

## MINIREVIEW

# Blood management in post-partum haemorrhage, including point of care coagulation tests

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**Abstract**

Postpartum haemorrhage (PPH) is the leading global cause of maternal mortality, and an important cause of morbidity and mortality in the UK. Management of PPH requires a patient centred team approach to ensure effective management. Early recognition is crucial, hence quantitative measurement of blood loss should be started as soon as bleeding is identified and continue throughout an evolving haemorrhage. Pregnancy is associated with haematological changes resulting in a pro-coagulant state. Blood management in PPH has moved away from the use of shock packs and fixed transfusion ratios. Most women are not initially coagulopathic and coagulopathy is uncommon in mild to moderate PPH, Practice has therefore moved towards goal directed transfusion of blood products informed by haematological investigations alongside clinical assessment. Fibrinogen tends to be the first coagulation factor to fall and Clauss fibrinogen is an important predictor of PPH severity. Transfusion of fibrinogen rich blood products such as cryoprecipitate and fibrinogen complex are more effective at rapidly increasing fibrinogen levels compared to FFP. Point of care (POC) coagulation tests such as rotational thromboelastometry (ROTEM) and thromboelastography (TEG) allow rapid bedside assessment compared to traditional laboratory tests. Surrogate markers of fibrinogen from POC tests can be used to both predict severity of PPH and inform blood transfusion. There is growing evidence that POC coagulation tests can be used to safely guide blood management in PPH, with its use associated with lower transfusion rates and possibly improved clinical outcomes. Further multi-centre studies are required to clarify debate surrounding their use. In this review we discuss blood management in PPH, with a focus on recent evidence regarding assessment of coagulopathy and the use of blood products.

**Keywords**

Postpartum haemorrhage (PPH); Blood management; Coagulopathy; Fibrinogen; Transfusion; Point of care (POC) tests; ROTEM; TEG

## 1. Introduction

Postpartum haemorrhage (PPH) is the loss of at least 500 mL of blood following birth. It can be classified by amount, timing and cause (Table 1) [1]. It is a leading cause of maternal mortality globally [2] and is associated with significant morbidity [3]. The 2017 MBBRACE report raised concerns that maternal mortality rates from haemorrhage were increasing. More recently these rates have fallen, whilst at the same time there has been increased focus on its recognition and treatment [4]. It is important to try to prevent PPH by identifying patients at risk, offering uterotonics for the third stage of labour and treating antenatal anaemia. If PPH occurs one should consider its cause, as this will direct management [1, 5].

The mainstay of treatment of established PPH involves recognition of severity, treatment of the underlying causes and supportive treatment to maintain oxygen delivery to tis-

ues and restore circulating volume [1]. There is growing evidence that the use of shock packs and fixed transfusion ratios of RBC : FFP of 1 : 1 or 1 : 2 often result in over-transfusion, particularly of fresh frozen plasma (FFP) [6, 7]. This practice was extrapolated from evidence in major trauma and is an outdated approach in obstetrics as it is associated with increased rates of serious complications from transfusion [6–9]. Blood management should be goal directed rather than based on volume of blood loss alone [6].

## 2. Haematological changes in normal pregnancy

Significant adaptive haematological responses during pregnancy occur to facilitate increased oxygen delivery to tissues, and create a prothrombotic state in preparation for bleeding associated with delivery. Plasma volume increases by 40-

TABLE 1. Classification of PPH.

Classification of PPH		
Amount	Timing	Cause '4 T's'
Minor: 500-1000 mL	Primary-within 24 hrs of birth	Tone: uterine atony Tissue: retained placental tissue or clots in the uterus
Moderate: 1000-2000 mL	Secondary-between 24 hrs and 12 weeks after birth	Trauma
Severe: > 2000 mL		Thrombin: primary or secondary coagulopathy

