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Amniotic Fluid Embolism: Clinical Challenges and Diagnostic Dilemmas

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Abstract

Amniotic fluid embolism (AFE) is an obstetric emergency accounting for 10% of maternal mortality in the United States. The understanding of the pathophysiology is incompletely understood, but is likely related to an inflammatory reaction to fetal components in the maternal circulation. There is evidence of serotonergic effects, complement activation and mast cell activation within maternal organs during the clinical presentation that support this pathophysiology. This abnormal maternal response is unpredictable. The quality of evidence is hindered by false diagnosis, which may account for 30% of reported cases and makes describing risk factors and directed treatments challenging. The aim of recent research efforts is to standardized the diagnosis so as to clarify the characteristics of AFE. The mainstay of treatment is supportive care and aggressive correction of coagulopathy. However, new therapies target the pro-inflammatory immune response. Additionally, some case reports describe successful utilization of extracorporeal membrane oxygenation. This review focuses on summarizing the literature with attention to the pathophysiology, uniform research diagnosis, and recent treatment modalities described in the current literature.

Keywords: Amniotic fluid embolism; Pathophysiology; Obstetric shock

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Introduction

Amniotic fluid embolism (AFE) continues to be an unpredictable and unavoidable obstetrical emergency. It was first described in the 1926 by Meyer and further elucidated in a case series in the 1940's [1]. Historically, it was called alternatively "obstetric shock" and "pulmonary embolism by amniotic fluid". Since then the low incidence has made AFE a difficult phenomenon to describe and study. The incidence is estimated to be approximately 1.9 - 6 per 100,000 women, although this is often confounded by diagnostic uncertainty. Knight et al found that prospective studies among developed countries estimated the incidence to be 1.9 – 2.5 in 100,000, while retrospective studies found an incidence of 5.5 – 6.1 in 100,000 [2]. The rates were especially increased when using ICD 9 codes without additional expert case review. This indicates the incidence of AFE may be overestimated due to a false positive diagnosis and differing methodologies in different reports. Of note, the incidence of AFE in the United States is approximately three-fold that of other countries. Fitzpatrick et al examined the incidence in the United Kingdom from 2005-2014 and reported it to be 1.7 in 100,000, lower than most estimates in the literature [3]. The mortality rate is estimated to be 0.4 – 1.3 in 100,000 in developed countries [2]. Mu et al found reported maternal mortality as 4.4/100,00 in 1996 with a decrease to 1.9/100,00 in 100,000 by 2013. However, this may represent epidemiologic differences between developed and underdeveloped regions as evidenced by a significant difference between rural and urban areas within China [4]. The case fatality has been estimated between 11-43 % [2]. Older reviews describe the mortality as high as 80% [5]. Despite variation in both incidence and mortality, the proportion of maternal death attributed to AFE has remained unchanged at 5-15% since 1990 [5,6].

Pathophysiology

Initially called "obstetric shock," AFE was associated with sudden maternal death without obvious etiology. Squamous cells were noted in the maternal pulmonary vasculature, leading to the hypothesis that the contents of amniotic fluid caused a physical obstruction within the maternal pulmonary circulation similar to a pulmonary embolus [2,5]. Despite many attempts at reproducing this effect in animal models, a similar clinical syndrome was not found. In fact, small amounts of amniotic fluid injected into women with ovarian cancer did not cause any hemodynamic instability

[7]. More recent research points to an acute immune response leading to inflammatory reaction similar to anaphylaxis and associated with pulmonary vasculature constriction. [6]. Endogenous mediators such as histamine and arachidonic acid metabolites provoke an acute phase reaction ultimately leading to the typical clinical presentation of AFE. Mass cell activation may attenuate this response by serotonergic effects on maternal vasculature and worsened vasoconstriction. Funk et al tried to answer the question as to whether mechanical obstruction played any part in the pathophysiology by estimated the number of fetal squamous cells in amniotic fluid and comparing this to volume of alveolar units in the maternal lungs. They conclude that the volume of fetal squamous cells would occupy less than one percent of alveolar units [8]. The pathogenesis of the coagulopathy associated with AFE is still poorly understood, but the current hypothesis is that procoagulants in amniotic fluid lead to a consumptive coagulopathy. [1]. Adding amniotic fluid to maternal blood samples leads to hypercoagulability as well as increased platelet activation [9]. Thromboxane within amniotic fluid may also play a role, and amniotic fluid has been shown to active tissue factor. In addition to these effects, AFE may cause DIC through complement activation which indirectly lead to thrombosis in the maternal circulation. [10].

