

Review Article

Amniotic Fluid EmbolismJonathan H Skerman¹, Khalil E Rajab²¹Department of Anaesthesia and Intensive Care and ²Department of Obstetrics and Gynaecology, College of Medicine and Medical Sciences, Arabian Gulf University, Bahrain and Salmaniya Medical Complex, Bahrain

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ABSTRACT

Amniotic fluid embolism, although fortunately rare, is one of the most catastrophic situations in obstetrics. It cannot be predicted nor prevented. The clinical events in this syndrome include respiratory failure, cardiopulmonary collapse, and disturbances of the clotting mechanism. Maintenance of oxygenation, circulatory support and correction of the coagulopathy can be life saving.

Although maternal and fetal prognosis is grave, death need not be the inevitable outcome if diagnosis is made early and is followed by prompt and aggressive management. Future efforts must be directed towards more clearly delineating the presentation, pathogenesis, diagnosis and outcome of amniotic fluid embolism.

KEY WORDS: amniotic fluid embolism, catastrophe, pregnancy

INTRODUCTION

Amniotic fluid embolism is a rare, unpredictable and unpreventable obstetric catastrophe. It is initiated by entry of amniotic fluid into the maternal circulation and is characterized by the sudden onset of severe dyspnea, tachypnea and cyanosis during labour, delivery or the early puerperium. Because randomised controlled trials are not possible, understanding the etiology and defining the risk factors have become the main foci^[1]. The management is empirical and will be discussed in detail.

Amniotic fluid embolism was first reported by Meyer in 1926^[2]. It was reported again in an experiment on laboratory animals by Warden in 1927^[3]. The importance of this condition and these early studies was not established until 1941, when Steiner and Lushbaugh noted the clinical and pathological findings of eight women who died suddenly during, or just after labor^[4]. They performed experimental studies on laboratory animals that produced the same severe disturbances of cardiopulmonary function following the entry of amniotic fluid into maternal circulation. Their study was documented with pathologic findings of pulmonary embolism caused by amniotic fluid particulate matter. Schneider in 1968 showed that lethal qualities of human amniotic fluid infused intravenously into dogs were enhanced greatly by the addition of meconium^[5]. The description by Steiner and Lushbaugh of a patient with amniotic fluid

embolism is classical in its detailed brevity. "Profound shock coming on suddenly and unexpectedly in a woman who is usually in severe labor or has just finished such a labor, especially if she is an elderly multipara with an excessively large, perhaps dead fetus and with meconium amniotic fluid, should lead to a suspicion of the possibility. If also, the shock is introduced by a chill which is followed by dyspnea, cyanosis, vomiting, restlessness and the like, and is accompanied by a pronounced fall in blood pressure and a rapid, weak pulse, the picture is more complete. If pulmonary edema now develops quickly in the known absence of previously existing heart disease the diagnosis is reasonably certain."^[4]

Their description is complete except for the development of disseminated intravascular coagulopathy in patients surviving the initial pulmonary insult.

INCIDENCE

The incidence of amniotic fluid embolism has been reported to be between 1:8000 to 1:80,000 pregnancies; a more realistic figure would be between these two extremes^[4-6]. The mortality rate is very high. Although it is a rare occurrence, it still remains a leading cause of maternal and fetal death. Morgan in 1979 reviewed 272 cases documented in the British medical literature and reported a mortality rate of 86%^[7]. From the same study, 25% of the deaths occurred within the first hour of the onset of symptoms indicating that even

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with optimum critical care management a high mortality rate persists. All sudden death in late pregnancy is not due to amniotic fluid embolism. We must be careful not to let this diagnosis become the bin for cases of unexplained death in labor, especially without confirmation by autopsy.

