

## ORIGINAL ARTICLE

# Acute obstetric coagulopathy during postpartum hemorrhage is caused by hyperfibrinolysis and dysfibrinogenemia: an observational cohort study

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## Abstract

**Background:** Postpartum hemorrhage (PPH) may be exacerbated by hemostatic impairment. Information about PPH-associated coagulopathy is limited, often resulting in treatment strategies based on data derived from trauma studies.

**Objectives:** To investigate hemostatic changes associated with PPH.

**Patients/Methods:** From a population of 11 279 maternities, 518 (4.6%) women were recruited with PPH  $\geq 1000$  mL or placental abruption, amniotic fluid embolism, or concealed bleeding. Routine coagulation and viscoelastometric results were collated. Stored plasma samples were used to investigate women with bleeds  $> 2000$  mL or those at increased risk of coagulopathy defined as placenta abruption, amniotic fluid embolism, or need for blood components. Procoagulant factors were assayed and global hemostasis was assessed using thrombin generation. Fibrinolysis was investigated with D-dimer and plasmin/antiplasmin complexes. Dysfibrinogenemia was assessed using the Clauss/antigen ratio.

**Results:** At 1000 mL blood loss, Clauss fibrinogen was  $\leq 2$  g/L in 2.4% of women and 6/27 (22.2%) cases of abruption. Women with very large bleeds ( $> 3000$  mL) had evidence of a dilutional coagulopathy, although hemostatic impairment was uncommon. A subgroup of 12 women (1.06/1000 maternities) had a distinct coagulopathy characterized by massive fibrinolysis (plasmin/antiplasmin  $> 40\,000$  ng/mL), increased D-dimer, hypofibrinogenemia, dysfibrinogenemia, reduced factor V and factor VIII, and increased activated protein C, termed acute obstetric coagulopathy. It was associated with fetal or neonatal death in 50% of cases and increased maternal morbidity.

**Conclusions:** Clinically significant hemostatic impairment is uncommon during PPH, but a subgroup of women have a distinct and severe coagulopathy characterized by

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hyperfibrinolysis, low fibrinogen, and dysfibrinogenemia associated with poor fetal outcomes.

#### KEYWORDS

coagulopathy, dysfibrinogenemia, fibrinogen, fibrinolysis, postpartum hemorrhage

## 1 | INTRODUCTION

Bleeding after childbirth (postpartum hemorrhage [PPH]) causes approximately 57 000 maternal deaths worldwide each year [1]. Obstetric bleeding may be exacerbated by hemostatic failure leading to massive PPH [2]. The characteristics of PPH-associated coagulopathy are poorly defined leading to some guidelines recommending the use of fixed ratios of red blood cells (RBCs), fresh frozen plasma (FFP), and platelets to resuscitate women [3–7], based on data derived from major trauma studies in nonpregnant adults [8,9].

Acute traumatic coagulopathy (ATC) is a complex dysfunction of hemostatic pathways driven by physical injury and shock. ATC is characterized by increased soluble thrombomodulin (sTM), which activates protein C, leading to inhibition of factor (F) Va and FVIIIa, whereas hyperfibrinolysis leads to clot breakdown, and increased thrombin generation drives fibrin formation contributing to hypofibrinogenemia. In addition, depletion and inhibition of coagulation factors due to dilution, hypothermia, and acidosis during resuscitation exacerbate trauma-induced coagulopathy (TIC) [10–12]. It is not known whether similar mechanisms occur during PPH.

PPH-associated coagulopathy has been described as a form of disseminated intravascular coagulation (DIC) where hemostatic changes are predominantly due to consumption of coagulation factors [13]. Management of DIC relies on the infusion of FFP and platelets [14], but whether this is appropriate for PPH is debated [2].

The hemostatic system at term differs from the nonpregnant state with increased procoagulant factors, including fibrinogen, FVIII, and von Willebrand factor (VWF), and reduced anticoagulants, such as protein S [15]. This results in an increased capacity to generate thrombin [16] and substantially enhanced clot firmness measured by viscoelastometric hemostatic assays (VHAs). Because of these changes, any evolving coagulopathy during PPH will start from a different hemostatic baseline to those associated with trauma or DIC in the nonpregnant state.

It is established that fibrinogen falls to critically low levels earlier than other coagulation factors during PPH [17] with levels <2 g/L predictive of progression to massive PPH [18–20]. Guidelines therefore recommend maintaining Clauss fibrinogen above 2 g/L, or Fibtan > 12 mm, during PPH [3–5,21]. Clauss fibrinogen < 2 g/L has been reported in 5% of cases of PPH of 1.5 L, increasing to 17% in PPH ≥ 2.5 L [22,23]. Prolongation of prothrombin time (PT) or activated partial thromboplastin time (APTT) is rare during PPH until bleeds exceed 3 L [17]. Formulaic treatment with FFP will therefore expose women with normal coagulation screens to unnecessary transfusion, while being inadequate to correct low fibrinogen [24].

### Essentials

- Hemostatic failure may exacerbate postpartum hemorrhage, but the coagulopathy is not well defined.
- This study described hemostasis in a cohort of women with postpartum hemorrhage (PPH) to inform evidence-based treatment.
- Hemostatic impairment was uncommon during PPH, but dilution of coagulation factors occurred with bleeds >3000 mL.
- Severe coagulopathy due to hyperfibrinolysis and hypodysfibrinogenemia occurred in 1/1000 cases.

In contrast, some women develop severe peripartum coagulopathy, which may be the main cause of hemorrhage. Classically this occurs in association with amniotic fluid embolism (AFE) [25] but may also be seen with placental abruption [13,26]. AFE-associated coagulopathy has been reported in small series and cases reports; these describe massive fibrinolysis, severe hypofibrinogenemia, moderate thrombocytopenia, and reduced FV and FVIII with normal levels of other procoagulant factors [27–29]. Recently, we reported a case of AFE with all these features and, in addition, an acute, acquired dysfibrinogenemia [30].

The mechanisms causing early fibrinogen depletion, relative to other coagulation factors, in PPH and the role of fibrinolysis are poorly understood. This study aimed to describe coagulation parameters during PPH and investigate PPH-associated coagulopathy to inform evidence-based treatment and improve outcomes for this potentially life-threatening complication of childbirth.

## 2 | METHODS

### 2.1 | Study subjects

Women were recruited at 1000 mL measured blood loss, or earlier for clinical suspicion of placental abruption, AFE, or concealed bleeding. All women giving birth had postpartum blood loss objectively measured, as opposed to estimated, by validated gravimetric and volumetric methods [31]. Consent to report clinical data and perform extended coagulation tests on stored samples was sought after the bleeding had stopped according to the ethical approval (REC16/WA/0282). Healthy-

term pregnant women ( $n = 37$ ) were recruited at the time of elective cesarean section to act as nonbleeding pregnant controls.

The causes of abnormal bleeding were recorded following review of the clinical notes and investigations such as placental histopathology. Many women had multiple causes of bleeding, and the study team determined the primary cause of PPH in collaboration with the treating clinicians. The primary causes of bleeding were categorized as follows: uterine atony, surgical/trauma (including surgical bleeds and genital tract trauma), placental abruption, placenta accretia/praevia, retained products of conception (including retained placenta or membranes), AFE (diagnosis of the single case was made the day after delivery following notes review), and coagulopathy of unknown cause (no significant obstetric cause for bleeding was found, and PPH was attributed to unexplained coagulopathy). Women were followed to discharge from the hospital. Information about all women who gave birth during the study period was obtained from the local maternity unit database.

## 2.2 | Laboratory testing

At recruitment, peripheral blood samples were taken for point-of-care testing, laboratory analysis, and extended testing. Point-of-care VHAs were performed using the Rotem Sigma (Werfen, Barcelona, Spain) [32]. PT, APTT, and Clauss fibrinogen were analyzed using an ACL TOP 700. Platelet-poor plasma was obtained from citrated blood samples and stored at  $-80^{\circ}\text{C}$  for further analysis. Samples in a subgroup of women were taken into lithium heparin for measurement of circulating activated protein C (aPC). If bleeding continued, blood sampling was advised at every 500 mL of blood loss or after infusion of coagulation products. Measured blood loss at the time of sampling was recorded where available.

