Amniotic fluid embolism: a diagnosis of exclusion in cases of maternal collapse

Amniotic fluid embolism is a rare but potentially catastrophic condition unique to pregnancy. As the fifth leading cause of direct maternal death in the UK (Knight et al, 2017) it is an important differential diagnosis in cases of maternal collapse and as such is relevant to medical professionals across all specialties. Amniotic fluid embolism is classically characterized by the clinical triad of haemodynamic collapse, coagulopathy and respiratory distress as a result of amniotic fluid or fetal antigens entering the maternal circulation. Although first defined in 1941, the exact pathophysiology of amniotic fluid embolism remains incompletely understood. The creation of national databases with clear diagnostic criteria (*Table 1*), such as the UK Obstetric Surveillance System, has led to improvements in maternal mortality through earlier recognition and management of cases of amniotic fluid embolism.

Table 1. Case definition of amniotic fluid embolism

The cases will be all women in the UK identified as having amniotic fluid embolism using the following definition:
Either a clinical diagnosis of amniotic fluid embolism (acute hypotension or cardiac arrest, acute hypoxia or coagulopathy in the absence of any other potential explanation for the symptoms and signs observed)
Or a pathological diagnosis (presence of fetal squames or hair in the lungs)

from UK Obstetric Surveillance System (2015)

Incidence

The true incidence of amniotic fluid embolism is unknown. A review of several national registries by Frati et al (2014) concluded that the mean incidence of amniotic fluid embolism was 5.5 per 100 000 pregnancies, with a range of 2–15 per 100 000. The UK Obstetric Surveillance System is currently investigating the UK incidence as a contemporary estimate is lacking. It is likely that the condition is under-reported as there is no specific diagnostic test other than identification at post-mortem. Non-fatal cases may therefore go undiagnosed and those confirmed events perpetuate the misconception that amniotic fluid embolism is almost universally fatal.

The latest MBRRACE-UK (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK) report cites amniotic fluid embolism as the fifth leading cause of direct maternal death after thromboembolism, haemorrhage, psychiatric disorders and sepsis (Knight et al, 2017). Neonatal outcomes are incompletely studied but mortality figures of up to 40% have been reported recently (Metodiev et al, 2018).

Risk factors

Although there are no risk factors for amniotic fluid embolism compelling enough to change obstetric clinical practice, there are several proposed associations. Seventy per cent of cases of amniotic fluid embolism occur during labour itself, although induction of labour, instrumental delivery and caesarean section are thought to increase the risk (*Table 2*).

Pathogenesis

The exact pathogenesis of amniotic fluid embolism is not established. It is widely accepted that the presence of amniotic fluid components and/or fetal antigens within the maternal circulation is a prerequisite for amniotic fluid embolism. As such, there are several proposed entry routes, most commonly the endocervical veins, uterine tears or placental attachment site.

Historically, it was thought that amniotic fluid entered the maternal circulation and caused a mechanical obstruction within the pulmonary vasculature, hence the name amniotic fluid embolism. However, this did not explain the physiological feature of disseminated intravascular coagulation associated with many cases of amniotic fluid embolism.

Clark et al (1995) noted the clinical similarities between amniotic fluid embolism and shock conditions such as septic shock and anaphylactic shock. Conde-Agudelo and Romero (2009) subsequently proposed a biphasic immune-mediated response to components of amniotic fluid and fetal cells within the maternal circulation. In phase one, biochemical mediators cause pulmonary artery vasospasm which in turn leads to right heart failure and hypoxia. In phase two, left ventricular failure leads to

Table 2. Risk factors

Maternal	Maternal age >35 years
	Multiparity
	Pre-eclampsia or eclampsia
	Ethnic minority
Placental or uterine	Placental abruption
	Placenta previa
	Polyhydramnios
Labour	Medical induction of labour
	Instrumental delivery
	Caesarean section

adapted from Knight et al (2012)

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Table 3. Symptoms and signs

System	Symptoms	Signs
Cardiovascular	■ Chest pain	■ Hypotension ■ Cardiac arrest ■ Placental abruption
Haematological		■ Deranged coagulation
Respiratory	■ Dyspnoea ■ Cough	■ Hypoxia ■ Cyanosis ■ Pulmonary oedema ■ Bronchospasm
Other	■ Altered mental status ■ Headache ■ Nausea	■ Fetal distress ■ Vomiting ■ Seizures

