Obstetrical and Pediatric Anesthesia

Amniotic fluid embolus: a review of the literature

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Purpose: To review the literature since 1979 to determine the natural history, etiology, diagnosis and potential treatment of amniotic fluid embolus (AFE).

Source: English language articles and books published between June 1976 and June 1998 were identified by a computerized medline search using the title or text word amniotic fluid embolus. This same search strategy was repeated and updated to October 1999 by an independent individual using both Medline and Embase. The search was also expanded to include Science Citation Index listing Morgan's 1979 review article. All relevant publications were retrieved and their bibliographies were scanned for additional sources.

Principal findings: Randomized controlled trials are not possible with amniotic fluid emboli. The majority of the literature consists of clinical reports combined with occasional limited reviews. Knowledge obtained from these reports suggests that amniotic fluid emboli present as a spectrum of disease that ranges from a subclinical entity to one that is rapidly fatal. Because cases are sporadic and the diagnosis is often unconfirmed, little progress has been made towards understanding its etiology or defining the risk factors. Present management is empirical and directed towards the maintenance of oxygenation, circulatory support and the correction of coagulopathy.

Conclusion: Amniotic fluid embolus continues to be a life-threatening but potentially reversible complication unique to pregnancy. It cannot be predicted nor prevented. Review of the literature reveals that there are no standardized investigational methods or protocols to confirm the diagnosis in suspected cases.

Objectif : Passer en revue la littérature depuis 1979 pour déterminer l'histoire naturelle, l'étiologie, le diagnostic et le traitement potentiel d'une embolie amniotique (EA).

Source : Des articles et des livres de langue anglaise, publiés entre juin 1976 et juin 1998, ont été sélectionnés lors d'une recherche informatisée de données médicales en utilisant les titres ou l'expression *amniotic fluid embolus*. La même méthode de recherche a été utilisée par un individu indépendant pour obtenir une mise à jour jusqu'en octobre 1999 avec Medline et Embase. La recherche a été étendue au Science Citation Index qui présentait la revue de Morgan de 1979. Tous les articles pertinents ont été retenus et leurs bibliographies examinées pour découvrir des sources supplémentaires.

Constatations principales : Les essais contrôlés et randomisés sur l'embolie amniotique sont impossibles. La plus grande partie de la documentation constituée de résumés cliniques combinés à des revues limitées occasionnelles. Les connaissances dégagées de ces résumés suggèrent que l'embolie amniotique se présente comme de multiples affections allant de l'entité subclinique à la maladie rapidement fatale. Les cas étant rares et le diagnostic souvent non confirmé, peu de progrès ont été réalisés pour mieux en comprendre les causes ou pour définir ses facteurs de risque. Le traitement actuel est empirique et vise à maintenir l'oxygénation, à entretenir la circulation et à corriger la coagulopathie.

Conclusion : L'embolie amniotique est toujours une complication grave mais potentiellement réversible, unique à la grossesse. On ne peut la prévoir ni la prévenir. Une revue de la littérature révèle qu'il n'existe pas de méthode ou de protocole normalisés d'évaluation qui permettent de confirmer le diagnostic chez des cas suspects d'embolie amniotique.

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Accepted for publication October 1, 2000.

THE entry of amniotic fluid into the maternal circulation was first described by Meyer in 1926.[1] However, it was not until 1941 that the clinical importance of this entity was appreciated. At that time, Steiner and Lushbaugh reported cases of unexpected death in the obstetrical population and reviewed their clinical presentation and histopathological findings.[2] Of these, eight patients became the major focus of their discussion. These women were found to have material consistent with amniotic fluid debris in the pulmonary vasculature and consequently became the basis of the earliest descriptions of the amniotic fluid embolus syndrome.

Following the initial descriptions of amniotic fluid emboli in humans, numerous investigators attempted to develop a suitable animal model to study the amniotic fluid embolus syndrome. These studies have been fraught with difficulty including the use of heterologous rather than autologous amniotic fluid and their findings, for the most part, are considered to be irrelevant to the human population.[3,4] Therefore, much of what is presently known about this entity has been derived from the numerous clinical reports.

The first major review of the literature was published by Morgan in 1979.[5] Prompted by three cases from his own institution, he reviewed the 272 cases reported in the English literature. This publication was important in that it was the first to challenge many of the traditional beliefs regarding amniotic fluid emboli. Since then, a national registry has been developed by Clark[6] in the United States and numerous clinical reports and reviews have accumulated. The purpose of this article is to review this literature in order to understand the present state of our knowledge regarding the natural history, etiology, diagnosis and treatment of AFE.

