrhagic phase of AFE [17].

Additional approaches to treatment of amniotic fluid embolism reported in the literature include extracorporeal membrane oxygenation (ECMO), plasma exchange transfusions, cardiopulmonary bypass, uterine artery embolization, continuous hemofiltration, pulmonary artery thromboembolectomy, intra-aortic balloon pump with ECMO, high-dose corticosteroids, C1 esterase inhibitors, and serum protease inhibitor therapy. There are no high-quality data available for many of the treatment approaches mentioned.

Aprotinin is a single-chain polypeptide derived from bovine tissues and is an inhibitor of proteolytic enzymes [9]. It is used in the treatment of hemorrhage associated with raised plasma concentrations of plasmin and may be effective for hemorrhage associated with AFE. Other fibrinolytic agents like tranexamic acid and aminocaproic acid are used in the management of hemorrhage and may be useful. Hysterectomy is necessary in individuals when uterine hemorrhage persists despite more conservative measures.

7. Outcomes

Mortality associated with amniotic fluid embolism appears to have declined which is likely associated with early diagnosis as well as improvements in critical care [4, 5, 9]. Disease severity (i.e., the presence or absence of cardiac arrest) is closely related to prognosis. Mortality rates vary greatly depending upon criteria used for diagnosis of AFE but have been reported as high as 60–70% [1, 9, 14]. The use of population-based studies appears to provide the best available evidence of the mortality rate associated with AFE. Analysis of a collection of 9 population-based studies published since 1999 which included more than 17 million births in 8 countries and 751 cases of amniotic fluid embolism revealed an overall mortality rate of 20.3% [7]. Morbidity, however, remains extremely high and can include serious neurologic impairment, renal failure, cardiac failure, arrhythmias, and myocardial infarction [5, 9].

Although limited data is available, neonatal survival rates are reported in the range of 70% [4, 5, 9]. Survival is dependent upon timing of delivery relative to onset of symptoms. Neonates delivered prior to onset of symptoms or soon after onset of symptoms have lower rates of morbidity and mortality.

There is no data to suggest that survivors of AFE have an increased risk of recurrence in a subsequent pregnancy. However, the risk of recurrence is unknown. There have been published case reports of successful pregnancies following an AFE.

8. Summary

Amniotic fluid embolism remains an elusive disease with catastrophic outcomes. The pathophysiology remains unclear even with new research developments over the last 10 years. However, the theory that the syndrome may be caused by an abnormal maternal proinflammatory response incited by fetal components is promising. The variation in maternal response to fetal and amniotic components present in the maternal circulation may provide useful information and requires further investigation. Various laboratory tests and biomarkers have been proposed that may aid in diagnosis of an AFE; however, there is no gold standard diagnostic test available at this time. AFE remains a diagnosis of exclusion and relies on clinical judgment. A high level of suspicion in laboring or postpartum women with acute cardiopulmonary compromise or coagulopathy is required for optimal maternal and fetal outcomes.

Methodology

A literature search was performed using PubMed. The term "amniotic fluid embolism" was used to search the database. The search was further narrowed using year of publication. Articles from 2005 to the present were selected. A combination of case reports, case series, population-based cohort studies, case control analysis, and review articles were included for review.

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