

Immune storm and coagulation storm in the pathogenesis of amniotic fluid embolism

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Abstract. – Amniotic fluid embolism (AFE) is a rare but severe obstetric complication with high mortality. To date, the pathogenesis of AFE has evolved from a simple theory of mechanical obstruction to an immunological theory. However, it is not yet fully understood. Here we elaborate on the immune storm and coagulation storm induced by the amniotic fluid entering the maternal circulation. These two storms contribute to a better understanding of the pathogenesis of typical and atypical AFE. Our theory needs to be confirmed by further clinical studies and basic research.

Key Words:

Amniotic fluid embolism, Pathogenesis, Immune storm, Coagulation storm.

Introduction

Amniotic fluid embolism (AFE) is a life-threatening obstetric complication. There is no publicly accepted pathogenesis of the disease to this day. There have been two main theories on AFE since it was first proposed in 1926.

- 1. Mechanical theory.** In 1941, Steiner and Lushbaugh¹ officially named the disease "AFE". It was systematically described that AFE pathogenesis is the pulmonary mechanical embolism caused by the physical components in the amniotic fluid, such as meconium, mucus, sebum, lanugo, and amniotic cell debris^{1,2}. However, this theory has not been supported by radiological evidence, autopsy results or animal models.
- 2. Immune-mediated theory.** In 1995, Clark et al³ found that AFE was more similar to anaphylaxis or septic shock⁴; therefore, he proposed to rename

AFE as "anaphylactoid syndrome of pregnancy"⁵. Benson et al⁴ found that some patients with AFE had negative tryptase results and no evidence of mast cell degranulation; moreover, the levels of C3 and C4 were decreased, indicating that complement activation may be one of the pathogeneses of AFE. It is currently thought that AFE results from immune activation secondary to exposure to numerous immunocompetent active and prothrombotic substances contained in the amniotic fluid.

The above two theories only partially explain the pathogenesis of AFE when used alone but give a complete picture when used in combination. There is a temporal relationship between the two theories during the dual hemodynamic phases of AFE from right heart failure to left heart failure⁵.

Uszyński⁶ proposed an integrated concept, including: (1) apoptosis-affected amniocytes play a unique role in the mechanical barrier of pulmonary blood flow and the initiation of disseminated intravascular coagulation (DIC) and (2) leukotrienes induce smooth muscle contraction in bronchial and pulmonary vessels.

Here we present the theories of immune storm and coagulation storm to help understand the various clinical manifestations of typical and atypical AFE.

Immune Storm Induced By Amniotic Fluid

Both allergic reactions and complement activation indicate the participation of immune factors in AFE. Recently, a growing body of research shows that immunological mechanisms may play a more critical role in the pathogenesis of AFE. Kanayama et al⁷ put forward the immune-in-

flammatory theory, and Clark et al⁸ proposed the "activated proinflammatory mediator theory" in the pathogenesis of AFE .

PAMPs and DAMPs in Amniotic Fluid

The immune system can be triggered by pathogen-associated molecular pattern molecules (PAMPs) or damage-associated molecular pattern molecules (DAMPs). PAMPs are microbial nucleic acids, lipoproteins, surface glycoproteins, and membrane components. DAMPs are usually released by cell necrosis or tissue damage, such as high-mobility group protein B1 (HMGB1), S100 proteins, heat shock proteins (HSP), hyaluronic acid, complement, ATP, uric acid, heparin sulfate, RNA, and DNA⁹.

Does amniotic fluid contain PAMPs or non-infected DAMPs? If the amniotic fluid is infected, it generally contains pathogen molecules belonging to PAMPs, such as bacteria or viruses. AFE

is sterile in most clinical cases, suggesting that DAMPs may play a significant role in the pathogenesis of AFE. Barber noted that amniotic fluid often contains free fetal nucleic acids (DNA or RNA) or hyaluronic acid from the extracellular matrix, which can enter the maternal circulation with amniotic fluid during labor and trigger the maternal immune system. Romero et al¹⁰ found that HMGB1 is significantly increased in infected and non-infected amniotic fluid. The author considered that this condition might be caused by amniotic epithelial cell damage.

