Amniotic fluid embolism: a leading cause of maternal death yet still a medical conundrum

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ABSTRACT

Amniotic fluid embolism (AFE) is a rare and potentially catastrophic condition that is unique to pregnancy. The presentation may range from relatively subtle clinical events to sudden maternal cardiac arrest. Despite an increased awareness of the condition, it remains a leading cause of maternal mortality. The underlying mechanisms of amniotic fluid embolism are poorly understood, but current theories support an immune-based mechanism which is triggered by potentially small amounts of amniotic fluid gaining access to the maternal circulation. This can result in a wide spectrum of clinical findings, with cardiovascular and haematological disturbances being prominent. The management of a suspected episode of amniotic fluid embolism is generally considered to be supportive, although in centres with specific expertise, echocardiography may assist in guiding management. Whilst outcomes after an episode of amniotic fluid embolism are still concerning, mortality would appear to have decreased in recent times, likely secondary to an improved awareness of the condition, advances in acute care and the inclusion of less severe episodes in case registries.

Keywords: Amniotic fluid embolism; Maternal mortality; Maternal morbidity; Pregnancy; Cardiac arrest; Disseminated intravascular coagulation

Introduction

Amniotic fluid embolism (AFE) is a rare, unpredictable and potentially catastrophic condition that is unique to pregnancy. The clinical syndrome of AFE was first described by Meyer in 1926, then again by Steiner and Luschbough in 1941. It has since been shown to encompass a wide spectrum of presentations, from subtle clinical events to sudden and fatal maternal cardiac arrest. It is characterised by the acute onset of combined cardio-respiratory compromise and coagulation disorders, occurring in the pregnant or recently pregnant state. Currently, AFE is a leading cause of maternal mortality in many developed countries and hence considerable effort is being made to advance the understanding of the condition, in the hope of improving the treatment and outcomes as has been seen with the other causes of maternal mortality. Despite this effort, there is still a relatively incomplete understanding of many aspects of AFE. Because of the infrequency of the condition and the lack of a reliable animal model, much of the information about AFE is derived from case reports, case series and registries. Consequently, there are significant variations in the reported incidence, risk factors and outcomes, which are also contributed to by different diagnostic criteria and potential false-positive cases.

This review aims to examine the current understanding of the underlying pathophysiology of AFE and to focus on recent advances in knowledge related to the diagnosis, management and outcomes.

Incidence

The published incidence of AFE varies widely, likely because of a number of factors such as the methodology used for case ascertainment (e.g. voluntary registries versus population-linked data), non-specific diagnostic criteria, uncertainty as to how the condition has been diagnosed, and differences in reporting as a result of varying levels of awareness (Table 1). Recent data suggest that the incidence ranges from 1:12 953 deliveries in the USA to 1:52 600 deliveries in the UK, with
Amniotic fluid embolism

Pathogenesis

Whilst the underlying mechanisms of AFE are poorly understood, it is relatively well accepted that the aetiology relates to the transfer of amniotic fluid into the maternal circulation, whereby an idiiosyncratic reaction is triggered. For amniotic fluid to gain access to the maternal circulation, whereby an idiosyncratic reaction is triggered. For amniotic fluid to gain access to the maternal circulation without any clinical consequences and in attempts to develop animal models of AFE, the injection of amniotic fluid has not reliably triggered a reaction. Amniotic fluid contains many vasoactive and procoagulant substances, such as platelet-activating factor, cytokines, bradykinin, thromboxane, leukotrienes and arachidonic acid, so it may require only small amounts of such substances to enter the maternal circulation to produce the events of an AFE. In addition, AFE reactions have been shown to be more common in women carrying a male fetus and in cases of rhesus iso-immunisation. Clark suggests that differences in the nature or severity of the presentation of AFE may be a result of variations in antigen exposure and individual response. Because of the similarities of some cases of AFE to anaphylaxis, Clark suggested that a more appropriate name for the condition is “anaphylactoid syndrome of pregnancy”.