POSSIBLE PREDISPOSING FACTORS

Maternal factors

The etiology of amniotic fluid embolism remains elusive. Associated factors include advanced maternal age, multiple pregnancies, macrosomic fetuses, short duration of labor and intense contractions often augmented with an uterine muscle stimulant such as oxytocin^[8]. Others suggest that fetal demise, meconium staining of amniotic fluid, amniotomy, PIH, caesarean section delivery, abruptio placenta, placenta previa, ruptured uterus, amniocentesis, insertion of an intrauterine pressure catheter, and pregnancy at term with the presence of an intrauterine device are also causative factors^[1,9-12]. Documentation of amniotic fluid embolism has also been reported following intrauterine injection of hypertonic saline to induce abortion.

Amniotic fluid embolus syndrome has been reported in association with a myriad of conditions. These conditions include first and second trimester abortion with saline, prostaglandins and urea, and hysterotomy. It has occurred during labor, at delivery, just after delivery, and one case even developed 32 hours postpartum. Most reported cases of amniotic fluid embolism occur during labor; a pattern of vigorous labor or hypertonic uterine contractions or labor further stimulated by use of oxytocin often has been implicated in the pathogenesis. Evidence for this association (use of an oxytocic) is primarily anecdotal and must be regarded with skepticism. In a review of this subject, Morgan concluded: "In view of the very wide use of accelerated labor and the rarity of amniotic fluid embolism, it must be concluded that there is no direct association between the two"^[7]. Placental abruption is present in up to 50% of cases and may contribute to the pattern of uterine hypertonus associated with amniotic fluid embolism. In 40% of cases, fetal death is reported prior to the acute clinical presentation.

In an analysis of data collected in another study^[8], the range of age was from 18 to 43 years, with 22 patients being 30 years old or older, and 12 patients over 35 years of age. The parity of patients ranged from one to eight; the majority of patients were greater than three; however, there were four cases documented in primipara. The duration of gestational age of the pregnancies in the patients who subsequently died ranged from 38 to 44

weeks. This of course excluded those patients that died from amniotic fluid embolism secondary to saline or other fluids injected intra-amniotically to induce abortion^[9].

The characteristics of the labor pattern varied. However, it is of interest to note that four patients developed amniotic emboli without being in labor^[10]. The majority of patients was in various stages of labor either spontaneously or augmented (in 22% labor had been induced and in 11% labor had been augmented with an oxytocic agent). The augmentation or induction of labor was instituted for the usual reasons: ruptured membranes without consistent uterine contractions; post-maturity; one patient due to pregnancy induced hypertension and one patient who was electively induced. In 10%, labor was augmented due to poor progress. Forty-four percent of patients in spontaneous labor had tumultuous and unusually short labors averaging less than one hour in duration. No comparably short labor or precipitous delivery was identified in the patients who received oxytocin stimulation, nor were tetanic contractions reported^[11].

The membranes were documented to be intact in three patients at the time the embolism or onset of symptoms occurred. In most cases studied, the membranes had ruptured either spontaneously or by amniotomy prior to the onset of symptoms. Simultaneous rupture of membranes with onset of symptoms of amniotic fluid embolus and meconium fluid was present in approximately 75% of these patients^[4,12].

Fetal factors

No clear pattern of fetal presentation, position or engagement could be ascertained; most cases documented indicated a vertex presentation. There was generally a lack of documentation associating station of the presenting part with onset of symptoms. It could be assumed, since the onset of symptoms occurred just prior to or during delivery, that the fetal presenting part was engaged.

The size of the infants varied from five to eleven pounds, but the exact weight of all infants was not available. There was a high incidence of demise and intrapartum death of infants and unfortunately of those few infants born alive, a very high percentage expired during the neonatal period. In one study of 21 infants on whom information was available, nine died with five deaths occurring during the intrapartum period. Ten live births were recorded in this particular study; however only two infants had survived. There was a disproportionately large number of stillbirths and some researchers felt that the presence of a dead fetus reduced the strength of the membranes as well as greatly increased the

quantity of particulate matter in the amniotic fluid^[4].

In order for amniotic fluid embolism to occur, the fluid must enter into the maternal circulation. Currently, there are three recognized conditions that must exist for this to result: amniotomy, laceration of endocervical or uterine vessels, and a pressure gradient sufficient to force the fluid into the maternal circulation.