Maternal Immune System Activation

During labor, PAMPs and DAMPs may enter the maternal circulation with the amniotic fluid and trigger the maternal immune system through any of the following three pathways. The three possible pathways of immune storm in AFE are illustrated in Figure 1.

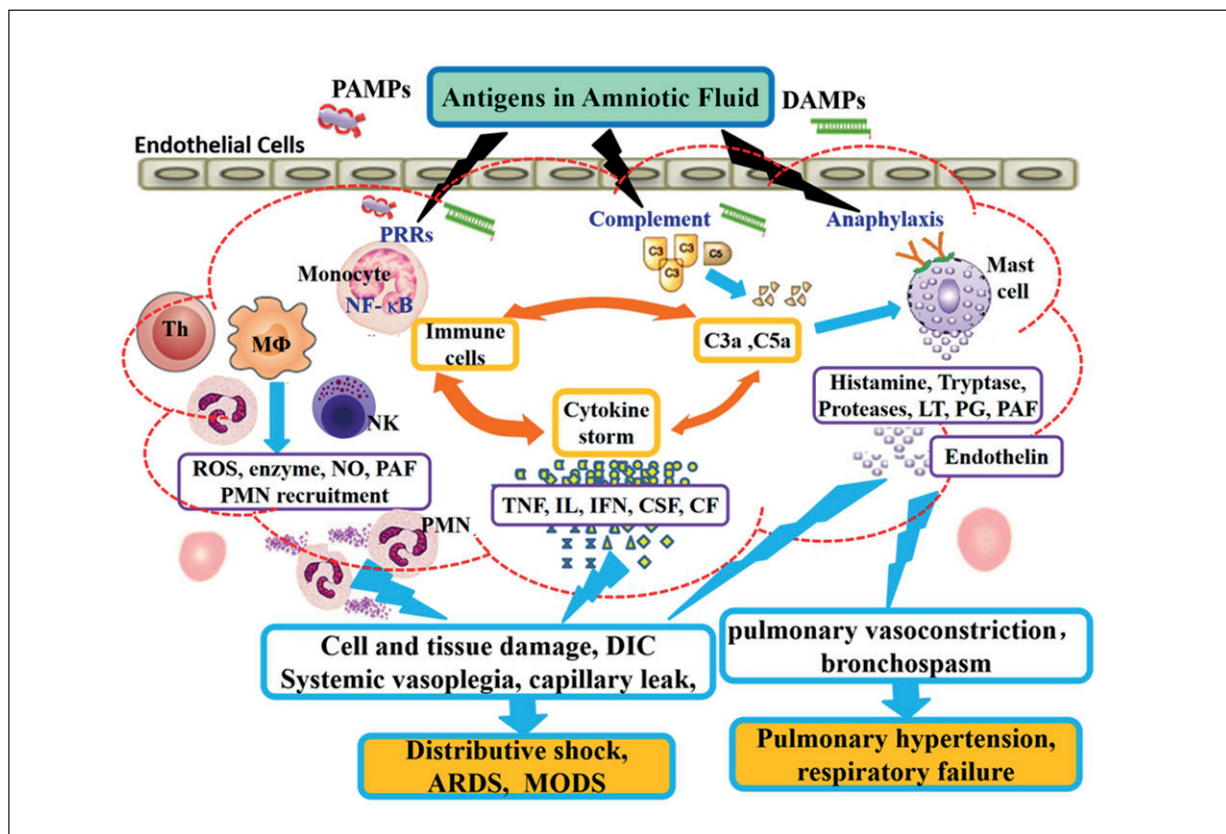


Figure 1. The three possible pathways of immune storm in AFE. PAMPs=pathogen associated molecular pattern molecules; DAMPs=damage associated molecular pattern molecules; PRR=pattern recognition receptor; NF-κB=nuclear factor κB; Th=T helper cell; MΦ=macrophage; NK=natural killer cell; PMN=polymorphonuclear cell; ROS=reactive oxygen species; NO=nitric oxide; TNF=tumor necrosis factor; IL=interleukin; IFN=interferon; CSF=colony stimulating factor; CF=chemotactic factor; DIC=disseminated intravascular coagulation; ARDS=acute respiratory distress syndrome; MODS=multi-organ dysfunction syndrome; LT=leukotriene; PG=prostaglandin; PAF=platelet activation factor.

