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The impact of antenatal factor XIII levels on postpartum haemorrhage: a prospective observational study

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Abstract

Purpose Postpartum haemorrhage (PPH) is a leading cause of maternal mortality and morbidity. Our aim was to investigate the relationships between antenatal factor XIII (FXIII), fibrinogen levels, and blood loss at childbirth.

Methods This prospective observational study evaluated an unselected cohort of pregnant women admitted for intended vaginal deliveries of singletons at term. To determine clotting factor levels, we obtained blood samples at a maximum of three days prior to vaginal delivery. A calibrated collecting drape was used to quantify blood loss in the third stage of labour. Moderate and severe PPH were diagnosed as blood losses ≥ 500 mL and ≥ 1000 mL, respectively. In a multiple logistic regression analysis, we determined whether coagulation factors and their interactions could independently predict (severe) PPH.

Results We analysed 548 vaginal deliveries that occurred during the study period. Of those, 78 (14.2%) lost ≥ 500 mL and 18 (3.3%) lost ≥ 1000 mL of blood. The mean pre-delivery FXIII activity in women with PPH (79.33% ± 15.5) was significantly ($p < 0.001$) lower than in women without PPH (86.45% ± 14.6). A receiver operating characteristic curve analysis detected antenatal FXIII cutoff levels of 83.5% and 75.5% for PPH and severe PPH, respectively. The multiple logistic regression analysis showed that FXIII alone ($p < 0.001$) and its interaction with fibrinogen ($p = 0.03$) significantly predicted PPH. FXIII was not significantly correlated with blood loss among patients with severe PPH.

Conclusion Our results suggested that antenatal FXIII levels may have a significant influence on PPH. The interaction between FXIII and fibrinogen might also provide slight advantages in forecasting PPH.

Keywords Factor XIII · Fibrinogen · Postpartum blood loss · Postpartum haemorrhage

Introduction

Postpartum haemorrhage (PPH) is one of the leading causes of maternal mortality and morbidity worldwide [1, 2]. Even when uterine atony is the main reason for PPH [3], a blood coagulation disorder, though rare, is an important potential contributor to increased blood loss at delivery [4–6]. A variety of studies have shown that reduced factor XIII (FXIII) levels were associated with increased blood loss after surgical treatments [7–9]. Pregnancy is associated with a progressive rise in most clotting factors, due to hormonal changes [10–12]. In contrast, FXIII levels do not increase significantly during pregnancy; in fact, there is some evidence that FXIII levels decline during pregnancy [13, 14]. No study has specifically focused on the prevalence of PPH among women with reduced FXIII levels. Recently, a case report described a woman with mild, congenital FXIII and fibrinogen deficiencies during pregnancy, labour, and postpartum,

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and they discussed potential management options for preventing PPH [15].

Previously, we showed that the median blood loss was 250 mL, the mean maternal haemoglobin content at admission was 11.9 ± 1.1 g/dL, and the average reduction in haemoglobin was 1.0 ± 1.1 g/dL after vaginal delivery [16]. Moreover, that study found significantly lower fibrinogen levels among women with severe PPH, but not in all women with PPH [17]. Finally, prepartum thromboelastometry-derived parameters (ROTEM) were not associated with postpartum blood loss [18].

Fibrinogen and FXIII are the major key proteins at the end of the coagulation cascade. Fibrinogen provides the matrix that is modified by activated FXIII. The interaction between fibrinogen and FXIII are essential for formation and stabilisation of the clot [19].

The present study aimed to investigate the association between antenatal FXIII activity and the measured blood loss during the third stage of labour in women delivering vaginally. Furthermore, we analysed whether the interaction between FXIII and fibrinogen was related to the prevalence of PPH.

Materials and methods

This prospective, observational study recruited 1083 women admitted for an intended vaginal delivery at the Department of Obstetrics, Charité University Hospital, Berlin, Germany, from January 2012 to May 2013. The study was approved by the local Ethics Committee (EA2/118/11), and all participants provided informed consent. Inclusion criteria were: a live singleton pregnancy; 37 completed gestational weeks; and the infant positioned in a cephalic presentation. Women were excluded, when they underwent a caesarean delivery during labour, when blood loss was not measured during the third stage, or when they had taken anticoagulation medication or had a known history of a bleeding disorder.

