Amniotic fluid embolism: the known and not known

Michael D Benson

Abstract

Amniotic fluid embolism was first recognized in 1926, in a Brazilian journal case report, on the basis of large amounts of fetal material in the maternal pulmonary vasculature at autopsy. The first English language description appeared in 1941 and consisted of eight parturients dying suddenly in which, once again, fetal material was seen in the pulmonary vasculature. A control group of 34 pregnant women dying of other recognized causes did not have fetal material in their lungs. The incidence of recognized, serious illness is on the order of two to eight per 100,000, with a mortality rate ranging from 13% to 35%. The diagnosis rests largely on one or more of four clinical signs: circulatory collapse, respiratory distress, coagulopathy, and seizures/ coma. The only confirmatory laboratory test remains autopsy findings although serum tests for fetal antigen, insulin-like growth factor binding protein-1, and complement are currently being investigated. One of the paradoxes of diagnosis is that fetal material in the pulmonary circulation at autopsy is specific for amniotic fluid embolism, while the same finding in the living is not. The mechanism of disease remains uncertain although the best available evidence suggests that complement activation might have a role. In contrast, mast cell degranulation probably is not a mechanism, so amniotic fluid embolism is not an anaphylaxis or anaphylactoid reaction as has been occasionally suggested. Perhaps the greatest unknown is not why 1 in 50,000 pregnant women develop what appears to be an immune response to their fetus, but rather why the other 49,999 do not?

Keywords

High-risk pregnancy, immunology, maternal-fetal medicine, maternal, mortality, perinatal medicine

Introduction

It has been more than eight decades since amniotic fluid embolism (AFE) was presumably first described in a case report written in Portuguese for a Brazilian medical journal by JR Meyer.¹ He described a woman with an intrauterine fetal demise for several weeks that ultimately experienced spontaneous labour. Febrile and septic (by current understanding), the patient progressed, but she suddenly became cyanotic, dyspneic, and then suffered a cardiorespiratory arrest in the space of a few minutes. Autopsy revealed the presence of numerous fetal squames in the maternal pulmonary vasculature.

Steiner and Luschbaugh,² two pathologists at the University of Chicago, provided the next description of AFE in two back-to-back papers in the same issue of the *Journal of the American Medical Association* in 1941. They described the autopsies of eight parturients who had sudden, unexpected deaths during labour, all of whom had large quantities of fetal squames in the maternal pulmonary vasculature at autopsy. In their series, it is noteworthy that two women were febrile and two were in labour with fetuses who had died beforehand—features similar to the JR Meyer case. What is less reported in the literature is that the pathologists had a control group of 34 parturients dying of other, recognized causes. None had fetal squames in their pulmonary vasculature.

In the subsequent decades, relatively little progress has been made in either understanding the mechanism of disease or developing specific treatments. Initially assigned a 90% mortality rate, it has become clear that the mortality rate is less, both due to an early predilection to diagnose only the most severe cases and general advances in support of acutely ill patients. This review will take a new look at diagnosis, incidence, risk factors, mortality rate, and disease mechanism.

Clinical diagnosis

In 1974, Courtney published one of the first clinical diagnostic criteria for AFE.³ He described “five cardinal signs”: respiratory distress, cyanosis, cardiovascular collapse, haemorrhage, and coma. He noted

that respiratory signs might be absent, even in fatal cases, but was less clear on whether a single cardinal sign or all were required for the diagnosis.

Since 1974, the clinical diagnostic criteria have coalesced into one or more of four categories, largely along the lines proposed by Courtney: (1) cardiovascular collapse, (2) respiratory distress, (3) seizures or coma, and (4) coagulopathy or disseminated intravascular coagulation (DIC).⁴ There is substantial consensus on this clinical definition as exhibited by agreement among American, British, and Japanese definitions.^{4–7} However, the British require maternal collapse and add acute fetal compromise and premonitory symptoms while the Japanese do not reference seizures. The presence of any one of these signs/symptoms is sufficient for the diagnosis in the absence of other explanations. An important nuance of the diagnosis is that the definition does not preclude other co-morbidities—just that these other illness not be responsible for the primary signs/symptoms of AFE.^{8,9} Also, uterine atony has been closely associated with AFE. However, it is not generally considered a diagnostic criteria and its relationship as a cause or a result of AFE is unknown.

One diagnostic criterion, coagulopathy, deserves special emphasis. At present, the best available evidence suggests that parturients with obstetric DIC/coagulopathy always merit a diagnosis of AFE with the possible exception of coagulopathies associated with hypertensive diseases of pregnancy. First, most clinical definitions of the disease permit the diagnosis of AFE on the basis of the single sign of a coagulopathy.^{4,6,7} It should be noted though that the British definition requires cardiovascular collapse in addition to DIC to merit a diagnosis of AFE and permit the diagnosis on the basis of haemorrhage as long as there was evidence of a coagulopathy (once again in the presence of

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cardiovascular collapse).⁵ Second, there are a number of case reports that make the diagnosis of AFE solely based on the presence of DIC.^{10–14} Finally, no one has suggested any distinguishing sign/symptoms, laboratory tests or pathophysiology to differentiate among DIC patients with abruptio, AFE, or retained fetal/placental material.

