Fibrinogen for the management of critical obstetric hemorrhage

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Abstract

Aim: In cases of critical obstetric hemorrhage leading to extreme hypofibrinogenemia, fibrinogen is the marker that indicates the critical severity, and early fibrinogen supplementation centering on hemostatic resuscitation is a vital treatment to stabilize a catastrophic condition. In this review, we investigated the effect of fibrinogen level on hemostasis and what we can do to treat hypofibrinogenemia efficiently and improve patients' outcome.

Methods: We reviewed numerous articles related to hypofibrinogenemia in critical obstetric hemorrhage. Especially, we performed a systematic review on target value of fibrinogen for hemostasis and effectiveness of fibrinogen concentrate. We also reviewed the articles about the methods for early normalization of fibrinogen level such as tranexamic acid, massive transfusion protocol, and point-of-care testing.

Results: The target value of fibrinogen calculated by needs for massive transfusion was 200 mg/dL or 10 mm of $A5_{FIBTEM}$. Although fibrinogen concentrate worked poorly on fibrinogen levels within the normal range, it improved the blood fibrinogen levels rapidly when it was administered to critical obstetric hemorrhage patients with serious hypofibrinogenemia. Hence, the volume of FFP transfused could be reduced along with a reduction in the frequency of pulmonary edema due to volume overload.

Conclusion: The patient group for which fibrinogen concentrate works most effectively is cases with severe hypofibrinogenemia. Further research is required in the light of evidence. The essence of the transfusion algorithm in critical obstetric hemorrhage is to approach the target value for obtaining hemostasis, ensure an accurate and prompt grasp of the severity using point-of-care testing, introduce a massive transfusion protocol and use tranexamic acid.

Key words: coagulopathy, critical obstetrical hemorrhage, disseminated intravascular coagulation, fibrinogen, fibrinogen concentrate, fresh frozen plasma.

Introduction

Critical obstetric hemorrhage (COH) is a collective term for obstetric hemorrhage related to the life of the pregnant woman, where there is a critical situation requiring rapid transfusion (not only red blood cell [RBC] concentrate but fresh frozen plasma [FFP] or platelet concentrate) and intensive team management. COH is still the largest cause of maternal death in Japan, above both thromboembolism and cerebrovascular disorder, and is responsible for 23% of maternal deaths.[1] In COH, coagulopathy easily develops due to the physiological change of blood coagulation and fibrinolytic function in pregnant women during late pregnancy,[2] and it is difficult to evaluate the severity due to the volume of blood loss.[3] Blood fibrinogen concentration has been suggested as an indicator of its severity.[4–6]

The mechanism of hemostasis includes primary hemostasis through platelet adhesion and aggregation and secondary hemostasis using coagulation factors.[7]

In COH, the frequency with which platelet transfusion is required for hemostasis failure due to abnormal platelet count is lower than the frequency of blood transfusion performed for coagulation factor supplementation in response to coagulopathy.[8]

The main condition of hemostatic failure in COH is coagulopathy, which is secondary hemostasis. There are two causes of the coagulation disorders seen in COH. One is consumption coagulopathy where tissue factors that flow into the maternal bloodstream activate the exogenous coagulation factors forming a complex with activated factor VII and consuming fibrinogen leading to a decrease in the blood concentration of fibrinogen. The second is dilutional coagulopathy,[9] in which there is large-scale loss of coagulation factors with reduced blood circulation due to massive blood loss. Furthermore, massive infusion to secure circulating blood volume or blood transfusion without coagulation factors further promotes the decrease in blood coagulation factor concentration.[10]

Although these conditions are not completely different from one another and are difficult to clearly distinguish during treatment, their commonality with consumption plus dilutional coagulopathy is that the fibrinogen concentration serves as a marker of critical severity,[5,6,11,12] and that early fibrinogen supplementation is vital to avoid coagulopathy in COH.

