Amniotic fluid embolism: the pathophysiology, diagnostic clue, and blood biomarkers indicator for disease prediction

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Summary
Objective: This article aims to review and provide more understanding of current knowledge of amniotic fluid embolism regarding pathophysiology, diagnostic criteria, risk factors, indicating biomarkers, treatment strategies and outcomes of some case reports. Study design: A systematic literature review was performed using the PubMed database, restricted to articles published in English from 1992 to 2018. Original research, case reports, guideline recommendations, and review articles were reviewed in this study. Summary: Amniotic fluid embolism (AFE) is a rare catastrophic obstetric condition defined by clinical manifestations of pregnancy with sudden onset of cardiopulmonary arrest, consumptive coagulopathy or neurological deficits without other explainable illnesses. The incidence varies from 1.7-14.8 cases per 100,000 worldwide. The current understanding of AFE pathophysiology includes fetal components obstructing maternal microvessels with subsequent anaphylactoid reaction. Maternal pulmonary vasospasm and hematologic activation occur later, followed by heart failure and sudden cardiovascular collapse. Some of the possible risk factors for AFE include; 1) Maternal risk: age over 35 years, hypertensive disorder and diabetes mellitus; 2) Fetal risk: polyhydramnios, multiparity, non-vertex at delivery, fetal distress and fetal macrosomia; 3) Obstetric risks: amniocentesis, artificial amniotic fluid injection, oxytocin infusion, and placental abruptio. Some of the useful biomarkers have been proposed including zinc coproporphyrin-1, squamous cell carcinoma antigen, carcinoembryonic antigen, cancer antigen 125, Siatyl Tn, monoclonal antibody TKH-2, C3, C4, tryptase, insulin-like growth factor binding protein-1, C1 esterase inhibitor. Management of AFE requires immediate basic life support and advanced cardiac life support. Adequate oxygenation, ventilation, coagulopathy correction, and appropriate vasopressors are recommended. However, the outcome prediction of AFE remains challenging.

Key words: Amniotic fluid embolism; Pathophysiology; Biomarker; Diagnosis; Cases.

Introduction
Amniotic fluid embolism (AFE) is a rare obstetric emergency condition. Despite its low incidence, maternal and perinatal mortality is still high. This high mortality could be explained by the limitation of disease prediction as well as a scarce diagnostic clue for AFE. Speculating the disease outcomes is also challenging. However, countless studies had been done over the past decades to improve the knowledge of the disease. This study attempts to improve the understanding of the condition and updated pathophysiology, risk factors, useful diagnostic markers, management, and case report outcomes.

Diagnostic criteria for amniotic fluid embolism and incidence
AFE was first described in 1926 by Meyer and recognized widely in 1941 [1]. It is defined by its fundamental features of sudden onset of cardiopulmonary arrest, consumptive coagulopathy, atonic bleeding, acute hypoxia, seizures, disturbed consciousness, acute hypotension, without other explainable illnesses or underlying diseases. However, the diagnostic criteria vary among nations as listed in Fig. 1 [2, 3, 4]. A study by Kobayashi, et al. showed that Japan criteria had a medium agreement with that of the UK (k = 0.538) and the USA (k = 0.453). This results in diagnosing different subgroups of patients [4]. Uterine AFE was considered to have occurred when fetal debris and amniotic fluid components were found in the uterus in pathological examination of cases of severe uterine hemorrhage after placental removal (eg. bleeding caused by uterine atony) in absence of other obstetric hemorrhagic complications such as abnormal placentaion, trauma during labor and delivery, and severe preeclampsia or eclampsia.

There is no consensus on the true incidence of AFE due to the rarity and variation of diagnostic criteria from countries to countries [5]. However, in the United States, the total cases of AFE have been estimated as 7.7 cases per 100,000 [6]. In Canada, the total rate of AFE in single and multiple birth deliveries was 14.8 and 6.0 per 100 000 singleton deliveries respectively [7]. Incidence of 1.7, 2.5 and 6.1 cases per 100,000 was reported in the United Kingdom, Netherlands, and Australia, respectively [8, 9]. The mortality rate reported by case studies is also varied from 20% to 60% [10].

