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A new approach to the pathomechanism of amniotic fluid embolism: unknown role of amniotic cells in the induction of disseminated intravascular coagulation

Mieczyslaw Uszyński*, Waldemar Uszyński

[1]*Department of Propedeutics of Medicine, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Poland*

[2]*Regional Hospital in Włocławek, Poland*

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ABSTRACT

There are four concepts (theories) of amniotic fluid embolism (AFE). The aim of the study was to perform their critical review and to popularize a novel integrated concept. We searched Medline (from its inception to 2011), using key words: amniotic fluid embolism, amniotic cells, tissue factor, leukotriene and microparticles. Articles most eligible for the study of etiopathomechanism of AFE were chosen by title and/or abstract contents. The analysis of the publications revealed that: (i) the integrated concept of AFE is an adequate tool to interpret the complication, being particularly useful for taking direct therapeutic decisions; (ii) disseminated intravascular coagulation (DIC) in this complication is induced not by tissue factor (TF) of amniotic origin but by spectacular procoagulant activity of apoptosis-affected amniotic cells. Descriptions of molecular processes were provided. In clonclusioin, there are two independent pathways of AFE-the DIC pathway and the leukotriene pathway. It is not the TF but the apoptosis-affected amniotic cells that are responsible for the process of DIC in AFE. 3. One of the therapeutic conclusions of the new approach to the concept of AFE indicates that attempts to use heparin in AFE are justified (at the onset of the complication).

1. Introduction

Amniotic fluid embolism (AFE) is a rare but extremely dangerous peripartal complication, which frequently leads to death of mother and baby (previously mother's mortality rate was 60%-80% as compared to the recent rate of 21%[1]). It is a cause of approximately 10% of all deaths of mothers in Poland[2], the USA[3], and possibly all over the world[4]. Since AFE appears suddenly and usually affects healthy women at labor, it also exerts a traumatic psychological effect, known as posttraumatic stress syndrome (PTSD), on dead woman's environment, including medical staff.

Life is threatened in AFE due to cardiopulmonary collapse (most frequently) or/and coagulation disturbances, including DIC and uterine hemorrhage (more seldom), and sometimes due to pulmonary complications (ARDS). It is well known that the therapeutic and emergency management should involve Basic Life Support and Advanced Life Support protocols in coordination with obstetric actions, e.g. caesarean section[5]. Undoubtedly, it is the concept of AFE pathomechanism approved by an obstetrician that underlies his actions.

The aim of the study was to provide a critical review of each of the four known concepts of AFE as well as to popularize a novel integrated concept and the resulting therapeutic implications.

2. Review

2.1. Four concepts of AFE

Four concepts attempt to provide information on the causes of AFE (Table 1). Briefly, according to the mechanical theory, fetal squames and other morphotic and amorphotic components of the fluid act as a causative factor, blocking the pulmonary circulation; the thromboplastin

*Corresponding author: Mieczysław Uszyński, MD, Professor, Department of Propedeutics of Medicine, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Poland.
Tel: +48 52 585 3939
Fax: +48 52 5853505
E-mail: kizproped@cm.umk.pl

theory states that the obstruction is due to disseminated intravascular coagulation (DIC), whereas the leukotriene theory emphasizes the role of leukotrienes in catastrophic pulmonary vasoconstriction. These first three concepts used to be competitive until the fourth one appeared, *i.e.*, the integrated concept of AFE.

There is also another concept described in literature, *i.e.*, anaphylactic concept of AFE; however, it is now considered a solved problem. Normal course of pregnancy and labor in women who have survived AFE is the major proof against the anaphylactic mechanism of AFE [11,12].

Table 1
Four concepts of amniotic fluid embolism (AFE).