Due to the physiological changes in coagulation and fibrinolysis unique to pregnant women, the necessary blood concentration of fibrinogen and the effect of fibrinogen concentrate for fibrinogen supplementation might be different in the field of obstetrics other than the field of cardiovascular surgery or trauma, and there is no specialized review in the field of obstetrics. In this paper, we will consider the physiological blood changes in pregnant women, provide a review specialized in the field of obstetrics and discuss the possibility that early normalization of fibrinogen can improve a patient's prognosis. Furthermore, the necessary blood concentration of fibrinogen and the effect of fibrinogen concentrate in pregnant women will be evaluated by a systematic review.

Hemostatic Resuscitation

If sufficient coagulation factor replenishment is performed at an early stage, the patient's prognosis may be improved. In a process called hemostatic resuscitation, 'local surgical hemostasis' and 'improvement of coagulopathy' are carried out simultaneously to improve the patient's condition.[13] Conventionally for hypotensive shock caused by massive hemorrhage, circulating blood volume is secured by maintaining blood pressure through administration of a crystalloid liquid.[14,15] On the other hand, a large infusion volume to maintain blood pressure can decrease the concentration of coagulation factor in the blood by dilution, making the coagulopathy severe and exacerbating hemorrhage due to the failure of thrombus formation.[16] It has been shown that even before dilutional coagulopathy caused by large-volume infusion occurs, tissue disorders manifest because of low blood reflux due to massive blood loss, which may result in severe coagulopathy.[17] That is, hypoperfusion into tissues due to massive blood loss increases the production of thrombomodulin in vascular endothelial cells; thrombomodulin binds with thrombin to form the thrombin-thrombomodulin complex (thrombin-TM-C). Although fibrinogen makes fibrin thrombus in the presence of thrombin, because thrombin is used for thrombin-TM-C as described above, the production of fibrin thrombus is reduced. Additionally, thrombin-TM-C promotes the activation of Protein C, and activated Protein C irreversibly inhibits factors Va and VIIIa and induces coagulopathy while suppressing plasminogen activator inhibitor-1 and promoting an increase in tissue plasminogen activator (tPA). Hence, plasmin production increases and promotes the enhancement of the fibrinogen-degrading fibrinolysis system (Fig. 1).

To prevent such conditions, coagulation factors should be supplemented in advance using FFP and concentrated coagulation factor preparations. It would be wise to focus on maintaining tissue reflux while at the same time using blood fibrinogen concentration, which has the strongest correlation with the severity of a coagulation disorder, as an indicator to improve the treatment for the coagulation disorder. Furthermore, it is possible that a patient's prognosis can be improved through treatments based on hemostatic resuscitation that abruptly raise blood fibrinogen concentration using a concentrated clotting factor preparation rather than FFP, thereby preventing a coagulation disorder.

Hypofibrinogenemia

To normalize fibrinogen at an early stage, it is necessary to know the fibrinogen level, which enables hemostasis in pregnant and parturient women. We conducted a comprehensive literature search for the

Figure 1 Mechanism of onset of coagulopathy in blood vessel due to low reflux. Hypoperfusion of tissues due to massive blood loss increases the production of thrombomodulin in vascular endothelial cells and promotes the activation of Protein C. Protein C irreversibly inhibits factors Va and VIIIa, causing coagulopathy and, at the same time, inhibiting plasminogen activator inhibitor-1 and promoting the enhancement of the fibrinolytic system.
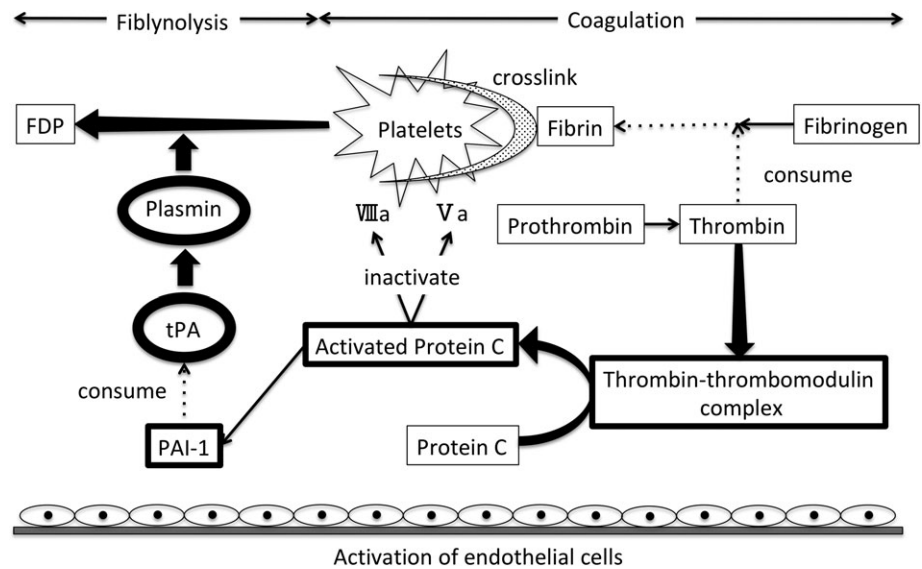
blood concentration of fibrinogen that could stop bleeding. In a PubMed search, 'fibrinogen concentrate' was confirmed in 674 papers, while fibrinogen was relevant in 59 120 papers. We targeted research work where more than 50% of the target patients were obstetrics patients and, in terms of the format of research, randomized controlled trials and quantitative systematic reviews were selected as interventional studies, while qualitative reviews were excluded. In the observational studies, case reports with less than five cases were excluded. The screening resulted in 12 studies that were confirmed as targeting obstetric patients.

