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Amniotic fluid embolism: Pathophysiology and new strategies for management

Naohiro Kanayama and Naoaki Tamura

Department of Obstetrics and Gynaecology, Hamamatsu University School of Medicine, Hamamatsu, Japan

Abstract

The registry program of amniotic fluid embolism (AFE) in Japan started in 2003. More than 400 hundred clinical diagnosed amniotic fluid embolism has been accumulated. Those data showed that there were two etiologies of AFE: the fetal materials create physical obstructions in the maternal microvessels in various organs, such as the lung; and (ii) the liquids cause an anaphylactoid reaction that leads to pulmonary vasospasm and activation of platelets, white blood cells and/or complements. The clinical findings showed that AFE was characterized mainly by cardiopulmonary collapse, the other involves the presence of disseminated intravascular coagulation (DIC) and atonic bleeding. Zinc coproporphyrin-1, sialyl Tn antigen (STN), complement C3, C4 and interleukin-8 have been used as serum markers of AFE. The levels of zinc coproporphyrin-1 and STN were increased in cardiopulmonary collapse type AFE, and a marked reduction of C3 and C4 was observed in DIC type AFE. At the primary medical institution, initial treatments for shock airway management, vascular management, fluid replacement, administration of anti-DIC therapy such as antithrombin, and administration of fresh frozen plasma should be provided. C1 esterase inhibitor activity in AFE cases was significantly lower than those of normal pregnant women. C1 esterase inhibitor may be a promising candidate of treatment of AFE.

Key words: amniotic fluid embolism, anaphylactoid reaction, atonic bleeding, C1 esterase inhibitor, disseminated intravascular coagulation, serum marker, rupture of the membranes.

Introduction

Amniotic fluid embolism (AFE) is one of the most serious complications of obstetrics, anesthetics and critical care. Despite earlier recognition and intensive critical care, the mortality of AFE remains high and has been estimated at between 5% and 15% of all maternal deaths.[1] Maternal mortality rates due to AFE have been estimated at between 37% and 80%.[2,3] Maternal death has been decreasing year by year in Japan, however, the incidence of maternal death due to AFE has remained unchanged. The maternal mortality rate due to AFE has increased to 24.3% in Japan.[4]

In August 2003, an AFE registry program was launched in Japan. Approximately 50 AFE cases are registered each year. The incidence of AFE seems to be five in every 100 000 deliveries, as approximately 1 million deliveries are reported each year. There is no marked difference in the incidence of AFE in Japan, Europe and the USA.

Definition of AFE in Japan

Amniotic fluid embolism was defined based on the Japan consensus criteria for the diagnosis of AFE based on the US/UK criteria (Table 1). Because the above diagnosis of AFE depended on clinical manifestations, we say that meeting these criteria is clinically diagnosed AFE (clinical AFE). If fetal debris and amniotic fluid components were found in the maternal

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Reprint request to: Dr Naohiro Kanayama, Department of Obstetrics and Gynaecology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashiku, Hamamatsu 431-3192, Japan. Email: kanayama@hama-med.ac.jp

Table 1 Japanese criteria of amniotic fluid embolism (AFE)

(1) If symptoms appeared during pregnancy or within 12 h of delivery.
(2) If any intensive medical intervention was conducted to treat one or more of the following symptoms/diseases:
  A) Cardiac arrest
  B) Severe bleeding of unknown origin within 2 h of delivery (≥1500 mL)
  C) Disseminated intravascular coagulation
  D) Respiratory failure
(3) If the findings or symptoms obtained cannot be explained by other diseases.

A clinical diagnosis of AFE can be made if the pathological condition meets the above three criteria. Because these diagnostic criteria serve the purpose of making a clinical diagnosis and being able to promptly provide treatment, the pathological conditions that meet them may include those other than AFE.

pulmonary arteries in addition to clinical AFE, we say that it is pathologically diagnosed AFE (AFE). As for clinical AFE, consumptive coagulopathy/disseminated intravascular coagulation (DIC) due to evident etiologies such as abnormal placentation (e.g. placental abruption), trauma during labor and delivery, and severe pre-eclampsia/eclampsia should be excluded from the criteria.

Definition of AFE in other countries

There are the variations in definitions of AFE used between countries and between data sources. The definitions of AFE in three nations are listed as below.[5] Basically, many countries diagnose by clinical symptoms.

The Netherlands

1 Reported as maternal mortality or severe maternal morbidity with AFE as diagnosis or in differential diagnosis.
2 One or more of the following severe enough to require medical treatment: hypotension (and/or cardiac arrest); respiratory distress; DIC; and coma and/or seizures.
3 Absence of any other clear medical explanation for the clinical course.

