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Amniotic fluid embolism

Felis S, Cremonini F, Primizia E

*Correspondence: Felis S

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Obstetrics &Gynecology Department - IRCCS San Martino Hospital-Genova -Italy

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Abstract

Amniotic fluid embolism remains one of the most devastating conditions in obstetric practice with an incidence of approximately 1 in 40,000 deliveries and a reported mortality rate ranging from 20% to 60%. The pathophysiology involves an abnormal maternal response to fetal tissue exposure associated with breaches of the maternal-fetal physiologic barrier during parturition. This abnormal response triggers a cascade of events similar to the systemic inflammatory response syndrome, involving the activation of proinflammatory mediators. Maternal treatment in cases of cardiopulmonary arrest is mainly supportive, focusing on resuscitation efforts and stabilizing the mother's condition. However, it is crucial to prioritize prompt delivery in order to improve the newborn's outcome.

Keywords: Amniotic fluid embolism; Cardiorespiratory arrest; Disseminated intravascular coagulopathy; Maternal death; Pregnancy.

INTRODUCTION

Amniotic fluid embolism is one of the most severe syndromes that can affect a pregnant woman. According to recent research, it is considered one of the leading causes of maternal mortality during pregnancy (1-5). For a long time, the causes and pathophysiology of this syndrome remained unknown, and only recently have we gained a better understanding of this dramatic condition (6,7).

Meyer described this syndrome in 1926 (8). Amniotic fluid embolism refers to the passage of amniotic fluid into the maternal circulation during or shortly after delivery. The incidence of this event is estimated at 14.8 cases per 100,000 in multiparous women

and 6 cases per 100,000 in nulliparous women, with a mortality rate ranging from 37% to 61% in various literature studies (9). Amniotic fluid embolism, in general terms, appears to be uncommon, but among women who die during pregnancy, the incidence of this condition is quite high. It is even more common among women who die after unexpected cardiovascular failure during labor (1-6).

Clinically, the typical triad of presentation of this condition consists of sudden onset of hypoxia, hypotension, and in many cases, coagulopathy. The presence of disseminated intravascular coagulation (DIC) has been confirmed in 83% of cases (10).

The systematic description of this syndrome was first documented in 1941 in a study involving 32 cases of women who died during labor due to "obstetric shock" (8,11).

Autopsies of eight women revealed the presence of squamous cells or other fetal debris in the maternal pulmonary arteries.

The authors concluded that the cause of death in these cases was pulmonary embolism of amniotic fluid.

In the following years, these claims were not contested. Many clinical cases with various symptoms were diagnosed as "amniotic fluid embolism" based on autopsy findings of fetal cells in the pulmonary arteries (6,7).

Since the introduction of pulmonary artery catheterization in clinical practice in the 1980s, numerous studies have identified similar pathological findings in pregnant women experiencing various symptoms that were not related to amniotic fluid embolism. Instead, these findings were associated with the presence of fetal cells entering the maternal circulation during labor (6,7,12). It became clear that the presence of fetal cells in the maternal circulation alone was not enough to diagnose amniotic fluid embolism, and relying solely on this diagnosis could not provide a convenient explanation for all cases of unexplained maternal deaths during labor.

Many studies followings the initial observations proposed a straightforward mechanism for this syndrome. According to one simplistic explanation, amniotic fluid would enter the maternal circulation, causing blockage of the pulmonary arteries due to the presence of amniotic cellular debris that was filtered by the pulmonary capillaries. This obstruction would then lead to hypoxia, right-sided heart failure, and ultimately death (6,7,13,14,15,16).

However, these studies demonstrated a wide variety of pathophysiological alterations in the studied animals, contradicting the traditional explanation of the presumed mechanical injury (6,7). In two studies (13,14) conducted on primates using autologous or homologous amniotic fluid, no adverse effects were observed despite the large volume of amniotic fluid used.

An objective evaluation shows that the entry of homologous amniotic fluid into the central circulation of primates or humans is generally harmless, even when large quantities are used (13-16). Therefore, progress in understanding this syndrome and its di-

agnosis and treatment has been limited. Only recently, with the introduction of pulmonary artery catheterization into clinical practice, the development of basic clinical research, and the establishment of a systematic registry for collecting all cases of amniotic fluid embolism, a better understanding of the pathophysiology of this syndrome has emerged (12,17-20).

PATHOPHYSIOLOGY

The pathophysiological origin of the hemodynamic alterations that occur during amniotic fluid embolism involves a complex sequence of pathophysiological reactions resulting from abnormal activation of the pro-inflammatory mediator system, similar to what occurs in the response to systemic inflammatory response syndrome (SIRS) (see Figure 1a-b).

