



## Recent Perspective of Amniotic Fluid Embolism: A Review Article

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### Authors' contributions

*This work was carried out in collaboration between all authors. Author TCO designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors TCO, COTE and LCI searched literature and reviewed the paper. All authors read and approved the final manuscript.*

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Review Article

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### ABSTRACT

**Background:** Amniotic fluid embolism (AFE) is a rare obstetric emergency with unclear aetiology, pathophysiology, diagnosis and management. The true incidence is unclear and diagnosed largely by exclusion. It can neither be predicted nor prevented and its management is fraught with controversy.

**Objective:** To provide clinicians with current knowledge regarding the epidemiology, pathophysiology and management of AFE.

**Methods:** This was a descriptive review of AFE. We searched several databases (Medline, Google scholar and Pubmed) with keywords, amniotic fluid, amniotic fluid embolism, amniotic fluid embolus and sudden postpartum collapse from inception to June 2014.

**Results:** Data regarding the presence of risk factors for AFE are inconsistent, complex and contradictory. No risk factor has been identified that would justify modification of standard obstetric practice to reduce the risk of AFE. Further understanding of this syndrome has been hampered by lack of universally accepted diagnostic criteria. Diagnosis of AFE is clinical, largely by exclusion,

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and maternal treatment is primarily supportive and not causative. Mortality is still high despite improved modalities for diagnosing AFE, and better intensive care support facilities.

**Conclusion:** AFE is a rare and dreadful obstetric emergency with a high morbidity and mortality rate. Our understanding of its aetiology and pathophysiology is incomplete and the criteria used to make its diagnosis are controversial. In spite of advances in the care of critically ill patients, no management interventions have been found to improve survival or long-term outcome of patients with AFE.

*Keywords: Amniotic fluid; amniotic fluid embolism; cardio respiratory collapse; coagulopathy; disseminated intravascular coagulation; pregnancy.*

## 1. INTRODUCTION

Amniotic Fluid Embolism (AFE) is a rare but catastrophic obstetric emergency that occurs as a result of entry of amniotic fluid and particulate matter into the maternal circulation leading to sequelae of this clinical syndrome. It is characterized by sudden cardiovascular collapse, altered mental status, nonreassuring fetal status and disseminated intravascular coagulation (DIC) [1-3]. AFE has a high mortality rate of 80% [3]. Fetal mortality is about 40% [4]. AFE, though a rare obstetric condition, is a relatively common cause of maternal mortality [5]. About half of patients that survive the initial insult develop DIC [3]. AFE presents two separate medical emergency life-threatening conditions that occur either simultaneously or in sequence such as cardio-respiratory collapse and coagulopathy [6].

The exact pathophysiology of AFE is still poorly understood [7]. Recently, despite little understanding of the pathophysiology, improved modalities for its diagnosis, and intensive resuscitation and care support facilities, fetomaternal outcomes are still poor. However, several aspects of this condition are fraught with controversy. The diagnosis is essentially one of exclusion based on clinical presentation. Although other causes of haemodynamic instability should always be borne in mind. The concept of the diagnosis of AFE traditionally made at autopsy, when fetal squames cells are commonly found in the maternal pulmonary circulation is not specific. It is certain that fetal squames cells are commonly found in the circulation of labouring patients who do not develop AFE. However, presence of fetal squames cells is suggestive of but not diagnostic of AFE [1,8]. Therefore, the aetiology and pathophysiology are still not very clear and its diagnostic criteria are fraught with controversy. Furthermore, despite advances made in management of critically ill patients of AFE, no approach appears to improve the survival or long-term outcome of these patients.

This review, however, examines the current knowledge regarding the epidemiology, pathophysiology and management of AFE.

## 2. METHODOLOGY

This was a 6-month descriptive review of Amniotic fluid embolism. Relevant literature search in this topic was from June 1st to December 31st 2014. A search of literature on AFE published in English was conducted. Relevant materials on AFE were selected. We searched several databases on AFE from inception to June 1<sup>st</sup> 2014 with keywords "Amniotic Fluid Embolism", amniotic embolus, amniotic fluid and sudden post-partum collapse. We also searched references in retrieved articles, book chapters, review articles, conference papers, technical reports, abstracts and internet articles using Medline, Google scholar, and Pubmed databases. These materials were critically reviewed and the inclusion of individual articles was based on scientific merit and clinical relevance.