UK

In the absence of any other clear cause, either:

1 Acute maternal collapse with one or more of the following features: acute fetal compromise; cardiac arrest; cardiac rhythm problems; coagulopathy; hypotension; maternal hemorrhage; premonitory symptoms (e.g. restlessness, numbness, agitation, tingling); seizure; or shortness of breath. (Excluding: women with maternal hemorrhage as the first presenting feature, in whom there was no evidence of early coagulopathy or cardiorespiratory compromise.)

Or:

2 Women in whom the diagnosis was made at post-mortem examination with the finding of fetal squames or hair in the lungs.

Australia

1 If not fatal, the hospital record had to include a diagnosis of one or more of the following: cardiac arrest; hypotension syndrome; respiratory distress; coagulation defects; coma and/or seizure; and an absence of other medical conditions or potential explanations of the symptoms and signs.
2 Where death was the outcome, AFE had to be listed as the cause of death.

Etiology

The condition that facilitates the inflow of amniotic components into maternal blood can be regarded as a risk for development of AFE. Other risk factors include amniocentesis, artificial amniotic fluid injection, multiple pregnancies, laceration during delivery, uterine scarring, induction of delivery, cesarean section and placenta previa. According to a report published in the UK in 2010, critical risk factors associated with the development of AFE were induction of delivery (odds ratio = 3.86), multiple pregnancies (10.9) and cesarean section (8.84). According to the total data reported in Japan in 2010, AFE associated with induction of delivery or cesarean section accounted for slightly more than 60% of all cases.

According to our data, onset of AFE seems to require two necessary conditions: (i) an influx of amniotic fluid into maternal circulation; and (ii) pulmonary embolus or anaphylactoid symptoms against the inflow of amniotic fluid. AFE develops after a relatively large amount of amniotic fluid containing fetal materials (e.g. meconium, squamous cells, lanugo, vernix, mucin) and liquids (e.g. protease in the meconium,

tissue factors) flows into the maternal circulatory system.[2] Amniotic fluid flows into the maternal circulatory system as follows. The amniotic components leak out of the lacerated egg membrane, flow out of the egg membrane and enter the ruptured vessels that are exposed in the lacerated uterine muscles or intrauterine cavity. The amniotic components flow into the maternal blood in accordance with the following scenarios. The fetal materials create physical obstructions in the maternal microvessels in various organs, such as the lung, while the liquids cause an anaphylactoid reaction that leads to pulmonary vasospasm and activation of platelets, white blood cells and/or complements.[6–8] AFE formed by the fetal materials as a physical embolus in the maternal pulmonary artery is shown on the left side in Figure 1. AFE resulting from an anaphylactoid reaction is shown on the right side in Figure 1. Accumulation of many inflammatory cells around the Alcian blue-positive image that is presented on the right side in Figure 1 reflects an anaphylactoid reaction caused by the amniotic fluid. The cases of AFE associated with a physical embolus are relatively few, while those of pulmonary vasospasm due to an anaphylactoid reaction are more frequently reported.

Amniotic fluid embolism also develops as a result of the flow of amniotic fluid into the uterus. The local flow of amniotic fluid into uterine tissues may cause an anaphylactoid reaction in the uterus, resulting in DIC or atonic bleeding. The severe cases of DIC or atonic bleeding which are refractory to various treatments are considered as mild AFE. The contact of amniotic fluid with allergy-associated cells, including mast cells in the cervix, results in the production of large amounts of bradykinin and inflammatory cytokines such as interleukin (IL)-8. Consequently, the uterine muscles relax and become edematous. Within the vessel, an anaphylactoid reaction promotes excessive coagulation and a fibrinolytic state. DIC progresses in this manner. From a clinical viewpoint, atonic bleeding derived from AFE accompanies sometimes incoagulable vaginal bleeding.

Pathological Conditions

One type of AFE is characterized mainly by cardiopulmonary collapse, with dyspnea, chest pain and symptoms of shock; the other involves the presence of DIC and atonic bleeding.[3,9–11] Patients with AFE with cardiopulmonary collapse (cardiopulmonary collapse type AFE) may suddenly complain of chest distress, become restless, and also develop cyanosis, dyspnea, cough and convulsive seizures. In some cases, this type occasionally starts with fetal distress before these cardiopulmonary symptoms. These patients account for 10–15% of those with AFE in our data. This type of AFE is serious because it develops into a life-threatening condition within a short time of onset. The laboratory findings on this type of AFE typically include left ventricular insufficiency associated with increased pulmonary wedge pressure, while the left ventricular work index and systemic vascular resistance decrease. During this process, pulmonary edema accompanying coarse rales rapidly progresses in the lungs. Few characteristic findings are observed in the chest X rays taken immediately after onset. Generally, edematous infiltration gradually expands from the center uniformly on both sides.