Clinical Presentation and Diagnosis

Despite decades of searching for specific biomarkers, pathologic or imaging findings that aid in the diagnosis of AFE, it remains a clinical diagnosis. It is characterized by the triad of hypoxia, cardiopulmonary collapse and DIC in the peripartum period [1,5]. Historically, the diagnosis was made by isolating squamous cells in maternal pulmonary vasculature. However, this is a finding in several other conditions such as severe hypertensive disorders and sepsis. [6]. Fetal components can be found in 21-100% of critically ill peripartum women without a clinical presentation consistent with AFE. Only 22-83% of patients with AFE will have DIC [11], and it typically occurs within hours of the initial clinical presentation. Non reassuring fetal status may be the first symptom and fetal bradycardia in combination with maternal hypoxia should raise the clinical suspicion for AFE and a concern for impending maternal cardiovascular collapse.

AFE frequently presents with hypoxia followed by hypotension and cardiac arrest. The cardiac sequela of this syndrome is typically biphasic, with initial right heart failure, dilated right ventricle which is then followed by left heart failure. The progression to left heart dysfunction is associated with pulmonary edema and adult respiratory distress syndrome (ARDS) which continues past the acute presetation. Coagulopathy may occur as an early or late feature. [1]. Premonitory symptoms such as altered mental status, a sense of distress, nausea and vomiting while not specific, commonly precede maternal collapse. [11]. The diagnosis of AFE is supported by transesophageal echocardiogram with an initially dilated, hypokinetic right ventricle [12]. Some recent case reports have shown strand-like material in the right atrium and ventricle during the acute phase of the illness which later disappears. [13,14]. These strands may represent a maternal immunologic response to the amniotic fluid. Laboratory findings consistent with coagulopathy support the diagnosis, but there is not specific biomarker that confirms an AFE. Clark et al has suggested standardized diagnostic criteria to aid in research of AFE. By creating uniform criteria, the authors aimed to exclude confounding findings with false positives. These criteria are: 1) Sudden onset of cardiorespiratory arrest, or both hypotension and respiratory compromise. 2) Documentation of Overt DIC following appearance of these initial signs and symptoms, but prior to significant blood loss. 3) Clinical onset during labor or within 30 minutes placental delivery. 4) No fever during labor [15] Stafford et al evaluated these criteria against expert review and found 78% of AFE cases identified by review were also identified by the uniform criteria [16]. Atypical cases were unlikely to be included, and cases without evidence of DIC were most likely to be excluded. With implementation of a uniform diagnostic criteria, new biomarkers and management strategies can be identified.

Management

There is no targeted therapy for AFE, and the management is supportive. During the initial disease course, treatment focuses on managing the respiratory failure, cardiac arrest, and coagulopathy. [4,6,11]. Patients with suspected AFE are monitored with telemetry and pulse oximetry. With worsening patient status, end-tidal CO_2, continuous blood pressure, pulmonary artery catheter, central venous pressure, systemic vascular resistance may all necessary. [11]. Transesophageal echocardiography has be useful. Laboratory evaluation should focus on correcting the coagulopathy and should include complete blood count, prothrombin time, fibrinogen, antithrombin III levels and blood type. Multiple units should be crossmatched. Arterial blood gases and electrolytes are help to guide resuscitative measures [12]. A multidisciplinary approach including critical care physicians, anesthesiologists and blood bank personnel is indispensable in cases of AFE. Treatment should occur within an intensive care setting [18]. The activation of the massive transfusion protocols is essential.