Investigative testing of coagulation was performed on women with any of the following criteria: bleeds  $\geq 2000$  mL, placental abruption, AFE, treatment with fibrinogen concentrate or FFP, or more than 1 blood sample taken during PPH. This group was selected to include women with the most severe bleeds and those most likely to be coagulopathic. Procoagulant factors FII, FV, FVII, FVIII, FIX, FX, and FXI were measured by single-stage clotting assay and FXIII antigen and von Willebrand factor antigen (VWF:Ag) by latex-enhanced immunoassay. The combined ability of coagulation factors to support hemostasis was assessed by thrombin generation measured on a Thrombinoscope (Thermo-Scientific) with peak thrombin and endogenous thrombin potential (ETP) reported. Dysfibrinogenemia was investigated by antigenic fibrinogen, measured by enzyme-linked immunosorbent assay (ELISA), and the ratio of functional (Clauss) to the total amount (ELISA) was calculated. Fibrinolysis was assessed by measurement of D-dimers (reported as D-dimer units), plasminogen measured by chromogenic assay, plasmin/antiplasmin (PAP) complexes (ELISA), and maximum lysis quantified on Extem. The protein C pathway was investigated through measurement of protein C (chromogenic), aPC (ELISA), and soluble thrombomodulin (sTM) (ELISA). Detailed methods for laboratory analyses are provided in [Supplementary Materials](#).

## 2.3 | Clinical management

Women were managed according to the OBS Cymru Rotem algorithm [33]. Briefly, if there was bleeding, the algorithm prompted infusion of fibrinogen concentrate if the Fibtex A5 was  $<12$  mm or Clauss fibrinogen  $<2$  g/L, FFP infusion if the Extem CT was  $\geq 75$  seconds or PT/APTT were above the nonpregnant normal range, and platelet transfusion if the platelet count was  $<75 \times 10^9/\text{L}$ . Intravenous tranexamic acid (1 g, repeated after 30 minutes if there was ongoing bleeding) was given at 1000 mL blood loss or earlier if there was concern of concealed bleeding. Obstetric management was according to the All Wales PPH management guideline [34] based on guidelines from the Royal College of Obstetrics and Gynaecology [4].

## 2.4 | Data analysis and statistics

Descriptive analyses used median, IQR, and range for continuous variables and number and percent for categorical variables. Missing data were not imputed. Differences between groups were analyzed using the Kruskal-Wallis test with Bonferroni correction and Mann-Whitney U-test or chi-squared test (Excel and SPSS version 27).

## 3 | RESULTS

Between May 6, 2017, and May 30, 2019, there were 11 279 maternities, and 518 (4.6%) women with PPH were recruited. The median (IQR), range total blood loss was 1500 (1200–1800), 200–8500 mL. [Table 1](#) shows the proportion of women eligible for the study that were recruited, and the proportion of women who had extended coagulation analyses performed ( $n = 148$ ). Of eligible women with  $\geq 2000$  mL blood loss, 101/106 (95.3%) were recruited and 83/101 (82.2%) had at least 1 extended blood test performed. The characteristics of recruited women are shown in [Table 1](#).

### 3.1 | Routine tests of coagulation and thromboelastometry at study entry

To investigate hemostatic changes early during the PPH, the blood samples taken at recruitment for routine laboratory and Rotem testing were analyzed, depending on the primary cause of bleeding ([Table 2](#)). At the time of the first testing, the median (IQR) blood loss was 1200 (1000–1400) mL.

#### 3.1.1 | Clauss fibrinogen

At study entry, Clauss fibrinogen was  $\leq 2$  g/L in 11/449 (2.4%) cases, 6/27 (22%) abruptions, and the cases of AFE and coagulopathy of unknown cause. Women with placental abruptions and praevia/accretia had lower Clauss fibrinogen levels on the first measurement

TABLE 1 Characteristics of women giving birth and recruited to the study

	All maternities N = 11 279	Women recruited N = 518	Extended tests performed N = 148	P value All women recruited vs extended tests group
Age, y	30 [26–34]	31.5 [28–35]	32.5 [28–35]	.31
Med [IQR]				
Body mass index Med [IQR]	26 [23–30]	26 [23–31]	25 [23–30]	.44
Gravida, N (%)	ND	2 (1–3)	2 (1–3)	.06
Parity, N (%)	ND	1 (0–2)	1 (0–2)	.33
Induction of labor, N (%)	ND	181 (35)	55 (37)	.62
Augmented labor, N (%)	ND	144 (28)	36 (24)	.7
<i>Mode of birth</i>				
Unassisted vaginal, N (%)	7056 (62.6)	165 (32)	39 (26)	.2
Instrumental vaginal, N (%)	1469 (13.0)	130 (25)	38 (26)	.89
Elective CS, N (%)	1397 (12.4)	80 (15)	24 (16)	.81
Nonelective CS, N (%)	1370 (12.1)	143 (28)	47 (32)	.32
<i>Primary cause of PPH<sup>1</sup></i>				
Abruption, N (%)	ND	31 (6)	20 (13.5)	.002
Atony, N (%)	ND	71 (13.7)	16 (10.8)	.36
Surgical/trauma, N (%)	ND	334 (64.5)	76 (51.4)	.004
Placental accretia/praevia, N (%)	ND	26/518 (5)	13 (8.8)	.09
Retained products of conception, N (%)	ND	54 (10.4)	21 (14.2)	.2
Amniotic fluid embolus, N (%)	ND	1 (0.2)	1 (0.7)	.34
Coagulopathy of unknown cause, N (%)	ND	1 (0.2)	1 (0.7)	.34
<i>Volume of PPH</i>				
Total measured blood loss, mL	350	1500	2000	<.001
Med (IQR)	(200–550)	(1205–1800)	(1585–2300)	
Not known, N (%)	503 (4.5)	0	0	NA
0–999 mL, N (%)	9783 (86.7)	23 (4.4)	7 (4.7)	NA
1000–1999 mL, N (%)	887 (7.9)	394 (76.1)	58 (39.2)	NA
2000–2999 mL, N (%)	89 (0.8)	86 (16.6)	70 (47.3)	NA
3000–3999 mL, N (%)	13 (0.1)	11 (2.1)	9 (6.1)	NA
≥4000 mL, N (%)	4 (0.04)	4 (0.8)	4 (2.7)	NA
<i>Transfusion</i>				
Any red blood cell transfusion N (%)	ND	133 (26)	72 (49)	<.001
Fibrinogen concentrate N (%)	ND	19 (3.7)	18 (12.2)	<.001
FFP transfusion N (%)	ND	3 (0.6)	3 (2)	.1
Platelet transfusion N (%)	ND	7 (1.4)	4 (2.7)	.26

<sup>1</sup>Primary cause of bleeding as assessed by the study team, many women had multiple causes of bleeding with atony contributing to 290 cases and surgical/trauma to 384. FFP, fresh frozen plasma; NA, not applicable; ND, no data available.

TABLE 2 Routine tests of coagulation and thromboelastometry performed at study entry