The characteristic course of AFE that starts with atonic bleeding and DIC (DIC type AFE) is as follows: incoagulable vaginal bleeding after delivery, which progresses to atonic bleeding and then severe bleeding, and then to shock. This type occasionally starts with fetal distress of an unknown origin accompanying

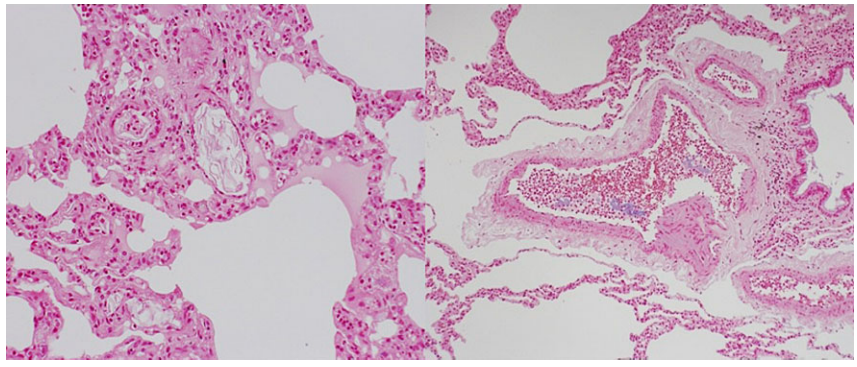

Figure 1 Left (hematoxylin–eosin), amniotic fluid embolism due to fetal debris. Right (Alcian blue staining), amniotic fluid embolism due to anaphylactoid reaction. Alcian blue-positive substance and many inflammatory cells are observed in pulmonary arteries (original magnifications: [left] × 200; [right] × 100).

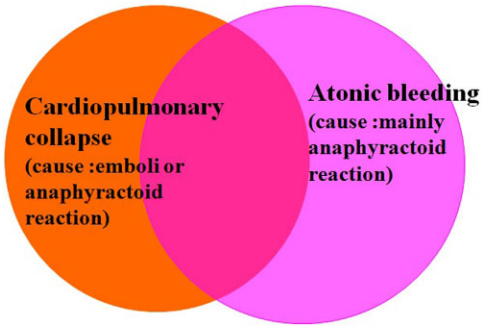

Figure 2 Pathophysiology of amniotic fluid embolism.

lower abdominal pain at the time of delivery. Following a detailed investigation of the autopsied cases, these patients were diagnosed with AFE, although generally they had been diagnosed with atonic bleeding/DIC of unknown origin in the ante mortem findings. AFE can be divided into the following two categories based on initial symptoms: (i) AFE that starts with cardiopulmonary collapse and characterized by pulmonary/respiratory symptoms; and (ii) AFE that starts with atonic bleeding/DIC. In the AFE registry program in Japan, one-third of the AFE cases reported are considered to be in the former category; the remaining two-thirds in the latter. The conceptual diagram of AFE is presented in Figure 2.

Analysis of AFE by the Japan Maternal Mortality Evaluation Committee

The causes of maternal deaths reported to the Japan Association of Obstetricians and Gynecologists have been analyzed by the Maternal Mortality Evaluation Committee (hereinafter referred to as the Evaluation Committee), organized by the members of Health and Labor Sciences Research. Maternal deaths have been registered, and almost all of them have been subjected to an analysis for cause of death since 2010. Of 75 maternal deaths analyzed from January 2010 to November 2012, 21 were caused by AFE. Of these cases, 10 involved cardiopulmonary collapse and 11 atonic bleeding/DIC. The clinical characteristics of each type were analyzed and the results are summarized below.

Clinical characteristics of cardiopulmonary collapse type AFE

The patients' mean age was 34.8 ± 4.1 years; four of them were primiparous. The initial symptoms were respiratory discomfort ($n = 4$), loss of consciousness ($n = 5$) and restlessness ($n = 1$). The time from symptom onset to cardiac arrest was extremely short (0–140 min; 37 min on average). Three patients experienced early rupture of the membranes, five induced delivery and three cesarean sections. Fetal distress of unknown origin was noticed before the appearance of cardiopulmonary collapse symptoms in four patients. Accordingly, AFE that involves cardiovascular collapse is a pathological condition that quickly becomes severe. As noted above, on average it rapidly progresses to cardiac arrest within 37 min. Because of the extremely short period from symptom onset to cardiac arrest, physicians find it difficult to provide life-saving medical treatment. Five patients experienced loss of consciousness as the initial symptom. Some patients who lost consciousness died because this symptom, which was taken for cerebral hemorrhage or eclampsia, was exacerbated during computed tomography scanning. Therefore, we should emphasize that the initial symptoms include loss of consciousness as well as respiratory discomfort and restlessness. Fetal dysfunction was noticed before the development of cardiopulmonary collapse in a relatively large number of cases. When we encounter a case of fetal dysfunction of unknown origin, we should consider AFE in the process of making a differential diagnosis list.

