Amniotic fluid embolism (AFE) is a catastrophic obstetric emergency that can present as sudden, profound, and unexpected maternal collapse associated with hypotension, hypoxaemia, and disseminated intravascular coagulation (DIC). It occurs when amniotic fluid, fetal cells, hair, or other debris enter the maternal circulation. The entry of the amniotic fluid was first described by Ricardo Meyer in 1926. The clinical consequences became established in 1941, after Steiner and Lushbaugh published a maternal mortality case series of eight women who had squamous cells and mucin, presumably of fetal origin, within their pulmonary vasculature at postmortem. They described it as a syndrome of sudden peripartum shock. Since then, a national registry has been developed by Clark in the USA\(^1\) and by Tuffnell in the UK, resulting in the accumulation of numerous clinical reports and reviews.

### Incidence

The true incidence of AFE is unknown, but has been reported to range from 1:8 000 to 1:80 000 pregnancies.\(^2\) The number of maternal deaths due to AFE has fallen significantly over the last 20 yr. In 1979, the suggested maternal mortality rate was 86%; in the triennial report of 2000–2002, the mortality was 25%.\(^3\) The national registry from the USA suggested a mortality rate of 61%. The changing mortality rates are due to better resuscitation techniques, intensive care facilities, and early recognition. However, despite this reduction, AFE still accounts for 4.7% of direct maternal deaths in the UK, 5.7% in France, 30% in Singapore, and up to 10% in the USA and Australia. The majority of patients with AFE die within the first hour of onset of symptoms and about 85% of those who survive have permanent neurological impairment. Elements of pre-existing fetal origin were detected in 73% of those undergoing autopsy and in 50% of those in whom such evidence was sought during life by the examination of pulmonary artery catheter aspirate. Neonatal mortality is ~70%.

If the fetus is alive at the time of event, nearly 70% will survive delivery but 50% of the survived neonates will incur neurological damage.

### Timing

Most cases of AFE (70%) occur during labour, 19% during Caesarean section, and 11% following vaginal delivery. It has also been reported during early gestation, second trimester abortions, during amniocentesis, or following closed abdominal injury.

### Risk factors

There are no proven risk factors. However, the following appear to be associated with a higher risk of developing AFE: advanced maternal age; multiparity; meconium stained liquor; intrauterine fetal death; polyhydramnios; strong frequent or tetanic uterine contractions; maternal history of allergy or atopy; chorioamnionitis; microsoma; uterine rupture; and placenta accreta.

### Pathophysiology

In AFE, amniotic fluid enters maternal circulation via ruptured membranes or ruptured uterine or cervical vessels down a pressure gradient from the uterus to veins. Although the site of placental implantation is one portal of entry, small tears in the lower uterine segment and endocervix are thought to be the most common site of entry.

The pathophysiology of AFE syndrome is unclear. In the past, it was thought to be due to fetal tissue/amniotic fluid forcibly entering maternal circulation causing transient pulmonary vasospasm, cardiac failure, hypoxaemia, and death. However, in 1995, Clark suggested that the syndrome arose from an immune rather than embolic process. According to Clark, AFE is caused by fetal antigens in the amniotic fluid stimulating a cascade of endogenous immunemediators, producing a reaction similar to anaphylaxis. Amniotic fluid contains various...
components that contribute to the pathophysiology of AFE in different ways (Table 1). Biochemical mediators found in the solution are thought to trigger the main features of anaphylactoid reaction with multi-system involvement. The products found in suspension are responsible only for the minor effects caused by actual mechanical obstruction. Clark suggested that ‘the syndrome of acute peripartum hypoxia, haemodynamic collapse and coagulopathy should be described as anaphylactoid syndrome of pregnancy’ and not AFE. There are also striking similarities between clinical and haemodynamic findings in AFE and septic shock, which suggests a common pathophysiological mechanism.

Clark described a biphasic response to AFE (Fig. 1):

**Table 1 Components of amniotic fluid**

<table>
<thead>
<tr>
<th>Solution (biochemical mediators)</th>
<th>Suspensions</th>
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<tbody>
<tr>
<td>Surfactant</td>
<td>Lamugo hair</td>
</tr>
<tr>
<td>Endothelin</td>
<td>Vernix caseosa</td>
</tr>
<tr>
<td>Leukotrienes C4 &amp; D4</td>
<td>Fetal squames</td>
</tr>
<tr>
<td>IL-1 &amp; TNF-a</td>
<td>Bile-stained meconium</td>
</tr>
<tr>
<td>Thromboxane A2</td>
<td>Fetal gut mucin</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Trophoblasts</td>
</tr>
<tr>
<td>Arachidonic acid</td>
<td></td>
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<tr>
<td>Thromboplastin</td>
<td></td>
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<tr>
<td>Collagen and tissue factor II</td>
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<tr>
<td>Phospholipase A2</td>
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</table>

**Phase 1:** Amniotic fluid and fetal cells enter the maternal circulation resulting in the release of biochemical mediators which cause pulmonary artery vasospasm followed by pulmonary hypertension. This results in elevated right ventricular pressures and right ventricular dysfunction, which will lead to hypoxaemia and hypotension with associated myocardial and capillary damage. Phase 1 may last up to 30 min.