To investigate the optimal blood concentration of fibrinogen, interventional studies that analyzed the outcome by keeping the blood fibrinogen concentration at a constant value is the most reliable method, but in practice it is difficult due to the ethical issues surrounding patient life-saving in COH. As for observational studies, we confirmed three prospective multicenter observational studies and two retrospective

observational studies (Table 1). In a prospective study, Charbit et al. analyzed the blood coagulation function parameters of 128 patients with post-partum hemorrhage (PPH) and reported that if the fibrinogen level at the time of a massive blood loss is less than 200 mg/dL, 100% of positive predictive value (PPV) cases develop into severe PPH (a case where Hb <4 g/dL, erythrocyte transfusion of ≥4 units, transcatheter arterial embolization (TAE) or vascular ligation, or a total hysterectomy was required).[11] Cortet et al. reported that 99.3% of PPV cases develop into severe PPH (a case where Hb <4 g/dL, erythrocyte transfusion, TAE or emergency surgical hemostasis, or intensive care unit admission was required) when fibrinogen at PPH onset falls below 200 mg/dL.[12] Collins et al. reported that for 356 patients with obstetric hemorrhage, $A5_{FIBMBTEM}$ (a parameter provided by a rotation thromboelastometry [ROTEM]) was an independent prognostic factor of blood loss of ≥2500 mL, ≥4 units of RBC transfusion and ≥8 units of allogeneic blood transfusion. Additionally, $A5_{FIBMBTEM}$

Table 1 Cut-off value of fibrinogen developing post-partum hemorrhage

Author	Country	Year	Cut-off value of fibrinogen	Risk factor	Number
Charbit et al.	France	2007	200 mg/dL	PPH	128
Cortet et al.	France	2012	200 mg/dL	PPH	323
Collins et al.	UK	2014	$A5_{FIBMBTEM}$ = 10 mm	PPH	356
Era et al.	Japan	2015	130 mg/dL	RCC 10 unit over	80
			200 mg/dL	FFP 10 unit over	
Wang et al.	Japan	2016	155 mg/dL	RCC 6 unit over	61
			120 mg/dL	FFP 10 unit over	

FFP, fresh frozen plasma; PPH, post-partum hemorrhage; RCC, red cell concentrate.

less than 10 mm or fibrinogen less than 200 mg/dL was related to prolonged bleeding, invasive surgery for hemostasis and transfusion treatment at an early stage.[18]

As a retrospective study, Era *et al.* reported that for 80 patients with COH, the fibrinogen cut-off value indicating a requirement of ≥10 units of RBC was 130 mg/dL, and the fibrinogen cut-off value indicating a requirement of ≥10 units of FFP was 200 mg/dL.[5] Wang *et al.* reported that for 61 patients with placental abruption, the predelivery fibrinogen cut-off values indicating a requirement of 6 and 10 units of RBC were 155 and 75 mg/dL, respectively, while the predelivery fibrinogen cut-off values indicating a requirement of 10 and 20 units of FFP were 120 and 98 mg/dL, respectively.[6]

