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Acute respiratory distress and amniotic fluid embolism in pregnancy

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A B S T R A C T

Respiratory failure in pregnant and postpartum women is uncommon, but it is one of the leading causes of maternal admission into the intensive care unit and is associated with high mortality. The underlying causes include sequelae of underlying medical conditions, such as congenital heart diseases, but it is more often related to acute respiratory distress syndrome from obstetric complications like pre-eclampsia, effect of treatment like tocolysis, coincidental to pregnancy like transfusion-related acute lung injury, and accidental like amniotic fluid embolism. The pathophysiological mechanisms involved in many of these conditions remain to be clearly established, but maternal inflammatory response and activation of the immune and complement systems appear to play leading roles. Prompt recognition of maternal respiratory distress and related manifestations and aggressive and adequate supportive treatment, especially cardiopulmonary resuscitation, ventilation, maintenance of circulation, and timely termination of the pregnancy, play key roles in achieving survival of both mother and foetus.

Introduction

Acute respiratory failure is the inability to maintain adequate gas exchange or ventilation and occurs in 0.1–0.3% of pregnancies, but the development of respiratory illness and need for mechanical ventilation is higher in the obstetric than the general population of similar age, being one of the most

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common reasons for admission to the intensive care unit (ICU) with the mortality of 9–44% [1–4]. Acute respiratory distress syndrome (ARDS) in obstetric patients is discussed below.

Acute respiratory distress syndrome in pregnant and postpartum women

Epidemiology, pathophysiology, and diagnosis

The group of ARDS has an overall incidence of 15.9–130 per 100,000 deliveries, higher than the 13.5 to 27.6 per 100,000 in the non-pregnant population [2–5]. Pregnancy predisposes to the development of pulmonary oedema due to increased cardiac output, and changes in systemic vascular resistance and colloid oncotic pressure, so that precipitating factors like pre-eclampsia and excessive infusion of intravenous fluid can easily precipitate the condition [1]. At autopsy, pulmonary oedema, alveolar collapse, and hyaline membrane involvement of the alveoli resembling neonatal hyaline membrane disease are found and represent the effects of systemic inflammation and diffuse endothelial damage to the lungs, with or without fluid overload [4,6]. Symptoms include dyspnoea, cough, fever, and fatigue, and clinical findings include tachypnoea, accessory muscle use, bilateral chest crackles on auscultation, jugular venous distension, cardiac flow murmurs, and S3, S4 gallop rhythm on auscultation, usually manifesting within 6–72 h following the appearance of the predisposing conditions and should prompt the diagnosis of ARDS [4]. Imaging with chest X-ray (CXR) or CT reveals diffuse bilateral lung infiltrates, or initial dependent lobar opacities evolving to bilateral involvement, while lung ultrasound can demonstrate the multiple B-lines of thickened interlobular septa and/or ground-glass opacities [4]. Undiagnosed underlying cardiac diseases can be ruled in or out by transthoracic echocardiography (TTE), and right heart catheterization can clarify the presence of cardiogenic oedema [4]. The diagnostic criteria of ARDS (Berlin Definition) and its causes [2,4,6,7] are shown in Table 1.

Pregnancy and ARDS

Mortality in pregnant and postpartum women is commonly due to respiratory failure, multiorgan failure, sepsis, complications from mechanical ventilation, and cardiac arrest, with the risk increasing with number of risk factors, while perinatal mortality is 20–30% [1]. The leading causes are infection (including non-obstetric and pneumonia), pre-eclampsia/eclampsia, postpartum haemorrhage (PPH),

Table 1
Acute respiratory distress syndrome (ARDS) – definition (Berlin criteria) and causes.

Berlin criteria	
Timing	Worsening or new respiratory symptoms within one week of known clinical process.
Chest imaging	Bilateral infiltrates that cannot be fully explained by atelectasis, lung nodules, or effusions
Origin of oedema	Not completely explained by cardiac failure or fluid overload
Oxygenation	Mild = 200 mmHg < PaO_2/FiO_2 ≤300 mmHg
	Moderate = 100 mmHg < PaO_2/FiO_2 ≤200 mmHg
	Severe = PaO_2/FiO_2 <100 mmHg
Non-obstetric causes	Pneumonia (bacterial, fungal, and viral), influenza A (H1N1)
	Sepsis (especially pyelonephritis)
	Blood product transfusion (transfusion-related acute lung injury)
	Haemorrhage, disseminated intravascular coagulation
	Trauma/contusion, fat emboli, air emboli
	Aspiration (Mendelson's syndrome) (11%*)
	Near drowning, inhalation injury, burns, reperfusion injury, pancreatitis
	Intracerebral haemorrhage
Obstetric causes	Pre-eclampsia/eclampsia (up to 22% of ARDS in pregnancy) (25%*)
	Puerperal infections and septic abortion (43%*)
	Amniotic fluid embolism
	Tocolytic therapy
	Retained gestational products

Compiled from Refs. [2,4,5,7], *% from Ref. [7]*.

