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ORIGINAL ARTICLE

The impact of prepartum factor XIII activity on postpartum blood loss

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Abstract

Background: Postpartum hemorrhage (PPH), a major cause of maternal mortality, has several known risk factors but frequently occurs unexpectedly. PPH incidence and related maternal morbidity and mortality are rising worldwide.

Objective: To evaluate the impact of defined prepartum blood coagulation parameters on postpartum blood loss.

Methods: This single-center, prospective cohort study analyzed prepartum activities of coagulation factors II and XIII and fibrinogen levels in 1300 women. Blood samples were obtained at labor onset and analyzed only after the last patient had delivered, to prevent a potential treatment bias. Blood loss was quantified using a validated technique. The influence of coagulation factors on measured blood loss was assessed by continuous outcome logistic regression.

Results: Prepartum factor XIII activity strongly influenced measured blood loss: every one unit (%) increase in prepartum factor XIII was associated with an odds ratio of 1.011 (95% confidence interval, 1.006-1.015; $P < .001$) to keep blood loss below any given cut-off level. For illustration, this suggests that a 30% increase in factor XIII activity increases the odds of not suffering PPH (defined as blood loss ≥500 mL) by 38.9%. This effect remained significant after stratification for the delivery mode, when correcting for other risk factors, and was independent of the statistical model used. Factor II but not fibrinogen had a partially comparable, but much less pronounced, effect.

Conclusion: In the largest population analyzed for the influence of prepartum coagulation factors on PPH to date, prepartum factor XIII activity had a strong impact on postpartum blood loss across every statistical model and clinical subgroup. Our hypothesis that early replenishment of factor XIII levels might constitute a new tool in the prevention and effective early treatment of PPH should be evaluated in future trials.

KEYWORDS

blood coagulation factors, factor XIII, fibrinogen, parturition, postpartum hemorrhage

Haslinger and Korte contributed equally to this article.

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1 | INTRODUCTION

Postpartum hemorrhage (PPH), defined as blood loss ≥500 mL within 24 hours after delivery, is a major cause of maternal morbidity and mortality worldwide[1-3] and is responsible for 30% of maternal deaths, equivalent to the deaths of 10 women every hour.[4] Although a particular burden in low-income countries, its complications are increasing in industrialized countries as well. The incidence of severe PPH in the United States, defined as PPH plus blood transfusion, hysterectomy, and/or surgical repair of the uterus, rose from 1.9 to 4.2 per 1000 deliveries between 1999 and 2008;[5] as explained, PPH makes up a relevant part of overall maternal mortality, which rose an alarming 26.6% from 2000 to 2014.[6]

Severe PPH may present without known and prenatally identifiable risk factors. In fact, 3% of women without prenatally identifiable risk factors will still have blood loss >1000 mL.[4,7] It is therefore compelling to search for and identify other pertinent risk factors. Coagulation factor XIII (FXIII), or fibrin stabilizing factor, plays an important role in the management of peri- and postoperative bleeding.[8-14] FXIII activity decreases in the second and third trimesters of pregnancy.[15,16] Peripartum data remain scarce but antenatal FXIII activity was recently shown to be significantly lower in women with PPH than in those without.[17]

The aim of this study was therefore to determine whether coagulation factors, and in particular prepartum FXIII activity, influence postpartum blood loss in previously asymptomatic women. Delivery stresses the coagulation system, above all if complicated by increased blood loss from causes such as uterine atony or retained placenta. Based on our earlier research,[8,10,18] we hypothesized that even slightly reduced FXIII activity might significantly aggravate blood loss given the importance of its cross-linking role in establishing mechanical clot stability and enhancing fibrinolytic resistance.[19,20] As the final steps of the coagulation cascade are also depending on factor II (FII) and fibrinogen, we thus evaluated the influence of fibrinogen, FII, and FXIII on postpartum blood loss.

Essentials

- Incidence of postpartum hemorrhage as well as associated maternal mortality is rising.
- Impact on postpartum blood loss of prepartum factors I, II, and XIII was assessed in 1300 women.
- Prepartum FXIII was the only factor to impact postpartum blood loss irrespective of the statistical model applied.
- Early replacement of factor XIII might reduce postpartum blood loss and needs to be evaluated.

The study was funded by University Hospital Zurich, CSL Behring Switzerland, the Center for Laboratory Medicine St. Gallen, and a private donor (a former patient). A written contract secured that funding entities not involved in performing the study (ie, CSL Behring and the private donor) had no influence on its design; the collection, management, analysis, or interpretation of data; the preparation, review, or approval of the manuscript; or publication.

2 | METHODS

2.1 | Study design and oversight

This single-center cohort study was performed at the Department of Obstetrics, University Hospital Zurich, Switzerland, between October 2015 and November 2016 following institutional review board approval (KEK-ZH 2015-0011, ClinicalTrials.gov registration NCT02604602). Patients gave written informed consent. Prospective data collection was performed by dedicated research personnel, using patient data from the general and obstetrics-specific clinical information systems.

Samples were analyzed at the Center for Laboratory Medicine, Hemostasis and Hemophilia Center, St. Gallen, Switzerland, only after the last patient was enrolled, thus preventing potential treatment bias.