	Nonpregnant healthy control	Pregnant term healthy controls N = 37	All PPH N = 518	Placental abruption N = 31	Atony N = 71	Surgical or Trauma N = 334	RPOC N = 54	Placenta accretia or praevia N = 26	AFE N = 1	Coagulopathy unknown cause N = 1
Measured blood loss at first sample (mL) Median (IQR), range	NA	None	1200 (1000-1400) 70-3000	600 (400-1100) 70-1300	1300 (1085-1500) 350-2200	1200 (1013-1460) 100-3000	1100 (1000-1300)	1000 (950-1290) 300-2320	2000	ND
Hb at first sample (g/L) Median (IQR), range	115-165	121 (116-126) 104-136	109 (100-119) 67-150	108 (100.5-128) 67-150	113 (101.5-122.5) 72-150	109 (99-118) 70-149	114 (105-124) 86-141	102.5 (94-109) 67-119	135	115
Clauss fibrinogen g/L Median (IQR), range N (%) $\leq 2$ g/L	2-4 <sup>1</sup>	5.0 (4.4-5.6) 3.5-7.9 0/37 (0%)	4.4 (3.7-5.2) 0.4-10.1 11/449 (2.4)	3.7 (2.7-4.5) 1.3-6.0 6/27 (22.2)	4.6 (3.7-5.7) 2.3/7.3 0/60	4.5 (3.8-5.3) 1.8-8.3 2/292 (0.7)	4.8 (4.1-5.1) 1.8-10.1 1/44 (2.3)	3.8 (3.6-4.6) 2.5-6.1 0/25 (0)	1.7 - - 1/1 (100)	1.4 - - 1/1 (100)
PT (sec) Median (IQR), range N (%) above NR	9-13 <sup>1</sup>	10.4 (9.9-10.6) 9.1-11.5	10.8 (10.4-11.3) 8.6-20.1 6/449 (1.3)	10.6 (10.2-11.4) 9.5-13.3 1/27 (3.7)	10.8 (10.5-11.3) 9.5-12.1 0/60 (0)	10.8 (10.4-11.3) 8.6-14.7 4/292 (1.4)	10.9 (10.5-11.3) 9.4-12.7 0/44 (0)	10.7 (10.4-11.3) 9.9-12.2 0/25 (0)	11.8 - - 0/1 (0)	20.1 - - 1/1 (100)
aPTT (sec) Median (IQR), range N (%) above NR	28-38.5 <sup>1</sup>	25.1 (23.4-26.0) 20-29.8	24.1 (22-25.9) 20-46.1 1/449 (0.2)	24.4 (22.7-26.2) 20-29.5 0/27 (0)	23.9 (20.0-25.6) 20-29.4 0/60 (0)	24.2 (22.1-26.1) 20-37.7 0/292 (0)	23.1 (20.3-25.2) 20-46.1 1/44 (2.3)	23.9 (21.2-25.6) 20-27.6 0/25 (0)	25.5 - - 0/1(0)	31.3 - - 0/1 (0)
Platelet count ( $\times 10^9$ /L) Median (IQR), range N (%) below NR	150-400 <sup>1</sup>	230 (181-279) 101-419 4/36 (11.1)	200 (163-237) 19-438 78/470 (16.6)	197 (173-262) 19-371 3/27 (11.1)	203 (166-238) 53-414 10/66 (15.1)	200 (161-235) 53-438 53/302 (17.5)	194 (173-253) 116-399 5/49 (10.2)	225 (142-193) 63-303 7/24 (29.2)	203 - - 0/1 (0)	180 - - 0/1 (0)
Fibtem A5 (mm) Median (IQR), range N (%) $< 12$ mm	ND	23 (21-26) 6.0-33	20 (17-24) 0-41 16/483 (3.3)	17 (12-22) 4-30 7/28 (25)	20 (16/23) 9-39 1/63 (1.6)	20 (17-24) 7-41 6/317 (1.9)	22 (19-25) 12-37 0/49 (0)	18 (15-22) 12-31 0/24 (0)	6 - - 1/1 (100)	0 - - 1/1 (100)
Extem CT (sec) Median (IQR), range N (%) $\geq 75$ s	ND	56 (52-62) 43-80	54 (50-59) 51-323 9/483 (1.9)	61 (50-71) 47-97 4/28 (14.3)	54 (52-58) 46-90 1/63 (1.6)	53 (50-57) 41-77 1/317 (0.3)	56 (52-60) 45-79 1/49 (2.0)	54 (50-59) 46-68 0/24 (0)	94 - - 1/1 (100)	323 - - 1/1 (100)
Extem Maximum lysis N (%) $> 15\%$	11 (2.5-17) 0-22	5 (2.0-8.5) 0-15 0 (0%)	5 (1-9) 0-25 4/481 (0.8)	2.5 (0.5-6.5) 0-11 0/28 (0)	5 (1-8) 0-15 0/63 (0)	6 (1-9) 0-25 3/316 (0.9)	5.5 (1-9) 0-12 0/48 (0)	5 (0-9) 0-19 1/23 (4.3)	4 - - 0/1 (0)	0 - - 0/1 (0)

Laboratory normal and reference ranges (NR)<sup>1</sup>. AFE, amniotic fluid embolism; ND, data not available; NA, not applicable; RPOC, retained products of conception; and includes retained placenta or membranes. Blood loss in the placental abruption group is lower because cases were recruited at the time of diagnosis rather than at 1000 mL, and it is likely that some bleeding was concealed.

compared with healthy-term pregnant controls ( $p < .001$ ). Results for Fibtex A5 were similar (Table 2).

### 3.1.2 | PT, APTT, and Extem CT

At study entry, the PT and APTT were above the nonpregnant laboratory normal range in 6/449 (1.3%) and 1/449 (0.2%) cases, respectively, and 9/483 (1.9%) women had an Extem CT  $\geq 75$  seconds. The median APTT in women with PPH was 4 seconds shorter than the lower end of the nonpregnant normal range.

### 3.1.3 | Platelet count

At study entry, 78/470 (16.6%) women had a platelet count below the normal range ( $150 \times 10^9/L$ ) with 7/470 (1.5%) less than  $75 \times 10^9/L$ . Further description of the results is given in [Supplementary Materials](#).

### 3.1.4 | Summary of routine test results at study entry

These results demonstrate that reduced levels of coagulation factors, sufficient to prolong PT/APTT, are uncommon in women with PPH of approximately 1200 mL except for fibrinogen in the context of placental abruption and AFE. Despite this, it is known that some women develop early severe hemostatic failure at the time of childbirth. Studies in AFE have highlighted that hyperfibrinolysis is an important component of these coagulopathies [27], and markers of this pathway were investigated.

## 3.2 | Fibrinolysis during postpartum hemorrhage

PAP complexes were measured to investigate recent plasmin generation in 130 women with the largest bleeds ( $>2000$  mL) and those most likely to have coagulopathy (abruption, AFE, or receipt of blood products). These women had higher PAPs compared with the healthy-term pregnant controls, median (IQR) 4760 (2531–16384) versus 1409 (1378–1481) ( $p < .0001$ ), nonpregnant normal range  $< 512$  ng/mL. D-dimers were higher in this group than healthy-term pregnant controls median (IQR) 1659 (930–2990) versus 599 (410–866),  $p < .0001$ , nonpregnant normal range  $< 350$  ng/mL consistent with activation of fibrinolysis during PPH.

A post hoc review of PAP distributions identified a distinct subgroup of 12 women who were significant outliers with PAPs  $> 40\,000$  ng/mL (Figure 1A, B). This group was defined as having acute obstetric coagulopathy (AOC). Women with AOC were compared with the other women who had had PAPs measured ( $n = 118$ ). Sequential samples had been taken from some women during the PPH, and coagulation parameters for the sample associated with the highest PAP were analyzed (Table 3).

### 3.2.1 | Laboratory features of AOC

D-dimers were  $>25$ -fold higher and platelets marginally lower in women with AOC compared with non-AOC. Factor V (Figure 1C) and FVIII were lower in AOC, whereas other coagulation factors were similar between the groups, suggesting specific rather than generalized depletion of coagulation factors. The VWF/FVIII ratio was much higher in the AOC group because FVIII was reduced, whereas VWF:Ag increased. Despite falls in FV and FVIII, ETP and peak thrombin were similar between the groups.

Clauss fibrinogen was 49% lower in the AOC group, reduced to a median (IQR) of 2.1 (1.6–3.0) g/L (Figure 1D), a level associated with clinically significant hemostatic impairment in the context of PPH [18,19,35]. Similarly, reduced fibrinogen function was seen in the Fibtex assay with a fall of 42%. In contrast to Clauss fibrinogen, fibrinogen antigen levels were reduced by 20% in the AOC group, and all had levels  $\geq 2$  g/L (Table 3). The Clauss/ELISA ratio was lower in the AOC group compared with non-AOC (Figure 1E) demonstrating that the reduced functional fibrinogen was caused by both a decreased amount of fibrinogen and acquired dysfibrinogenemia. The non-AOC group had Clauss/ELISA ratios indistinguishable from healthy-term pregnant controls and nonpregnant controls (Table 3). Plasminogen and FXIII levels were decreased in the AOC group.