aspiration, and haemorrhage, but uncommon and non-obstetric conditions like lymphoma and status epilepticus have been reported [5,8], while 60% of the cases ventilated after 26 weeks had preterm birth (PTB) [5]. For obstetric and non-obstetric conditions, the incidence of ARDS was 3.8% and 33.3%, respectively, renal replacement was 5.7% and 22.2%, respectively, and ICU mortality was 3.8% and 11.1%, respectively, but there was no significant difference in the neonatal outcome except meconium aspiration syndrome (3.8% and 33.3%, respectively) and sepsis (5.7% and 33.3%, respectively), with higher incidence in the former for abnormal Denver Development Screening Test (24.5% and 5.6%, respectively) [8]. Recent data showed a significant increase in mechanical ventilation from 36.5/100,000 live births in 2006 to 59.6/100,000 live births in 2012, with an overall mortality of 9% [9], which was lower than the 39.3% reported before [5]. Mortality risk was associated with prolonged mechanical ventilation (aOR 1.69), need for haemodialysis (aOR 3.40), liver failure (aOR 1.71), amniotic fluid embolism (AFE, aOR 2.31), influenza infection (aOR 2.26), septic obstetric emboli (aOR 2.15), and puerperal infection (aOR 1.86), whereas tobacco use (aOR 0.53) and pneumonia (aOR 0.70) were associated with reduced risk [9]. One study found a third (9/28) of the cases might have been preventable, while 10 of the mothers with living foetuses in the third trimester required ventilation with 9 of them delivering within 4 days [5]. Furthermore, of the 6 infants delivered for foetal heart rate abnormalities, 1 died and 3 had asphyxia [5].

Management of ARDS in pregnant and postpartum women

General management

This requires a multidisciplinary team with maternal-foetal medicine (MFM) obstetricians and anaesthetists/intensivists, and the patient is managed in an intensive care setting. The key is the identification, control, and treatment of the inciting cause, including timely administration of antibiotics. Fluid resuscitation is given judiciously to avoid worsening of lung compliance, and supplemental oxygen is provided by face mask or high-flow nasal cannula to maintain the SpO_2 at $\geq$88% [4]. The roles of pharmacological therapies, including corticosteroids and nitric oxide (NO), remain controversial. Following recovery, 5-year outcomes are generally normal, but there may be reduction in 6-min walk test as predicted for age and long-term psychiatric outcomes [4]. If the maternal condition improves with treatment, delivery can await in preterm gestation, and prompt delivery is indicated with foetal compromise or obstetric indications, but delivery per se is not effective in improving maternal respiratory function, recovery, or survival [1,7].

Respiratory support and mechanical ventilation

During pregnancy, the decreased lung functional residual capacity (FRC) predisposes to rapid onset of hypoxia, hypercapnia, and acidosis after short periods of apnoea, the physiological chronic compensated respiratory alkalosis reduces the buffering capacity in the blood and the ability for further respiratory compensation when maternal metabolic acidosis develops, and the foetal need for oxygen increases maternal oxygen requirement [1]. These factors interact to increase the risk of development of maternal respiratory failure and the need for respiratory support. The goals of respiratory support are to maintain the SaO_2 at $\geq$95%, PaO_2 at >70 mmHg, $PaCO_2$ at <45 mmHg, tidal volume of 6–8 mm/kg ideal body weight, maternal pH > 7.30, and peak or plateau pressures <35 cmH_2O, and the inability of achieving these goals reflect impending respiratory failure [1,7]. Non-invasive positive pressure ventilation (NIPPV) reduces complications associated with intubation and sedative medications and is indicated when supplemental oxygen cannot improve oxygenation, the criteria being adequate respiratory drive, ability to control and protect one's own airway to avoid aspiration and tolerating tight-fitting mask, haemodynamic stability, and short-term need for ventilator support [1,7]. A lack of clinical improvement 30–45 min later would call for invasive mechanical ventilation [2].

Invasive mechanical ventilation should follow a lung-protective ventilation strategy with low tidal volume (TV) and lower positive end-expiratory pressure (PEEP) ventilation [4] to avoid lung over-

distension and ventilator-associated lung injury and reduce barotrauma and mortality [2,7]. Fibre-optic guided intubation is recommended due to the 8-fold increase in failed intubation [1]. Initial settings are the respiratory rate of 10–14/min, TV $\leq$ 6 mL/kg non-pregnant predicted lean body weight {calculated as 45.5 + 0.91(height in cm − 152.4)}, minute ventilation <115 mL/kg, FiO_2 beginning at 100% and weaning to <50% as tolerated while maintaining oxygen saturation of >94%, targeted inspiratory plateau pressure of $\leq$30 cmH_2O, and using extrinsic PEEP only when necessary [1,2,7,10], while pH and $PaCO_2$ can be maintained by increasing respiratory rate [7]. The judicious use of PEEP to provide PaO_2 of 65–90 mmHg increases FRC and recruits dependent lung regions and collapsed non-aerated alveoli [2], while minimizing the worsening of haemodynamic performance from increased intrathoracic pressure and decreases in preload [7]. Whether to use volume- or pressure-regulated TV depends on the situation, as the former can ensure TV and reduce atelectasis at the expense of increased work of breathing for the patient and lung trauma, whereas the latter can improve ventilation-perfusion (V/Q) matching and less likely to cause lung trauma but increases the difficulty to achieve desired constant minute ventilation [1]. As well, PEEP can compromise cardiac output and increase intracranial pressure, and high-level PEEP can even be associated with hypotension and hypoxaemia [1].