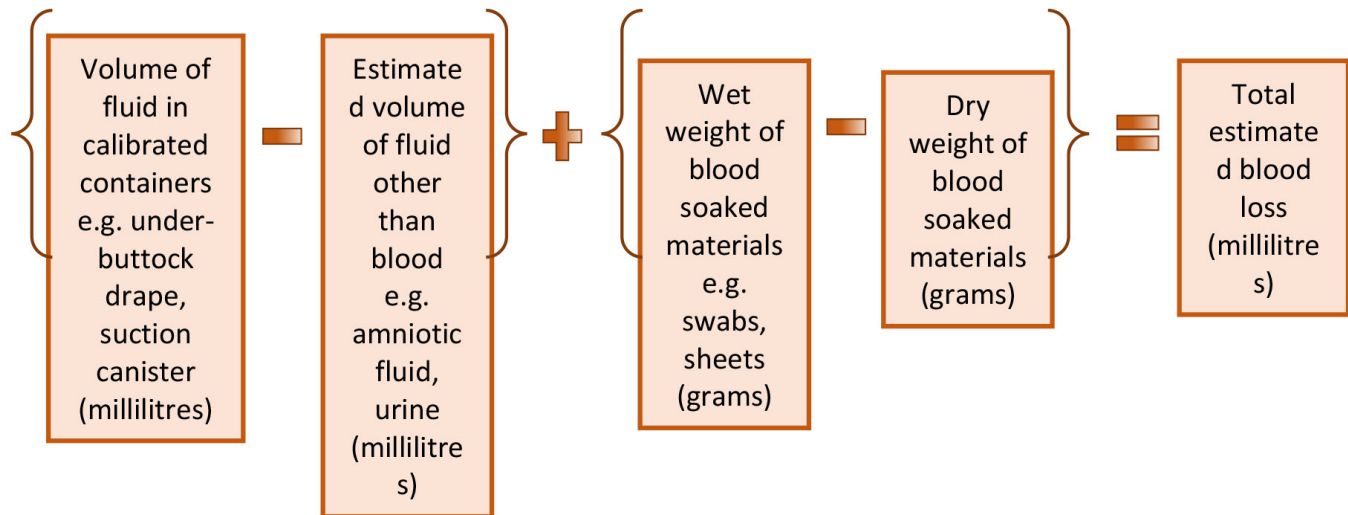


FIGURE 1. Quantitative assessment of blood loss [20].

50% and red blood cell mass increases by 20% resulting in a dilutional physiological anaemia. There is an overall increase of up to 2000 mL in blood volume compared with the non-pregnant individual. As a result pregnant patients usually compensate well for blood loss. By the time classical symptoms and signs of hypovolaemia occur more than 1500 mL of blood may have already been lost [10].

There is immense upregulation of the majority of pro-coagulant factors [11]. Fibrinogen levels in particular rise significantly and steadily increase from 2-4 g/L to 4-6 g/L [12, 13]. As the precursor for fibrin it is vital for clot formation and stability [14]. By the end of pregnancy fibrinogen makes up the vast majority coagulation factors in the plasma [12]. This is accompanied with suppressed endogenous anticoagulation activity [12, 15] and reduced fibrinolytic activity [16]. Overall these changes result in a prothrombotic state [11, 17] and this affects the rate and pathophysiology of coagulopathy in PPH compared to major haemorrhage in the non-obstetric population [18]. Platelet count falls slightly but this does not usually impact coagulation [13].

### 3. Measuring blood loss

Visual estimation of blood loss in PPH is now widely accepted to be inaccurate [19, 20]. It often leads to underestimation of blood loss with increasing inaccuracy as volume of blood loss increases [21]. Measuring blood loss has been shown to be associated with higher rates of PPH due to improved detection

rates, thereby legitimising its importance [19]. Quantitative assessment of blood loss requires teamwork and should be started immediately after delivery (Fig. 1). This should be repeated at regular time intervals, so ongoing blood loss can be recorded and acted upon [20]. It is important to review areas where blood loss can go unnoticed, such as under the drapes, and appreciate that there may also be internal bleeding or blood within the uterus which cannot be easily quantified [22]. Therefore measuring blood loss should occur in conjunction with ongoing clinical assessment of the patient [23].

### 4. Coagulopathy in PPH

Coagulopathy is uncommon in mild and moderate PPH [13] and most women with PPH do not become clinically coagulopathic [12]. The underlying pathophysiological processes are influenced by the cause and volume of bleeding, and are different to those in major haemorrhage in the non-obstetric population. Coagulopathy is caused in varying degrees by dilution of existing coagulation factors during resuscitation with intravenous fluid and a consumptive process that is either localised at the placenta or disseminated [18, 24, 25]. PPH caused by trauma or uterine atony is usually associated with late onset coagulopathy when blood loss is 2000 mL. It is predominantly a dilutional coagulopathy although consumption of coagulation factors can contribute in severe cases [15]. PPH associated with retained products can result in either an early or late coagulopathy. Dilutional coagulopathy predominates

in most cases but local consumption of coagulation factors can also play a role [18]. Disseminated intravascular coagulopathy (DIC) is not a common cause of coagulopathy in PPH with the exception of amniotic fluid embolus, placental abruption, severe pre-eclampsia, sepsis and ongoing massive haemorrhage [6, 18].