Name of concept	Pathogenic factor according to the respective concept	Pathomechanism of AFE according to the respective concept	Authors of the concept
Mechanical concept (theory)	Fetal squames, cell debris, mucus bands, fatty droplets	Mechanical blockade of pulmonary artery induce cardiopulmonary collapse	Stein and Lushbaugh 1941[4]
Thromboplastic concept (theory)	Tissue factor (TF), formerly known as tissue thromboplastin	Microemboli formed in the process of DIC cause blockade of blood flow through the lungs and lead to consumptive coagulopathy	Weiner et al 1953[5] Albrechtsen 1964[6]
Leukotriene concept (theory)	Leukotrienes and other metabolites of arachidonic acid cascade	Catastrophic pulmonary artery vasoconstriction and blockade of pulmonary function	Clark 1990[7]
Integrated concept of AFE	Two factors: a/ procoagulant-like activity of the apoptosis-affected amniotic cells; b/ leukotrienes and other metabolites of arachidonic acid cascade	Two pathways: a/ DIC-pathway; b/ leukotriene pathway	Uszyński 2011[8]

2.2. Mechanical theory

Pioneer researchers of AFE, Steiner and Lushbaugh[6], believed that cardiopulmonary collapse was caused by disseminated pulmonary embolism of amniotic components of fetal origin (squamous cells, lanugo hairs, mucus threads and fat droplets), and not by biochemical components of the amniotic fluid. They based their assumptions on pathomorphological examinations of parturients who had died suddenly, and on experimental data. The researchers were able to reproduce embolic phenomena by intravenous administration of native amniotic fluid to an experimental animal, but not when filtered fluid, *i.e.*, free of amniotic cells, was applied. Similar studies were later conducted by other authors who always confirmed this intriguing observation- the fluid that was filtered did not induce DIC in animals[13].

Comment: (i) Protagonists of the mechanical theory believed that the obstructed blood flow through the lungs was caused only by amniotic cells and other morphotic elements of the amniotic fluid. Also microthrombi produced by intracellular coagulation formed additional blockade and caused pulmonary vasoconstriction. (ii) Lack of apoptotic amniotic cells in the filtered amniotic fluid resulted in a negative outcome of the experiment (see further).

2.3. Thromboplastic theory

At first, Reid, Weiner and Roby[7] in 1953 grounded their explanations of the pathomechanism of AFE on the activity of tissue factor (TF; formerly called tissue thromboplastin), a procoagulant, which they estimated to occur in high concentrations in the amniotic fluid. When the amniotic TF gets to the pulmonary arterioles, it induces, as they thought, intravascular coagulation, hypofibrinogenemia and obstetric hemorrhages. However, laboratory findings of the subsequent 20 years showed that the levels of TF and other coagulation factors in the amniotic fluid were too low to make the embolic portion of the fluid induce DIC in the circulating maternal blood[13,14]. McMillan[15] in 1968 stated in his spectacular calculations that the pathogenic amount of TF could be found in 7 liters of the fluid, whereas the volume of a genuine embolus was estimated at 10-100 mL. Meta-analysis of our study of 2003[16] also showed that TF contained in 100 mL supernatant could cause only a statistically insignificant increase in TF concentration in maternal blood (not exceeding standard deviation).

Comment: In the light of the above studies, the thromboplastic theory became outdated and the question concerning the pathomechanism of coagulation disturbances in AFE remained open for a long time. Nevertheless, one of the assumptions of the theory was right, namely that DIC in AFE is TF-dependent. Newly reported cases of AFE, with detected pulmonary artery or intracardiac thrombi[17-20], are undisputed arguments for the existence of DIC in amniotic fluid embolism.

2.4. Leukotriene theory

The premises of the leukotriene theory of AFE were first described in the years 1985 and 1986[21], though an overview of the theory contents was provided in 1990 by Clark[9]. In animal studies, infusion of leukotrienes resulted in severe pulmonary hypertension followed by systemic hypotension with negative inotropic effect and decreased cardiac output. It was assumed that the action observed in animals could occur in humans as well. According to this theory, metabolites of the arachidonic acid cascade- mainly leukotrienes, previously known as slow-reacting substance, but also thromboxan A2 (TXA2) and others-cause catastrophic pulmonary vasoconstriction in AFE. These metabolites either pass to the lungs with the amniotic fluid

or are formed in loco after the fluid gets to the pulmonary vessels.

Comment: (i) The leukotriene concept is the ground for satisfactory elucidation of pulmonary vasoconstriction. However, it does not relate to DIC and other coagulation disturbances. (ii) Its popularity, especially among anesthesiologists, can explain why other AFE concepts are frequently neglected in the diagnosis and therapy of the complication.