2.2 | Participants

Women admitted to the labor ward before vaginal delivery or cesarean section were eligible if they were ≥18 years of age and their pregnancy at ≥22 weeks. Patients with known congenital disorders of hemostasis, on anticoagulant therapy, and women with preeclampsia or eclampsia were not eligible. Enrolment was consecutive. The blood sample was drawn in the 36 hours preceding the onset of delivery, defined as regular contractions or membrane rupture, whichever occurred first. Patients were offered the possibility to discuss the study at three different time points before they were asked for written informed consent.

2.3 | Procedures

Our institution uses a proprietary, validated quantitative system to measure vaginal delivery blood loss.[21,22] Immediately after clamping the cord, the midwife places a fresh drape under the woman's pelvis to collect blood. The drape is regularly checked and if continued bleeding is observed, the drape is weighed on a neonatal balance installed in every suite. If the overall weight (ie, fluid minus drape) exceeds 300 g, a plastic bag with a quantitative scale is placed under the pelvis for blood collection and exact measurement.[21,22] Cesarean blood loss is estimated by the obstetrician; all fluid between hysterotomy and clamping the cord is collected in a pouch and presumed to be mostly amniotic in origin. Fluid collected in the pouch thereafter is added to the volume of blood lost, as is the volume of all blood-soaked surgical cloths. As published, this measurement technique is more accurate in vaginal delivery but also correlates well with hemoglobin loss in cesarean delivery.[22]

Blood was collected from an antecubital vein into Vacutainer® tubes (6.0 mL, 9:1 diluted with 0.105 mol/L buffered sodium citrate) and processed without delay on a 24/7 basis: plasma was centrifuged at 2800 *g* for 10 minutes at 17°C, 2 mL supernatant aliquots were snap-frozen and stored at −80°C before being couriered to the laboratory on dry ice.

2.4 | Analysis of coagulation factors and hemoglobin

Fibrinogen concentration (Clauss assay) and FII activity (one-stage clotting assay) were determined on an ACL 500 coagulation analyzer (Instrumentation Laboratory) according to the manufacturer's recommendations; FXIII activity was measured by chromogenic assay (Berichrome) on an XP analyzer (Siemens), also according to the manufacturer's recommendations. Prepartum hemoglobin (low levels of which may influence postpartum blood loss[4,7]) was analyzed on an ADVIA (Siemens) or XN-20 (Sysmex) instrument.

2.5 | Outcome

We evaluated the impact of prepartum fibrinogen concentration and FII and FXIII activity on measured postpartum blood loss (measured blood loss [MBL], in mL).

2.6 | Statistical analysis

Baseline demographic, fetomaternal and perinatal characteristics, and prepartum coagulation factor values were stratified by mode of delivery and presented using descriptive statistics. Continuous MBL data and the depending probabilities (%) of remaining below a certain cut-off (mL) were presented graphically, stratified by mode of delivery.

In a first step, the conditional distribution of MBL in relation to prepartum hemoglobin (g/L), fibrinogen (g/L), FII (%), and FXIII (%) was estimated by continuous outcome logistic regression.[23,24] In this model, all possible binary logistic regression models for all MBL volumes were estimated, thus allowing us to apply this model to any blood loss cut-off point (ie, the regression coefficients were treated as constants). The regression coefficients describe the odds ratio and assess the change associated with a one-unit increase in one of the four evaluated prepartum blood parameters; this was done simultaneously for all potential blood loss cut-off points. Thus, the calculated odds ratios describe the effect of a one-unit increase in the respective prepartum parameter on the probability to remain below any MBL cut-off chosen. Appropriateness of the models was assessed by comparison against a Tobit model assuming the normality of MBL (details in Appendix S1 in supporting information).

In our analysis, all singular MBL measured were interval-censored (interval widths 50 mL for blood losses ≤1000 mL, 100 mL for larger blood losses, in order to reflect any potential inaccuracy of the actual measurements). The null hypothesis of all regression coefficients being zero was tested using the likelihood ratio test (at nominal level $\alpha = 0.05$); 95% Wald-type confidence intervals for odds ratios are reported without multiplicity adjustment.

In a second step, the impact of potential effect modifiers on the odds ratios of prepartum blood parameters was assessed using model-based recursive partitioning.[25] Two models were calculated: first, a model with the variables available prepartum only (eight variables). This information is important as it can be used for designing subsequent clinical trials investigating the role of the coagulation factors; and second, a model with all variables available (the 24 variables available preas well as postpartum), which can be used as verification of the role of coagulation factors when also postpartum available information (such as important risk factors for PPH like uterine atony, retained placenta, etc) are included in the analysis. The effect of prepartum blood parameters on blood loss was evaluated in diverse subgroups; subgroup-specific odds ratios are reported (details are given in the Appendix S1).

All analyses were performed using the add-on packages partykit, version 1.2-3[26] and mlt, version 1.0-5,[27] to the R System for Statistical Computing (version 3.5.3, R Core Team[28]). Raw data and all codes are given in the Appendix S1, which is open to other interested groups.

3 | RESULTS

The study recruited 1500 women from October 2015 through November 2016. One hundred ninety-one patients were excluded from further analysis as blood was not taken within the prespecified time range (n = 133) or the sampling tube was not adequately filled (n = 58). Nine further women were excluded as the results for one or more coagulation factors were missing. Table 1 shows baseline characteristics and prepartum blood values stratified by delivery mode (missing data in the Appendix S1). Figure 1 shows MBL distribution stratified by delivery mode.

