The Science of Amniotic Fluid Embolism

Yifei Xu*

Department of Biological Sciences, University of California Davis, Davis, United States

* Corresponding Author Email: fyfxu@ucdavis.edu

Abstract. With many countries around the world facing aging populations and declining birth rates, governments are encouraging women to have children. However, few countries are really concerned about the effects of pregnancy on women, and society is hiding the risks and symptoms of pregnancy and postpartum complications as if to get more women to have children by hiding these facts. What I believe is that only when women truly understand the process and risk factors of pregnancy can they be prepared to give birth with confidence. People are always afraid of the unknown. This article systematically analyzes the disease with the highest mortality rate during pregnancy, amniotic fluid embolism (AFE). Hopefully, this article will make more people aware of this rare but highly fatal disease. This article introduces various aspects of AFE, the most central part of which should be the analysis of the causes of AFE and the current treatment methods. The author hopes that after reading this article, the reader will be able to eliminate as many questions as possible about AFE.

Keywords: Amniotic fluid embolism; pregnancy; female; obstetrics.

1. Introduction

AFE had been first described from Ricardo Meyer in 1926. [1]. AFE is an uncommon condition and a major contributor to the cause of maternal mortality. Despite its rarity and extremely high mortality rate, the underlying pathophysiological etiology of AFE continues to plague researchers to this day. What is clear, however, amniotic fluid in the autopsy report was able to find amniotic fluid material in the pulmonary vessels of the deceased which in turn led to obstruction of the pulmonary circulation.

The entering of amniotic fluid into the maternal circulation causes anaphylaxis, or hypersensitivity reaction. In which immune cells, complement, and Cytokines begin to interact and activate, leading to an overactive immune system. This may lead to systemic vasospasm, capillary leakage, pulmonary vasoconstriction, DIC (Disseminated Intravascular Coagulation) and cardiopulmonary failure. This immune response is also known as an immune storm. It can lead to damage to various organs and tissues. Procoagulant substances are found in amniotic fluid, which has rapid and strong procoagulant activity. Amniotic fluid accelerates the production of thrombin and activates the aggregation of platelets in the blood to produce clots. Because amniotic fluid also contains anticoagulant substances, the mother's coagulation status is balanced. The maternal coagulation system is triggered by excessive procoagulant substances or insufficient anticoagulant substances in the amniotic fluid. However, it is difficult to determine in advance whether a coagulation storm will occur because of the different genetic diversity among individuals and the different maternal susceptibilities and coagulation functions. The more advanced the DIC (Disseminated Intravascular Coagulation), the more advanced the thrombosis. The more severe the DIC, the more severe the thrombosis. Typical manifestations of the onset of AFEvare sudden hypoxia, hypotension and a triad of coagulation, including the presence of an immune storm and a coagulation storm. Pulmonary vasoconstriction leads to obstruction of blood flow to the lungs, resulting in the development of pulmonary hypertension and pulmonary failure. In cardiopulmonary AFE, there is no coagulation storm and thus no DIC, but there is an immune storm, distributive shock and ARDS (acute respiratory distress syndrome). In the DIC type of AFE, a coagulation storm occurs, producing consumptive coagulopathy, without pulmonary hypertension and right heart failure because of the shortage of thrombus, and without the formation of an immune storm [2].

The motivation for this article is that China is currently advocating for more births and more children, but few people really consider the risks and traumas that women suffer during childbirth.

Only by truly informing women about the problems, risks, and after-effects of pregnancy can women feel more comfortable giving birth. Instead of going through the birth without knowing anything about the pregnancy process, this can lead to increased mental risks in the postpartum period, such as severe postpartum depression. This is because many pregnant women find out after the birth that the pregnancy to postpartum process is not what they thought it would be, causing a strong psychological gap. This article analyzes the fact that AFE is a disease that can only occur in women who have a high mortality rate while pregnancy. The pathogenesis, symptoms, sequelae, risk factors, mortality, treatment and recurrence are explained in detail.

