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Fibrinogen concentrate in the management of postpartum hemorrhage: a narrative review

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Abstract

Postpartum hemorrhage remains an important cause of mortality and morbidity, representing 27.1% of maternal deaths. Primary coagulopathy and dilutional coagulopathy occur regularly and require aggressive treatment. Tranexamic acid is identified as essential in the management of obstetric hemorrhage. The crucial role of fibrinogen is established as well. Although definite proof of the efficacy is lacking, fibrinogen concentrate is widely used to treat postpartum hemorrhage and peripartum coagulopathy. The goal of this narrative review is to summarize the existing literature regarding the use of fibrinogen during postpartum hemorrhage. We will also discuss the role of point of care testing during peripartum hemorrhage for both diagnosis and guidance of coagulation therapy. Finally, we will evaluate the role of fibrinogen administered as a concentrate or as free fresh plasma.

Keywords: **Postpartum hemorrhage, fibrinogen, coagulation disorders, point of care test.**

Introduction

Postpartum hemorrhage (PPH) is a leading cause of maternal mortality[1]. Worldwide PPH is the leading direct cause of maternal mortality, representing 27.1% of maternal deaths[2]. In high resource countries such as the United Kingdom and the United states it is no longer the leading cause of mortality but still is responsible for up to 12% of maternal deaths[3]. In developing nations, including Africa and Asia, peripartum hemorrhage is responsible for 30% of all direct maternal mortality[2]. Uterine atony, retained placental tissue and lacerations of the genital tract are the most important causes of hemorrhage[4]. Early onset coagulopathy and dilutional coagulopathy are rare but are responsible for 2-5% of major bleeds[4]. Low fibrinogen levels at delivery before hemorrhage occurs have a 100% positive predictive value to predict hemorrhage[5]. Dilutional coagulopathy is an aggravating factor of blood loss during PPH. Especially plasma fibrinogen is susceptible to a rapid drop in ongoing blood loss[6]. Obstetric hemorrhage is characterized by rapid deterioration. Rapid identification of causes and rapid evaluation of therapy are essential to guide appropriate treatment. Since classic laboratory testing yields results with significant delay, there is a rising interest in the use of viscoelastic testing such as rotational thromboelastography (ROTEM) to determine the utility of fibrinogen transfusion[7].

Methods

We performed a review of the literature in Pubmed database using following MESH search terms: 'postpartum hemorrhage', 'fibrinogen', 'thromboelastography', rotational thromboelastography, coagulopathy and 'blood coagulation disorders'. The search was limited to articles published since 2002 and published in the English language. Screening was performed in November 2022. An update of the search was performed by March 15th 2023 and the literature was updated. We included randomized controlled trials, retrospective studies, observational studies, case series, narrative and systematic reviews that dealt with fibrinogen and peripartum hemorrhage and that evaluated rotational thromboelastometry in the obstetric setting. The papers where we could

not obtain a full text were excluded from the search list. We found 51 papers and retained 32.

Results

We identified 32 papers.

Literature definition of postpartum hemorrhage: The World Health Organization defines PPH as a blood loss of 500 mL or more within 24 hours of birth[8]. In some studies a distinction in definition between vaginal birth and cesarean delivery is made. Blood loss has to be more than 500 mL in vaginal delivery and more than 1000 mL in a cesarean delivery to be defined as a PPH. The American College of Obstetrics and Gynecology redefined PPH in 2017 as a cumulative blood loss greater than 1000 mL with signs and symptoms of hypovolemia within 24hours of the birth process, regardless of the route of delivery[9].

Blaha et all., reviewing the definitions of PPH worldwide, summarize different definitions based on several factors. Some definitions are based on the volume of blood loss; others are based on the pathoyphysiological changes and the last group of definitions is based on the need of an intervention[10]. Hence PPH is defined as "a cumulative blood loss equal or greater than 1000 mL or any blood loss associated with clinical and/or laboratory signs of shock/tissue hypoperfusion within 24h after birth[10].