3.1 | Influence of prepartum blood parameters on MBL

MBL distribution was significantly influenced by prepartum blood parameters ($X^2 = 33.65$, $df = 4$, $P < .001$). Higher prepartum FII and FXIII were both associated with lower postpartum MBL. For every one-unit increase in prepartum FII, the odds ratio for keeping postpartum MBL below a defined cut-off (possible for any of the MBL volumes) was 1.007 (95% confidence interval [CI], 1.001-1.013; $P = .02$). For prepartum FXIII, the odds ratio for keeping postpartum MBL below a defined cut-off (possible for any of the MBL measured) was 1.011 (95% CI, 1.006-1.015; $P < .001$) with every one-unit increase in prepartum FXIII (Table 2). Prepartum fibrinogen had no detectable influence on postpartum MBL (odds ratio 0.930 [95% CI, 0.828-1.044, $P = .22$]). As the odds ratios per singular coagulation factor unit increase are somewhat difficult to interpret in a clinical setting, we also modelled

TABLE 1 Fetomaternal and perinatal characteristics, prepartum hemoglobin and blood coagulation factors, stratified by mode of delivery

Variable	Vaginal delivery (N = 677)	Elective cesarean delivery (N = 409)	Unplanned cesarean delivery (N = 223)
Measured blood loss, mL	350 (300-500)	500 (400-600)	500 (400-700)
Prepartum hemoglobin, g/L	128.0 (121.0-135.0)	124.0 (118.0-131.0)	127.0 (120.0-134.0)
Prepartum fibrinogen, g/L	4.5 (3.9-5.1)	4.3 (3.9-4.8)	4.5 (3.9-5.2)
Prepartum factor II, %	128.0 (118.0-140.0)	128.0 (115.0-138.0)	128.0 (115.0-140.0)
Prepartum factor XIII activity, %	98.5 (86.0-117.8)	93.0 (82.0-107.0)	93.0 (80.2-111.0)
Number of colloids	0 (0-0)	1 (1-1)	1 (0-1)
Spontaneous delivery	566	–	–
Vacuum delivery	111	–	–
Unplanned cesarean delivery (non-urgent)	–	–	210
Unplanned cesarean delivery (emergency)	–	–	13
Gestational age, days	280 (273-285)	267 (265-270)	277 (268-284)
Maternal age, years	32 (29-35)	34 (30-37)	33 (30-36)
Multiparity	310 (45.8%)	254 (62.1%)	70 (31.4%)
Body mass index, kg/m^2	23.2 (20.5-26.8)	25.1 (21.7-28.8)	23.4 (21.0-26.4)
Duration of second stage labor, minutes	51 (18-121)	–	173 (119-207)
Multiple fetus pregnancy	6 (0.9%)	32 (7.8%)	13 (5.8%)
Induction of labor	263 (38.8%)	4 (1.0%)	85 (38.1%)
Induction of labor >48 hours	22 (3.2%)	1 (0.2%)	18 (8.1%)
Chorioamnionitis	1 (0.1%)	0	9 (4.0%)
Neonatal weight, g	3370 (3090-3650)	3200 (2890-3510)	3340 (2945-3690)
Uterine rupture	0	0	3 (1.3%)
Uterine atony	42 (6.2%)	7 (1.7%)	4 (1.8%)
Retained placenta	24 (3.5%)	0	0
Retained placental tissue	26 (3.8%)	1 (0.2%)	0
Morbidly adherent placenta	1 (0.1%)	3 (0.7%)	1 (0.4%)
Placenta previa	0	9 (2.2%)	4 (1.8%)
Bleeding from laceration	49 (7.2%)	0	0
Placental abruption	2 (0.3%)	2 (4.9%)	6 (2.7%)

Note: Data are median (interquartile range) or n (%).

what would happen to postpartum MBL if clinically relevant changes in prepartum coagulation factors would occur. It showed that a 10% rise in prepartum FXIII activity increased the odds of postpartum MBL to remain below a defined cut-off by 11.6%, while a 30% rise of FXIII activity increased the odds of keeping blood loss under any defined cut-off by 38.9%. In other words, the model derived from our cohort indicates that the risk to develop PPH might be reduced by roughly 40% if prepartum FXIII activity is increased by 30%.

The results were unaffected by deviations from the model assumptions. In particular, distribution regression[29,30] models and a selection of binary logistic regression models using MBL cut-offs of 500, 750, and 1000 mL did not change the model fit substantially (details in Appendix S1). Graphic assessment indicated that the interpretation of constant effects for all MBL cut-offs was appropriate (Figure 2). Estimated odds ratios for prepartum FII and FXIII and corresponding CIs could be reproduced by looking at a binary logistic regression model for the selected cut-off point of 500 mL MBL, which defines PPH, as well (Table 2).

We also stratified the model estimation by delivery mode. The models for vaginal delivery and cesarean section gave similar results for FXIII, as in the unstratified analysis outlined above. However, FII showed to have an effect only in the cesarean section stratum, indicating that the effect observed in the overall cohort does not apply to patients with vaginal delivery. As in the overall cohort, no influence of fibrinogen was observed, neither in the vaginal delivery nor in the cesarean section stratum (Table 3).