Pattern Recognition Receptor (PRR) Pathway

PAMPs and DAMPs are mainly recognized by various PRRs on the membranes of innate immune cells. After PAMPs or DAMPs are identified by the various PRRs of immune cells, a violent cytokine storm can occur via pathways such as the transcription factor NF- κ B (nuclear factor- κ B) activation pathway. Proinflammatory cytokines, such as tumor necrosis factor α (TNF- α), interleukins 1 and 6 (IL-1, IL-6), and interferon (IFN), promote the activation and aggregation of macrophages and polymorphonuclear cells, thereby releasing reactive oxygen species (ROS), protease, nitric oxide (NO) or more cytokines. Cytokine storm can also activate platelets, which produce blood clots to eliminate PAMPs or DAMPs⁹. However, if the cytokine storm is too intense, it can damage autologous cells, tissue or organs, which leads to clinical manifestations, such as capillary leakage, distributive shock, acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome (MODS), or DIC^{9,11,12}.

Romero et al¹⁰ found that in two separate AFE cases, serum TNF- α concentrations were significantly increased to 1 ng/mL and 10 ng/mL (the lethal dose is 0.1 ng/mL). Although the author did not dynamically monitor the level of TNF- α changes after the occurrence of AFE, the report indicated that cytokine storm might participate in the process of AFE.

Anaphylaxis Pathway

Anaphylaxis may take part in the pathogenesis of AFE. Anaphylaxis is a general term for both IgE-mediated immediate hypersensitivity reactions and non-IgE-mediated anaphylactoid reactions^{13,14}. Clark et al³ proposed that anaphylactoid reaction to fetal antigens may participate in AFE. Fineschi et al¹⁵ found the evidence of mast cell degranulation containing tryptase-positive material extracellularly in the bronchial wall of AFE patients, which may be caused by complement activation¹⁶. Regarding multiparous delivery, the maternal immune system may be sensitized by fetal antigens during previous labor, and IgE may trigger severe anaphylaxis when maternal blood is re-exposed to fetal antigens.

Anaphylaxis can trigger mast cells or basophils to release inflammatory mediators (histamine, tryptase, leukotrienes), causing smooth muscle contraction, systemic vasodilation, in-

creased vascular permeability, and edema^{14,16}. Leukotrienes and endothelins can induce pulmonary vasoconstriction and bronchoconstriction^{6,17}.

Complement Pathway

Some DAMPs can also be identified by the maternal native IgM, which activates complement through the classic antibody-dependent pathway. Benson et al⁴ found decreased C3 and C4 levels during AFE, and Fineschi et al¹⁵ found C3a expression and mast cell degranulation in the bronchial wall of AFE patients. Complement activation appears to be the initial immune response leading to secondary degranulation of mast cells, and the complement pathway seems to be more promising than anaphylaxis as a possible mechanism of disease¹⁸.

C3a and C5a, the products of complement activation, are anaphylatoxins that can bind to the high-affinity Ig E receptor expressed on mast cell membranes and determine their degranulation¹⁶. Complement activation and subsequent mast cell degranulation can produce a damaging inflammatory response leading to tissue damage.

The rarity of AFE demonstrates differential maternal sensitivity to PAMPs or DAMPs. Some studies^{19,20} have suggested that cytokine storm occurrence is determined by the differences in the innate immunogenetics of normal individuals.

Immune Storm

When amniotic fluid enters the maternal circulation, DAMPs or PAMPs may activate the maternal immune response of sensitive individuals through the PRR pathway, anaphylaxis pathway or complement pathway. Complement, immune cells and cytokines can activate each other, leading to excessive activation of immune system. As a result, a large number of cytokines, enzymes, reactive oxygen species, histamine and leukotriene are released in a short period of time, leading to systemic vasoplegia, capillary leakage, DIC, pulmonary vasoconstriction, and even cardiopulmonary failure.