### 2.1 Historical Perspective

The presence of amniotic fluid and fetal particulate matter in the pulmonary blood vessels of a mother who had died suddenly in labour was first reported by Meyer [9] in 1926. Another report was made in 1927 in an experiment on laboratory animals by Warden [10]. This syndrome was first described and characterized by Steiner and Lushbaugh [11] in 1941. The histopathology of the pulmonary vasculature of the women included, mucin, amorphous eosinophilic material, lanugo hairs, fat droplets and squamous cells. These findings presented the classic pathology findings in AFE. The pathophysiology was thought to involve embolization of animal debris of fetal origin but evidence has shown that the syndrome results from bronchial mediators that are released after embolization. Clark et al. [12] proposed renaming

the syndrome “anaphylactoid syndrome of pregnancy” because of the humoral and immunologic factors implicated in this condition. Current data from the National Amniotic Fluid Embolus Registry suggest that the process is more similar to anaphylaxis than to embolus and hence the name “anaphylactoid syndrome of pregnancy” because the fetal tissue or amniotic fluid components are not universally found in women who presented with signs and symptoms attributable to AFE [12].

AFE is a rare obstetric condition and due to low frequency of the condition, it is difficult for it to be studied and hence poorly understood. However, Clark et al. [12] in the United States and Tufnell [13] in the United Kingdom established a national registry for suspected AFE. The diagnostic criteria are the presence of the following 4 signs or symptoms [12-14]:

1. Acute hypotension.
2. Acute hypoxia.
3. Coagulopathy or severe clinical haemorrhage in the absence of other explanations.
4. All of these occurring during labour, caesarean delivery or dilatation and evacuation or within 30 minutes postpartum with no other explanation for the clinical findings.

Currently, the diagnosis is clinical. It is essentially one of exclusion based on clinical presentation. However, other causes of haemodynamic instability should be borne in mind.

The Leukotriene concept of AFE was described by Clark [15] in 1985, then Azegami and Mori [16] in 1986. Later in 1990, Clark provided an overview of the Leukotriene theory of AFE [17]. The basis of Clark description was that infusion of amniotic debris of fetal origin on experimental animals resulted in severe pulmonary hypertension followed by systemic hypotension with negative inotropic effect and decreased cardiac output [17]. Clark assumed that the action observed in experimental animal could occur in humans as well. This theory believes that Leukotrienes (thromboxane A<sub>2</sub>) cause fetal pulmonary vasoconstriction in AFE. The Leukotriene theory concept of AFE has dominated other concepts. Recently, the search for potent vasoconstrictors and bronchoconstrictors in amniotic fluid that could induce embolic phenomenon is still on-going. Currently, the roles of arachidonic acid (Leukotriene) [18], endothelin-1[19], Brady-kinin

[20], Thrombin [21], contained in amniotic fluid in causation for AFE are the subject of research to discover the most potent vasoconstrictors and bronchoconstrictors.

## 2.2 Origin of Amniotic Fluid (AF)

Amniotic fluid takes its origin from both mother and the fetus. As a result of its mixed origins the following mechanisms have been described. In the first trimester (1) Primitive cells around the amniotic vesicle (2) Active secretion from the amniotic epithelium. (3) Transudate from maternal circulation across placental surface and fetal membranes. (4) Transudate of fetal extracellular fluid which is formed through the fetal skin and across surface of umbilical cord.

In the later part of pregnancy from 2<sup>nd</sup> trimester, the skin becomes Keratinized and waterproof: there is an increasing contribution from fetal urine and fetal lung secretions. As the fetus develops an ability to swallow, a circulation of fluid occurs with the result that the fluid excreted from the kidneys is passed through the bladder into the amniotic pool. The fluid is now swallowed, digested and re-excreted. Apart from tracheobronchial secretion and transfer across fetal skin prior to its keratinization, additional contributions to amniotic pool, comes from amniotic membrane secretions.

