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AMNIOTIC FLUID EMBOLISM OR ANAPHYLACTOID SYNDROME OF PREGNANCY? A NARRATIVE UPDATE

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Abstract: The term amniotic fluid embolism (AFE) is dating from 1941, when a pathological description, made 20 years before, received clinical significance and a name. It is a very rare obstetrical emergency with poor prognosis. Many studies have shown that the AFE is a misnomer, representing not a true embolism, but an anaphylactoid reaction associated with pregnancy, characterized by sudden cardiovascular collapse, hypoxia and disseminated intravascular coagulation. Along with pathophysiology, diagnosis and management, the authors also present the legal considerations of AFE.

Keywords: amniotic fluid, embolism, anaphylaxis, pregnancy.

INTRODUCTION

Amniotic fluid embolism (AFE) represents a life-threatening obstetric emergency, characterized by a triad of symptoms: sudden cardiovascular collapse, hypoxia and disseminated intravascular coagulopathy (DIC) [1].

Despite the fact that AFE was first described almost 100 years ago by J.R. Meyer, a Brazilian pathologist in 1926 [2], its real significance was only recognized in 1941 when Steiner and Lushbaugh published an article detailing a series of 32 pathology reports in which pregnant patients died due to a sudden shock during labor. In 8 out of these patients, at autopsy they found squamous cells and mucin particles in the maternal pulmonary arterial circulation, hence the term "amniotic fluid embolism" [3]. However, published data in the US National Amniotic Fluid Embolism Registry may show that AFE is a misnomer, as the underlying process responsible for this entity resembles more an inflammatory process, similar with anaphylaxis, so Clark and his colleagues recommended to use the term "anaphylactoid syndrome of pregnancy" (ASP), instead of AFE [1]. Due to the lack of specific tests to diagnose this disease, these terms are used in the literature, so both AFE and ASP appear in reviews and case reports.

Incidence

The incidence of AFE varies significantly between 1 in 8,000 and 1 in 80,000 deliveries. There are inconsistent definition criteria that varies between both countries and registries. The UK Obstetric Surveillance System (UKOSS) register, published by Fitzpatrick and colleagues, shows an incidence of 1.7 per 100,000 deliveries, with a case fatality of 19% [4]. The data published by Knight *et al*. reported incidences anywhere between 5.5-6.1 per 100,000 deliveries in USA and Netherlands, with a case fatality of 18% and 11%, respectively [5]. All this data points to a significant geographic difference in incidence, with the US rate being almost three times higher than in Europe [6]. In the 2013-2015 MBRACE-UK report, AFE represents the fifth direct cause of maternal mortality, following thromboembolism, hemorrhage, suicide and pregnancy-related sepsis [7].

Risk factors

Fitzpatrick and colleagues published, recently, a multi-country, population-based cohort looking at

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the risk factors for AFE. The odds of having AFE rose significantly with increasing maternal age, in women who had a multiple pregnancy, polyhydramnios, placenta previa, placental abruption and induction of labor using any method [8]. Other factors suggested to increase the risk of AFE in the post-delivery period include both Cesarean section and operative vaginal delivery, either by forceps or vacuum [9], as well as fetus male sex, fetal distress, fetal macrosomia (for fetal factors), amniocentesis, premature rupture of membranes, cervical laceration, uterine rupture, preeclampsia and eclampsia, as obstetric risk factors [10-12].