As FXIII was the only variable associated with any volume of MBL and in any stratum evaluated, it is adequate to calculate the overall prevalence for PPH (defined as MBL ≥500 mL) as a function of prepartum FXIII (with prepartum levels of 127 g/L for hemoglobin, 4.5 g/L for fibrinogen, and 128% for FII representing the equivalent median values in the study population). This is shown in Figure 3. Such an

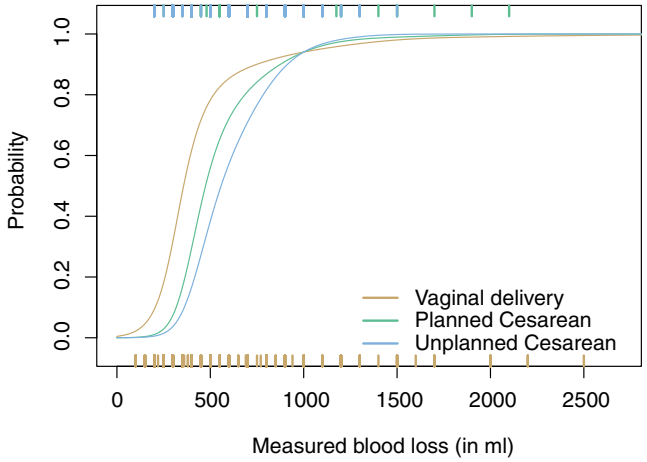


FIGURE 1 Distribution of measured blood loss (mL) stratified by mode of delivery. Rugs indicate measured blood loss observations, stratified by mode of delivery. The line presents the probability (%) that measured blood loss remains below a certain cut-off (mL). One vaginal delivery with blood loss of 5700 mL not shown

evaluation is not adequate for the other variables, as they are neither invariably associated to MBL, nor have they influence in all strata.

3.2 | Identification of effect modifiers

The second step of the analysis assessed the influence of other PPH risk factors on the demonstrated effect of prepartum FXIII on postpartum MBL. The prepartum model indicated that higher prepartum FXIII corresponded to lower postpartum MBL in all subgroups. The effect seemed most prominent in a subgroup of women with a singleton pregnancy, body mass index >20.7 kg/m^2, and maternal age ≤28 years (Figure 4, subgroup 5). In this subgroup, the probability of MBL >500 mL was 24%, of MBL >750 mL 7%, and of MBL >1000 mL 3%. According to our model, an absolute increase of prepartum FXIII activity by 50%, will reduce the probability for a postpartum MBL >500 mL from 24% to 9%, for >750 mL from 7% to 2%, and for >1000 mL from 3% to 1%, respectively (Figure 5). Potential results and probabilities without or with prepartum FXIII therapy for different subgroups, according to our model, are given in Table 4. This modeling will help us in the design of a prospective clinical trial.

4 | DISCUSSION

This prospective study in 1300 women showed a strong effect of FXIII on postpartum blood loss. The higher the prepartum FXIII activity, the lower the probability of PPH, defined as a postpartum MBL ≥500 mL; this also held true for any other arbitrarily chosen threshold. The effect was independent of the statistical model applied, continued to be present after stratification by delivery mode and also after considering other risk factors for PPH, whether prepartum or both pre- and postpartum. The overall consistency of the association of FXIII with blood loss is robust and statistically significant. However, even more important seems the assumed clinical relevance: the selective administration of FXIII is possible; and in our model, an increase in FXIII activity by 30% associates with a decrease of the probability to suffer from PPH by 39%; for an increase of FXIII activity by 50%, this number increases to 73%.

Such robust results from statistical models are of great clinical interest: they indicate a high likelihood that the increase of peripartum FXIII levels might reduce postpartum blood loss. This seems a reasonable and feasible approach to evaluate, as various FXIII concentrates are commercially available. For now, and according to our model including prepartum available risk factors for PPH, women with a singleton pregnancy, body mass index >20.7 kg/m^2, and maternal age ≤28 years seem to constitute the risk group most appropriate to target for an early interventional therapy. However, given the sound results regarding the association of prepartum FXIII activity with postpartum blood loss in the overall population and all subgroups, the question arises if a prepartum FXIII cut-off can be identified that is associated with PPH and would thus allow the substitution of FXIII before delivery. Therefore, the prevalence of PPH as a function of prepartum FXIII was calculated (Figure 3) for a hypothetical subject with prepartum hemoglobin 127 g/L, prepartum fibrinogen 4.5 g/L, and prepartum FII 128% (these values reflect the

TABLE 2 Continuous outcome ("all") and binary (for cut-off point 500 mL) logistic regression models for impact of prepartum blood parameters on measured postpartum blood loss

Cut-off	Prepartum blood parameter	Odds ratio	95% confidence interval	*P*
All	Hemoglobin	1.008	0.999-1.018	.07
	Fibrinogen	0.930	0.828-1.044	.22
	Factor II	1.007	1.001-1.013	.02
	Factor XIII	1.011	1.006-1.015	<.001
500 mL	Hemoglobin	1.007	0.996-1.018	.20
	Fibrinogen	0.921	0.807-1.051	.22
	Factor II	1.009	1.002-1.016	.01
	Factor XIII	1.009	1.003-1.014	.002

Note: Odds ratios for remaining below a certain cut-off point for measured blood loss, induced by a one-unit increase in one of the four prepartum blood parameters: "all" or 500 mL. "All" refers to all cut-off points simultaneously via continuous outcome logistic regression.