Fluid homeostasis is vital, balancing between adequate organ and placental perfusion against the accumulation of extravascular fluid in the lungs; thus, pulmonary artery catheter, arterial lines, or central venous pressure catheter haemodynamic monitoring is often recommended [1]. Positioning on the left or right lateral position prevents inferior vena cava compression by the uterus [1]. Analgesia and sedation, as well as nutritional support, may be required. Methylprednisolone, β-sympathetic agonist, and inhaled nitric oxide are not recommended [2]. In refractory hypoxaemia, the use of extracorporeal membrane oxygenation (ECMO) has been associated with survival rates of 66%–78% for parturients with ARDS and infants home discharge rate of 71% [2]. The important causes of ARDS in obstetric patients are discussed below.

Tocolytic pulmonary oedema

Many tocolytic agents have been associated with pulmonary oedema, the incidence varying between 0.3% and 9%, and usually presents $\geq$24 h after treatment initiation [3,6]. Most commonly associated with β-adrenergic agonists, ARDS occurs less frequently with magnesium and calcium channel blockers [6]. The mechanisms include prolonged exposure leading to myocardial dysfunction, increased capillary permeability, excessive intravenous fluid administered, and reduced osmotic pressure, and fluid retention could be compounded by simultaneous glucocorticoid administration [6]. Treatment includes the discontinuation of the tocolytic agent, administer oxygen and diuretic, and restrict fluid infusion, failing all of which calls for mechanical ventilation, but other differential diagnoses should be considered if pulmonary oedema persists for $\geq$24 h [6].

Pulmonary oedema due to pre-eclampsia (PE)/eclampsia

Pulmonary oedema occurs in up to 3% of women with PE, more common in obese, chronically hypertensive women with 70% presenting in early puerperium (mean time of 71 h post-delivery), the mechanisms include hydrostatic oedema from increased afterload, left ventricular (LV) systolic and diastolic dysfunction, reduced serum oncotic pressure, abnormal vascular permeability, excessive fluid administration (oxytocin infusion for labour induction and magnesium sulphate infusion), and autotransfusion from the uteroplacental circulation after the third stage of labour, with older, multigravida patients with a history of hypertension being more prone [2,3,6,11,12]. Clinical findings could include normal or low LV preload, increased afterload, and a normal or low cardiac output [3,6]. In this situation, ARDS is aggravated by disseminated intravascular coagulation (DIC), acute kidney injury, and cerebral oedema [2].

Gestational trophoblastic disease (GTD)

This uncommon condition can follow trophoblastic pulmonary embolism in benign hydatidiform mole, and contributory factors include fluid overload, LV dysfunction, systemic inflammatory response,

and thyrotoxicosis due to molar pregnancy [6]. It usually presents during uterine evacuation and resolves within 48–72 h with supportive treatment.

Gastric acid aspiration (Mendelson syndrome)

Gastric acid aspiration is a non-obstetric and rare condition in pregnancy, its occurrence being more common during labour and delivery, especially at the induction of general anaesthesia for emergency caesarean delivery (CD) even if the mother has been fasted, due to increased intra-abdominal pressure, progesterone-induced lowering of the oesophageal sphincter tone and prolonged gastric emptying time, and adopting the supine position during labour and delivery [6,13]. The incidence is 1:3216, being higher for emergency procedures [14]. Its severity and development of ARDS depend on the amount of material aspirated, its acidity, patient age, and comorbidities, and large objects causing airways obstruction lead to acute respiratory distress, cyanosis, and even death, whereas smaller particles can cause wheezing, dyspnoea, cough, and atelectasis, and chemical pneumonitis is more likely if the gastric contents pH is < 2.5 and volume is ≥ 0.3 mL/kg [15]. Neutrophil recruitment and release of proinflammatory cytokines cause respiratory embarrassment [16]. While pulse oximetry may show oxygen desaturation and tachycardia, many do not develop clinical and radiological abnormalities, the latter primarily on the right dependent pulmonary segments if present. Medications used for the prevention and minimisation of the effects of gastric acid aspiration during labour and delivery include oral sodium citrate (30 ml) given every 3 h, and the histamine receptor-2 antagonist ranitidine, to alkalinise the stomach contents and reduce gastric acid secretion. An oral prokinetic agent (metoclopramide) can reduce gastric volume and peripartum nausea and vomiting and increase lower oesophageal tone [17]. Recommended duration of fasting is 2 h for clear liquids, 6 h for a light meal, and 8 h for a solid fatty meal [17]. Treatment involves putting the patient in the Trendelenburg position, providing oropharyngeal suction, and swift intubation with insertion of a suction catheter to prevent the dislodgment of aspirated material further into the lungs with positive pressure ventilation, or bronchoscopy and pulmonary lavage. Hypoxia is treated by mechanical ventilation.