Search criteria

A computerized Medline search of the English language literature published subsequent to Morgan's review was undertaken. The initial search was conducted from June 1976 to June 1998 using the title or text word amniotic fluid embolus. This same search strategy was repeated and updated to October 1999 by an independent individual using both Medline and Embase. The search was then expanded to include Science Citation Index listing Morgan's 1979 review article. All relevant publications were retrieved, read and their bibliographies scanned for additional sources. One hundred and ninety one related publications were identified. The majority of these consisted of clinical reports combined with occasional limited reviews or analyses of maternal mortality statistics. Although some overlap may have occurred between the clinical reports and the patients included in the mortality statistics, where available, the data within these publications revealed an additional 286 cases of suspected or confirmed amniotic fluid embolus reported since Morgan's review. Taken collectively, it is now believed that, similar to other embolic syndromes, amniotic fluid embolus (AFE) is not an all or nothing phenomenon. Rather, it is a spectrum of disease that ranges from a subclinical entity to one that is rapidly fatal.[3] In those patients who are symptomatic, the presentation can be quite variable and will depend on the predominant physiological aberration.

Natural history

Incidence and mortality

The incidence ranges between 1 in 8,000 to 1 in 80,000 pregnancies, with various estimates between these two extremes.[5] With such a variation, one can only conclude that the true incidence is not known. There are many reasons for this. First, there are a number of inaccuracies in reporting the cause of maternal death.[1] Secondly, the presentation can be variable and the number of nonfatal or subclinical episodes is unclear. Finally, in those patients who do survive or in whom no autopsy was performed, it is often quite difficult to confirm the diagnosis.[1,7]

The mortality continues to be high for patients who are symptomatic. There were only 39 survivors in Morgan's series of 272 patients: a mortality rate of 86%.[5] In Clark's registry the mortality was 61%.[6] Among the survivors only 15% were neurologically intact. All deaths occurred within five hours of collapse, the timing dependent on the length of resuscitation efforts.[6]

Clinical presentation

The classic presentation of amniotic fluid embolus syndrome was described as sudden, profound and unexpected shock followed by cardiovascular collapse and, in most cases, death.[2] The syndrome was thought to more likely occur in the elderly multiparous patient who had an unusually strong or rapid labour or who had just delivered following such a labour. The use of uterine stimulants, meconium staining of the amniotic fluid or the presence of a large or dead fetus were also felt to increase the risk. Subsequent experience has shown that there are a number of exceptions to this classical description.[1]

Although multiparous patients accounted for 88% of the reported cases at the time of Morgan's review, there were no other identifiable predisposing factors.[5] Clark also found no identifiable maternal risk factors,

including parity, in his analysis of the national registry.[6] Although both authors noted that patients were most likely to present during labour or shortly thereafter, there are several case reports of amniotic fluid emboli occurring during Cesarean sections and therapeutic abortions[8] as well as occasional cases in the late postpartum period, or very rarely in a non labouring patient[3,7,10] Other cases have been associated with abdominal trauma, ruptured uterus or intrapartum amnioinfusion.[9]

In order to explain those cases presenting in the late post partum period, Courtney[11] suggested that amniotic fluid may become trapped in the uterine veins during contraction of the uterus at delivery. This fluid may then be released into the circulation later, during normal postpartum uterine involution. A similar mechanism was suggested by Margarson.[1,2] In this case it was postulated that trapped amniotic fluid was mobilized following return of sympathetic tone and spontaneous movement in a patient who had been given a spinal anesthetic for Cesarean section. Alternatively, similar to fat emboli, the late onset of symptoms may be due to the passage of amniotic fluid debris into the central circulation via the transpulmonary route or through a patent foramen ovale.[1,3] Distribution to major organs such as the brain or heart may then contribute to the pathophysiology and the clinical picture we observe. Finally, it is conceivable that the initial event was either transient or subclinical and went unrecognized. This, in turn, could account for the delayed or atypical presentations reported in the literature.