Venous blood samples (BD Vacutainer®, Becton Dickinson GmbH, Franklin Lakes, NJ, USA) were collected from the antecubital vein. For all enrolled patients, we evaluated serum maternal FXIII and fibrinogen levels just upon admission for delivery or at a maximum of three days prior to birth. FXIII was measured with the latex photometric immunoassay (HEXAMATE FXIII, Medical and Biological Laboratories Co. Ltd. Nagoya, Japan; reference range 65–125%). Fibrinogen was quantified according to the Clauss method, with the STA Fibrinogen Reagent (Roche Diagnostics GmbH, Mannheim, Germany). Further routine coagulation assays included the activated partial thromboplastin time [coagulation method, STA APTT (Roche), STA Evolution (Roche)], the prothrombin time [coagulation method, Neoplastin (Roche), STA Evolution Roche)], and platelet levels (impedance method, Sysmex XN series). EDTA tubes were used for platelet count and citrate blood was used for coagulation analyses. All tests were performed by Labor Berlin-Charité Vivantes GmbH.

During delivery, clinicians were blinded to the clotting results for FXIII and fibrinogen. Blood loss during childbirth was systematically measured with a graduated collecting drape (Brenner-Medical GmbH, Putzbrunn, Gemany) placed under the pelvis of each woman, in the third stage of labour. All women prophylactically received a bolus of three international units of oxytocin via intravenous injection after the baby was born. The blood collection bag remained in situ until the midwife or obstetrician was no longer concerned about bleeding. In general, mothers were observed for 2 h postpartum in the delivery suite. Health care providers examined the drape and recorded the level of blood collected. According to World Health Organization guidelines [20], we divided the PPH group into two subgroups: non-severe PPH (blood loss ≥ 500 mL and <1000mL) and severe PPH (blood loss ≥ 1000 mL). When PPH occurred, the staff applied a clinical stepwise multidisciplinary management protocol formulated by an interdisciplinary expert committee, which comprised members from Germany, Austria and Switzerland [21, 22].

Maternal serum coagulation factor content was again routinely assessed on the first day after delivery. We excluded participants that had received red blood cell transfusions and those lost to follow-up. We recorded basic patient data and medical information, including maternal age, gravity, parity, gestational age at delivery, body mass index (BMI), induction of labour, mode and duration of delivery, birth injuries, and birthweight.

Statistical analysis

Results are presented as raw numbers, rates, medians (interquartile range), or means (± SD), when a normal distribution was confirmed with the Kolmogorov–Smirnov test. Simple linear regression and Spearman's rank correlation was used to evaluate the relationship between blood loss and FXIII levels. P values < 0.05 were considered statistically significant. We maximized the sum of sensitivity and specificity curves with Euclidean distances in receiver operating characteristic (ROC) curve analyses to determine optimal cutoff values. To identify independent predictors of PPH, we used the model of purposeful selection of variables in multiple logistic regression analyses. All statistical analyses were performed with IBM SPSS Statistics (Version 22, SPSS, Inc., Chicago, IL, USA) or R (Version 3.1.2, The R Foundation for Statistical Computing).

Results

We initially enrolled 1083 patients in the current study. The two main reasons for excluding participants were caesarean delivery in labour ($n = 203$) and incomplete blood sampling ($n = 145$) (Fig. 1). In 548 cases we performed correlation analyses between coagulation factors and postpartum blood loss. Of these 548 women, 78 (14.2%) lost ≥ 500 mL of blood and 18 (3.3%) lost