Pathophysiology of amniotic fluid embolism
Until now, the pathophysiology of AFE remains unclear. Recent studies have proposed that the onset of AFE requires two actions. First, an amniotic fluid containing fetal com-
ponents including squamous cells, vernix, lanugo, meco-
nium inflow into the maternal circulation. These materials
then enter the exposed and ruptured vessels in the intrauter-
ine cavity or lacerated uterine muscles. The components are
capable of obstructing maternal microvessels and can end up as pulmonary emboli. Second, the maternal anaphy-
lactoid reaction occurs against the influx of amniotic fluid in
maternal circulation which can activate pulmonary vasospa-
som and create platelets, factor VII, white blood cells and complement stimulation. This hemostatic activation can
initiate disseminated intravascular coagulopathy and sub-
sequent coagulation cascade followed by ischemic dis-
tal organ dysfunction and multi-organ failure. This process
may induce other hemorrhagic complications such as he-
maturia, bleeding from venipunctures, gastrointestinal bleed-

The presence of fetal materials or amniotic fluid in
myometrium can cause a maternal local immune reaction
which might interfere with myometrial function, leading
to uterine atony and postpartum hemorrhage which may
present as incoagulable vaginal bleeding in some cases
[3, 11]. Embolization may contribute to pulmonary hy-
pertension, right-sided heart failure leading to left ven-
tricular failure and sudden cardiovascular collapse [3, 5,
12]. Regarding immunological reactions, the previous
studies revealed some relevant mediators such as tryptase,
bradykinin, histamine, endothelin, arachidonic metabolites,
and leukotriene. Nevertheless, the laboratory results do
not show a significant elevation of these mediator levels
[5, 13, 14]. The mechanism of AFE is summarized in Fig. 2.

Risk factors

AFE is a potentially catastrophic condition as it is an un-
predictable and unpreventable syndrome. Many attempts
have been made to identify the risk factors to overcome
or prevent the occurrence of AFE. The risk factors which
have been repeatedly reported are as follows: maternal age
over 35 years, induction of labor, cesarean section, forcelps
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| Maternal Risk | Fetal Risk | Obstetric Risk |
|---------------|------------|----------------|
| - Age over 35 years | - Polyhydramnios | - Amniocentesis |
| - Hypertensive disorder | - Multiparity | - Artificial amniotic fluid injection |
| - Pre-eclampsia or eclampsia | - Non-vertex at delivery | - Oxytocin infusion |
| - Diabetes | - Male fetus | - Cesarean section |
| | - Fetal distress | - Forceps or vacuum-assisted delivery |
| | - Fetal macrosomia | - Uterine rupture or laceration |
| | - Intrauterine death | - Placenta previa |
| | | - Placental abruption |
| | | - Cervical laceration |

Figure 2. — Mechanism of AFE.

or vacuum-assisted vaginal delivery, uterine rupture or laceration, placenta previa, placental abruption, polyhydramnios, pre-eclampsia, and eclampsia as summarized in Table 1 [6, 15, 16]. However, this may only alert physicians to immediately manage or avoid these risk factors to reduce the prevalence of AFE but also to lower the fatality rate. Oi et al. have proposed eight parameters including dyspnea, cardiac arrest, loss of consciousness, serum sialyl Tn > 47U/mL, serum interleukin-8 > 100 pg/ml, vaginal delivery, multiparity, and term delivery as potential factors to predict mortality rate and more accurate prognosis [1, 12, 17]. In 2018, a systematic review and analysis from a data pool by Indraccolo et al. revealed that among all risk factors, only oxytocin infusion during labor can increase fatality in typical AFE cases [18].

AFE can occur during the first or second trimester of pregnancy as it is also believed to be a complication after amniocentesis and artificial amniotic fluid injection. However, Drukker et al. revealed that over the past 55 years, there were only two cases of AFE identified after performing amniocentesis in the English literature [15]. However, despite multiple risk factors given, none of them is adequately established to alter standard obstetric care [12].

Biomarkers: the predictor of AFE

The early diagnosis for AFE remains challenging as there is no universal biomarker used for screening AFE. To the current knowledge, some of the useful biomarkers have been proposed as summarized in Table 2. Those primitive markers identified include sialyl Tn (STN) and Zincoproporphyrin-1 (ZnCP1) which were proven to be over-expressed in meconium and amniotic fluid [19, 20, 21]. Serum squamous cell carcinoma antigen is also a potentially useful marker as it is only present in amniotic fluid, not in maternal serum [22].

