

Indication and utilization of fibrinogen replacement therapy in postpartum hemorrhage:
a single-center retrospective descriptive study

Hisako Okada¹, Shuko Nojiri², Yakhup Adila³, Shoko Okahara⁴, Atsuo Itakura⁵, and Hiroyuki Sumikura⁴

1Department of Anesthesia and Pain Medicine, Juntendo University Urayasu Hospital, 2 Medical Technology Innovation Center Clinical Research and Trial Center, Juntendo University Faculty of Medicine, 3 Department of Anesthesia and Pain Medicine, Juntendo University Graduate School of Medicine, 4Department of Anesthesia and Pain Medicine, Juntendo University Hospital, 5 Department of Obstetrics and Gynecology, Juntendo University Hospital.

Introduction: Postpartum hemorrhage (PPH) is a leading cause of maternal mortality worldwide. Hypofibrinogenemia is the major cause of PPH, and fibrinogen value is recognized as predictive factor for severe PPH. National guidelines of PPH management have substantial variations, thus better evidence is required. The trigger and target plasma fibrinogen level in PPH is recommended around 150-200 mg/dL^{1,2}. Either fibrinogen concentrate or cryoprecipitate is recommended for fibrinogen replacement therapy (FRT) . The purpose of this study is to evaluate whether FRT was properly performed for acquired hypofibrinogenemia in PPH. The primary outcome is an implication of proper FRT, which was defined as follows; 1) plasma fibrinogen level was measured before FRT and below 200 mg/dL, 2) no additional intervention was performed after FRT. Secondary outcomes are to assess the inverventional treatment and comorbidities. As we utilize point-of-care testing (POCT) device of plasma fibrinogen value, correlation of plasma fibrinogen value with POCT and the Clauss method was evaluated.

Methods: After IRB approval (H20-0258), we extracted the obstetric patients who received FRT from April 2015 to August 2020. Inclusion criteria were obstetric patients who was administered fibrinogen concentrate and/or cryoprecipitate. Exclusion criteria was inheriting hypofibrinogenemia, abortion and patient with missing data.

Results: Within 6,610 women who delivered in our institution, 28 patients received FRT and 3 patients were excluded. Both fibrinogen concentrate and cryoprecipitate were administered for severe PPH in 10 patients (group FC). Eleven patients were administered fibrinogen concentrate alone (group F), and 4 patients were administered cryoprecipitate alone (group C). One patient in group F had 2 bleeding episodes. We analyzed 12 episodes of FRT for group F(Figure 1). Characteristics of women and PPH are shown in Table 1. Prepartum data did not indicate any coagulation abnormality (Table 2). All patient had life-threatening bleeding or acquired hypofibrinogenemia (Table 3). The plasma fibrinogen level was below 150 ml/dL in 65.4% and below 200 mg/dL in 88.5% of the patients. After FRT, 65.4% of the patients had plasma fibrinogen level more than 200 mg/dl, and of the patients more than 200 mg/dL (Table 4) . In group F, plasma fibrinogen level more than 200 mg/dL was significantly achieved than other groups. In four patients in group F, it was above 300 mg/dL and deemed excessive (Table 4). Interventional treatment was performed in 9 cases (34.6%) in total and more frequent in group FC. Comorbidities such as lung edema or thrombosis were similar among the groups (Table 6). Good correlation was found between fibrinogen POCT device and the conventional Clauss method in severe PPH (Figure 2).

Discussion: Our high successful management of fibrinogen replacement therapy may be achieved by the use of fibrinogen POCT device, which enabled us to evaluate plasma fibrinogen level with whole blood within several minutes^{3,4}. However, in some cases in our study, the fibrinogen level was excessive even if we evaluated it with accessible POCT.

Limitation: Selection bias, small sample size, no second dose of the same product.

Conclusion: Our study demonstrated that about 90 % of patients with life-threatening PPH who needed FRT found to have an acquired hypofibrinogenemia as low as 200 mg/dL. After FRT, two-thirds of the patients achieved plasma fibrinogen level above 200 mg/dL, but hemostasis was achieved in most of the cases. However, FRT deemed excessive or insufficient in some cases. More strict compliance for FRT in severe PPH may be necessary.