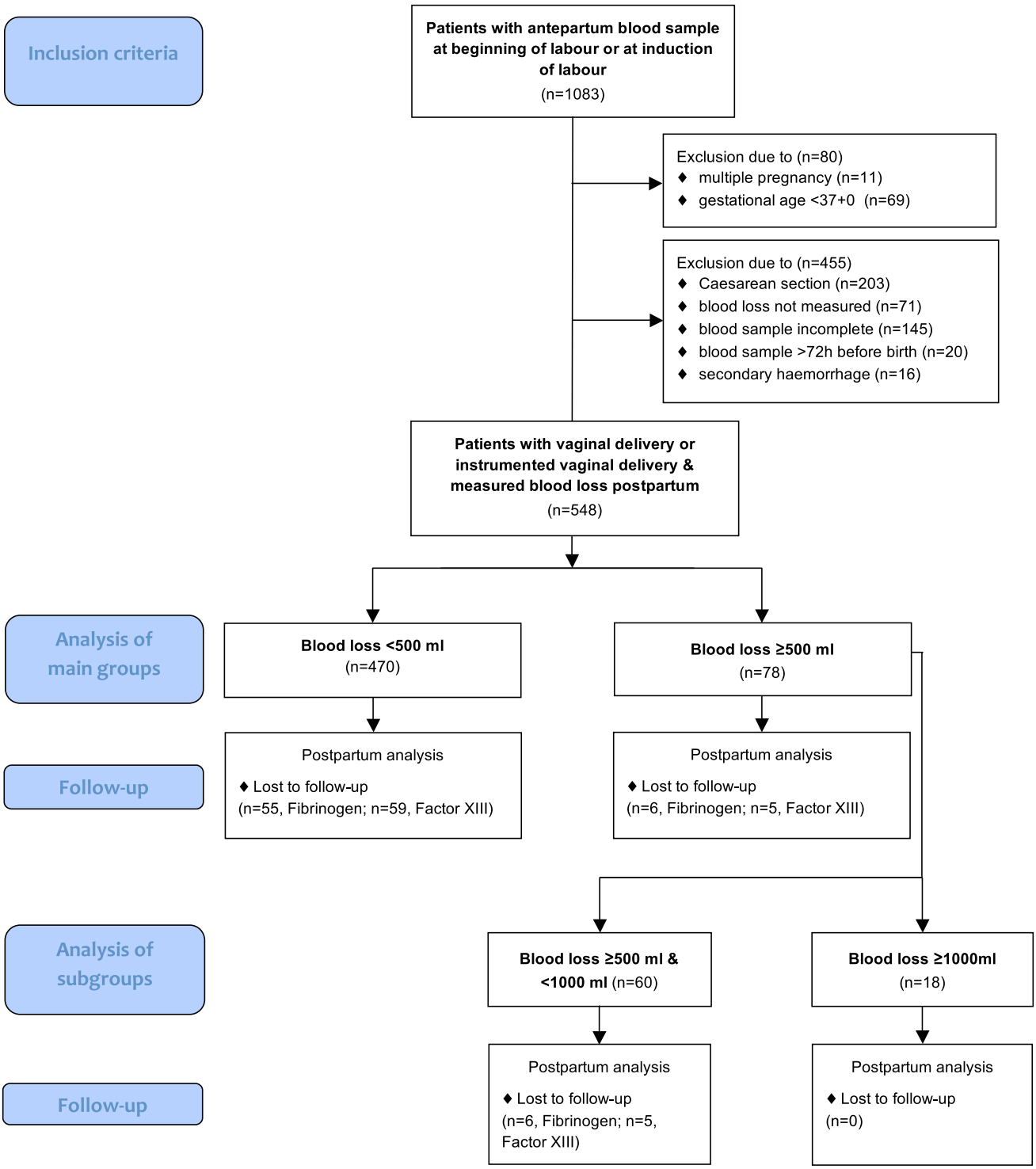

Fig. 1 Flow diagram of the selection of study participants and the analysis of samples

≥ 1000 mL of blood. Five women with severe PPH received transfusions of red-cell concentrates. No maternal death occurred due to severe bleeding in our cohort.

We found that PPH was significantly associated with parity, instrumental vaginal delivery, birthweight, induction of labour, labour durations more than 12 h, and severe birth injuries. Tables 1 and 2 summarise the demographic and clinical characteristics of patients in the study group. The mean antenatal maternal FXIII and fibrinogen contents were 85.44% ± 14.97 and 4.59 ± 0.73 g/L, respectively. No patient had antenatal FXIII levels below 38%.

The mean pre-delivery FXIII activity in women with PPH (79.33% ± 15.5) was significantly ($p < 0.001$) lower than that in women without PPH (86.45% ± 14.6; Table 3). However,

Table 1 Demographic and clinical characteristics of the study population, divided into groups of patients without PPH (blood loss < 500 mL) and with PPH (blood loss ≥ 500 mL)

Characteristics	Total	*n*	Blood loss < 500 mL	*n*	Blood loss ≥ 500 mL	*n*	*p* value
Age (years)	29.4 ± 6.0	548	29.6 ± 6.1	470	28.4 ± 5.3	78	0.091[1a]
Gravidity	2 (1;3)	548	2 (1;3)	470	2 (1;2)	78	0.002[2]
Parity	1.5 (1;2)	548	2 (1;2)	470	1 (1;2)	78	< 0.001[2]
BMI (kg/m^2)	27.9 (25.8;30.9)	510	27.9 (25.7;31.1)	440	27.9 (26.1;30.3)	70	0.849[2]
Gestational diabetes	31 (5.8%)	531	23 (5.1%)	454	8 (10.4%)	77	0.064[3a]
Gestational age (days)	278 ± 7.9	548	278 ± 7.9	470	279 ± 7.8	78	0.291[1a]
Induction of labour	195 (35.6%)	547	160 (34.1%)	469	35 (44.9%)	78	0.045[3b]
Labour duration > 12 h	94 (18.3%)	514	75 (16.9%)	442	19 (26.4%)	72	0.044[3b]
Mode of delivery (instrumented vaginal delivery)	90 (16.4%)	548	67 (14.3%)	470	23 (29.5%)	78	0.001[3b]
Childbirth injuries	396 (72.3%)	548	324 (68.9%)	470	72 (92.3%)	78	< 0.001[3b]
Severe childbirth injuries[4]	248 (45.3%)	548	197 (41.9%)	470	51 (65.4%)	78	< 0.001[3b]
Birthweight (g)	3439 ± 444	548	3417 ± 448	470	3517 ± 395	78	0.002[1b]