Adapted from Thongrong et al (2013)

Table 4. Differential diagnoses

	Differential diagnosis	Specific investigations
Pregnancy-related	Eclampsia	
	Obstetric haemorrhage	
	Peripartum cardiomyopathy	Echocardiogram
		Cardiac magnetic resonance imaging
		Cardiac protein assays
	Uterine rupture	
Anaesthetic-related	High spinal anaesthesia	Sensory level testing (cold spray)
	Local anaesthetic toxicity	
Other	Pulmonary embolism	Computed tomography pulmonary angiogram
		Echocardiogram
	Air embolism	Echocardiogram
	Anaphylaxis	Mast cell tryptases
		Complement levels (C3/C4)
	Septic shock	Blood cultures
	Myocardial infarction	Troponin I/T
	Arrhythmia	
	Transfusion reaction	
	Toxins	
	Metabolic causes	Thyroid function tests
		Cortisol levels

From Thongrong et al (2013)

pulmonary oedema while the continued release of biochemical mediators culminates in disseminated intravascular coagulation. These mechanisms provide a better unifying explanation for the haemodynamic collapse, respiratory distress and deranged coagulation described in many case reports of amniotic fluid embolism.

More recently, a hybrid of these two theories has been proposed where tissue factor within amniotic fluid entering the circulation triggers the activation of the clotting cascade (Uszyński, 2011). This generates microthrombi within the pulmonary circulation resulting in hypoxia and disseminated intravascular coagulation. Additionally, reduced C3 and C4 levels in affected individuals implicate complement proteins in mediating mast cell degranulation in the lungs, resulting in respiratory distress (Benson, 2012). Inflammatory mediators cause vasodilation and shock, completing the clinical picture.

Clinical features

Amniotic fluid embolism classically presents with the triad of sudden onset respiratory distress, profound cardiovascular collapse and coagulopathy (*Table 3*). However, it is increasingly accepted that not all of these features are consistently present (Sadera and Vasudevan, 2015). Additional premonitory signs and symptoms such as breathlessness, chest pain, light-headedness, restlessness, distress, pins and needles, or nausea and vomiting may be early warning signs for those at risk of amniotic fluid embolism collapse.

Cardiovascular symptoms

As described previously, the amniotic fluid and fetal cells increase pulmonary and systemic vascular resistance. This leads to acute pulmonary hypertension and right heart failure. Left ventricular failure follows with the interventricular septum being pushed into the left atrium or ventricle. This is exacerbated by myocardial ischaemia secondary to the associated hypoxia. This left heart failure, in combination with the immune-mediated vasodilatation, produces the clinical sign of profound hypotension and shock.

Haematological changes

Activation of the clotting cascade leads to a consumptive coagulopathy reflected by a rise in prothrombin time and activated partial thromboplastin time and a fall in fibrinogen levels. The clinical manifestation of this is disseminated intravascular coagulation

with or without massive haemorrhage and haemodynamic collapse.

Respiratory symptoms

Initially, hypoxia is likely to be the result of pulmonary vasoconstriction as described above and pulmonary oedema associated with acute left heart failure. Ongoing respiratory compromise is thought to be the result of capillary leak from the immune-mediated process, causing non-cardiogenic pulmonary oedema.

Diagnosis

Amniotic fluid embolism is a diagnosis of exclusion and, as such, the UK Obstetric Surveillance System has set out diagnostic criteria based on the absence of any other clear cause for entry onto their registry (*Table 1*). There is no test available to confirm amniotic fluid embolism and verification may only be sought at post-mortem. Owing to its heterogeneous clinical presentation there are a range of differential diagnoses to consider in the acute scenario, particularly those with specific treatments (*Table 4*). However, there are several investigations routinely performed in the critically unwell patient which may support a diagnosis of amniotic fluid embolism (*Table 5*).

Management

A supportive approach is the mainstay of management for suspected cases of amniotic fluid embolism, and therefore a definitive diagnosis is not needed in the acute setting. Symptoms and signs should be managed as they present without the need for investigative results. Expedition of delivery may be necessary on account of fetal distress and a multidisciplinary approach with senior clinicians present is essential. Patient care post-amniotic fluid embolism is best provided in a high dependency setting. In the event of maternal collapse an obstetric arrest or peri-arrest call should be initiated as per local protocols. This ensures the presence of all essential personnel for successful maternal and fetal resuscitation as necessary.