## 5. Coagulation tests

### 5.1 Laboratory tests

Traditional laboratory coagulation studies including prothrombin time (PT), international normalised ratio (INR), activated partial thromboplastin time (aPTT) were designed to test specific aspects of the clotting cascade in order to assess the effects of specific anticoagulants [11]. In practice, the long turnaround time, poor correlation with severity of blood loss and inability to predict progression of PPH limits their use in a rapidly evolving PPH scenario [26–28]. Derangement of PT, INR and aPTT in the context of PPH usually does not occur until 4000–5000 mL blood loss [13] suggesting these are imperfect tests of coagulation in PPH [26–28]. It is imperative to not be falsely reassured by normal PT, INR & aPTT. If these results are abnormal one must be alerted to the possibility that either significant blood loss has occurred or the patient has an underlying coagulopathy, both of which need to be addressed urgently in the context of ongoing bleeding.

Clauss fibrinogen level should be tested early in the management of PPH and repeated regularly if there is ongoing haemorrhage [1, 13]. Fibrinogen has been shown to be a reliable early marker for risk of severe PPH [13, 28, 29]. When coagulopathy occurs the first factor to fall significantly is fibrinogen [13]. A study of women with PPH > 1500 mL showed that, compared to aPTT and PT, fibrinogen correlated best with level of blood loss [26]. Studies have also shown that low levels of fibrinogen are an independent risk factor for the development of severe PPH. A fibrinogen level of < 2 g/L has been shown to be associated with 12 times increased risk of severe PPH and a 100% positive predictive value for progression to severe PPH [28, 29]. Fibrinogen levels 2–3 g/L have also been shown to be associated with increased risk of severe PPH, but to a smaller degree [27, 29]. With this growing evidence, the correction of coagulopathy has become more centred on the replacement of fibrinogen in the first instance. The threshold for initiating replacement and dose required remain uncertain and under investigation [9] however current best evidence indicates levels should be kept > 2 g/L [1, 13, 28].

### 5.2 Point of care coagulation Tests

Viscoelastometry tests including rotational thromboelastometry (ROTEM) and thromboelastography (TEG) allow rapid and comprehensive point of care (POC) assessment of all stages of coagulation at the patient's bedside. Measurements of clot formation all the way through to and including breakdown are taken [12, 30]. Whole blood samples are mixed with different reagents to isolate and measure specific parts of the coagulation cascade and allow goal directed transfusion of blood products [12, 31]. Use outside of obstetrics have shown that they may

better predict bleeding risk compared with standard laboratory tests [32, 33]. ROTEM has the largest evidence base in regards to PPH, however further research is required to clarify debate surrounding their use [13, 31].

ROTEM has been shown to safely guide transfusion of blood products in evolving PPH [13]. Normal values in pregnancy have been identified for ROTEM parameters [34–36]. The FIBTEM test involves a platelet inhibitor reagent which allows the contribution of fibrinogen in clot formation to be measured in isolation [31]. FIBTEM A5 is a measure of clot firmness after 5 minutes [37] and can be used as a surrogate measure of fibrinogen level [31]. High degrees of correlation between FIBTEM A5 and Clauss fibrinogen have been observed within the obstetric population and thus FIBTEM A5 can also be used to predict progression of PPH [31, 38]. OBS-2 a multicentre double-blinded RCT showed that fibrinogen replacement when FIBTEM A5 < 15 mm (fibrinogen concentrate) had no beneficial outcome. They did however find on subgroup analysis that there may be a benefit of fibrinogen replacement when FIBTEM A5 < 12 mm however this lacked statistical significance [39]. A prospective study comparing shock packs and ROTEM guided transfusion (using FIBTEM A5 < 12 mm trigger for fibrinogen replacement) found less blood products were used, with no increase harm and reduced rates of transfusion related complications [7]. A FIBTEM A5 < 12 mm can be used interchangeably with fibrinogen < 2 g/L when guiding fibrinogen replacement [13], as FIBTEM A5 12 mm roughly correlates with 2.2 g/L fibrinogen [40]. There is some evidence to suggest that earlier measured values from ROTEM could be used as an indication of fibrinogen levels. This would allow earlier detection and correction of coagulopathy [41].