Values represent the mean ±SD, the median (IQR), or the number of patients (%)

[1] *p* value determined with Student's *t* test; [a] two-sided; [b] one-sided

[2] *p* value determined with Wilcoxon–Mann–Whitney test (two-sided)

[3] *p* value determined with exact Fisher-test; [a] two-sided; [b] one-sided

[4] Perineal laceration of third and fourth grades, episiotomy, or vaginal laceration

Table 2 Demographic and clinical characteristics of the study population, divided into groups of patients without severe blood loss (< 1000 mL) or with severe PPH (blood loss ≥ 1000 mL)

Characteristics	Blood loss < 1000 mL	*n*	Blood loss ≥ 1000 mL	*n*	*p* value
Age (years)	29.5 ± 6.0	530	27.2 ± 5.3	18	0.103[1a]
Gravidity	2 (1; 3)	530	2 (1; 2.75)	18	0.547[2]
Parity	2 (1; 2)	530	1 (1; 2)	18	0.635[2]
BMI (kg/m^2)	27.9 (25.8; 31.0)	494	27.8 (25.2; 29.4)	16	0.274[2]
Gestational diabetes	30 (6.0%)	513	1 (5.6%)	18	1[3a]
Gestational age (days)	278 ± 7.8	530	278 ± 8.6	18	0.957[1a]
Induction of labour	185 (35.2%)	529	10 (55.6%)	18	0.064[3b]
Labour duration > 12 h	90 (18.0%)	498	4 (25%)	16	0.333[3b]
Mode of delivery (instrumented vaginal delivery)	85 (16.0%)	530	5 (27.8%)	18	0.157[3b]
Childbirth injuries	381 (71.9%)	530	15 (83.3%)	18	0.217[3b]
Severe childbirth injuries[4]	238 (44.9%)	530	10 (55.6%)	18	0.256[3b]
Birthweight (g)	3436 ± 447	530	3526 ± 336	18	0.149[1b]

Values represent the mean ±SD, the median (IQR), or the number of patients (%)

[1] *p* value determined with Student's *t* test; [a]two-sided; [b]one-sided

[2] *p* value determined with Wilcoxon–Mann–Whitney test (two-sided)

[3] *p* value determined with Fisher's exact test; [a]two-sided; [b]one-sided

[4] Perineal laceration of third and fourth grades, episiotomy, or vaginal laceration

Table 3 Antenatal maternal blood coagulation parameters in groups of patients without PPH (< 500 mL) and with PPH (≥ 500 mL)

Coagulation factors	Total	*n*	Blood loss < 500 mL	*n*	Blood loss ≥ 500 mL	*n*	*p* value
Fibrinogen (g/L)	4.59 ± 0.73	548	4.60 ± 0.71	470	4.61 ± 0.88	78	0.871[1b]
Factor XIII (%)	85.44 ± 14.97	548	86.45 ± 14.65	470	79.33 ± 15.50	78	< 0.001[1b]
Haemoglobin (g/dL)	12.0 ± 1.1	546	12.0 ± 1.1	468	12.0 ± 1.0	78	0.855[1a]
aPTT (s)	30.5 ± 2.6	547	30.5 ± 2.6	529	31.1 ± 2.3	78	0.176[1b]
Prothrombin time (s)	108.0 (100.0; 115.0)	547	108.0 (100.0; 115.0)	469	108.0 (100.0; 115.8)	78	0.693[2a]
Platelets (/nL)	215 (178; 254)	546	217 (179; 256)	468	206 (172; 244)	78	0.067[2b]

Values represent the mean ±SD or the median (IQR)

[1]*p* value determined with Student's *t* test; [a]two-sided; [b]one-sided

[2]*p* value determined with Wilcoxon–Mann–Whitney test (two-sided)

this finding was inconsistent; there was no significant difference ($p = 0.118$) in pre-delivery FXIII levels between women with severe PPH (80.61% ± 17.0) and women with less than 1000 mL blood loss (85.6% ± 14.88; Table 4). Interestingly, women that developed severe PPH showed significantly ($p = 0.005$) lower median platelet counts (178.5/nL) before birth than women with less than 1000 mL blood loss (217/nL). Moreover, we observed a trend ($p = 0.06$) of lower pre-birth platelet counts in all women with PPH (206/nL) compared to all women without PPH (217/nL). Postnatal coagulation measurements in these groups are available as supplemental data (Tables S1 and S2).