2.5. Integrated concept of AFE

According to the integrated concept of AFE[10], the fluid bolus induces two independent pathogenic pathways: (i) the intravascular coagulation pathway with formation of microthrombi, mainly in the pulmonary circulation (DIC), and sometimes macrothrombi (pulmonary artery or intracardiac thrombi), resulting in hemodynamic diorders and consumption coagulopathy; (ii) the leukotriene pathway with the arachidonic acid cascade and action of its products, leading to catastrophic pulmonary vasoconstriction. The blockade of the pulmonary function can be caused by the mechanisms of one of the pathways or both. Clinical symptoms include acute respiratory, circulatory and clotting abnormalities. Cardiopulmonary collapse with cardiac arrest is the most dangerous sequence of the complication (Figure 1).

Comment: (i) Casuistic descriptions providing evidence for lung obstruction due to pulmonary artery or intracardiac thrombi[17-20], or catastrophic pulmonary vasoconstriction[22-24] make up the grounds for the integrated concept of AFE. (ii) Novel laboratory findings (see below) allow explanation of the thrombogenic potential of the amniotic fluid and elucidation of the mechanism of DIC in amniotic fluid embolism.

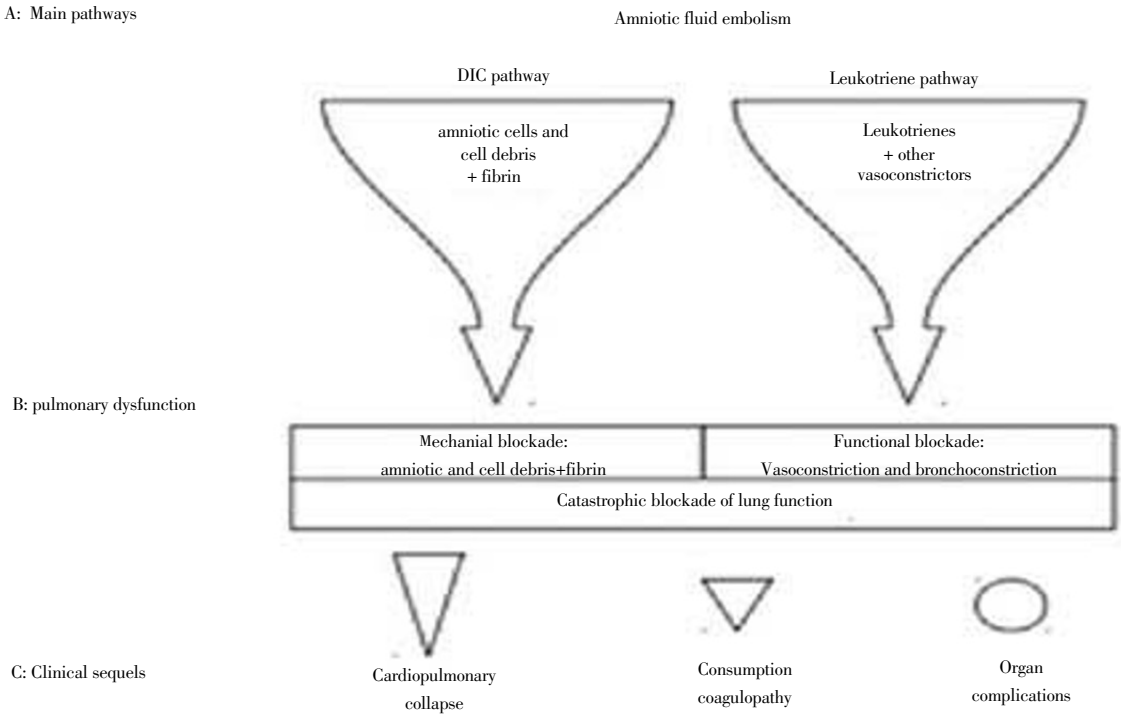

Figure 1. The mechanism of respiratory and circulatory disorders in amniotic fluid emboliom: two pathogenic pathways (A) leading to catastrophic blockade of lung function (B), and clinical sequels (C) (from [8]).