Although the activation pathways mentioned above may not occur simultaneously, they are intertwined and interacted. The various strong immune responses that lead to tissue and organ damages during the pathogenesis of AFE are collectively referred to as the "immune storm". The term "immune storm" can fully express the importance of the immunological mechanism in the pathogenesis of AFE.

Although the immune storm is induced by amniotic fluid antigens that enter the maternal circulation, the main reason for its incidence is individual high sensitivity and excessive activation of the immune system. The maternal immune system may provoke an uncontrolled immune response that occasionally damages autologous organs to remove the invading antigens. Therefore, AFE can be regarded as an “acute autoimmune disease”.

Coagulation Storm Induced by Amniotic Fluid

The Procoagulants in Amniotic Fluid

There are procoagulant substances in amniotic fluid. Hayami et al²¹ mixed 0.1 mL of amniotic fluid with 5 mL of venous blood from 16 healthy pregnant women; the ACT was significantly reduced in the samples and some samples were even wholly clotted. This result shows that the amniotic fluid exhibits a rapid, vigorous procoagulant activity and DIC may occur even if very little amniotic fluid enters the maternal blood. Lockwood et al²² found that increased tissue factors in amniotic fluid using an immunodetection method. Tissue factors exhibit a procoagulant activity that converts prothrombin to thrombin, and DIC may occur if these factors enter the maternal circulation.

Amniotic fluid can enter the maternal circulation during labor. High concentrations of tissue factors, microparticles and coagulation factors can also enter the maternal circulation along with amniotic fluid to activate the maternal coagulation system through the extrinsic and intrinsic coagulation pathway²³. Oda et al²⁴ found that amniotic fluid can accelerate thrombin production and activate platelet aggregation in whole blood producing soft and fragile clots by rotational thromboelastometry.

Amniocytes gradually and inevitably undergo apoptosis during pregnancy and acquire the properties of particular types of procoagulants. The discovery of amniocytes in thrombin generation is the key to elucidate the mechanism of DIC in AFE⁶.

The Anticoagulants in Amniotic Fluid

Although amniotic fluid contains high concentrations of coagulation factors and the entry of amniotic fluid into the maternal circulation is a common phenomenon, the incidence of coagulation storm is very low, which is worth exploring.

Sarig et al²⁵ simultaneously detected tissue factor and tissue factor pathway inhibitor (TFPI) in the amniotic fluid of pregnant women and found that the two increased synchronously; furthermore, the increase in TFPI was greater than tissue factor. In addition to TFPI, there are other anticoagulants such as antithrombin, protein C and S and thrombomodulin in amniotic fluid⁶. Lacroix et al²⁶ proposed that there are not only procoagulant factors but also anticoagulant factors and factors with fibrinolytic activity on the amniotic fluid microparticles, which achieve a dynamic coagulation/anticoagulation balance.

Coagulation Activation

Although procoagulant factors can enter the maternal circulation with amniotic fluid, anticoagulant factors are also present in the amniotic fluid at the same time so that maternal coagulation state is balanced and coagulation activation is avoided. The maternal coagulation system is activated only when there is an excess of procoagulant factors entering the maternal circulation, or insufficient anticoagulant factors in the amniotic fluid.

C1 esterase inhibitors can inhibit the activation of plasma kallikrein and factors XII and XI. Tamura et al²⁷ found that amniotic fluid C1 esterase inhibitor activity was significantly lower in AFE cases (n=106) than the standard control group, suggesting that a reduction in inhibitors levels in amniotic fluid is another factor controlling the incidence of DIC.

Furthermore, coagulation is also associated with maternal susceptibility. It has been shown that coagulation risk varies significantly due to genetic polymorphisms among individuals^{28,29}.