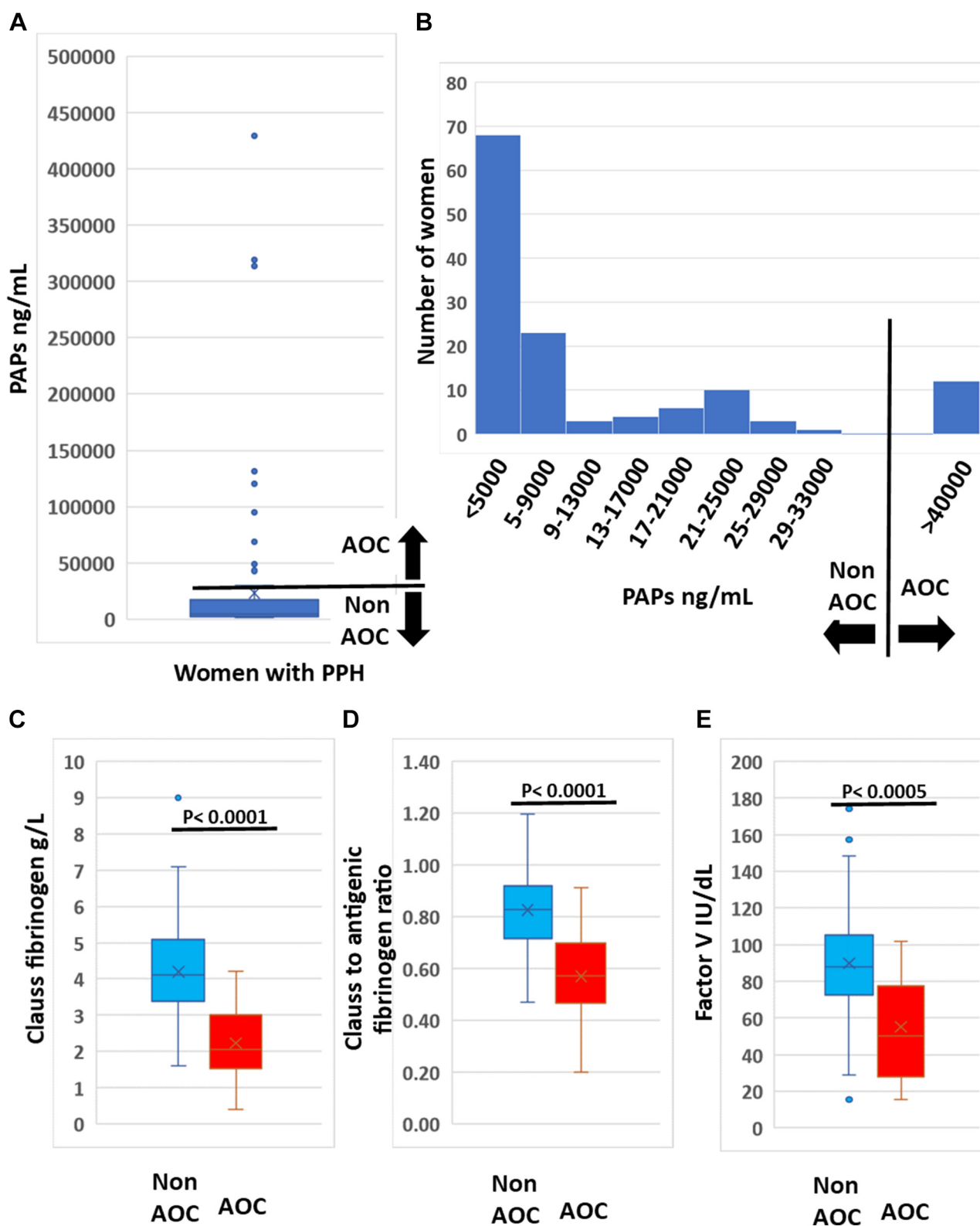
Due to the unavailability of sample tubes at the start of the study, aPC was only measured in 60 women with PPH. It increased from a median of 11 ng/mL in healthy-term pregnant control women to 19.6 ng/mL in the non-AOC women with PPH ( $p < .00001$ ) (nonpregnant normal range 1.6–4.2 ng/mL). aPC was increased 4.5-fold in the AOC group compared with the non-AOC group ( $p = .0007$ ) (Table 3). Soluble thrombomodulin was higher in the healthy-term pregnant controls than women with PPH ( $p < .001$ ), and there was no difference between the AOC and non-AOC groups.

### 3.2.2 | Clinical features of AOC

The clinical characteristics and maternal and neonatal outcomes of the 12 women who had evidence of AOC are shown in Table 4. AOC was associated with placental abruption in 5/12 cases and the case of AFE. The primary cause of bleeding for the other women was diverse.

At the time of the highest PAP, there was no difference in blood loss, lactate, or shock index between the AOC and non-AOC groups (Table 3). Preeclampsia, smoking and lower gestation were more common in AOC but there was no association with clinical suspicion of sepsis (Table 4). AOC was associated with maternal admission to the high-dependency unit on delivery suite, increased RBC transfusion, and infusion of fibrinogen concentrate. There was a markedly increased incidence of intrauterine and neonatal deaths in the AOC group.





**FIGURE 1** Plasmin/antiplasmin (PAP) complexes, factor V and dysfibrinogenemia in women with postpartum hemorrhage. The highest PAP levels in 130 women with severe postpartum hemorrhage are shown. A distinct group of outliers with PAPs > 40 000 ng/mL defined the group of women labeled as acute obstetric coagulopathy (AOC) in the further analyses (A, B). The levels of factor V (FV), Clauss fibrinogen, and Clauss to antigenic fibrinogen ratio are shown in the 118 non-AOC and 12 AOC women are shown (C-E). Women with AOC had reduced FV and an acquired dysfibrinogenemia.

TABLE 3 Hemostatic variables and indices of shock in acute obstetric coagulopathy

	Nonpregnant healthy controls (laboratory normal range or reference ranges)	Nonbleeding term pregnancy controls N = 37	Nonacute obstetric coagulopathy group Median (IQR) Range N = 118	Acute obstetric coagulopathy group Median (IQR) Range N = 12	P Non-AOC vs AOC
Blood loss when samples taken (mL) Median (IQR), range	NA	0	1500 (1125–2000) 875–5700	1350 (1085–2300) 595–5500	.9
Shock index when samples taken Median (IQR), range	NA	NA	0.85 (0.73–1.0) 0.4–1.75	0.81 (0.60–0.91) 0.51–0.94	.35
Lactate when samples take (mmol/L) Median (IQR), range	0.5–1.6	ND	2.3 (1.9–2.8) 1.1–7.5	2.1 (1.5–2.7) 0.9–3.5	.14
D-dimer (ng/mL) Median (IQR), range	<350	599 (410–866) 239–2226	1702 (915–2726) 240–17 438	43915 (14 283–58 085) 10 607–64 145	<.0001
Plasminogen (IU/dL) Median (IQR), range	80–120	ND	103 (91–120) 37–173	82 (70–100) 54–124	<.05
Platelets ( $\times 10^9/L$ ) Median (IQR), range	150–400	230 (181–279) 101–419	187 (150–251) 19–435	149 (109–172) 98–184	<.01
aPTT (s) Median (IQR), range	27–38.5	25.1 (23.4–26.0) 20–29.8	24.5 (22.2–26.4) 20–63.3	27.2 (24.8–29.6) 22.9–34.8	<.05
Clauss fibrinogen (g/L) Median (IQR), range	2.8 (2.5–3.3) 1.8–4.9	5.9 (4.4–5.6) 3.5–7.9	4.1 (3.4–5.0) 1.6–9.0	2.1 (1.6–3.0) 0.4–4.2	<.0001
Fibtem A5 (mm) Median (IQR), range	ND	23 (21–26) 6.0–33	20 (16–24) 7–37	11.5 (8–14) 0–21	<.0001
Fibrinogen ELISA (g/L) Median (IQR), range	3.5 (3.2–4.1) 2.0–7.2	6.4 (5.8–7.4) 4.7–8.5	5.0 (4.3–5.9) 1.8–10.1	4.0 (3–4.5) 2–5.6	<.005
Fibrinogen Clauss/ELISA ratio Median (IQR), range	0.80 (0.76–0.87) 0.66–0.96	0.76 (0.72–0.84) 0.57–10.4	0.83 (0.72–0.92) 0.47–1.20	0.57 (0.48–0.68) 0.21–0.91	<.0001
Factor II (IU/dL)	50–200	145 (132–155) 92–172	109 (97–123) 32–177	96 (71–119) 61–161	.10
Factor V (IU/dL) Median (IQR), range	50–200	108 (99–118) 74–222	88 (73–105) 16–174	50 (32–77) 16–102	<.0005
Factor VII (IU/dL) Median (IQR), range	50–200	188 (173–204) 123–232	141 (118–161) 48–239	169 (119–187) 98–217	.14
Factor VIII (IU/dL) Median (IQR), range	50–200	205 (162–263) 108–496	262 (179–351) 86–908	159 (59–315) 50–440	<.05
VWF:Ag (IU/dL) Median (IQR), range	50–200	283 (266–309) 163–587	357 (273–442) 78–950	439 (299–711) 259–1783	.08