In light of the high mortality in Morgan's series, it is not surprising that cardiorespiratory collapse was almost invariably present.[5] However, the presenting symptom in 51% of patients was respiratory distress. In the remainder, the first indication of a problem was hypotension in 27%, a coagulopathy in 12% and seizures in 10%. Clark[6], on the other hand, found that, of those women presenting prior to delivery, 30% had seizures or seizure-like activity while 27% complained of dyspnea. Fetal bradycardia (17%) and hypotension (13%) were the next most common presenting features. Of the 13 patients who developed symptoms after the delivery of the infant, seven (54%) presented with an isolated coagulopathy manifested by postpartum hemorrhage. Several additional case reports have suggested that the presentation of an amniotic fluid embolus can be quite variable in regards to timing, presenting symptoms and subsequent course.[14–43] These reports highlight the need to consider the differential diagnosis carefully while, at the same time, maintaining a high index of suspicion for this disorder (Table I).

Etiology

Normal anatomy and physiology

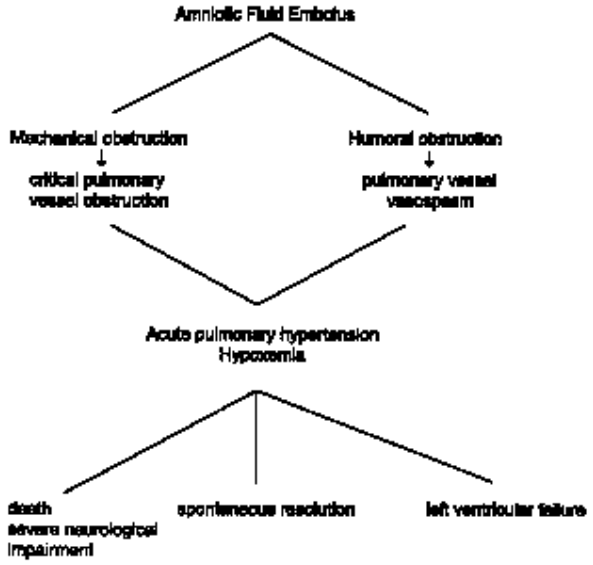
Amniotic fluid and the surrounding sac provide important protective mechanisms for the developing fetus. Throughout gestation, intact fetal membranes isolate amniotic fluid from the maternal circulation. At delivery, uterine vessels on the raw surface of the endometrium become exposed following placental separation. Normally, uterine contractions are very effective in collapsing these veins. Therefore, in addition to ruptured membranes, in order for AFE to occur there must be a pressure gradient favouring the entry of amniotic fluid from the uterus into the maternal circulation.[1] Although the placental implantation site is one potential portal of entry, particularly with partial separation of the placenta, this is otherwise unlikely if the uterus remains well contracted. On the other hand, small tears in the lower uterine segment and endocervix are common during labour and delivery and are now thought to be the most likely entry site.[1,3] In support of this concept, Bastein *et al.* reported a case of amniotic fluid embolus where postmortem examination revealed marked plugging of both the cervical vasculature and the lungs by various amniotic fluid elements.[2,7]

Throughout the literature there are references to the concept that amniotic fluid routinely enters the maternal circulation at delivery. This misconception arose from the belief that the presence of squamous cells in the pulmonary vasculature was a marker signaling the entry of amniotic fluid into the maternal circulation. Studies have now shown that squamous cells can appear in the pulmonary blood of heterogenous populations of both pregnant and non-pregnant patients who have undergone pulmonary artery (PA) catheterization.[44–48] The presence of these cells is thought to have resulted from contamination by either exogenous sources during specimen preparation or by epithelial cells derived from the entry site of the PA catheter.[44,45] Since it is difficult to differentiate adult from fetal epithelial cells, the isolated finding of squamous cells in the pulmonary circulation of pregnant patients *without* amniotic fluid embolus is most likely a contaminant and not indicative of maternal exposure to amniotic fluid.

TABLE I Clinical presentation

• Acute cardiorespiratory collapse
• Acute respiratory distress
• Hypotension
• Hemorrhage / coagulopathy
• Seizures
• Fetal distress

TABLE II Proposed hemodynamic pathophysiology



Further examination of blood specimens taken from pregnant patients, with and without a clinical diagnosis of amniotic fluid embolus reveals that, although squamous cells may be present in both groups, only the former had evidence of other fetal debris such as mucin, vernix and lanugo. In these patients, squamous cells and other granular debris were frequently coated with leukocytes, suggesting a maternal reaction to foreign material. Where other occasional unidentifiable debris was detected, the authors stated that the material present in the patients who did not have an AFE was "clearly different" from that seen in the AFE sample.[48]