Clinical characteristics of DIC type AFE

In every patient, the initial symptom was incoagulable vaginal genital bleeding after placental delivery (or during cesarean section). Uterine atony developed nearly simultaneously. The time from symptom onset to cardiac arrest was 102 min, on average. The typical laboratory finding was rapid and marked decrease in fibrinogen levels (to <100 mg/dL within 2 h after initial symptom onset in all six patients in whom it was measured: 81, 47, <50, <30, <50 and <50 mg/dL, respectively). Five of the 11 patients did not undergo an examination of the coagulation system, including the measurement of fibrinogen. In a conference to investigate cause of death, delay in transfusion therapy (particularly when using fresh frozen plasma [FFP]) was pointed out in nine of 11 patients. Five patients suffered DIC/atonic bleeding accompanied by pulmonary edema.

Labor-inducing/promoting drugs were used in six of 11 patients and Caesarean section was performed in two of them.

In patients with AFE involving atonic bleeding/DIC, the mean time from initial symptom onset to cardiac

arrest was 107 min, slightly longer than that in the patients with AFE involving cardiopulmonary collapse. Premature ablation of a normally implanted placenta is said to progress to serious DIC within 5–6 h. Compared with this case, DIC associated with AFE progresses rather quickly. Unless any appropriate action is taken to control DIC within 2 h after incoagulable vaginal bleeding, a fatal outcome can be expected. Immediate control of DIC is indispensable in ensuring patients' survival. In the typical laboratory findings, fibrinogen levels decreased in the early stages. In all six patients whose fibrinogen levels were measured, the levels declined to less than 100 mg/dL within 2 h of bleeding. If incoagulable bleeding is noticed after delivery, blood cell count and measurement of fibrinogen should be performed as the first step of treatment. In nine of 11 patients, delayed transfusion therapy (particularly using FFP) was pointed out. Early transfusion with higher doses of FFP is indispensable for controlling DIC associated with AFE. To be able to administer FFP without delay, we should measure fibrinogen levels and make a diagnosis of DIC as soon as possible.

Autopsy Findings on Patients with AFE

Of 21 patients with AFE, five with AFE involving cardiopulmonary collapse (cardiopulmonary collapse type AFE) and four with DIC were subjected to autopsies. The pathological findings were evaluated and compared. The findings from the lungs and uteruses of patients with AFE involving cardiopulmonary collapse are listed in Table 2. In all of the patients with AFE of this type, amniotic and fetal materials were detected in the pulmonary vessels. The conventional or typical pathological image of AFE was found in these patients.

The clinical and pathological findings of the lungs and uteruses obtained from patients with the type of AFE with DIC (DIC type AFE) preceding are listed in Table 3. Amniotic components/fetal materials were detected in the pulmonary vessels in all of the patients with AFE involving cardiopulmonary collapse. The conventional or typical pathological image of AFE was observed in these. No remarkable findings in the uterus were obtained from four of the five patients with AFE involving cardiopulmonary collapse. Uterine atony and inflammatory cell infiltration were clearly recognized in the one remaining patient. In cardiopulmonary collapse AFE, the amniotic components/fetal materials probably formed emboli primarily in the pulmonary artery, which resulted in shock or loss of consciousness. A relatively large volume of amniotic fluid is likely to flow into the maternal circulatory system with this type of AFE.

Uterine atony (a large, edematous uterus) was macroscopically observed and amniotic components microscopically observed in the uterine vessels in all of the patients with DIC type AFE. Uterine atony reflects a marked edematous uterus. Histologically, in some cases, edema existed as if it divided the uterine smooth muscle cells. Amniotic components were detected in the lungs in only one patient with DIC type AFE; however, pulmonary edema was detected in 50% of these patients. Compared to the presence of amniotic components, pulmonary edema seemed to be a more suitable pulmonary finding that characterizes DIC type AFE. In a conference to investigate cause of death, a

Table 2 Autopsy findings from patients with cardiopulmonary collapse type amniotic fluid embolism

	Lungs	Uterus	Time from symptom onset to cardiac arrest
Case A	Many amniotic materials were detected in the branches of the pulmonary artery and capillaries throughout the lungs.	No remarkable findings.	76 min
Case B	Dilation of pulmonary capillaries, congestion and fetus-derived cells were recognized.	No remarkable findings.	35 min
Case C	Fetus-derived keratin was observed in the pulmonary microvessels.	No remarkable findings.	13 min
Case D	Alcian blue-positive parenchymas were detected in the pulmonary artery and microvessels.	No remarkable findings.	3 min
Case E	Alcian blue-positive, cytokeratin-positive and sialyl Tn antigen-positive images were observed in the pulmonary vessels. Marked inflammatory cell infiltration was recognized.	Uterine atony and inflammatory cell infiltration was definitely observed.	60 min

