Factor XIII in the Acute Care Setting and Its Relevance in Obstetric Bleeding

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Keywords

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Abstract

Background: Major hemorrhage is one of the main causes of preventable mortality in either severe trauma, high-risk surgical patient, or the obstetric population. As underlined by the cell-based coagulation model, a resistant and stable clot is essential to prevent or to stop an ongoing bleeding. Coagulation factor XIII (FXIII) stabilizes the newly formed clot by cross-linking the fibrin monomers into a three-dimensional network and by impeding fibrinolysis. Thus, FXIII is an essential coagulation factor in the acutely bleeding patient. ***Summary:*** Acquired FXIII deficiency is much more common than the inherited form. On the basis of acute tissue injury which leads to major bleeding, acquired FXIII deficiency is traditionally considered to be secondary to consumption. However, recent evidence in the field of obstetrics and high-risk surgery suggests that it might be an associated factor rather than a consequence of the bleeding, which would mean that early replacement of FXIII could potentially improve outcomes. However, FXIII measurement is not universally available. Assessing FXIII through viscoelastic assays seems feasible, though likely it is not yet accurate. Moreover, the target population at risk and the aimed FXIII level required to achieve hemostasis in each condition are yet to be defined. ***Key Messages:*** FXIII should be assessed and replaced if necessary in the acutely bleeding patient. We recommend FXIII to be included in an escalating scheme of hemostatic therapies in the acute care setting.

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Introduction

In the acute care setting, hemorrhage continues to be the leading cause of preventable mortality, being to some extent unexpected and unexplained [1]. In trauma, while traumatic brain injury is the main cause of mortality, uncontrolled hemorrhage is the predominant cause of early preventable deaths [2]. In obstetrics, postpartum hemorrhage (PPH) is the most important cause of preventable maternal deaths globally [3], and perioperative bleeding comes with a considerable increase in morbidity and mortality [4]. Therefore, it is of utmost importance to better predict and characterize patients at risk of significant bleeding and which the best treatment approach is.

Physiological hemostasis lies on creating a stable platelet-fibrin clot that prevents bleeding and promotes wound healing [5]. Plasma coagulation factor XIII (FXIII) is essential for both. Thus, in the acutely bleeding patient, FXIII is key to optimize hemostasis. In this review, we will develop the potential importance of FXIII in the acute care setting with a special focus in obstetric management.

Importance of FXIII in the Acute Care Setting

FXIII is present in plasma as a tetrameric pro-transglutaminase composed by two proenzymes (A) and two carrier proteins (B) subunits. This is an exception as all other coagulation factors are serine proteases (factor II, III, VII, IX, X, XI, and XII) or glycoproteins (factors V and VIII). The A-subunits contain the active center with a main function in hemostasis while B-subunits are thought

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to stabilize the A-subunits extending the circulating half-life of the active A-subunits from 3 to 11 days and to regulate the rate of transglutaminase formation by thrombin [6]. FXIII is activated by thrombin in the presence of calcium during the initiation phase. It has a crucial role in stabilizing a new formed clot by covalent cross-linking of soluble fibrin monomers and polymers into a three-dimensional insoluble fibrin network and conferring further additional clot resistance to fibrinolysis by incorporating α2-antiplasmin [7]. Beyond the role of hemostasis, FXIII has important physiological functions in wound healing and angiogenesis through downregulation of thrombospondin-1, bacterial immobilization by cross-linking fibrin to the surface of bacterial proteins within the plasma clot [8], and inflammation by cross-linking of fibrinogen after being activated by human neutrophil elastase [9, 10]. In experimental models, it has also been associated with a reduction in multiple organ dysfunction caused by ischemia reperfusion [11] and with a potential antioxidant role [12] likely secondary to its endothelium stabilizing effect [13].

FXIII deficiency can be inherited or acquired. Inherited FXIII deficiency is a rare bleeding disease affecting approximately 1 per 1–3 million people. It is associated with bleeding symptoms as umbilical bleeding early after birth, soft tissue bleeding after trauma or even life-threatening spontaneous intracranial hemorrhage, and non-bleeding symptoms as delayed wound healing and miscarriage [14]. In this setting, the cut-off for replacement is believed to be at 5% [15]. However, the largest prospective replacement trial in congenital deficiency rather suggested a safe and effective threshold of 20% for prophylaxis [16].

Acquired FXIII deficiency is much more common, being caused by FXIII consumption or hyposynthesis or by autoimmune conditions [17, 18]. It has also been associated with bleeding after neurosurgery, heart surgery, abdominal oncology surgery, and orthopedic surgery [4, 19–23], increased transfusion requirements in noncardiac surgery [1] and in the intensive care unit [24], short-term outcome after acute ischemic stroke [25, 26] and acute myocardial infarction [27], and recently with COVID-19 infection [28].