The volume of AF varies according to gestational maturity. Its volume is about 50 ml at 12 weeks, 400 ml at 20 weeks and peaks to about 1000ml at 38 weeks with a rapid fall in volume at post-term (800 ml at 40 weeks: 350 ml at 42 weeks). The reason for this reduction in AF volume in post-term is not clearly explained [22,23].

## 2.3 Composition of AF

AF is heterogenous in composition and has a neutral pH. In the first half of pregnancy, the composition of AF is the same as maternal plasma except for a much lower concentration of protein [22]. As pregnancy advances, the composition and volume of the liquor amnii change. It contains cells and cellular debris with insoluble materials suspended in a clear solution. The osmolarity decreases as pregnancy progresses. At term it contains three main types of cells (fetal epithelial cells, amniotic cells and dermal fibroblasts). Nitrogenous waste (urea, creatinine and uric acid) increases in concentration towards term reflecting the increasing function of the fetal kidneys. Other constituents are proteins (Albumin, globulins),

lipids in form of free fatty acids and lecithin and carbohydrates. Inorganic salts, Na<sup>+</sup> and Cl<sup>-</sup> concentrations are high while K<sup>+</sup>, Ca<sup>++</sup>, Mg<sup>++</sup>, P<sub>04</sub> are low. AF has antibacterial activity due to its pH and the presence of lysozyme, peroxidase and ∞-interferon [23].

At term AF consists of 98-99% water and 1 – 2% solid constituents. The solution consists of organic substances like protein, lipid and carbohydrates. It also contains hormones, enzymes, inorganic constituents like Na<sup>+</sup>, Cl<sup>-</sup>, K<sup>+</sup> and suspended particles like epithelial cells, vernix caseosa, exfoliated amniotic epithelial cells and exfoliated cells from the tracheobronchial tree, vagina and bladder of the fetus.

AF is pale straw coloured or faintly turbid, milky, having a low specific gravity of 1010. It is highly hypotonic to maternal serum at term. The AF is measured in quantity, colour and consistency [22]. The normal pale straw colour of AF may be altered under certain circumstances. It may appear turbid due to presence of vernix caseosa. Abnormal appearance may be as follows: greenish due to presence of meconium indicative of past or present fetal distress in presentations other than breech or transverse lie. Golden-yellow, may be seen in presence of bilirubin resulting from fetal cell haemolysis as a result of Rh-Incompatibility. Greenish-yellow, may be seen in post maturity. Dark-Maroon, observed in altered blood in accidental haemorrhage. Prune juice, observed in presence of retained dead fetus. Blood stained, freshly blood stained and bright red in Vasa praevia or low lying placenta [22,23].

## 2.4 Procoagulants and Anticoagulants in AF

Tissue Factor (TF) is the predominant procoagulant in the AF. Tissue factor and a few coagulation factors are in active forms (IIa, VIIIa, and Xa) [24]. Amniotic fluid does not contain fibrinogen, factors V and VII. AF has all other

coagulation factors: II, TF, VIII, IX, X, XI, XII, XIII, Prekallikrein and higher molecular kininogen (HMK) and anticoagulants tissue factor pathway inhibitor (TFPI): antithrombin protein C and S, thrombo modulin (TM) (Table 1).

The levels of coagulants and anticoagulants are very low compared to plasma (3% - 5% of plasma). The level of tissue factor in amniotic fluid is higher than that in the maternal plasma [25]. The higher molecular weight form of tissue factor (46,000) predominates in Amniotic fluid (in tissues 40,000 – 46,000) [24]. The major source of tissue factor in AF is assumed to be the cells of desquamated epidermis of the fetus. There is evidence to support activity of the coagulation cascade in the AF but due to lack of fibrinogen this activity is incomplete. High thrombin markers such as fragments of prothrombin F1+2 and thrombin-antithrombin complex indicate that thrombin is generated in the AF. Thrombin substrates in loco include protein C and Pro-TAFI (procarboxypeptidase B), the anticoagulant called activated protein C (APC) and thrombin activatable fibrinolysis inhibitor (TAFI), a spectacular link between/coagulation and fibrinolysis are formed in AF [25].