(Continues)



TABLE 3 (Continued)

	Nonpregnant healthy controls (laboratory normal range or reference ranges)	Nonbleeding term pregnancy controls N = 37	Nonacute obstetric coagulopathy group Median (IQR) Range N = 118	Acute obstetric coagulopathy group Median (IQR) Range N = 12	P Non-AOC vs AOC
VWF/FVIII ratio Median (IQR), range	ND	1.38 (1.05–1.88) 0.59–2.58	1.29 (1.05–1.69) 0.28–5.60	3.57 (2.26–5.29) 1.34–8.54	<.0001
Factor IX (IU/dL) Median (IQR), range	50–150	173 (159–188) 74–267	158 (133–178) 56–275	122 (111–158) 68–277	<.05
Factor X (IU/dL) Median (IQR), range	50–150	159 (142–179) 122–283	115 (99–132) 31–203	98 (79–117) 62–183	.12
Factor XI (IU/dL) Median (IQR), range	50–150	108 (92–120) 59–163	82 (66–96) 19–195	78 (58–96) 36–172	.66
Factor XIII (IU/dL)	64–136	54 (43–81) 22–98	54 (43–65) 15–136	45 (34–51) 19–60	<.01
Peak thrombin generation (nM) Median (IQR), range	238 (206–295) 110–408	397 (347–446) 194–532	382 (330–426) 138–561	355 (302–355) 264–673	.68
Endogenous thrombin potential (nM/min) Median (IQR), range	1527 (1372–1750) 624–2644	2067 (1944–2367) 1273–3008	2030 (1738–2381) 1015–3435	2089 (1886–2379) 1224–3808	.58
Soluble thrombomodulin (pg/mL) Median (IQR), range	16.5 (15.0–20.0) 12.0–25.3	42.7 (34.0–45.2) 26.5–53.8	29.6 (23.1–36.3) 8.7–117.3	29.7 (27.2–46.0) 19.2–48.4	.32
Protein C (IU/dL) Median (IQR), range	70–151	134 (118–150) 84–196	92 (790–110) 23–172	82 (65–106) 48–171	.35
Highest activated protein C (IU/dL) during bleeding Median (IQR), range	2.4 (2.0–3.3) 1.6–4.2 <sup>1</sup> N = 70	11 (9.7–12.3) 3.1–17.5 N = 21	19.6 (15.2–34.9) 2.4–172 N = 54	88.7 (46.4–121) 38–993 N = 6	.0007

<sup>1</sup> The normal range for aPC was performed in a different laboratory to the study samples and so may not be directly comparable. Results in the AOC and non-AOC groups correspond to the time of the highest plasmin/antiplasmin complex except for activated protein C where the highest recorded level is reported. AOC, acute obstetric coagulopathy; ND, data not available; NA, not applicable; VWF, von Willebrand factor.

### 3.3 | Tests of coagulation dependent on the volume of postpartum hemorrhage

In addition to sample collection and testing at study entry, further samples were collected as bleed volume increased. Hemostasis results, dependent on measured blood loss at the time of sampling, are shown in Table 5 and median data are summarized in Figure 2. Women with AOC are excluded from these analyses.

#### 3.3.1 | Fibrinogen

Clauss fibrinogen was significantly lower at each bleed volume compared with healthy-term pregnant controls ( $p < .002$ ). Data are

influenced by the local treatment algorithm, which prompted infusion of fibrinogen concentrate if the Fibrin A5 was <12 mm or Clauss fibrinogen <2 g/L leading to higher fibrinogen levels than if a replacement had not happened, especially at larger bleed volumes.

#### 3.3.2 | Prothrombin time and APTT

The PT in women with PPH was marginally longer than the non-bleeding pregnant control group at all bleed volumes with a statistically significant increase in PT with larger bleed volumes ( $p < .001$ ). However, the number of women with PT above the nonpregnant normal range was small, 10/506 (2.0%). The APTT was similar to healthy-term pregnant controls until bleeds were >3000 mL. In bleeds

TABLE 4 Clinical features of mother and neonate in the acute obstetric coagulopathy group

	All nonacute obstetric coagulopathy N = 506	Nonacute obstetric coagulopathy with PAPs performed N = 118	AOC N = 12	p All nonacute obstetric coagulopathy vs AOC
Age (y)	31.5 (28–35) 16–49	32 (28–35) 16–45	30.5 (27–35) 21–45	.8
BMI, Median (IQR, range)	26 (23–31) 16–55	25 (23–30) 17–53	24 (24–29) 20–41	0.5
Parity: Median (IQR, range)	1 (0–2) 0–10	1 (0–2) 0–5	2 (1–2) 0–5	.045
Gestation (wk) Median (IQR, range)	40 (38–41) 17–42	40 (37–41) 17–42	36.5 (29.7–39) 20–40	.0002
Induction of labor: N (%)	180 (35.6)	49 (41.5)	1 (8.3)	.05
Multiple births: N (%)	24 (4.7)	8 (6.8)	1 (8.3)	.6
Smoker: N (%)	35 (6.9)	9 (7.6)	3 (25)	.02
Preeclampsia: N (%)	41 (8.1)	11 (9.3)	4 (33.3)	.01
<i>Mode of birth</i>				
Vaginal unassisted: N (%)	160 (31.6)	30 (25.4)	5 (41.7)	.5
Instrumental vaginal: N (%)	129 (25.5)	33 (28.0)	1 (8.3)	.2
Elective CS: N (%)	78 (15.4)	16 (13.6)	2 (16.7)	.9
Nonelective CS: N (%)	139 (27.5)	39 (33.1)	4 (33.3)	.7
<i>Cause of postpartum hemorrhage</i>				
Placental abruption: N (%)	26 (5.1)	15 (12.7)	5 (41.7)	.008
AFE: N (%)	0 (0)	0 (0)	1 (8.3)	NA
Coagulopathy: N (%)	0 (0)	0 (0)	1 (8.3)	NA
Atony: N (%)	70 (13.8)	9 (7.6)	1 (8.3)	.93
Surgical: N (%)	333 (65.8)	67 (56.8)	1 (8.3)	.001
Praevia/accrete: N (%)	24 (4.7)	9 (7.6)	2 (16.6)	.28
RPOC: N (%)	53 (10.5)	18 (15.3)	1 (8.3)	.52
Total blood loss (mL) Median (IQR, range)	1500 (1222–1800) 200–8500	2000 (1600–2378), 200–8500	1525 (1050–2650), 200–5500	.9
Red blood cell transfusion (units) Median (IQR, range)	0 (0–0) 0–19	0 (0–2) 0–16	1.5 (1–2.5) 0–9	<.0001
Fibrinogen concentrate infusion: N (%)	9/506 (1.8%)	8/118 (6.8)	10/12 (83.3)	<.0001
Sepsis pathway: N (%)	72 (14)	23 (19)	1 (8)	.6
HDU admission N (%)	304/485 (62.7)	104 (88.1)	12 (100)	.03
ICU admission: N (%)	1 (0.2)	0 (0)	1 (8.3)	<.0001
Hysterectomy: N (%)	4 (0.8)	3 (2.5)	0	NA
Intra-uterine death: N (%)	1 (0.2)	1 (0.8)	5 (41.7)	<.0001
Neonatal death: N (%)	1 (0.2)	0 (0)	1 (8.3)	<.0001
Intrauterine or neonatal death: N (%)	2 (0.4)	1 (0.8)	6 (50)	<.0001

AOC, acute obstetric coagulopathy; AFE, amniotic fluid embolism; BMI, body mass index; HDU, high-dependency unit on delivery suite; ICU, intensive care unit; NA, not applicable; RPOC, retained products of conception.