Pathogenesis

Initial opinions made presence of the amniotic fluid or fetal cell in the maternal circulation a prerequisite for AFE. There is a disruption of the maternal-fetal interface and the passing of lanugo, trophoblasts, bile-stained meconium or fetal squamous cells into the maternal circulation [3, 13]. The suspected sites of entry of the amniotic fluid are the endocervical veins, uterine trauma sites and trauma of the utero-placental unit. There needs to be a pressure gradient, in order for the amniotic fluid to enter from the uterus into the maternal circulation [6]. However, there are many women who, despite being exposed to either amniotic fluid or fetal cells, may not show any signs of AFE, which makes the exact mechanism unclear. Which brings into discussion an abnormal activation of humoral or immunological processes, leading to the release of vasoactive and procoagulant substances, similar to the systemic inflammatory response syndrome and anaphylaxis [14]. This is why Clark *et al*. proposed the new term "Anaphylactoid Syndrome of Pregnancy" (ASP) [1]. The vasoactive substances include cytokines, thromboxane, bradykinin, leukotrienes, platelet-activating factor and arachidonic acid [15]. The concentration of procoagulant products, like tissue factor and tissue factor pathway inhibitor, that trigger intravascular coagulation, is increased in amniotic fluid, compared with the maternal serum [16].

Complement activation has also an important role in the respiratory insufficiency that appears in AFE [17], as the amniotic fluid does activate complement in some experimental models [18].

Japanese researchers have identified several serum biomarkers that can help in understanding AFE's pathophysiology: zinc-coproporphyrin-1 [19], sialyl TN antigen [20], complement C3, C4 and interleukin 8 [21]. Recently high levels of insulin-like growth factor-binding protein 1 [22] and squamous cell carcinoma antigen [23] have also been identified as new markers of amniotic fluid presence into the maternal circulation.

Clinical Findings

Timing for onset of symptoms

In the great majority of cases, AFE occurs during labor and delivery or within 30 minutes postpartum. Clark's analysis of the AFE national registry showed that 70% of cases happened during labor, 11% during vaginal delivery and 19% during cesarean delivery [1].

Rarely, AFE can appear following first or second trimester abortions, miscarriage, amniocentesis or abdominal/uterine trauma. The incidence is rare, having been described mostly in case reports [24-27].

Signs and symptoms

The clinical presentation for the great majority of patients with AFE is abrupt and catastrophic. The sign and symptoms could be divided into two phases, with some parturients experiencing an aura or precursory symptoms. These precursory symptoms may consist of agitation, numbness, feeling cold, sense of sudden doom, lightheadedness, chest pain, nausea and vomiting, panic, anxiety or change in mental status immediately preceding the event [14,28,29]. The prodromal symptoms usually lead to the sudden cardiorespiratory failure or arrest (the initial phase of the AFE), which include acute dyspnea and cyanosis, severe abrupt hypotension from cardiogenic shock, arrythmia, cardiac arrest, respiratory failure, seizures, unconsciousness or coma and fetal compromise [30]. The second phase of AFE shows involvement of left ventricular failure, major clotting dysfunction leading to disseminated intravascular coagulation (DIC), seen in about 80% of patients [31], noncardiogenic pulmonary edema and reactive hypovolemia [8, 14].

Laboratory and imaging

As already mentioned, DIC is the main laboratory abnormality, so a coagulation profile will show an elevated D-dimers, thrombocytopenia and low fibrinogen appearing in most patients [31-35], usually with 30 minutes from the onset of the cardiopulmonary collapse. In certain situations, these laboratory abnormalities may occur even without cardiorespiratory compromise or can be delayed up to 48 hours from initial presentation [36]. Rotational thromboelastometry (ROTEM) and thromboelastography (TEG) have been found to identify and diagnose the coagulopathy in parturients with AFE (even when there are no overt signs of bleeding), as well as help in the management of

these patients [24, 35, 37, 38]. A complete blood count (CBC) may show nonspecific values, together with anemia secondary to the hemorrhage and sometimes an elevated white blood cell (WBC) count, however many laboring or postpartum parturients may present normally with a WBC over 20,000 cells/microL. An arterial blood gas (ABG) analysis is significant for both hypoxemia and sometimes hypercapnia, due to the respiratory compromise. The patients with significant hypotension and cardiac arrest will also show some metabolic acidosis. Chest X-ray imaging may be initially normal, but in some cases, there are bilateral infiltrates consistent either with pulmonary edema or acute respiratory distress syndrome. ECG will show sinus tachycardia, as well as potential arrythmias leading to cardiac arrest. Echocardiography which can reveal increased pulmonary pressures, followed by left ventricular failure may guide management of AFE cases [39, 40].