Table 3 Autopsy findings of DIC type amniotic fluid embolism (AFE) patients

Clinical symptoms	Lungs	Uterus	Time from symptom onset to cardiac arrest
Case A Initial event of disseminated intravascular coagulation (DIC); no respiratory symptoms other than coughing until death.	Pulmonary edema	Uterine atony, many Alcian blue-positive images in the uterine veins	Approximately 60 min
Case B Initial event of DIC; no respiratory symptoms until death.	No pulmonary finding	Uterine atony, many Alcian blue-positive images in the uterine veins	Approximately 60 min
Case C Initial event of DIC; subsequent events (chest pain, respiratory failure).	Keratin-positive images in the pulmonary vessels	Uterine atony, keratin-positive images in the uterine veins	115 min
Case D DIC during cesarean section due to placenta previa.	Pulmonary edema, no amniotic materials in the lungs.	Uterine atony, Alcian blue-positive and keratin-positive cells in the vessels from the cervix to the isthmus of the uterus, small round cell infiltration under the vascular endothelium	63 min

pathologist described a pulmonary finding for a case of DIC type AFE as 'pulmonary edema that looked like a damp rag wrung out'. The findings that characterize DIC type AFE are edematous lesions mainly in the uterus and lungs. The amniotic fluid flows into the maternal circulatory system and comes in contact with certain organs, including the uterus and lungs. Edematous changes are more frequently observed in these organs. Even in patients with DIC type AFE for whom autopsies were not performed, atonic bleeding was observed nearly consistently. The characteristic of DIC type AFE is edematous changes mainly in the uterus or lungs resulting from the inflow of amniotic fluid. The possibility exists that the mechanism of the sudden occurrence of edematous changes may be closely related to the etiology of DIC type AFE.

Treating Clinical AFE with no Evidence of Amniotic Components in the Lungs

Deceased patients can be definitively diagnosed with AFE if the presence of amniotic components/fetal materials in the lung tissue is confirmed during autopsy. Alcian blue staining and the measurement of zinc coproporphyrin-1 (Zn-CP1) levels are useful in detecting acidic mucin in amniotic fluid.[12] Moreover, fetal skin-derived keratin staining and staining of TKH-2, glycoprotein derived from mucin contained in the meconium/amniotic fluid (sialyl-Tn [STN] staining) are also useful.[13] Villus cell-derived cells are occasionally detected in maternal lungs during a normal pregnancy. Amniotic components, however, are rarely detected or stained in maternal lungs during the normal course of pregnancy. Therefore, Alcian blue-positive or Zn-CP1-positive result in the lungs is an important finding suggestive of AFE.[14]

As mentioned before, neither amniotic components nor fetal materials were detected in the lungs of some patients with DIC type AFE, among clinical cases of AFE. In the UK, detection of amniotic components/fetal materials in the pulmonary vessels is required for making a pathological diagnosis of AFE. According to UK diagnostic criteria, a pathological condition that meets the criteria for clinical AFE but has no evidence of amniotic components in the lungs is not regarded as AFE. A pathological condition with no evidence of amniotic components/fetal materials in the lungs (no amniotic components/fetal materials detected in the excised section) but meets the criteria for clinical AFE (uterine atony and amniotic components in the uterine

vessels) should be differentiated from conventional types of AFE. We propose that this form of AFE be called amniotic fluid embolism of uterine type (uterine type AFE) (Fig. 3). Onset of uterine type AFE resembles uterine atony, however, uterine type of AFE rapidly advances DIC and shock, and its histological findings mentioned above are different from those of conventional uterine atony. A patient may undergo a total hysterectomy because of clinical AFE. We propose this case should be called uterine type AFE if the above uterine findings are obtained. Based on the results of an investigation by the Evaluation Committee, many cases of uterine type AFE could be clinically judged to be DIC type AFE. If a patient undergoes a hysterectomy, a diagnosis of uterine AFE can be made according to the pathological findings of the uterus and clinical evidence.

Disseminated intravascular coagulation type AFE is characterized by uterine atony that can be macroscopically observed in the pathological examination, with a large, edematous uterus. Histologically, Alcian blue-positive amniotic components were observed in the uterine vessels in all of the patients with DIC type AFE. Amniotic components were detected in the pulmonary vessels in one of four patients. Pulmonary edema was recognized in two of four patients.

Serum Markers

Serological methods are available for making an auxiliary diagnosis of AFE. In Japan, we use Zn-CP1 and STN to detect the substances specific to amniotic fluid in maternal blood.[12,15] Currently, Legrand *et al*. recommend other various useful amniotic markers, such as insulin-like growth factor binding protein 1.[16]

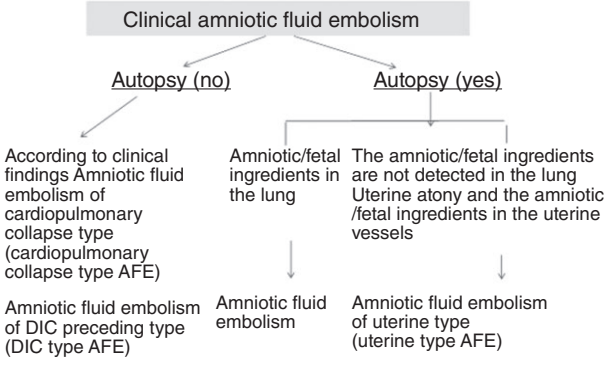

Figure 3 Classification of amniotic fluid embolism (AFE) in Japan. AFE, disseminated intravascular coagulation.