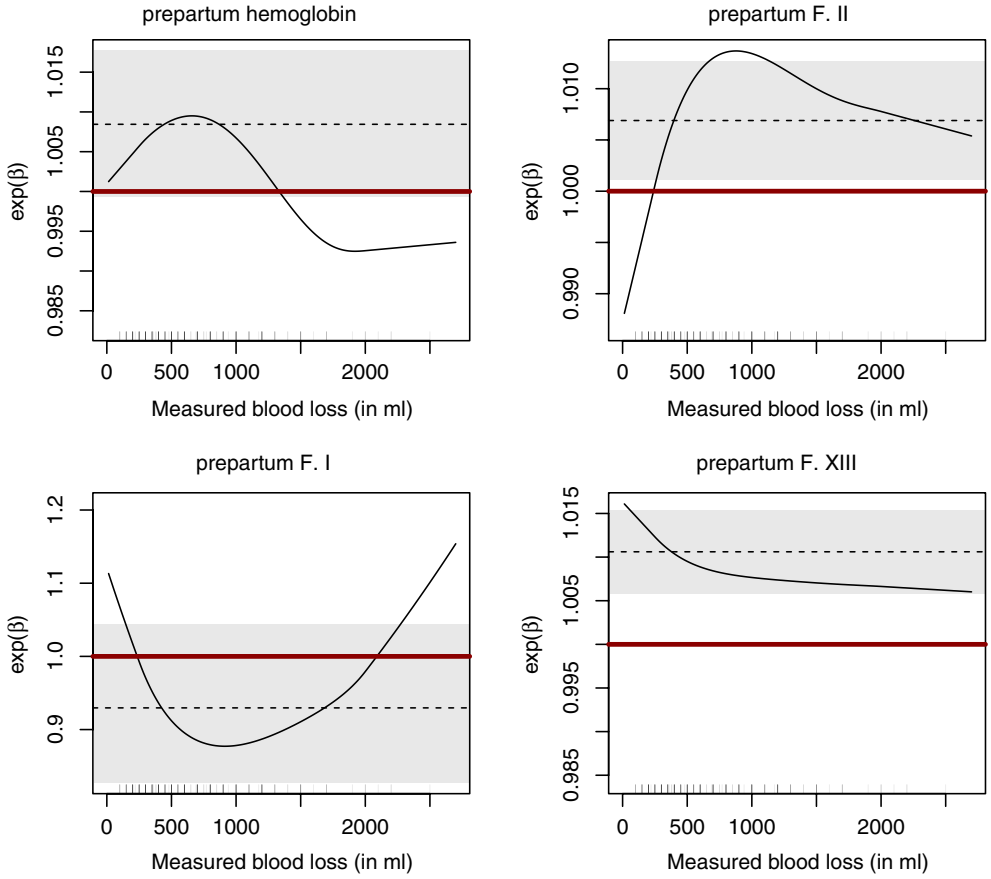


FIGURE 2 Odds ratio (as a curve, for every prepartum variable evaluated) for remaining below a certain amount of postpartum blood loss based on MBL cut-off-dependent regression coefficients. Dashed lines: postpartum blood loss-constant regression coefficients (on the exp-scale) from the continuous outcome logistic regression model; gray area: confidence interval pertaining to the constant regression coefficients; red line: absent effect (odds ratio 1.0); continuous black line: blood loss-cut-off-specific logistic regression coefficients. If the measured blood loss (MBL)-constant regression coefficient (dashed line) with its confidence interval (gray area) remains above the OR of 1 (red line), the probability increases to remain below any blood loss-cut-off (in other words: the more far away the dashed line is, the bigger is the impact on blood loss). The same is true for MBL-cut-off-specific regression coefficients: the variable effect depending on the chosen blood loss-cut-off is represented by the continuous line. The factor XIII (FXIII) odds ratio graph is the only one not to cross the red line representing nil effect, ie, FXIII is the only parameter with a statistically significant impact on blood loss for any blood volume measured: the higher the prepartum FXIII activity, the higher the probability of remaining below any blood loss cut-off. This is the case neither for fibrinogen nor factor II. Fibrinogen is the only parameter with a regression coefficient mostly far below 1.0, representing an unfavorable (albeit statistically nonsignificant) effect on postpartum blood loss

median values of the study population). The graph confirms once again the firm and continuous association of prepartum FXIII levels with blood loss; however, an explicit cut-off is difficult to define. Our hypothesis, which needs to be confirmed in an interventional trial, is that early replenishment of FXIII might be useful above all in patients with obstetric bleeding complications such as uterine atony or retained placenta. Women with a rather low FXIII activity might still not suffer from PPH as long as they are not confronted with obstetric complications. However, as long as results of prospective, controlled intervention trials are not yet available, early replenishment of prepartum FXIII might be discussed if prepartum FXIII activity is below 50% as the probability for PPH then seems to exceed 50% (Figure 3).

Albeit that the calculated odds ratios seem somewhat challenging to interpret at first sight in the given setting, the continuous analysis of a large dataset including clinical and laboratory data entails indisputable advantages: to the best of our knowledge, this study is the first to examine the influence of prepartum coagulation factors over the whole spectrum of precisely measured postpartum blood loss levels, which were continuously obtained by an evaluated blood loss measurement system. This is an important difference from studies that only analyzed predefined cut-off values for postpartum blood loss—using cut-offs for analysis is prone to loss of information in clinical data sets.

Our findings are consistent with those of a recent study in 548 women showing significantly lower FXIII activity in those patients suffering from PPH, defined as MBL ≥500 mL, compared to those without PPH. No differences for FXIII activity were observed in the subgroup with MBL ≥1000 mL, but it seems likely that this evaluation was underpowered due to the small group size (n = 18).[17] Two even smaller studies (longitudinal study in 44 women,[16] cross-sectional study in 128 women in the third trimester of pregnancy[15]) found no significant correlation between FXIII activity and estimated blood loss, again possibly due to inadequate sample sizes.