Diagnostic criteria

AFE is a clinical diagnosis of exclusion, due to the fact that there are no specific laboratory tests that can make the diagnosis. The UK Obstetric Surveillance System (UKOSS) set out certain diagnostic criteria, used in the British national registry. They include: either acute maternal collapse with one or more of the following features: acute fetal compromise, cardiac arrest, cardiac arrythmias, coagulopathy, hypotension, maternal hemorrhage, premonitory symptoms, seizure and shortness of breath (and excluding women with maternal hemorrhage as the first presenting feature in whom there was no evidence of early coagulopathy or cardio-respiratory compromise) or women in whom the diagnosis was made at post-mortem examination, finding squamous cells or hairs in the lungs [4, 41]. In the US, Clark and his colleagues convened a working group under the auspices of the "M in Maternal Fetal Medicine Committee" of the Society for Maternal-Fetal Medicine (SMFM) and the Amniotic Fluid Embolism Foundation to develop uniform diagnostic criteria for the research reporting of AFE [42, 43], as listed in Table 1. In Japan, the consensus criteria for the diagnosis of AFE include the following: 1. If symptoms appeared during pregnancy or within 12 hours from delivery; 2. If any intensive medical intervention was conducted to treat one or more of the following symptoms/diseases: cardiac arrest, severe bleeding of unknown origin within two hours from delivery (≥1500mL), disseminated intravascular coagulation, respiratory failure; 3. If the findings or symptoms obtained could not be explained by other diseases; 4. As for AFE, consumptive coagulopathy/DIC due to evident etiologies such as abnormal placentation, trauma during labor and delivery and severe preeclampsia/eclampsia, should be excluded [44].

There seems to be some substantial overlap between the three diagnostic criteria, mostly due to the fact they are all based on the clinical presentation. At the same time, using these criteria may produce different estimates for the AFE diagnosis, as there were recently several case reports of isolated coagulopathy associated with maternal hemorrhage, but without cardiopulmonary collapse [45, 46]. This lack of international consensus between clinicians and researchers makes it difficult to be able to compare maternal death rates worldwide [47]. In a follow-up study after the publication of the US criteria, looking at 115 cases extracted from the AFE Registry, Stafford and Clark, along with their colleagues from Baylor College of Medicine in Houston, Texas (where the AFE Registry was established), showed the fact that even if a lot of AFE cases will be diagnosed using these criteria, there could be up to 21% of atypical AFE cases, which may be excluded [48]. A very recent study from France tried to test the validity of these criteria in a population-based cohort with a strong clinical suspicion for AFE. They found out that only 43% of patients presented all four diagnostic criteria from the SMFM definition. All patients presented with a hemodynamic collapse, but 57% of them were lacking respiratory symptoms, while 71% checked the criteria for biological DIC, with clinical coagulopathy and massive postpartum hemorrhage. All

Table 1. Uniform diagnostic criteria for research reporting of amniotic fluid embolism [40]

1. Sudden onset of cardiorespiratory arrest, or both hypotension (systolic blood pressure <90 mm Hg) and respiratory compromise (dyspnea, cyanosis, or peripheral capillary oxygen saturation [S_pO_2] <90%).
2. Documentation of overt DIC following appearance of these initial signs and symptoms, using scoring system of Scientific and Standardization Committee on DIC of the ISTH, modified for pregnancy – see Table 2 (41). Coagulopathy must be detected prior to loss of sufficient blood to itself account for dilutional or shock-related consumptive coagulopathy.
3. Clinical onset during labor or within 30 minutes of delivery of placenta.
4. No fever (≥ 38.0°C) during labor

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

patients also presented premonitory symptoms. As such, the authors proposed a modified version of the SMFM criteria, based only on clinical criteria:

1. Premonitory signs including neurological signs (seizure, confusion, agitation, fainting or anxiety and imminent death feeling), abnormal fetal heart rate, respiratory signs (dyspnea, cough, shortness of breath), and atypical signs (nausea and/or vomiting, arterial blood hypertension, skin rash, thoracic or abdominal pain);

2. Sudden hypotension (systolic blood pressure <90 mmHg) or sudden cardiorespiratory arrest. Suddenness is a subjective criterion that involves a brutal hemodynamic change.