In the entire population, we found a significant correlation between the antenatal FXIII levels and blood loss ($p = 0.01$; $r = -0.11$) as well as fibrinogen ($p < 0.0001$; $r = 0.29$). A ROC curve analysis indicated that antenatal FXIII cutoff levels were 83.5% (area under the curve (AUC) 0.63, 95% CI 0.56–0.70, sensitivity 63%, specificity 58%) and 75.5% (AUC 0.60, 95% CI 0.45–0.75, sensitivity 50%, specificity 76%) for predicting PPH and severe PPH, respectively (Fig. 2a, b). We also found a platelet count threshold of 217.5/nL for predicting severe PPH (AUC 0.62, 95% CI 0.53–0.71, sensitivity 48.5%, specificity 79.3%). We performed multiple logistic regressions to test the predictive value of antenatal risk factors for PPH and severe PPH (Tables 5, 6). We found that PPH could be predicted by the FXIII level (OR 3.79, $p < 0.001$) and by the interaction between FXIII and fibrinogen (OR 3.81, $p = 0.038$). When the antenatal FXIII level was below 83.5%, the risk of developing PPH increased from 11.7 to 33.5% ($p < 0.01$). Indeed, 49 out of 78 women with PPH had antenatal FXIII concentrations below 83.5%. We found that, of 83 women with FXIII (< 83.5%) and fibrinogen levels (< 4.14 g/L) below the cutoff values, 20 developed PPH. Thus, the antenatal activity of FXIII (< 75.5%; OR 2.97, $p = 0.024$) and the antenatal fibrinogen level (< 4.08 g/L; OR 2.63, $p = 0.036$), but not the combination, were significant predictors of severe PPH. Among women with FXIII activity below 75.5% before birth, the risk of a severe PPH was nearly threefold higher (1.2% vs. 3.5%) than among women with FXIII activity above 75.5% ($p = 0.06$) (Fig. 3a). The importance of platelet count was illustrated by the finding that, out of 18 women with severe PPH, 16 had platelet levels between 150 and 217.5/nL. When platelets fell below 217.5/nL, the risk of severe PPH increased from 0.78% to 5.4% ($p = 0.003$) (Fig. 3a).

The subgroup analysis that focused on PPH severity showed that FXIII (OR 2.97) and fibrinogen (OR 2.63), but not their interaction, were significantly associated with severe PPH. Furthermore, the antenatal maternal platelet count significantly predicted severe PPH (OR 7.33, $p = 0.001$). When platelets fell below the threshold of 216/

Table 4 Antenatal maternal blood coagulation parameters in groups of patients with non-severe blood loss (< 1000 mL) and with severe PPH (≥ 1000 mL)

Coagulation factors	Blood loss < 1000 mL	*n*	Blood loss ≥ 1000 mL	*n*	*p* value
Fibrinogen (g/L)	4.60 ± 0.73	530	4.24 ± 0.79	18	0.035[1b]
FXIII (%)	85.6 ± 14.88	530	80.61 ± 17.06	18	0.118[1b]
Haemoglobin (g/dL)	11.9 ± 1.1	528	12.2 ± 1.0	18	0.334[1a]
aPTT (s)	30.5 ± 2.6	529	31.1 ± 2.3	18	0.161[1b]
Prothrombin time (s)	108.0 (100.0; 115.0)	529	108.0 (99.75; 119.0)	18	0.621[2a]
Platelets (/nL)	217 (179; 255)	528	178 (172; 204)	18	0.005[2b]

Values represent the mean ± SD or the median (IQR)

[1]*p* value determined with Student's *t* test; [a]two-sided; [b]one-sided)

[2]*p* value determined with Wilcoxon–Mann–Whitney test (two-sided)