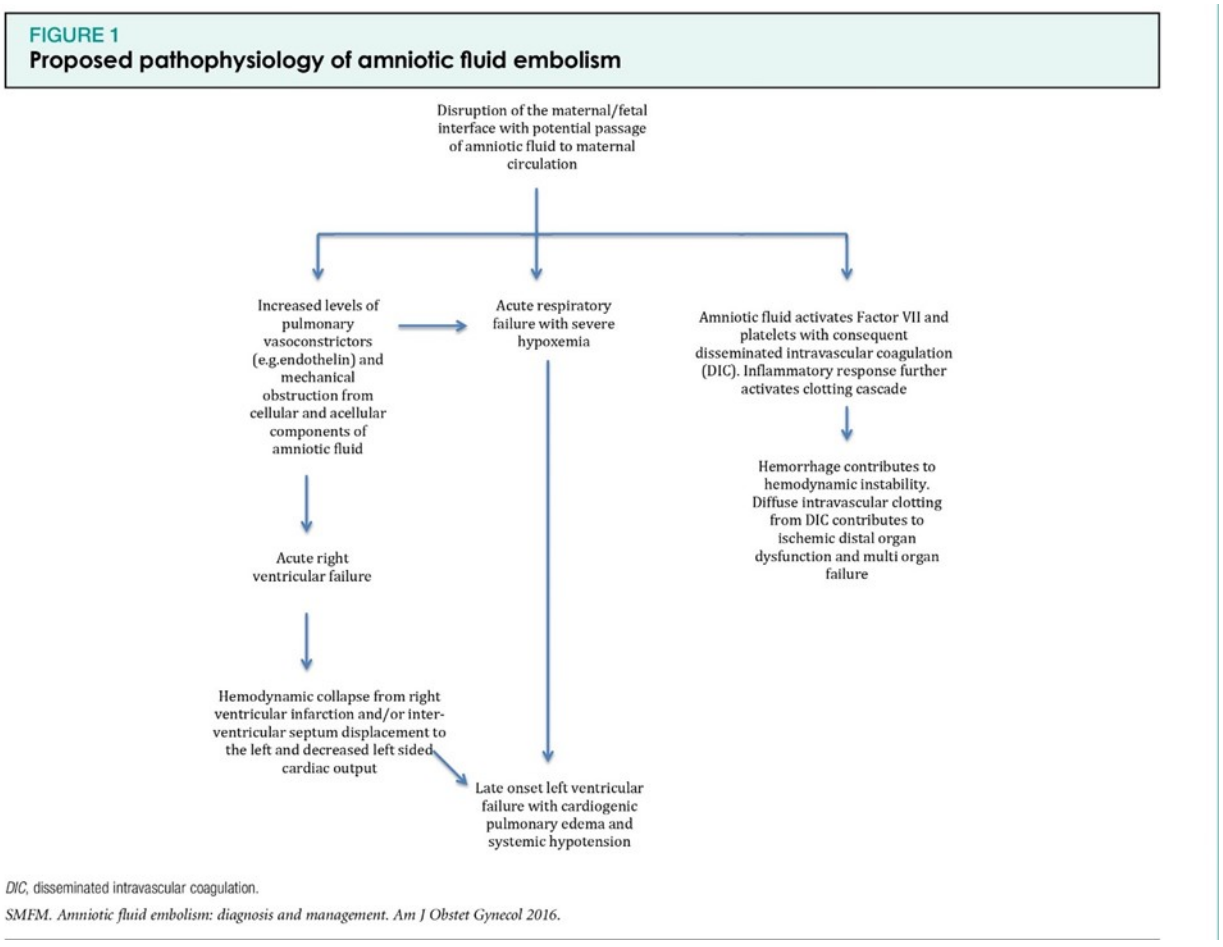

Fig. 1 a. Proposed mechanism for amniotic fluid embolism. SIRS, Systemic Inflammatory Response Syndrome