**Phase 2:** This occurs in patients who survive the initial insult. Left ventricular failure and pulmonary oedema occurs. Biochemical mediators trigger DIC leading to massive haemorrhage and uterine atony.

**Signs and symptoms**

AFE may present with maternal collapse, associated with breathlessness, cyanosis, hypotension, dysrhythmias, and DIC. However, it is becoming increasingly clear that the presentation can be more subtle than this. It can be preceded by fetal distress. The main signs and symptoms of AFE are summarized in Table 2. Other non-specific symptoms (e.g. vomiting, complaints of chills, anxiety) may be seen in some patients.

The differential diagnosis includes: obstetric causes (e.g. eclampsia, placental abruption, peripartum cardiomyopathy) and non-obstetric conditions (e.g. anaphylaxis, pulmonary embolus, pulmonary aspiration, septic shock, haemorrhagic shock, myocardial infarction, drug toxicity, total spinal anaesthesia).

**Systemic changes**

**Haemodynamic**

Amniotic fluid and fetal cells cause an increase in both systemic and pulmonary vascular resistances resulting in acute pulmonary hypertension. Survivors of this response develop left ventricular failure and pulmonary oedema. The cause of myocardial dysfunction is not clear. It may be due to ischaemic insult from the initial acute hypoxaemia or the effect of a direct myocardial depressant factor present in the amniotic fluid. The presence of endothelin (a potent vasoconstrictor) and humoral factors such as histamine, prostaglandins, serotonin, thromboxane, and leukotrienes causes myocardial depression, decrease in cardiac output, pulmonary hypertension, and DIC. Similar mechanisms exist in anaphylaxis and septic shock.

**Pulmonary**

Pulmonary vasospasm and ventricular dysfunction cause rapid and profound hypoxaemia, which may result in permanent neurological impairment. Initial profound shunting and rapid recovery may occur in some patients. In survivors, primary lung injury often leads to acute respiratory distress syndrome (ARDS).

**Coagulation**

Up to 83% of patients develop some form of DIC with or without clinically significant bleeding. Amniotic fluid contains activated coagulation factors II, VII, and X. It also has a direct factor X activating property, induces platelet aggregation, releases platelet factor III, and has a thromboplastin-like effect. Lockwood and colleagues suggested that amniotic fluid contains a tissue factor, which is a procoagulant. The source of procoagulant is sloughed fetal skin and respiratory, gastrointestinal, and genitourinary epithelia. Tissue factor is responsible for activating the extrinsic pathway by binding with factor VII. This complex in turn triggers clotting by activating factor X. Once clotting is triggered within pulmonary vasculature, local thrombin generation can then cause vasoconstriction and microvascular thrombosis and release of vascular endothelin. Endothelin depresses myometrial and myocardial contractility. The end results include massive haemorrhage and haemodynamic collapse.

**Diagnosis**

There is still no pathognomic marker of AFE. The diagnosis is one of the exclusion criteria. The presence of fetal squamous cells in pulmonary vasculature was once considered diagnostic, but it is now considered to be neither sensitive nor specific. The presence of fetal squamous cells in the broncho-alveolar lavage may support the diagnosis.

Diagnosis is aided by non-specific and specific diagnostic tests which are summarized in Table 3. Non-specific tests include a full differential diagnosis includes: obstetric causes (e.g. eclampsia, placental abruption, peripartum cardiomyopathy) and non-obstetric conditions (e.g. anaphylaxis, pulmonary embolus, pulmonary aspiration, septic shock, haemorrhagic shock, myocardial infarction, drug toxicity, total spinal anaesthesia).
Amniotic fluid embolism

Mechanical block  Release of endogenous mediator

↓  ↓

Pulmonary vessel obstruction  Pulmonary vessel vasospasm

Acute pulmonary  Hypoxaemia  Right heart failure

Hypertension

Death

Survive

Left ventricular failure  Pulmonary oedema  Neurological impairment  DIC

Survive (40–75%)  Death (25–60%)

Fig. 1 Proposed pathophysiological mechanisms of AFE.

blood count and coagulation screen to demonstrate low haemoglobin and abnormal coagulation. Arterial blood gases may show hypoxaemia. Chest X-ray does not often show any abnormality in the early stages before ARDS develops. ECG may demonstrate a right ventricular strain pattern in the early stage. Ultrasound is useful to demonstrate either right or left ventricular dysfunction.

Diagnostic tests include cytological analysis of central venous blood and broncho-alveolar fluid, Sialyl Tn antigen test, zinc coproporphyrin concentration, and serum tryptase concentrations.