Forming a stable and resistant fibrin clot is the pivot around which the hemostasis revolves in the acute bleeding patient, as it is emphasized in the cell-based coagulation model. Therefore, FXIII is crucial in this setting [29]. Of note, when assessing the importance of acquired FXIII deficiency in the acute care setting, several issues arise.

First, it is difficult to distinguish if low FXIII levels are a consequence of bleeding by hyper-consumption or conversely an associated factor for bleeding. If that would be the case, rather than wait for bleeding to occur, a more appropriate approach might be to measure FXIII activity or surrogate markers for decreased FXIII activity in patients at risk. However, defining the target population that might be at risk of acquired FXIII deficiency may be challenging. Based on our retrospective analysis [30], we have previously hypothesized that this high-risk population could be stratified per patient characteristics (being frail, plenty of co-morbidities, or oncological patients which would be at higher risk) and per procedural kinds (being emergent and/or major procedures that need intensive care unit admission and are linked to increased inflammatory response, the ones of higher risk).

Second, FXIII, or fibrin stabilizing factor, participates in the last step of the clotting process, so patients with FXIII deficiency typically show normal values in conventional coagulation screening (thrombin time, prothrombin time, and activated partial thromboplastin time) as they only reflect the initiation phase. Moreover, given the long half-life (3–11 days) of circulating FXIII, bleeding due to FXIII deficiency can be evident several days after the tissue injury. Thus, FXIII deficiency is difficult to diagnose which could end up in delaying appropriate treatment.

Third, the level of FXIII activity required achieving effective hemostasis is to be determined, though we have recently reported it might has to be well above 30% in a mixed medical and surgical population [30], being then higher than in the inherited forms as previously suggested [13].

Fourth, given that FXIII measurement is not universally available, one might postulate that FXIII deficiency could be indirectly investigated through fibrinogen measurement as FXIII circulates in a complex with it [31]. Unfortunately, fibrinogen, which assessment is commonly accessible, is no predictor of FXIII deficiency [30, 32]. Viscoelastic assays are also used to optimize clinical management at bedside monitoring. Attempts to measure FXIII using the ApTEM assay with rotational thromboelastometry (ROTEM), which uses aprotinin to inhibit fibrinolysis and estimates FXIII activity based on a maximum lysis value, have not proven successful [33]. Nonetheless, impaired clot firmness in the ExTEM assay (which activates hemostasis via the activator tissue factor) and the FibTEM assay (which measures the fibrin part of the clot) has been shown to correlate with FXIII concentrations in several clinical studies [32, 34, 35]. Ex vivo inhibition of FXIII decreases clot firmness and increases fibrinolysis, which can be used for assessing FXIII activity [36]; conversely, in vitro FXIII supplementation increases clot firmness [37]. Thus, viscoelastic assays can be used to detect FXIII, though taking in account that they lack endothelium, flow, and local tissue milieu [38], which seems fundamental in FXIII biology.

Fifth, it is of great interest that both in unexplained intraoperative bleeding [39] and severe trauma bleeding [40, 41], thrombin generation might be upregulated indi-

cating that insufficient activation of the coagulation cascade is not the reason for the bleeding to occur. Wettstein [42] demonstrated in a clinical study that elevated perioperative levels of soluble fibrin monomer and decreased FXIII availability per unit of generated thrombin result in an early and significant loss of clot firmness in thromboelastography. This might indicate that relative or absolute FXIII deficiency results in inadequate cross-linking of soluble fibrin into a stable clot, leading to a fragile clot that breaks easily which is unable to stop bleeding. This could be the underlying cause of hemorrhage in the acute setting, though elevated thrombin generation. In addition, FXIII subunit A is also present in platelets. Recently, it has been found that histone H4, a damaged-associated molecular pattern released after tissue injury, leads to platelet ballooning [43], which provides a large surface for assembling clotting factors being a potential reason for the elevated thrombin generation during acute bleeding. The hypothetical relationship between platelet ballooning and FXIII is yet to be established.

Finally, altered hemostasis can be the cause or at least a concomitant factor for an ongoing severe bleeding (the patient can die because he/she is bleeding). However, hemostasis is likely a forgotten "organ," and as such losing the hemostatic capacity might be the result of an organ failure (the patient is bleeding because he/she is dying), [44]. Therefore, in the severe bleeding patient, early diagnose and treatment (by surgical control of the hemorrhage and hemostatic therapies) is essential before this condition becomes irreversible, which in addition frequently leads to huge blood transfusion and resources wastage.