Previous studies that defined hypofibrinogenemia used a method to calculate the cut-off value of fibrinogen as a factor which predicts the progression to massive blood loss and massive transfusion. In the five studies that investigated the cut-off value of fibrinogen, the definitions of cut-off value, number of units of transfusion and the volume of blood loss in massive blood loss are somewhat different. However, what has been calculated is the cut-off value when massive transfusion is required for massive blood loss, and the general opinion is that this value is when fibrinogen is less than 200 mg/dL or $A5_{FIMBTEM}$ is less than 10 mm. Although some variation is plausible depending on the condition of mass blood loss, we would recommend these values be used as a warning. Normal blood concentration of fibrinogen in pregnant women in their third trimester rises close to 500 mg/dL.[19–21] The minimum amount of fibrinogen necessary for hemostasis is 40–50% of the normal concentration, whereas the minimum amount of coagulation factors other than fibrinogen is 20–25%.[22] Even when considering the normal amount of fibrinogen specific to pregnant and parturient women, the observations agree with the results of this research.

Effectiveness of Fibrinogen Concentrate

Rapid normalization of the blood fibrinogen level decreases the volume of blood loss.[23] FFP is currently used in Japan to replenish coagulation factors, but the amount of fibrinogen in FFP is smaller than that in fibrinogen supplementation.[24] When coagulation factors are supplemented using only FFP, a large amount of FFP that exceeds the volume of RBC transfused would be required.[8] When supplementing coagulation factors using only FFP, several issues are encountered: A large amount of FFP for supplementation of coagulation factors frequently causes pulmonary edema due to increases in circulating blood volume[5]; FFP melting requires manpower and time, and quick replenishment of coagulation factors is thus difficult; and mass blood loss would be further prolonged if the administration of FFP is delayed which would exacerbate coagulopathy.[25] To rapidly raise blood fibrinogen level, fibrinogen concentrate has been approved and is being used in developed countries within Europe such as Austria, Germany and the Netherlands,[26] and its use is also recommended in the guidelines.[26,27] There are no insurance indications in Japan, and there is little distribution of fibrinogen concentrate that can be used. As fibrinogen concentrate seems to be useful for efficient coagulation factor supplementation, we carried out a comprehensive literature search looking for the effects of the administration of fibrinogen concentrate.

We confirmed two interventional studies and five retrospective observational studies (Table 2) that examined the effect of fibrinogen concentrate in the field of obstetrics. In interventional studies, Wikkelso *et al.* reported that the volume of blood loss was ≥500 mL with vaginal delivery and ≥1000 mL with cesarean section, and that prophylactic administration of 2 g of fibrinogen concentrate had no effect on the 249 patients with obstetric hemorrhage and normal blood fibrinogen levels.[28] Collins *et al.* reported that, despite randomized double-blind placebo-controlled

Table 2 Evidence on the effectiveness of fibrinogen concentrate for post-partum hemorrhage

Author	Country	Year	Type of study	Comparison with non-users	Number	Effectiveness
Wikkelso *et al.*	Denmark	2015	RCT	+	249	−
Collins *et al.*	UK	2017	RCT	+	55	−
Bell et al	UK	2010	Case reports	−	6	+
Ahmed *et al.*	Ireland	2012	Retrospective	+	77	+
Kikuchi *et al.*	Japan	2013	Retrospective	−	18	+
Makino *et al.*	Japan	2015	Retrospective	−	101	+
Matsunaga *et al.*	Japan	2017	Retrospective	+	137	+

RCT, randomized controlled trial.

tests performed in 55 patients of critical obstetrics hemorrhage with $A5_{FIMBTEM}$ less than 12 mm and the volume of blood loss between 1000 to 1500 mL, fibrinogen concentrate did not prove efficacious in reducing the volume of blood transfusion and blood loss.[29] In this study, there were as few as seven patients with fibrinogen <200 mg/dL, excluding cases with amniotic fluid embolism (a representative disease that causes extreme hypofibrinogenemia).

