

## Factor VIIa treatment of DIC as a clinical manifestation of amniotic fluid embolism in a patient with fetal demise

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### Abstract

**Introduction** A pregnant patient, with term intrauterine fetal demise, who developed cardiopulmonary arrest during labor, followed by disseminated intravascular coagulation (DIC) secondary to amniotic fluid embolism (AFE) that was treated with Recombinant Factor VIIa, is presented.

**Case report** A 22-year-old Turkish woman was admitted to our antenatal clinic at 39 weeks 6 days of gestation with a complaint of decreased fetal movements for the previous 3 days. Shortly after presentation, she was noted to have circumoral cyanosis with shortness of breath and sudden loss of consciousness. After a 3,220 g macerated male fetus was delivered, persistent bleeding occurred in the mother and was managed with Recombinant Factor VIIa at a dose of 90 mcg/kg. She died 8 days after the admission due to multiple organ failure.

**Conclusion** Recombinant Factor VIIa may be a treatment option for hemorrhage in patients with DIC related to AFE.

**Keywords** Hematologic and clotting ·  
Critical care obstetrics · Postpartum hemorrhage ·  
Cardiovascular diseases · Stillbirth

### Introduction

Amniotic fluid embolism (AFE) is a rare but catastrophic complication of pregnancy. The incidence of AFE ranges from 1/8,000 to 1/80,000 pregnancies with a mortality rate of 61–86% [1, 2]. It accounts for 10% of maternal deaths and is the fifth most common cause of maternal mortality [1]. It has a variable presentation ranging from mild symptoms of organ dysfunction to hypoxia, sudden cardiovascular collapse, disseminated intravascular coagulation (DIC) and death. Historically, cardiovascular collapse was believed to result from mechanical obstruction of the pulmonary circulation by amniotic fluid debris [3]. But more recent articles suggested that AFE results from an anaphylactoid reaction to fetal antigens [4]. Suspected risk factors include hyperstimulated labor, multiparity, increased gestational age, fetal death, oxytocin and other uterine stimulant use [2, 5].

Amniotic fluid embolism usually presents during labor, but there are reports that describe the occurrence during cesarean section and second trimester pregnancy termination [6, 7]. AFE is a diagnosis of exclusion in a pregnant patient presenting with cardiovascular collapse.

In this report we present a patient, with term intrauterine fetal demise, who developed sudden hypoxic respiratory failure, cardiopulmonary arrest, and heavy uterine bleeding related to DIC that was managed with Recombinant Factor VIIa.

### Case report

A 22-year-old, gravida 1, para 0, Turkish woman was admitted to our antenatal clinic for the first time at 39 weeks 6 days of gestation with a complaint of decreased fetal movements for the prior 3 days. Ultrasonographic examination revealed a fetus with sonographic measurements

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concordant with 34 weeks of gestation and without cardiac activity. She was admitted to hospital and induction with low dose oxytocin was started. Cervical dilatation was 2 cm with 60% effacement at her admittance with a blood pressure of 110/70 mmHg and heart rate of 80 beats per min. Physical examination was normal except for 1(+) pretibial edema and petechial lesions around the medial malleolus of the right leg. A baseline blood coagulation panel that consisted of INR, PT, aPTT, fibrinogen, hemoglobin, and platelet count was all normal, and her urinalysis demonstrated no proteinuria. Her past medical history was insignificant, with no history of allergy or epileptic seizures.

Two and half hours after starting oxytocin induction, cervical dilatation was at 10 cm, effacement was at 100%, and the fetal head was at +3 station. She was taken to the delivery room and was noted to have circumoral cyanosis with shortness of breath and sudden loss of consciousness. Subsequent hypoxic respiratory failure ensued, bag mask ventilation started, and a 3,220 g macerated male fetus was delivered. Post-delivery, peripheral pulses were lost and an electrocardiogram (ECG) revealed arrhythmia without pulse, endotracheal intubation was achieved and cardiopulmonary resuscitation (CPR) was started. Epinephrine 1 mg and atropine 1 mg were given intravenously along with crystalloid infusion. The patient had 2 min of CPR prior to recovery. But 10 min later, ECG revealed asystole again and CPR was restarted. Advanced cardiac life support (ACLS) continued for 45 min. After the patient was stabilized, a profound vaginal bleeding was noted and 40 units of oxytocin was added to lactated ringers solution and given over 15 min. Additionally, methergine 0.2 mg was given by intramuscular injection to secure uterine tone. A Foley catheter was placed and gross hematuria was noted. Immediate blood coagulation panel study revealed that PTT and PT levels were within undetectable ranges, fibrinogen and D-dimer levels were 25 mg/dl and >20 ng/ml, respectively. Based on the laboratory and clinical signs it was thought that bleeding was due to DIC. Arterial blood gas analysis levels of pH, 7.54; pO<sub>2</sub>, 84 mmHg; pCO<sub>2</sub>, 24.8 mmHg; HCO<sub>3</sub>, 24.8 mEq/l; and PaO<sub>2</sub>, 98% indicated respiratory acidosis. Since the patient was still unconscious, mannitol infusion and dexamethasone were started. The patient was transferred to the operating room and bimanual uterine massage was started for ameliorating vaginal bleeding; 13 units of fresh frozen plasma, 3 units of platelet and 3 units of packed red blood cells were given. Since the blood pressure dropped to 70/43 mmHg and vaginal bleeding still persisted, an additional four units of fresh whole blood were given and an intrauterine tamponade soaked with adrenalin was placed. In spite of aggressive crystalloid infusion and blood product replacement vaginal bleeding did not cease and the blood pressure dropped to 50/30 mmHg with a heart rate of 165 beats per min. Due to persistent bleeding Recombinant Factor VIIa at a dose of