AF also contains other enzymatic systems that have cascade dynamics namely Leukotrienes (arachidonic acid cascade), and Kinins (Kallikrein-Kinin cascade). It also contains proteins of the fibrinolytic system and products suggesting plasmin activation [26].

## 2.5 Incidence

The true incidence of AFE is uncertain because of inaccurate diagnosis and inconsistent documentation of mild cases. The diagnosis of AFE remains one of exclusion with possible under reporting of mild cases. However, with recent large population – based studies, the incidence of AFE ranges between 1 in 13,000 deliveries in USA [27,28] to 1 in 57000 in the UK [29,30]. Maternal mortality approaches 80% and

**Table 1. Procoagulants and anticoagulants in AF**

Procoagulants	Anticoagulants
(1) Tissue Factor (TF)	(1) Tissue Factor pathway inhibitor (TFPI)
(2) Coagulant factors: II, TF, VIII, IX, X, XI, XII, XIII, Prekallikrein, high molecular kininogen (HMK)	(2) Antithrombin (AT)
	(3) Protein C and S
	(4) Thrombomodulin (TM)

\* AF does not contain fibrinogen, factors V and VIII

the morbidity is also high [7]. There is a drop in maternal mortality rate as a result of AFE. Reported figures range from 37% - 61% [12,13]. The reasons for the low reported figures may be due to early diagnosis and advances in intensive care centres and better resuscitation techniques. Majority of women with AFE die within the 1<sup>st</sup> hour of onset of symptoms and about 85% of those who survive have permanent hypoxia induced neurological impairment [6,31].

Neonatal out-come is poor with a mortality rate of 20-25%, among the survivors, 50% may be neurologically intact [12,13]. The onset of AFE cannot be predicted or prevented because there are no proven risk factors [7]. No racial or ethnic predilection exists.

AFE typically occurs during labour, soon after vaginal or caesarean delivery or during second-trimester dilatation and evacuation procedures [6,12,31]. Seventy percent of AFE occur during labour, 19% during caesarean delivery and 11% following vaginal delivery. AFE is also reported during early pregnancy, second trimester abortions, during amniocentesis or following closed abdominal injury [12,31].

## 2.6 Risk Factors

There are no proven risk factors for AFE. Risk factors that are significantly associated with an increased risk of AFE are maternal age of 35 years or older, caesarean section, instrumental vaginal deliveries, placenta praevia, abruptio placentae, eclampsia and fetal distress. Other significant risk factors are polyhydramnios, cervical laceration or uterine rupture [27,28,32], amniocentesis [33], removal of placenta [34], therapeutic abortion [34], abdominal trauma [35], intrapartum amnio infusion [32] and African American race [28].

Other documented risk factors are multiparity, meconium stained liquor, intrauterine fetal death, strong frequent or tetanic uterine contractions, maternal history of allergy or atopy and chorioamnionitis [31].

## 2.7 Pathophysiology

The pathophysiology is still poorly understood because of limited human studies on AFE. Documented reviews have been speculative with a lot of published theories. Three theories are postulated to explain the pathophysiology of cardio-respiratory disorders and coagulation disturbances in AFE, each of which have

different premises: (1) the mechanical theory postulates that fetal squames and other components of the AF act as a causative factor blocking the pulmonary circulation. (2) The Thromboplastin theory postulates that the obstruction is due to disseminated intravascular coagulation (DIC). (3) The Leukotriene theory postulates that it is the Leukotrienes that cause catastrophic pulmonary vasoconstriction [18].

Clark et al. [12] proposed that AFE arose from an immune process rather than embolic process. Steiner and Lushbaugh [11] in their early work on AFE reported the presence of Mucin, amorphous eosinophilic material and squamous cells in women with AFE, consistent with the presence of amniotic fluid. They hypothesized that amniotic fluid was forced into the maternal circulation during contractions leading to the embolic event. Clark et al. [12] speculated that the least likely time for transfer of AF is during tumultuous labour or during uterine tachysystole. Lee et al. [36] demonstrated that fetal squamous cells can be found in the pulmonary circulation of women without clinical evidence of AFE and other investigators could not reproduce the syndrome in two separate animal models, mini pigs and monkeys, by injecting AF directly into their circulation [37]. Clark et al. [12] in their registry documented that 19% of women first manifested symptoms during caesarean delivery when there is no tumultuous labor.