Notably, if AFE presents antepartum with a viable fetus, delivery is indicated for fetal and maternal indications [12]. The placenta is not well perfused during cardiorespiratory resuscitation. A gravid uterus adversely impacts blood pressure and preload further compromising cardiac output. If advanced cardiac life support is attempted in a gravid woman, the patient should be in left-lateral tilt to ameliorate these effects. In order to decrease the incidence of neurologic impact and long-term sequelae, rapid correction of maternal hemodynamics is necessary using standard advanced cardiac life support protocols. Hypotension is corrected with inotropic agents, but intravenous fluids are limited. Vasopressors, antiarrhythmic agents, and defibrillation are used in a similar manner to other critically ill patients [1,11,12] Management of hypoxia and respiratory failure is dictated by the severity of symptoms. It may include noninvasive oxygen supplementation, but most often necessitates intubation and ventilation. Oxygen saturations should be kept above 90% to prevent neurological complications. By limiting fluid resuscitation during the acute phase, the risk of pulmonary edema is decreased [19]. Pulmonary edema and ARDS often occur after the initial cardiac symptoms. In addition to a cardiopulmonary arrest, DIC is associated with approximately half of all cases of AFE [5,12]. The management is the same as in other clinical scenarios with the activation of massive transfusion protocols and the replacement of red cells, platelets and coagulation factors. Blood products are transfused in a grouped fashion – 1 unit packed red blood cells, 1unit of fresh frozen plasma or cryoprecipitate, and 1unit of platelets. Unfortunately, as DIC develops, the risk of atony and catastrophic maternal hemorrhage increases. Surgical management with cesarean hysterectomy was necessary in 25 percent of women in one review [3]. Factor VII should not be used in the initial management of hemorrhage, as it is associated with worsened survival in women with AFE [3,11]. Agents

that decrease pulmonary vascular resistance have been suggested but have not been definitively shown to improve outcomes in these patients. Sildenafil, prostacyclin, and inhaled nitrous oxide have been utilized in case reports with some success [17].

In the most recent ten years, multiple case studies have described cases of AFE where veno-arterial extracorporeal membrane oxygenation (ECMO) has been utilized successfully [20-22]. As anticoagulation is necessary for ECMO use, ECMO is not recommended by the society of maternal fetal medicine. A recent case study describes a case that was notable for heparin-free ECMO during the initial 48 hours after cardiopulmonary collapse in the setting of hemorrhagic shock and DIC [20]. Atropine, ondansetron and ketorolac (A-OK) have been used together to decrease the serotonergic affects during AFE. Rezai et al. describe a case where this protocol – called A-OK – was used and the patient had an uneventful recovery [23]. This case was confounded with evidence of sepsis prior to cardiovascular collapse, which may indicate that this was not a true case of AFE.

Prognosis

Women who survive AFE have increased mortality. Fitzpatrick et al found a rate of 13% for neurologic deficits in survivors [3]. Knight et al found that 20% of survivors in the UK had cerebral infarcts after AFE [2]. Cardiac arrest and advanced cardiac life support were associated with increased rates of neurologic sequelae. This is likely a representative of the consequences of hypoxia during the resuscitation. In addition, the rate of fetal demise is 7-38% [2]. Fetal compromise may be an early feature of AFE, and maternal hemodynamic instability directly affects fetal oxygenation [25]. Unfortunately, there is no data on long term outcomes for survivors. Women report that AFE affects their future reproductive choices, and 52% report of patients that their obstetrician recommended against future pregnancies [25]. When compared to age-matched cohorts, women who had survived AFE were half as likely to have a subsequent pregnancy [25]. This is despite the absence of evidence that there is no known risk of recurrence [11].

Conclusion

Although AFE has been described for over one hundred years, the understanding of the pathogenesis, diagnosis, directed treatment and most importantly prevention is incomplete. The rate of misdiagnosis of AFE is approximately 30%, impacting our ability to understand and describe this disease process. New research using uniform criteria could help exclude false positives and allow clinicians to develop targeted treatment and prevention strategies. AFE accounts for approximately 10% of maternal mortality, and improved understanding of this phenomenon may help address the maternal mortality. With mounting evidence that a complex inflammatory process better explains the pathogenesis of AFE, further research targeting these inflammatory mediators may lead to directed treatments.

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