2.6. Phenomenon of the thrombogenic potential of the amniotic fluid

Interestingly, the thrombogenic action of the amniotic fluid occurs despite low concentrations of TF, a known initiator of coagulation, and of other coagulation factors in the fluid[14-16]. How in that case can we explain the thrombogenic effect of the amniotic fluid? In the light of studies of the last decade, during embolism the amniotic cells not only block mechanically the pulmonary vessels but also play an active pathogenic role, by inducing intravascular coagulation in the form of microthrombi (DIC) in pulmonary circulation, and sometimes – macrothrombi (pulmonary artery and intracardiac thrombi).

Amniotic cells acquire spectacular procoagulatory properties (procoagulant-like activity) in the process of apoptosis, which they permanently undergo. As Zhou *et al.*[25] showed, membranes of apoptotic amniotic cells are the site of thrombin generation. If these cells flow with blood into the pulmonary vessels, they become the site of DIC and can be compared to burning flares that kindle fire, as postulated by Uszyński in his integrated concept of AFE[10].

The molecular mechanism of thrombin generation on the surface of the amniotic cells (for ref. see[25]) is as follows: apoptosis leads to externalization of the aminophospholipid, phosphatidylserine (PS) – from the inner layer of the cell membrane to its external layer. Due to its negative charge, PS can accumulate TF and other coagulation factors on the cell membranes, *e.g.*, those factors which obtained positive charge in interaction with calcium ions (Ca^{++}). At that time, there are optimal conditions for interaction between coagulation factors (proximity, area). Thus, interaction of TF

with VIIa factor yields the TF/VIIa complex and later the TF/VIIa/X tenase complex, which in the presence of calcium ions (prothrombinase) transforms prothrombin into the active serine enzyme, thrombin (Figure 2).

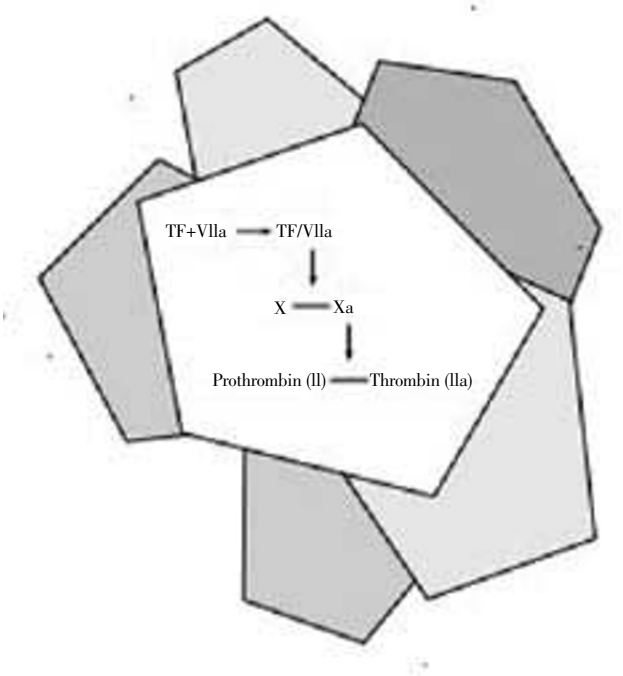

Figure 2. A simplified scheme of thrombin generation on the surface of apoptosis-affected amniotic cells.
The surface of apoptosis-affected amniotic cells becomes the accumulation site for coagulation factors: tissue factor, TF, factor VIIa, factor X and prothrombin (factor II), which interact giving rise to thrombin. TF: tissue factor; VII: factor VII (activated form: VIIa); X: factor X (activated form: Xa).

It can be easily noticed that the mechanism of coagulation initiation in the amniotic cells as described by Zhou *et al*.[25] is similar to the cell-based model of hemostasis, as postulated by Hoffman and Monroe in 2001[26]. The only difference refers to the cells that show thrombin generation, *i.e*., amniotic cells in AFE, whereas normally, the reaction occurs on the surface of blood platelets and fibroblasts.

Conflict of interest statement

We declare that we have no conflict of interest.

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