Atear or rent in the membranes as in amniotomy has been associated with proven embolism^[10]. Various sites of entry of amniotic fluid into maternal circulation have been suggested. Laceration of endocervical veins can occur during the normal process of cervical dilation and effacement, although more severe lacerations may occur with a very rapid and tumultuous labor or vigorous cervical manipulation during vaginal examination. Uterine vessels can be damaged through surgical procedures such as caesarean section or amniocentesis. Trauma is also responsible for causing damage to the uterine vessels^[11]. According to Thomson^[13], an abnormal opening of the uterine vessels, either decidual or myometrial which occurs with uterine rupture, placenta accreta, caesarean section, or retained placenta may provide a portal of entry for amniotic fluid. Abruptio placenta, whether marginal or complete, as well as any degree of placenta previa could also provide a route of entry. If amniotic fluid finds an open maternal venous sinus, it could be pumped by a vigorous contraction through the disrupted amniotic membrane, with resultant embolization.

Intra-amniotic injections of fluid, i.e. hypertonic saline, saline, or urea cause a rise in intrauterine pressure which may be greater than that associated with normal labour. Frost in 1967, reported a patient with a hydatidiform mole who died from trophoblastic embolization of the lungs following injection of intra-amniotic hypertonic saline^[14]. A review of deaths following legal abortions in the United States from 1972 to 1978 revealed 15 (12%) were due to amniotic fluid embolus; all of these followed intra-amniotic injections, and none followed uterine curettage^[14]. Clinically, the symptoms exhibited in these patients were the same as in those with embolism occurring at term. This study also revealed gestational age to be a significant factor. No deaths occurred below 12 weeks of gestation; however the mortality was 7.2 per 100,000 at 21 weeks or more, representing a risk factor 24 times greater after 21 weeks gestation^[14]. Due to the rarity of the condition combined with the fact that diagnosis is most often made during the post mortem examination, it is difficult to determine a definite cause and effect with this catastrophic obstetrical event.

Pathophysiology

The two life threatening consequences of amniotic fluid embolism, cardiopulmonary collapse and disseminated intravascular coagulation, may occur in sequence or together. The physiology of amniotic fluid embolism results in pulmonary hypertension with a sudden reduction of blood flow to the left heart, decreased left ventricular output, and subsequent peripheral vascular collapse. The sudden development of pulmonary hypertension precipitates acute cor-pulmonale and congestive heart failure which thereby causes pulmonary edema. The derangement of the ventilation-perfusion ratio of the lungs produces hypoxemia and tissue hypoxia. Multiple emboli are usually necessary to cause this acute onset of symptoms.

The toxicity of intravenously infused amniotic fluid appears to vary remarkably depending upon the particulate matter it contains; this is especially true of meconium fluid. The particulate materials found in amniotic fluid and especially in meconium stained fluid, according to some authors, may account for the cause of sudden death associated with this syndrome^[15].

Meconium includes shed fetal squamous cells (squames), fetal hairs, vernix caseosa and mucin. If the severe pulmonary vascular obstruction and cor-pulmonale which develops is not immediately fatal, hemorrhage will soon be evident. The etiology of disseminated intravascular coagulopathy is controversial. Evidence suggests a potent thrombolytic action of amniotic fluid that causes disseminated deposition of fibrin clots and activation of the lysis system. These hemodynamic processes defibrinate the blood, resulting in afibrinogenemia, coagulopathy and subsequent hemorrhage^[16,17]. The powerful thromboplastin effects of trophoblasts are well established; systemic release of trophoblastic material may play an even greater role in the coagulopathy of amniotic fluid embolism than has been appreciated.

Kitzmilller has shown that amniotic fluid collected during labor as compared to fluid collected prior to labor has greater toxicity when infused into rabbits^[17]. The particular substance mediating this reaction is still unknown. Prostaglandins and leukotrienes produce many of the hemodynamic and hematologic effects present in patients with amniotic fluid embolism and have been implicated by some researchers^[18]. These metabolites of arachidonic acid are present in increased quantities during labor^[19].

