Amniotic fluid embolism

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Abstract

Amniotic fluid embolism (AFE) is a rare but severe complication of pregnancy characterised by a catastrophic systemic dysfunction involving the respiratory, cardiovascular and haematological systems. Its incidence in the UK is approximately 1 in 59,000 maternities, but despite its overall rarity AFE is responsible for a significant proportion of the maternal deaths across the developed world and was the third leading direct cause of maternal deaths ascertained by the UK confidential enquiry 2009–2011. However, it should no longer be considered as resulting in inevitable mortality, and increasing evidence shows that good supportive care can result in improved outcomes for mother and baby. Current data puts case fatality rates for AFE in the UK at around 19%, much lower than previously thought. This review collates the latest literature looking at how and when AFE occurs, its presentation, diagnosis and management.

Keywords amniotic fluid embolism; maternal collapse; maternal mortality

Incidence

Amniotic fluid embolism (AFE) remains an extremely rare condition. Because of this very rarity, and the fact that it is a diagnosis of exclusion, the true incidence is particularly difficult to determine. Combined with internationally differing definitions of AFE, as well as differing methodologies for reporting and recording data, this results in a great range of reported incidence rates between countries. The International Network of Obstetric Survey Systems (INOSS) have recently produced a consensus definition of AFE as '*an acute cardio-respiratory collapse within 6 hours after labour, birth or ruptured membranes, with no other identifiable cause, followed by acute coagulopathy in those women who survive the initial event*,' that it would recommend is used in future.

In the UK, AFE is researched through the UK Obstetric Surveillance System (UKOSS). The system is designed to study rare disorders using robust diagnostic criteria, to ensure specifically that false-positive cases are not included. UKOSS collected data on all the women diagnosed with AFE between 2005 and 2014 and estimates the total UK incidence as 1.7 per 100,000 maternities; one of the lower reported incidence rates in the developed world. The fatality rate of AFE is 0.3 per 100,000. In comparison, recent data from the Australasian Maternity Outcomes Survey estimate an incidence of up to 5.4 per 100,000, and a North American population study of 3 million births produced a 6.7 per 100,000 incidence.

The lowest incidence rates have generally been seen in countries using validated case identification (such as the UK), whereas the higher rates tend to come from retrospective analysis of large population discharge databases, especially if no additional criteria are applied to exclude false positive cases. For example, AFE may be considered as a differential in a woman who collapses, and is recorded as such in her notes even if a more likely cause for the collapse is found subsequently. However, the diagnosis of AFE could conceivably remain coded in the patient's records at discharge and create an over-estimation of true cases when the database is interrogated.

Both the total and fatal incidence rates from in the UK currently remain stable, with no significant temporal trend in the last 10 years.

Pathogenesis

There are a number of theories that may explain the transfer of amniotic fluid from the fetal to the maternal circulation, and the consequent features of AFE. It is suggested that a breach occurs in the barrier between these two circulations, most likely in the form of small tears in the lower uterine segment and the veins in the endocervix during labour and delivery. An osmotic gradient between the uterus and the maternal circulation is created. Since multiple studies have now found that the passage of amniotic and fetal cells into maternal circulation is extremely common during normal pregnancy and delivery, the question is raised as to why only a very few women experience the clinical picture of AFE in response, but most do not.

The traditional model of amniotic debris causing an obstructive pathology within the maternal pulmonary circulation is highly debated, not least because of there has been no consistent evidence to support any physical obstruction (radiologically, in autopsies, or experimentally), but also due to the inability to reliably reproduce this in animal models and the extremely variable presentation and course of the condition. Instead, there have been several theories concerning an abnormal maternal immunological response to account for the signs and symptoms of AFE.

Pathophysiology

Uncertainty also remains around the exact pathophysiology underlying AFE. Once amniotic fluid enters the maternal circulation, there are thought to be a number of humoral, haemodynamic, and coagulopathic changes that occur and lead to the signs and symptoms of the syndrome.

Haemodynamic changes

The mechanisms of these changes in the maternal circulation are incompletely understood, but seem to involve a complex sequence of abnormal activation of endogenous proinflammatory mediator systems similar to those seen in anaphylaxis or the systemic inflammatory response syndrome (SIRS). Current evidence suggests that the haemodynamic response to AFE is biphasic, with the initial onset of severe pulmonary hypertension as a result of the vasospasm leading to acute right ventricular failure with a left deviation of the inter-atrial and inter-

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ventricular septum. This leads to left ventricular failure due to reduction in pre load, and to systemic hypotension. This is turn may decrease coronary perfusion and ischaemic injury to the myocardium, aggravating cardiogenic shock in addition to the likely predominate distributive shock of the condition. In addition, recent literature has shown *in vitro* that amniotic fluid may act as a cardiac depressant, i.e. it decreases the contractility of myometrium, and could potentially affect the myocardium similarly. Hypoxaemia may be a result of the severe ventilation-perfusion mismatch due to intense vasoconstriction in the pulmonary vessels that occurs during the initial phase.