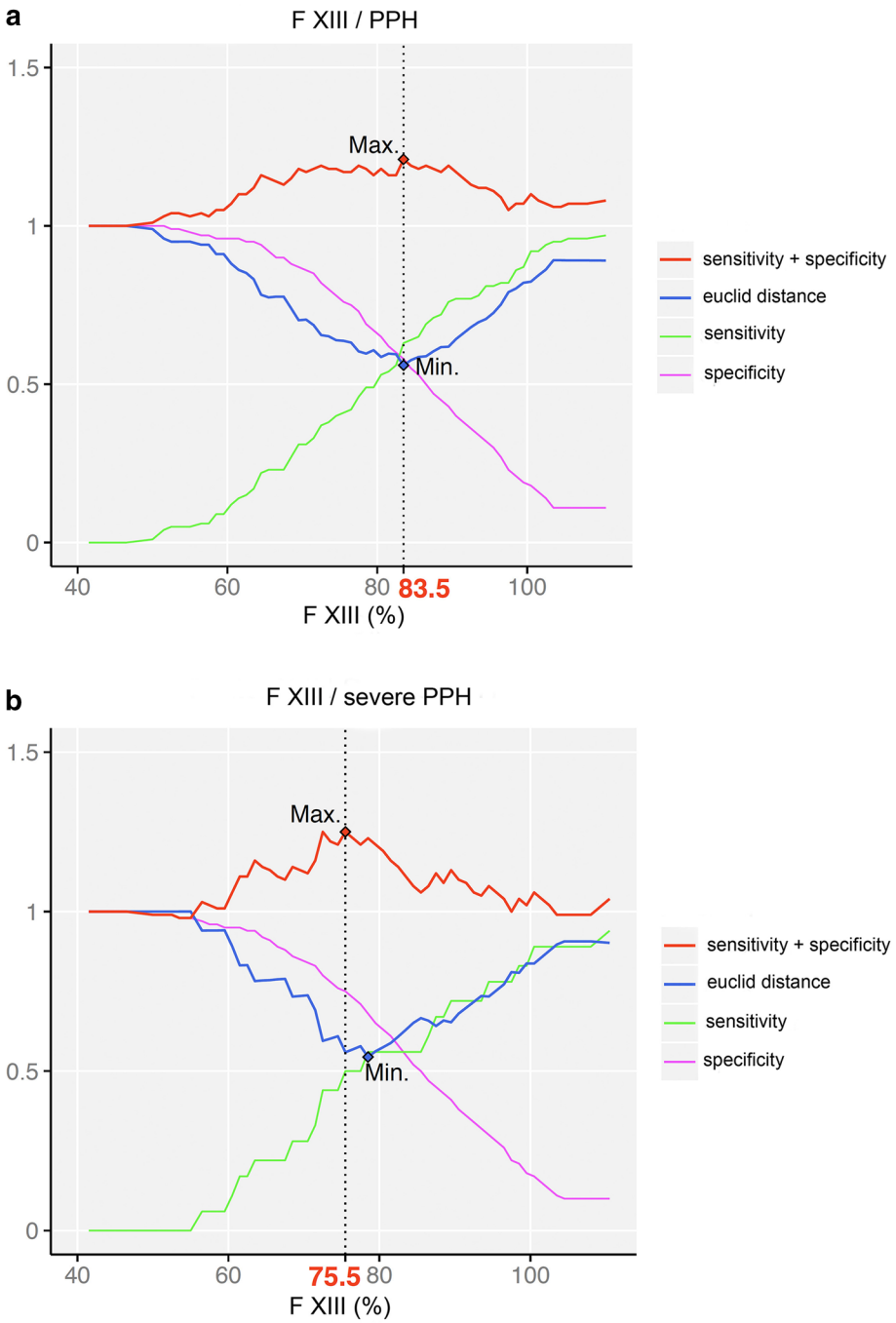

Fig. 2 Maximization of the sum of sensitivity and specificity of FXIII on a ROC curve. Euclidean distances were used to determine the optimal FXIII cutoff values for predicting PPH (**a**) and severe PPH (**b**)

nL, the risk of severe PPH significantly ($p < 0.001$) increased from 5.0 to 47.3% (Fig. 3b). Of 18 women in the severe PPH group, 15 had platelets below 216/nL before giving birth.

Discussion

This large, single-centre, prospective study produced two main results. First, we found that the probability of PPH increased significantly with declining FXIII activity. Second, we found that the interaction between FXIII and fibrinogen provided slight advantages in forecasting PPH.

Few previous studies have investigated the impact of FXIII activity on postpartum blood loss. In contrast to our findings, Karlsson et al. found no significant correlation between blood loss in the third stage of labour and the antenatal FXIII activity, fibrinogen concentration, or platelet count [13]. Their results were derived from 44 women, and blood loss volumes during delivery were estimated by weighing surgical sponges and pads and measuring collected

Table 5 Multiple regression analysis results for identifying predictors of PPH

Potential predictive factors	OR	95% CI	*p* value
Fibrinogen	1.03	0.55–∞	0.465
FXIII	3.79	2.03–∞	< 0.001
Parity	0.59	–	–
Maternal height	1.30	–	–
Maternal blood group	1.88	1.20–∞	0.011
Gestational diabetes	3.23	1.39–∞	0.011
Mode of delivery	2.09	1.23–∞	0.012
Severe childbirth injuries	1.80	1.08–∞	0.029
Birthweight	1.31	1.02–∞	0.04
FXIII–fibrinogen interaction	3.81	1.11–∞	0.038

P values are one-tailed

Table 6 Multiple regression analysis results for identifying predictors of severe PPH

Potential predictive factors	OR	95% CI	*p* value
Fibrinogen	2.63	1.09–∞	0.036
FXIII	2.97	1.21–∞	0.024
Platelets	7.33	2.50–∞	0.001
Maternal age	0.60	–	
Maternal height	1.93	–	
FXIII–fibrinogen interaction	0.62	0.11–∞	0.326

P values are one-tailed

blood. However, they described a significant positive correlation between FXIII and fibrinogen, consistent with our data. Sharief and coworkers investigated the changes in FXIII level during pregnancy [14]. They measured a mean FXIII activity of 90 ± 19 IU/dL in 128 women between 29 and 42 weeks. There was no significant relationship between FXIII and estimated blood loss during delivery. The difference between the designs of these studies and ours complicated a comparison with the results of the present investigation.