Some researchers postulate that an acute anaphylactoid reaction may play a part in the development of the cardiovascular collapse^[20]. For a true anaphylactic reaction to occur, sensitization is required, but evidence for this is inconclusive.

The most significant pathologic findings at autopsy are limited to the lungs. Grossly, the lungs show evidence of pulmonary edema (in 70% of the cases)^[21]. Alveolar hemorrhage and pulmonary embolism of amniotic fluid materials are present; the presence of embolic particles is essential for diagnosis, but on histology they may be missed because of their small size^[15,22-24]. They are composed of amorphous debris, epithelial squames, and mucin (from meconium). They tend to lodge in small arteries, arterioles, and capillaries of the lungs^[22]. Since uterine trauma is a significant factor in the pathogenesis, signs of uterine laceration or uterine rupture may be evident^[23]. Acute right ventricular dilation is usually present. Amniotic fluid elements are sometimes found in uterine vessels and the right side of the heart, and careful evaluation of the other organs may also identify the magnitude of embolization with the finding of particulate matter in the maternal brain, kidneys, liver and spleen. The hypothalamus is also an area that deserves special evaluation.

Clinical and Laboratory Diagnosis

In a small percentage of patients the onset of symptoms before labor was clinically evident. The majority of patients developed symptoms during the latter part of the first stage of labor and a lesser number became acute during birth. There have been two cases documented associated with delivery of the placenta and only one case has been documented to occur as late as 32 hours postpartum.

Prodromal symptoms in amniotic fluid embolism are sudden chills, shivering, sweating, anxiety, and coughing followed by signs of respiratory distress, shock, cardiovascular collapse, and convulsions^[1]. All patients were conscious during the onset of symptoms. Respiratory difficulty, evidenced by cyanosis, tachypnea, and bronchospasm, frequently culminates in fulminant pulmonary edema. Hypoxemia explains the cyanosis, the restlessness, the convulsions and coma. Reflex tachypnea results from the decreased arterial oxygen saturation and cardiovascular collapse, heralded by hypotension, tachycardia and arrhythmia may end in cardiac arrest. Convulsions may be an early manifestation of CNS involvement combined with cerebral ischemia and eventually may lead to coma and death. If the patient survives this initial episode, bleeding occurs secondary to disseminated intravascular coagulopathy and uterine atony.

In all cases studied, bleeding was never documented as one of the first symptoms. A definitive diagnosis is usually made at examination by demonstration of amniotic fluid material in the maternal circulation and the small arteries,

arterioles, and capillaries of the pulmonary vessels. In the living patient, diagnosis can be made by identification of lanugo or fetal hair and fetal squames in an aspirate of blood from the right heart^[24]. Fetal squames have been recovered in the maternal sputum in some cases^[25]. Additional diagnostic tools for confirmation of amniotic fluid embolism suspected by the classic clinical picture include: 1. chest X-ray, which may show enlarged right atrium and ventricle and prominent proximal pulmonary artery (in massive pulmonary embolism) and pulmonary edema; 2. lung scan, which may demonstrate some areas of reduced radioactivity in the lung field; 3. central venous pressure (CVP), with an initial rise due to pulmonary hypertension and eventually a profound drop due to severe hemorrhage; and 4. measurement of blood coagulation factors. Normally in pregnancy, blood coagulation factors are increased. However, with amniotic fluid embolism, evidence of disseminated intravascular coagulopathy ensues with failure of blood to clot, decreased platelet count, decreased fibrinogen and afibrinogenemia, prolonged PT and PTT, and presence of fibrin degradation products.