References: 1) Int J Hematol. 2021; 114: 18-34, 2) Bjog. 2017; 124: e106-e149, 3) JA Clin Rep. 2021; 7: 23, 4) J Obstet Gynaecol Res. 2018; 44: 788-791.

Figure 1. patient flow

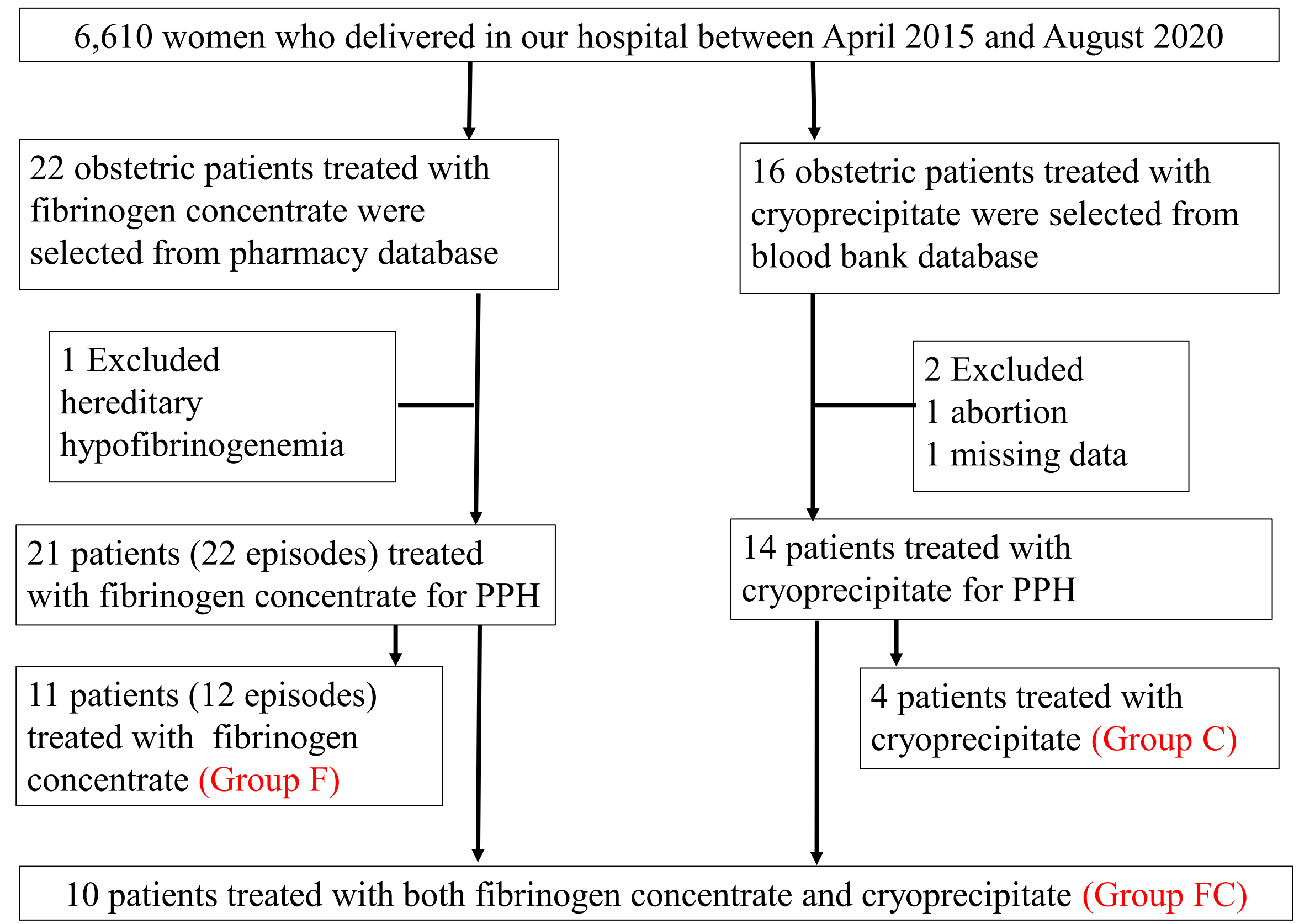


Table 1. Characteristics of Women and Characteristics of PPH treated with FRT (N= 25 women with 26 episodes).