Clark et al. [12] recognized that the clinical course and haemodynamic changes of AFE were similar to patients with anaphylactic shock and proposed that AFE was more of an immunologic than embolic phenomena. AF contains numerous vasoactive and procoagulant substances, such as platelet activating factor, cytokines, bradykinin, thromboxane, leukotrienes and arachidonic acid and entrance of minute amounts of these substances into the maternal circulation could cause the syndrome [38]. This explained why fetal cells were not always found in women who suffered AFE. Clark et al. [12] proposed renaming the syndrome (AFE) to "anaphylactoid syndrome of pregnancy" because of the various humoral and immunologic factors implicated. To support this immunologic theory is the finding that AFE is commoner in women carrying male fetuses and these women are at increased risk for Rh iso-immunization, another immunologic based condition [39]. There are also striking similarities between clinical and haemodynamic findings in AFE and septic shock, which suggest a common pathological mechanism. Gei and

Hankins proposed a pathophysiological course [40]. Further support for an immune basis is that complete activation, another component of the immune response, may play a role in the pathogenesis of AFE. Specifically, C3 and C4 levels are markedly decreased in women with AFE [41].

Three distinct response or a combination responses to circulating fetal debris are suggested. The initial respiratory reaction begins with transient pulmonary vasospasm [17] and leads to pulmonary hypertension, intrapulmonary shunting bronchoconstriction and severe hypoxia [42]. The maternal mediators may have an influence in this manifestation [42,43,44].

The 2<sup>nd</sup> manifestation includes negative inotropism and left ventricular failure resulting in increasing pulmonary oedema and hypotension leading to shock. The 3<sup>rd</sup> manifestation is a neurological response to the respiratory and haemodynamic injury which may include seizures, confusion, or coma [40].

About 45% of patients that survive to this point have severe coagulopathy usually DIC with uncontrollable uterine bleeding along with bleeding from puncture sites such as intravenous insertion sites and epidural catheters [40]. This coagulopathy is precipitated by several procoagulant components of AF, e.g. thromboplastin which initiates the extrinsic pathway of the clotting cascade and results in excessive fibrinolytic activity [40].

Most patients of AFE may die of severe lung, or brain injury, multiple organ failure or from an infection acquired in the intensive care unit [17].

## 2.8 Clinical Presentation

AFE occurs intrapartum or in the immediate postpartum period [7]. The classical clinical presentation of AFE is in two forms (1) Typical (classic) with 3 phases; phase 1: respiratory and circulatory disorders, phase 2: coagulation disturbances of maternal haemostasis, phase 3: acute renal failure and acute respiratory distress syndrome (formerly adult respiratory distress syndrome ARDS) and (2) Atypical form, without the phase of respiratory circulation disorders, beginning with haemostasis disorders in the mother e.g. uterine haemorrhage or sometimes ARDS and Renal failure [18]. The symptoms are often sudden and protean. The prodromal symptoms in AFE are sudden chills, shivering, sweating, anxiety and coughing followed by signs

of respiratory distress, shock, cardiovascular collapse and convulsion [7,33]. Respiratory difficulty evidenced by cyanosis, tachypnoea, and bronchospasm, frequently culminates in fulminant pulmonary oedema.

Hypoxemia explains the cyanosis, restlessness, convulsions and coma. Reflex tachypnoea results from the decreased arterial oxygen saturation and cardiovascular collapse, heralded by hypotension, tachycardia, and arrhythmia may end in cardiac arrest.

Convulsion is an early manifestation of central system involvement combined with cerebral ischaemia and may lead to coma and death. However, it may be difficult for the patient to survive this initial episode, which occurs as a result of DIC and uterine atony. DIC is present in more than 83% of patients with AFE [7]. The onset can occur within 30 minutes from onset of symptoms or may be delayed for up to 4 hours [45]. AF contains tissue factor that acts as a procoagulant and may account for the coagulopathy [24].