In the differential diagnosis of amniotic fluid embolism, the following entities are to be considered^[25]:

1. Thrombotic pulmonary embolism, which is usually caused by a thrombus originating from the lower extremities or pelvic veins, is usually associated with chest pain. However, it generally occurs later in the postpartum period, and may occur with evidence of venous thrombosis^[26].
2. Air embolism, which may follow a ruptured uterus, blood transfusion under pressure, or manipulation of placenta previa can occur during labor or caesarean section. It is associated with chest pain, but an important differentiating factor from amniotic fluid embolism is the auscultation of a typical "water-wheel" murmur over the pericardium^[24].
3. Aspiration of gastric contents into the lungs causes cyanosis, tachycardia, hypotension, and pulmonary edema (similar to amniotic fluid embolism). However, acid aspiration is usually seen in an unconscious patient with loss of the cough reflex or during induction or emergence from general anesthesia^[26].
4. Eclamptic convulsions and coma in a pregnant patient may resemble this syndrome, but the state of shock in amniotic fluid embolism and presence of hypertension, proteinuria, and edema in the eclamptic patient differentiate these two conditions^[27].
5. Convulsions from a toxic reaction to local anesthetic drugs may be confused with this

syndrome. However, the close temporal relationship between the onset of symptoms and administration of the drug is an important differentiating factor^[27]. Also, hypertension is usually present in the clinical picture of drug toxicity.

6. Acute left heart failure (seen most commonly in pregnant patients with rheumatic heart disease) may simulate an amniotic fluid embolism, but the history of previous disease with ECG changes and other clinical symptoms, i.e., cardiac murmur, helps in the diagnosis.
7. A cerebrovascular accident may be considered in the differential diagnosis, but it is distinguished from amniotic fluid embolism by the absence of cyanosis, hypotension, and pulmonary edema. Also, examination of cerebrospinal fluid should help in the diagnosis.
8. Finally, hemorrhagic shock in an obstetric patient, which is usually associated with ruptured uterus, uterine inversion, abruptio placenta and placenta previa, may lead to the erroneous diagnosis of amniotic fluid embolism. A careful history and physical examination, absence of cyanosis and presence of low CVP with hemorrhagic shock should lead to the correct diagnosis.

OBSTETRIC AND ANESTHETIC MANAGEMENT

To prevent amniotic fluid embolism, trauma to the uterus must be avoided during maneuvers such as insertion of a pressure catheter or rupture of membranes. Incision of the placenta during cesarean delivery should also be avoided if possible^[7]. Since one of the most frequent predisposing factors is considered to be tumultuous labor that may occur naturally, excessively strong and frequent uterine contractions should be controlled by administration of intravenous α -adrenergic drugs^[7] or magnesium sulfate^[28,29]. Also, oxytocic drugs, which can precipitate excessive tetanic uterine contractions must be used appropriately and judiciously.

In most cases no therapy has proven effective. Whenever unexplained cyanosis and shock develops during labor, a diagnosis of amniotic fluid embolism should be considered^[30]. Assuming a diagnosis could be made prior to death, supportive measures should be focused at cardiopulmonary resuscitation, blood volume replacement, and treatment of coagulopathy.

Resuscitation should begin with endotracheal intubation and mechanical ventilation using inspired oxygen concentrations of 50 to 100% delivered by positive pressure and PEEP. With the use of PEEP, functional residual capacity will hopefully increase and if oxygenation improves, as evidenced by pulse oximetry or ABGs, a

lowered PEEP setting may be tried. However high PEEP may produce a decrease in cardiac output due to increased intrathoracic pressure and may subsequently decrease tissue perfusion. Improved oxygenation will hopefully reduce pulmonary capillary fragility and thereby decrease the severity of pulmonary edema. To date, there has been no documentation in the use of hyperbaric oxygen and some authors feel it would be worth a try in treating the severe tissue hypoxia. To prevent and/or recognize further deterioration careful monitoring is essential. Placement of an arterial line to monitor arterial blood gases and other pertinent chemistries, as well as a central venous or Swan-Ganz catheter to monitor cardiac status and state of hydration are of enormous value.