An additional cause for the confusion regarding whether or not amniotic fluid routinely enters the maternal circulation centres around the importance of trophoblastic embolization to the maternal lung. Trophoblastic cells are normally free floating in the intervillous space and therefore have direct access to the maternal circulation.[1] Consequently, their presence in the maternal peripheral or central vascular system is not surprising nor indicative of an amniotic fluid embolus. Attwood and Park found evidence of trophoblastic embolism to the lungs in 43% of women dying in the peripartum period but microscopic evidence of amniotic fluid embolus in less than 1%.[1] Similarly, earlier studies were able to identify trophoblastic cells in the broad ligament veins at cesarean section but none noted any other amniotic fluid debris.[1]

Further evidence that amniotic fluid does not normally enter the maternal circulation can be found from autopsies of parturients who died from various complications of pregnancy. Roche and Norris[49] compared lung specimens obtained from 20 toxemic patients with an equal number who had clinical evidence of amniotic fluid embolus. Utilizing a specific stain for acid mucopolysaccharide (AMP), they were able to confirm the presence of mucin in the lung sections from all of the amniotic fluid embolism patients. None of the sections from the toxemic patients stained positive. In an earlier study of 109 maternal deaths, Bradwell and Toy found microscopic evidence of amniotic fluid debris in only two cases.[1]

In summary, the presence of squamous or trophoblastic cells in the maternal pulmonary vasaculature must not be equated with the entry of amniotic fluid into the maternal circulation. There is no conclusive evidence at present to support the suggestion that amniotic fluid embolus is a common physiological occurrence.

Pathophysiology

Once amniotic fluid has entered the maternal circulation, a number of physiological changes occur that contribute to the syndrome that we observe. In essence, the pathophysiology is multifactorial and the clinical presentation will depend on the predominant physiological aberration.

Hemodynamic changes

The early reliance on experimental animal models for amniotic fluid emboli led to the traditional view that acute, severe pulmonary hypertension was the major pathophysiological change.[4] This was believed to be due either to critical obstruction of the pulmonary vessels by embolic material or to pulmonary vasospasm secondary to the response of the pulmonary vasculature to fetal debris resulting in acute asphyxiation, cor pulmonale and in turn sudden death or severe neurological impairment.[3,4]

Human hemodynamic data generally do not support sustained periods of pulmonary hypertension.[50,51] In 1990, Clark[4] reviewed the available hemodynamic data from the published cases of amniotic fluid embolus in humans and found only mild to moderate elevations in pulmonary artery pressures, whereas all patients had evidence of severe left ventricular dysfunction. Calculation of pulmonary vascular resistance further revealed that, with one exception, all were either normal or in a range that was reflective of isolated left heart failure.[4]

An excellent case report documenting left ventricular dysfunction was published by Girard *et al.* in

1986.[52] A 25-yr-old previously healthy prima gravida suffered acute cardiorespiratory collapse during the second stage of labour. The diagnosis of amniotic fluid embolus was made on the basis of a typical clinical presentation combined with fetal debris aspirated from the pulmonary artery catheter. Hemodynamic measurements and echocardiography revealed severe left heart failure. Because of the extent of the myocardial impairment, endomyocardial biopsy was performed to rule out peripartum cardiomyopathy. No evidence for this was found and a repeat echocardiogram 10 days later was within normal limits.

Similar to Girard's report, subsequent published cases have also supported left ventricular failure as the major hemodynamic aberration.[33,51,53] However, more recently, there have been two case reports in which amniotic fluid embolus was accompanied by massive thrombotic pulmonary embolus.[35,54] This suggests that, in a minority of patients, critical obstruction of the main branches of the pulmonary arteries can occur.