Transfusion-related acute lung injury

The literature on this complication in pregnant [19,20] and postpartum women [21] is scanty, but transfusion-related acute lung injury (TRALI) is the leading cause of transfusion-related morbidity and mortality and is differentiated from other transfusion-related complications such as transfusion-associated circulatory overload and transfusion-associated dyspnoea [22]. Diagnosis is by acute hypoxaemia (SpO_2 <90% on room air or $PaO_2/FiO_2 \leq 300$ mmHg), bilateral pulmonary oedema on imaging, no evidence of left atrial hypertension, and onset during or within 6 h of transfusion of a blood product and is classified into TRALI type 1 (no temporal relationship to an ARDS risk factor) and type 2 (with risk factors for, or already having mild, ARDS with stable respiratory status for $\geq$12 h preceding the transfusion) [22,23]. It is attributed to anti-HLA or anti-human neutrophil antibodies (HNA) present in transfused plasma, so that all blood products, but especially plasma-rick products (whole blood, platelet concentrates, plasma) are implicated, and the pathophysiology mechanisms include antibody-mediated and a “two-hit” model in which a first hit due to clinical risk factors such as infection promoting inflammatory activation of pulmonary endothelium, followed by a second hit from biological response modifiers or antibodies in the transfused blood product, resulting in the release of cytokines and reactive oxidative species which cause pulmonary endothelial damage, capillary leak, and lung injury [22,23]. Risk factors in obstetrics include surgery, sepsis, PPH, massive blood transfusion, positive fluid balance, and thrombotic microangiopathy [22,23]. Management includes supportive care and corticosteroid.

Pulmonary embolism

This is covered in another chapter and is not repeated here.

Amniotic fluid embolism

Epidemiology

The estimated incidence is between 1:15,200 and 1:53,800 deliveries in North America and Europe [24], and 1.9/100,000 and 6.1/100,000 maternities in the UK and Australia, respectively [25]. An earlier Canadian study found the rate of AFE to be 14.8 and 6.0 per 100,000 multiple-birth and singleton deliveries, respectively [26], but a later study included only cases with additional features of cardiac arrest, shock/severe hypotension, respiratory distress, mechanical ventilation, coma, seizure, or coagulation disorder could confirm only 40% (120/292) diagnosed cases to have AFE, yielding an incidence of 2.5/100,000 deliveries [27]. Data from the UK Obstetric Surveillance System (UKOSS) for February 2005 to February 2009 revealed an incidence of 2.0/100,000 deliveries [28], while extension to January 2014 gave an incidence of 1.7/100,000 deliveries [29]. In New South Wales, Australia, the incidence was 3.3/100,000 for January 2001–December 2007 [30]. Thus, the reported incidence would be influenced by whether only singleton pregnancies or all pregnancies were included, whether the diagnosis was validated, and the time period and location of the data collection, although in the later UK study [29], no temporal trends in either incidence or risk factors were found.

More importantly, AFE was the first, second, and third leading cause of maternal death in Australia, the USA, UK, and China, as well as in France and Poland, respectively [24]. In the Canadian studies, case-fatality rate was 13% fatality in singleton deliveries [26] and 27% overall (33/120) in the later study, with the mortality rate of 0.8/100,000 [27]. In the UK studies, the earlier [27] reported 20% case-fatality rate, the later [28] reported 19% case-fatality rate, with 7% of the surviving women having permanent neurological injury [28]. Perinatal mortality was 135/1000 total births [27]. In the Australian study, case-fatality rate was 35% and mortality rate was 1.2/100,000 [30]. In developed countries overall, a 2009 report [24] provided case-fatality rates of 13.3% for Canada, 21.6% for the USA, 24.0% for the UK, and 44.0% for Sweden, whereas a 2012 review reported case-fatality rate being highest at 43% in Victoria, Australia, and lowest at 11% in the Netherlands, while the national figures for the UK, USA, Canada, and Australia were 19%, 18%, 13%, and 14%, respectively [25]. A report from Japan in 2014 gave fatality rate of 24.3% [31]. Indeed, the case-fatality rate dropped from 85% to 61% in 1995 in the USA and from 37% in 1997–2004 to 20% in 2005–2009 in the UK, as well as 35% and 13% for Australia in 2001–2007 and Canada in 1991–2002, respectively [32]. Although by no means conclusive, these figures suggested progressively declining mortality from AFE. Furthermore, underreporting of nonfatal cases was suspected [24] so that the actual case-fatality rate was probably lower than the maternal mortality ratio of 0.5–1.7 per 100,000 live births [24]. Therefore, the true incidence of AFE was likely underestimated with the majority of affected parturients surviving without sequelae.