3. Clinical early massive obstetric hemorrhage or clinical DIC.

4. Clinical onset during labor or within 30 minutes of delivery [49].

Differential diagnosis

As AFE has no reliable or definite tests to support its diagnosis, the possible differential diagnoses can be divided in obstetric and non-obstetric ones, as shown in Table 3. AFE should always be considered in the differential diagnosis of sudden cardiorespiratory compromise in any pregnant or recently postpartum patient [14].

Management

The most important steps in the management of an acute AFE event include prompt and effective cardiopulmonary resuscitation of the parturient and rapid evacuation of the fetus.

Cardiopulmonary resuscitation (CPR)

Most experts agree that a high-quality CPR should include rapid and forceful chest compressions (100/minutes and 2-inch depth) with adequate chest recoil and only short interruption of 5-10 seconds, as documented in the latest American Heart Association (AHA) guidelines [50]. This should be part of the recent recommendations for treatment of critical obstetric conditions, including basic life support (BLS) and advanced cardiac life support (ACLS) protocols [51-53]. High quality CPR should be combined with effective left uterine displacement. Older techniques have recommended using a firm backboard, with a 30-degree tilt to the left, however this may make CPR more difficult and less effective. The current guidelines recommend manual uterine displacement with two hands to the left with the patient in supine position on a hard surface to relieve any compression of the periumbilical uterus (after 20 weeks of gestational age), while maintaining high-quality chest compressions [50]. If available, continuous waveform capnography should also be used, as it ensures efficient chest compressions,

Table 2. Modified International Society on Thrombosis and hemostasis scoring system for overt disseminated intravascular coagulation in pregnancy [41]

Platelet count: >100,000/mL = 0, <100,000/mL = 1, <50,000/mL = 2
Prolonged prothrombin time or international normalized ratio (INR): <25% increase = 0, 25-50% increase = 1, >50% increase = 2
Fibrinogen level: >200mg/L = 0, <200mg/L = 1
Score ≥3 is compatible with overt disseminated intravascular coagulation in pregnancy.

Table 3. Modified International Society on Thrombosis and hemostasis scoring system for overt disseminated intravascular coagulation in pregnancy [41]

Obstetric causes	Non-obstetric causes
Eclampsia	Pulmonary embolism
Uterine rupture	Air embolism
Placental abruption	Fat embolism
Acute hemorrhage	Pulmonary edema
Peripartum cardiomyopathy	Tension pneumothorax
Uterine inversion	Heart Failure
	Myocardial infarction
	Anaphylaxis
	Sepsis
	Aspiration pneumonia
	High spinal anesthesia
	Local anesthetic toxicity
	Transfusion reaction
	Asthma exacerbation
	Intracranial hemorrhage