There is still no specific laboratory to test for the clinical definition of AFE. It can only be determined by excluding other causes and by clinical symptoms. For example, the sudden onset of maternal cardiovascular collapse or death during delivery should be considered for the presence of AFE. The current treatment for AFE is to secure the airway, adjust positive end-expiratory pressure, control coagulation status, provide red blood cell concentrate and fresh frozen plasma depending on the amount of blood loss, platelet replacement, stabilize hemodynamics, and correct hemostatic disorders. Because individual physicians' judgment and the patient's condition vary, the agents and treatments used vary. Next the author will describe the specific treatment by specifying the course of treatment in two cases [3].

2. Mainbody

2.1. Amniotic fluid embolism pathogenesis

The pathogenesis of AFE was attributed to amniotic fluid pulmonary embolism by many researchers in the decades prior to the 1970s, as fetal mucin and squamous cells have been found from pulmonary vessels in autopsies of many deceased women. Starting in the 1980s, intensive care obstetrics added pulmonary artery catheters. As the examination of lung tissue sections became more frequent and through examination of animal models a pathologic cause was derived, namely that amniotic fluid was in some way compelled to enter the maternal circulation and that amniotic fluid cellular debris was filtered by the pulmonary capillaries leading in obstruction of pulmonary artery blood flow. This triggers hypoxia, right venous heart failure and death [4].

Here is a case of death determined by autopsy results to be attributable to an AFE. The case was a 33-year-old female who entered a private hospital for delivery at 37 weeks of pregnancy. Fifteen minutes after the delivery of a 2.8 kg baby, she developed tonic-clonic seizures, had difficulty breathing, also together with lost awareness. After being transferred to a triple-A care hospital, the patient was managed to breathe, but she died after 6 hours of hospitalization. The family filed a claim against the hospital for the abrupt death of a pregnant, healthy mother. After police and forensic intervention, the autopsy report had tissue slices of various organs. No pathological abnormalities were found in the tissue slides of the uterus, but fetal squamous cells, hairs and mucus were present in the tissue slides of the lungs. This is a distinctive feature of the occurrence of AFE and the histology of the lungs showed pulmonary edema and capillary congestion [5]. However, fetal cells in the pulmonary vasculature cannot be used as a very reliable criterion for the diagnosis of AFE, this is because fetal cells are detectable in 21% to 100% of pregnancies in females without AFE [6].

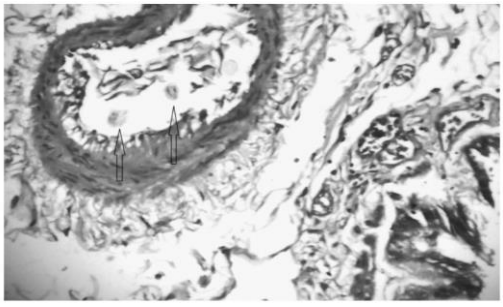

Figure 1. The arrow points to the baby's cellular tissue and hair [5]

2.2. Symptoms of the onset of amniotic fluid embolism

The onset of symptoms of AFE varies considerably from person to person. Starting with the most obvious coagulation disorders and cardiopulmonary failure, headache, chest pain, dizziness, hypoxia, and shortness of breath may also be existing. In amniotic fluid embolism: pathophysiology and new & strategies for management by Kanayama N and Tamura N, the authors state that two-thirds of cases present with atonic bleeding, and only one-third present with cardiopulmonary [7]. In general, the symptoms of AFE can be classified into three phases.