Pathophysiological mechanisms, clinical features, and risk factors

One or more breaches in the physical barriers between the maternal and foetal compartments at the endocervical veins, uterine trauma sites, and the placental attachment site allow entry of amniotic fluid and its contents into the maternal circulation in the presence of a pressure gradient [24,33]. Depending on the total volume passed and nature and amount of its contents (foetal squames, meconium, lanugo, vernix, mucoin, protease, and tissue factor), reactions consequent to activation of platelets, white cells, complements, and coagulation, production and release of bradykinin and inflammatory cytokines from mast cells, and abnormal activation of the proinflammatory mediator systems similar to the systemic inflammatory response syndrome (SIRS) can occur leading to effects from physical obstruction to vasospasm in the maternal pulmonary microvasculature [31,32,34].

The development of AFE has been described (or regarded) as biphasic, but the author's view is that AFE probably develops (or evolves) in four stages which may be distinct and evolve gradually over hours or are compressed into a rapid sequence or merged in a catastrophic manifestation. In the majority of cases, the first stage starts during labour when the intermittent transfer of small amounts of amniotic fluid occurs through minor disruptions in the foetal-maternal interface, thus explaining the prodromal symptoms (aura) and the foetal distress presenting before overt maternal manifestation in 47% [28] and 32% [32], respectively. Prodromal symptoms include breathlessness, chest pain, feeling

cold, nausea, vomiting, numbness/tingling, lightheadedness, restlessness, agitation, distress, panic, and change in mental state, which can appear as early as 4 h before frank AFE [24,32,34]. Unfortunately, these symptoms were usually overlooked, only recognized in retrospect.

The second stage is when materials from amniotic fluid arrive in bulk at the pulmonary vasculature, causing increasing pulmonary vasoconstriction, pulmonary hypertension, acute right ventricular (RV) failure, even RV infarction resulting in haemodynamic collapse and/or interventricular septum displacement to the left thus decreasing left-sided cardiac output. The third stage then follows with LV failure secondary to impaired LV filling, ischaemic injury to the myocardium, myocardial depressant effect (from amniotic fluid), and hypoxaemia from severe ventilation-perfusion mismatching in the lungs [24,34]. The hypoxaemia, systemic hypotension, and persistent tachycardia together reduce further coronary perfusion and myocardial oxygenation, aggravating LV failure and causing cardiogenic pulmonary oedema and further increasing the severity of hypoxaemia. The foetus becomes more hypoxaemia, eventually ending in foetal demise. Meanwhile, intravascular coagulation is activated by amniotic fluid contents and SIRS, resulting in DIC with consumption of clotting factors, fibrinogen, and platelets, thus predisposing to subsequent PPH, further haemodynamic instability, metabolic acidosis, and eventual multiorgan dysfunction and failure. Unless the condition is corrected or reversed before this point, the mother would most likely succumb.

The speed of progression and the range and severity of manifestations of AFE are probably related to the site(s) and number and size(s) of the opened maternal veins exposed to amniotic fluid, and the amount and nature of residual amniotic fluid transferred from the fetal compartment into the maternal uterine venous circulation following delivery, which in turn are influenced by the type of labour and route and mode of delivery. The permutations of these factors create the myriad of manifestations which vary from relatively mild and slowly progressing dyspnoea, oxygen desaturation on pulse oximetry, cough, and hypotension to sudden catastrophic collapse and irreversible shock, convulsive seizures, and cardiac arrest. This can explain why the majority of cases occurred during labour or within 8 min of delivery, that hypotension and foetal distress were almost universal, and 93% were had respiratory failure (pulmonary oedema or ARDS), 87% suffered cardiopulmonary arrest, and coagulopathy was present in 83% [10], and why the majority of the survivors of the initial insult developed non-cardiogenic pulmonary oedema [2]. Thus, AFE hardly ever presents during the uneventful pregnancy until events such as labour or interventions such as medical induction or CD creates the opportunity for disruption of the foetal-maternal interface to occur and allows the transfer of amniotic fluid down the pressure gradient, thus relating the presentation to events such as labour and delivery [35,36], and second-trimester pregnancy termination [37]. In timing, 70%, 11%, and 19% presented during labour, after vaginal delivery, and during CD, respectively [38], while a later review reported 56% being diagnosed before delivery [32].

This sequence could account for the consistency of some but not all risk factors in the literature, due to commonality in some of the mechanisms (e.g., CD) and differences in other factors related to obstetric practice (e.g., labour induction), which influences the population-attributable risk. For example, 35% for labour induction suggested that assuming causality, cases would be reduced by 35% without induction, and the 8-fold increased odds of CD for postnatal presentation suggested that avoiding CD would also reduce the risk [32]. As well, the outcome could influence the association between a particular risk factor and AFE, such as the adjusted odds ratio (aOR) for medical induction was 1.8 overall but 3.5 for the fatal cases [26]. Some factors could be associated with a significantly reduced risk, such as age <20 years (aOR 0.2–0.4) [25] and non-cephalic presentation (aOR 0.5) [27], but the latter was also shown to be associated with increased risk (aOR 6.8) [25]. Confounding conditions, such as presentation as cardiac arrest, Black or other ethnic minorities, shorter interval between AFE event and hysterectomy, and lower likelihood of receiving cryoprecipitate, have been associated with maternal death/neurological injury [29]. It is likely that some risk factors are merely surrogates for common essential factors which are related to the mechanisms of AFE (Table 2).