## 2.9 Diagnosis

The diagnosis of AFE is clinical and is one of exclusion. The diagnosis of AFE is suspected in a woman who presents with 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 conditions or potential explanation for the symptoms and signs presented [41].

Laboratory tests (a complete blood count, coagulation profile, arterial blood gases cardiac enzymes and electrolytes) are non-specific [1,2]. No specific laboratory tests are available for making a diagnosis of AFE, however, several tests have been proposed to increase the index of suspicion for this diagnosis or support this diagnosis. The identification of squamous cells in central venous blood [46], and detection of squamous cells in pulmonary arterial blood is not pathognomic for AFE since it is equally identified in 21 – 100% pregnant women without AFE [36] and in non pregnant women [8]. The detection of squamous cells in the maternal pulmonary arterial circulation is not sufficient for the diagnosis of AFE. The identification of squamous cells in the maternal pulmonary arterial circulation is supportive of the diagnosis, and /or they are accompanied by other fetal debris [36,46].

Diagnostic makers for AFE (zinc coproporphyrin, sialyl, tryptase and complement factors C3 and C4 [47-49]) based on peripheral blood sample have also been suggested. These serum diagnostic markers are promising but still require larger studies and are not currently available in tertiary hospitals in Africa and most centres worldwide. Therefore, at present time, there is no test that can reliably confirm the diagnosis of AFE in suspected cases.

## 2.10 Differential Diagnosis of AFE

Since squamous cells have been found in the circulation of patients with and without the AFE syndrome, the diagnosis is clinical and one of exclusion based on presenting symptoms and clinical course, not based on laboratory or pathology findings [7]. Sudden onset of dyspnoea with cardiovascular collapse and DIC in a patient should lead the clinician to suspect AFE and initiate treatment [7].

The differential diagnosis of AFE includes obstetric causes, non obstetric causes and anaesthetic causes. Obstetric causes are acute haemorrhage, placental abruption, uterine inversion, uterine rupture, uterine atony, eclampsia and peripartum cardiomyopathy. Haemorrhagic shock seen in these conditions differentiates them from AFE except in eclampsia and peripartum cardiomyopathy. A careful history, physical examination, presence of low CVP with haemorrhagic shock and absence of cyanosis should lead to the correct diagnosis. Eclampsia is characterised by hypertension, proteinuria and oedema but the state of shock in AFE differentiates it from eclampsia [50].

Non obstetric causes include pulmonary embolism, air embolism, anaphylaxis, sepsis/septic shock, and cardiovascular accident. Patients with pulmonary embolism present with chest pain and it may occur with evidence of venous thrombosis in the lower limbs. It occurs later in postpartum period [51]. Patients with air embolism present with chest pain and auscultation of a typical "water wheel" murmur over the pericardium differentiates air embolism from AFE [52]. Patients with CVA may present with hypotension, pulmonary oedema and absence of cyanosis. Examination of CSF will help in the diagnosis.

Anaesthetic causes include high spinal anaesthesia or total spinal anaesthesia, local anaesthetic toxicity and aspiration of gastric

contents into the lungs. The administration of local anaesthetic drug with onset of symptoms is an important differentiating factor [50]. The presentation of cyanosis, tachycardia, hypotension and pulmonary oedema in aspiration of gastric content into the lungs is similar to that seen in AFE, except that aspiration of gastric content is usually seen in an unconscious patient with loss of cough reflex or during induction or emergency from general anaesthesia [51].

## 2.11 Management

Management of AFE is primarily early recognition, prompt resuscitation, delivery of the fetus and supportive on rapid maternal cardiopulmonary stabilization and adequate oxygenation to the vital organs and correcting coagulopathy. The management is multidisciplinary approach that involves input of consultants (Anaesthesiologist, Obstetrician, haematologist and neonatologist). After initial stabilization, these patients need to be managed in an intensive care unit. Intravenous access with large bore intravenous catheters is of paramount importance. Arterial catheterization should also be considered for accurate arterial blood pressure monitoring and frequent blood sampling. If the presentation is before delivery, expeditious delivery of the fetus in the resuscitation process will increase the chances of perinatal survival without neurologic sequelae [12], and also aid in the maternal resuscitation efforts by improving venous return to the right heart [7].