TABLE 5 Coagulation tests by blood loss at the time of testing

	0 mL <sup>1</sup>	<999 mL	1000–1999 mL	2000–2999 mL	>3000 mL
Clauss fibrinogen (g/L)	5.1	4.1	4.5	3.6	2.5
Median (IQR),	(4.6– 5.6)	(3.7–4.7)	(3.7–5.3)	(2.8–4.6)	(2.1–3.3)
range	3.8–7.2	2.4–7.6	1.8–10.1	1.6–9.0	1.7–5.1
		N = 59	N = 367	N = 55	N = 14
PT (s)	10.4	10.7	10.8	11.1	11.6
Median (IQR),	(9.9–10.6)	(10.3–11.2)	(10.4–11.3)	(10.6–12.0)	(11.0–14.1)
range	9.1–11.5	9.7–12.6	8.6–14.7	9.5–13.6	10.2–18.2
		N = 59	N = 367	N = 55	N = 14
APTT (s)	25.1	24.5	24.1	24.5	27.6
Median (IQR),	(23.4–26.0)	(20.9–26.4)	(22.2–25.9)	(22.4–28.2)	(25.3–35.0)
range	20–29.8	20–31.4	20.0–37.7	20.0–34.4	20.0–63.3
		N = 59	N = 367	N = 55	N = 14
Platelet count ( $\times 10^9/L$ )	230	195	201	172	127
Median (IQR),	(181–279)	(162–235)	(161–244)	(138–206)	(92–162)
range	101–419	63–419	53–438	85–336	67–217
		N = 64	N = 378	N = 59	N = 14
D-dimer (ng/mL)	599	1248	1739	1768	1019
Median (IQR),	(410–866)	(705–1938)	(876–2895)	(841–3021)	(560–2121)
range	239–2226	192–3883	240–17438	286–20176	265–7436
		N = 18	N = 104	N = 45	N = 11
PAP (ng/mL)	1409	2304	3197	3396	4103
Median (IQR),	(1378–1481)	(2014–3102)	(2140–7844)	(2483–5869)	(1899–7415)
range	1284–2119	2304–16643	1136–97424	1176–23975	1657–9160
	N = 20	N = 15	N = 95	N = 41	N = 10
Factor II (IU/dL)	145	127	113	97	79
Median (IQR),	(132–155)	(113–136)	(97–124)	(83–109)	(46–94)
range	92–172	88–142	47–177	43–145	32–119
		N = 18	N = 104	N = 45	N = 11
Factor V (IU/dL)	107	99	93	71	51
Median (IQR),	(99–118)	(84–123)	(78–104)	(55–98)	(23–73)
range	74–222	62–189	29–174	34–144	16–137
		N = 18	N = 104	N = 45	N = 11
Factor VII (IU/dL)	188	148	147	122	99
Median (IQR),	(173–204)	(127–168)	(119–166)	(101–156)	(89–123)
range	123–232	88–300	59–232	52–196	46–153
		N = 18	N = 104	N = 45	N = 11
Factor VIII (IU/dL)	205	226	253	248	180
Median (IQR),	(162–263)	(172–354)	(169–329)	(147–358)	(106–302)
range	108–496	57–551	50–908	53–559	57–492
		N = 18	N = 104	N = 45	
Factor IX (IU/dL)	173	156	155	135	94
Median (IQR),	(159–188)	(125–191)	(136–178)	(111–166)	(72–163)
range	74–267	102–246	42–155	74–247	56–190
		N = 18	N = 104	N = 45	N = 11
Factor X (IU/dL)	159	127	117	99	68
Median (IQR),	(142–179)	(106–137)	(103–132)	(80–112)	(47–89)
range	122–283	86–191	44–203	42–166	31–113
		N = 18	N = 104	N = 45	N = 11
Factor XI (IU/dL)	107	85	79	68	51
Median (IQR),	(92–120)	(66–97)	(64–95)	(50–88)	(31–79)
range	59–163	42–112	24–153	27–126	19–131
		N = 18	N = 104		N = 11

(Continues)

TABLE 5 (Continued)

	0 mL <sup>1</sup>	<999 mL	1000–1999 mL	2000–2999 mL	>3000 mL
Factor XIII (IU/dL)	54	52	52	44	27
Median (IQR),	(43–81)	(37–64)	(44–56)	(31–53)	(25–38)
range	22–98	30–92	15–136	14–135	15–50
		N = 20	N = 104	N = 45	N = 11
VWF:Ag (IU/dL)	283	306	362	316	258
Median (IQR),	(266–309)	(271–380)	(273–439)	(258–450)	(174–286)
range	163–587	168–646	78–950	162–640	140–388
		N = 18	N = 104	N = 45	N = 11
Peak thrombin (nM)	397	390	382	340	289
Median (IQR),	(347–446)	(347–427)	(329–426)	(301–376)	(203–326)
range	194–532	265–482	117–538	193–561	161–350
		N = 18	N = 107	N = 38	N = 9
Endogenous thrombin	2067	2083	2011	1932	1814
potential (nM/min)	(1944–2367)	(1834–2580)	(1738–2381)	(1676–2223)	(1667–2029)
Median (IQR),	1273–3008	1501–3433	1025–3435	1015–3006	1431–2250
range		N = 18	N = 107	N = 38	N = 9
Soluble thrombomodulin (pg/mL)	42.7	32.2	29.5	25.3	24.3
Median (IQR),	(34.0–45.2)	(25.4–36.5)	(22.4–36.7)	(22.6–31.1)	(12.5–37.7)
range	26.5–53.8	15.1–43.6	14.6–117.3	11–107.1	7.0–46.3
		N = 15	N = 94	N = 41	N = 10
Activated protein C (IU/dL)	11	33.7	19	17.9	13
Median (IQR),	(9.7–12.3)	(12–36.6)	(15.2–28.4)	(11.4–27)	(8.6–15.9)
range	3.1–17.5	8.8–69.2	7.3–136	2–52.2	8.5–16.5
	N = 21	N = 7	N = 35	N = 15	N = 5

An individual woman may contribute data to multiple-bleed volume brackets. Data for bleeds < 1000 mL are not representative, because women were recruited before a 1000 mL bleed for clinical concern of an abruption, AFE, or concealed bleeding. The results are not adjusted for the administration of fibrinogen concentrate ( $n = 9$ ) or FFP ( $n = 3$ ). This means that the data will tend to overestimate the fibrinogen level, because the treatment algorithm aimed to maintain the fibrinogen > 2 g/L if bleeding was ongoing. FFP replacement will have had minimal effect. *N* relates to the number of samples not the number of women. AFE, amniotic fluid embolism; APTT, activated partial thromboplastin time; VWF, von Willebrand factor; FFP, fresh frozen plasma.

<sup>1</sup> The 12 women with acute obstetric coagulopathy have been excluded from this table data. Samples taken before elective cesarean section.

> 3000 mL, the APTT was higher than the healthy-term pregnant controls ( $p < .005$ ), however, only 1 woman had APTT above the nonpregnant normal range. This woman had a bleed of 8500 mL due to undiagnosed placenta accrete. The APTT became abnormal at 5700 mL of blood loss, at which time she was given 2 units of FFP, and the APTT returned to the normal range.

### 3.3.3 | Platelet count

The platelet count fell with increasing bleed volume and was statistically significantly lower than the healthy-term pregnant controls for bleeds > 2000 mL. These data are affected by the unit policy to transfuse platelets if they were below  $75 \times 10^9/L$ . In total 6/506 (1.2%) women received platelets.

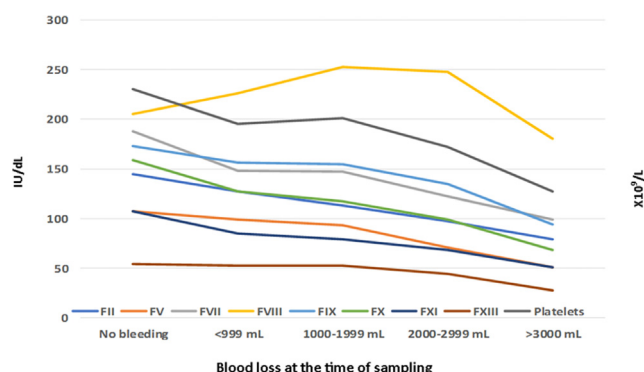
### 3.3.4 | Individual coagulation factors and thrombin generation

Median values of FII, VII, VIII, IX, and X in the healthy-term pregnant women were higher than the midpoint of the laboratory reference

range (Table 3), whereas factor V and XI levels were not raised. These changes were associated with increased peak thrombin and ETP and shortened PT and APTT (Table 3). FXIII was reduced in the healthy-term pregnant controls to a median level of 54 IU/dL (laboratory normal range, 64–136 IU/dL) (Table 3).

