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Running Head: Excessive fibrinolysis in amniotic fluid embolism
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Abstract

Amniotic fluid embolism (AFE) is a catastrophic condition in the peripartum period and still remains as a leading cause of maternal death. Although over 80% of cases of AFE cases are accompanied by coagulopathy, the pathology of disseminated intravascular coagulation is not well understood not only because of its rarity but also because of the limited availability of laboratory testing in emergent clinical settings. We describe a case of AFE whose characteristic data for coagulation and fibrinolysis were timely depicted with sequential thromboelastography. We believe that the point-of-care, which provides information for both coagulopathy and fibrinolysis, may provide crucial data not only for the treatment of postpartum hemorrhage in daily clinical practice but also for the elucidation of AFE pathophysiology.

Amniotic fluid embolism (AFE) is a catastrophic condition in the peripartum period and still remains as a leading cause of maternal death despite its rarity. Clinical manifestation of AFE varies from sudden cardio-respiratory collapse to postpartum hemorrhage (PPH) [1]. Although it is presumed that over 80% of cases of AFE cases are accompanied by coagulopathy [1], the pathology of disseminated intravascular coagulation (DIC) is not well understood not only because of rarity of AFE but also because of the limited availability of laboratory testing in emergent clinical settings. Recently, point-of-care viscoelastometric methods, such as thromboelastography (TEG®) and rotational thromboelastometry (ROTEM®), have been used to monitor blood coagulation in obstetrics [2-6], although sufficient data on serial TEG/ROTEM measurements in normal patients during immediate postpartum period are not established yet. We describe a case of AFE whose characteristic data for coagulation and fibrinolysis were timely depicted with sequential TEG.

A 36-year-old healthy multiparous woman, who conceived spontaneously, was referred to our hospital at a 30-week gestational age (GA) due to low-lying placenta. Her coagulation laboratory data at 36w GA showed completely normal values (platelet count: 193000/μL, prothrombin time (PT): 11.5 sec, activated partial thrombin time (APTT): 24.3 sec, fibrinogen: 417 mg/dL, and fibrinogen degenerated product (FDP): 7.4 μg/mL). Although the placental location was normalized during her subsequent pregnancy course, labor induction was scheduled because the fetal weight was estimated as large-for-dates. The mother delivered a healthy boy vaginally by the induction of labor with oxytocin at 39w GA (3650 g with Apgar score 9 and 9, 1 minute and 5 minutes, respectively) and the placenta was delivered smoothly 4 minutes later. Although she did not complain of dyspnea, percutaneous monitoring of oxygen saturation (SpO_2) suddenly dropped to 88 %, which recovered promptly to 97% with deep breathing in room air. In the meantime, uterine bleeding supposedly caused by uterine atony continued reaching approximately 1000mL at 28 mins after delivery. A Bakri balloon was then inserted into the uterine cavity, and a venous blood sample was taken for laboratory testing including for TEG (TEG 6s, Haemonetics Corporation, Braintree, MA). The TEG tracing revealed excessive fibrinolysis as LY30 (percent clot lysis at 30 minutes) for 35.8% (normal range: 0.0 – 2.6%) at that moment, although maximum amplitude (MA), which indicates maximum clot strength, was slightly lower at 49.2 mm and Angle, which reflects the formation rate of blood clot and the function of fibrinogen, still stayed normal at 65.1 degree (Figure1a. Normal ranges are 52-69mm and 63-78 degree, for MA and Angle, respectively). Because the bleeding continued even with the insertion of the Bakri-balloon, uterine artery embolization by the percutaneous procedure was attempted by the radiologists. The

patient, however, developed shock vital signs with heart rate 180 bpm and systolic blood pressure 50 mmHg during radiological procedure. A hysterectomy was subsequently performed with the placement of intra-aortic balloon occlusion for the sake of stabilizing maternal circulation and minimizing bleeding during the operation. The results of the TEG tracings just at the time of the hysterectomy 3.5 hours after delivery, as well as the other tracings after maternal vital signs had stabilized at 6 hours post-delivery are shown in Figure1b and 1c. Note that normalized fibrinolyses were observed, although the indices for coagulation, including MA and Angle, had not normalized yet in both moments. Estimated total blood loss was about 11,000mL, and total administration of blood products were 600mL autologous blood, 38 units RBC, 14units FFP, 20 units PC, and 5 packs of cryoprecipitate. The patient's subsequent postpartum course was uneventful, and she was discharge from hospital 12 days after delivery and without any further complications.

There has been much controversy as to whether a consumptive coagulopathy rapidly occurs, or an excessive fibrinolysis precedes, regarding the cause of massive hemorrhage in AFE. Because fibrinogen/fibrin degradation products and D-dimers indirectly reflect fibrinolysis, these parameters are not able to give answers that settle this controversy. On the other hand, point-of-care, including TEG and ROTEM, readily visualize fibrinolytic activity. Collins. et. al. firstly observed hyper-fibrinolysis in the very early phase of an AFE case where the patient had undergone a cesarean delivery at 29w GA due to a fully dilated uterine cervix with the fetus in a transverse position [2]. Interestingly, resolution of hyper-fibrinolysis was observed just 1 hour after the initial ROTEM tracing. Their observation is quite similar with ours regarding the detection of hyper-fibrinolysis and its prompt resolution after adequate treatment. However, another four reports of AFE assessed blood samples with ROTEM did not detect hyper-fibrinolysis [3-6]. This discrepancy might be explained by the rather late timing of blood sampling in the latter four reports, because the phase of the disease might progress in extremely rapid fashion. Taken together with the facts mentioned above, our observation in this case strongly suggests that excessive fibrinolysis might precede coagulopathy in the process of AFE pathology and that hyper-fibrinolysis might not be observed any more after devastating degeneration of the fibrinogen and fibrin. In other words, obstetricians should keep in mind that the timing of blood sampling is very important for understanding the phase of a disease which progresses in extremely rapid fashion. Otherwise, one might just see the final condition after the chain reaction like a domino falling, which is thought to be triggered by contact with fetal material. In this sense, Annecke et. al. wisely advocated ' Stop hyper-fibrinolysis ' in the therapy algorithm for acquired coagulopathy in

postpartum hemorrhage [3]. We believe that the point-of-care, which provides information for both coagulopathy and fibrinolysis, may provide crucial data not only for the treatment of PPH in daily clinical practice but also for the elucidation of AFE pathophysiology. Case accumulation is further needed to establish adequate treatment for AFE.

