Commentary

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Amniotic Fluid Embolism (AFE) in China: Are maternal mortality and morbidity preventable?

Xiuting Mo[1,*], Aihua Feng[1,2,*], Xiaoyan Liu[1,3], Ruoyan Gai Tobe[1,]**

[1] *School of Public Health, Shandong University, Ji'nan, China;*
[2] *Obstetric Division, The Fourth People's Hospital of Jinan, Ji'nan, China;*
[3] *Qilu Hospital of Shandong University, Ji'nan, China.*

Summary **A case of hospital-patient conflict has occurred in China that has lifted billows in the public and highlighted the lethality of amniotic fluid embolism (AFE). AFE is a rare but severe obstetric complication with high maternal mortality and morbidity. Globally, the incidence of AFE is estimated to be approximately 2 to 6 per 100,000 deliveries. The maternal mortality rate (MMR) attributable to AFE ranges between 0.5 to 1.7 deaths per 100,000 deliveries in the developed world and 1.9 to 5.9 deaths per 100,000 deliveries in the developing world. In developed countries, AFE often accounts for a leading cause of maternal mortality; whereas the proportion of maternal death caused by AFE tends to be not as dominant compared to common perinatal complications in developing countries. With the mechanism remaining to be elucidated, AFE can neither be predicted nor prevented even in developed countries. Treatment requires a set of highly intensive advanced emergency obstetric care, challenging obstetric care in developing countries. Although this complication is currently far from preventable, China has potential to improve the prognosis of AFE by strengthening the emergency obstetric care system.**

Keywords: Amniotic Fluid Embolism (AFE), maternal mortality, obstetric complication, China

In August of this year in China, a case of hospital-patient conflict occurred in Xiangtan County Maternal and Child Hospital which highlighted lethality of amniotic fluid embolism (AFE), a rare but severe obstetric complication, characterized by sudden cardiovascular collapse, altered mental status, and disseminated intravascular coagulation (*1*). When an expectant mother died from AFE during her delivery, her family was enraged and the mass media sensationally directed its spearhead against the hospital, underlying which is the unprecedentedly intensified contradiction between hospital and patients in China. For most non-professional people, it was probably the first time to hear the new word "amniotic fluid embolism". They never knew that high maternal mortality and morbidity from such a fatal condition is far from preventable. Even for a large number of medical professionals, the relevantly rare incidence of less than 10 per 100,000 deliveries makes AFE only appear as a term in their textbooks but not a real experience in their clinical practices. Such a fatal case has lifted awareness in the public.

Globally, the incidence of AFE is estimated to be approximately 2 to 6 per 100,000 deliveries (*1-4*). The maternal mortality rate (MMR) attributable to AFE ranges between 0.5 to 1.7 deaths per 100,000 deliveries in the developed world and 1.9 to 5.9 deaths per 100,000 deliveries in the developing world. Based on the reported data, risk factors associated with an increased risk of AFE include advanced maternal age (older than 35 years), placental abnormalities, cesarean/instrumental vaginal delivery, placenta previa, eclampsia, polyhydramnios, cervical lacerations and uterine rupture (*1-7*). The estimation is based on large-scale epidemiological data in North American and European developed countries and the figure varies according to different studies. In most developed countries, AFE often accounts for a leading cause of

*These authors contributed equally to this works.
***Address correspondence to:*
Dr. Ruoyan Gai Tobe, School of Public Health, Shandong University, No.44 Wen-hua-xi Road, Jinan 250012, China.
E-mail: ruoyangtobe@sdu.edu.cn

maternal mortality: for example, in Japan, where MMR is the lowest in the world, it is the highest cause of maternal death and accounts for as much as 24.3% of all fatal cases (*8*). In contrast, the pattern of causes of maternal mortality varies by regions in the world and the proportion of maternal death caused by AFE tends to be not dominant compared to common perinatal complications such as hemorrhage, hypertensive disorders and sepsis in most developing countries (*9,10*). The priority of reduction of MMR to achieve the Millennium Development Goals in the developing world remains in measures tackling common perinatal complications contributing to maternal mortality and morbidity, which are preventable and avoidable by effective facility-based and population-based interventions with good cost-effectiveness.