It has been mentioned that a FXIII deficiency is the most underestimated haemorrhagic diathesis, because these patients typically show normal values in routine coagulation screening tests (prothrombin time, activated partial thromboplastin time, and thrombin time) [23]. Furthermore, the prenatal management of FXIII deficiency also raises the limitation of FXIII measurement. A variety of methods for measuring FXIII have been described; in this study, we used the photometric immunoassay (5.10 Euro per analysis). Previous case reports that studied congenital FXIII deficiencies pointed out that pregnancies with a favourable outcome were only observed after FXIII substitution treatment. However, the optimal FXIII activity in these women remains an issue of debate. The desired level of plasma FXIII is thought to be 30% during labour, and a booster dose of 1000 IE is recommended before childbirth, to prevent severe obstetric haemorrhagic complications [24–26]. Congenital FXIII deficiency is an autosomal recessive disorder [27]. Women that are homozygous for a mutation that causes FXIII deficiency have FXIII levels less than 1% of normal levels, and they are symptomatic [28]. The estimated prevalence of FXIII deficiency is 1 in 3–5 million [29]. In contrast, women that are heterozygous for a mutation that causes FXIII deficiency have about 30–60% residual clotting factor activity; these women are typically asymptomatic [28]. However, they may demonstrate significant bleeding symptoms under special conditions, such as childbirth. The lowest FXIIII level in this study was 38%. Recently, Kaveney et al. published a case report that showed the course of a mild FXIII deficiency during pregnancy, labour, and after labour [15]. They described a 50% decline in the patient's FXIII activity, which reached a nadir of 26% during labour. The patient had a missense mutation in the FXIII gene, which was first described in that study. The patient received 1470 IU of FXIII during labour, and she had an uneventful vaginal delivery. In general, around 100 mutations have been identified in the FXIII gene locus.

The identification of more prenatal maternal risk factors for peripartum bleeding could promote the prevention of PPH in women. We should keep in mind that most maternal deaths due to PPH have involved delayed or substandard care in the diagnosis and management of peripartal bleeding [30]. Healthy women in labour can typically tolerate acute blood losses of up to 1000 mL, without significant haemodynamic problems [31]. However, every attempt should be made to prevent severe, potentially life-threatening PPHs. We lack studies on the benefits and costs of screening and administering substitutions for women with mild FXIII deficiencies.

Strengths and limitations

The strengths of this study included the large sample size. Our cohort comprised over 500 women in labour. Another strength was the uniform study methodology, implemented at a single referral university centre. To our knowledge, this was the first prospective study to investigate FXIII activity in a large number of pregnant women, and to examine the correlation between clotting factor levels and measured blood loss during a vaginal delivery. FXIII photometric immunoassay is independent of the fibrinogen plasma level, thus allows isolated FXIII results interpretation. Moreover, we also examined associations between these measurements and the antenatal fibrinogen content.

Our study also had some limitations. We excluded 49.4% of the initially enrolled women owing to a variety of reasons

