Feasibility to recruit to a pilot study, the effect of upfront administration of Fibrinogen concentrate in Obstetric Haemorrhage (FibUpFront PPH) :

Difficulties with recruitment in this very dynamic and rapidly changing environment.

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Background: As a leading cause of maternal morbidity and mortality, postpartum haemorrhage (PPH) is an obstetric emergency that warrants rapid recognition and management. This includes identifying and treating any coagulopathy, with particular attention to fibrinogen, which may fall to critically low levels during the course of the bleeding and thereby further worsen the haemorrhage. The measurement of fibrinogen levels using the traditional Clauss method can take up to 60 minutes, and so point-of-care tests such as rotational elastometry (ROTEM) are being used to provide a more rapid, real-time assessment of coagulation. Fibrinogen concentrate may be a safe, efficacious alternative to fresh frozen plasma (FFP) and cryoprecipitate for the replacement of fibrinogen but this is yet to be established in the obstetric setting. The OBS2 trial likely offers us the most up to date information and liaison with the group has confirmed similar difficulties in recruitment.

Methods/design: This study aimed to primarily assess the feasibility of FIBTEM-guided fibrinogen concentrate administration and whether its administration would reduce the requirement for blood products in severe PPH among recruited patients. It was a single-centre (initially planned as multi-centre but King Edward Memorial in Perth unfortunately withdrew from the pilot) double-blind randomised control trial in which 50 women required to be randomised if they met the following inclusion criteria: age 18 years or over, FIBTEM A5 ≤15 mm on ROTEM POC testing, estimated blood loss greater than 1500 ml less than four hours postpartum and not responsive to first line uterotonic therapy/manual uterine rubbing with ongoing evidence of haemorrhage at the time of randomisation. Participants with a FIBTEM A5 12-15 mm received standard of care plus 4 g of fibrinogen concentrate (reconstituted with sterile water to make a 200 ml solution). Participants with a FIBTEM A5 between 8-11 mm will receive 6 g of fibrinogen concentrate (reconstituted with sterile water to make a 300 ml solution). Participants in the control group will receive standard of care and either 200 or 300 ml of normal saline (i.e. placebo).

Discussion:
The main challenge during this pilot study was that despite a large number of eligible patients for enrolment due to logistics for example time of day, short notice due to urgency of cases and limited research staff resources limited our ability to screen and recruit patients difficult. The ROTEM is not a familiar device in our department, we use TEG but to have standardisation across sites included ROTEM as our primary device to accommodate King Edward Memorial but also to compare results with OBS 2 trial. This added another dimension of complexity because not all our Anaesthetic technicians were familiar on how to operate the ROTEM. PPH is a dynamic situation demanding lots of interventions that occupy staff's time and resources. There was a steep learning curve associated with mixing Fibrinogen concentrate versus availability of Cryoprecipitate, we do however use Fibrinogen

Concentrate in our Code Crimson Trauma calls and our experience in Maternity help streamline their process of preparing Fibrinogen Concentrate currently.

BACKGROUND

Postpartum haemorrhage (PPH) is a leading cause of maternal morbidity and mortality worldwide. It remains a leading cause of maternal mortality in both low-resource and developed countries (1). Estimates suggest over 100,000 women die each year as a result of severe PPH. Postpartum women with ongoing bleeding over 1000 mL are at a higher risk of adverse clinical outcomes (2).

It is imperative that persistent PPH is recognised promptly, and managed aggressively, to reduce maternal morbidity and mortality (2). Coagulopathy is often an early feature and may worsen the blood loss. The coagulation disturbance tends to occur even before the dilution of clotting factors, with tissue hypoperfusion and acidosis precipitating fibrinogen consumption and hyperfibrinolysis (2, 3).

Baseline fibrinogen levels are higher (4 – 6 g/L compared to 2 – 3 g/L) in pregnancy (4) and studies have shown a greater propensity to severe PPH in bleeding postpartum women with fibrinogen concentrations below 2 g/L (5, 6). As bleeding continues, the fibrinogen concentration may fall to critically low levels. Supplementation of fibrinogen has therefore been a focus of recent research, in an attempt to manage the global problem of PPH (7, 8).