Risk factors

A large number of risk factors for AFE have been identified. These include maternal age over 35 years, multiple pregnancy, caesarean birth, assisted delivery, placenta praevia, placental abruption, eclampsia, fetal distress, polyhydramnios, uterine rupture and ethnic minority. Labour induction has received recent particular attention as a possible risk factor. Data from the UK Obstetric Surveillance System (UKOSS) suggested that induction of labour greatly increased the risk of AFE (OR 3.86, 95% CI 2.04–7.31). This finding supported a Canadian study that also showed an increased risk (OR 1.8, 95% CI 1.3–2.7). However, a large USA population study of 3 million births and 227 cases of AFE did not find a significant association (adjusted OR 1.5, 95% CI 0.2–2.3). The plethora of associations means that identification of risk factors for AFE has an exceptionally low positive predictive value and is of no benefit in the acute setting. Further, as many risk factors are not potentially modifiable, identification may not prove useful in reducing the incidence of AFE.

Pathophysiology and clinical manifestations

Amniotic fluid embolism can present with a wide range of symptoms and signs, from cardiac arrest through to decreased cardiac output with consequent maternal collapse – hence the term “embolism”. However, this theory fails to support all of the clinical manifestations of AFE and whilst a physical obstruction to pulmonary blood flow may be a component of a reaction, especially with meconium-stained amniotic fluid, it does not appear to be the primary mechanism.

The second theory is that the reaction is immune-mediated, this being supported by a number of factors. Amniotic fluid has been shown to be present in the maternal circulation without any clinical consequences and in attempts to develop animal models of AFE, the injection of amniotic fluid has not reliably triggered a reaction. Amniotic fluid contains many vasoactive and procoagulant substances, such as platelet-activating factor, cytokines, bradykinin, thromboxane, leukotrienes and arachidonic acid, so it may require only small amounts of such substances to enter the maternal circulation to produce the events of an AFE. In addition, AFE reactions have been shown to be more common in women carrying a male fetus and in cases of rhesus iso-immunisation.

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### Table 1 Incidence of amniotic fluid embolism and case fatality rates in published series

<table>
<thead>
<tr>
<th>Year published</th>
<th>Incidence (per 100 000 maternities)</th>
<th>Case fatality rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knight</td>
<td>2012</td>
<td>1.9-6.1</td>
</tr>
<tr>
<td>Kramer</td>
<td>2012</td>
<td>2.5</td>
</tr>
<tr>
<td>Knight</td>
<td>2010</td>
<td>2.0</td>
</tr>
<tr>
<td>Ot</td>
<td>2010</td>
<td>Not reported</td>
</tr>
<tr>
<td>Roberts</td>
<td>2010</td>
<td>3.3</td>
</tr>
<tr>
<td>Abenhaim</td>
<td>2008</td>
<td>7.7</td>
</tr>
<tr>
<td>Samuelsson</td>
<td>2007</td>
<td>1.9</td>
</tr>
<tr>
<td>Kramer</td>
<td>2006</td>
<td>6.1</td>
</tr>
<tr>
<td>Tuffnell</td>
<td>2005</td>
<td>Not reported</td>
</tr>
<tr>
<td>Yang</td>
<td>2000</td>
<td>Not reported</td>
</tr>
<tr>
<td>Gilbert</td>
<td>1999</td>
<td>4.8</td>
</tr>
<tr>
<td>Clark</td>
<td>1996</td>
<td>Not reported</td>
</tr>
<tr>
<td>Burrows</td>
<td>1995</td>
<td>3.4</td>
</tr>
<tr>
<td>Hogberg</td>
<td>1985</td>
<td>Not reported</td>
</tr>
<tr>
<td>Morgan</td>
<td>1979</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Australia reporting a figure within this range of 1:16 393. Knight et al. noted the variation in the incidence of AFE between countries based on the methodology used for case ascertainment. The lowest rates of AFE were obtained with prospective case identification, suggesting there may be a significant number of false-positive cases reported. They recommended that future comparisons of incidence data between countries be based on use of similar methodology and case definitions.
relatively minor or possibly sub-clinical events. In Clark’s initial analysis of clinical features, hypotension and fetal distress were universal findings, with cardiac arrest, pulmonary oedema and coagulation disturbances also common (Table 2). With improving awareness and recognition of the condition, it is evident that the presenting features may not be dramatic, with Knight et al. reporting that the most common manifestations are premonitory symptoms (30%), shortness of breath (20%) and acute fetal compromise (20%). However, as the condition progresses or when it is more severe, other features typical of AFE may be apparent, particularly maternal haemorrhage, hypotension, marked dyspnoea, severe coagulopathy and acute fetal compromise.