The median levels of individual coagulation factors and platelets varied according to bleed volume (Figure 2) (full data in Table 5). Median levels of FII, V, VII, IX, X, XI, and platelets fell linearly and in similar proportions as bleed volume increased. At bleed volumes > 3000 mL, coagulation factors remained within the normal range except in 2 cases that had bleeds of 3000 and 8500 mL. Median FVIII did not reduce and tended to increase during PPH, although this was not statistically significant ( $p < .28$ ). Factor VIII was within or above the population normal range in all women with PPH at all times. Median VWF:Ag increased in bleeds of 1000–1999 mL compared with the nonbleeding pregnant controls ( $p < .001$ ). VWF:Ag was above 100 IU/dL in all cases of PPH at all times. In women with PPH, FXIII decreased in bleeds > 2000 mL ( $p < .0005$ ) compared with healthy-term pregnant controls and was a median of 27 IU/dL for bleeds > 3000 mL (Table 5 and Figure 3).

The combined effect of procoagulant factors was assessed using thrombin generation. Peak thrombin was reduced in bleeds > 2000 mL



**FIGURE 2** Coagulation factor levels and platelet number dependent on the volume of bleed. Lines represent the median values of each parameter for women at the specified bleed volume. Full data are given in Table 5. Women with acute obstetric coagulopathy have been excluded. The “no bleeding” group are samples taken before elective cesarean section. An individual woman may contribute data to multiple-bleed volume brackets. Data for bleeds < 1000 mL are not representative because women were recruited at less than 1000 mL bleed for clinical suspicion of a placental abruption, amniotic fluid embolism (AFE), or concealed bleeding. The results are not adjusted for administration of fibrinogen concentrate ( $n = 9$ ) or fresh frozen plasma (FFP) ( $n = 3$ ). This means that the data will overestimate the fibrinogen level because the treatment algorithm aimed to maintain the fibrinogen > 2 g/L if bleeding was ongoing. FFP replacement will have minimal effect. Y axes are for coagulation factors on the left and platelets on the right.

compared with healthy-term pregnant controls ( $p < .001$ ) (Table 5), but it remained increased compared with nonpregnant controls in bleeds up to 3000 mL ( $p < .0001$ ) and was similar for bleeds >3000 mL ( $p = .4$ ). The lowest peak thrombin in the PPH group was 161 nM, which is within the nonpregnant normal range. There were no statistically significant differences between the ETP of women of different bleed volumes or with healthy-term pregnant controls. The ETP was >1000 nM/min and within the nonpregnant normal range in all cases of PPH. These data confirm that there were adequate amounts of coagulation factors to support thrombin generation even at high bleed volumes.

### 3.3.5 | D-dimer and plasmin/antiplasmin complexes

D-dimers were used as a potential marker of DIC in women without AOC. D-dimers were raised compared with healthy-term pregnant controls for bleed volumes <999, 1000–1999, and 2000–2999 mL ( $p < .005$ ) but not for bleeds > 3000 mL. There was no statistically significant difference in D-dimer concentrations between PPHs of different volumes. These results, combined with the linear decreases in individual coagulation factors and platelets, are compatible with loss due to bleeding and dilution being the main mechanism of coagulopathy associated with very large PPH.

PAPs were increased at all bleed volumes compared with healthy-term pregnant controls ( $p < .0001$ ). There was a nonstatistically significant trend for PAPs to increase as bleed volume increased.

### 3.3.6 | Soluble thrombomodulin and activated protein C

sTM was decreased in women with PPH at all bleed volumes compared with healthy-term pregnant controls ( $p < .002$ ) with no differences between bleed volumes. There was an increase in aPC for bleeds ≤ 999 mL and 1000–1999 mL compared with healthy-term pregnant controls ( $p < .001$ ). The level of aPC for bleeds ≥ 2000 mL was similar to term controls.

## 4 | DISCUSSION

This study, performed in a large number of women with PPH, showed that abnormalities of coagulation are relatively uncommon in the context of treatment using our local monitoring and blood product replacement algorithm [36,37]. Most women maintain adequate hemostasis until large volumes of blood loss. In very large bleeds (>3000 mL measured blood loss) evidence for an evolving dilutional coagulopathy was seen. We identified a small subgroup of women with PPH who had a distinct, severe coagulopathy characterized by hyperfibrinolysis and dysfibrinogenemia.

Hemostatic impairment early during PPH (median 1200 mL blood loss) was uncommon, with only 2.4% having a Clauss fibrinogen <2 g/L and 1.3% an abnormal PT/APTT, although reduced fibrinogen was more common in placental abruption, seen in 22% of cases, confirming findings from previous studies [19,23,35]. Thrombin generation in our study was increased at term similar to previous findings [16]. In this situation, early replacement with fresh frozen plasma (FFP) would not be expected to improve coagulation factor levels or hemostatic competence [38,39].

In women with PPH who do not have AOC, the linear relationship between the fall in coagulation factors, except for FVIII, and platelets with bleed volume, suggests depletion and consumption of coagulation factors due to bleeding and clot formation and dilution due to resuscitation [40,41]. This is supported by the finding that, as coagulation factors declined, D-dimers did not increase suggesting that, in the non-AOC cases, DIC was not a prominent cause of the falling levels. The study did not measure thrombin/antithrombin complexes and so the amount of thrombin generated is not known. Individual coagulation factors remained within the nonpregnant normal range until bleeds were larger than 3000 mL and even above that volume, most coagulation factors were normal. Factor V and XI were below the nonpregnant normal range in many cases, but it is unlikely that this would have contributed to hemostatic impairment because thrombin generation remained normal. Normal thrombin generation potential, despite decreased levels of coagulation factors, is explained in part by stress-related increased FVIII. These findings suggest that FFP is unlikely to improve hemostasis except in very few cases, and in our cohort only 3/518 (0.6%) women received FFP. The safety of withholding FFP based on VHAs has been shown previously [42].

Lower levels of FXIII before labor, although remaining within the population normal range, are associated with an increased risk of PPH, independent of fibrinogen levels [43,44], however, the FXIII level required for hemostasis during PPH is not known. Guidelines in inherited bleeding disorders recommend maintaining a level of above 20 IU/dL [45]. In bleeds > 3 L, all women had FXIII below the nonpregnant normal range, although only 1 woman, with total blood loss of 8500 mL, had a level < 20 IU/dL. The impact of these findings on in vivo hemostasis is unknown and investigation of the role of FXIII replacement, with cryoprecipitate or FXIII concentrate, during severe PPH is required. Fibrinogen concentrates contain different amounts of FXIII, and their effect on in vitro hemostatic tests varies [46]. Cryoprecipitate reduced bleeding during PPH when given at the time of RBC transfusion, although it was challenging to give the cryoprecipitate in a timely manner [47].

Despite most women having normal hemostasis during PPH, it is recognized that a subgroup of women develop severe early hemostatic impairment that can precipitate massive PPH. In our study, 12/518 (2.3%) subjects (1.06/1000 maternities) had a specific coagulopathy, defined based on massive hyperfibrinolysis (PAPs > 40 000 ng/mL), which we have called AOC. Women with AOC formed a distinct group compared with other women with PPH in our study, with approximately a 30-fold increase in PAP levels and 25-fold increase in D-dimer confirming the presence of massive fibrinolysis. Ducloy-Bouthors et al. [48] investigated 144 women with PPH, without evidence of significant coagulopathy (mean fibrinogen above 3 g/L), and found average PAP levels of approximately 1000 ng/mL. In major trauma studies, PAPs above 20 000 ng/mL are used to define the most severe group [49,50].

Women with AOC had a characteristic hemostatic profile with evidence of an acquired dysfibrinogenemia that was not present in other women with PPH. This means that reduced Clauss fibrinogen and Fibrin A5 in the AOC group were due to both decreased absolute levels and impaired function. We have recently reported dysfibrinogenemia in the context of severe PPH-associated with AFE [30]. The mechanism for dysfibrinogenemia in AOC is not known but may be related to high levels of fibrin degradation products interfering with fibrin polymerization [51].

AOC was associated with reduced FV, FVIII, and FXIII, but other procoagulant factors were preserved. Thrombin generation was normal or increased, and there was a small decrease in platelet count. These hemostatic changes suggest a specific rather than generalized consumption of coagulation factors. Although FVIII was reduced in AOC, this would not be clinically significant because it remained above 100 IU/dL in all cases. The FVIII level was influenced by the rise in VWF, and the relative depletion of FVIII was more obvious when VWF/FVIII ratios were investigated.

FV and FVIII fell by similar amounts, 43% and 39%, respectively, suggesting that depletion may have been due to a shared mechanism. Depletion of FV and FVIII may have been caused by aPC as seen in ATC [10–12,52]. Additionally, plasmin directly cleaves FV and FVIII [53,54], and this may have been a contributing mechanism given the massive excess of this enzyme in the AOC group. FXIII was

approximately 17% lower in the AOC group compared with other women with PPH, and nonbleeding healthy-term pregnant women are known to have reduced FXIII levels [55].