by measuring the partial pressure of carbon dioxide (CO_2) in the expired respiratory gases and displaying the end-tidal CO_2 ($ETCO_2$). Several studies have also showed an association between presence of $ETCO_2$ and return of spontaneous circulation (ROSC) during cardiac arrest [54]. The chest compressions should be part of the complete algorithm of ABCD (Airway -securing the airway (intubation), Breathing-effective ventilation, Circulation-blood circulation and control of hemorrhage and Defibrillation, Drugs, Delivery – defibrillate if cardiac arrest, pharmacological agents to support circulation and fetus delivery) [51, 52]. Securing the airway could be difficult in the parturient, especially in cardiac arrest situations. The intubation should be done by the most experienced provider and additional equipment and personnel should be immediately available in case a difficult airway is encountered, including video-laryngoscopy devices [50]. To minimize fixation errors about risk of aspiration in pregnancy, cricoid pressure is no longer recommended in general in cardiac arrests, but can help in assisting intubation, if necessary [52]. In the event of maternal cardiac arrest, early defibrillation of shockable rhythms is recommended, while chest compressions should be immediately resumed after delivery of the electric shock [50]. The energy requirements for pregnant patients is similar with that for non-pregnant patients, with escalating shock energy if the initial shock was not effective [50]. After intubation, large-bore intravenous catheters should be placed for infusions. Pulmonary artery pressure wedge (Swan Ganz) catheters will measure left atrial and pulmonary artery pressures as well as cardiac output and help in management of the critical situations. Pulmonary artery blood aspiration may reveal the presence of fetal blood components, but not always. When a Swan Ganz catheter is not available, cardiac echocardiography may give similar information and may help in managing these patients [39, 40]. The most recent AHA guidelines recommend that drug administration during ACLS should adhere to the standard adult dosing guidelines without concern for teratogenicity [50]. Changed from the previous guidelines [55] is the removal of vasopressin use as an alternative to epinephrine during CPR for the parturient [50]. Vasopressor support should include dopamine, dobutamine or epinephrine, but norepinephrine could also be used for persistent hypotension. Inhaled nitric oxide can be helpful in reducing right ventricle afterload in cases associated with pulmonary hypertension [56]. Sildenafil and epoprostenol have also been used for their pulmonary artery vasodilation properties [57-59].

At the same time, in certain circumstances, the maternal cardiac arrest could be caused by large amounts of local anesthetics that cause systemic toxicity (LAST). The algorithm for management of LAST leading to cardiac arrest includes, besides ACLS, the administration of 20% lipid emulsion (initial bolus of 1.5mL/kg lean body weight, followed by an infusion of 0.25 mL/kg/min or repeat bolus in case of persistent cardiovascular collapse). This regimen may be life saving for the parturient [60, 61].

In parturients who do not show improvement and continue with severe hemodynamic instability, extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass (CPB) should be considered [62]. ECMO has clearly advantages over CPB as it can be installed at bedside, does not require a sternotomy and has fewer potential complications [63]. Veno-arterial (VA) and veno-venous (VV) ECMO have been successfully used in parturients with AFE who do not respond to initial resuscitation [64-67]. VV ECMO is usually used in cases of severe hypoxemic respiratory failure (like acute respiratory distress syndrome or pulmonary hypertension without severe right ventricular failure) (Table 4) [68]. As such, most AFE cases require VA ECMO, due to the impending cardiac arrest. VA ECMO provides both respiratory support, as well as hemodynamic support in patients with severe transient hemodynamic instability caused by reversible causes (Table 5). The success of instituting any ECMO device therapy depends significantly on the availability of the ECMO procedural team, which usually consists of representatives from critical care medicine, cardiothoracic surgery, cardiac anesthesiology and perfusion medicine. The logistics of activating the ECMO team, followed by rapid cannulation of the patient and the success of this process, is based with having the ECMO team physicians accustomed to cannulating in any off-site locations, to decrease the time from decision to actual placement of the cannulas. In certain scenarios, if activating the ECMO team is estimated to take a long time, it has been reported successful inter-hospital transfer to a regional or local ECMO center with a shorter time for ECMO placement [69, 70]. Good communication between medical centers is essential for the success of such endeavor. Prolonged ECMO increases the risk of complications (Table 6), so patients should be weaned from ECMO as early as possible to avoid these complications [68]. The risk of thromboembolic events should be weighed against the risk of major bleeding with systemic coagulation and using high circuit flows may mitigate this risk.

Other invasive techniques used for the management of AFE cases and reported in the literature include intra-aortic balloon counter-pulsation [71], resuscitative endovascular balloon occlusion of the aorta – REBOA [72, 73], pulmonary artery thromboembolectomy [74], hemofiltration [75] and plasma exchange transfusion [76]. Efficiency of plasma exchange transfusion may be linked to removal of chemical mediators and cytokines responsible for the anaphylactoid reaction. Based on the new biomarkers identified in cases of AFE, Akasaka *et al.* have recently used C1 esterase inhibitor concentrates for the treatment of AFE cases [77].

