AMNIOTIC FLUID EMBOLISM (AFE):
PATHOPHYSIOLOGY, CLINICAL FEATURES,
DIAGNOSIS, THERAPY

INTRODUCTION

The occurrence of the amniotic fluid embolism syndrome is a rare and often fatal obstetric complication [1]. The amniotic fluid embolism (AFE) was described in 1926 by Meyer [2] as reported by Clark et al. [3] but it was not until 1941 before it became recognized as a clinical entity after the publication by Steiner and Lushbaugh [4]. Classically, AFE is a sudden event characterized by acute respiratory failure with severe maternal hypoxia, cardiovascular collapse, and coagulopathy [3]. AFE occurs when amniotic fluid and/or fetal elements (including fetal squamous cells, mucin, meconium, vernix caseosa, and lanugo hairs) enter the maternal blood stream, and is confirmed by proving their existence in the maternal pulmonary vascularisation at autopsy [5,6]. Amniotic fluid embolism occur in 1/8000 to 1/80000 deliveries but with a maternal morbidity ranging from 26% in a recent report to 86% in earlier ones [7,8]. In the USA, this condition is the most common cause of peripartum maternal death and is responsible for

SUMMARY:
Amniotic fluid embolism (AFE) is an unpredictable, unexpected, and for the most part, an untreatable obstetric emergency. Management of this condition includes prompt of the signs and symptoms, aggressive resuscitation efforts, and supportive therapy. Any delays in diagnosis and treatment can result in increased maternal and/or fetal impairment or death. Whereas once the invariable outcome of AFE was death of the mother, today the prognosis is some what brighter thanks to increased awareness of the syndrome and advances in intensive care medicine. In any case, intensive care nurses are called on to provide, life saving care the patient and her fetus.

Key words: amniotic fluid embolism, pathophysiology, diagnosis, management

EMBOLIA PRIN LICHID AMNIOTIC (ELA): PATOFIZIOLOGIE CLINICĂ, DIAGNOSTIC, TERAPIE

Rezumat
Embolsul lichidului amniotic este în mare parte (în cele mai multe cazuri), o urgență obstetrică neașteptată, nepredictibilă și netratabilă. Managemnetul acestor situații include observarea rapidă a semnelor și simptomelor, eforturilor de resuscitare agresivă și terapia suportivă. Orice întârziere a diagnosticului și tratamentului duce la creșterea riscului matern și/sau fetal sau la moarte. În trecut evoluția AFE se solda invariabil cu moartea mamei, astăzi prognosticul este mai bun datorită unui diagnostic mai precoce și a îngrijirilor medicale avansate. În orice caz asistentele de la terapie intensivă sunt implicate în măsurile pentru susținerea vieții mamei și a fătului.

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roughly 10% of all maternal deaths [3]. This special report showed that 70% of AFE occurred during labor but before delivery 11% after vaginal delivery (81% in spontaneous delivery) and 19% during cesarean section. Even today, AFE is the leading cause of death during labor and the first few postpartum hours [9] and it remains a deadly and unexpected obstetric emergency [10]. The fetal mortality rate although better than the maternal rate, is a dismal 21% and 50% of the surviving neonate experience permanent neurological injury [3].

**ETIOLOGY**

Normally, amniotic fluid does not enter the maternal circulation because it is contained safely within the uterus, sealed off by the amniotic sac. AFE occurs when the barrier between amniotic fluid and maternal circulation is broken and, possibly under a pressure gradient, fluid abnormally enters the maternal venous system via the endocervical veins, the placental site (if placenta is separated) or a uterine trauma site [11]. Why this entry into maternal circulation occurs in some women and not in others is not clearly understood. The devastating consequence of circulating fetal debris (carried by amniotic fluid) occurs only rarely, even though during normal labor and delivery, cesarean deliveries, and minor traumatic procedures fetal tissue may pass into maternal circulation and cause no symptoms [12]. That AFE develops in only a minute proportion of these women suggests that either it is an effect of the mount of exposure to fetal debris or the type of fetal debris (containing meconium or not) or that some maternal factors may play a significant role [3]. Clark et al. [3] contend that AFE more closely resemble an anaphylactic reaction to fetal debris than an embolic event, and they propose the term “anaphylactoid syndrome of pregnancy” instead of AFE. The exact mechanism of this anaphylactoid reaction to amniotic fluid is not clearly understood.