In a retrospective observational study, Bell et al. reported that fibrinogen concentrate used for six patients with COH and hypofibrinogenemia improved their fibrinogen levels and that its administration would be rapid at small volumes.[30] Ahmed et al. identified 77 patients with COH whose dose of fibrinogen concentrate had a stronger correlation with a rise in blood fibrinogen level than cryoprecipitate. These results suggested that, while there was no significant difference, this would tend to reduce the volume of blood loss and the amount of blood transfusion required.[31] Kikuchi et al. reported that in 18 patients with COH, administration of 1 g of fibrinogen concentrate raised fibrinogen levels by 40 mg/dL and no adverse events were observed.[32] Makino et al. conducted a nationwide survey of the usage status of fibrinogen concentrate in Japan and reported that, in 99 patients with COH, the administration of 1 g of fibrinogen concentrate raises the blood fibrinogen concentration by 32.9 ± 34.5 mg/dL.[33] We report that in 137 patients with COH and hypofibrinogenemia (fibrinogen <150 mg/dL), the administration of fibrinogen concentrate increased the blood fibrinogen level in a dose-dependent manner and reduced the ratio of FFP transfusion volume/RBC transfusion volume. Through subgroup analyses, it has been reported that for cases of super massive blood loss that required more than 18 units of RBC and in cases of placental abruption, fibrinogen concentrate reduced the volume of FFP transfusion required and decreased the incidence rate of pulmonary edema that is a complication of high-dose FFP administration.[34]

Although it is thought to be an ethical reason to ensure patient safety, interventional studies targeted patients with normal fibrinogen concentration that do not show the therapeutic significance of administering fibrinogen preparations, and we cannot identify the effect. Although fibrinogen concentrate works poorly on blood fibrinogen levels that are within the normal range, as shown by observational studies, when it is administered to COH patients with serious hypofibrinogenemia, the blood fibrinogen levels rapidly improve. Hence, the volume of FFP transfused is reduced along with a reduction in the frequency of pulmonary edema due to volume overload. With respect to obstetric hemorrhage, the patient group for which the efficacy of fibrinogen concentrate is most significant is severe cases with severe levels of coagulopathy.

Usefulness of Point-of-Care Testing to Grasp the Fibrinogen Level

To quickly replenish coagulation factors for coagulopathy, there are other things that can be done including the rapid measurement of blood fibrinogen level by point-of-care testing (POCT). There is a possibility that patient prognosis can be improved by quickly identifying low fibrinogen plasma levels and performing early intervention. TEG,[35] ROTEM[36] and dry hematology[37] are available as devices that can evaluate fibrinogen by POCT. These POCT are able to measure the fibrinogen level in approximately 10–20 min and correlate well with conventional fibrinogen quantitation using the Clauss's method.[38–40] Therefore, it is possible to grasp the severity of a patient's coagulopathy based on the fibrinogen levels at an early stage, estimate the volume of transfusion necessary and carry out appropriate transfusion therapy without an excess or deficiency. Although dilutional coagulopathy is thought to correlate somewhat with the volume of blood loss and fibrinogen levels, severe hypofibrinogenemia that is not associated with the blood loss volume is observed in consumption coagulopathy.[6] Recent analysis of the amniotic fluid embolism registry and Maternal Death Evaluation Committee recognizes 'DIC type (uterine type) amniotic fluid embolism' as a cause of COH, and the number of related reports is increasing.[41] However, it has been pointed out that even this disease can develop extreme hypofibrinogenemia that does not correspond to the volume of blood loss. It is difficult to estimate the severity of coagulopathy in the field of obstetrics from the clinical features such as the volume of blood loss.[3,42,43] Therefore, instead of examining the hypofibrinogenemia after developing to significant blood loss, the blood fibrinogen level should be tested as a screening mechanism in patients that can develop COH.