Management of coagulopathy and hemorrhage.

Rapid transfusion of blood and blood components should be done immediately as hemorrhage and coagulopathy appears in AFE cases. Massive transfusion protocol guidelines should be followed when a diagnosis of AFE is suspected [78]. Administration of packed red blood cells (PRBC), along with fresh frozen plasma (FFP), platelets in a 1:1:1: ratio should be done until bleeding is controlled [79]. Cryoprecipitate should be given to maintain fibrinogen levels > 200mg/dL [33], or fibrinogen concentrate, when available [80]. Tranexamic acid (TXA), an antifibrinolytic agent, has been used both in AFE cases [81], but also to decrease obstetric hemorrhage-induced maternal mortality, part of the WOMAN study [82]. Recombinant factor VIIa has been also studied in patients with AFE, but it was associated with a worse outcome and higher mortality, so it is not recommended at present time [83].

Some anecdotal evidence and case reports suggest that a combination of atropine, ondansetron and ketorolac (so called A-OK protocol) has been successfully used in AFE cases [84], but it remains investigational and reserved for refractory cases. Another recently published report mentioned the successful use of rivaroxaban, a direct factor Xa inhibitor, in lieu of both heparin or warfarin (due to potential heparin-induced thrombocytopenia and slow action of warfarin), as a consumption coagulopathy required anticoagulation [85].

Obstetrical management

If the parturient is undelivered at the time of the cardiac arrest, expeditious delivery should be done if the fetus has reached a viable age (≥ 23 weeks). Some authors recommend moving this threshold to 20 weeks, to improve maternal perfusion and chances of survival, but there is no clear evidence that it will improve outcomes of AFE cases [50]. The so-called

Table 4. Indications for VV-ECMO support during pregnancy and postpartum [66]

1.	Severe (but potentially reversible) respiratory failure
2.	Hypercapnia with severe respiratory acidosis despite optimal conventional mechanical ventilation with respiratory rate increased up to 35 breaths/min
3.	PaO_2/FiO_2 ratio less than 100 with inspired fraction of oxygen ≥ 0.9 and PEEP ≥ 10 cm H_2O despite optimal ventilator support and use of usual adjunctive methods (cisatracurium, recruitment maneuvers, prone ventilation and adequate PEEP).

Table 5. Indications for VA-ECMO support during pregnancy and postpartum [66]

1.	Refractory left ventricular failure from peripartum cardiomyopathy, myocardial infarction, myocarditis
2.	Bupivacaine intoxication requiring prolonged cardiopulmonary resuscitation
3.	Refractory right or left ventricular failure in suspected cases of amniotic fluid embolism
4.	Inability to wean from cardiopulmonary bypass after heart surgery
5.	Massive pulmonary embolism with refractory right ventricular failure
6.	Need for prolonged cardiopulmonary resuscitation (at least 10 minutes) with a potentially reversible precipitating condition

Table 6. Common complications with VA-/VV-ECMO support [66]

Circuit thrombosis	Prevent with systemic anticoagulation (most commonly with unfractionated heparin)
Bleeding	Etiology is multifactorial, including anticoagulation, thrombocytopenia, acquired Von Willebrand disease secondary to destruction of large multimers in the extracorporeal circuit. Threshold to transfuse varies among centers. Maintain hemoglobin above 7-8 g/dL
Infection	Some centers advocate broad-spectrum antibiotics while on ECMO support despite limited evidence
Hemolysis	Some degree of hemolysis may occur from the negative pressure generated by the pump. Excessive hemolysis may be due to cannula malposition or hypovolemia with less venous return to the circuit
Thrombocytopenia	May require transfusion of platelets if active bleeding or less than 20,000/mm^3