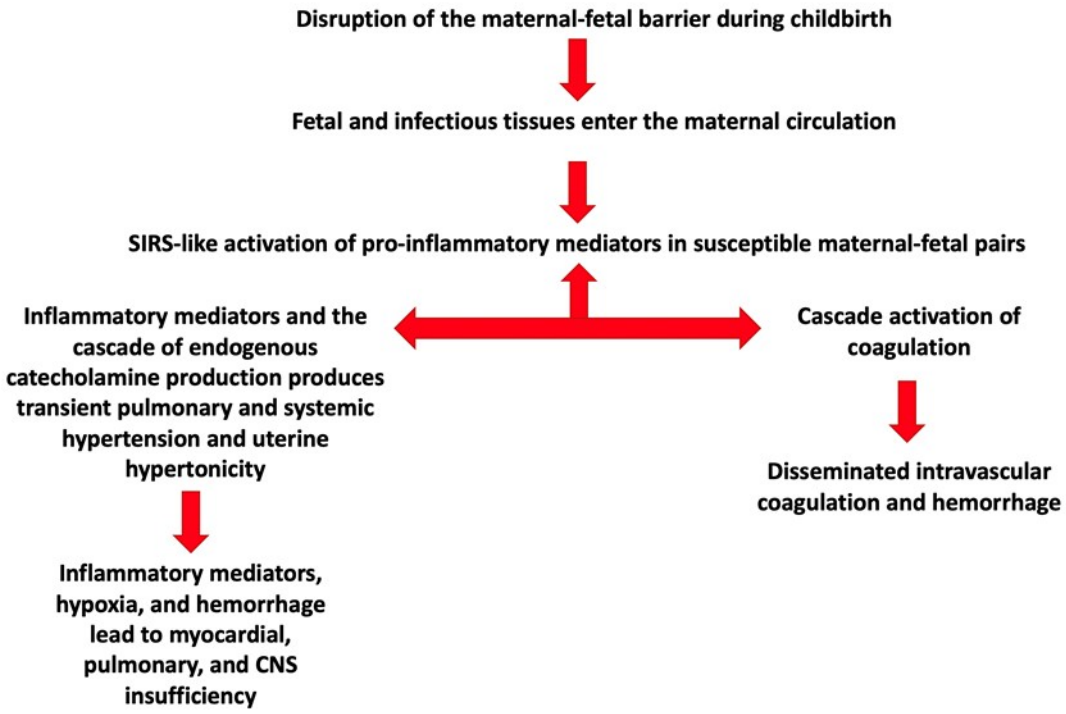

Fig. 1 b. Proposed mechanism for amniotic fluid embolism. SIRS, Systemic Inflammatory Response Syndrome

The pathogenesis of the syndrome has not yet been fully understood, although recent studies have excluded the possibility that it is solely based on pulmonary mechanical obstruction, as animal models have been unable to reproduce the described symptoms. Instead, it appears that the syndrome is due to immunological/inflammatory processes that affect predisposed individuals (13). Although some authors have described the finding of amniotic fluid components (such as fetal epithelial squames, lanugo, fat material, vernix caseosa, bile, etc.) in the pulmonary arterial circulation as nonspecific, this finding remains a key element in post-mortem examinations to confirm that a woman was affected by the syndrome (9).

There is an initial transient period characterized by systemic and pulmonary hypertension (16). However, the predominant hemodynamic alteration is severe left ventricular dysfunction with normal pulmonary pressures (19,20). Myocardial insufficiency can lead to secondary myocardial hypoxia due to amniotic fluid embolism, causing lung injury, cardiac arrest, coronary artery spasm, and direct myocardial ischemia (17,21). The pulmonary symptoms of hypoxia originate from an initial period of severe hemodynamic shift, often followed, in survivors, by lung injury and acute respiratory distress syndrome. In patients whose initial clinical signs do not include cardiac arrest, coagulopathy often develops, which can result in death. Coagulopathy is the third component of the classic triad of signs and symptoms that are part of amniotic fluid embolism syndrome (6,7,17).

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A certain number of patients develop severe disseminated intravascular coagulation at the time of delivery without evident primary cardiorespiratory dysfunction (6,7). Amniotic fluid causes in vitro shortening of coagulation time, platelet aggregation with release of platelet factor III, and activation of both factor X and the complement cascade (6,7). Amniotic fluid also causes transient thrombocytopenia. However, it remains uncertain and unknown how much procoagulant factor in clear amniotic fluid is sufficient to cause clinically significant coagulopathy (6,7,22).

The two only situations in obstetrics that classically lead to severe acute consumptive coagulopathy are amniotic fluid embolism and rare cases of massive placental abruption. In both cases, there is likely a release of fetal tissues and placental thromboplastin into the maternal circulation. In some cases of placenta accreta, there may be maternal cardiovascular collapse and coagulopathy before significant blood loss or shock occurs to cause such a severe condition. It can be inferred that in cases of placenta accreta, placental abruption, and amniotic fluid embolism, a similar sequence of events occurs involving the activation of inflammatory mediators, cascade activation of the coagulation system, or both as a secondary response to fetal antigen exposure.

