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Amniotic fluid embolism: retrospective study about 12 patients

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Abstract

Amniotic embolism is a serious complication. The symptoms associated with amniotic embolism (EA) result from the passage into the maternal circulation of fetal and amniotic material, most often during labor or in immediate postpartum. His prognosis remains gloomy. His diagnosis is difficult and his treatment is just symptomatic. We reviewed 12 files of patients with probable or autopsy-confirmed amniotic embolism.

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Introduction

Amniotic embolism corresponds to the passage of amniotic fluid in the maternal circulation, it is a rare but potentially catastrophic affection it is a pregnancy-specific disease. Its real incidence is difficult to evaluate, because some cases pauci or asymptomatic are not recognized and can go unnoticed [1]. The incidence of amniotic fluid embolism (AFE) is estimated at 1/53 800 deliveries in Europe and it is an obstetric emergency involving maternal and fetal prognosis. In France, AFE is the second leading cause of maternal death, with a maternal mortality ratio of 1.2 per 100,000 deliveries. The understanding of its pathophysiology has progressed in recent years, but remains poorly understood due to the rarity of this condition. AFE should be considered in mothers with acute onset of cardiorespitory collapse. The confirmation of this disease relies on amniotic fluid debris of histological findings at different levels: a central venous blood sample, bronchoalveolar lavage fluid (BALF), examination of the hysterectomy specimen or autopsy [2]. Once the diagnosis is brought up, the management must be multidisciplinary and intensive.

Methods

This is a retrospective study based on the exploitation of the files of 12 patients with serious complications of childbirth including cardiopulmonary arrest, acute respiratory distress, whether or not associated with hemorrhage of delivery and coagulopathy, and who are diagnosed as a probable or confirmed AFE by the microscopic study, collated in the services of "El HAROUCHI Maternity", "Lala Meryem Maternity", "Maternal intensive care", "pathology department" and "Forensic Medicine" of Ibn Rochd University Hospital Center Casablanca for a period of ten years, from April 2008 to February 2018.

Results

Twelve suspect AFE cases were reported from 2008 to 2018 including six cases confirmed by autopsy. The mean age was 29.6 years. Four out of 12 patients were multiparae, three of whom had a history of cesarean delivery. No atopic pregnancy or intrauterine intervention during pregnancy has been described. All patients were admitted for delivery of a full term pregnancy, with an intrauterine fetal death reported in three cases. Labor had taken place spontaneously in 5 patients while the other 7 were triggered by oxytocin infusion. Five of the twelve patients had an artificial membrane rupture, three with tinted amniotic fluid. AFE clinical presentation was variable, disseminated intravascular coagulation (DIC) was the leading syndrome, with severe post-partum hemorrhage, and cardiovascular collapse. Early symptoms (weakness, cyanosis, vomiting) have been described in five patients with three case of cardiac arrest.

Four patients had generalized seizures, being the initial clinical manifestation in one two. The acute respiratory distress syndrome was reported in four patients. These symptoms occurred during labor in four patients leading to emergency cesarean section including one during resuscitation maneuvers, giving birth to 4 female newborns, two with Apgar 1/10, remained the same after 5 min and died despite pediatric resuscitation, the two others was an intrauterine fetal death. For the other 8 cases, the symptoms occurred in the aftermath of vaginal delivery, two with the use of forceps, giving birth to eight healthy male newborns. As for the blood work, hemostasis disorders associated with acute anemia have been described in all patients and hepatic cytolysis objectified in 8 patients. AFE management was mainly symptomatic using CPR and transfusion. Concerning postpartum hemorrhage management, hypogastric arteries ligation was performed in seven patients; a triple ligation was performed in five and three patient required hysterectomy. The outcome was fatal for all

patients including 8 by cardiac arrest and 3 by cerebral anoxia despite resuscitation measures.

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Discussion

The AFE was first described in 1926 [1-3]. The incidence of AFE, estimated at 1/53 800 deliveries in Europe, is very difficult to approach because of its rarity. In recent years, the prognosis of AFE has further improved thanks to better initial multidisciplinary management [4]. However, this improvement doesn´t concern the most serious forms such as those observed in the Clark registry [5], which reported a survival rate of 39%, neurological impairments recorded in 85% of survivors [6]. Morgan considers AFE to be the most fatal condition in obstetrics [5]. In the US registry, death occurred within five hours after the onset of symptoms in 63%. Cardiorespiratory arrest is the main cause of poor prognosis and maternal neurological sequelae. Few data specify the fetal prognosis. In the US registry, the death rate of newborns during the event is 22% and neurological impairment rate of 61%. The pathophysiology of AFE is incompletely understood. The transition of amniotic fluid to maternal circulation involves the coexistence of an amniovascular gap and a decreasing pressure gradient. This passage can be done through three recognized pathways, which are the blood vessels of the cervix, the placental implantation site and a traumatic uterine lesion. The embolus is made of fetal epithelial squamous cells, hair, intestinal secretions (mucin) or even meconium.