perimortem cesarean delivery (PMCD) should be done while CPR is ongoing. A PMCD theoretically may improve the survival chances of the fetus, as well as assist in the maternal resuscitation by relieving the aorto-caval uterine compression. The present AHA, SOAP and RCOG guidelines recommend starting the PMCD within 4 minutes from the maternal cardiac arrest (if spontaneous circulation has not returned after instituting CPR) and delivering the fetus by 5 minutes. However, several studies published recently showed that the number of fetuses delivered by PMCD within 5 minutes of arrest was quite low, even less than 10% [86]. As such, it is advised for the PMCD to occur at the site of the maternal arrest, to minimize interruptions in CPR and avoid a potential delay in delivery of the fetus [87-89]. Rose and his colleagues have published a call to action several years back, challenging the term PMCD, trying to focus both on maternal and fetal benefits of the procedure and renaming it resuscitative hysterotomy [90]. Their approach has however a confusing suggestion that a non-shockable rhythm would prompt with an immediate PMCD/resuscitative hysterotomy, whereas a shockable rhythm such as ventricular fibrillation should defer delivery and instead attempt defibrillation. A group of experts who authored both the recent SOAP and AHA guidelines disagreed with Rose and colleagues, as their suggestion may confuse the providers involved in the patient's resuscitation and lead to a delay in delivery [91].

Postcardiac arrest management

After successful resuscitation, the post arrest management is of vital importance. Patients may be hemodynamically unstable, requiring both fluids and vasopressors or inotropes. The goal is to maintain a mean arterial pressure above 65 mm Hg [92]. Oxygen administration should be reduced from 100%, as hyperoxia can worsen the ischemia-reperfusion injury. The pulse oximetry value should be maintained around 94-98% [92]. Glucose levels should also be kept between 140-180 mg/dL, using insulin infusions if necessary [93]. Mild therapeutic hypothermia has been commonly used to improve neurological outcome after different types of hypoxic injuries and in the treatment of post-anoxic injury after cardiac arrest [92]. Therapeutic hypothermia in pregnant patients has been reported in several cases with positive outcomes [94,95,96]. The main concern limiting its use in these parturients is the potential increased risk of hemorrhage. This means that for patients with AFE that do not demonstrate significant DIC and bleeding, therapeutic hypothermia could be considered.

Prognosis and recurrence risk

The recurrence of AFE is quite difficult to define, as the number of cases is reasonably small, with a high mortality rate. There have been multiple case reports of uneventful subsequent pregnancies and no cases of recurrence were reported [97,98,99]. A recent review from the AFE Registry from Steven Clark *et al*. looked at reproductive decisions in patients who survived an AFE event [100]. About 30% of survivors achieved subsequent pregnancies, most of them with only one subsequent pregnancy. Out of those pregnancies, half of them were delivered by Cesarean section, one quarter had spontaneous vaginal deliveries and the other quarter spontaneous/elective abortions [100]. One important detail related to all these surviving patients showed a lack of psychiatric or psychological consultations after their initial AFE event. It has been previously shown that there is a reduction in subsequent reproductive capacity in women who have experienced a maternal near-miss during pregnancy [101]. The women who experience near-death events like severe postpartum hemorrhage suffer from long-term psychological and emotional complications, with the realization that childbearing may sometimes be associated with potentially life-threatening consequences [102].

Legal considerations of AFE cases

Even if AFE cases are rare, the associated morbidity and mortality is extremely serious. Several authors have listed potential risk factors [8], whose presence should make clinicians more aware of a potential complication. However, as there are no warning signs and certain cases happen in the absence of these risk factors, AFE remains unpredictable and unpreventable. This makes the resuscitation efforts and quick diagnosis extremely important in managing these difficult situations. A recent study of the results from the French confidential enquiry into maternal deaths from AFE in France between 2010-2012 showed that 35% of those deaths were deemed "preventable" and with substandard care due to delay in diagnosis, absence of quick surgical control of the hemorrhage and lack of aggressive treatment of the associated coagulopathy [103]. The other important points for the clinicians included: thinking about AFE in the presence of premonitory signs in parturients with ruptured membranes, having access to quick diagnostic tests when a suspicion of AFE presents, availability of adequate resources and a multidisciplinary team for an aggressive resuscitation of the patient, understanding the level of urgency and gravity of the disease through a clear communication