The causes of pulmonary edema have been variably ascribed to vigorous fluid resuscitation, increased pulmonary capillary permeability, and cardiac decompensation due to hypoxia and tachycardia. The severity of pulmonary edema certainly plays an important role in the initial gas exchange abnormality.

At present there is no clear regime of drug therapy to reverse the symptoms and complications of amniotic fluid embolism. Drug therapy and other treatment have been supportive and aimed at improving ventilation/perfusion ratio, maintaining adequate blood pressure and treating the disseminated intravascular coagulopathy.

The drug used to treat pulmonary complications such as bronchospasm and vasoconstriction of pulmonary arterioles is terbutaline, especially if the patient has not delivered and has a live fetus. Isoproterenol also relieves pulmonary vasoconstriction and improves cardiac function, although it can cause peripheral vasodilation, which will exacerbate the hypotension. Dopamine in low dose may be preferable to isoproterenol, since it improves cardiac function and increases peripheral and renal perfusion. High dose of dopamine decreases renal perfusion. Administration of aminophylline for its bronchodilation and cardiac stimulation effects is controversial, especially because of the tachycardia it produces. Hydrocortisone in pharmacologic doses up to 2 g/24 hrs reduces pulmonary vasospasm and pulmonary edema and potentiates the cardiac response to catecholamines. In the event of heart failure, digitalization with a rapid acting agent is recommended^[31]. Diuretics can be used if pulmonary wedge pressure is elevated. Indomethacin has been effective in treating severe pulmonary hypertension in laboratory animals and should be considered for use. In a condition with such a high rate of mortality, there would be nothing to lose.

Hypotension should be treated first by left uterine displacement if the patient is undelivered.

This can be accomplished easily by insertion of a wedge under the right hip. The vasopressor of choice is ephedrine because it does not decrease uterine perfusion. However, if the fetus has expired or has already been delivered, isoproterenol or dobutamine can be used. The fluid of choice should be lactated Ringers since its pH is close to that of blood; the rate of infusion will depend upon the CVP values or filling pressures if a Swan-Ganz catheter is in place. If acidosis is present, as evidenced by blood gas values, sodium bicarbonate should be administered.

Treatment of the bleeding diathesis requires blood replacement using fresh whole blood when available, as the clotting factors are intact. Cryoprecipitate and platelet infusions are also required to help combat the coagulopathy. Heparin therapy is controversial; some patients have been documented to survive with its use but there is documented survival without using heparin.

Uterine bleeding in a patient already delivered should be controlled by massage and use of intravenous oxytocin. If uterine bleeding is unresponsive to these methods, one should consider exploration for retained placenta or membranes or a search for cervical or uterine lacerations. Methylergonovine is also a strong uterine stimulant and can be given very slowly intravenously. The use of prostaglandins (Hemabate[®] Upjohn and Company) to control hemorrhage is controversial and may cause bronchospasm and/or pulmonary hypertension.

The use of ϵ -aminocaproic acid and aprotinin is not well documented in treatment of amniotic embolism, but they can be used when rapid reversal of the lytic state is needed before delivery^[32]. Aprotinin (Trasylol) should be the drug of choice if the fetus is still viable since it does not cross the placenta whereas ϵ -aminocaproic acid does, and is teratogenic as well^[33]. In cases of intractable hemorrhage which does not respond to the above measures uterine artery embolization can be life-saving^[34]. Continuous hemodiafiltration has been reported to have affected a dramatic response in cases of disseminated intravascular coagulation due to amniotic fluid embolism^[35].

When amniotic fluid embolism occurs prior to delivery, the accompanying respiratory distress, cardiovascular collapse and hemorrhagic tendency are contraindications to any regional anesthetic techniques; if severe shock develops, general anesthetics must be administered with extreme caution. Since immediate delivery is indicated, emergency caesarean section is usually required. The choice of anesthetic agents will depend upon the patient's condition, and aggressive cardiopulmonary resuscitation may be all that the anesthetist can

provide. Anesthetic agents that produce myocardial depression must be avoided.

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