90 mcg/kg was initiated; 30 min after the bolus, vaginal bleeding ceased and the coagulation panel improved. Another 90 mcg/kg bolus was given in order to preserve hemostasis, and the intrauterine tamponade was taken out 6 h later. Since the patient remained unconscious and neurologic symptoms did not improve, computed tomography of the brain was taken and revealed minimal edema without bleeding. The patient was transferred to the neurology intensive care unit, and she died 8 days after admission due to multiple organ failure. Autopsy could not be performed because of the objection of the patient's family.

## Discussion

Amniotic fluid embolism, also known as anaphylactoid syndrome of pregnancy, was first described by Meyer in 1926 [6]. However, it was brought to prominence by Steiner and Lushbaugh [7] who reviewed eight cases of unexpected death and found material that consisted of amniotic fluid debris in the pulmonary vasculature. The incidence of AFE ranges from 1/8,000 to 1/80,000. The variability in the incidence is attributed to the differences in clinical presentation and in confirming the diagnosis. The mortality rate of AFE is 61–86% with only 15% of survivors that remain neurologically intact [1, 2].

The diagnosis of AFE should be suspected in females after delivery, especially those with ruptured membranes, who develop sudden onset of dyspnea with hypoxia, cardiovascular collapse, and coagulopathy [8].

Amniotic fluid embolism occurs when there is a breach in the barrier between amniotic fluid and maternal circulation. The routes of entry have been proposed through the endocervical veins, placental site or at the site of uterine trauma [9]. Small tears at the lower uterine segment and endocervix are now thought to be the most likely entry sites [6, 10]. Precipitate labor and forceful uterine contractions may cause cervical tears which can be a risk factor as it was in the case presented.

Historically it was believed that AFE was due to an obstruction of pulmonary vessels by embolic material or pulmonary vasospasm in response to fetal debris (squamous cells, mucin) that resulted in an acute asphyxiation, cor pulmonale, sudden death or neurological impairment [10, 11]. Current data suggest that rather than being a simple embolic phenomenon, physiologic and haematologic sequela of AFE resembles a type I hypersensitivity reaction with mechanisms similar to anaphylaxis and septic shock. After the foreign substance enters the maternal circulation, a cascade is initiated that releases primary and secondary mediators, which in turn cause a myocardial depression, pulmonary hypertension and DIC. The nature and severity of the clinical syndrome appears to depend on the variation of the

antigenic exposure and the individual response, which explains the variety of symptoms. Clark proposed a biphasic model to explain the development of AFE. He suggested that pulmonary vasospasm and right heart failure with accompanying hypoxia was the initial hemodynamic response resulting in sudden death and neurological impairment. If the patient initially survives and enters the second phase; left heart failure, pulmonary edema and DIC develop [1].

There is no specific test that can confirm the syndrome. In postmortem examinations, amniotic fluid components can be identified with special stains and immunohistochemistry [12]. Fetal squamous cells have been recovered from the pulmonary circulation of women who had undergone pulmonary catheterization for other reasons and showed no clinical evidence of AFE [13]. More recently, studies involving monoclonal antibody TKH-2 and maternal plasma concentrations of zinc coporphyrin seem promising in the rapid diagnosis of AFE. Immunohistochemical staining employing antibody TKH-2 is a sensitive method for histological diagnosis of AFE [14, 15].

The management of AFE is supportive and is directed towards the maintenance of oxygenation, circulatory support, and the correction of the coagulopathy. If the fetus is mature and undelivered at the time of the maternal cardiac arrest, Cesarean section should be instituted as soon as possible [1, 16]. Even though 79% fetal survival rate has been reported, only 39% of them survive neurologically intact [1]. Among maternal survivors, the next serious problem will be DIC and uterine atony which should be treated with aggressive fluid and blood product replacement. The Recombinant Factor VIIa may be utilized to maintain hemostasis before operative measures such as hypogastric artery ligation or hysterectomy are undertaken especially in young patients whose fertility preservation is important [17–20]. Aprotinin, also known as bovine pancreatic trypsin inhibitor, BPTI (Trasylol, Bayer) is a protein, that is used to reduce bleeding during complex surgery by inhibiting the fibrinolysis. Trasylol was entirely and permanently withdrawn in May 2008 although a case that was effectively managed with aprotinin to control the coagulopathy associated with AFE was reported by Stroup et al. [21].