AFE can occur at any time during pregnancy or in the immediate postpartum period, with reports of cases also at the time of amniocentesis, at induction of labour for miscarriage and termination of pregnancy. Knight et al. noted that in their UK study population of 60 cases, AFE generally occurred between two hours before delivery and four hours after delivery. In 56% of cases AFE presented at or before delivery and when it occurred after delivery, 73% of cases were at caesarean delivery, making this a significant risk factor (adjusted OR 8.84, 95% CI 3.70–21.1).

Cardiovascular changes associated with AFE may be complex and the detail is open to debate. The increasing availability of echocardiography, which allows earlier and more rapid assessment of underlying cardiovascular changes than pulmonary artery catheterisation, has generated new insights into circulatory abnormalities. Currently, it is thought that there is likely to be a biphasic response. In the initial phase of an AFE reaction there may be severe pulmonary hypertension associated with acute right ventricular failure, which can lead to severe impairment of left ventricular filling due to deviation of the inter-ventricular septum into the left atrium and ventricle. These findings are likely to explain the sudden cardiovascular collapse seen in some AFE reactions. If the patient survives this initial insult, the second phase is thought to involve continuing left ventricular failure, without severe pulmonary hypertension. Clark et al. found only mildly increased pulmonary artery pressures and increased central venous and pulmonary capillary wedge pressures. The mechanism of the on-going left ventricular failure is unclear, but has been postulated to be a result of myocardial ischaemia or the presence of substances that depress myocardial function.

A number of vasoactive mediators are present in amniotic fluid and may explain the potential for pulmonary hypertension. Hankins et al. were able to demonstrate that the injection of homologous amniotic fluid into the maternal circulation of goats caused marked increases in both the pulmonary and systemic vascular resistances. This response was more intense in the presence of meconium. This may explain why in Clark et al.’s initial case series, worse maternal outcomes were seen in women with meconium-stained amniotic fluid. Endothelin has also been implicated in the pathophysiology, because amniotic fluid contains high concentrations, which may be sufficient to generate the vasoconstriction seen during AFE. Other humoral factors such as proteolytic enzymes, histamine, serotonin, prostaglandins and leukotrienes may also have a role.

Coagulation disorders in AFE occur in the majority of cases, occurring in over 80% of cases and are sometimes the presenting feature. The coagulopathy seen with AFE is postulated to occur as a result of both procoagulant and anticoagulant factors and is likely to be multifactorial. Amniotic fluid contains a number of factors that influence coagulation, including activated clotting factors II, VII and X and tissue factor. It is not clear whether the coagulopathy is due primarily to a consumptive process or massive fibrinolysis. The procoagulant thromboplastin is found in amniotic fluid and might contribute to a consumptive coagulopathy. Significant early-onset hyperfibrinolysis has recently been demonstrated in a case of AFE and may be secondary to increased levels of urokinase-like plasmin activator, thrombin-antithrombin complexes and plasminogen activator inhibitor-1 found in amniotic fluid. Respiratory symptoms are a feature of AFE and can range from mild dyspnoea to respiratory arrest. Intra-pulmonary shunting is seen acutely in many women, leading to low arterial oxygenation despite oxygen therapy. In severe reactions pulmonary oedema may be a consequence of left ventricular failure or potentially from capillary damage.

