Interpretation of Chinese expert consensus on diagnosis and management of amniotic fluid embolism

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Amniotic fluid embolism (AFE) is a rare but potentially lethal condition characterized by an abrupt onset, unpredictability, and high fatality rate. The Society for Maternal-Fetal Medicine (SMFM) published clinical guideline No. 9 “Amniotic fluid embolism: diagnosis and management” in 2016.[3] Based on this guideline and other relevant studies, the Obstetrics Group of the Chinese Society of Obstetrics and Gynecology, Chinese Medical Association, developed a consensus on the diagnosis and treatment of AFE in December 2018, aiming to standardize its diagnosis and management, and to improve maternal and perinatal outcomes.[3]

The design of the Chinese consensus was based on a systematic literature review performed using several databases. The search was restricted to English- and Chinese-language articles published from 1983 through to January 2017. Priority was given to original research articles. Review articles, commentaries, evidence reports, and published guidelines were also reviewed. This article aims to document the Chinese consensus and review the SMFM guideline No. 9 and relevant recent articles.

Epidemiology and Pathophysiology of AFE

In a population-based study of 3 million births in the United States, the incidence of AFE was 7.7 per 100,000 births.[3] According to an epidemiological study of 111,767 obstetrical cases randomly selected from 19 tertiary and 20 secondary hospitals in 14 provinces of China in 2011, the incidence of AFE was six per 10,000 births.[4] This higher incidence of AFE in China is partly because different diagnosis criteria were used in different regions, and the study was conducted among tertiary and secondary hospitals where patients are more likely to have high-risk factors. Overall, the maternal mortality rate of AFE is 19% to 86%,[3,5-7] 70% of cases of AFE occur during labor, 11% after vaginal delivery, and 19% during a cesarean delivery.[8] AFE usually occurs during or immediately after delivery, mostly between 2 h before the delivery of the fetus and 30 min after the delivery of the placenta.[1,5] In rare instances based on case reports, AFE can occur following induced abortion, transabdominal amniocentesis, blunt abdominal trauma, surgical trauma, or removal of a cervical suture.[9-14]

The pathogenesis of AFE is still unclear. It is generally believed that when the maternal-fetal barrier is damaged, amniotic fluid components enter the maternal circulation. They not only cause mechanical obstruction, but also react with the maternal immune system and activate inflammatory mediators, which can lead to a cascade of immune reactions and systemic inflammation.[5,15,16] In this process, activation of the immune complement system can play an important role.[17] These processes lead to acute respiratory failure, pulmonary edema, and acute right ventricular failure. Hemodynamic collapse from right ventricular infarction and/or displacement of the interventricular septum to the left cause a decrease in left-sided cardiac output and late onset left ventricular failure.[1]

Diagnosis

AFE is a clinical diagnosis that cannot be made based solely on laboratory tests,[1,8] Based on a retrospective review and analysis of medical records of the United States national AFE registry,[8] the recommended diagnostic criteria are as follows.

1. To diagnose AFE, the following five criteria should all be met.
(1) Acute hypotension or cardiac arrest.
(2) Acute hypoxemia: dyspnea, purpura, or respiratory arrest.
(3) Coagulopathy: laboratory evidence of consumption coagulopathy factors or fibrinolysis, or clinical manifestations of severe bleeding, but with no reasons to explain.
(4) The symptoms occur during labor, cesarean section, curettage or shortly after delivery (mostly within 30 min after delivery of the placenta).
(5) The findings cannot be explained by other diseases.

2. Under these conditions, AFE should be suspected, including acute maternal respiratory and circulatory

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failure with one or more of the following conditions that cannot be explained by other reasons such as hypotension, shortness of breath, convulsions, acute fetal distress, cardiac arrest, coagulopathy, maternal hemorrhage, and prodromal symptoms (irritability or tingling). Doctors should be alert and act as soon as possible. These features do not include postpartum hemorrhage without coagulopathy or cardiac failure from other causes.\textsuperscript{[6]} 

**Clinical Manifestations and Management Protocols**

The typical presentation of AFE includes a triad of sudden hypoxia and hypotension, followed in many cases by coagulopathy, mainly occurring during labor or after delivery.

**Prodromal symptoms**

30% to 40% patients with AFE have non-specific prodromal symptoms, mainly manifested as dyspnea, cough, chest pain, nausea, vomiting, anxiety, agitation, irritability, and changes in mental status.\textsuperscript{[15,18]} In cases occurring before delivery, electronic fetal monitoring has demonstrated decelerations and loss of variability. Severe fetal bradycardia can be the first manifestation of AFE.\textsuperscript{[7,13]} Urgent attention should be paid to these prodromal symptoms. A multidisciplinary team including the fields of anesthesia, respiratory therapy, critical care, and maternal-fetal medicine should be involved in the ongoing care of women with AFE.

**Respiratory and circulatory failure**

Patients may experience sudden dyspnea and/or lip cyanosis, decreased oxygen saturation, early onset crackles at the lung base, tachycardia, hypotensive shock, convulsions, and loss of consciousness or coma. In severe cases, ventricular fibrillation, pulseless ventricular tachycardia, and cardiac arrest might occur, leading to death within a few minutes.\textsuperscript{[8]} Hypoxia, acidosis, and hypercapnia should be avoided because they increase pulmonary vascular resistance and lead to further heart failure.\textsuperscript{[13]}

**Management protocols**

(1) Respiratory supportive management: keep the airway open, supply adequate oxygenation and effective ventilation as soon as possible.