ROTEM can also be used to guide FFP transfusion through use of the ExTEM test. ExTEM CT (clotting time) gives a broader assessment of clotting status including fibrinogen, platelets and other coagulation factors [31, 40]. An observational study using ROTEM in PPH showed that abnormal ExTEM CT > 100 s occurred in women with severe PPH. This was also associated with very low FIBTEM A5 suggestive of significant global coagulopathy. This study also showed that implementation of a ROTEM based algorithm using FIBTEM A5 ≤ 12 mm and ExTEM CT > 100 seconds was associated with reduced FFP transfusion, no incidence of transfusion related circulatory overload (TACO) and reduced intensive care admissions [40].

There are currently fewer studies using TEG in the setting of PPH compared to ROTEM [31]. One study has shown that TEG parameters demonstrate a coagulopathy with EBL > 2000 mL and that there is a correlation between TEG-MA (measure of clot strength) and fibrinogen levels as PPH progresses. This study used a TEG reagent that is designed to look at the intrinsic clotting pathway rather than isolate fibrinogen contribution to clot formation [42]. Recent studies looking at FLEV-TEG, designed to measure the contribution of fibrinogen, have raised concerns that it may overestimate fibrinogen levels and if used as a transfusion guide could lead to under treatment [43, 44]. Small studies have described the benefit of using TEG in PPH [33, 45] and TEG algorithms have been published based on normal values gained from healthy pregnant women [46]. It is our opinion that robust clinical

evidence is required to validate routine use of TEG in PPH scenarios.

Older machines including ROTEM delta and TEG 5000 require manually pipetting blood samples into small cups and adding different reagents in order to examine different aspects of the clotting cascade [33]. Although still faster than laboratory tests it remains time consuming and is prone to human error and inaccuracies [47]. Newer machines, ROTEM sigma and TEG 6s, have the advantage of a pre-filled cartridge. This reduces human error, user training and time to results [47, 48]. Studies outside the obstetric population have shown good correlation between the two machines apart from when measuring clot breakdown [49]. More comparative data in the pregnant population is needed to establish whether changes to existing PPH treatment algorithms are required [33]. ROTEM sigma may be better suited than TEG 6s for algorithms where early identification of low fibrinogen activity is advantageous, such as in PPH [50]. This is probably due to simpler transfusion algorithms associated with ROTEM.

It is important to be aware of some of the limitations pertaining to the use of ROTEM and TEG in PPH. There can be significant variability in precision of results between different machines and internal and external quality control is imperative to ensure accuracy of results [33, 51, 52]. These machines cannot assess the effect of hypothermia that can occur during PPH [31]. And although these tests may present advantages when managing obstetric patients with particular disorders of coagulation, more evidence is required to allow the broader use of viscoelastometric tests in obstetric care [33].

The Association of Anaesthetists of Great Britain and Ireland (AAGBI) and Obstetric Anaesthetist Association (OAA) both advocate the use of point of care testing in the setting of PPH to assess and guide management of coagulopathy [1, 6]. NICE guidance states there is insufficient evidence to recommend routine use in PPH [1, 54]. However more recently ROTEM has been introduced into national PPH guidance in Wales [55].

## 6. Blood management

Blood management is an important component of a wider comprehensive care package that should be delivered in PPH scenarios [1, 55, 56]. Blood product transfusion should be informed by regular assessment (every 30 minutes) and be goal directed to maintain [1, 55]:

- Haemoglobin > 80 g/L [1]
- Fibrinogen > 2 g/L [1, 55]
- FIBTEM A5  $\geq$  12 mm [55]
- ExTEM CT < 75 seconds [55]
- PT & aPTT < 1.5 times normal [1]
- Platelets >  $75 \times 10^9/L$  [1, 5, 55]

### 6.1 Correcting anaemia

Major obstetric haemorrhage protocols should allow O negative blood to be available with switch of group specific blood as soon as possible. It is essential to closely liaise with blood bank for these patients in order to prevent delays in blood transfusion, especially if red cell antibodies are present [1, 55]. There is little evidence to support routine use of cell salvage

[57, 58] however guidelines support its use in emergency PPH scenarios [1, 5, 58]. A large randomised controlled trial showed low complication rates and no occurrence of amniotic fluid embolus. Serious complications were associated with leukodepletion filters and the authors suggest avoiding their use [57].