	Group C	Group F	Group FC	<i>P</i> -value
n	4	11	10	
Age (years)	37.5 [33.8 – 40.5]	36.0 [32.5 -40]	38.0 [32.0 – 43.3]	0.821
BMI (kg/m ²)	23.4 [22.5 – 24.4]	23.5 [21.2 – 25.0]	22.4 [20.9 - 23.4]	0.294
Parity (null/para)	4/0	7/4	5/5	0.211
Gestational age (weeks)	37.5 [35.5 – 39.5]	37.5 [29.5 – 40.0]	38.0 [36.8 – 40.0]	0.720
Mode of delivery				
Normal vaginal	0	2 (18.2%)	0	0.796
Instrumental	1 (25.0%)	3 (27.3%)	4 (40.0%)	
Cesarean	3 (75.0%)	6 (54.5%)	6 (60.0%)	
Primary PPH	3 (75.0%)	9 (75.0%)	8 (80.0%)	1.000
Comorbidity				
Uterine atony	3 (75.0%)	2 (18.2%)	7 (70.0%)	0.020*
Intrapartum cesarean section	0	0	3 (30.0%)	0.066
Placenta abruptio	0	3 (27.3%)	0	0.138
Placenta accreta	1 (25.0%)	1 (9.1%)	3 (30.0%)	0.417
Multiple pregnancy	1 (25.0%)	1 (9.1%)	1 (10.0%)	0.770
miscellaneous	0	AFE, Ruptured pseudoanrysm	AFE	-

Data are presented as median [interquartile range, Q1–Q3] or number (%) (column proportion). For analysis, Kruskal-Wallis test was used for continuous data, and Fisher’s exact test was used for categorical data.

Table 2. Prepartum laboratory data

	Group C	Group F	Group FC	<i>P</i> -value
n	4	12	10	
Hemoglobin (g/dL)	10.1 [9.3 – 10.2]	11.0 [10.2-12.1]	10.7 [10.2 – 11.6]	0.126
Platelet count (10 ⁹ /L)	265 [82.2 – 384.8]	208 [183 – 249]	203.5 [187.8 – 224.3]	0.440
Fibrinogen (mg/dL)	474 [427 – 483]	388 [348 – 477]	410 [348 – 483]	0.300
FDP (μg/mL)	3.5 [1.9 – 5.9]	1.85 [1.35 – 3.18]	5.6 [3.3 – 5.7]	0.071

Data are presented as median [interquartile range, Q1–Q3]. Kruskal-Wallis test was used for analysis. FDP: fibrinogen/fibrin degradation products.

Table 3: Blood loss, FRT, tranexamic acid, and blood transfusion.