Coagulation Storm

Consumptive coagulopathy in AFE refers to the formation of microthrombi or even thrombi once the coagulation system is activated, followed by activation of fibrinolytic system and subsequent DIC. More attention was paid to coagulopathy and bleeding, while thrombosis was overlooked in the past. The more severe the DIC is, the more severe the thrombosis and fibrinolysis may be. Unlike consumptive coagulopathy in other diseases, which usually develops gradually in systemic microcirculation, thrombosis in AFE occurs concentrating in the venous system between uterus and heart in a short time. Although microthrombi is common, large clots can be observed in some individuals³⁰⁻³⁵.

There are three characteristics of thrombosis in AFE. Firstly, the thrombosis forms in limited space (mainly inferior vena cava) quickly so that a mass effect and mechanical obstruction occur in the right heart and pulmonary vessels. Secondly, the thrombosis formation usually accumulates on the amniotic cell debris, forming a particular mass of mixed emboli (amniocytes and other physical components + thrombi and microthrombi), which doubles its mass effect. Thirdly, unlike the old thrombi in pulmonary thromboembolism, the thrombi and microthrombi in the mixed emboli are fresh and unstable. When fibrinolysis occurs, the thrombi and microthrombi will rapidly and partially dissolve. So, the mass of mixed emboli is usually transient, and the final emboli that can be found in pulmonary vessels at autopsy are mainly the physical components of amniotic fluid with less residual thrombi and microthrombi. Several studies have identified transient masses (i.e., mixed emboli) in the maternal right heart by echocardiography at the beginning of AFE with cardiopulmonary failure³²⁻³⁵. The masses were highly mobile, heterogeneous with a gelatinous appearance, and disappeared after minutes to hours, followed by DIC. Although not all patients with AFE have such masses, their appearance

indicates that massive intravascular thrombosis during the initial phase of AFE may be the missing link in the pathogenesis of this syndrome.

As mentioned above, there is a rapid dynamic process from massive thrombosis to rapid fibrinolysis in maternal inferior vena cava, corresponding to the clinical manifestation of AFE from cardiopulmonary collapse to DIC. We refer to this rapid and massive thrombosis/fibrinolysis process as the "coagulation storm". Unlike the typical coagulation cascade, "coagulation storm" can lead to mechanical obstruction of pulmonary vasculature before severe DIC occurs. The rapid and catastrophic nature of thrombosis and fibrinolysis associated with AFE is well reflected by the term "coagulation storm". (The coagulation storm in AFE is illustrated in Figure 2).

Immune Storm and Coagulation Storm in the Pathogenesis of AFE

The Intersection of Immune Storm and Coagulation Storm

These two storms can be intertwined to form a vicious circle, ultimately leading to MODS. Recent studies have shown that procoagulant and