Laboratory diagnosis—autopsy

Currently the only widely accepted laboratory confirmation of AFE is the finding of fetal material in the maternal pulmonary vasculature at time of autopsy. This needs to be distinguished from finding fetal material in the maternal circulation of the living, which is not considered specific for AFE. Finally, work is being done on serum markers for AFE but, thus far, there is no well-established test that has a consensus about sensitivity and specificity suitable for clinical use.

The first evidence for the specificity of autopsy findings comes from Steiner and Lushbaugh.² They found fetal squames in eight out of eight AFE patients and none in 34 women in the third trimester dying from other causes. It should be noted that they did find fetal mucin in one pulmonary capillary in the control group and that seven women in the control group died of post-partum haemorrhage. This is noteworthy because the authors did not separately identify coagulopathy and because haemorrhage itself (without DIC) would qualify for AFE under the British definition.⁵ Thus, the finding of fetal squames seems fairly specific for AFE at autopsy but may not be highly sensitive.

In 1998, Japanese investigators used an immunohistochemical stain for a fetal antigen, STN, to make a diagnosis of AFE at autopsy.¹⁵ All four AFE patients had positive staining of the pulmonary vasculature while the control group of four women who died from non-AFE causes did not. A second study of 29 maternal deaths found fetal material in 100% of the seven AFE patients and none in those 22 parturients dying of non-AFE causes.¹⁶ It should be noted that the study findings were nuanced since the authors began with the assumption that any fetal material in the maternal vasculature was diagnostic of AFE. They also used a variety of stains in addition to routine Hematoxylin and Eosin, used three pathologists to examine the histology from each case, and took an average of seven lung sections. With that said, they did not find fetal material in any cases that were obviously not AFE such as traumatic injury. They observed, however, that the fetal material was not uniformly distributed through the lung vasculature in the AFE cases. Other studies similarly found fetal material in the pulmonary vasculature in AFE patients at autopsy while not finding it in pregnant women dying of other causes.^{17,18}

Laboratory diagnosis—living patients

Unlike with autopsy, the presence of fetal material in the maternal circulation while the mother is still alive does not establish the diagnosis. This lack of specificity comes from two types of evidence—studies looking for fetal squames in the maternal pulmonary circulation and those looking for fetal material elsewhere in the circulation.

In the 1980s, at least two studies were done in which pulmonary artery samples were taken from critically ill pregnant patients, looking for fetal material.^{19,20} Any number of these aspirates had fetal material, ranging from squames to mucin to lanugo in women who did not have AFE.

There are also studies in which fetal material has been found elsewhere in the maternal circulation in women who did not have AFE. Perhaps the earliest report is a case in the early 1960s in which fetal material was found in the maternal circulation of the uterus at the time of peripartum hysterectomy in a woman who did not have AFE.²¹ More recently, a study of 57 archived peripartum hysterectomy specimens demonstrated fetal material in 20% to 33% of the population, in each of the seven diagnostic categories.²² There was no difference between the rate of intravascular material for the DIC group and all others.

In any event, it is clear that finding intravascular fetal material among the living is not specific or diagnostic for AFE. Similarly, no diagnostic criteria for the disease require its presence. Why there should be a difference in specificity between the living and those who succumb is unclear. The obvious explanation that the disease is presumably more severe in those who die still does not explain why fetal material can be found in the lungs of those who do not have the disease.

Beyond histology studies, there are at least three laboratory tests that have been described specifically for the diagnosis of AFE. The first such test utilizes an antibody against a fetal antigen common in meconium, Sialyl Tn.^{15,23} This assay has been used in both serology and histology (autopsy) studies of AFE patients. Higher levels have been associated with higher mortality.⁶ This antibody assay is not commercially available.

Another test that has been used for the diagnosis of AFE is serum complement. Investigators found markedly decreased complement levels in eight out of eight AFE patients.²⁴ Levels in controls remained in the normal range although they did drop slightly over the course of labour. It is worth emphasizing that the complement research was intended to elucidate the mechanism of disease rather than develop a diagnostic test. The sensitivity and specificity of complement for the diagnosis of AFE remains uncertain.