Insulin-like growth factor binding protein-1(IGFBP-1) has been considered as a valuable biomarker due to its high
### Table 2. — Biomarkers and tests proposed for AFE diagnosis.

| Author, Year | Marker | Abnormal finding | AFE cases | Non-AFE cases | Sensitivity | Specificity |
|--------------|--------|------------------|-----------|---------------|-------------|-------------|
| Kanayama N, 1992 [20] | Zinc Coproporphyrin-1 | Serum level > 35 nmol/L | 4 | 50 | 100% | 98% |
| Sarandakou A, 1992 [31] | CEA | Serum level, Umbilical cord blood, Amniotic fluid level > 5 ng/ml | 0 | 56 | - | - |
| | CA-125 | Serum level, Umbilical cord blood, Amniotic fluid level > 35 U/ml | 0 | 56 | - | - |
| | Squamous cell carcinoma antigen | Serum level, Umbilical cord blood, Amniotic fluid level > 2.5 mg/ml | 0 | 56 | - | - |
| Kobayashi H, 1993 [19] | Sialyl Tn | Serum level > 50 U/mL | 4 | 32 | 100% | 96% |
| Kobayashi H, 1997 [29] | Monoclonal antibody TKH-2 | Positive staining | 4 | 4 | 100% | 100% |
| Benson M, 2001 [14] | C3 | Serum level < 70 mg/dL | 6 | 22 | 87.50% | 100% |
| | C4 | Serum level < 16 mg/dL | 6 | 22 | 100% | 100% |
| | Tryptase | Serum level > 2 SD | 9 | 22 | 0% | - |
| | Sialyl-Tn | Serum level > 47 U/ml | 127 | 74 | 25.80% | 97.30% |
| | Zinc coproporphyrin-1 | Serum level > 1.6 nmol/L | 127 | 74 | 45.90% | 73% |
| Iwai K, 2011 [21] | Insulin-like growth factor binding protein-1 | Serum level > 104.5 pmol/ml | 25 | 94 | 92% | 97.80% |
| Legrand M, 2012 [23] | Insulin-like growth factor binding protein-1 | Serum activity level | 106 | 88 | - | - |
| Tanura N, 2014 [25] | C1 Esterase inhibitor | Serum activity level 25% | 70 | 74 | 60.00% | 89.20% |

Concentration in amniotic fluid. It could be detected in maternal serum even in case of amniotic fluid leakage into maternal circulation in only a very small amount. IGFBP-1 level is low in normal pregnancy and was proven to rise after the onset of AFE [23]. A case report by Wernet et al. revealed that alpha-fetoprotein (AFP) and insulin-like growth factor binding protein-1 were increased fourfold during the onset of AFE after performing dilatation and curettage in the first trimester. This might be helpful in early diagnosis and rapid management of AFE [24].

Furthermore, numerous reports have demonstrated that the complement system plays a role in AFE resulting in decreased maternal complement levels. C1 Esterase inhibitor (C1INH) activity levels are significantly lower in AFE cases and lowest in fatal A FE patients indicating that C1INH is a potential prognostic factor [25]. C3 and C4 levels are significantly depressed in AFE from previous studies [1, 14]. Regarding subsequent mast cell activities, the tryptase levels are inconsistent and relatively unpredictable among studies and therefore cannot be used as a diagnostic tool for AFE [14, 26]. Campanharo et al. reported a case of maternal SLE with AFE measuring a decrease of the C3a level. This indicated that the complement activation was secondary to the patient’s SLE. For this reason, patients with autoimmune disease should be observed with closed surveillance [27].

Some specific cytokines including Interleukin 6 (1500-2000 pg/ml), interleukin 8 (500-700pg/ml) and tumor necrosis factor alpha-soluble receptor p55 (sTNFp55) are detected in amniotic fluid. These unique markers are useful in identifying AFE in cases with systemic inflammatory response syndrome [16, 28].

AFE can also be histologically diagnosed by specific staining. The TKH-2 is an antibody that reacts with meconium and amniotic fluid-derived mucin-type glycoprotein. The TKH-2 immunostaining is present in the pulmonary vasculature of patients with AFE, which can be easily missed by the conventional hematoxylin-eosin stain. Moreover, it was reported that no TKH-2 staining was found in non-AFE patients. Therefore TKH-2 has been considered as a potential sensitive method to diagnose AFE [16, 28, 29]. The presence of amniotic components using concentration in amniotic fluid.
hematoxylin-eosin, alcian blue and sialyl-Tn in the uterine vasculature was also evaluated in DIC-type PPH. Nevertheless, the result showed no significant finding [30].