### Diagnosis

Historically, the diagnosis of AFE was usually made at autopsy when fetal squames were found within the

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Signs and symptoms of amniotic fluid embolism</th>
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</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>100%</td>
</tr>
<tr>
<td>Fetal distress</td>
<td>100%</td>
</tr>
<tr>
<td>Pulmonary oedema or ARDS</td>
<td>93%</td>
</tr>
<tr>
<td>Cardiopulmonary arrest</td>
<td>87%</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>83%</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>83%</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>49%</td>
</tr>
<tr>
<td>Seizure</td>
<td>48%</td>
</tr>
<tr>
<td>Uterine atony</td>
<td>23%</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>15%</td>
</tr>
<tr>
<td>Transient hypertension</td>
<td>11%</td>
</tr>
<tr>
<td>Cough</td>
<td>7%</td>
</tr>
<tr>
<td>Headache</td>
<td>7%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>2%</td>
</tr>
</tbody>
</table>

Adapted from Clark SL; ARDS: adult respiratory distress syndrome.
In the absence of any other clear cause the diagnosis of AFE is made by:

Either

Acute maternal collapse with one or more of the following features:
- Acute fetal compromise
- Cardiac arrest
- Cardiac rhythm problems
- Coagulopathy
- Hypotension
- Maternal haemorrhage
- Premonitory symptoms, e.g., restlessness, numbness, agitation, tingling
- Seizure
- Shortness of breath

Excluding women with maternal haemorrhage as the first presenting feature in whom there was no evidence of early coagulopathy or cardio-respiratory compromise

Or

Women in whom the diagnosis was made at post-mortem examination with the finding of fetal squames or hair in the lungs

Fig. 1  Diagnostic criteria for amniotic fluid embolism.
Similarly, the use of selective pulmonary embolisation for the management of haemorrhage, whilst a potential indicator of severity, is associated with reasonable survival rates of between 30–39%. A Japanese study identified a number of potential risk factors for mortality, including term gestation, multiparity, vaginal delivery, cardiac arrest, dyspnoea, loss of consciousness and higher maternal STN levels.

Despite this encouraging news in regards to fatality risk, AFE remains a significant contributor to maternal mortality in developed countries and is currently the leading cause of direct maternal death in both Australia and New Zealand and consistently in the top five causes of direct maternal death in the USA and UK. The decreased case fatality rate associated with AFE in recent times is not fully explained but is likely to be secondary to a combination of factors. Awareness of the condition has increased significantly amongst obstetric care providers so it is likely that women experiencing less severe episodes of AFE that may not have been diagnosed previously are now being included in registries. In addition, advances in resuscitation and intensive care may mean that women who previously may not have survived the event now have an improved chance of survival. Of particular relevance to the obstetric anaesthetist, multidisciplinary obstetric resuscitation simulation training has been associated with improved management of uncommon obstetric emergencies. This is likely to have contributed to reductions in maternal morbidity and mortality, although evidence of clinical benefit is difficult to ascertain.

The morbidity associated with AFE in those women who survive may be considerable although advances in care appear to have improved outcomes. In Clark’s initial registry data, 61% of women had a persisting neurological impairment. However, recent data from the UK document an incidence of cerebral injury in only 6% and in Australia the incidence of cerebral infarction was 20%. An indicator of significant morbidity is the extent of supportive therapy required and in the UK, tress syndrome (ARDS) picture and hence lung protection strategies may be beneficial. Similar to the degree of circulatory support required can vary widely. The management of hypotension often involves the optimisation of preload with fluid administration, and vasopressor and inotropic drugs. As the underlying pathophysiology may vary from case to case, advanced haemodynamic monitoring may employ here to further guide fluid and inotropic therapy. Both respiratory and haemodynamic compromise are likely to be worsened in the presence of a gravid uterus. Patients who are difficult to ventilate or who are receiving maximal haemodynamic support in the intensive care unit may benefit from urgent delivery.

Coagulation abnormalities and maternal haemorrhage should be anticipated from the outset. Blood and blood product transfusion with fresh frozen plasma, cryoprecipitate and platelets is often required. The increasing use of point-of-care coagulation testing with thromboelastometry or thromboelastography may aid the precise targeting of coagulation disturbances. Recombinant factor VIIa has been used in a number of cases of AFE, but poorer maternal outcome due to massive intravascular thrombosis has been reported so this is not recommended as a routine. Hyperfibrinolysis may be a significant contributor to the coagulopathy but it is difficult to detect with traditional coagulation testing. Both tranexamic acid and aprotinin have been used in cases of AFE.