We simultaneously measure serum levels of complement C3 (C3) and complement C4 (C4) to examine whether an anaphylatoxin-like reaction is involved, and IL-8 to check for increased cytokine (Table 4). Exposure of the blood sample to light results in degeneration of Zn-CP1. Therefore, serum should be obtained from the blood sample collected and the serum sample should be covered with aluminum foil for light shielding. Although these marker levels frequently increase in cardiopulmonary collapse type AFE, these are not sensitive markers for DIC type AFE. On the other hand, C3 and C4 levels generally become extremely low regardless of AFE type (Fig. 4). Our data suggest that the excessive activation of complement system may be crucially involved in pathophysiology of AFE. The measurement of C3 and C4 is important in assessment of severity of AFE. Benson *et al*. reported that serum levels of C3 and C4 complement had a sensitivity between 88% and 100%, and a specificity of 100% for the diagnosis of AFE.[17] We propose that if AFE is suspicious from clinical symptoms and amniotic markers, a marked decrease of C3 and C4 would strongly confirm AFE. Benson described that the presence or the absence of fetal material in the maternal circulation of living women cannot either confirm or refute the diagnosis of AFE and that it is unclear why there should be a difference in the sensitivity and specificity of intravascular fetal material between the living and the dead. He commented that previous serum markers do not seem entirely satisfactory on

Table 4 Serum markers for an auxiliary diagnosis of amniotic fluid embolism

(1) Zinc-coproporphyrin-1 (Zn-CP1). Normal value, <1.6 pmol/mL.
High-performance liquid chromatography is used to measure Zn-CP1 contained in the meconium. This substance emits fluorescence at wavelengths of 580 nm and 630 nm with excitation light having a wavelength of 405 nm.
(2) Sialyl-Tn. Normal value: <46 IU/mL.
This sugar chain of the mucin-type glycoprotein recognizes mucin in the meconium.
(3) Complement C3 and C4. Normal values: 80–140 and 11–34 mg/dL, respectively.
These enzymes that complement antigen–antibody reaction are activated by inflammation or allergy.
(4) Interleukin-8. Normal value: <20 pg/mL.
This inflammatory cytokine increases in the event of disseminated intravascular coagulation, systemic inflammatory response syndrome or acute respiratory distress syndrome.

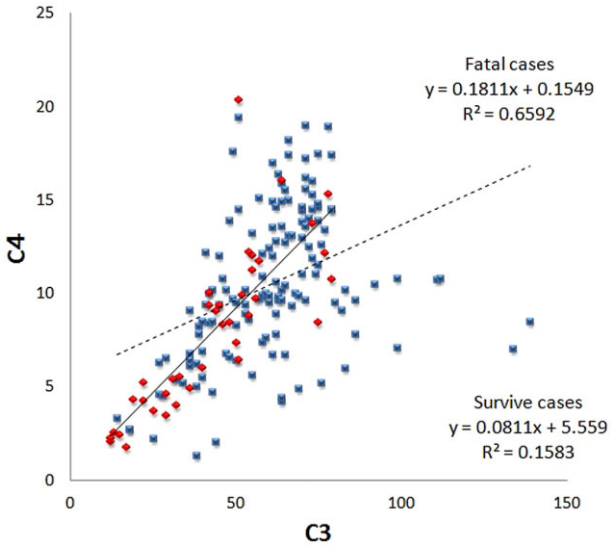

Figure 4 Levels of C3 and C4 in clinical amniotic fluid embolism. ■, survived; ◆, died.

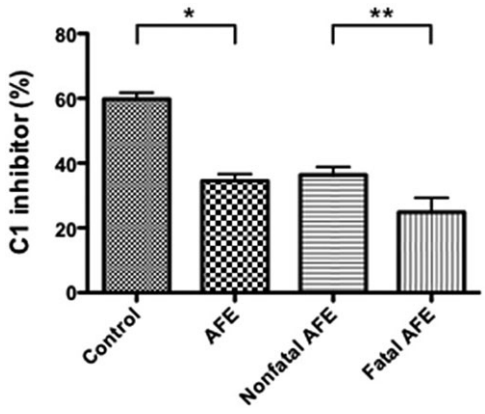

Figure 5 C1 inhibitor level and amniotic fluid embolism (AFE). Non-fatal AFE, surviving AFE patients; fatal AFE, deaths due to AFE. $^{**}P < .001$, $^{*}P < 0.05$.