In the first stage patients present with systemic hypertension and transient pulmonary, leading to the first hematotoxicity and possible progression to right heart failure. In the second stage, the patient's left ventricular function decreases and acute pulmonary edema develops in the lungs. In the third stage patients have coagulopathy, heart failure, acute lung injury and acute respiratory distress syndrome (ARDS) [8]. In addition, if the fetal is not delivered at the time of AFE, the fetal heart rate may be abnormal. This is due to fetal hypoxia and reduced uterine blood flow [9]. AFE can also lead to sequelae, with up to 80% of survivors of AFE having permanent neurological sequelae, such as brain damage and seizures due to hypoxia [10]. The associated risk of AFE is placental abruption, multiple pregnancies, placenta praevia, and the use of induction of labor are more likely to occur in pregnant women. The use of prostaglandins for induction of labor also increases the likelihood of amniotic fluid embolism. In addition, the probability of amniotic fluid embolism increases as the age increases [10]. In Risk Factors, Management, and Outcomes of Amniotic Fluid Embolism: A Multicountry, Population-Based Cohort and Nested Case-Control Study this article, a library review was performed on PubMed and the resulting mortality rate for amniotic fluid embolism was derived from data of pregnant women in 8 countries, namely Australia, the United Kingdom, the United States, Canada, China, France, Netherlands and New Zealand. In total, there were 17 million deliveries, and out of these, amniotic fluid embolism occurred in 751 cases, with a mortality rate of 20.4%. But in fact, half of these 751 cases of amniotic fluid embolism had a 100% mortality rate. However, because amniotic fluid embolism is rare and a random sample of cases cannot be used, this data has the limitation that it cannot be applied to the general population [11].

2.3. Case study of amniotic fluid embolism

When a female, 37 years old was 39 weeks pregnant and had a history of labor and delivery 5 years earlier. She entered the hospital with irregular contractions of the uterus. When the patient's blood pressure falls and heart rate accelerates, and the fetus' heart rate also dropped, the doctor used forceps to deliver the patient immediately. After the placenta was out and delivery was complete, the patient suddenly began to experience massive blood loss. Unconsolidated blood flowed out of the vagina in large quantities, and the blood loss reached 2,100 ml in 1 hour. The total blood loss was about 3,000 mL. The bleeding was controlled after 6 hours after the patient was given a large amount of red blood cell suspension, plasma and hemostatic drugs through intravenous infusion, along with hemodialysis and placement of a ventilator. The laboratory report showed a significant decrease in platelets and hemoglobin leading to abnormal coagulation. After continuous blood transfusion for one week, hemofiltration, and plasma transfusion, the patient was still unstable and had two cardiac arrests. The patient's hemoglobin was elevated, but the results of platelet, routine coagulation D-dimer and fibrin degradation were still not encouraging. These results indicated that the platelets and coagulation factors were over depleted and caused injury to the heart, liver, kidneys, respiratory system, and the coagulation system. After discussions among the treatment units, they ruled out the use of heparin and warfarin, which would have caused a further decline in platelets, making the situation worse. The final treatment plan was to treat the patient with rivaroxaban, the safest and most effective blood anticoagulant available for the treatment of venous thromboembolism. After two daily oral doses of 15 ml of rivaroxaban, the patient's dyspnea improved after 4 days, after 7 days the parameters started to normalize, and after 10 days the platelet and coagulation test results returned to normal. During the rest of the recovery, the patient took rivaroxaban orally for a total of 3 months and did not experience any discomfort on the 30th and 60th day of treatment. rivaroxaban is a drug

used for the prevention and treatment of venous thromboembolism and can be used as an anticoagulant for patients. In this patient, who suffered from AFE, which led to DIC (Disseminated Intravascular Coagulation), the use of rivaroxaban brought a good anticoagulant effect, which led to a therapeutic effect [13].