In addition to these strategies, a number of case reports describe other management approaches, although these are highly dependent on the local resources and expertise available. Examples include the use of pelvic embolisation for the management of haemorrhage, cardio-respiratory support in the form of cardiopulmonary bypass, pulmonary artery thromboembolectomy, extracorporeal membrane oxygenation and intra-aortic balloon counterpulsation, haemofiltration and exchange transfusions. The use of selective pulmonary vasodilators to assist in the acute management of severe pulmonary hypertension is also described.

### Outcomes

In keeping with the variation seen in the incidence and severity of AFE, the mortality associated also varies considerably. Thirty years ago AFE was associated with a very high mortality rate, with a reported case fatality of 86%. Such mortality, and the unpredictable nature of the condition, has almost certainly contributed to the fear with which the condition is associated. In recent times the case fatality rate appears to have decreased significantly, with the lowest incidence since 1999 being 11% and most series reporting a much lower mortality than that originally reported. Risk factors for a fatal outcome from AFE have not been extensively studied. Cardiac arrest, whilst a potential indicator of severity, is associated with reasonable survival rates of between 30–39%.

A differential diagnosis for amniotic fluid embolism can include:

- **Obstetric causes:**
  - Eclampsia
  - Uterine rupture
  - Placental abruption
  - Acute haemorrhage
  - Peripartum cardiomyopathy

- **Non-Obstetric causes:**
  - Emboli (air, fat, thrombus)
  - Cardiac (myocardial infarction, cardiomyopathy)
  - Anaphylaxis
  - Sepsis
  - Local anaesthetic toxicity
  - High spinal anaesthesia
  - Transfusion reaction
  - Aspiration

### Fig. 2 Differential diagnosis for amniotic fluid embolism.
Obstetric Surveillance System data, 25% of women who survived required a hysterectomy and more than 50% required a blood transfusion.  

Neonatal outcome is dependent on a number of factors, mostly linked with maternal status. Fetal distress is a common presenting feature of AFE, and if the condition manifests with the fetus in utero the neonatal outcomes may be poor. A number of complications may occur, including stillbirth, early neonatal death, hypoxic ischaemic encephalopathy and seizures. Mortality rates approaching 40% are reported, and Clark found that neonatal neurological morbidity was close to 50%. In keeping with improved maternal outcomes, this may no longer be accurate and the impact of perimortem caesarean delivery is unclear. It is worth reinforcing the point that appropriate resuscitation of the mother, with prompt restoration of maternal cardiac output and hence utero-placental blood flow, is likely to optimise outcomes for the neonate.

Future pregnancies

With an increasing number of women surviving an episode of AFE and going on to another pregnancy, the question of whether these women are at an increased risk of a repeat AFE is highly relevant. There are a number of case reports of successful pregnancies after AFE and to date no confirmed cases of a woman suffering another AFE in a subsequent pregnancy. While numbers are comparatively small, it has been suggested that the risk of recurrence is likely to be very low, because AFE appears to be related to the specific antigenic makeup of the index pregnancy, with subsequent pregnancies likely to be antigenically dissimilar.

Conclusions

AFE continues to be a feared condition in obstetric anaesthesia, due in part to the unpredictable nature of the condition, the potential severity of the presentation and the associated maternal and neonatal morbidity and mortality. Despite an increased awareness and significant research into the condition, our understanding of the underlying mechanisms remains incomplete. Differences in the reporting of the condition make conclusions in relation to the incidence, risk factors and outcomes difficult to compare between groups and standardised methods are required. The management of a suspected episode of AFE remains essentially supportive. Assessment of significant cardiovascular compromise with echocardiography may allow more accurate tailoring of haemodynamic therapy, whilst transfusion requirements may be substantial and should be anticipated. Currently, no widely available diagnostic test is available although a number of promising biochemical markers are being investigated.

Disclosure

Nolan McDonnell is the lead investigator for the Amniotic Fluid Embolism Project for the Australasian Maternity Outcomes Surveillance System (AMOSS).

References