	Group C	Group F	Group FC	<i>P</i> -value
n	4	12	10	
Estimated blood loss				
Total (g)	3,197 [2,546 – 3,976]	3,243 [1,964 – 5,870]	5,704 [4,858 – 7,765]	0.013*
Before starting FRT (g)	2,517 [1,682 – 2,795]	3,110 [1,548 – 5,335]	4,683 [3,566 – 5,657]	0.067
Fibrinogen replacement therapy				
Cryoprecipitate (bag)	2 [1.25 – 2]	0	2.5 [1 – 3]	-
Estimated Fibrinogen from Cryoprecipitate (mg)	879 [539 – 957]	0	842 [405 – 1370]	-
Fibrinogen (g)	0	3,000 [3,000 – 3,000]	3,000 [3,000 – 3,000]	-
Estimated total fibrinogen given (mg)	879 [539 – 957]	3,000 [3,000 – 3,000]	3,842 [3,405 – 4,369]	0.0001*
Plasma fibrinogen level (mg/dL)				
Prepartum	474 [427 – 483]	388 [348 – 477]	410 [348 – 483]	0.300
Pretransfusion (nadir fibrinogen level)	122 [72.5 – 161.8]	129 [72.5 – 210]	118.5 [40.8 – 142]	0.558
Pretransfusion (min-max)	63 - 168	43 - 233	20 - 178	-
Posttransfusion	175 [150 – 219]	249 [214 – 331]	202 [123 – 242]	0.026*
Posttransfusion (min-max)	143 - 233	151 - 379	110 - 283	-
Anti-fibrinolytic				
Tranexamic acid	2 (50.0%)	7 (58.3%)	5 (50.0%)	1.000
Blood transfusion				
RBC total (U)	9 [6.5 – 11.5]	11 [6.5 – 16]	16 [13.5 – 20.5]	0.017*
FFP total (U)	7 [4.5 – 12.5]	11 [6.5 – 17.5]	17 [13.5 – 20]	0.040*
PLT total (U)	0 [0 – 0]	0 [0 – 20]	10 [0 – 20]	0.126
Transfusion volume before starting FRT (mL)	1,400 [532 – 1,690]	2,490 [1,710 – 3,872]	3,495 [3,055 – 4,958]	0.005*
Transfusion volume after starting FRT (mL)	660 [340 – 2,300]	540 [0 – 1,310]	880 [360 – 1,770]	0.632

Data are presented as median [interquartile range, Q1–Q3] or number (%) (column proportion). For analysis, Kruskal-Wallis test was used for continuous data, and Fisher’s exact test was used for categorical data. The mean value of fibrinogen concentration of cryoprecipitate was adopted in calculation for unmeasured cryoprecipitate.

Table 4: Plasma fibrinogen level before and after FRT.

	Group C	Group F	Group FC	Total	P-value
n	4	12	10	26	
Lowest plasma fibrinogen level before FRT (mg/dL)					
< 150	2 (50.0%)	7 (58.3%)	8 (80.0%)	17 (65.4%)	0.331
150 - 200	2 (50.0%)	2 (16.7%)	2 (20.0%)	6 (23.1%)	
> 200	0	3 (25.0%)	0	3 (11.5%)	
Plasma fibrinogen level after FRT (mg/dL)					
< 200	3 (75.0%)	1 (8.3%)	5 (50.0%)	9 (34.6%)	0.030*
200 - 300	1 (25.0%)	7 (58.3%)	5 (50.0%)	13 (50.0%)	
> 300	0	4 (33.3%)	0	4 (15.4%)	

Fisher’s exact test was used for analysis.

Table 5. Primary outcome: Implementation of proper FRT.

	Group C	Group F	Group FC	Total	<i>P</i> -value
n	4	12	10	26	
Fbg < 200 mg/dL	4 (100%)	9 (75%)	10 (100%)	23 (88.5%)	0.253
No additional intervention	4 (100%)	12 (100%)	9 (90%)	25 (96.2%)	0.539
Proper FRT	4 (100%)	9 (75%)	9 (90%) #	22 (84.5%)	0.625

Definition of proper FRT is that if both the criteria met; 1) Fbg < 200mg/dL before FRT, 2) No additional intervention after FRT. # Hemostasis was achieved by hysterectomy after FRT in 1 patient.

Table 6: Secondary outcome : interventional treatment and complications

	Group C	Group F	Group FC	Total	<i>P</i> -value
n	4	12	10	26	
Interventional treatment*	0	2 (16.7%) ^a	7 (70.0%) ^b	9 (34.6%)	0.009*
Comorbidity					
ALI	0	4 (33.3%)	2 (20.0%)	6 (23.1%)	0.375
ICU admission	0	4 (33.3%)	5 (50.0%)	9 (34.6%)	0.205
Thrombosis	0	0	1 (10.0%)	1 (3.8%)	0.435
AKI	0	5 (41.7%)	2 (20.0%)	7(26.9%)	0.528

a: compression suture and TAE, b: 3 hysterectomy, 3 compression suture, and 1 TAE. ALI: acute lung injury, AKI: acute kidney injury.

Figure 2. Correlation of plasma fibrinogen level between the conventional Clauss method and point-of-care testing device.