These elements can be found both in the pulmonary capillary vessels and in the uterine vessels. According to data from many studies, there are three associated clinical responses: respiratory, hemodynamic and neurological [7]. The initial respiratory response is pulmonary capillary obstruction

resulting in pulmonary arterial hypertension (PAH), intra pulmonary shunting and severe hypoxia [5,8-10]. The early PAH could be explained by two mechanisms, a pure mechanical phenomenon with pulmonary capillary obstruction by the insoluble elements of the amniotic fluid, associated with pulmonary vasoconstriction due to the presence in this fluid of endothelin, a powerful vasoconstrictor and other insoluble elements (leukotrienes, thromboxane A2) and arachidonic acid. Direct toxicity of the amniotic fluid by negative inotropism alters the left ventricular systolic function which is already disturbed by dilation of the right ventricle, resulting in initial collapse [2]. Finally, respiratory and hemodynamic distress leads to neurological distress which includes seizures, confusion or coma. The often serious hemorrhagic syndrome observed in AFE is probably due to a DIC triggered by the amniotic fluid rich in activating factors of coagulation. The symptoms are most often diffuse hemorrhages for which no obstetric cause is found.

Hemodynamic changes and coagulation disorders in AFE may be mediated by humoral factors including histamine, serotonin, prostaglandins, leukotrienes and proteolytic enzymes. All these mediators are involved in septic and anaphylactic shocks, hence the term "anaphylactoid syndrome of pregnancy" by Clark [5]. The brutal and unpredictable clinical presentation usually begins during labor or immediately after the birth of the baby. According to Morgan [5], AFE occurs in 90% of cases during labor versus 70% compared to Clark [6]. Some suspected cases of AFE have been reported, either during an abortion of the second trimester [6] or exceptionally during pregnancy [9]. In our study, the clinical presentation started in 4 out of 12 patients during labor (40%). Risk factors include older maternal age (≥35 years of age), multiparity, cesarean section, macrosomia, male baby, use of oxytocin and long labor. Artificial rupturing of membranes, instrumental extraction, uterine rupture, genital tract injury, hydramnios, are significantly associated with increased risk of AFE. Intrauterine fetal death and meconium in amniotic fluid are also risk factors of poor prognosis.

In our study, the risk factors observed were: multiparity in 4 patients out of 12, a history of cesarean section, an intrauterine fetal death, the use of oxytocin in 7 patients, membrane rupture in three patients, tinted amniotic fluid in a three patient. There were eight male newborns. Many signs and symptoms are indicative of possible AFE: dyspnea, cyanosis, cough, chest pain, agitation, headache, nausea ... AFE remains an exclusion diagnosis and should always be suggested in case of an obstetric emergency with hypotension and / or cardiovascular collapse, acute respiratory distress, DIC, coma and / or seizures during labor or within 48 hours post-delivery, in the absence of a health problem or other potential explanation for the observed symptoms. The frequency of AFE symptoms reported in large series is summarized in Table 1. Other differential diagnoses should also be considered (Table 2). Maternal death usually results from sudden cardiorespiratory arrest, massive bleeding, or multiple organ failure. Due to the acute onset of AFE, it primarily requires an immediate supportive and resuscitative treatment that temporarily excludes any para-clinical investigation. Similarly to clinical symptoms, the results of biological and / or radiological examinations are non-specific. They diagnose complications, guide the therapeutic approach [2] and can help with differential diagnosis.

Leukocytosis can be observed. The diagnosis of DIC is based on a prolonged prothrombin time, a decrease in fibrinogen and / or the presence of thrombocytopenia. Cardiac enzymes can be elevated and hypoxemia is objectified by the measurement of arterial blood gases. Non-specific lung abnormalities may be observed on chest radiography. Transthoracic or ideally transesophageal echocardiography is useful for diagnosis. If performed in the early phase of AFE, it can sometimes highlight intracardiac thrombus or embolus in the right heart. The presence of amniotic epithelial cells in the

blood or maternal BALF is not pathognomonic for amniotic embolism, but their absence is has a significant negative predictive value. The measurement of serum tryptase allows a better understanding of the pathophysiology of AFE, especially the anaphylactoid theory [6], without being able to pinpoint the triggering factor of this anaphylactic reaction, whether it is infectious, drug-related or amniotic, but the elevation of this enzyme was inconsistently found [3,5]. Other blood substances have been suggested as AFE markers: zinc-coproporphyrin complex, meconium component, serum syalil Tn antigen, complement factors (C3, C4), IGFBP1 (insulin-like growth factor binding protein-1), fetal fibronectin and alpha-fetoprotein [11].