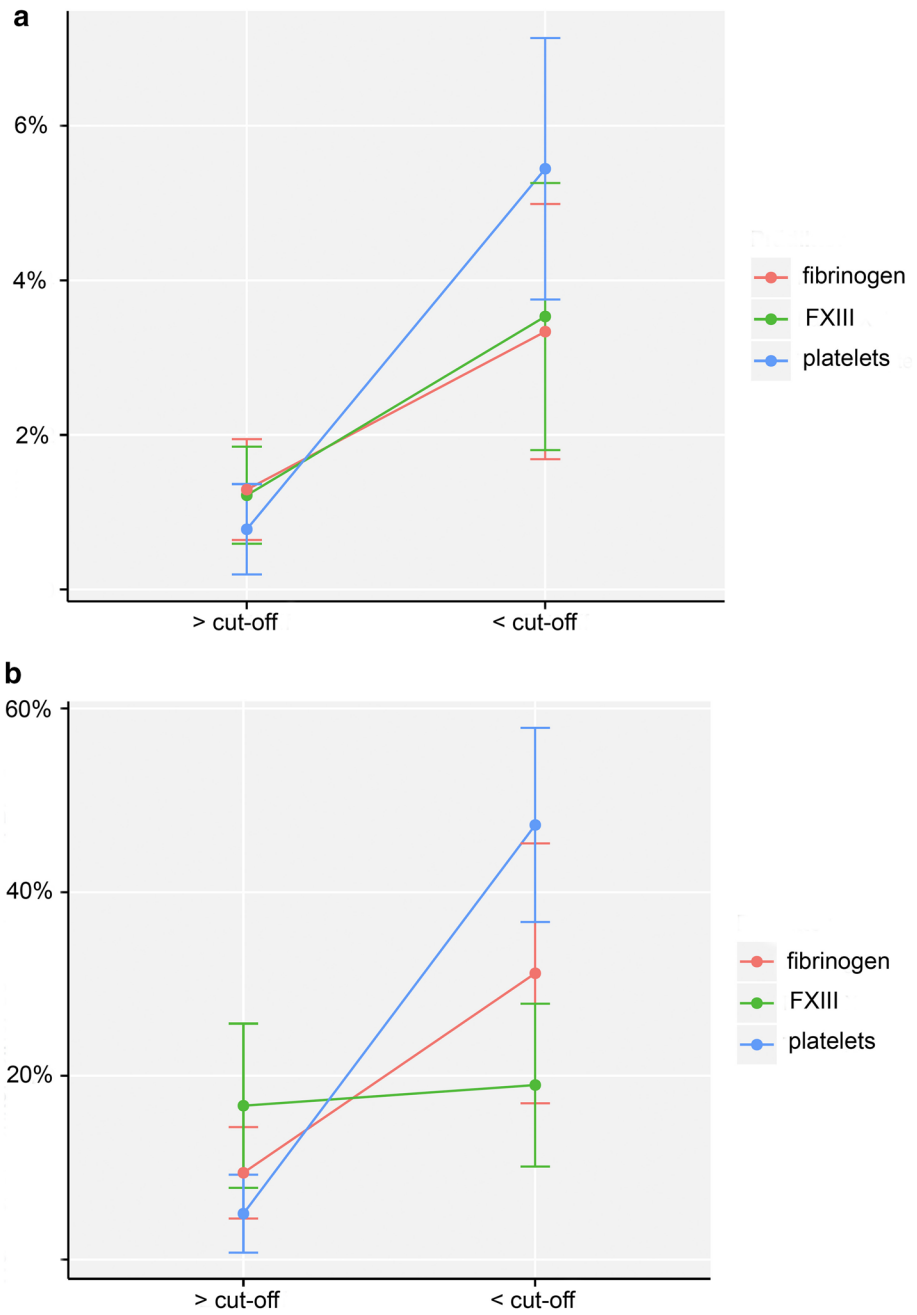

Fig. 3 Risk of development of severe PPH in the entire population (**a**) and in the bleeding group (**b**) depending on pre-delivery cutoff levels for fibrinogen (4.08 g/L), FXIII (75.5%), and platelets (217.5/nL)

and our cohort included only 18 patients with blood loss ≥1000 mL. This may be the reason for the non significant correlation between FXIII and severe bleeding. The present study cannot determine whether other obstetric factors (instrumental vaginal delivery, increased birthweight, induction of labour, labour duration, and severe birth injuries) are more important than FXIII activity for bleeding at delivery. From a practical point of view antenatal FXIII cutoff levels for predicting PPH (83.5%) and severe PPH (75.5%) were still within the reference range and the AUC was only 0.63 and 0.60, respectively. Furthermore, we did not perform a FXIII mutational analysis in patients with (severe) PPH or patients with reduced antenatal FXIII activity. Finally, the commercial diagnostic FXIII activity kits currently available apply different methods for measuring FXIII levels; however, it was difficult to compare our findings to those previously published in the literature. Therefore our results must be generally interpreted with caution and further studies are needed.

Conclusions

Previous studies have indicated that labouring women with a mild FXIII deficiency might benefit from an antenatal diagnosis of this blood coagulation disorder. Moreover, for those women, FXIII replacement therapy represents a potential management option for preventing increased blood loss during labour. Our results suggested that antenatal FXIII levels might have a significant influence on (severe) PPH. Further, the interaction between FXIII and fibrinogen improved forecasting of PPH. This raises the question whether FXIII should be routinely or under certain conditions determined before delivery and in cases with low values a more intensive care in the third stage of labour is recommended. We also found that maternal platelet levels showed the highest OR (7.33) for predicting severe PPH in the bleeding subgroup, which underlined the importance of their role in the clotting system during a vaginal delivery. However, the impact of pre-delivery platelets counts on the development of PPH has not been adequately investigated and we hope that our results would stimulate further research on this topic.

Author contribution CB: manuscript writing, data analysis, LM: manuscript writing, data collection, AH: data collection, KND: data collection, LK: manuscript editing, CvH: manuscript editing, WH: project development, FP: data analysis.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest related to this study. Trial registration: German Clinical Trials Register (7873).

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