The clinical and laboratory symptoms present in amniotic fluid embolism, as well as in anaphylactic shock or endotoxin-mediated shock, are very similar (7,17,23). In these situations, there is an abnormal host response following exposure to various foreign antigens, resulting in the release of endogenous mediators that cause and guide the specific clinical syndrome. Therefore, from a pathophysiological perspective, amniotic fluid embolism appears similar to systemic inflammatory response syndrome (SIRS) and clinical conditions such as septic shock, where an abnormal host response with stimulating antigenic action is responsible for the clinical manifestations (24).

The nature of the antigenic stimulus and the endogenous release of mediators are the causes of the clinical manifestations and their severity. A sudden disinhibition of generalized immunosuppression, present during pregnancy due to exposure to inflammatory cytokines, can lead to the state of "immune storm" seen in amniotic fluid embolism. Since the passage of fetal tissues into the maternal circulation, even early in pregnancy, is almost normal, it is es-

sential to identify those women who are particularly at risk for this abnormal response (23).

Since amniotic fluid itself is harmless and the pathophysiology of this syndrome is NOT embolic, it seems reasonable to conclude that the term "Amniotic Fluid Embolism" is incorrect. It would be more appropriate to use terminology that highlights the anaphylactic-like clinical manifestations, such as Pregnancy-Related Anaphylactoid Syndrome (17).

RISK FACTORS

Several risk factors have been examined (23-29). The most common ones are: advanced maternal age (>35 years) (42.86%) or young age (<20 years) (4.76%), parity, race (especially Hispanic and African American), cigarette smoking, male fetus, medical induction of labor, cesarean section, instrumental operative delivery, cervical trauma, placenta previa and placental abruption, hypertension, polyhydramnios, diabetes, manual removal of the placenta (25-31). Many studies have found an association between these risk factors and amniotic fluid embolism, while others have refuted such an association (25,31). The presence of uterine tachysystole or uterine tetany has been linked to the occurrence of this syndrome. In such cases, the endogenous release of norepinephrine (which occurs as a physiological hemodynamic response to any physiological insult) has a uterotonic effect. However, increased uterine activity, commonly present in these situations, is a manifestation of the progression of amniotic fluid embolism rather than its cause. The American College of Obstetricians and Gynecologists has concluded that there is no causative link between uterine stimulation and amniotic fluid embolism (25,32). Currently, no demographic or clinical risk factors have been identified as predictive of amniotic fluid embolism, and this syndrome remains unpreventable and unpredictable.

CLINICAL PRESENTATION

The diagnosis of amniotic fluid embolism remains primarily clinical. Recent research (33) and subsequent work by E. Offer (34) have established criteria for case selection to accurately identify cases resulting from amniotic fluid embolism. These criteria incorporate clinical observations reported by various authors (11).

TABLE 1

International criteria for diagnosis of amniotic fluid embolism

United Kingdom:	
Clinical diagnosis of AFE (acute hypotension or cardiac arrest, acute hypoxia, or coagulopathy in absence of any other potential explanation for signs and symptoms observed) OR pathologic diagnosis of fetal squames or hair in lungs.[14]	
Australia:	
Clinical diagnosis of AFE (acute hypotension or cardiac arrest, acute hypoxia, or coagulopathy in absence of any other potential explanation for signs and symptoms observed) OR pathologic/postmortem diagnosis (presence of fetal squames/debris in pulmonary circulation).[15]	
Japan:	
1	Symptoms appeared during pregnancy or within 12 h of delivery;
2	Intensive medical intervention was conducted to treat ≥1 of following symptoms/diseases: (a) cardiac arrest, (b) severe bleeding of unknown origin within 2 h of delivery (≥1500 mL), (c) DIC, or (d) respiratory failure; and
3	If findings or symptoms obtained could not be explained by other diseases. Consumptive coagulopathy/DIC due to evident etiologies such as abnormal placentation, trauma during labor, and severe preeclampsia/eclampsia should be excluded.
Uterine AFE was considered to have occurred when fetal debris and amniotic fluid components were found in uterus in pathological examination of cases of severe uterine hemorrhage after placental removal (eg, atonic bleeding) in absence of other obstetric hemorrhagic complications such as abnormal placentation, trauma during labor and delivery, and severe preeclampsia/eclampsia.[16]	

AFE, amniotic fluid embolism; *DIC*, disseminated intravascular coagulation.

TABLE 2

Uniform diagnostic criteria for research reporting of amniotic fluid embolism

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 or symptoms, using scoring system of Scientific and Standardization Committee on DIC of the ISTH, modified for pregnancy.[19] 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 min of delivery of placenta.
4	No fever (≥38.0°C) during labor.