further examination because the amount of fetal material in fatal AFE cases was not necessarily massive and indeed present only in microscopic amounts.[18]

New Marker: C1 Esterase Inhibitor

C1 esterase inhibitor (C1INH), which is mainly synthesized in hepatocytes and endothelial cells and belongs to the serpin family, is a major inhibitor not only of C1 esterase, but also of FXIIa and kallikrein.[19–21] Its deficiency is know to be a specific cause of hereditary angioedema (HAE).[22] Because C1INH is capable of not only inhibiting the complement system, but also modulating the coagulo-fibrinolytic and kallikrein-kinin systems, we hypothesized that C1INH was key in the pathophysiology of AFE.[23] We discovered that C1 esterase inhibitor (C1 inhibitor) decreased in patients with AFE.[24] We found that many deceased patients had C1 inhibitor levels far below 25% (Fig. 5). C1 inhibitor inhibits the complement system and has a direct effect on the kinin and fibrinolytic systems. We found that a decrease in C1 inhibitor resulted in the development of various pathological conditions associated with AFE, including uterine atony (uterine edema), DIC and an anaphylactoid reaction. Although early FFP transfusion therapy has been known to be effective for treating AFE, C1 inhibitor contained in FFP seems to contribute to improvement of the pathological condition. Because a C1 inhibitor (Berinert P, CSL Behring, Marburg, Germany) is included as a drug for hereditary angioedema on the National Health Insurance (NHI) list, its application for AFE can be expected.

In addition, the chronological assessment of C1INH activity levels in two AFE patients indicated that their basal C1INH activity levels before onsets were also lower than those of healthy pregnant controls during labor. Thus, we proposed that low C1INH activity levels before onset of AFE could be a predictive factor, as well as low levels at onset and the persisting low levels of C1INH activity could be prognostic factors of AFE.

Treatment

At the primary medical institution, initial treatments for shock (airway management, vascular management, fluid replacement, administration of an antishock agent) and DIC (administration of antithrombin, administration of FFP if possible) should be provided. The patient should then be transferred to an advanced medical institution. At the secondary medical institution, the patient should be treated in the intensive care unit as soon as possible. The treatment protocol should be in accordance with guidelines for managing critical obstetric bleeding. In the case of hypotension, epinephrine, dopamine hydrochloride or dobutamine hydrochloride (1–5 μg/kg per min) should be administrated to maintain blood pressure and urine volume. High-dose adrenocorticosteroid hormone (500–1500 mg in the form of hydrocortisone) is occasionally effective.

Antithrombin (3000 units) should be administrated as soon as possible because severe DIC frequently develops in the early stages. FFP (≥10–15 units) should be administrated. FFP is preferable to red blood cell products. Red blood cell products should be administrated while monitoring bleeding volume. The target ratio between FFP and red cell concentrate should be adjusted to a level exceeding 1.5. In instances of DIC associated with AFE or the premature ablation of a normally implanted placenta, coagulation factor replacement therapy is first priority because the activation of coagulation factors enables the production of intravascular thrombi.

Recently, we reported that C1INH activity levels in AFE cases were significantly lower than those of normal pregnant women. Furthermore, when we compared fatal cases to non-fatal cases of AFE, the C1INH activity of fatal cases was significantly lower than that of non-fatal cases.[24] Many published works have reported that the rapid administration of FFP or cryoprecipitates was sufficient to extricate the patient from a critical situation. According to our study, the meaning of administration of FFP does not only supply coagulating factors but also C1INH. One hundred units of C1INH are contained in FFP derived from 200 mL blood. Clinically, the use of 500–1500 units of human plasma-derived C1INH concentrates can revert HAE in C1INH-deficient patients. Because AFE patients certainly have significant lower levels of C1INH activity, similar to a C1INH deficiency, the clinical application of human plasma-derived C1INH concentrates may become one of the promising candidates for the treatment of AFE.

Platelet transfusion should be considered while monitoring DIC. If the platelet count exceeds 20 000/μL, platelet transfusion in not needed immediately. If the above treatments are ineffective for improving DIC, the use of recombinant factor VII, which is not included on the NHI list but whose efficacy has been demonstrated in Japan and overseas, can be considered. Conventionally, heparin has been recommended for treating patients suspected of having AFE with DIC. Generally, DIC associated with AFE rapidly progresses and causes severe bleeding, and thus the use of heparin is not recommended.

Actions to be Taken in the Event of a Fatal Outcome

An autopsy should be performed on all deceased patients. Their families may decline to accept this proposal; however, the importance of the investigation into the cause of death should be explained and sufficient efforts should be made to receive their consent. Notification of maternal death is submitted to the Japan Association of Obstetricians and Gynecologists and Prefectural Associations of Obstetricians and Gynecologists. An additional form with the specific details of the case is submitted to the Japan Association of Obstetricians and Gynecologists. The treating physician reports the case to the head of the medical institution and takes the appropriate actions in accordance with the institution's investigation protocol.