In an attempt to reconcile clinical and experimental findings, Clark[4] proposed a biphasic model to explain the hemodynamic abnormalities that occur with amniotic fluid emboli. He suggested that acute pulmonary hypertension and vasospasm may be the initial hemodynamic response. The resulting right heart failure and accompanying hypoxia could account for the cases of sudden death or severe neurological impairment. He further speculated that in those patients who initially survived, this phase of pulmonary hypertension was not sustained but rather was replaced by the onset of left ventricular failure. The transient nature of the initial pulmonary hypertension is seen in experimental animal models which have measured central hemodynamic parameters and have used autologous amniotic fluid. Reis *et al.*,[55] using the pregnant ewe model, demonstrated changes in the pulmonary circulation consistent with acute pulmonary hypertension and found that these had, in most cases, returned to normal within 10 min of injection. In a more recent study, Hankins *et al.*[56] injected pregnant goats with autologous amniotic fluid and found marked increases in both pulmonary and systemic vascular resistance. These effects were considerably increased with meconium stained amniotic fluid. All changes were noted within 10 min of injection and, for the most part, had resolved by 30 min. Since the pressor responses occurred simultaneously in both the pulmonary and systemic circulations, the authors concluded that this was consistent with the presence of a potent vasoconstrictor in amniotic fluid. They found that neither filtration nor boiling of the injectate altered the hemodynamic changes. This provided further support for the belief of a humoral cause for this early phase as opposed to mechanical obstruction. Despite the attractiveness of the biphasic model, Clark[4] cautioned that the existence of an initial phase of transient pulmonary hypertension in humans was speculative. The lack of supportive clinical data in humans is likely due to the obvious delay in collecting hemodynamic parameters following the initial presentation (Table II).

Several mechanisms for myocardial dysfunction have been suggested. At the present time, the origin remains unclear. One possibility is ischemic injury to the myocardium in those presenting with acute respiratory distress and hypoxemia.[50] Alternatively, hypoxic injury could result from a leftward shift of the intraventricular septum secondary to acute right ventricular dilatation. The decline in cardiac output subsequent to impaired left ventricular filling could then result in decreased coronary artery perfusion.[50]

A more recent hypothesis is that amniotic fluid contains a direct myocardial depressant. This suggestion was initially based on the *in vitro* observation that amniotic fluid caused a decrease in myometrial contractility and, therefore, might have a similar effect on the myocardium.[4] Endothelin, a vasoconstrictive peptide synthesized in certain vascular endothelial cells, has been implicated as a possible causative factor. Following its discovery in 1988, increased plasma concentrations of endothelin have been noted in several acute clinical conditions such as myocardial infarction, cardiogenic shock, subarachnoid hemorrhage and air embolism.[57] Similarly, amniotic fluid has been found to contain high concentrations of endothelin as compared to maternal plasma concentration.[58] The occurrence of amniotic fluid embolus could result in a sudden increase in maternal plasma endothelin levels.

Experimental animal models and *in vitro* studies have shown that endothelin has a powerful constrictor effect in coronary and pulmonary arteries as well as in human bronchi.[58] In the canine model, infusions of

TABLE III Diagnosis of amniotic fluid embolus

- Diagnosis of Exclusion
- Differential Diagnosis
  - thrombotic embolus
  - air embolus
  - septic shock
  - acute myocardial infarction
  - peripartum cardiomyopathy
  - anaphylaxis
  - aspiration
  - placental abruption
  - transfusion reaction
  - local anesthetic toxicity

endothelin increased total peripheral vascular resistance and left atrial pressures while decreasing cardiac output.[57] Hankins *et al*.[56] found hemodynamic evidence that amniotic fluid contains a potent vasoconstrictor. Clark[6] noted initial transient systemic hypertension in five of the patients from the national registry in whom early blood pressure recordings were available. The only study which has attempted to determine if endothelin is the vasoconstrictor present in amniotic fluid is that by Maradny and colleagues.[58] Following the injection of human amniotic fluid into rabbits they were able to demonstrate an elevation of plasma endothelin concentrations. Unfortunately, the applicability of a heterologous amniotic fluid model to the human clinical situation is limited since one is not able to determine if the animals' response was to the amniotic fluid or to antigenically dissimilar material. To be meaningful this work needs to be repeated using autologous amniotic fluid.