(2) Circulatory supportive management:

(a) The provision of immediate high-quality cardiopulmonary resuscitation with standard basic cardiac life support and advanced cardiac life support protocols in patients who develop cardiac arrest associated with AFE is recommended.\textsuperscript{[1]} The most critical immediate action is to start chest compressions before breathing resuscitation is administered. Patients who have not yet given birth should be tilted to the left lateral decubitus position or, preferably, have the gravid uterus displaced laterally by an assistant to prevent aortocaval compression.\textsuperscript{[19]}

(b) Fluid resuscitation: excess fluid administration should be avoided, or it will exacerbate right heart failure and pulmonary edema.\textsuperscript{[20]}

(c) The use of vaspressors and inotropic agents: right ventricular output can be improved by using inotropes such as dobutamine (2.5–5.0 μg/kg per min by intravenous pump)\textsuperscript{[21]} and milrinone (0.25–0.75 μg/kg per min by intravenous pump).\textsuperscript{[1,22]} These agents will also lead to pulmonary vasodilation, making them the first choice for treating AFE. Other specific interventions aimed at decreasing pulmonary vascular resistance include sildenafil (20 mg t.i.d., orally, or through nasogastric/orogastric tube), inhaled or intravenous prostacyclin (epoprostenol: 10–50 ng/kg per min, inhaled; iloprost 10–20 μg inhaled, 6–9 times per day), and inhaled nitric oxide (5–40 part per million).\textsuperscript{[1,23]} Hypotension in this phase should be mainly treated with vasopressors such as norepinephrine (0.05–3.30 μg/kg per min by intravenous pump) or vasopressin. Different from theSFMF guideline, the Chinese consensus stated that papaverine can also be used as an alternative pulmonary vasodilator, especially in low-resource regions.

(d) The use of glucocorticoids is still under debate.\textsuperscript{[1]} The Chinese consensus has recommended that the early use of large doses of glucocorticoids might be an effective attempt based on experience in clinical practice.\textsuperscript{[6,16]}

(e) New circulation support strategy: for patients with AFE with intractable shock, irreversible to vascular active drugs, extracorporeal membrane oxygenation,\textsuperscript{[24]} intra-aortic balloon counter-pulsation,\textsuperscript{[25]} and other strategies have been reported to be effective in many cases.

(f) If the patient has still not delivered a neonate at the time of cardiac arrest, expeditious delivery is indicated if the fetus has reached an age of potential viability (more than 23 weeks). An operative vaginal delivery (forceps or vacuum-assisted) should be performed in patients while in labor for whom obstetrical conditions support such an intervention. If vaginal delivery is not an option, emergency cesarean delivery is generally indicated. Classically, the indication for a cesarean delivery has been a failure to obtain spontaneous circulation after 4 min of cardiopulmonary resuscitation to reduce the profound fetal hypoxia occurring during maternal cardiac arrest.\textsuperscript{[1,19]}

**Coagulation dysfunction**

Disseminated intravascular coagulation (DIC) is present in up to 83% of cases.\textsuperscript{[1,8]} DIC can be the first manifestation of AFE. It presents as non-coagulating severe postpartum hemorrhage after delivery with no reasons.

Management protocols including the early assessment of clotting status are recommended. Postpartum hemorrhage and DIC caused by AFE tend to be very severe and should be treated actively by early transfusion of blood products according to standard massive transfusion protocols and clotting factors (eg, fresh frozen plasma, cryoprecipitate, fibrinogen, or platelets). Simultaneous anti-fibrinolytic treatment, such as tranexamic acid is recommended. There is clinical controversy on the use of heparin in the treatment of DIC caused by AFE. Heparin treatment is not recommended, unless there is evidence for early hypercoagulability.\textsuperscript{[1,5,6,15]}
Obstetric management

Uterine atony is common with AFE and should be managed aggressively with uterotonics such as oxytocin, ergometrine, and prostaglandins. Ischemia and poor perfusion of the uterus can play an important role in uterine atony, so it is essential to maintain a stable circulation and restore the blood supply to the uterus.

Cases of refractory postpartum hemorrhage might require uterine tamponade, bilateral uterine artery ligation, or B-Lynch suturing. Hysterectomy is not necessary for the treatment of AFE and should not be implemented prophylactically. However, if postpartum hemorrhage is difficult to control and endangers the patient’s life, rapid removal of the uterus is necessary.

Multiple organ dysfunction

Acute renal failure, acute respiratory distress syndrome, hypoxic-ischemic brain damage, and severe sepsis often occur after a successful first resuscitation of a patient with AFE. It is essential to maintain maternal vital signs and internal environment stability, and to protect the central nervous system and perform hypothermic treatment when needed.

Summary

The diagnosis of AFE is one of exclusion, based on clinical manifestations. Rapid initiation of treatment aided by early diagnosis is important. Maternal mortality caused by AFE has declined significantly recently, mainly thanks to the comprehensive management of this syndrome. Timely and effective multidisciplinary cooperation is essential for successful maternal rescue and improving the prognosis. Treatment of AFE is mainly supportive and involves the delivery of the fetus when indicated, respiratory support, and hemodynamic support with the judicious use of fluids, vasopressors, cardiotonics, and pulmonary vasodilators.

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Conflicts of interest

None.

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