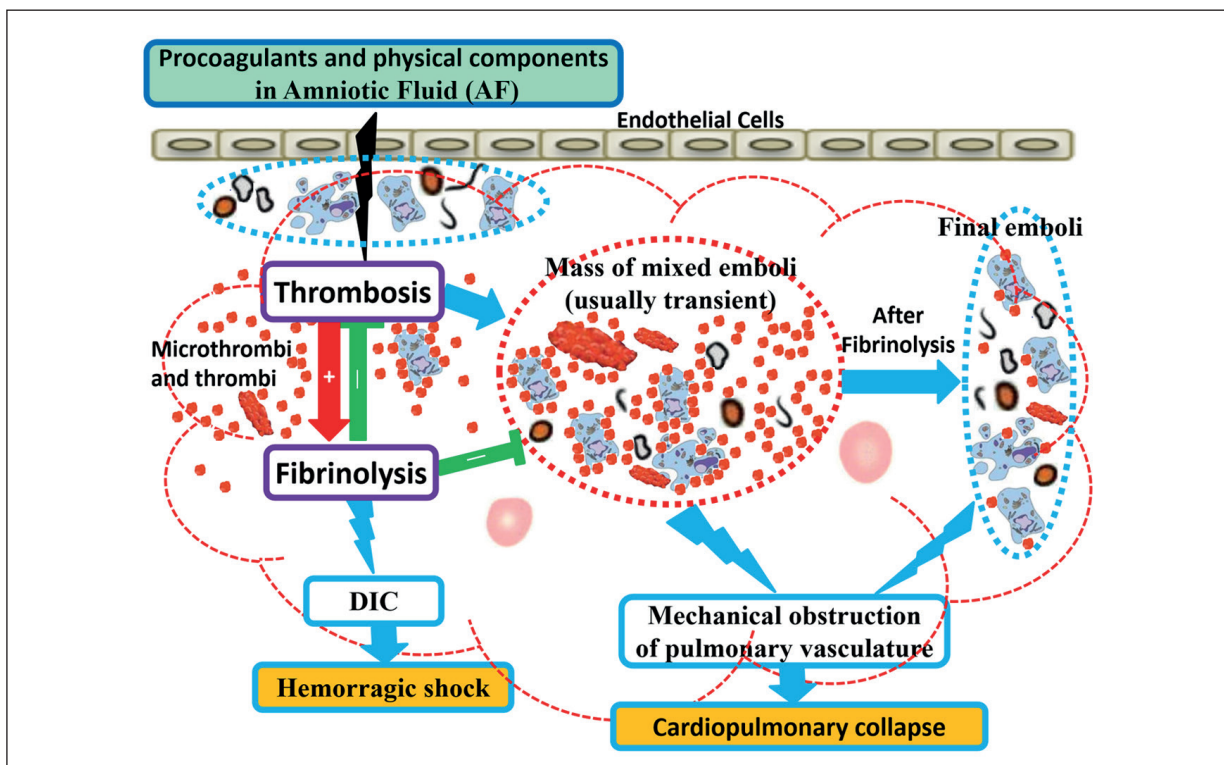


Figure 2. The coagulation storm in AFE.

proinflammatory factors can promote each other. As the initiating factor of the contact system, factor XII plays a significant role in the intrinsic coagulation pathway and promotes inflammation³⁶. On the other hand, DAMPs and PAMPs can induce cytokine storms, thrombosis, and DIC³⁷.

The Two Storms in the Pathogenesis of Typical AFE

The presentation of typical AFE includes a triad of sudden hypoxia, hypotension, and coagulopathy followed by in many cases. The typical AFE usually consists of both immune and coagulation storms. The obstruction of blood flow through the lungs is a direct cause of pulmonary hypertension and cardiopulmonary failure. The occlusion occurs due to mechanical obstruction of mixed emboli deriving from coagulation storm and pulmonary vasoconstriction caused by immune storm⁶. ARDS and distributive shock emanating from the immune storm aggravate the respiratory and circulatory failure in AFE. (The immune storm and coagulation storm in the pathogenesis of AFE are shown in Figure 3)

Because fibrinolysis is a secondary reaction to massive thrombosis in the coagulation storm, DIC usually comes after the cardiopulmonary collapse in typical AFE.

The Two Storms in the Pathogenesis of Atypical AFE

In clinical practice, in addition to typical AFE, atypical AFE can also be encountered. For instance, cardiopulmonary type AFE without apparent consumptive coagulopathy, DIC type AFE without respiratory-circulatory disorders^{7,38,39}.

In cardiopulmonary type AFE, the immune storm occurs as distributive shock or ARDS, but DIC does not happen due to lack of the coagulation storm.

In DIC type AFE, the coagulation storm is activated and manifests as consumptive coagulopathy, but immune storm does not form. Although coagulation storm develops in this type of AFE, few physical components in amniotic fluid enter maternal circulation so that pulmonary hypertension and right heart failure do not occur because of lack of emboli.