Compliance of Ethical Standards

Conflict of Interest: The authors have no conflict of interest to declare.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from the patient included in this article.

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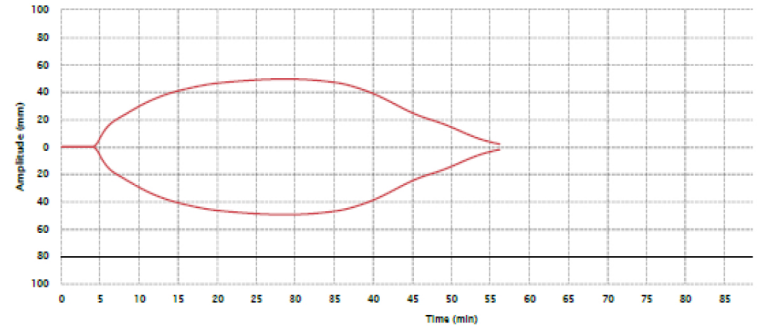
Figure Legends

Thromboelastgraphy (TEG) traces in this case. TEG trace showing excessive hyper-fibrinolysis and almost normal coagulation (LY30: 35.8%, MA: 49.2 mm, and Angle 65.1 degree) at 28min after delivery (a) and laboratory data were; platelet count: 208000/μL, prothrombin time (PT): 11.8 sec, activated partial thrombin time (APTT): 34.3 sec, fibrinogen: 198 mg/dL fibrinogen degenerated product (FDP): 633.6 μg/mL, and d-dimer: 232.7μg/mL. TEG trace with normalized fibrinolysis and disturbed coagulation (LY30: 0%, MA: 29.5, and Angle: 53.2 degree) after 3.5 hour with massive transfusion and hysterectomy (b), and laboratory data were; platelet count: 90000/μL, PT: 18.9 sec, APTT: 91.7 sec, fibrinogen: 54 mg/dL FDP: 271 μg/mL, and d-dimer: 119μg/mL. TEG trace with normal fibrinolysis and decreased coagulation (LY30: 0%, MA: 44.4, and Angle: 60.3 degree) after 6 hour with stable vital signs (c), and laboratory data were; platelet count: 233,000/μL, PT: 12.3 sec, APTT: 34.2 sec, fibrinogen: 176 mg/dL FDP: 95.9 μg/mL. The normal ranges of each TEG parameters are 0.0-2.6%, 52-69 mm, and 63-78 degree, for LY30, MA, and Angle, respectively).

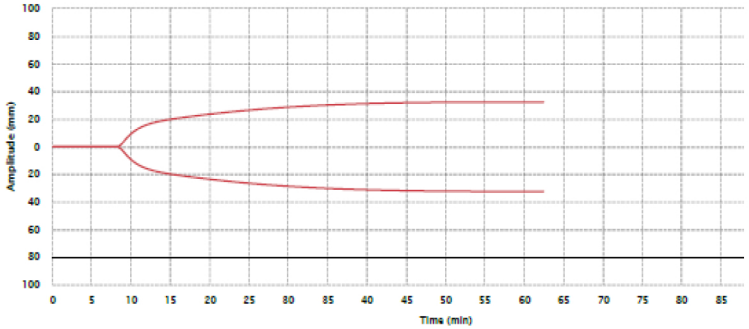
Figure1

(a)



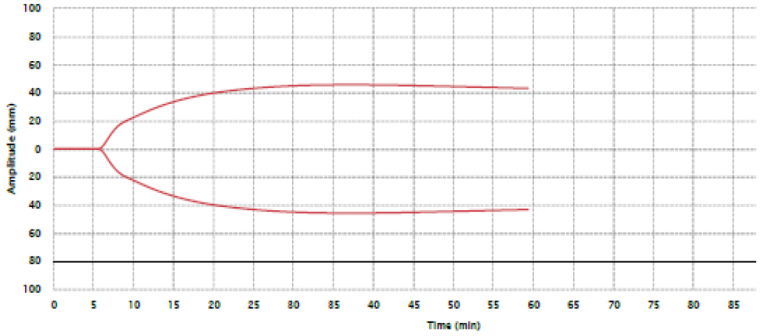
	TEG-ACT (sec)	R (min)	K (min)	ANGLE (deg)	MA (mm)	LY30 (%)
CK		4.6	2.5	65.1	49.2	35.8
		4.6 - 9.1	0.8 - 2.1	63 - 78	52 - 69	0.0 - 2.6

(b)



	TEG-ACT (sec)	R (min)	K (min)	ANGLE (deg)	MA (mm)	LY30 (%)
CK		8.8	6.4	53.2	29.5	0.0
		4.6 - 9.1	0.8 - 2.1	63 - 78	52 - 69	0.0 - 2.6

(c)



	TEG-ACT (sec)	R (min)	K (min)	ANGLE (deg)	MA (mm)	LY30 (%)
CK		6.2	2.9	60.5	44.8	0.7
		4.6 - 9.1	0.8 - 2.1	63 - 78	52 - 69	0.0 - 2.6