Predisposing factors once considered to be associated with AFE include placental abruption, uterine overdistention, fetal death, trauma, tumultuous or oxytocin-stimulated labor, multiparity, advanced maternal age, and rupture of membranes [10]. The occurrence of AFE in twin pregnancy is extremely rare [1]. Öney et al. [13] described the first case in 1982 at 39 weeks of pregnancy during normal labor. Recently a third case of AFE in twin pregnancy was describer during preterm uterine contraction with ruptured membranes despite tocolytic therapy [14]. de Rooij et al. [1] reported the occurrence of AFE in a twin pregnancy at 29 weeks during preterm uterine contraction with tocolytic therapy before vaginal loss of amniotic fluid (28-year-old healthy female).

**CLINICAL FEATURES AND PATHOPHYSIOLOGY**

One of the major factors that makes AFE so devastating is its total unpredictability. Although most cases occur after the onset of labor, some incidents have occurred outside of labor. As mentioned earlier, several clinical conditions seem to be associated with AFE, but essentially there are no definitive clues, warning signs, or associated conditions that indicate the risk of AFE may increase. Most experts agree that AFE, as it is known now, cannot be predicted or prevented [15].

According to Gei and Hankins [15] the initial signs and symptoms have a typical chronology, and the morbidity and mortality of the manifestations steadily decreases with time. Most often, respiratory distress and cyanosis occur suddenly within the first minute and are quickly followed by hypotension, pulmonary edema, shock, and neurological manifestations such as confusion, loss of consciousness, and seizures. More than 80% of patients experience cardiorespiratory arrest within the first few minutes [11]. Approximately 50% of patients do not survive this onslaught of cardiopulmonary injury, but of those who do, 40% to 50% have coagulopathy and hemorrhage up to 4 hours later [16]. Porter et al. [17] noted that in some patients, coagulopathy may be the first indication of AFE, whereas Clark et al. [3] reported that seizure activity may at times be the first manifestation.

The pathophysiology of AFE is speculative. The initial respiratory reaction possibly begins with transient pulmonary vasoconstriction [18]. Although this possible transient vasoconstriction has not been documented (probably because the signs and symptoms appear so abruptly in a seemingly healthy person who is not being monitored via invasive methods), vasoconstriction may be caused by amniotic microemboli that trigger the release of arachnoid acid metabolites [19], and lead to pulmonary hypertension, intrapulmonary shunting, bronchoconstriction and severe hypoxia [18]. Exactly which components of amniotic fluid actually cause this effect is unknown, but Clark [18] suggests that abnormal components such as meconium may play a role. Many experts speculate that maternal mediators also may have an influence: amniotic fluid activates complement [20], leukotrienes [21,22], endothelin [23], syncytiotrophoblastic cells and megakaryocyte in pulmonary vessels.
DIC, pulmonary mast cell tryptase [25]. The second manifestation includes negative inotropism and left ventricular failure resulting in increasing pulmonary edema and hypotension quickly leading to shock. The third manifestation is a neurological response to the respiratory and hemodynamic injury, which may include seizures, confusion, or coma [15].

About 40% to 50% of patients who survive to this point have severe coagulopathy, usually disseminated intravascular coagulation (DIC), which results in uncontrollable uterine bleeding along with bleeding from puncture sites such as insertion sites for intravenous and epidural catheters [15]. This coagulopathy is thought to be precipitated by several procoagulant component of amniotic fluid, most notably thromboplastin, which initiate the extrinsic pathway of the clotting cascade and result in excessive fibrinolytic activity [15,26,27]. The distinction between primary fibrinogenolysis and DIC with secondary fibrinolysis is often difficult to draw [28]. It is complicated by the changes in the coagulation and fibrinolytic systems during normal pregnancy. However, the absence of clinical evidence of systemic thrombosis (hepatic and renal tests remain normal) and some biological data may suggest predominant fibrinogenolysis: a normal platelet count, a very low fibrinogen level and factor V level in contrast to normal factor II, VII, X ones, the absence of soluble fibrin, a high level of fibrin degradation products, and very low plasmin inhibitor level with high values of t-PA (tissue-plasminogen activator). Antithrombin levels decreased slightly during pregnancy reaching values published in the literature ranging from 40 to 132% during the third trimester [29].

Possibly before the onset of maternal signs and symptoms, but most certainly as they appear, initial changes in fetal heart rate pattern become evident on the electronic fetal monitor. The changes are due to the electronic fetal uterine perfusion and the resultant decreased placental blood flow associated with maternal hypotension [15]. A decrease in fetal oxygenation, in this situation due to maternal hypotension and hypoxia, can rapidly lead to the appearance of nonreassuring pattern in fetal heart rate [30].