Currently, the research for fetal cells in maternal blood and BALF, combined with the serum tryptase dosage, provide valuable diagnostic indications. In the event of a fatal outcome, the macro and microscopic autopsy examinations make it possible to confirm with certainty the diagnosis of AFE by highlighting the presence of fetal elements in the pulmonary arterial circulation, but also other organs: the hysterectomy specimen, kidney, brain, heart, and spleen. The management of AFE is mainly symptomatic, there is no etiological treatment. The coordination of obstetrical and resuscitation measures should allow jointly, and in the shortest possible time, the extraction of the fetus and the stabilization of the maternal vital signs. The maternal resuscitation is based on three axes: the maintenance of an effective oxygenation with intubation and administration of 100% oxygen and positive pressure ventilation. The reestablishment of a stable hemodynamic status calls for a rapid volume infusion and the use of positive inotropic drugs. Finally the correction of hemostasis disorders through the administration of labile blood products (red blood cells concentrates, fresh frozen plasma and platelet concentrates) and fibrinogen. Several articles in the literature describe the use of recombinant activated factor VIIa (rFVIIa) in AFE with hemorrhage secondary to a coagulopathy. However, the meta-analysis of these cases shows a significant increase in thromboembolic complications and deaths in women with AFE and receiving rFVIIa compared to those who did not receive it [12]. Hemostasis hysterectomy can be performed in case of uterine atony resistant to medical treatment. Other adjuvant treatments have been described as the effective use of inhaled nitric oxide for the management of high blood pressure and right heart failure associated with AFE [13]. Clark has proposed the use of steroids, considering his support for the anaphylactoid theory [6], but there´s insufficient data to conclude to the benefits of this therapeutic approach. Hemofiltration or plasmapheresis techniques have been successfully used for isolated cases of AFE [14].

Conclusion

Amniotic fluid embolism is a rare and catastrophic disease because of its poor prognosis for both mother and baby. Its pathophysiology is uncertain, and the diagnosis is difficult to establish. Any isolated acute incident during delivery should be suggestive of the diagnosis. As soon as AFE is suspected, a multidisciplinary management must be carried out to insure an effective cardiorespiratory resuscitation, to avoid a coagulopathy and to allow the rapid extraction of the fetus. An autopsy must be done in case of death to confirm the diagnosis. If in spite of a clear explanation the family of the deceased refuses this verification, it´s necessary to create a national registry of the cases observed, to collect these cases and publish them, to discuss them, in order to better understand the epidemiology and pathophysiology of this dreadful complication.

What is known about the topic

- Amniotic embolism corresponds to the passage of amniotic fluid in the maternal circulation;
- The confirmation of this disease relies on amniotic fluid debris of histological findings at different levels;

- The management must be multidisciplinary and intensive.

What this study adds

- It sets an idea about incidence rate in the Moroccan context as well as management and complication rate.

Competing interests

The authors declare no competing interest.

Authors' contributions

The patients were seen first by OB/GYN team (Kenza Lebbar, Rachida Sabiri, Mehdi Bouslikhane, Karima Fichtali, Mustapha Benhessou, Said Bouhya), then transferred to critical care unit(Amine Hanzaz, Adil Ouboukhliq, Lina Berrada, Rachid Elharrar) who made the diagnosis with collaboration with cardiology team (Amal Moukhliss, Soukaina Safir, Marwa Abdulhakeem, Rihab Machtache, Rachida Habbal). M.Abdelhakeem: made the traduction of the article. All the authors have read and agreed to the final manuscript.

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Tables

Table 1: symptoms of AFE recorded in large series

Table 2: differential diagnosis of AFE

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Table 1: symptoms of AFE recorded in large series	
General symptomatology	Hypoxia, acute respiratory distress syndrome, respiratory arrest
	Hypotension, cardiogenic shock then hemorrhagic Cardiac arrest
	Obstetrical bleeding, hematuria, ENT bleeding, gastro-entestinal bleeding, etc.
	Headache, confusion, convulsive seizure, cerebral thrombosis, coma
Obstetrical symptoms	Postpartum hemorrhage
	Paratonia, hemorrhage from the operating site
	Foetal signs, foetal heart rate abnormalities isolated or associated with hypertonia or hypercinesia
	Multivisceral complications or failures Maternal and foetal deaths

Table 2: differential diagnosis of AFE	
Obstetric causes	Acute hemorrhage
	Rupture or placental retention
	Uterine rupture
	Eclampsia,
	Peripartum cardiomyopathy
Anesthetics	Local anesthetic systemic toxicity
	Total spinal anesthesia
	Pulmonary inhalation toxicity.
Respiratory	Pulmonary embolism (gas, fat, thrombosis)
	Pneumothorax
	Pulmonary edema (cardiogenic or non-cardiogenic)
	Asthma attack...
Cardiac	Myocardial infarction
	Arrhythmias
Neurologic	Epilepsy
	Stroke
	Cerebral hemorrhage
Other	Septic
	Hemorrhagic and anaphylactic shocks; Hypoglycemia