TABLE 3 Continuous outcome logistic regression for the impact of prepartum blood parameters on postpartum measured blood loss, stratified by mode of delivery

Prepartum blood parameter	Mode of delivery	Odds ratio	95% confidence interval	*P*
Hemoglobin	Vaginal	0.994	0.981-1.007	.37
	Cesarean	1.006	0.993-1.020	.35
Fibrinogen	Vaginal	1.010	0.851-1.200	.91
	Cesarean	0.862	0.736-1.009	.07
Factor II	Vaginal	1.002	0.994-1.011	.57
	Cesarean	1.011	1.002-1.019	.01
Factor XIII	Vaginal	1.010	1.003-1.016	.004
	Cesarean	1.008	1.001-1.014	.02

Note: Odds ratios for remaining below any cut-off point for measured blood loss, induced by a one-unit increase in one of the four prepartum blood parameters.

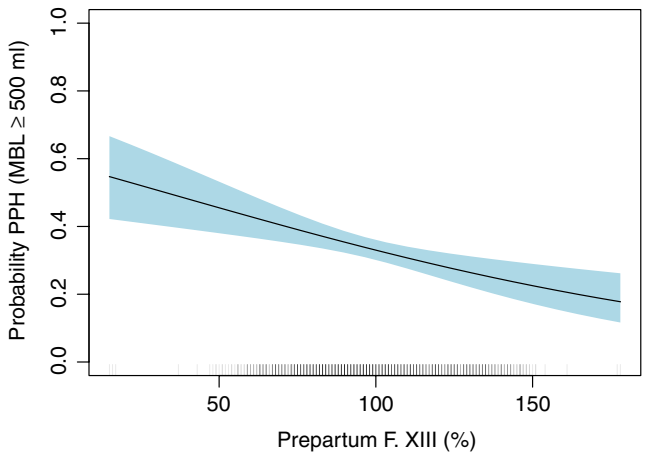


FIGURE 3 Prevalence of postpartum hemorrhage (PPH) as a function of prepartum factor XIII (FXIII). Prevalence curve of PPH (defined as measured blood loss [MBL] ≥ 500 mL) as a function of prepartum FXIII for a hypothetical subject with prepartum hemoglobin 127 g/L, prepartum fibrinogen 4.5 g/L, and prepartum factor II 128%. The line represents the probability for a patient to suffer from PPH, the blue area represents the 95% confidence band. Rugs on the horizontal axis indicate actually measured prepartum FXIII activities (%); the brightness of a rug reflects the number of measurements of a certain value (the darker a rug is, the more frequent this specific activity was measured in a patient)

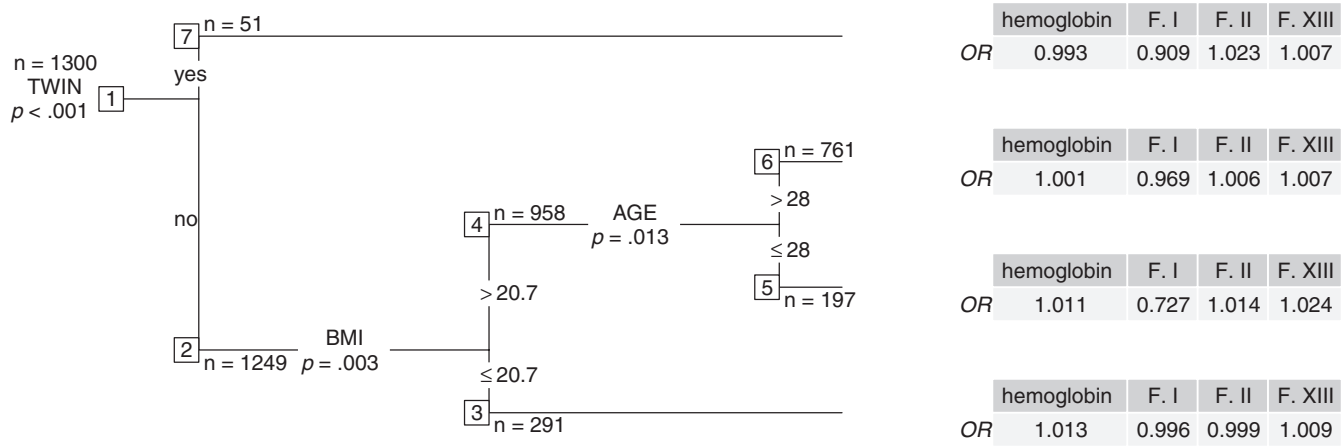
Specialties other than obstetrics have provided some evidence on the importance of FXIII, eg, in the surgical setting. Two randomized placebo-controlled studies showed that FXIII increases clot firmness and reduces blood loss or dependence on blood transfusion.[8,12] Decreased FXIII activity is associated with unexplained intraoperative bleeding and reduced clot firmness[10] as well as postoperative hemorrhage in neurosurgical patients.[11,31]

Given their contribution to the final steps of the clotting cascade, we also evaluated fibrinogen and FII in addition to FXIII.