Prevention

Risk factors found in several studies to be significantly associated with an increased risk of AFE included maternal age of 35 years or older, cesarean delivery, forceps/vacuum delivery, placenta previa, abruption placenta, eclampsia and fetal distress.[5] It is assumed that the rupture of the membranes followed by the inflow of amniotic fluid into maternal circulation occurs easily in cases of cesarean delivery, forceps/vacuum delivery, placenta previa, abruption placenta and eclampsia because these conditions are ascribed to injury of the birth canal or injury of trophoblasts. The amniotic membrane and chorion membrane form an important barrier that prevents amniotic fluid from flowing into the maternal circulatory system. The egg membrane, especially the amniotic membrane, restricts contact of the amniotic fluid with maternal allergy-associated cells. In the event of rupture of the egg membrane, an anaphylactoid reaction is likely to occur in the mother's body, and routine delivery management should be employed. Unless the membrane is ruptured, the maternal allergy-associated cells, including mast cells, eosinophils and basophils, are not exposed to a large amount of amniotic fluid. If the membrane is ruptured and amniotic fluid flows into the vagina, the possibility of contact with maternal allergy-inducing cells decreases because, as with the skin, the vagina is lined by thick, stratified, squamous epithelium and rarely comes into contact with maternal immune cells. If the membrane is ruptured, and amniotic fluid comes into contact with the cervical tissues or uterine muscles, either major or minor allergic-like reactions are induced in some parts of the uterus. In the event of rupture of the membrane, the contact between the amniotic fluid and the mother's body should be prevented as much as possible. Timely rupture of the membrane, which is defined as 'complete dilation of

the uterine cervix followed by rupture of the membrane', is regarded as normal. This conventional process ensures safe delivery management. Artificial rupture of the membrane at the higher station of the presenting part of the fetus or rupture of the membrane without effacement of the cervix enables contact with the endocervical columnar epithelium or stroma (in the presence of laceration) and increases the possibility of allergic reaction. Therefore, obstetricians should recognize the increased risk of inflow of amniotic fluid into maternal blood in the event of an injury, vacuum delivery and forceps delivery. The pathological conditions that increase the risk for development of AFE include pregnancy accompanying allergy-related condition, pregnancy-induced hypertension syndrome, low-lying placenta and placenta previa. Treating obstetricians should carefully follow-up with pregnant women with these risks and direct special attention to the progress in the event of rupture of the membrane.

Important Considerations for Preventing AFE

Based on those risk factors of AFE we manage the patients during labor to prevent AFE as below:

1 Measuring the volume of bleeding is not reliable. Always consider the possibilities of internal bleeding and blood leakage toward the back, which makes it difficult to measure volume accurately. Measuring the volume of bleeding during delivery also is occasionally inaccurate.
2 Direct special attention to the pulse and shock index. Carefully consider pulse rate. Make it a rule to calculate the shock index as a matter of routine practice. A timely diagnosis of shock cannot be made if attention is directed only to blood pressure.
3 Restlessness, respiratory discomfort, severe lower abdominal pain and fetal dysfunction of unknown origin appear before AFE manifests.
4 Check for atonic bleeding and incoagulable vaginal bleeding of unknown origin. In the obstetric field, patients suffer severe bleeding characteristic of DIC after uterine atony or incoagulable vaginal bleeding resulting from consumption of coagulation factors.
5 Pay particular attention to a rupture of the membrane that can result in AFE. Carefully observe the mother and her baby for some time after the rupture of the membrane.
6 Do not rupture the membrane using a non-physiological or artificial technique. As mentioned before, contact of the amniotic fluid with the lumen of the cervix entails the risk for AFE. Therefore, rupture of the membrane at stations higher than station 1 and artificial rupture in a state of insufficient dilation of the uterine cervix (<5 cm) should be avoided.
7 In the event of early rupture of the membrane, induced delivery should be carefully monitored. Because amniotic fluid easily flows into maternal blood, this type of delivery should be managed as a high-risk delivery.

In conclusion, there are two etiologies of AFE: (i) the fetal materials create physical obstructions in the maternal microvessels such as lung; and (ii) an anaphylactoid reaction that leads to pulmonary vasospasm and activation of platelets, white blood cells and/or complements. The clinical findings showed two types of AFE: (i) cardiopulmonary collapse type AFE; and (ii) DIC type AFE. Zinc coproporphyrin-1, STN, C3 and C4 have been used as serum markers in Japan. In addition to them, C1INH could be a sensitive marker to reflect the pathophysiology of AFE. C1INH may be a new treatment for AFE. Regarding prevention of AFE, obstetricians must take care of the appropriate time of the rupture of membranes and reduce lacerations of the birth canal.

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