Symptoms and diagnosis: Untreated PPH can lead to hypovolemic shock, multi-organ dysfunction and maternal death, so early identification and treatment of women with PPH is a key factor for maternal survival[11]. The diagnosis of PPH is primarily based on the identification of excessive blood loss. This identification is generally based on a visual estimation of blood loss and has been associated with an underestimation of the amount of blood loss, making it a limitation in the diagnosis of PPH[12]. To become a good estimation of the ongoing blood loss there are different methods of quantitation of blood loss (QBL), including gravimetry, volumetric analysis and colorimetry[13]. The gravimetric method consists of weighing blood-soaked materials and registering the wet mass minus the dry mass being equal to the volume of blood loss. Disadvantages are overestimation due to contamination with amniotic fluid or irrigation fluids[14]. A volumetric analyses is done by using suction canisters and plastic drapes, but this method has similar disadvantages as the gravimetric method[15]. In a hybrid system the gravimetric and volumetric methods are combined. Finally, the colometric method evaluates the hemoglobin content in blood-soaked materials and accounts for non-blood contamination[16]. This method can be used to trigger hemorrhage alerts through the integration of a hemorrhage protocol. But further studies are needed to determine whether the use of this system has any meaningful improvement in maternal outcome compared with the other methods[17].

Another way of making the diagnosis is based on clinical signs and symptoms. Signs and symptoms such as pallor, light-headedness, weakness, palpitations, tachycardia, diaphoresis, restlessness, confusion, air hunger, syncope, fatigue and oliguria could be potentially present. The shock index seems to be a promising indicator of the severity of blood loss[11]. Before clinical signs of hypotension and tachycardia are present already 1500 mL blood loss has occurred.

Etiology: Bleeding in PPH is precipitated by obstetric causes but can be exacerbated by haemostatic impairment[18]. Uterine atony is the most common obstetric cause of hemorrhage (70- 80%) followed by abnormal placentation (15-20%), genital tract trauma (0.5-3%) and coagulation disorders[4]. There are no exact numbers regarding the incidence of coagulation disorders being the cause of PPH. Acquired coagulopathy is a major aggravating factor of blood loss. During PPH, plasma fibrinogen is the first coagulation factor to drop precipitously due to bleeding, hyperfibrinolysis (consumption) and haemodilution[19].

Hemostasis: During pregnancy, the hemostatic system shifts towards a prothrombotic state, with increased levels of procoagulant factors, particularly fibrinogen, von Willebrand factor, and factor VIII20. The level of fibrinogen is typically between 4 to 6 g/L, which is higher than the normal range of 2 to 4 g/L in non-pregnant women[21]. Around the time of delivery, the fibrinogen levels further increase to 6-8 g/L. These changes result in shorter prothrombin and activated partial thromboplastin times (PT/aPTT) , sometimes even below the normal laboratory range, and there is a significant increase in thromboelastographic parameters[22]. Although the platelet count may decrease during pregnancy (gestational thrombocytopenia), it is usually not low enough to substantially increase the risk of bleeding[6].

Fibrinogen is an essential endogenous component of hemostasis with rising concentrations during pregnancy[21]. Blood loss on the other hand results in coagulopathy and reduced fibrinogen levels. Massive transfusion is often needed to treat an ongoing hemorrhage, but can itself result in dilutional coagulopathy. Studies have shown that fibrinogen is the first coagulation factor to decrease to a critically low level during major blood loss and

replacement with RBC[23]. Observational studies of patients with PPH have revealed that low fibrinogen concentration in the early stage of PPH or even just before delivery is linked to excessive bleeding and the need for blood transfusions[24]. It has been found that fibrinogen is an early biomarker for worsening of PPH. The risk of progression to severe PPH increases almost three-fold for each 1g/L decrease in fibrinogen concentration, independently of the other laboratory indicators. The specificity of a fibrinogen level <2g/l for the prediction of PPH was 99.3% (95% CI = (98.4-1.00))[25].

Important to know is that bleeding persists because of the obstetric cause and not because of the reduced fibrinogen. Nonetheless the reduction in fibrinogen level can contribute to the continuation of the bleeding. Notice that a severe PPH can occur with normal fibrinogen levels25.