Potential Importance of FXIII in Obstetric Bleeding

As any acquired bleeding diathesis, PPH is not a diagnosis by itself but a symptom of an underlying condition [45]. Obstetric reasons for PPH are mainly uterine atony (tone), genital tract trauma (trauma), retained products of conception (tissue), and more rarely coagulopathy (thrombin). PPH is defined as a blood loss >500 mL within 24 h whatever the mode of delivery [46]. It has sustained a notable increase in the industrialized countries in the past decade due to the growing frequency of uterine atony [47]. However, PPH can often occur without identifiable risk factors [48] which emphasizes the need of timely diagnosis (involving FXIII determination) and a multidisciplinary (surgical and hemostatic) treatment approach [49]. Thus, a fully understanding of the cause of bleeding is urgently needed in order to decrease the incidence of PPH and its associated mortality.

Secondary to hormonal changes, coagulation factors levels increase during pregnancy. Indeed, clot strength measured with viscoelastic assays has been shown to be higher during pregnancy from gestational week 10 till 40 compared to 8 weeks postpartum [50]. However, FXIII shows a consistent decrease from the first trimester till the partum, though being within the reference range, beginning to increase again during the postnatal period. It has been hypothesized that this reduction is related to maternal transfusion of FXIII to the fetus and to the placenta growth [51].

Bamberg et al. [52], in a large single-center observational prospective study of over 500 pregnant women, found that 3 days before birth, FXIII levels, though being within the reference range, were significantly lower in women with PPH (86.45% ± 14.6 in women experiencing a blood loss <500 mL during delivery (n = 470) versus 79.33% ± 15.5 in women whose blood loss during delivery was >500 mL (n = 78), $p < 0.001$). These authors have not found significant differences in FXIII levels in the subgroup of women with a blood loss greater than 1,000 mL likely due to the small sample size of this subgroup (n = 18). Similarly, Karlsson et al. [53] found significantly lower FXIII levels at the onset of labor in women with a subsequent PPH compared to women without (0.98 kIU/L ± 0.2 vs. 1.05 kIU/L ± 0.17, $p = 0.0006$), being more evident when excluding obstetric complications, thus, relying only on the hemostatic capacity.

In this line, in the largest published sample to date on 1,309 pregnant women, in which postpartum blood loss and coagulation factors (fibrinogen, FII, and FXIII) were objectively measured, Haslinger et al. [54] identified prepartum FXIII levels to be the only factor impacting postpartum blood loss across the whole sample. Their model suggests that increasing FXIII levels significantly decrease the likelihood of PPH in any mode of delivery (vaginal or cesarean). Specifically, the odds ratio for maintaining blood loss below 500 mL was 1.009 (95% confidence interval, 1.003–1.014; $p = 0.002$) with every one-unit increase in antenatal FXIII levels. Even more binding, FXIII significantly influenced measured postpartum blood loss independently of any cut-off, which supports the hypotheses that FXIII is an associated factor for postpartum blood loss and not a consequence of it. This has important clinical implications showing FXIII as a potentially modifier factor to decrease PPH by measuring and administering FXIII before delivery. In surgical patients at high risk for bleeding, the intraoperative use of FXIII has already been postulated as potentially beneficial reducing blood loss [55] and transfusion requirements [21]. Likewise, in congenital FXIII deficiency, FXIII prophylaxis has demonstrated to be effective in achieving pregnancy [56, 57].

However, as in the previously mentioned studies [52, 53], prepartum FXIII levels in the Haslinger paper [54] were also within the reference range (median FXIII activ-

ity 98.5% in women with vaginal delivery [*n* = 677], 93% in women experiencing elective cesarean section [*n* = 409], and 93% in unplanned cesarean section [*n* = 223]). What is more, the measured blood loss in the three settings (median blood loss of 350 [300–500] mL in vaginal delivery, 500 [400–600] mL in elective cesarean section, and 500 [400–700] mL in unplanned cesarean section) is common during partum and more importantly, it does not usually require hemostatic intervention. In addition, the incidence of major bleedings (>1,500 mL) was not reported in this study. Consequently, the target population and the level of FXIII required to avoid PPH are yet to be defined by further trials investigating larger samples of patients with higher blood losses.

In the meantime, based on the study by Haslinger et al. [54] where a statistical model suggests that blood loss will increase with a decrease in prepartum FXIII levels (shown in Fig. 1), early replacement of FXIII is likely beneficial in the setting of acute PPH in which obstetric and surgical management of a given condition (mainly uterine atony,
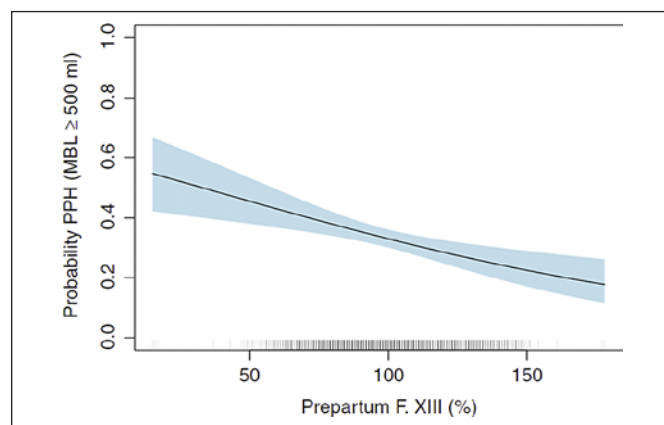