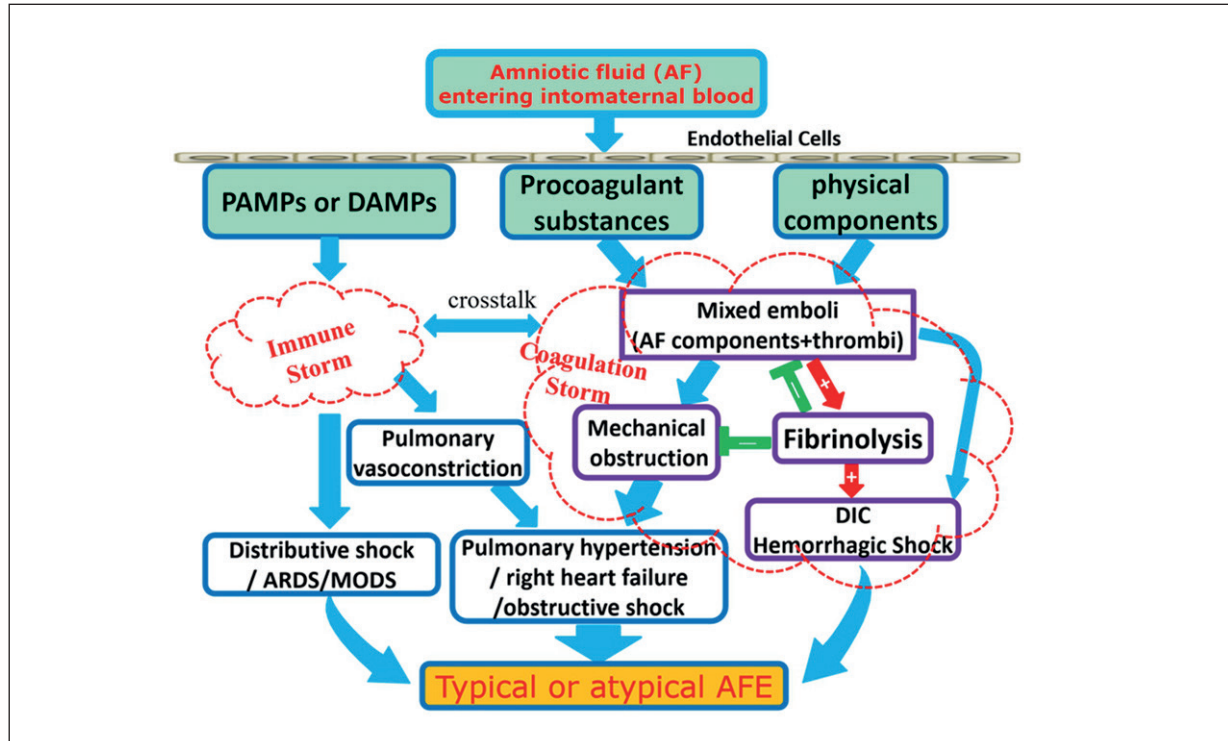


Figure 3. The immune storm and coagulation storm in the pathogenesis of AFE. PAMP=pathogen associated molecular pattern; DAMP=damage associated molecular pattern; DIC=disseminated intravascular coagulation; MODS=multi-organ dysfunction syndrome; AFE=amniotic fluid embolism.

Occasionally, particular types of AFE occur with more complex clinical manifestations. When the amniotic fluid is infected, an immune storm is activated by PAMPs, and AFE may occur with fever and septic shock as the primary clinical manifestations^{13,40}. Conflicting AFE types occur when the mother has a patent oval foramen or an atrial septal defect^{30,31,41,42}. Among these conflicting AFE types, mixed emboli are formed due to the coagulation storm, and some of which lead to embolic syndrome of the brain or other organs through the defect site from the right heart to the left heart⁴³.

Further situations can occur in which only mild changes occur to the maternal immune system or coagulation system due to amniotic fluid components, and these changes are too mild to constitute a storm; clinically, only mild clinical symptoms or laboratory abnormalities may be found, and these are often overlooked by clinicians or explained by other causes.

Conclusions

AFE is a complicated and dangerous obstetric complication, and its pathogenesis is still not entirely exact. Previous studies have confirmed that mechanical obstructions and immune factors may play important roles in the pathogenesis of AFE. In this review, we present a theory of immune and coagulation storms which help to understand the pathogenesis of AFE better. Further clinical and basic research on its pathogenesis is needed to understand AFE.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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