Diagnosis and investigations

Diagnosis of AFE is clinical and often by exclusion. There is consensus regarding the manifestations not being explained by condition or disease which may be present or known, and maternal

Table 2
Clinical features, risk factors, and outcome of amniotic fluid embolism.

Clinical features	% in series/report	RR/aOR
Cardiac arrest	30–87%, 40%[‡]	–
Shock/severe hypotension	32.5%, 63%[‡]	–
Respiratory distress, SOB[‡]	14.2%–72%, 62%[‡]	–
Coma/seizure	1.7%/15%[‡], 10–48%	–
Disseminated intravascular coagulation, haemorrhage	22–83%, 62%–65%[‡]	–
Foetal distress/compromise	43%[‡], 50–100%	–
Risk factors - Age ≥35 years	5.7%, 38%#	2.3, 2.15#, 1.9[†], 4.8[⁋]
African/other American (versus White American)	–	2.4/2.3[Ψ]
Polyhydramnios	19.0%	3.8, 3.0[†]
Blunt abdominal trauma and surgical trauma	–	–
Procedures—pregnancy termination, amniocentesis, etc.	–	–
Pre-eclampsia/eclampsia (pre-existing hypertension)	7.0%/75.5%	1.7/16.3, 1.4/11.5[†], 7.3/29.1[Ψ], (9.5) [Ψ]
Induction of labour (all methods)	41%#, 47%[‡]	2.53#, 3.86[‡], 3.5/5.6[Ψ]
Medical induction of labour	4.9%	1.9, 1.8[†],1.9/3.4[⁋1]
Placenta praevia/abruption	21.6%, 3%#	5.0, 5.75#, 3.5[†], 10.5/13.3[⁋2],15.6/17.3 [Ψ], 30.4/8.0 [Ψ]
Foetal distress	6.5%	1.5, 1.7[†]
Instrumental delivery	4.8%	7.6, 5.9/2.9[†2], 40.6[⁋3], 1.9/2.9/4.3/5.9/8.9/11.6/36.0 [Ψ]
Vaginal breech delivery	–	15.1 [Ψ]
Caesarean delivery	7.4%	11.7, 12.5/8.6[†1], 23.3[Ψ], 8.1/48.5[⁋4], 8.84[‡]
Cervical laceration/uterine rupture	56.2%	12.7, 3.8[†]
Manual removal of placenta	25%	19.4[⁋]
Multifoetal pregnancy	9.3%, 12%#, 8%[‡]	2.5, 5.3 [Ψ], 7.75#, 10.9[‡]
Gestational age <37 weeks	–	9.7 [Ψ]
Postdated pregnancy	5.1%	1.8
Foetal macrosomia (≥4500 g)	4%#	–

Compiled from Refs. [24–30]. Source of figures as indicated [Ψ] [25], [†] [26] ([†1]cephalic/non-cephalic, [†2]forceps/vacuum), [‡] [28], # [29], [⁋] [30] ([⁋1]medical induction (ns)/vaginal PGE_2 induction, [⁋2]placenta praevia/abruption, [⁋3]instyrumental/breech, [⁋4]caesareran section before (ns)/after labour), unmarked from Refs. [24,27].

haemorrhage as the first presenting feature without evidence of early coagulopathy or cardiorespiratory compromise (Table 3) [29,34,38–40]. Differential diagnoses include myocardial infarction, pulmonary embolism, air embolism, anaesthetic complications (related to regional anaesthesia), anaphylaxis, eclampsia, and sepsis, which on scrutiny would not satisfy the recommended diagnostic criteria [34]. Indeed, a stricter review with the inclusion of features of cardiac arrest, shock/severe hypotension, respiratory distress, mechanical ventilation, coma, seizure, or coagulation disorder could actually exclude 60% of 292 cases labelled as AFE in a national database [27]. Another point is that clinical presentation within a specified time frame, such as within 30 min of delivery, is a widely recognized character [24]. Although foetal debris can be detected in the capillaries of multiple organs [24], and postmortem finding of foetal squames/hair in the pulmonary arterial circulation is regarded as diagnostic [29], this was not invariably found in all cases of AFE [24,32], whereas this was also identified in 21–100% of pregnant women without AFE so that this is not pathognomonic [24].

Echocardiography performed during pulmonary vasospasm would reveal severe pulmonary hypertension, dilated hypokinetic right ventricle, tricuspid regurgitation, and leftward deviation of the

Table 3
Diagnosis of and investigations in amniotic fluid embolism.