The third laboratory test for the diagnosis of AFE was studied by a French group from the outset as a diagnostic test with sensitivity and specificity as a key outcome measure.²⁵ The investigators used the British AFE definition but added as a criteria for diagnosis the presence of fetal squames on bronchoalveolar lavage. Insulin-like growth factor binding protein-1 is found in high concentrations in amniotic fluid and was tested to see if it could discriminate among women with AFE and those without. In all, 25 AFE patients were assessed along with a post-partum haemorrhage group of 24 patients, healthy labour group of 50 patients, and pulmonary embolism group of 20 patients. The AFE group had a mean level of 234 micromoles/liter while the non-AFE groups had a mean of 56 micromoles/liter, and the ranges did not overlap between the two groups. The test is commercially available, though not on a rapid basis.

Incidence

The estimated incidence of the disease has varied considerably, ranging from a high of one per 600 to a low of two per 100,000 (Britain).^{5,26} Population-based studies have generally fallen in between. Two American studies found an incidence of 5.0 and 7.7 per 100,000.^{27,28} A Canadian study found a rate in between of 6.0/100,000 while an Australian study had the lowest incidence—3.3 per 100,000.^{29,30}

The British study had the best methodology as all hospitals in Britain were actively surveyed monthly for AFE cases, and the cases that were reported had additional vetting.⁵ Beyond a difference in methodology, the authors note that there might be some differences in national obstetrical practices that can impact the risk of AFE such as induction and Caesarean rates and thereby the reported incidence.

Risk factors

In considering risk factors, the distinction between non-causal associations and causation is frequently (and unfortunately) blurred in the medical literature on AFE. For the life-threatening manifestations of AFE that occur between 1 in 20–50,000 pregnancies, determining risk factors among an array of related variables is a daunting (impossible?) task. Due to their well-known propensity for ascertainment bias, very little can be learned regarding risk from case series. Population-based studies are an improvement but some of the methodology and interpretation problems can be seen in the previously cited, two separate studies of 3,000,000 women apiece in North America.

The first study, of 3,000,000 Canadian deliveries found an association between medical induction of labour and AFE (odds ratio of 1.8).²⁹ The authors suggested that women contemplating elective induction should be informed of this risk (an absolute risk of 1 in 10,000). Remarkably, a very similar study of 3,000,000 US deliveries using the same methodology (and even sharing one author) found no statistically significant association between labour induction and AFE although some of the other associations (Caesarean delivery) remained robust.²⁸ The most important point of these studies is that even an analysis of several million deliveries at a time might not produce consistent associations, let alone permit cause and effect deductions. The disease is rare, there are numerous confounding variables, and although there may be a consensus about diagnostic criteria in the medical literature, it is easy to surmise that this knowledge is not uniform among practicing obstetricians.

With these caveats in mind, British investigators have probably the best data and analytic methods with which to measure clinical associations with AFE.^{5,31} They used a customized database, specifically assessed potential AFE cases, and used control patients from women delivering in the same hospital immediately before the index case. They found an association with labour induction (adjusted odds ratio 3.86), older, ethnic minority women (adjusted OR 9.85), and multiple pregnancy (adjusted OR 10.9). Caesarean section was associated with postnatal AFE (adjusted OR 8.84). A regression model was developed in an effort to sort out confounding variables. Although a much more rigorous treatment of clinical associations of AFE in a large population than other studies, cause and effect relationships should still be treated with caution. In particular, it is unclear why age should be associated with AFE—but only for ethnic minorities and not Caucasians. (The strength of this relationship was almost three times stronger than with induction of labour.)

Mortality rate

Until the past 15 years or so, the mortality rate was consistently reported as well over 50%.³ However, all of these reports comprised individual cases or case series in which doctors collected cases and then reported characteristics of the population. As noted before, case series typically have problems with ascertainment bias. Specifically, the reported cases in no way reflect a random sample of the disease population. As is obvious, case series tend to collect the sickest patients with the worse outcomes—conditions necessary to make the patients worth the effort of reporting in the first place.

In more recent times, with the development of computerized databases by insurance companies and governments, population-based studies have been used to examine the mortality rate of AFE. In the last 15 years, at least five such studies looking at both incidence and mortality rates (two American, one Canadian, British, and Australian each) have been reported, comprising millions of deliveries.^{5,27–30} In all five studies, the mortality rate of AFE has ranged from 13% to 35%. (Four out of five studies reported a mortality rate of 26% percent or under. Only the Australian study reported the rate of 35%.) Although these studies still reflect some bias toward reporting only the sickest patients, they are a big improvement over case series. Thus, AFE is not necessarily a death sentence and the majority of patients will survive.

Certainly some will die, even with proper medical care. There is no specific treatment unique to AFE. Rather treatment is based on generally applied approaches to cardiovascular collapse, respiratory arrest, coagulopathy, and whatever else the manifestations of the individual's disease process.

Mechanism

The pathophysiology of AFE remains unknown. There is a growing recognition that the disease may not be “embolic” in the traditional

sense. That is, the clinical manifestations might not be entirely or even primarily the result of a physical obstruction of pulmonary vessels by fetal material but rather a maternal immunologic response to fetal antigen.