Massive Transfusion Protocol

A paper on massive transfusion protocol (MTP) in the field of trauma was published in 2007. A high FFP:RBC ratio of 1.4:1.0 for patients bleeding from trauma was an independent survival-related factor, and it
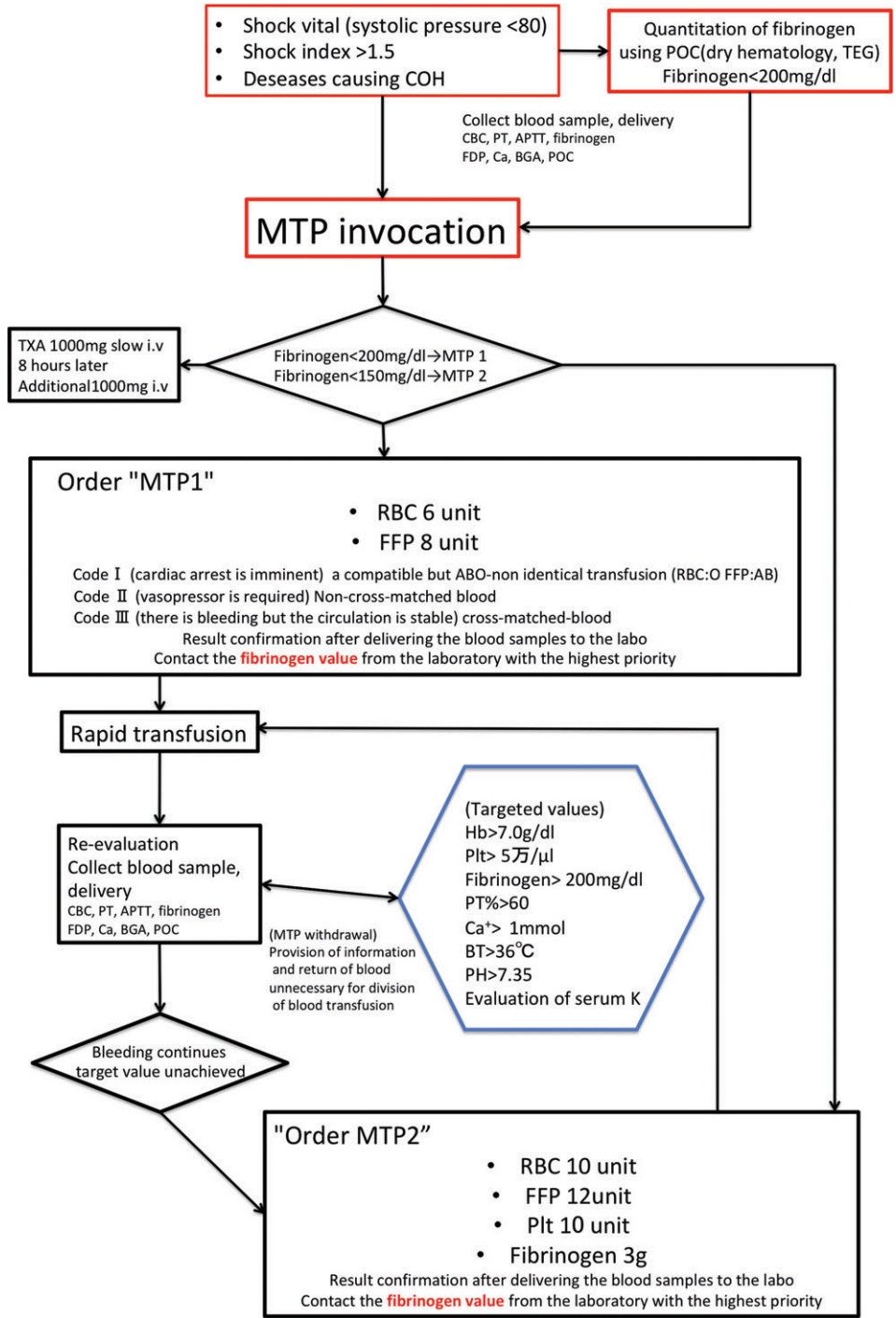
Figure 2 Massive transfusion protocol.

was recommended that FFP:RBC be administered at 1:1.[44] There are related reports in the field of obstetrics as well, and most of these reports conclude that FFP:RBC should be administered at 1:1 or more, or are preparing these protocols.[8,45–50]