Diagnostic criteria
Recommended in the USA and the UK [38–40]
1. Acute hypotension or cardiac arrest
2. Acute hypoxia
3. Coagulopathy or severe clinical haemorrhage in the absence of other explanations
4. All of these occurr during labour, caesarean delivery, or dilation and evacuation, or within 30 min postpartum with no explanation for the findings
UKOSS and Australian criteria [32]
Acute maternal collapse with acute foetal compromise, cardiac arrest/rhythm problems, coagulopathy, hypotension, haemorrhage, premonitory symptoms, seizures, shortness of breath (excluding haemorrhage as presenting features without evidence of coagulopathy or cardiorespiratory compromise); or Finding of foetal squames or hair in the lungs at autopsy
Diagnostic criteria in Japan [31]
Symptoms during pregnancy or within 12 h of delivery, medical treatment required for cardiac arrest, bleeding ≥1500 mL of unknown origin within 2 h of delivery, DIC, respiratory failure, and symptoms not explained by other diseases
Investigations [24,31,32,34]
Echocardiogaphy (transthoracic or transoesophageal) - assess right and left ventricular function and cardiac disorders to guide fluid resuscitation
Electrocardiography - display tachycardia, right ventricular strain pattern, and ST and T wave abnormalities, arrhythmia, asystole, pulseless electrical activity, and myocardial infarction
Chest X-ray - detect pulmonary oedema and exclude other disorders
Maternal blood tests - complete blood count and coagulation profile, renal and liver function, blood electrolytes, arterial pH and blood gas, glucose, and cardiac enzymes
Zinc-coproporphyrin-1 (Zn-CP1) (<1.6 pmol/L) - from meconium, detection suggests amniotic fluid embolism, need to shield blood sample from light to prevent degeneration
Sialyl-Tn (STN) (<46 IU/mL) - from mucin in meconium, detection suggest the diagnosis
Complement 3 (80–140 mg/dL) and 4 (11–34 mg/dL) - decreased levels from inflammation or allergy and in amniotic fluid embolism
Interleikin-8 (<20 pg/mL) - level increased by DIC, SIRS, or ARDS
C1 esterase inhibitor (C1INH) - inhibitor of C1 esterase, Factor XIIa and kallikrein, and is decreased in AFE

Abbreviations: UKOSS = United Kingdom Obstetric Surveillance System, DIC = disseminated intravascular coagulation, SIRS = systemic inflammatory response syndrome, ARDS = acute respiratory distress syndrome.

interatrial and interventricular septum and can be diagnostic. Blood tests such as arterial blood gas, renal and liver function, and complete blood count and coagulation profile are essential for maternal assessment and management, but there are as yet no specific diagnostic tests (Table 3) [24,31,34,35].

Monitoring and management and treatment

Maternal intact survival following AFE is attributed to timely recognition, appropriate management, and aggressive resuscitation and treatment in an intensive care setting [34–37]. The mother should be managed as for ARDS [3–6,34]. The principle of management is supportive, including timely initiation of treatment for shock, airway management, vascular management, fluid replacement, and correction of coagulopathy, all of which are dependent on adequate and appropriate assessment and monitoring. The goals are the rapid correction of haemodynamic instability and hypoxia, preventing additional hypoxia and end-organ failure, and judicious fluid therapy to avoid increasing the risk of a right-sided myocardial infarction and distention of the RV leading to LV obliteration and compromising cardiac output [34], while refractory hypotension is corrected by vasopressors (norepinephrine) and inotropes, and selective pulmonary vasodilators for treatment of severe pulmonary hypertension [24]. When LV failure and cardiogenic pulmonary oedema become prominent, non-invasive mechanical ventilation or endotracheal intubation should be considered and left-sided heart failure be treated by optimizing cardiac preload, the use of vasopressors to maintain blood pressure and coronary perfusion pressure, and inotropes to increase LV contractility [34]. Invasive arterial pressure monitoring, central venous, and pulmonary artery catheters may be required in providing continuous cardiac (including blood

Table 4
Monitoring and treatment of amniotic fluid embolism.

Monitoring	Remarks
Foetal well-being (cardiotocography)	During antepartum AFE, for evidence of foetal distress and decision of when to deliver in a viable pregnancy
Pulse oximetry	Instant information on pulse rate and oxygen saturation to guide treatment, goal to maintain reading at 94–98%
Blood pressure	Allow detection and guide treatment of hypotension, to maintain mean arterial pressure around 65 mmHg
Blood count and coagulation test, fibrinogen level	Maintaining platelet count >50,000/mm^3, normal INR and aPTT, fibrinogen ≥2.0 g/L
Blood glucose	Maintain at 7.8–10.0 mmol/L (140–180 mg/dL)
Arterial pH and blood gases	To look out for hypoxia, acidosis, and hypercapnia
Temperature	Maintain at 32–36 °C, especially after cardiac arrest
Treatment	
Norepinephrine	Maintain blood pressure and coronary perfusion pressure
Inotropes (dobutamine, milrinone)	Treatment of heart failure, improve ventricular contractility, maintain pulmonary vasodilation
NO, prostacyclin, sildenafil	Reduce pulmonary afterload
Fluid resuscitation, diuretics	Avoid overload, remove excessive fluid
Transfusion of blood products	Replenish lost blood, correct coagulopathy, giving packed red blood cells, fresh frozen plasma, and platelets at the ratio of 1:1:1
Cardiac defibrillation	In case of asystole, ventricular fibrillation, etc.
Mechanical ventilation	Non-invasive or endotracheal intubation for pulmonary oedema
ECMO	Successful cases reported but risk of bleeding due to need for anticoagulation during ECMO
Prevention and treatment of postpartum haemorrhage	Oxytocic agents, repair lacerations, uterine tamponade and brace sutures, hysterectomy as last resort