Humoral factors

As in sepsis and other causes of distributive shock, a number of reactive mediators have been implicated in the circulatory changes in AFE. These include prostaglandins, leukotrienes, histamine, serotonin and proteolytics. Key amongst these is endothelin, a powerful vasoconstrictor found in significantly high levels in amniotic fluid. There is evidence to show *in vitro* and *vivo* that endothelin also constricts the pulmonary bronchi and causes depression of myometrial and myocardial contractility, but there is little direct evidence to show that it is the endothelin in amniotic fluid that directly causes the clinical signs of AFE.

Coagulopathy

AFE is almost always associated with a form of disseminated intravascular coagulopathy (DIC) which is likely to be consumptive rather than fibrinolytic. Support for this comes from findings that amniotic fluid contains activated coagulation factors II, VII and X. Amniotic fluid is known to induce platelet aggregation, release platelet factor III and activate the complement cascade. A mechanism proposed by Lockwood et al is that tissue factor found in amniotic fluid triggers the extrinsic pathway of the coagulation cascade which binds to factor VII and activates factor X which, in turn, triggers coagulation. It is the coagulation that leads to vasoconstriction of the microvasculature and thrombosis. This produces thrombin which secretes the endothelin which may lead to the changes seen in AFE.

Risk factors

As with incidence data, there is difficulty in verifying and quantifying risk factors for developing AFE due to the nature of the condition and the lack of international consensus of methods for identifying and recording AFE data. A 2012 review by Knight et al examined data from the UK, USA, Canada, Australia and the Netherlands and identified very little consistency between countries in risk factors for occurrence of AFE; none of the suggested risk factors were consistently related to mortality from the condition. The only factors associated with AFE in all five countries were induction of labour and increasing maternal age.

The UKOSS 2005–2014 data suggest that induction of labour gives a six-fold increased odds ratio for women induced with prostaglandins and a two-fold increased odds ratio for AFE among those receiving oxytocin or oxytocin plus prostaglandin.

The other significant risk factors identified from the UKOSS were caesarean section, vaginal instrumental delivery, multiple pregnancy and placenta praevia. Previous studies have suggested a clear association between caesarean section and AFE, but it has been unclear as to whether these modes of delivery were cause or consequence of AFE. The UKOSS study differentiated between cases of AFE diagnosed prior to caesarean section and those diagnosed after, and found that postnatal presentation of AFE had a sixteen-fold increase in the odds of Caesarean delivery, indicating a likely causal relationship. Similarly, for vaginal instrumental delivery the odds ratio was 9.51 (95% CI 3.17 −28.51). Whilst this suggests that if induction, instrumental delivery and caesarean section were avoided, the incidence of AFE would be significantly reduced, there are clearly other benefits to these interventions.

Of note, despite the temporal increases in factors such as caesarean rates and maternal age over the last decade, no corresponding temporal trend was noted in incidence rates in the UKOSS study, possibly due to lack of power in the study and low absolute incidence rates of AFE.

Historically it has been suggested that polyhydramnios, placental abruption, cervical laceration, hyperstimulation and uterine rupture are all risk factors that lead to an increased risk of AFE but there is a lack of data to confirm this. There has also been concern that use of cell salvage in obstetrics could lead to passage of fetal debris into maternal circulation and so to AFE. This has not been found to be the case and cell salvage should not be considered a risk factor.

Since AFE cases are both rare and difficult to predict, there has never been enough clear evidence and consensus about risk factors to justify specific changes to obstetric care.

Presentation

It is important to consider AFE as a differential diagnosis in any woman who presents with sudden collapse in pregnancy or the puerperium, although this differential will often be ruled out later as specific signs or results uncover the true cause. AFE presents in all cases with a sudden change in either maternal or fetal condition. Table 1 describes the current UKOSS case definition for AFE. Analysis of the UKOSS data found that women had a median of four, (range one to nine), of these features at presentation. Approximately 53–60% of AFE cases present prior to the birth of the baby and tend to occur during labour, although there are reported cases of presentation pre-labour, during induction of labour, following uterine evacuation, cervical suture removal, amniocentesis, or blunt abdominal trauma. The remainder of cases occurs shortly after delivery, generally within 30 minutes.

Approximately 47% of women who experience AFE have a premonitory sign or symptom prior to collapse. Commonly reported premonitory symptoms are numbness, tingling, agitation, pins and needles, lightheadedness, chest pain, breathlessness, and feeling cold. In 36% of patients, there was concern about fetal compromise prior to a change in maternal condition; likely due to compensated or unrecognised maternal hypoxia and hypotension. Cardiac arrest as a presenting feature is recorded in 60 −80% of registered cases. There may commonly be excessive bleeding, but this is not often the first presenting feature, and in cases of this where there is no early coagulopathy or cardiorespiratory compromise a different diagnosis should be sought (Table 1).

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