Although it is considered one of the ways of practicing the theory we described in the hemostatic resuscitation section, our hospital has also created a massive blood transfusion protocol for obstetrical hemorrhage based on the aforementioned theory

Table 3 Key points

1	When coagulopathy caused by massive blood loss occurs, supplementation of coagulation factor (FFP) is necessary from the early onset in order not to worsen the disease condition.
2	The administration shall be continued to maintain an FFP:RBC ratio greater than 1:1.
3	It is desirable that supplementation of fibrinogen should be carried out at a small volume, as rapidly as possible, toward a hemostatic fibrinogen level (>200 mg/dL).
4	For serious hypofibrinogenemia, it would be ideal to replenish fibrinogen using fibrinogen concentrate.
5	In the event of coagulopathy, in the field of obstetrics, fibrinolysis too is accelerated, and administration of 1000 mg tranexamic acid is required within 3 h after onset. If bleeding continues, it is desirable to administer an additional 1000 mg dose.

FFP, fresh frozen plasma; RBC, red blood cells.

(Fig. 2). It is a therapeutic strategy focusing on the improvement of coagulopathy caused by tissue damage due to low reflux through the preliminarily supplementation of coagulation factors using FFP and fibrinogen concentrate.

The decrease in fibrinogen is due to the differences between consumption coagulopathy and dilution coagulopathy, and more FFP is required to normalize the decreased blood fibrinogen level while supplementing circulating blood volume. We administer MTP1 and MTP2, because fibrinogen concentrate can efficiently raise the blood fibrinogen level.[34] Screening of fibrinogen level is conducted using targeted POCT. Depending on the extent of the decrease in circulating blood volume, preparation for an emergency transfusion is graded from a compatible but ABO-non identical transfusion to the cross-matched compatible blood. The essence of the transfusion algorithm with COH plus extreme hypofibrinogenemia is to establish a target value that enables hemostasis, repeat rapid transfusion and evaluate the transfusion plan, in order to bring each parameter closer to the target value. We would appreciate if this can be used as one example. Creating an MTP and informing each facility promotes blood transfusions with a continued supply of transfusion preparations until completion of hemostasis,[51] thereby realizing timely transfusion therapy and a reduction in transfusion volume and treatment cost[52] (Table 3).

Tranexamic Acid

As mentioned earlier, low reflux due to mass blood loss promotes enhancement of the fibrinolytic system that increases plasmin production and promotes degradation of fibrinogen. In consumption coagulopathy, amniotic fluid and placenta-derived tissue thromboplastin form a complex with factor VII and excessively convert fibrinogen to fibrin to form microthrombi that decrease the blood concentration of fibrinogen.[53] Fibrin thrombus formation rapidly activates the fibrinolytic system and degrades fibrinogen. Plasmin and tPA are released into the blood in large amounts due to the enhancement of the fibrinolytic system. Normally, plasminogen and tPA also accelerate the degradation of fibrinogen in the presence of thrombin resulting in a further decrease of the fibrinogen blood concentration. Hence, the production of fibrinogen degradation product (FDP) – the degradation product of fibrin and fibrinogen – increases, and the FDP in the tissue inhibits the contraction of uterine smooth muscle.[54,55] Activated plasmin produces bradykinin through the degradation of polymeric kininogen.[56] Bradykinin has a smooth muscle relaxing effect and exacerbates secondary relaxation hemorrhage.

Tranexamic acid binds to the lysine-binding site of plasminogen and inhibits fibrin binding of plasminogen, thereby suppressing the enhanced fibrinolytic system. It has also been reported that it is possible to decrease the volume of blood loss and transfusion using tranexamic acid concomitantly,[57–59] where administration within 3 h of onset is said to improve patient prognosis.[60] Efficacy and safety were confirmed with a large-scale randomized controlled trial in the field of obstetrics, but in this study, 1 g of tranexamic acid (10 mg/mL/min) was slowly administered intravenously over 100 min, and when hemostasis did not take place, 1 g of tranexamic acid was administered additionally.[59] The possibility that this drug may cause thromboembolism or renal impairment and the possibility that it may induce convulsions have also been pointed out, so caution must be taken during administration.

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Disclosure

None declared.

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