It is important to prevent further hypoxia and end-organ hypoperfusion and organ system failure. Therefore, endotracheal intubation and administration of 100% oxygen with positive pressure ventilation should be performed immediately. Fluid resuscitation is needed to counteract hypotension and haemodynamic instability. Transthoracic or transesophageal echocardiography may guide fluid therapy with evaluation of left ventricular filling [53,54].

Vasopressors and inotropic support are needed for refractory hypotension. Central venous access should be established for vasopressor infusion and monitoring. Epinephrine may be ideal agents because of the additional  $\beta$ -adrenergic effects, which improve cardiac function in addition to the  $\alpha$ -adrenergic vasoconstrictor effects. Vasopressin may be used as primary therapy or as an adjunct to other inotropic therapies and has the benefit of sparing

the pulmonary vasculature from vasoconstriction, especially at low doses [55]. When there is right heart failure, milrine or other phosphodiesterase inhibitors should be considered.

Mortality from DIC may be up to 75%. Specific coagulation laboratory abnormalities are treated with fresh frozen plasma, cryoprecipitate, fibrinogen and/ or factor replacement [56]. The successful use of rFVIIa has been reported [57-59], although it has also been associated with massive intravascular thrombosis [60]. Recently, newer therapies have been described in the treatment of AFE such as (Aprotinin [61]), aminocaproic acid and tranexamic acid (antifibrinolytic agents) in the management of obstetric haemorrhage [62], and menorrhagia [63]. Other newer novel approaches are also reported in the treatment of AFE [64-66]. These newer approaches have only been reported anecdotally and in very small case reports [64-66].

## 2.12 Prognosis

The prognosis in AFE is very poor. Up till date, AFE cannot be predicted or prevented since the aetiology is unknown. AFE is a lethal and most feared complication of pregnancy. Recently, the prognosis and mortality of AFE have improved from early diagnosis, prompt and aggressive treatment by a multidisciplinary approach [6,67]. Although the mortality rate has declined, morbidity remains high among survivors with severe complication such as neurologic impairment [1,6,12,13].

The mainstay of a successful management remains the identification of high risk patients. AFE requires a high index of suspicion, multidisciplinary approach, early recognition and rapid resuscitation efforts in order to have a better outcome [68,69].

## 2.13 Recurrence

The available information on AFE is limited. There is evidence that AFE is not a recurrent syndrome. A total of 9 cases of successful pregnancy outcome following AFE have been documented with no report of recurrent AFE in the medical literature [70,71]. However, corticosteroid therapy may be administered before amniocentesis and delivery to minimize the theoretical potential of a recurrence [72]. It is important to document that patients with a known

history of atopy or anaphylaxis are also at a high risk of AFE. The reason is that a known history of drug allergy and atopy was found in 41% of the 46 patients with AFE in the National Amniotic Fluid Embolism Registry [12].

## 2.14 Issues and Controversies

Documented information on AFE is mainly based on case reports or case series. Limited researches are on risk factors and some diagnostic tests. However, there is no information based on a high level of evidence and observational studies. There is need for systematic review of case reports and case series to support evidence on such a rare syndrome as AFE. There is need for working diagnostic criteria which should be clearly defined to reflect worldwide standard in such a rare condition.

AFE is still associated with a high maternal and perinatal morbidity and mortality, but the pathophysiology is fairly understood in recent times. There is need for further researches on promising serum diagnostic tests (zinc coproporphyrin, sialyl Tn Antigen and C3 and C4 compliment). Future researches on pathophysiology, diagnosis and management should focus on the role of inflammatory mediators such as histamine, prostaglandins, leukotrienes, whose biologic activity can explain the events that occur with AFE.

## 3. CONCLUSION

AFE is a rare and dreadful obstetric emergency with a high morbidity and mortality rate. Our understanding of its aetiology and pathophysiology is incomplete and the criteria used to make its diagnosis are controversial. In spite of advances in the care of critically ill patients, no management interventions have been found to improve survival or long-term outcome of patients with AFE.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.



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