Compared to common perinatal complications worldwide, AFE can neither be predicted nor prevented as cases occur sporadically with a broad spectrum of clinical manifestations that vary widely (*11*). The pathological mechanism of onset of AFE remains unclear. Globally, without reliance on laboratory markers, the current diagnosis is based on one or more of four key typical symptoms: cardiovascular collapse, respiratory distress, coagulopathy, and/or coma/seizures. The accurate laboratory test is only operated at forensic autopsy (after death of the mother) to detect fetal materials in the maternal pulmonary circulation. The definition of AFE isn't clarified. Current ongoing clinical research on the pathological mechanism has shifted from embolism toward a maternal immune response to the fetus, amniotic fluid-dependent anaphylactic reaction and complement activation, with the hypothesis raising from pregnant women's immune tolerance on the presence of foreign antigen within both their uterus and their circulation; whereas no related theory based on robust evidence has been widely accepted nor have amniotic fluid-specific markers been developed, so far (*12,13*). With the mechanism remaining to be elucidated, it is difficult to identify effective practices and actions. No study has proved the effectiveness of typical interventions such as an antenatal care package and high-risk pregnancy management on reduction of mortality and morbidity caused by AFE, though they are effective to reduce MMR. Therefore, even in developed countries, AFE remains a difficult clinical problem and a higher level of evidence rather than case reports or case series is necessary. An inclusive hospital record database worldwide with uniform diagnostic criteria should be created for addressing numerous unanswered questions (*1*).

Based on suggestions of case series, survival of AFE cases crucially relies on early identification and quick clinical operation response (*14*). The management of AFE is supportive and directed towards maintenance of oxygenation, cardiac output and blood pressure, and correction of the coagulopathy, and the initial goal of the treatment is the rapid correction of maternal hemodynamic instability (*1*). For a good prognosis outcome, treatment needs to ideally take place in an intensive care unit (ICU) by a multidisciplinary team, and the necessary rescue healthcare includes a series of technique-intensive therapeutic measures, such as cardiopulmonary resuscitation, uterine evacuation, continuous cardiac telemetry/respiratory/blood pressure monitoring, pulmonary artery catheter, transesophageal echocardiography, administration of oxygen, fluid therapy, recombinant activated factor VIIa, transfusion, *etc* (Table 1). Such highly intensive advanced emergency obstetric care remains a tremendous challenge in developing countries and the situation can be explained

Table 1. Major treatment of AFE in ICU

Measures of treatment	Purposes
Cardiac telemetry monitoring, Respiratory monitoring, Blood pressure monitoring, Pulmonary artery catheter Transesophageal echocardiography	*Evaluation of cardiac and respiratory function*
Cardiopulmonary resuscitation Uterine evacuation when resuscitation failed Cardiopulmonary bypass	*Maintenance of cardiac and respiratory function*
Oxygen administration Optimization of preload Fluid therapy Vasopressors	*Correction of hemodynamic instability*
Transfusion of blood products Recombinant activated factor VIIa Intravenous oxytocin Serine proteinase inhibitor FOY Hysterectomy Heparin therapy	*Correction of coagulopathy and disseminate intravascular coagulation (DIC)*

by a much higher MMR due to AFE there compared to the figure in developed countries.

Although this complication is currently far from preventable, China has the potential to improve the prognosis of AFE by strengthening the emergency obstetric care system. As China has been characterized by a huge geographical diversity in health resources and health outcomes, AFE occurring in diversified regions probably has different treatment outcomes and opportunities to survive. With advancement of maternal healthcare, maternal mortality caused by AFE has largely declined (*15-17*). Most successful survival cases of AFE have been reported in top-level tertiary comprehensive hospitals of large capital cities, which represent the highest level of medical technology and treatment outcomes of the country. For the latest reported case successfully rescued in Shanghai, it's reported that more than 10,000 cc packed blood products were assembled from all blood centers of the metropolitan city with a population of over twenty million. The success of the resuscitation definitely was attributed to a well-functioning emergency obstetric care system and social infrastructure, whereas the fatal case which occurred in Xiangtan County Maternal and Child Hospital seemed not be favored with these resources. Moreover, as the onset of AFE cannot be avoided and the prognosis depends on health professional's quick response to the emergency, a training program and simulation experience needs to be conducted for improving the knowledge, attitude and skill of obstetric health professionals.

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