The clinical utility of laboratory fibrinogen to predict progression of PPH is limited because results take 60-90min to become available. Therefore point of care viscoelastometric tests, such as rotational thromboelastometry (ROTEM©), provide results within 10 minutes[18]. The fibrinogen based thromboelastometry (FIBTEM) measures the effect of fibrinogen by eliminating the contribution of platelets to clot strength, through the addition of cytochalasin D. The normal value for FIBTEM maximum clot firmness (MCF) are 15-19mm in the third trimester of pregnancy, these are significantly higher than in the non-pregnant population (10-12mm). The MCF result is available after 30-40min, but earlier studies have shown that clot firmness results available after 5min (A5) had a close correlation with the subsequent MCF[26].

In the study of Collins et al, early fibrinogen concentrate in women experiencing moderate to severe PPH who had a FIBTEM A5 < 15mm did not lead to a statistically significant reduction in transfusion requirement or blood loss. Subgroup analyses did suggest that early fibrinogen infusion had an effect on blood product usage and bleed size at a FIBTEM A5<12mm or fibrinogen < 2.5g/L[18]. Historically transfusion guidelines, recommended fibrinogen replacement with levels less than 1g/L, but recent in vitro studies suggest that fibrinogen levels of 2.5g/L are associated with optimal clot formation, supporting the subgroup analysis of Collins et al[27].

There are several potential options for fibrinogen supplementation such as cryoprecipitate, fresh frozen plasma (FFP) and fibrinogen concentrate. FFP is not preferred for fibrinogen supplementation because large volumes are necessary to effectively increase the plasma fibrinogen level[13]. Additionally, plasma fibrinogen is derived from non-pregnant donor blood. Hence, fibrinogen is available in a concentration of 2-2.5 g/L. Administration of FFP therefore might result in a paradoxical dilution of the fibrinogen. Cryoprecipitate is the concentrated precipitate produced after thawing and centrifugation of FFP and it contains fibrinogen and other coagulation proteins. Disadvantages of cryoprecipitate are thawing of the product, the risk of blood-borne related complications such as transmissions of infections and the need of a cross-match[28]. Fibrinogen concentrate undergoes subsequent processing to reduce the risk of viral transmission. This further treatment removes or inactivates potentially contaminating viruses, antibodies and antigens (Table I).

Protocol: In response to increasing rates of maternal morbidity and mortality in the United States the National partnership for Maternal Safety (2020) developed a series of maternal safety bundles. The goal of the bundle is to provide a set of straightforward, evidence-based practice recommendations to improve care and outcomes for preventable causes of maternal mortality and morbidity. The bundle is organized in the four R actions: Readiness, recognition and prevention, response and reporting and systems learning[29].