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

In its classic clinical presentation, a woman in labor or after vaginal delivery or cesarean section may experience acute dyspnea and desaturation, or dyspnea and desaturation followed by sudden cardiovascular collapse. The most common early symptoms in cases of amniotic fluid embolism include:

- Hypotension (100%)
- Dyspnea (49%)
- Cyanosis (83%)
- Frothy mouth discharge
- Abnormal fetal heart rate (100%)
- Loss of consciousness
- Cardiac arrest (87%)
- Uterine or surgical incision bleeding (83%)
- Uterine atony (23%)
- Seizures (48%)
- Pulmonary edema or acute respiratory distress syndrome (ARDS) (93%)
- Bronchospasm (15%)
- Transient hypertension (11%)
- Cough (7%)
- Headache (7%)
- Chest pain (2%)

Cardiovascular failure is usually followed by cardiac arrest, coagulopathy, or a combination of both. Coagulopathy can result in death despite optimal management of cardiovascular failure and bleeding. In women who experience cardiac arrest, classic arrhythmias such as ventricular fibrillation, asystole, and pulseless electrical activity can occur. These patterns, reflecting different mechanisms of arrest, are due to hypoxia, direct myocardial depression, or severe coagulopathy (17). In women who survive the initial hemodynamic failure and coagulopathy, lung damage and acute respiratory distress syndrome may manifest. Women who have experienced cardiac arrest often develop multiorgan failure, including hypoxic brain damage.

If the fetus is still in utero at the onset of amniotic fluid embolism, abnormalities in fetal heart rate are common and indicative of hypoxia. Decelerations, particularly prolonged acute decelerations, are frequently observed (17). To cope with the hemodynamic insult, the mother may redirect oxygenated blood from the peripheral and splanchnic vascular beds to the cardiac and cerebral circulation, often at the expense of uterine blood flow. Therefore, fetal heart rate abnormalities are a consequence of this hypoperfusion and are usually not accompanied or preceded by maternal symptoms attributable to am-

niotic fluid embolism (17).

DIAGNOSIS

The diagnosis is made if there is a sudden maternal collapse associated with one or more of the following signs:

- Pulmonary thromboembolism
- Transfusion reaction
- Hemorrhage
- Anaphylaxis
- High spinal anesthesia
- Placental abruption
- Air embolism
- Peripartum cardiomyopathy
- Myocardial infarction
- Eclampsia
- Septic shock
- Uterine rupture

The necessary characteristics to make a differential diagnosis with pathologies characterized by symptoms similar to those described for amniotic fluid embolism are highlighted in Tables n. 3 and n. 4.

Differential diagnosis of amniotic fluid embolism

	Amniotic fluid embolism	Hemorrhage	Sepsis	Anesthetic accident	Pulmonary thromboembolism	Systemic anaphylaxis
Hypotension	+++	+++	+++	+++	++	+++
Hypoxia	+++	+/–	+	+++	+++	+++
Coagulopathy	+++	+	+	No	No	No
Sudden onset	Yes	No	No	Yes	Yes	Yes
Prior fever	No	No	Yes	No	No	No
Recognized antecedent event	No	Hemorrhage	Chorioamnionitis	Anesthetic administration	No	Medication administration

SPECIFICITY
SIGNS AND SYMPTOMS OF AMNIOTIC FLUID EMBOLISM
• HYPOTENSION **• SHORTNESS OF BREATH** **• CYANOSIS** **• LOSS OF CONSCIOUSNESS** **• CARDIAC ARREST** **• GENITAL BLEEDING** **• UTERINE ATONY** **• CONVULSIONS**

CLINICAL MANAGEMENT

Initially, it is recommended to perform the following laboratory tests in women presenting with clinical symptoms of amniotic fluid embolism:

- Complete blood count with platelet count
- Cross-matching for blood transfusion
- Serum electrolytes
- Arterial blood gas analysis
- Cardiac enzymes
- Coagulation profile (PT, PTT, INR, fibrinogen)
- ECG
- Echocardiogram
- Chest X-ray

It is not necessary to confirm the presence of amniotic fluid embolism since the treatment is primarily supportive and based on clinically observable pathophysiological data. After a cardiac arrest, the "Standard Basic Cardiac Life Support and Advanced Cardiac Life Support Algorithm" should be followed. In the case of maternal hypotension with a risk of cardiac arrest, fluids and vasopressor medications should be administered to maintain adequate blood pressure levels. Oxygen should be administered in case of dyspnea, hypoxia, or both. Although endotracheal intubation may not be necessary in all cases, the immediate presence of an anesthesiologist-resuscitator is required for potential intubation. The administration of oxygen should be guided by pulse oximetry saturation levels and the results of blood gas analysis or both.