between all members of the team, being wary of the potential for massive coagulopathy, even without bleeding and for in-hospital arrest, being prepared for a prolonged cardiorespiratory resuscitation and contacting the ECMO team as soon as possible [103]. Several Italian authors looked at the malpractice lawsuits for deaths or injuries due to amniotic fluid embolism. In order to file a suit, three requirements had to be met: accidental nature of the misconduct on the part of the hospital personnel, existence of proven damage and a causal relationship between the above two factors [104, 105]. Most of the cases judged against the physicians involved did not focus on the misdiagnosis of AFE, but on the lack of a timely and appropriate emergency assistance. In one of the cases, the obstetrician was held responsible for having waited for the anesthesiologist, instead of providing CPR. The hospital was also held liable for not providing a well-equipped delivery room (no oxygen, defibrillator or emergency surgical kit) [104]. The conclusion is that in all these critical situations a multidisciplinary team needs to communicate efficiently and avoid any delays in management of the AFE event, to improve and give chances of survival for both the mother and her fetus.

In conclusion, at the end of this article we include the most recent AFE algorithm published by the Anesthesia Informatics and Media Lab from Stanford University as part of the Obstetric Anesthesia Emergency Manual, which is free to download and use by all interested clinicians [106, 107].

DIAGNOSIS:

Triad

Premonitory symptoms

- Hypoxia
- Restlessness
- Hypotension
- Agitation
- Consumptive coagulopathy

CALL FOR HELP: OB RAPID RESPONSE IMMEDIATE:

- Team leader: Identify
- Airway: Clear?
- Breathing: SpO_2 + Respiratory rate + Auscultation
- Circulation: Heart rate + Blood pressure + Urine output
- Conscious level: Adequate?
- Position: Left uterine displacement
- Fetal heart rate: Monitor
- IV access: 2 large bore IV's, 16 GA
- Invasive monitoring: Arterial line, central line
- Labs: CBC, Coag screen, Fibrinogen, BMP, ABG, TEG/ROTEM

TREATMENT:

Oxygen: 100% (10 L/min) *via* non-rebreather facemask or ETT

Hypotension: Cautious IV fluid bolus. Administer vasopressor boluses PRN

- Phenylephrine 100-200 mcg IV
- Ephedrine 5-10 mg IV
- Epinephrine 10-100 mcg IV

Consider vasopressor infusion

- Epinephrine 0.01-0.1 mcg/kg/min IV
- Norepinephrine 0.01-0.1 mcg/kg/min IV
- Vasopressin 0.01-0.04 units/min IV

Coagulopathy: At risk for massive hemorrhage/ DIC

- Initiate MTP if symptoms of DIC or ongoing hemorrhage or atony
- Early administration of PRBC's, FFP, Plts, Cryo or Fibrinogen concentrate
- Consider tranexamic acid 1 gm IV (over 10 mins)

Emergent delivery: Consider

Additional treatment: Consider hydrocortisone 100 mg IV bolus

Iloprost 2.5 mcg NEB for pulmonary vasoconstriction

OTHER:

1. Definitive airway: Intubate if developing hypoxia / pulmonary edema
2. Invasive monitoring: Place arterial line, consider central line
3. EKG, CXR, TEE/TTE
4. ICU consult
5. Consider ECMO or balloon pump in patients with severe left ventricular failure

DIFFERENTIAL DIAGNOSIS:

1. Anaphylaxis
2. Sepsis
3. Hemorrhage
4. Embolism (PE, air)
5. Eclampsia
6. Medication reaction (LAST)
7. Myocardial infarction

Conflict of interest

The authors declare that they have no conflict of interest.

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