Low fibrinogen levels had previously been incriminated in severe PPH:[32,33] however, in a randomized controlled trial in 249 patients with severe PPH, preemptive treatment with fibrinogen concentrate reduced neither red cell transfusion nor any secondary outcome.[34] Likewise, viscoelastometric-guided (Fibtem A5 ≤ 15 mm) infusion of fibrinogen concentrate in women with postpartum blood loss of 1000-1500 mL and ongoing bleeding did not improve outcomes in a double-blind randomized controlled trial.[35] Unlike other non-intervention studies[32-33,36,37] and in accordance to the aforementioned two prospective intervention trials, our study found no association of prepartum fibrinogen levels with postpartum blood loss. We cannot exclude that such an association exists in populations with a high prevalence of unequivocally identified fibrinogen deficiencies. However, fibrinogen deficiencies were rare in our study population with fibrinogen levels <1.5 g/L in 0.15% and <2 g/L in 0.31% of women. Therefore, we speculate that low fibrinogen concentrations measured in postpartum hemorrhage shown to be associated with severe PPH,[32-33,36,37] reflect a consequence (due to ongoing consumption) rather than a preexisting (risk) factor. This would also help to explain why preemptive or early fibrinogen therapy did not prevent or improve PPH in the prospective trials.[34,35] In line with this, a recent study found no consistent effect of fibrinogen on blood loss, with a potential effect being dependent on the cut-off chosen.[17] This again highlights the importance of our finding that FXIII significantly influences postpartum blood loss at any MBL observed, independent of any cut-off. For clinical use (ie, FXIII replenishment), however, intervention limits or target populations at risk will need to be defined.

Little is known about the effect of FII on postpartum blood loss. Lower FII activity has been reported in patients with severe versus non-severe PPH,[32] but other data were inconclusive.[33] In our study, higher prepartum FII activity was associated with lower postpartum MBL, but the effect was markedly less important than that of FXIII, and it was not seen in all subgroups: there was no influence of prepartum FII activity on postpartum MBL in the group of patients that had a vaginal delivery.

Albeit the major strengths of our study as explained above (no treatment bias, precise measurement of blood loss, use of continuous regression models), potential weaknesses have to be recognized. Although we used the actually probably most precise, clinically feasible methodology for blood loss measurement in vaginal delivery, blood loss measurement in cesarean delivery always harbors a potential for inaccuracy, as in any other study evaluating



	hemoglobin	F. I	F. II	F. XIII
OR	0.993	0.909	1.023	1.007

	hemoglobin	F. I	F. II	F. XIII
OR	1.001	0.969	1.006	1.007

	hemoglobin	F. I	F. II	F. XIII
OR	1.011	0.727	1.014	1.024

	hemoglobin	F. I	F. II	F. XIII
OR	1.013	0.996	0.999	1.009

FIGURE 4 Subgroup model for the effect of blood parameters on measured blood loss including prepartum available information (gestational age, maternal age, multiparity, body mass index, multiple fetus pregnancy, estimated fetal weight as proxy for neonatal weight, induction of labor, and chorioamnionitis). Twin: multiple fetus pregnancy; BMI: body mass index; Age: maternal age. Subgroup 3: single fetus pregnancy and body mass index ≤20.7 kg/m^2. Subgroup 5: single fetus pregnancy, body mass index >20.7 kg/m^2 and maternal age ≤28 y. Subgroup 6: single fetus pregnancy, body mass index >20.7 kg/m^2 and maternal age >28 y. Subgroup 7: multiple fetus pregnancy