Any coagulopathy and resulting bleeding should be intensively treated through blood and clotting factor transfusions. The use of recombinant factor VIIa appears to worsen the clinical picture by inducing intravascular clot formation. Perhaps the use of recombinant factor VIIa should be reserved for women with severe coagulopathy who continue to have bleeding despite adequate blood transfusion therapy.

If the fetus has reached an appropriate gestational age, immediate delivery is indicated. Although some studies suggest that delivery may improve the maternal condition, there is no valid justification for such a claim. The poor prognosis in this condition, even after immediate delivery, does not change. Immediate delivery is essential for the survival of the fetus.

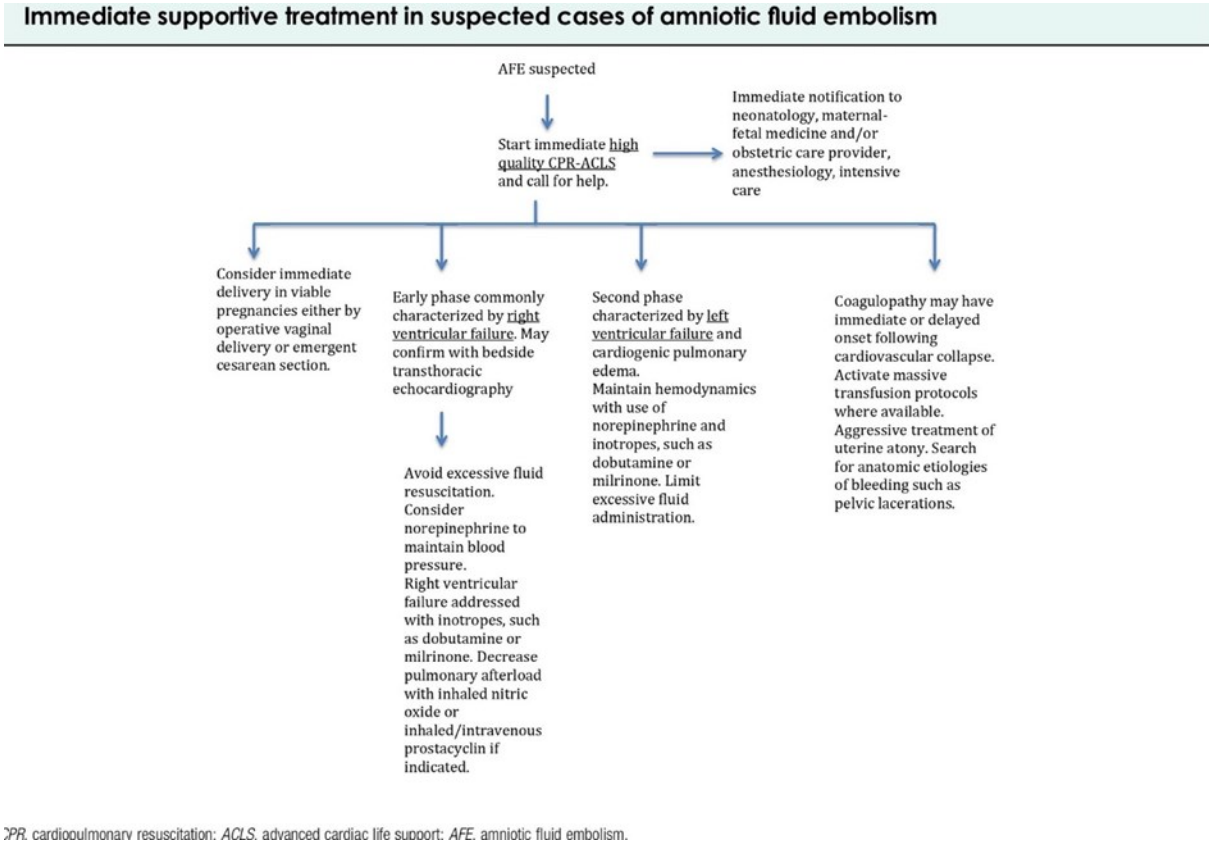
The time between cardiac arrest and delivery (minutes)	Neurologically intact	With neurological deficits	Percentage without neurological deficits
0-5	11	1	91
5-15	4	47	50
>15	7	12	37

Figure n.2: Cardiac arrest, time interval to delivery, and neurological outcome (15,35)

From the moment an optimal cardiopulmonary resuscitation (CPR) achieves a cardiac output of 1/3 of normal, the performance of optimal CPR at term pregnancy is always challenging due to the venocaval obstruction of the gravid uterus. Uteroplacental perfusion during CPR is likely to be very poor or absent. Therefore, in the case of cardiac arrest, regardless of the cause, an emergency cesarean section is indicated if the fetus has reached a viable gestational age. In women with cardiac ar-

rest, immediate delivery improves the chances of a good neonatal outcome.