This is a 34-year-old pregnant woman in labor. She came to a private hospital in the 41st week of pregnancy due to obstructed labor. The mature male baby was delivered with the help of oxytocin injection and a vacuum machine. The patient's total bleeding was 1510 grams during the recovery of the perineal incision and deep vaginal laceration performed after delivery, but the bleeding was completely stopped. However, 1 hour and 10 minutes after delivery, the patient developed temporary respiratory distress and a slight decrease in oxygen saturation, which later resolved on its own. Two hours after delivery, the patient again developed respiratory distress, decreased oxygen to 90% and developed uterine bleeding, non-coagulable blood 890g, urethral bleeding and low consciousness, and was later taken to this rescue hospital in shock and with photic shock. A few minutes later the patient's consciousness dropped to a coma level and was given oxygen and artificial pressure support ventilation. The colloid solution was also injected. At this point, the uterus contracted and the genitalia bled, and after a few minutes, the uterus lost its tone. The injection of ergo- meter maleate and prostaglandin F2a did not restore uterine contractions. To reduce genital bleeding, the uterus and descending aorta were still pressed towards the posterior part of the body. Arrived at the emergency hospital 10 minutes later 3000 units of antithrombin (AT)-III was administered intravenously to the patient. 12 minutes after arrival at the hospital, tracheal intubation was performed and manual positive pressure ventilation was maintained. Aspiration out of the patient's trachea revealed a scant, bloody, bubbly secretion in the lungs, indicating diffuse alveolar hemorrhage. Arrived at the hospital 14 minutes later, the carotid artery could not be palpated, and 1 mg of epinephrine was immediately injected. Fifteen minutes after reaching the hospital, a rapid transfusion of concentrated red blood cells and fresh frozen plasma was started for the patient. A total of 2.25 mg of epinephrine, 33units of red blood cell concentrate and 57 units of fresh frozen plasma, 1000 mL of hydroxyethyl starch solution, 500 mL of 5% albumin, and 2000 mL of crystalloid solution were administered during the two hours of resuscitation because of repeated pulseless electrical activity and cardiac compressions. red blood cell concentrate, 17 units of fresh frozen blood, and 40 units of platelet concentrate. One hour later, after being admitted to the intensive care unit, the patient experienced a contraction of the uterus, which continued to be accompanied by bleeding. Another 1250 units of danaparoid and 3000 units of AT-III were injected to the patient and the bleeding gradually stopped. A CT scan of the chest showed significant bilateral pulmonary consolidation, indicating an active lung damage. The patient's head CT showed a mass lesion, which was confirmed to be temporary intracranial edema by an alarm MRI. The patient was then administered dobutamine to improve right venous dysfunction, as a lack of respiratory motion and moderate tricuspid regurgitation were observed. Four days later, the patient was transferred from the ICU ward to the regular ward, and the intracranial hemorrhage was relieved. She was discharged after 16 days with no sequelae [14].

2.4. The recurrence of amniotic fluid embolism

In Amniotic Fluid Embolism – Implementation of International Diagnosis Criteria and Subsequent Pregnancy Recurrence Risk this passage, the authors studied the recurrent problem of AFE in 12 survivors who experienced and were successfully treated for AFE. Nine of the 12 patients developed AFE before delivery. The other 3 had AFE during surgery for fetal death in the middle of pregnancy. Four of the 12 survivors had 11 subsequent pregnancies that failed and were treated without further AFE. The other six gave birth to newborns again and at full term. The remaining two did not have further pregnancies due to neurological damage from the first AFE. As we know from the subsequent pregnancies of these 10 survivors, recurrence of AFE is rare and the presence of AFE in one pregnancy does not increase the incidence of subsequent pregnancies [15].

3. Conclusion

This article provides a basic overview of AFE in a scientific perspective. It contains the principles of AFE pathogenesis, its symptoms, specific treatment and the possibility of recurrence. The mechanism of the pathogenesis of AFE remains unknown, how the amniotic fluid enters the maternal circulation and what specific groups of people are acutely allergic to fetal antigens are unknown. However, what is clear is that amniotic fluid entering the maternal circulation and causing pulmonary embolism is the main etiology. The symptoms of AFE can vary in the early stages of the disease, so that patients with coma, unconsciousness, shortness of breath, lack of oxygen and chest pain should be aware of the symptoms of AFE in advance so that they can make emergency preparations. The current treatment for AFE is broadly based on replenishing blood loss, ensuring oxygenation and controlling coagulation status. The limitation is the interpretation of mortality, which is not applicable to the general population due to the small probability of AFE and the high mortality rate, as well as the genetic differences between individuals and the severity of symptoms between cases. The significance of this study is to help lay people understand the basics of AFE and to popularize the risk of AFE, which is extremely high even though the probability of its occurrence is low. In the future, it is denhoped that the underlying causes of AFE and the groups of people who develop it, which pregnant women have hypersensitivity reactions, and which pregnant women have clotting storms or immune storms, will be clarified soon. In this way, we can prepare and develop treatment measures in advance, so that pregnant women can avoid AFE and be treated at the first time and reduce the mortality rate.