### 6.2 Replacing Fibrinogen

Fibrinogen should be replaced either by giving cryoprecipitate or fibrinogen concentrate [1, 55]. Both contain higher concentrations of fibrinogen compared to FFP, which has relatively low concentrations of fibrinogen and can dilute down existing fibrinogen within the circulation [13]. A multicentre double-blinded RCT in primary PPH showed outcomes were not improved when fibrinogen was empirically replaced [59]. 2 pools of cryoprecipitate or 4 g of fibrinogen concentrate should be transfused if FIBTEM A5 7-11 mm or Clauss fibrinogen is < 2 g/L. If FIBTEM A5 < 7 mm then 3 pools of cryoprecipitate or 6 g fibrinogen concentrate should be transfused [55]. Cryoprecipitate requires thawing, which can delay transfusion. Fibrinogen concentrate does not require thawing and so can be more rapidly transfused [13]. If these transfusion triggers are met but bleeding has stopped and there is no clinical concern then fibrinogen replacement can be withheld [40, 55].

### 6.3 Replacing other coagulation factors using FFP

Further research is required to confirm ROTEM threshold values in PPH [31, 34]. For now 15 mg/kg of FFP can be transfused if ExTEM CT is  $\geq$  75 seconds or if PT or aPTT are abnormally elevated [55]. If no haemostatic testing is available and there is ongoing bleeding 12-15 mg/kg FFP should be administered after 4 units of red blood cells have been given. It is important to consider earlier FFP use in situations such as amniotic fluid embolus, placental abruption, pre-existing coagulopathy or delayed recognition of severe PPH [1].

### 6.4 Platelet transfusion

Platelet count is sufficient in the majority of PPH cases [13]. 1 pool of platelets should be transfused if levels fall <  $75 \times 10^9/L$  to maintain levels of >  $50 \times 10^9/L$  [1]. There is scope for the use of viscoelastic tests but more evidence is required to confirm this [31, 33].

### 6.5 Antifibrinolytics

The WOMAN study examined the role of intravenous tranexamic acid in the treatment of PPH and showed a statistically significant reduction in deaths due to bleeding [60]. Following this the World Health Organisation (WHO) strongly recommended the early use of intravenous tranexamic acid for women with PPH [61]. One gram is generally given and this can be repeated after 30 minutes if there is ongoing bleeding [1, 55]. Tranexamic acid should not be withheld on the basis of viscoelastic tests [33]. Although they can identify states of hyperfibrinolysis [53], there is no robust data to support goal directed use of antifibrinolytic agents [31, 33].

## 7. Venous thromboembolism (VTE)

PPH is a risk factor for venous thromboembolism, particularly if blood loss is > 1000 mL. This risk increases further if surgery is required to control bleeding [62, 63]. Red blood cell transfusion alone has also been shown to be a risk factor for VTE [64] and the risk increasing with every unit transfused [65]. Once bleeding has stopped all patient risk factors for VTE should be considered in conjunction with the risk of bleeding to assess the prevention measures for VTE [66]. ROTEM and TEG can identify hypercoagulable states associated with pregnancy [31, 33]. In future, with more evidence, there may be a role for viscoelastometric tests in VTE risk stratification, prevention and treatment [51].

## 8. Summary

PPH is a potentially life threatening condition which continues to be a worldwide problem [2, 3]. Improved understanding of PPH associated coagulopathy allows for targeted and judicious transfusion of appropriate blood components. The importance of fibrinogen and measuring Clauss fibrinogen is now well established in the management of PPH. Fibrinogen replacement is indicated if levels fall below 2 g/L [1, 55]. However laboratory coagulation tests take time to reach the lab and be processed. POC tests have a more rapid turn around time and have the added benefit of being carried out close to patient. There is growing evidence that they can be used to safely guide blood product transfusion. The use of ROTEM based algorithms in PPH is associated with reduced rates of transfusion of blood products and improved clinical outcomes [13, 17]. However debate around their use remains, as there is a lack of studies comparing ROTEM and TEG to standard coagulation tests in PPH. Multi-centre comparison data, including cost analysis, is required to establish the most beneficial way of guiding blood management in PPH [13, 31].

## AUTHOR CONTRIBUTIONS

All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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