Various authors have suggested that other humoral factors including proteolytic enzymes, histamine, serotonin, prostaglandins and leukotrienes may contribute to the hemodynamic changes and consumptive coagulopathy associated with amniotic fluid embolus.[4,7,59] All of these mediators have been implicated in other shock states which have similar clinical and hemodynamic derangements, most notably anaphylaxis and sepsis.[6] Clark[6] was the first to note the similarities between these clinical states and suggested that they may share pathophysiological mechanisms. In both anaphylaxis and sepsis, a foreign substance enters the circulation and causes the release of various primary and secondary mediators. These mediators, in turn, can cause profound myocardial depression, decreased cardiac output, pulmonary hypertension and DIC; changes essentially identical to those described with amniotic fluid emboli. Clark further suggested that the name amniotic fluid embolus be discarded and the entity be renamed as the "anaphylactoid syndrome of pregnancy". This model more accurately describes the variations in clinical presentation and outcome since the severity of the clinical symptoms depends, in part, on the individual host response to foreign antigen. In addition, the antigenic potential of amniotic fluid would vary in each case, depending on the cellular content. For example, women carrying a male fetus are more likely to be affected.[6] Similarly, fluid containing thick meconium may be more toxic than clear amniotic fluid.[6] Animal studies have suggested that this is true.[56] Human data have also shown that, although most patients dying from amniotic fluid emboli have had clear amniotic fluid, there is a shorter time from the initial presentation to cardiac arrest and an increased risk of neurological damage or death in the presence of meconium or a dead fetus.[6] Further indirect evidence for an immunological basis is the occurrence of fatal amniotic fluid emboli during first trimester abortions. This suggests that under the right circumstances, maternal exposure to even small amounts of amniotic fluid can initiate the syndrome.[6]

Benson *et al.*[60] have suggested that if amniotic fluid syndrome represents an anaphylactoid reaction to fetal antigens, maternal serum tryptase levels should be increased in suspected cases. Tryptase, a serine protease, is released in large quantities during mast cell degranulation. It is detectable within 30 min after an inciting event, peaks in one to two hours, has a half-life of two hours and is fairly stable in serum. Unlike histamine which has a half-life of two minutes, the authors suggest that tryptase is a more convenient marker for mast cell degranulation. Further research in this area is obviously desirable in order to support Clark's hypothesis.

Coagulopathy

The development of a consumptive coagulopathy is common with amniotic fluid emboli. This was first appreciated in 1950 when Warner and Reid[5] reported on the coagulation changes associated with this syndrome. In Morgan's 1979 review, 12% of patients presented with a bleeding diathesis while one subsequently developed in an additional 37%.[5] More recent reviews found an even higher incidence. Clark[6] reported that 83% of the cases in the national registry had either clinical or laboratory evidence of a consumptive coagulopathy. The remaining 17% died before the clotting status could be assessed by either clinical or laboratory techniques. Similarly, in 15 cases of fatal amniotic fluid emboli associated with induced abortion, two patients presented with a coagulopathy and an additional 75% of the initial survivors went on to develop disseminated intravascular coagulation (DIC).[61] It now appears that amniotic fluid embolus is almost always associated with some form of DIC, with or without clinically significant bleeding. Isolated DIC causing maternal hemorrhage may be the first indication of the problem in a small number of patients.[38,62] Although successful treatment of these cases has been reported, overall the mortality rate is high, similar to that seen with the more classical syndrome. Porter[63] reviewed the eight cases from the national registry that presented with an acute isolated coagulopathy and found that six women exsanguinated despite appropriate management.

The etiology of the coagulopathy remains somewhat obscure. Investigations which have attempted to clarify the mechanism have yielded inconclusive and some-

times contradictory results. Although amniotic fluid contains activated coagulation factors II, VII and X, their concentrations are well below those found in maternal serum at term.[64] On the other hand, amniotic fluid has been shown to have a direct factor X activating property and thromboplastin like effect. Both of these increase with gestational age. Lockwood *et al*.[64] suggested that tissue factor may be responsible for these effects and found substantial quantities of tissue factor in amniotic fluid. Potential sources include sloughed fetal skin and epithelial cells derived from the fetal respiratory, gastrointestinal, and genitourinary tract mucosa. Tissue factor activates the extrinsic pathway by binding with factor VII. This complex in turn triggers clotting by activating factor X. The authors further speculated that once clotting was triggered in the pulmonary vasculature, local thrombin generation could then cause vasoconstriction and microvascular thrombosis as well as secretion of vascular endothelin. As previously discussed, this vasoactive peptide can depress both myometrial and myocardial contractility and may primarily or secondarily contribute to the hemodynamic changes and uterine atony that have been observed in this syndrome.