References

[1] Meyer JR. Embolia pulmonar amnio-caseosa. Braz Med. 1926; 2:301-3.

[2] R.-L. YANG, M.-Z. LANG, H. LI, X.-M. QIAO. Immune storm and coagulation storm in the pathogenesis of amniotic fluid embolism. European Review for Medical and Pharmacological Sciences, 2021; 25: 1796-1803

[3] Rath, Werner H, Stefan Hoferr, and Inga Sinicina. “Amniotic Fluid Embolism: An Interdisciplinary Challenge: Epidemiology, Diagnosis and Treatment.” Deutsches Ärzteblatt international 111.8 (2014): 126–132.

[4] Shamshirsaz, Amir A., MD; Clark, Steven L., MD. Amniotic Fluid Embolism. Obstetrics and gynecology clinics of North America, 2016, Vol.43 (4), p.779-790

[5] Shantilal Mohanlalji Sisodia, MD, Kiran Arun Bendale, MD, and Wasif Ali Zafar Ali Khan, MD. Amniotic Fluid Embolism: A Cause of Suddden Maternal Death and Police Inquest

[6] Conde-Agudelo A, Romero R: Amniotic fluid embolism: an evidence- based review. AJOG 2009; 201: 445.

[7] Kanayama N, Tamura N. Amniotic fluid embolism: pathophysiology and new & strategies for management. J Obstet Gynaecol Res 2014; 40:1507-1517.

[8] Balinger KJ, Chu Lam MT, Hon HH, et al. Amniotic fluid embolism: despite & progress, challenges remain. Curr Opin Obstet Gynecol 2015; 27:398 - 405. Obstetrics and gynecological perspective on incidence, treatment, risk factors, and future research into AFE.

[9] Amir A. Shamshirsaz, MD, Steven L. Clark, MD. Amniotic fluid embolism. Obstet Gynecol 2014; 123:337 - 348. &Review highlighting research on animal models of AFE and pathophysiology of anaphylactoid response.

[10] O’Shea, Aidan, and Sunil Eappen. “Amniotic Fluid Embolism.” International anesthesiology clinics 45.1 (2007): 17–28.

[11] Fitzpatrick, Kathryn E. et al. “Risk Factors, Management, and Outcomes of Amniotic Fluid Embolism: A Multicountry, Population-Based Cohort and Nested Case-Control Study.” PLoS medicine 16.11 (2019): e1002962–e1002962.

[12] Kramer, Michael S. et al. “Incidence, Risk Factors, and Consequences of Amniotic Fluid Embolism.” Paediatric and perinatal epidemiology 27.5 (2013): 436–441.

[13] Wu, Hai-Di et al. “Successful Treatment of Amniotic Fluid Embolism Complicated by Disseminated Intravascular Coagulation with Rivaroxaban: A Case Report.” Medicine (Baltimore) 99.4 (2020): e18951–e18951.

[14] Hosono, Kanako et al. “Successful Recovery from Delayed Amniotic Fluid Embolism with Prolonged Cardiac Resuscitation.” The journal of obstetrics and gynaecology research 37.8 (2011): 1122–1125. Web.

[15] Cahan, Tal et al. “Amniotic Fluid Embolism – Implementation of International Diagnosis Criteria and Subsequent Pregnancy Recurrence Risk.” Journal of perinatal medicine 49.5 (2021): 546–552.