Hypoxia should be managed with 100% oxygen via a non-rebreathe mask and early consideration should be given to tracheal intubation and mechanical ventilation. This decision should be based on the degree of respiratory failure and having considered the increased risk of a difficult airway and gastric aspiration in the pregnant patient.

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Cardiovascular collapse should be managed with fluid resuscitation (bearing in mind the potential for cardiac failure and pulmonary oedema), invasive arterial monitoring, vasopressor and inotropic support. Assessment of cardiac status may be achieved with bedside echocardiography or cardiac output monitors if the skill set and equipment is available. If the patient is invasively ventilated, a transoesophageal echocardiogram is likely to produce higher quality images for interpretation.

Coagulopathy may be suspected clinically in the event of haemorrhage or identified on point-of-care testing such as thromboelastometry. Laboratory results are likely to show a prolonged activated partial thromboplastin time and prothrombin time with hypofibrinogenaemia. A massive obstetric haemorrhage call should be initiated to enable transfusion of blood products in line with hospital protocols. In general, packed red cells, platelets, fresh frozen plasma and cryoprecipitate may be required and ratios should be guided by local guidelines, ongoing clinical assessment and haematological advice.

Additional therapies to consider include tranexamic acid, intraoperative cell salvage and clotting factor concentrates. Tranexamic acid in particular reduces mortality in all-cause post-partum haemorrhage and should therefore be given in the event of hypofibrinogenaemia relating to amniotic fluid embolism (Shakur et al, 2017).

If cardiac arrest occurs, the Resuscitation Council (2016) guidelines for maternal cardiopulmonary resuscitation should be followed. Modifications to the algorithm for all pregnant patients (>20 weeks' gestation) include manual displacement of the uterus or application of a left lateral tilt to prevent aortocaval compression, early intubation, alternate hand positioning for performing chest compressions and consideration of perimortem caesarean section at 4 minutes if return of spontaneous circulation is not achieved.

Table 5. Investigations and results supportive of amniotic fluid embolism

Investigation	Supportive of amniotic fluid embolism
Arterial blood gas	Hypoxaemia
	Elevated arterial partial pressure of carbon dioxide ($PaCO_2$)
Full blood count	Low haemoglobin
Coagulation profile	Increased prothrombin time
	Increased activated partial thromboplastin time
	Low fibrinogen
	Low platelets
Chest X-ray	Pulmonary oedema
	Cardiomegaly
Electrocardiogram	Right heart strain
Transoesophageal echocardiogram	Pulmonary vasoconstriction
	Right ventricular dilatation
	Leftward deviation of septum
	Left ventricular collapse

from Metodiev et al (2018)

KEY POINTS

- Amniotic fluid embolism is a leading cause of direct maternal death in the UK, making it an important topic for medical professionals across a range of specialties.
- The pathophysiology of amniotic fluid embolism is incompletely understood but there are continued efforts to identify the exact process underlying the clinical presentation.
- Risk factors are numerous but none are definitive enough to change current clinical practice. Awareness of the associations may help to inform a diagnosis.
- The heterogeneous presentation of amniotic fluid embolism lends itself to multiple differential diagnoses which must all be considered in cases of sudden maternal collapse.
- Routinely performed investigations are useful in supporting a diagnosis of amniotic fluid embolism, while more specific tests can rule out pathologies with a similar clinical presentation.
- Management is largely supportive and should focus on treating the triad of hypoxia, cardiovascular collapse and coagulopathy. A multidisciplinary approach is essential.
- Presumed and confirmed cases of amniotic fluid embolism should be submitted to the UK Obstetric Surveillance System database to support the ongoing research effort.

Conclusions

Amniotic fluid embolism is an uncommon but life-threatening complication of pregnancy. No significant risk factors have been identified to help predict and prevent cases of amniotic fluid embolism in clinical practice, making cases more challenging to treat when they occur. Early and aggressive resuscitation is undoubtedly essential for positive maternal and neonatal outcomes and this is best achieved using a multidisciplinary approach to both acute management and post-resuscitation care. Careful consideration should be given to alternate diagnoses because of the non-specific and diverse presentations of amniotic fluid embolism. Following a suspected case, data should be submitted to the UK Obstetric Surveillance System database to help with information gathering for this incompletely understood syndrome. **BJHM**

Conflict of interest: none.

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