Abbreviations: ECMO = extracorporeal membrane oxygenation, INR = international normalized ratio, aPTT = activated partial thromboplastin time, NO = nitric oxide.

pressure) and respiratory (including pulse oximetry or with an end-tidal CO_2 monitor) monitoring, and the occasional need for pulmonary artery catheter to guide haemodynamic management and monitoring of blood gases [24]. The aim is to maintain mean arterial pressure around 65 mmHg, low-normal temperature (≤36 °C), pulse oximetry at 94–98% (to minimize ischaemia-reperfusion injury to the brain), blood glucose at 7.8–10.0 mmol/L with glucose or insulin infusion if necessary, and normal haemoglobin and coagulation function [34]. Transfusion of FFP at 15 mL/kg body weight to correct coagulopathy, and replacement with fibrinogen concentrates or cryoprecipitate may be necessary if severe hypofibrinogenaemia (<1 g/L) persists after FFP transfusion as fibrinogen level correlates with the severity of bleeding [41]. The use of recombinant activated factor VII in DIC could lead to excessive thrombosis and multiorgan failure and therefore only as a last resort, while antifibrinolytic agents such as tranexamic acid may help in case of excessive fibrinolysis [34]. ECMO has been used successfully with complete recovery [36,42]. Not to be overlooked are foetal monitoring before delivery and prevention and treatment of PPH afterwards [Table 4].

Other and subsequent management

Antibiotic treatment may be required for both prophylaxis and treatment of suspected sepsis. Nutritional support facilitates recovery, especially if anaemia has developed. Psychological support is recommended especially if there is perinatal mortality or poor outcome, or hysterectomy, and/or other

end-organ damage requiring treatment (e.g., haemodialysis) to avoid postpartum depression. Long-term follow-up may be necessary, although the recurrence of AFE has not been reported.

Conclusion

Although ARDS in pregnant women is rare, there is significant maternal morbidity and mortality. Many of the aetiological conditions and risk factors can be identified during antenatal and intrapartum management, and the awareness of which would allow timely diagnosis and appropriate management under a multidisciplinary team in an ICU setting thus optimizing maternal and perinatal outcome.

Summary

Respiratory failure occurs rarely in pregnant and postpartum women, but this is a serious condition, a leading cause of maternal admission to intensive care, and as a group a leading cause of maternal and perinatal mortality. It may be related to an underlying chronic medical condition like congenital heart disease. However, it is more often related to ARDS, which is related to or consequent of obstetric complications like pre-eclampsia and eclampsia, antenatal treatment like tocolysis, incidental to pregnancy like sepsis and transfusion-related acute lung injury, and accidental like AFE. In some instances, the development of ARDS is related to the obstetric management in specific situations where much room for improvement could be found. The awareness of the possibility of ARDS and prompt recognition of maternal respiratory distress and related manifestations, including foetal distress, are the vital initial steps in preventing maternal and perinatal mortality. Treatment is not necessarily related to the specific diagnosis as it is essentially supportive, including cardiopulmonary resuscitation, maintenance of the airway, oxygenation, circulation and end-organ perfusion, and correction of other related and sequential or consequential conditions, such as coagulopathy. If ARDS presents before delivery, it is important to monitor foetal well-being and decide the optimal timing and mode of delivery of the foetus to optimize perinatal survival, and delivery could also contribute to successful maternal resuscitation. A multidisciplinary team approach with management in an intensive care setting is critical in ensuring successful management and minimizing maternal mortality and other related sequelae.

Declaration of competing interest

The author has no conflict of interest to declare.

Practice points

- Acute respiratory distress syndrome is uncommon in obstetric patients but is associated with a significant risk of maternal morbidity and mortality.
- Intravenous fluid administration should be tightly monitored in many obstetric complications to avoid fluid overload and iatrogenic pulmonary oedema.
- In obstetric patients receiving a transfusion of blood products in the management of obstetric complications, transfusion-related acute lung injury must be included in the differential diagnosis if respiratory distress develops.
- Risk factors for amniotic fluid embolism may emerge only in the course of labour and its management so that vigilance is vital in early recognition and treatment.
- The diagnosis of amniotic fluid embolism is clinical, and a multidisciplinary team working in an intensive care setting is critical in maternal survival.

Research agenda

- The limited information on pulmonary effects of obstetric complications and their management, especially for pre-eclampsia, calls for prospective and systematic studies in this area.
- The risk factors and predisposing conditions of amniotic fluid embolism should be captured in a consensus global database and analysed in depth to segregate the surrogate from the genuine risk factors which are linked to the pathophysiological mechanisms.
- Prospective studies on blood tests which could identify amniotic fluid components rapidly and help to predict the high-risk cases for amniotic fluid embolism should be designed and organized.

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