The inconsistencies with AFE as an embolic event have been previously described.³² In brief, acute respiratory distress syndrome, a common sequelae of AFE, is not typically seen with pulmonary embolism, and there are no characteristic findings on radiologic studies. Animal models using amniotic fluid emboli have not consistently reproduced the disease. The coagulopathy and neurological aspects of AFE cannot be explained by a physical circulatory obstruction, and complement activation is not seen in pulmonary embolism.

The possibility that AFE could be an anaphylactic reaction to fetal antigen, and that this hypothesis was testable, was suggested in a brief paper in 1996.³³ Subsequently blood assays for serum tryptase and/or urinary histamine were negative in a series of seven patients with AFE.²⁴ This provided strong evidence that the primary mechanism underlying the disease was not anaphylaxis.

Since this study, other investigators have found elevated serum tryptase levels in fatal cases of AFE. Of the five cases reported thus far in the literature, one patient had normal tryptase levels, another three had slightly elevated levels, and one had substantially elevated levels.^{34–38} Again, these results, taken together, suggest that mast cell degranulation probably does not have a primary role to play in the mechanism of AFE.

The evidence is a bit more confusing when it comes to histology-based searches for the disease mechanism in autopsy findings. Two studies did find evidence of either increased mast cell counts or extracellular tryptase in AFE patients compared with pregnant women with traumatic death.^{18,36} These results are hard to reconcile with the unimpressive serum findings of tryptase since presumably elevated circulating levels of histamine would be created for systemic effects beyond the lungs.

At this point a bit of terminology discussion is in order. The term “anapylactoid syndrome of pregnancy” was proposed as an alternative name to AFE.^{39,40} Although the name never really caught on, an occasional author still makes reference to it. The term “anapylactoid” as distinct from “anaphylaxis” refers to a non-antibody-mediated degranulation of mast cells, releasing histamine (and tryptase). Clinically indistinguishable from anaphylaxis, both processes involve the release of large amounts of histamines—just from different underlying mechanisms. “Anapylactoid syndrome of pregnancy” is thus a misnomer for two reasons. First, the best working hypothesis for AFE remains a maternal immune response to fetal antigen leaking into the circulation (i.e. one involving antibody). Thus, a non-antibody response implied by the term anapylactoid is not appropriate. Second, since the case series failed to find any evidence for mast cell degranulation (whether immune or non-immune mediated), it is premature to assign the disease a name implying this specific mechanism.

Finally, the same series of AFE patients that found no evidence for mast cell degranulation/anaphylaxis found that eight out of eight patients had very depressed serum complement levels, suggesting complement activation as a possible mechanism for AFE.²⁴ Of note was the fact that a control group of healthy labouring women also experienced a slight, but statistically significant, decrease in complement levels. The significance of this remains unknown.

However, C3 levels were low normal, while only C4 levels were depressed in another series of AFE patients from Japan.⁶ The Italian group who previously found histology evidence for mast cell degranulation looked for evidence of complement activation in their next paper.³⁶ Depressed amounts of C3a consistent with complement activation was found in the pulmonary circulation of eight AFE patients compared with six pregnant women dying of trauma. One of the complexities in considering either mast cell degranulation or complement activation as a possible mechanism of AFE is the fact that these immune pathways are interrelated.⁴¹

AFE—the known

1. The clinical diagnosis generally rests on one or more of the following clinical signs/symptoms: (1) cardiovascular collapse, (2) respiratory distress, (3) coagulopathy, and (4) seizures/coma.
2. The most widely accepted laboratory diagnosis of AFE is the finding of fetal material in the maternal pulmonary circulation at autopsy. A promising test is serum insulin-like growth factor 1, which in early investigations seems specific and sensitive. Finding fetal material in the circulation of the living is not diagnostic, and the absence of such material at autopsy is not proof of absence of disease.
3. The incidence of life-threatening AFE is on the order of one in 20,000 to 50,000. More mild forms of the disease might be more common—and probably are—but there is no consensus on how to identify these more mild cases.
4. The reported mortality rate has dropped over the years to between 16% and 35%, depending on the study—due in part to better, population-based studies and reporting as well as improvements in critical care medicine.
5. The primary mechanism of the disease is probably not anaphylaxis.
6. There is no basis for using the term “anaphlactoid,” specifically denoting a non-immune-mediated mast cell degranulation.

AFE—the unknown

1. There is some serologic and histologic evidence that the disease might be complement-mediated, but the data is too preliminary to be conclusive.
2. Why fetal material in the maternal pulmonary circulation should be specific for AFE in death but not in life remains unexplained.

Perhaps the greatest question of all about AFE, should it prove to be a maternal immune response to the fetus, is not “Why is it so rare?” Rather, the better question is, “Why is it not much more common?”

Conflict of interest

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