The coagulopathy in the AOC cohort is indistinguishable from that described in women with AFE where severe fibrinolysis and reduced fibrinogen, FV and FVIII, and dysfibrinogenemia are reported [27–30]. Yet in the cohort of 12 women with AOC described in this study, only 1 was diagnosed with AFE. This diagnosis was made by the study team on notes review and not by the clinical team during the acute episode. The case of “coagulopathy of unknown cause” fits the UKOSS definition of AFE (<https://www.npeu.ox.ac.uk/ukoss/current-surveillance/amf>, accessed August 16, 2022), although not the more strict criteria of Clark et al. [56]. This diagnosis was not considered because the woman did not have circulatory collapse or hypoxia. AFE was reported in 3.3/100 000 women with a 35% maternal mortality in a population-based study [57] and a literature review identified rates between 2.1 and 6.1/100 000 depending on study methodology (<https://www.npeu.ox.ac.uk/research/projects/66-afe-comparative-study>, accessed August 16, 2022). These incidences are much lower than the 1.06/1000 women who developed AOC in our study, although subclinical AFE is a possible explanation. Five women with AOC had placental abruption, and hypofibrinogenemia is a known association. However, there were 26 other women with an abruption in our study with no evidence of AOC (average fibrinogen 4.1 g/L, PAPs 4733 ng/mL, and D-dimer 2384 ng/mL) demonstrating that most abruptions are not affected. There were no fetal or neonatal deaths in these 26 cases. The remaining women with AOC had diverse causes of bleeding indicating that the coagulopathy can present in a variety of situations. These findings are clinically important because AOC cannot be predicted by the cause of bleeding, unless an AFE is diagnosed; and the only way to identify cases in an acute bleed is a low fibrinogen (Clauss or point-of-care) together with very high D-dimers (>20 000 ng/mL), if this test is rapidly available.

AOC was associated with very poor fetal and neonatal outcomes when compared with other cases of PPH (50% (6/12) fetal/neonatal mortality vs 0.4% (2/506)). This is partly explained by the high incidence of placental abruption in the AOC group, and poor outcomes are also reported in cases of pregnancy-related coagulopathy [58]. Whether the fetal and neonatal deaths were caused by or were precipitated by AOC requires further study. AOC was not associated with sepsis, a known risk factor for pregnancy-associated coagulopathy [13]. Despite having similar volumes of blood loss to other women with PPH, morbidity in women with AOC was increased, and they were more likely to receive RBC transfusion, suggesting concealed bleeding, for example, into the uterine wall, and be admitted to high-dependency care on the obstetric unit and intensive care, although their shock index and lactate were similar to non-AOC cases. The clinical outcomes described in this article should be considered in the context of the local PPH treatment algorithm, which includes VHAs to detect low functional fibrinogen and guide replacement during cases of AOC. It is not possible to assess the likely outcomes in centers without access to early detection of hypofibrinogenemia, and there is the risk of progression of bleeding if fibrinogen replacement is



delayed. The amount of fibrinogen needed to restore hemostasis in cases of AOC cannot be assessed from the data available if there is no access to VHAs, but higher doses than those required for dilutional coagulopathy may be necessary because of ongoing depletion and dysfibrinogenemia.

The very high levels of PAP complexes and D-dimers show that excessive amounts of plasmin had been generated, which cleaved crosslink fibrin. It is not known what precipitated the activation of plasminogen to plasmin or the activator responsible. A possible mechanism is that decreased levels of plasminogen activator inhibitors (PAI-1 or PAI-2) contributed, although it is unlikely that the excessively high PAPs seen in the AOC group would have been caused through failure of inhibition alone.

In trauma, increased aPC is thought to be mediated by increased circulatory sTM associated with shock [10–12]. This does not seem to be the case in AOC because, aPC was raised compared with other women with PPH, whereas sTM was not increased; and also bleed volume, shock index, and lactate were similar between the AOC group and other women with PPH. The mechanism for the raised aPC in AOC requires further study.

The coagulopathy described in AOC suggests that treatment should be with antifibrinolytics, such as tranexamic acid [59], and fibrinogen replacement with cryoprecipitate or fibrinogen concentrate [35,47]. Despite the severe coagulopathy, the volume of bleeding between the AOC group and the non-AOC group was similar, suggesting that the treatment protocol used in our center, which used early tranexamic acid and rapid identification and correction of low functional fibrinogen [36,37], was effective in preventing bleed progression, and there were no examples of AOC that were exacerbated by dilutional coagulopathy. Prospective studies are required to investigate this further.

This study has a number of limitations. Sample collection and storage performed outside of routine hours was challenging, and not all women had samples available from every time point. In addition, extended tests of coagulation were performed on a subgroup of cases selected for bleed severity and likelihood of coagulopathy. It is not possible to exclude that cases of AOC were missed in the women who did not have extended testing, but this is unlikely because women with low Clauss fibrinogen or Fibtex A5 were tested.

This was an exploratory study to investigate PPH-related coagulopathy. The women with AOC were categorized retrospectively because they were found to be outliers based on markers of hyperfibrinolysis. The coagulopathy described will need to be investigated further in prospective cohorts to establish whether the findings are reproducible. The mechanisms that precipitated very high levels of PAPs and raised aPC were not determined and require further study. We were unable to analyze aPC in the complete cohort because of the initial lack of appropriate blood bottles; therefore, the aPC data are limited and should be interpreted with caution.

In conclusion, in a large cohort of women with PPH, that included the large majority of women in our institution with bleeds > 2000 mL, very few develop hemostatic impairment early during the bleed. Women without AOC have a linear reduction in coagulation factors

and platelets with increasing bleed volume, compatible with consumption into clots and dilution, although no woman had reduced thrombin generation.

We identified a cohort of women (1.06/1000 maternities) who had a distinct and severe early coagulopathy, that we termed AOC. This coagulopathy was indistinguishable from that previously reported for AFE. The AOC group was not identifiable by clinical presentation alone and recognition and treatment of this coagulopathy depends on availability of timely coagulation results. The local treatment protocol of tranexamic acid infusion and maintaining fibrinogen > 2 g/L appeared to be effective in limiting progression of PPH-associated with AOC. The implications of reduced FXIII levels in pregnant women at term and during PPH are unclear and require further investigation. Overall, our results suggest that empirical fixed ratio treatment of PPH with early FFP is unlikely to improve coagulation in most women with PPH and will lead to large numbers receiving unnecessary blood products and undertreatment of women with established coagulopathy. Emphasis for correction of PPH-related coagulopathy should be on the administration of antifibrinolytic agents and replacement of fibrinogen. How and when to test for fibrinogen during a PPH, and the optimal source for replacement, requires further study.

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## AUTHOR CONTRIBUTIONS

L.de.L. was the study's principal investigator, led the ethical approval, designed the study, collated data, interpreted data, and co-wrote the first draft of the manuscript.

P.V.J. designed the study, led the laboratory investigations, interpreted data and co-wrote the first draft of the manuscript. S.F.B. designed the study, collated data, interpreted data, and co-wrote the first draft of the manuscript. N.J.M. interpreted data and critically reviewed the manuscript. J.F. performed the thrombin generation



assays, collated data, interpreted data, and critically reviewed the manuscript. P.M.B. developed and provided materials for the aPC test, interpreted data, and critically reviewed the manuscript. D.J. co-led the consenting of women, developed and maintained the study database, collated data, interpreted data, and critically reviewed the manuscript. AR co-led the consenting of women, collated data, interpreted data, and critically reviewed the manuscript. L.C., T.R., and V.F. collated data, interpreted data and critically reviewed the manuscript.

R.E.C. and P.W.C. designed the study, collated data, interpreted data, and co-wrote the first draft of the manuscript. The manuscript has been read and approved by all authors.

## DECLARATION OF COMPETING INTERESTS

L.de.L. has received research support Haemonetics. S.F.B. has received research support and paid consultancies from Werfen and Haemonetics. N.J.M. has received research support and paid consultancies from Alveron Pharma, LFB Group, and STAGO. R.E.C. and P.W.C. have received research support and paid consultancies from CSL Behring, Werfen, and Haemonetics. None of the other authors have conflicts to declare.

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#### SUPPLEMENTARY MATERIAL

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