The treatment for suspected amniotic fluid embolism should follow the algorithm provided below (11).



CPR, cardiopulmonary resuscitation; *ACLS*, advanced cardiac life support; *AFE*, amniotic fluid embolism.

At present, the therapy to be initiated for patients with amniotic fluid embolism is solely supportive. The treatment aims to maintain oxygenation, restore blood pressure, and initiate cardiopulmonary resuscitation as early as possible. Calling for help and involving the anesthesiologist-intensivist is mandatory to ensure advanced resuscitative support and intensive monitoring. Immediate administration of high-flow oxygen is essential to prevent cerebral hypoxic damage. Ventilatory support should be provided, considering tracheal intubation and mechanical ventilation. Circulatory support should be achieved by establishing two large-bore venous accesses and a central venous catheter for fluid and vasopressor administration.

Bleeding due to disseminated intravascular coagulation should be managed with packed red blood cell transfusion and platelet transfusion if there is associated thrombocytopenia. Specific coagulation factor deficiencies should be addressed by administering fresh frozen plasma, cryoprecipitate, fibrinogen, and factor VII in cases of massive and uncontrollable bleeding. Massive hemorrhage resulting from coagulopathy and uterine atony requires treatment with uterotonics, blood transfusions, and po-

tentially hysterectomy. Despite therapy, amniotic fluid embolism has a poor prognosis with severe neurological deficits in the few surviving patients.

Modified International Society on Thrombosis and Hemostasis scoring system for overt disseminated intravascular coagulation in pregnancy

- Platelet count: >100,000/mL = 0, <100,000/mL = 1, <50,000/mL = 2
- Prolonged prothrombin time or international normalized ratio: <25% increase = 0, 25-50% increase = 1, >50% increase = 2
- Fibrinogen level: >200 mg/L = 0, <200 mg/L = 1

Score ≥3 is compatible with overt disseminated intravascular coagulation in pregnancy

OUTCOMES

If a diagnostic criterion based on the presence of all three classic symptoms of the syndrome is adopted, the mortality rate exceeds 60% (17). In cases where cardiac arrest is present, survival is even lower, with less than 10% of patients surviving cardiac arrest treated in the hospital. When less severe cases with milder symptomatic pathology are included in the statistical-clinical analysis, the mortality rate is approximately 20% (7,29,31). The presence of experienced healthcare personnel in managing patients in critical clinical conditions significantly improves the likelihood of survival for these women. Prognosis appears to be closely correlated with the severity of the disease and the occurrence of cardiac arrest rather than specific treatment.

In suspected amniotic fluid embolism, simultaneous with adequate resuscitation, the following should be performed:

1. Prepare red blood cells, fresh frozen plasma or cryoprecipitate, and platelets (even before clinical signs of coagulopathy manifest or laboratory confirmation is obtained).
2. If the patient is unconscious or experiencing severe hypoxia or desaturation, intubation and ventilation with 100% oxygen should be performed.
3. During CPR and in preparation for delivery, the patient should be placed on her side to achieve lateral displacement of the uterus, improving maternal venous return.
4. Crystalloid solutions should be administered rapidly, keeping in mind that among surviving patients, there is a high likelihood of acute lung injury and pulmonary edema.