A pulmonary microvasculature blood sample can be taken in patients with established central venous access. A pulmonary artery (PA) catheter is floated into a wedged position. Ten millilitres of dead space blood is slowly withdrawn from the distal lumen of PA catheter and discarded. An additional 10 ml is then withdrawn, heparinized, and saved for analysis. Two-to-three-millilitre
Aliquots of blood are passed through nucleopore filters, which are then stained. The presence of squamous cells, specially if they are coated with neutrophils and found in significant large numbers along with fetal debris such as mucin or hair, is suggestive of AFE.

The Sialyl Tn antigen test was described by Kobayashi and colleagues, who showed that monoclonal antibodies TKH-2, MA54, B72.3, and CC49 react with meconium and amniotic fluid-derived mucin. TKH-2 has the ability to detect the lowest concentration of the antigen. Sialyl is a mucin-type glycoprotein that originates in fetal and adult intestinal and respiratory tracts. It is a major component in meconium (10% by weight) and is also present in clear amniotic fluid. Using a sensitive anti-mucin antibody TKH-2, the authors found no difference in the serum levels of Sialyl Tn antigen in pregnant patients throughout gestation or in early post-partum period when compared with non-pregnant controls. In contrast, the antigen concentrations were significantly elevated in patients with AFE. The monoclonal antibody TKAH-2 may eventually prove useful in rapid, non-invasive diagnosis of AFE.

Plasma concentration of zinc coproporphyrin, a characteristic component of meconium, has shown to be greater in patients with suspected AFE. At present, clinical experience with the Sialyl Tn antigen and zinc coproporphyrin is limited and further studies are needed to assess the reliability and utility of these tests.

**Table 2** Presenting signs and symptoms of AFE (in order of frequency)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
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<tbody>
<tr>
<td>Dyspnoea</td>
<td>Hypotension</td>
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<tr>
<td>Cough</td>
<td>Fetal distress</td>
</tr>
<tr>
<td>Headache</td>
<td>Pulmonary oedema/ARDS</td>
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<tr>
<td>Chest pain</td>
<td>Cardiopulmonary arrest</td>
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<tr>
<td></td>
<td>Cyanosis</td>
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<tr>
<td></td>
<td>Coagulopathy</td>
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<tr>
<td></td>
<td>Seizures</td>
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<tr>
<td></td>
<td>Uterine atony</td>
</tr>
<tr>
<td></td>
<td>Bronchospasms</td>
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<tr>
<td></td>
<td>Transient hypertension</td>
</tr>
</tbody>
</table>

The suggestion that AFE may be related to anaphylaxis led Nishio and colleagues to measure tryptase concentrations. They reported concentrations of 67.2 ng ml\(^{-1}\) (normal <10 ng ml\(^{-1}\)). However, others have found normal tryptase but low complement concentrations.

**Management**

The key factors in the management of AFE are early recognition, prompt resuscitation, and delivery of fetus. The input of consultants (anaesthetists, obstetricians, haematologists intensivists) must be enlisted early.

**Oxygenation**

Maintaining oxygenation may necessitate intubation and ventilation. CPAP or PEEP may be indicated.

**Haemodynamic stability**

Rapid intravenous filling, direct acting vaspressors such as phenylephrine and inotropes may be necessary to improve cardiac output. Invasive monitoring, including PAWP, if indicated, can be hazardous due to rapid developing coagulopathy. During cardiopulmonary resuscitation, left uterine displacement must be maintained if the patient is still pregnant. Surgical intervention may be necessary to control haemorrhage.

**Uterine tone**

Uterine tone should be maintained in the usual way using oxytocin, ergometrine, and prostaglandins such as carboprost and misoprostol as indicated. Bimanual uterine massage and uterine packing may help to reduce blood loss.

**Coagulation**

Clark reported that 83% of his cases had either clinical or laboratory evidence of a consumptive coagulopathy. Early involvement of haematologists is essential. Plasma, cryoprecipitate, and platelets are frequently required. Recombinant factor VII has been used to treat uncontrollable massive obstetric haemorrhage and perhaps should be considered in consultation with haematologists if haemorrhage becomes difficult to control.

**Delivery of baby**

The baby should be delivered as quickly as possible. If the mother is undergoing cardiopulmonary resuscitation, surgical delivery should be performed within 5 min for improved maternal outcome. Once stabilized, most patients will require transferring to ICU. Steroids, prostacyclin, nitric oxide as well as plasma exchange, haemofiltration, and cardiopulmonary bypass have been used in patients with AFE.
UKOSS Amniotic fluid embolism register

Amniotic fluid embolism continues to be a leading cause of maternal death. As a result, a database of voluntary notifications has been established in the UK to collect information on epidemiology and management of AFE. The entry for this register is via the national perinatal epidemiology unit website: http://www.npeu.ox.ac.uk/ukoss. The entry criteria include acute hypotension, cardiac arrest, acute hypoxaemia and coagulopathy in the absence of any other potential explanation for the symptoms and signs observed or a pathological diagnosis (presence of fetal squames and hair in the lungs).

References