Fig. 1. Prevalence of PPH as a function of prepartum FXIII. It was calculated considering that the other antenatal hemostatic risk factors are kept within normal range (hemoglobin = 127 g/L, fibrinogen = 4.5 g/L, and FII = 128%). These values reflect the median values of the study population [54]. The line represents the probability of having PPH defined as measured blood loss >500 mL and the blue area the 95% confidence interval. This figure is reproduced with permission of Haslinger and coauthors [54].

Fig. 2. Scalating scheme of hemostatic therapeutic options for PPH. This figure is modified with permission from Lier and coauthors [49].

retained placenta, or bleeding from cervical or vaginal tears) is essential. Of note, prospective, randomized, and interventional trials are needed to prove that statistical model.

Conversely, in Haslinger paper [54], fibrinogen did not show any detectable influence on postpartum blood loss while FII had only an influence on postpartum blood loss in the cesarean delivery subgroup. Accordingly, in the peripartum setting, neither preemptive fibrinogen replacement in patients with normofibrinogenemia [58] nor even fibrinogen substitution with thromboelastometric-guided fibrinogen infusion (FibTEM A5 ≤15 mm) in women with ongoing PPH 1,000–1,500 mL [59] has demonstrated to reduce transfusion requirements or blood loss. However, as in other settings [60], fibrinogen below 2 g/L should be treated as it may be associated with increased bleeding. These results likely show that the early decrease in fibrinogen levels observed in PPH [61] represents a consequence of that bleeding due to consumption as occurs in traumatic hemorrhagic shock where fibrinogen is the first coagulation factor to reach critical levels [62]. Second, FXIII replacement after cardiopulmonary bypass has not improved outcomes in terms of transfusion avoidance in cardiac surgery [63]. However, in this setting FXIII deficiency was not previously linked to an increased risk of postoperative bleeding [64]. We will await the results from the ongoing first randomized trial assessing the early administration of cryoprecipitates (which contain FXIII) versus standard care in pregnant women at >24 weeks gestation who are actively bleeding and require blood transfusion [65].

Surprisingly, the recently published PPH guidelines from the Network for the Advancement of Patient Blood Management, Hemostasis and Thrombosis (NATA) [46] do not mention FXIII. However, in the German PPH guidelines, FXIII replacement is indicated in an ongoing bleeding at a dose of 15–20 IU per kg intravenously in an escalating scheme of hemostatic therapies with strong consensus of the committee (shown in Fig. 2) [49]. In other contexts, FXIII replacement is indicated if a decrease of FXIII activity is confirmed or suspected. In the trauma setting, FXIII replacement is indicated in an ongoing bleeding with FXIII activity <60% at a dose of 15 IU per kg intravenously [66] and suggested if FXIII deficiency is suspected by viscoelastic assays (clot instability not related to hyperfibrinolysis after having replaced with other hemostatic agents) already 1 decade ago [67]. The European Society of Anesthesiology guidelines for severe perioperative bleeding [68] also suggest the administration of FXIII concentrate (30 IU per kg) in case of bleeding and FXIII activity <30%. Of note, replacement with FXIII concentrate has proved to be safe with a low risk of adverse drug reactions [69].

Conclusion

Severe bleeding is the main cause of preventable mortality in the acute care setting. Bleeding is the symptom of an underlying situation (mainly tissue injury) in which hemostatic impairment plays an essential role. However, it is sometimes challenging to distinguish when altered hemostasis is an associated factor or, conversely, a consequence of consumption. This difference is fundamental due to the potential of an associated factor to modify a given condition. Physiological hemostasis depends on creating a stable clot as it is underlined in the cell-based coagulation model and assessed with viscoelastic assays. FXIII stabilizes a recently formed platelet-fibrin clot making it resistant to fibrinolysis. Consequently, FXIII deficiency might be an associated factor for acute bleeding in high-risk surgery, severe trauma, and obstetrics despite upregulation of thrombin generation. In order to better understand and treat the acutely bleeding patient, FXIII should be thoroughly assessed and replaced if necessary. Hopefully, this will be soon endorsed across all the guidelines that make recommendations about the acutely bleeding patient. In this sense, we recommend including FXIII assessment and replacement in an escalating scheme of hemostatic therapies in the acute care setting. However, the target population and the level of FXIII required to achieve hemostasis in each situation remains to be elucidated.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

P.D. has drafted the article and approved the final version. W.K. has reviewed critically the article for important intellectual content and approved the final version.

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