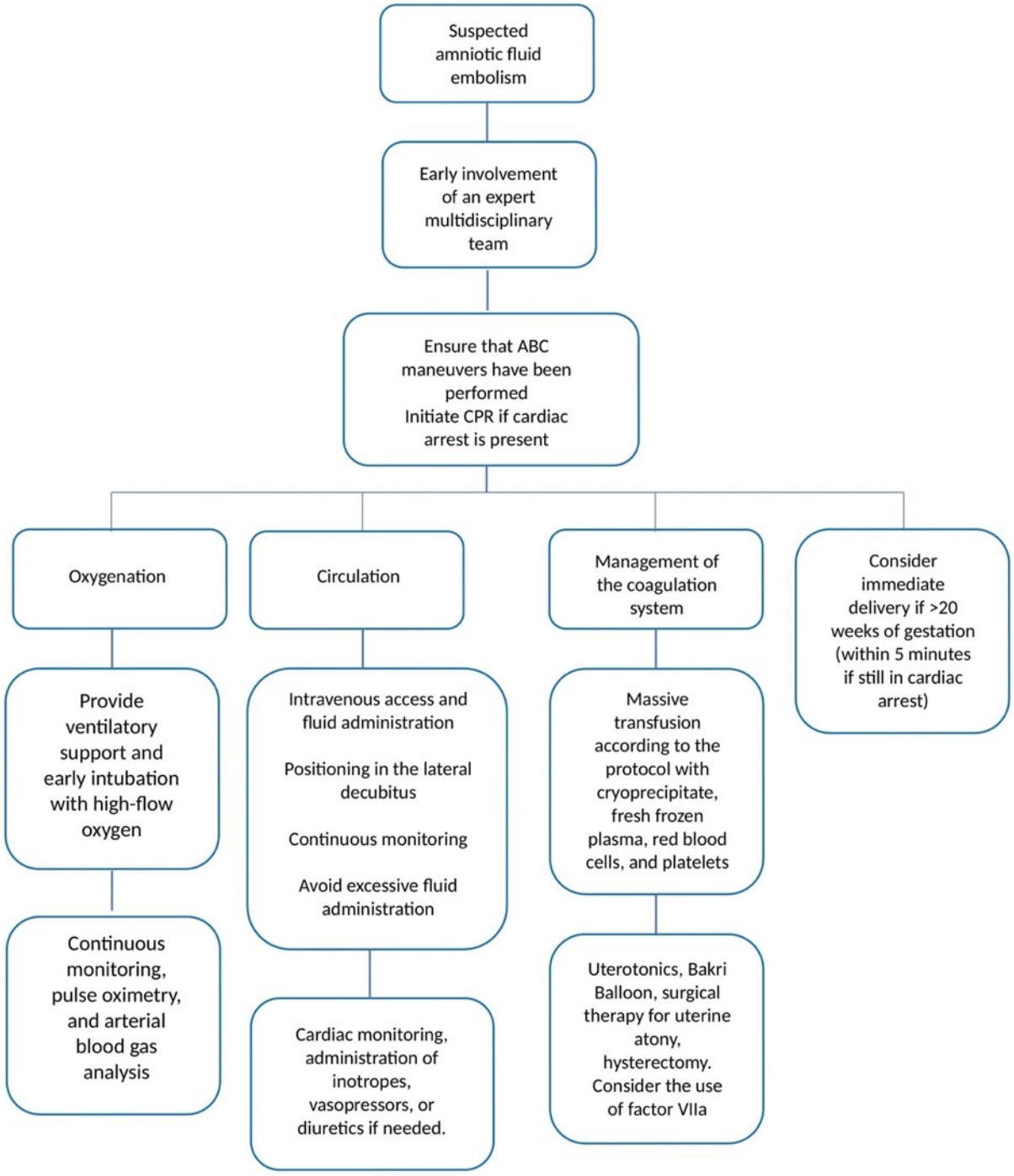
Summary of Recommendations

Number	Recommendations	GRADE
1	We recommend consideration of AFE in the differential diagnosis of sudden cardiorespiratory collapse in the laboring or recently delivered woman.	1C Strong recommendation Weak-quality evidence
2	We do not recommend the use of any specific diagnostic laboratory test to either confirm or refute the diagnosis of AFE; at the present time, AFE remains a clinical diagnosis.	1C Strong recommendation Weak-quality evidence
3	We recommend the provision of immediate high-quality cardiopulmonary resuscitation with standard BCLS and ACLS protocols in patients who develop cardiac arrest associated with AFE.	1C Strong recommendation Weak-quality evidence
4	We recommend that a multidisciplinary team including anesthesia, respiratory therapy, critical care, and maternal-fetal medicine should be involved in ongoing care of women with AFE.	Best practice
5	Following cardiac arrest with AFE, we recommend immediate delivery in the presence of a fetus ≥23 weeks of gestation.	2C Weak recommendation Weak-quality evidence
6	We recommend the provision of adequate oxygenation and ventilation and, when indicated by hemodynamic status, the use of vasopressors and inotropic agents in the initial management of AFE. Excessive fluid administration should be avoided.	1 C Strong recommendation, Weak-quality evidence
7	Because coagulopathy may follow cardiovascular collapse with AFE, we recommend early assessment of clotting status and early aggressive management of clinical bleeding with standard massive transfusion protocols.	1C Strong recommendation, Weak-quality evidence

ACLS, advanced cardiac life support; *AFE*, amniotic fluid embolism; *BCLS*, basic cardiac life support; *GRADE*, Grading of Recommendations Assessment, Development, and Evaluation.

SMFM. Amniotic fluid embolism: diagnosis and management. Am J Obstet Gynecol 2016.

Algorithm for the management of amniotic fluid embolism



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