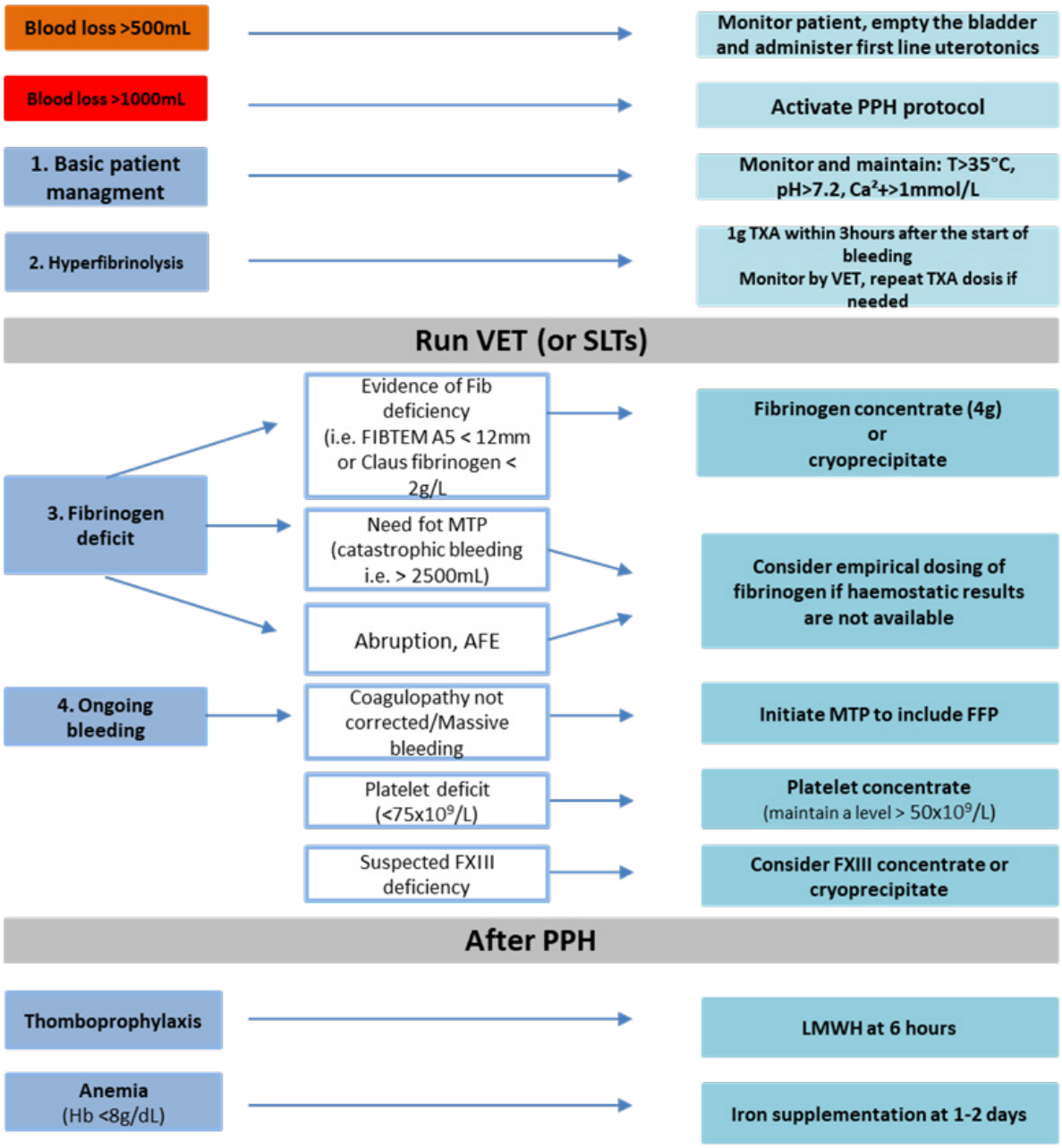
The purpose of PPH protocols is to establish uniformity in identifying and treating PPH (including achieving hemostasis and for the resuscitating the patient), diminish cognitive biases through standardized responses, and help teams have a common understanding of the pathway to stop hemorrhage[30].

In California investigators compared the rates of severe hemorrhage-related morbidity among deliveries in hospitals preceding and following the

Table I.

Fibrinogen supplementation	Advantages	Disadvantages
Cryoprecipitate	High concentration of fibrinogen	Thawing of the product Transmission of infections Need of cross-match
Fresh frozen plasma	Cost-effective	Large volumes Low concentration of fibrinogen
Fibrinogen concentrate	Inactivation of potentially contamination viruses, antibodies or antigens	Expensive

Table II.



VET: ViscoElastometric Tests – MTP: Massive Transufsion Protocol – SLT: standard laboratory tests

implementation of a PPH protocol and found that participation in the collaborative was associated with a 20.8% reduction in hemorrhage-related morbidity[31].

When fibrinogen is reduced we refer to the recent paper by Hofer et al. as a guide for a simple algorithm to be used[32] (Table II).

Conclusion

The administration of fibrinogen during massive transfusion protocol because of ongoing hemorrhage is already well-established. It is for some years that there's a rising interest for the fibrinogen administration during PPH, but the modified thrombotic state makes it more difficult to determine the timing and efficiency of fibrinogen administration. Since the use of point of care testing, such as ROTEM, it is more predictable to determine the timing of administration of fibrinogen. It is of great interest to know that an ongoing PPH is not over after the administration of fibrinogen, the primary cause needs to be under control, but an altered coagulative state also needs to be treated. The anesthesist has a crucial role in this matter. At the end, more randomized controlled trials are necessary to help us determine the timing and utility of administration of fibrinogen .

As important as the administration of fibrinogen is the recognition of an ongoing bleed and the use of

a PPH-protocol. Every center needs such a protocol combined with trained doctors, nurses and other paramedics. Only this way it will make it possible to lower the incidence of maternal mortality and morbidity.

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