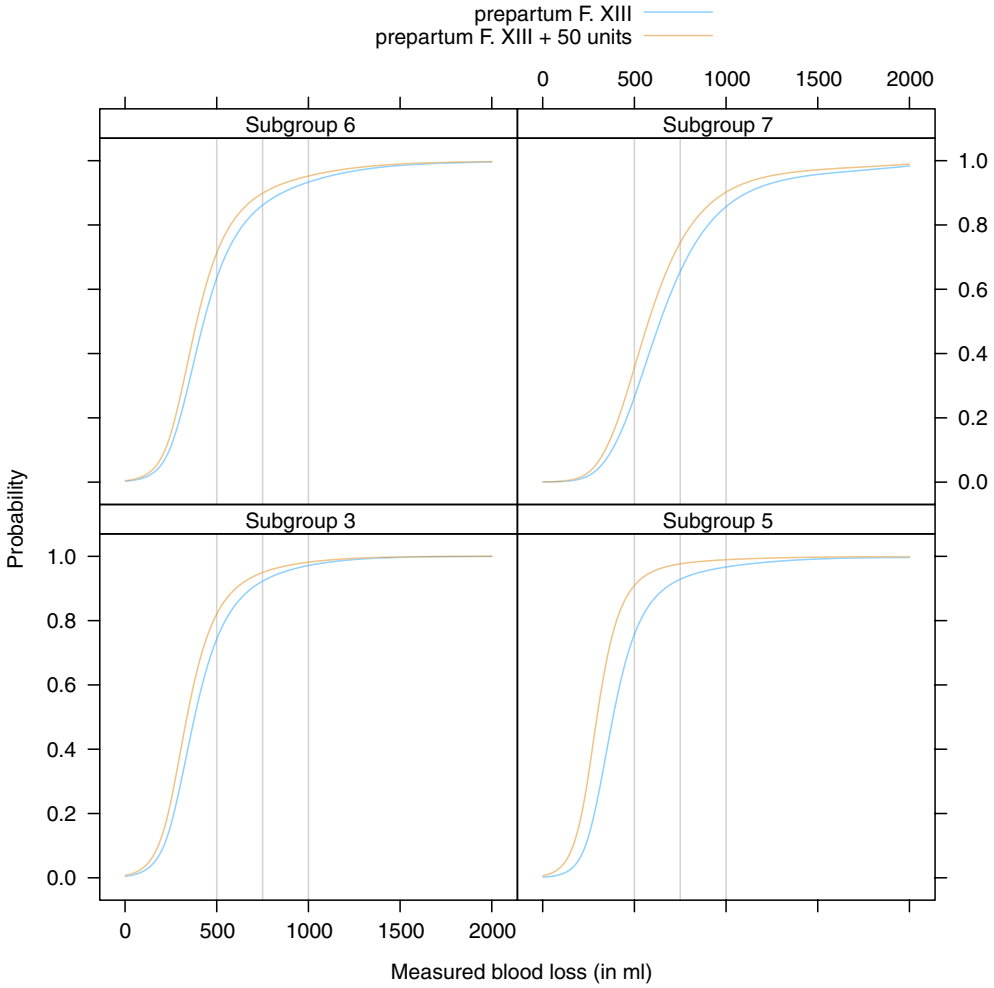


FIGURE 5 Conditional distribution of measured blood loss in the subgroups given in Figure 4 for original factor XIII (FXIII) measurements (blue lines) and under hypothetical increase of FXIII activity of 50% (yellow lines). Vertical gray lines indicate 500, 750, and 1000 mL measured blood loss. Subgroup 3: single fetus pregnancy and body mass index ≤20.7 kg/m^2. Subgroup 5: single fetus pregnancy, body mass index >20.7 kg/m^2 and maternal age ≤28 y. Subgroup 6: single fetus pregnancy, body mass index >20.7 kg/m^2 and maternal age >28 y. Subgroup 7: multiple fetus pregnancy

TABLE 4 Probability (in %) of measured blood loss over a certain, hypothetical cut-off in the subgroup model including prepartum available information without (untreated) and with hypothetical increase of factor XIII by 50% (plus F XIII)

	MBL >500 mL		MBL > 750 mL		MBL > 1000 mL	
Subgroup	Probability	95% Interval	Probability	95% Interval	Probability	95% Interval
3						
Untreated	25.6	21.1-30.6	7.7	5.4-11.0	2.8	1.6-5.0
Plus FXIII	17.8	10.8-28.1	5.0	2.7-9.3	1.8	0.8-3.9
5						
Untreated	24.1	19.0-30.1	7.1	4.6-11.0	3.3	1.7-6.4
Plus FXIII	9.0	4.5-17.1	2.3	1.0-5.3	1.1	0.4-2.8
6						
Untreated	36.3	33.3-39.5	13.9	11.8-16.3	6.6	5.2-8.4
Plus FXIII	28.6	22.2-36.0	10.1	7.2-14.0	4.7	3.2-7.0
7						
Untreated	73.4	60.5-83.2	34.5	23.3-47.9	14.2	7.6-25.1
Plus FXIII	64.2	31.0-87.8	25.6	7.7-58.7	9.7	2.4-32.5

Note: Subgroup 3: single fetus pregnancy and body mass index ≤ 20.7 kg/m^2; Subgroup 5: single fetus pregnancy, body mass index >20.7 kg/m^2 and maternal age ≤28 y; Subgroup 6: single fetus pregnancy, body mass index >20.7 kg/m^2 and maternal age >28 y; Subgroup 7: multiple fetus pregnancy. FXIII, factor XIII

this parameter. However, the technique used here has previously been validated in our institution,[22] showing reasonable correlation with calculated blood loss; it has to be stressed once more that the overall results with regard to FXIII were very robust as they are essentially unaffected by the delivery mode (with or without cesarean section).

In summary, our study combines an unbiased analysis of prepartum coagulation parameters with a robust peri- and postpartum clinical data set in the, to the best of our knowledge, largest population of women prospectively assessed for potential prepartum PPH risk factors including coagulation factors to date. Prepartum FXIII had a consistent and highly significant effect over the whole spectrum of postpartum MBL, across all patient strata and statistical analyses; other coagulation factors showed no such effect. We believe that these results help to explain why recent randomized controlled trials with early or pre-emptive treatment of fibrinogen for PPH were negative.[34,35] Our results might also be helpful in order to reconsider and potentially adapt clinical PPH guidelines[38-40] with regard to the importance of FXIII. Our results strengthen the case for initial enzyme (FXIII) over substrate (fibrinogen) replacement, and/or the order in which they are given. Given the increasing incidence of PPH, its associated morbidity and mortality, and the number of severe cases that occur unheralded, we must aim to better identify the women at risk. In an attempt to effectively reduce postpartum blood loss further, our next step is to determine whether our hypothesis can be confirmed in a prospective randomized intervention study, employing FXIII in patients at risk.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

R. Zimmermann suggested the initial study outline. C. Haslinger, W. Korte, and R. Zimmermann designed and planned the study in detail. C. Haslinger and R. Brun collected data and performed its quality control. W. Korte performed the analysis of coagulation factors. T. Hothorn performed the statistical analysis and wrote Appendix S1. C. Haslinger and W. Korte wrote the first draft of the manuscript. T. Hothorn, R. Brun, C. Greenberg, and R. Zimmermann participated in the drafting and revising of the manuscript and contributed to its intellectual content.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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