In conclusion, AFE is a devastating, unpreventable and unpredictable complication of pregnancy with high mortality and morbidity rates for both the mother and the fetus. A high index of suspicion of AFE and the prompt institution of resuscitative measures may improve outcomes.

**Conflict of interest statement** None.

## References

- Clark SL, Hankins GDV, Dudley DA, Didly GA, Porter TF (1995) Amniotic fluid embolism; analysis of the national registry. *Am J Obstet Gynecol* 172:1158–1169. doi:10.1016/0002-9378(95)91474-9
- Morgan M (1979) Amniotic fluid embolism. *Anaesthesia* 34:20–32. doi:10.1111/j.1365-2044.1979.tb04862.x
- Davies S (2001) Amniotic fluid embolus: a review of the literature. *Can J Anaesth* 48:88–98
- Benson M, Lindberg R (1996) Amniotic fluid embolism, anaphylaxis, and tryptase. *Am J Obstet Gynecol* 175:737. doi:10.1053/ob.1996.v175.a74918
- Steiner PE, Lushbaugh CC (1941) Maternal pulmonary embolism by amniotic fluid. *JAMA* 117:1340–1345
- Mason RG (1992) Amniotic fluid embolism. *Clin Chest Med* 13:657–665
- Steiner PE, Lushbaugh CC (1986) Maternal pulmonary embolism by amniotic fluid as a cause of obstetric shock and unexpected deaths in obstetrics. *JAMA* 255:2187–2203. doi:10.1001/jama.255.16.2187
- Ray BK, Vallejo MC, Creinin MD, Shannon KT, Mandel GL, Kaul B, Ramanathan S (2004) Amniotic fluid embolism with second trimester pregnancy termination: a case report. *Can J Anaesth* 51(2):139–144
- Courtney LD (1974) Amniotic fluid embolism. *Obstet Gynecol Surv* 29:169–177. doi:10.1097/00006254-197403000-00001
- Mc Doughall RJ, Duke GJ (1995) Amniotic fluid embolism syndrome: case report and review. *Anaesth Intensive Care* 23:735–740
- Clark SL (1990) New concepts of amniotic fluid embolism: a review. *Obstet Gynecol Surv* 45:360–368. doi:10.1097/00006254-199006000-00003
- Marcus BJ, Collins KA, Harley RA (2005) Ancillary studies in amniotic fluid embolism: a case report and review of the literature. *Am J Forensic Med Pathol* 26:92–95. doi:10.1097/01.paf.0000154255.67466.8e
- Clark SL, Pavlova Z, Greenspoon J, Horenstein J, Phelan JP (1986) Squamous cells in the maternal pulmonary circulation. *Am J Obstet Gynecol* 154:104–106
- Kobayashi H, Ohi H, Terao T (1993) A simple non invasive, sensitive method for diagnosis of amniotic fluid embolism by monoclonal antibody TKH-2 that recognises NeuAc2-6GalNAc. *Am J Obstet Gynecol* 168:848–853
- Kanayama N, Yamazaki T, Naruse H, Suminoto K, Horiuchi K, Terao T (1992) Determining zinc coproporphyrin in maternal plasma- a new method for diagnosing amniotic fluid embolism. *Clin Chem* 38:526–529
- Lawson HW, Atrash HK, Franks AL (1990) Fatal pulmonary embolism during legal induced abortion in the United States from 1972 to 1985. *Am J Obstet Gynecol* 162:986–990
- Lim Y, Loo CC, Chia V, Fun W (2004) Recombinant Factor VIIa after amniotic fluid embolism and disseminated intravascular coagulopathy. *Int J Gynaecol Obstet* 87(2):178–179. doi:10.1016/j.ijgo.2004.08.007
- Segal S, Shemesh I, Blumental R, Yoffe B, Laufer N, Mankuta D, Mazor M, Zohar S, Schiff E, Martinovitz U (2004) The use of Recombinant Factor VIIa in a severe postpartum hemorrhage. *Acta Obstet Gynecol Scand* 83:771–772. doi:10.1111/j.0001-6349.2004.00501.x
- Boehlen F, Morales MA, Fontana P, Ricou B, Irion O, Moerloose P (2004) Prolonged treatment of massive postpartum hemorrhage with recombinant factor VIIa: case report and review of the literature. *BJOG* 111:284–287. doi:10.1111/j.1471-0528.2004.00058.x
- Mato J (2008) Suspected amniotic fluid embolism following amniotomy: a case report. *AANA J* 76(1):53–59
- Stroup J, Haraway D, Beal JM (2006) Aprotinin in the management of coagulopathy associated with amniotic fluid embolus. *Pharmacotherapy* 26(5):689–693