Some tumor markers (squamous cell carcinoma [SCC] antigen, carcinoembryonic antigen [CEA], and cancer antigen-125 [CA-125]) have been found significantly elevated in amniotic fluid when compared to those in umbilical cord blood and maternal serum. Hence, further considerable efforts should be made to introduce these markers as a diagnostic tool for AFE [31]. Moreover, there are some proteins that specifically present in amniotic fluid, including Procollagen type I N-terminal propeptide (PINP), Pro-early placenta insulin-like peptide (ProEPIL), Annexin I, Brain Natriuretic Peptide (BNP), Pro-Opiomelanocortin (POMC), Chromogranin A (CgA). (However, these are not conventional markers and more research is need to eluci-date their potential roles in AFE [28].

It is recognized that coagulopathy is one of the predominant features of AFE which occurs in a remarkably short period. Early measurement of fibrinogen levels may help reduce the risk of maternal death from AFE [32].

### Amniotic fluid embolism: management and outcomes

According to Society for Maternal-Fetal Medicine guidelines, AFE should be one of the differential diagnosis for the case of any pregnant woman or recently postpartum patient with sudden cardiopulmonary compromise or cardiac arrest, in which basic life support and advanced cardiac life support protocols should be immediately activated and performed as in a non-pregnant individual manner.

The additional components in rescuing cardiac arrest pregnant women include: 1) Lateral displacement of the...
A FE should be diagnosed based on clinical features and immediately managed. No laboratory test is required for confirming AFE. A multidisciplinary team (anesthesia, respiratory therapy, critical care, and maternal-fetal medicine) should be involved.

After successful resuscitation, a postcardiac arrest patient must be closely monitored and targeted as follows: 1) Mean arterial pressure of 65 mmHg, 2) Pulse oximetry at the value of 94-98%, 3) The serum glucose level at 140-180 mg/dL, and 4) Body temperature at 32-36°C for 12-24 hours to improve neurological outcomes.

In the early phase, transthoracic and/or transesophageal echocardiography can be applied, monitor ongoing right ventricular failure. Hypoxia, hypercapnia, and acidosis should be avoided. After the right heart function improves, left ventricular failure along with cardiogenic pulmonary edema usually follow in a later phase [12]. Adequate oxygenation, ventilation, and appropriate vasopressors or inotropic drugs are recommended. High-dose adrenocortico-steroid is effective on some occasions [3]. Excessive fluid administration should be avoided. Dialysis may be indicated in severe pulmonary congestion unresponsive to diuretic drugs [12].

Disseminated intravascular coagulation usually presents either shortly after a cardiovascular collapse or in the later phases. Therefore, early assessment of coagulopathy and aggressive management of clinical bleeding with standard transfusion protocols is recommended. It has been reported that rapid transfusion of cryoprecipitates or FFP can alleviate patients in critical condition. A platelet count above 50,000/mm3 and normal (or close to normal) activated partial thromboplastin time and international normalized ratio should be maintained [12]. It was previously suggested to administer heparin in AFE with DIC patients. However, heparin may induce severe bleeding. Therefore using heparin is not currently recommended [3]. In cases of uterine atony, uterotonic agents such as oxytocin, ergot derivatives, and prostaglandins are appropriate as indicated. Other surgical management such as uterine tamponade, uterine artery ligation, B-Lynch stitch or hysterectomy may be required in more severe cases of postpartum hemorrhage [12].

The mortality rate has been reported to be varied between 20% and 60% [10, 33]. Maternal mortality rate per 100,000 live births has been estimated to be 0.4 in the Netherlands, 0.5 in the United Kingdom and Sweden, 0.7 in Canada, 1.5 in Australia and 1.0-1.7 in the United States [9, 33]. However, the understanding of AFE has improved in the last decade. Some available case reports and the following outcomes are in Table 3.

**Conclusion**

AFE is a rare condition but often leads to lethal consequence and the current knowledge is still limited. Over the past few decades, a lot of attempts have been made to gain more understanding of the disease. Pathophysiology, some risk factors, and diagnostic markers are identified and reviewed here in this article. A high quality basic and advanced life support, adequate oxygenation and coagulopathy correction along with a multidisciplinary team approach should be performed. Further investigations and research is required to improve the understanding of the disease. This review has offered some useful clinical points and management which should be applied in a case-by-case manner.

**Acknowledgment**

This work was partially supported by the Chiang Mai University Fund (TT).

**Conflict of interest**

There is no conflict of interest to declare.

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