**DIAGNOSIS**

Immediate recognition and diagnosis of AFE is essential to improve maternal and fetal outcomes. Until recently, the diagnosis of AFE was made only after autopsy of the mother revealed squamous cells, lanugo hair, or other fetal and amniotic material in the pulmonary arterial vascularisation [15,31]. Although laboratory data may indicate that AFE is likely, as noted previously, no single laboratory or clinical finding can be used to diagnose or exclude it [11,12]. Diagnosis therefore, must be based on clinical features and AFE should not be confused with other pregnancy-related complications or medical conditions.

**MANAGEMENT**

Once the signs and symptoms are recognized and a presumptive diagnosis is made, supportive measures should be implemented promptly. In the event of cardiac arrest, the resuscitation team should follow standard Advanced Cardiac Life Support protocols for obstetric patients [26]. Ideally, overall management of AFE should take place in an obstetric intensive care unit. Many hospitals lack obstetric intensive care units and so the patients must be cared for in a medical or surgical intensive care unit [30].

The 3 main goals of treatment are (1) oxygenation, (2) maintaining cardiac output and blood pressure, and (3) correcting coagulopathy.

**1) Oxygenation**

The fetus is very vulnerable to maternal hypoxia [31], which is initially profound in AFE. Therefore, the first priority is resuscitation of the mother [10] and administration of oxygen by any means available at concentrations of 100% [12].

A more aggressive approach includes securing an airway through endotracheal intubation, providing mechanical ventilation for the patient with a high inspired fraction of oxygen (>60%) and the addition of positive end-expiratory pressure (PEPP) [11,12,15]. Positive end-respiratory pressure is typically started at 5 cm H₂O are increased by increment of 2 to 3 cm H₂O until satisfactory levels of PaO₂ are reached [15]. The goal of oxygen therapy is the maintain arterial PaO₂ higher than 60 mmHg and arterial oxygen saturation (SaO₂) at 90% or higher [11,27,32].

**2) Circulation control**

Maintaining cardiac output and blood pressure involves several simultaneous interventions. Gei and Hankins [15] recommend positioning the patient flat or in a slight Trendelenburg position to improve to venous blood return and perfusion of the central nervous system. Supportive measures include the initiation of fluid therapy, administration of pharmacological agents (inotropic agents to maintain cardiac output and blood pressure: dopamine, dobutamine, norepinephrine) and
electrocardiographic monitoring to detect and treat arrhythmias; most patients with AFE initially have electromechanical dissociation or bradycardia [3]. Placement of a pulmonary artery catheter is highly recommended for monitoring cardiac output, central venous pressure, and pulmonary artery pressure.

Volume replacement with isotonic crystalloid solution is a first-line therapy for maintaining blood pressure [27]. Fluid therapy should be based on the findings of central venous monitoring, so as to avoid overhydration in these patients, who are predisposed to pulmonary edema [11]. Therapy for left ventricular dysfunction should be directed toward improving inotropy [33]. Gillie and Hughes [34] recommend several inotropic agents as drug of choice for maintaining cardiac output and blood pressure (dopamine, dobutamine, norepinephrine). A clinical guideline for supporting critically ill obstetric patients is to maintain systolic blood pressure at or higher than 50 mmHg [27], with acceptable organ perfusion, as indicated by a urine output of 25 ml/h or more [32].

(3) Control of hemorrhage and coagulopathy

The results of hemostatic studies can be used to diagnose and monitor the course of bleeding and disseminated intravascular coagulation (DIC). According to Martin et al.[26] control of uterine bleeding can often be accomplished with uterine massage and the administration of pharmacological agents. If bleeding is profuse and pharmacological intervention is unsuccessful, a hysterectomy may be necessary. Administration of blood transfusions and blood components is considered the first line of treatment for correcting coagulopathy associated with AFE [11]. Blood products include packed red blood cells, fresh-frozen plasma, platelets, and cryoprecipitate to maintain organ perfusion and urinary output until bleeding due to DIC resolves [32]. Cryoprecipitate is particularly useful in AFE because it can be used to replenish clotting factors in lieu of fresh-frozen plasma in volume restricted patients. In addition, cryoprecipitate contains both fibrinogen and fibronectin, which facilitate the removal of cellular and particulate matter (eg. amniotic fluid debris) from the blood via the reticuloendothelial system [11]. McCance and Huether [35] explain that the reticuloendothelial system, now referred to as the mononuclear phagocyte system, consists of line of cells that ingest and destroy (by phagocytosis) unwanted material in the blood.

Another pharmacological interventions is the use of intravenous steroids. Amniotic fluid not only displaces blood and reduces oxygen and waste exchange but also introduces antigens, cells, and protein aggregates that trigger inflammation within the bloodstream [30]. In consideration of the potential inflammatory response and similarities to anaphylaxis, the administration of corticosteroids may be helpful in AFE [3,15,27].

REFERENCES
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