TABLE IV Laboratory investigations

Non specific	*Specific*
complete blood count	cervical histology
coagulation parameters including FDP, fibrinogen	serum tryptase
arterial blood gases	serum sialyl Tn antigen
chest x-ray	zinc coproporphyrin
electrocardiogram	PMV analysis (if PA catheter *in situ*)
V/Q scan	
echocardiogram	

TABLE V Management

1. Symptomatic – (depends on severity)
2. Goals and Treatment
   a) *Maintenance of oxygenation*
      supplemental O_2
      intubation
      ventilation
      diuretics
   b) *Circulatory support*
      CPR protocol
      delivery of fetus
      volume
      inotropes
      afterload reduction
   c) *Correction of the coagulopathy*
      fresh frozen plasma
      packed RBC
      platelets
      cryoprecipitate
3. Possible additional measures
      high dose corticosteriods
      epinephrine
      cardiopulmonary bypass
      nitric oxide
      inhaled prostacyclin

Diagnosis

There is no routine diagnostic scheme to confirm the presence of an amniotic fluid embolus. Rather, it is a diagnosis of exclusion. Any condition that presents as acute cardiorespiratory collapse or massive hemorrhage in the peripartum period must be systematically evaluated. The differential diagnosis includes air or thrombotic pulmonary emboli, septic shock, acute myocardial infarction, cardiomyopathy, anaphylaxis, aspiration, placental abruption, eclampsia, uterine rupture, transfusion reaction and local anaesthetic toxicity[1,3] (Table III).

Depending on the clinical presentation, laboratory investigations which may be useful include complete blood count, coagulation parameters, arterial blood gases, serum tryptase, chest x-ray, VQ scan, ECG and echocardiogram. A thorough histological examination of the cervix for amniotic fluid debris in hysterectomy specimens or at autopsy may be helpful in confirming the diagnosis[65] (Table IV).

In those cases where central venous access has been obtained, blood from the pulmonary vasculature should be collected using the method described by Mason.[1] He suggested that in order to minimize the possibility of maternal or exogenous contamination, a more representative sample of the pulmonary microvasculature (PMV) can be obtained if blood is drawn from the distal lumen of a wedged pulmonary artery catheter. After discarding the first 10 ml of blood, an additional 10 ml is drawn, heparinized and analyzed utilizing Papanicolaou's method. This technique was used to compare samples from ten non pregnant control patients with two patients who developed peripartum ARDS thought to be secondary to an amniotic fluid embolus.[47] Both patients had several components of amniotic fluid in their blood including squamous cells and mucous strands while none of these elements were found in any of the control patients. Further experience with the technique has led Mason to conclude that, although PMV preparations may occasionally be contaminated by maternal squames, when squamous cells are found in large numbers in such a sample it is clinically significant and strongly supportive of the diagnosis of amniotic fluid embo-

lus.[47] This is particularly true if the squamous cells are coated with neutrophils or if they are accompanied by other fetal debris such as mucin or hair. Similarly, Lee *et al.*[46] suggested that a more reliable method of confirming the diagnosis might centre on the identification of other amniotic fluid elements in the maternal pulmonary vasculature as opposed to squamous cells.

More recently, two studies have attempted to develop simple, noninvasive, sensitive tests for diagnosing amniotic fluid emboli utilizing peripheral maternal blood. Kobayashi *et al.*[66] studied maternal serum sialyl Tn antigen levels in four women with clinical amniotic fluid emboli and compared them to both pregnant and non pregnant controls. Sialyl is a mucin-type glycoprotein that originates in fetal and adult intestinal and respiratory tracts. It is present in both meconium and in clear amniotic fluid. Using a sensitive antimucin antibody, TKH-2, the authors found no difference in the serum levels of pregnant patients throughout gestation or in the early postpartum period when compared to healthy non-pregnant controls. In contrast, the antigen levels in the amniotic fluid embolus group were elevated. Moreover, since serum sialyl concentrations were not altered in patients with other critical illnesses, the elevation observed is unlikely to result from local ischemia secondary to maternal cardiovascular collapse. The authors therefore concluded that the test was a promising simple, non-invasive method for diagnosing amniotic fluid emboli.

A second study from the same institution measured maternal plasma concentrations of zinc coproporphyrin, a characteristic meconium component, and found they were higher in patients with amniotic fluid emboli and those with amniotic fluid emboli-like symptoms than in either pregnant or non pregnant controls.[67] At present, clinical experience with both of these tests is limited. Further studies are needed in order to assess their utility and reliability.

Management

The management of amniotic fluid embolus is basically symptomatic and directed towards the maintenance of oxygenation, circulatory support and correction of the coagulopathy (Table V). Depending on the clinical presentation, full cardiopulmonary resuscitation (CPR) protocol may be indicated. If the fetus is sufficiently mature and is undelivered at the time of maternal cardiac arrest, Cesarean section should be instituted as soon as possible.[68] Regardless of the presentation, oxygen should be administered to all patients, in concentrations adequate to maintain normal oxygen saturation. PEEP or CPAP. can be added as required. In severe cases, the initial hypoxemia is often so profound that irreversible neurological injury may result despite appropriate resuscitative measures.

Treatment of hemodynamic instability includes optimization of pre-load with rapid volume infusion. During the early stages, direct acting vasopressors such as phenylephrine may be useful in restoring aortic perfusion pressure.[69] Once this is accomplished, other inotropes such as dopamine or dobutamaine can be added to improve myocardial function. When clinically feasible, pulmonary artery catheterization can be instituted to help guide therapy. In some cases, afterload reduction may be beneficial in restoring cardiac output, providing pre-load is adequately preserved. In others, diuretics are useful for mobilizing pulmonary edema fluid.

Treatment of the coagulopathy associated with amniotic fluid embolus involves the administration of blood component therapy. Since this is frequently associated with massive hemorrhage, replacement of blood loss with packed red blood cells is the first priority in order to maintain oxygen delivery to the tissues. O negative or group specific blood can be used if cross-matched blood is unavailable. Plasma and platelets are given to replace the clotting factors, antithrombin III and the platelets that are consumed in the clotting process. As circulatory volume is restored, the accompanying improvement in cardiac output will, in turn, enhance the liver's ability to aid in further restoration of normal hemostasis by clearing fibrin degradation products from the circulation.[71] There are no absolute transfusion thresholds or factor concentrations on which to base blood component replacement. Instead, ongoing therapy should be guided by the clinical condition of the patient and laboratory evidence of a coagulopathy.

Although cryoprecipitate is not a first line therapy for treating the coagulopathy, it may be useful in circumstances where fibrinogen is low and volume overload is a concern. It has also been reported to be useful in a patient with severe ARDS secondary to amniotic fluid embolus.[72] Following administration of cryoprecipitate, the patient's cardiopulmonary and hematological status improved dramatically, leading the authors to suggest that it may be useful in cases where conventional medical therapy appears to be unsuccessful in maintaining blood pressure, oxygenation and hemostasis. This recommendation was based on similar treatment protocols for severely ill patients with multiple trauma, burns and postoperative sepsis. In these clinical settings, it is believed that there is an impairment in the clearance of circulating microaggregates and immune complexes by the reticuloendothelial system leading to the development of cardiopulmonary insufficiency and DIC.

Cryoprecipitate is rich in opsonic alpha 2 surface-binding glycoprotein, also known as fibronectin, which aids the reticuloendothelial system in the filtration of antigenic and toxic particulate matter. Depleted levels of this glycoprotein have been reported in severely ill patients, with marked improvement in the clinical status following repletion of fibronectin levels.[72]

Isolated reports of other less common treatment modalities for amniotic fluid emboli have been reported. For example, in one patient a serine proteinase inhibitor, FOY, was utilized in the treatment of an associated DIC.[73] In another, cardiopulmonary bypass and pulmonary thromboembolectomy were successful in treating a moribund patient who had sustained a sudden postpartum cardiopulmonary arrest secondary to amniotic fluid embolus.[35] Others have reported the use of nitric oxide[74] or inhaled aerosolized prostacyclin[75] to treat refractory hypoxemia. Clark has suggested that, in light of the similarities to anaphylaxis, high dose corticosteroids and epinephrine may be useful therapeutic adjuvants.[6]

Summary

Amniotic fluid embolus continues to be one of the most feared and devastating complications of pregnancy. It can be neither predicted nor prevented. Its presentation is variable and, similar to other embolic phenomena, it is believed to encompass the spectrum of disease from a subclinical entity to one that is rapidly fatal. Medical management is essentially supportive and depends on the predominant physiological aberration. Although there has been some promising research conducted since Morgan's review, there are many unanswered questions. If we are to further our knowledge of this tragic complication, we need to develop standardized diagnostic protocols and apply them to all cases of suspected amniotic fluid embolus. In addition, we must develop national and international registries and encourage collaboration between research centers. Without a specific method to confirm the diagnosis and registries to collect the data, our understanding of the natural history, etiology and treatment will continue to be hampered.

Acknowledgment

The author wishes to thank Drs. Judith Littleford and Susan Palmer for their suggestions regarding the revision of this manuscript, Ms. Nicole Brockhurst for her assistance with the literature search and Ms. Josephine Sham for her secretarial support.

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