Options for fibrinogen replacement include fresh frozen plasma (FFP), cryoprecipitate or fibrinogen concentrate. Each of these products vary in efficacy and safety profile (3). FFP includes an only slightly higher fibrinogen concentration than the target concentration of 2 g/L. Therefore, large infusion volumes of FFP are required to deliver sufficient doses of fibrinogen when a severe haemorrhage occurs. There is therefore a risk of fluid overload and pulmonary oedema, which obstetric patients are more susceptible to given their increased vascular permeability (3). Cryoprecipitate is preferred over FFP for fibrinogen replacement as it contains a much higher concentration (approximately 15 g/L). Both FFP and cryoprecipitate are allogeneic blood products that require cross-matching and thawing prior to administration. There is also a risk of exposure to blood-borne pathogens as they do not undergo viral inactivation processes (3).

Fibrinogen concentrate is a lyophilized powder derived from human plasma. Each vial contains approximately 1 g of fibrinogen that is reconstituted with 50 mL of sterile water to provide a low-volume, high-concentration solution that can be administered promptly, without the need for thawing. As it undergoes viral inactivation and pasteurization, the risk of pathogen transmission with fibrinogen concentrate is very low (3).

A number of non-obstetric studies have demonstrated improved coagulation results and reduced transfusion requirements in patients receiving fibrinogen concentrate during severe haemorrhage (3). There is a paucity of data on its use in the obstetric setting, however one recent Danish study failed to show a benefit from the administration of fibrinogen concentrate in 249 women who were randomised to receive either placebo or 2 g of fibrinogen concentrate. However, the volume of blood loss for inclusion was relatively low

(1000 mL) and the trial did not specifically target patients with low fibrinogen levels. The dose of fibrinogen concentrate administered was also relatively low. What's more, this study did not routinely use point-of-care (POC) coagulation testing (8).

POC tests can assist the clinician to make prompt, real-time assessments of coagulation. In contrast, it can take up to 60 minutes to obtain results using the traditional Clauss method for fibrinogen measurement. This is too long to inform clinical decisions during acute haemorrhage. POC tests also give an indication of the functional status of fibrinogen.

Rotational thromboelastometry (ROTEM) is a POC technology that is widely used in the obstetric setting. Components of this test correlate well with laboratory fibrinogen levels and results are available within about 10 minutes (9,10). The FIBTEM assay performed using ROTEM measures clot strength after platelet inhibition (9). Huissoud et al published ROTEM results in non-bleeding patients at different stages in pregnancy. They demonstrated a median FIBTEM A5 (amplitude after 5 minutes) of 15 mm (IQR 5 – 15 mm) in the third trimester (11). Collins et al examined FIBTEM values in PPH. They found that the FIBTEM A5 was an independent predictor for an obstetric haemorrhage > 2500 ml, with a median FIBTEM A5 of 12 mm (IQR 7 – 17 mm) in women progressing to severe PPH (9).

In an attempt to better manage obstetric haemorrhage and reduce PPH-related morbidity and mortality, this study aims to investigate the feasibility of ROTEM-guided administration of fibrinogen concentrate. We hope it will address the relative lack of evidence supporting the use of fibrinogen in this setting and that it ultimately leads into a large-scale clinical trial.

What's new since our final protocol design 2016:

Women Trial [15] published 2017 - use of Tranexamic acid :
Interpretation: Tranexamic acid reduces death due to bleeding in women with post-partum haemorrhage with no adverse effects. When used as a treatment for postpartum haemorrhage, tranexamic acid should be given as soon as possible after bleeding onset.
Conclusions: Although TXA use reduces bleeding deaths by almost one third, mortality rates similar to those in high income countries will not be achieved without tackling late presentation, maternal anaemia, availability of blood for transfusion and poor infrastructure.

OBS 2 Trial[16] published 2017:
Conclusions: Infusion of fibrinogen concentrate triggered by Fibtem A5 15 mm did not improve outcomes in PPH. Pre-specified subgroup analyses suggest that fibrinogen replacement is not required if the Fibtem A5 is > 12 mm or Clauss fibrinogen >2 g litre, but an effect below these levels cannot be excluded. The raised fibrinogen at term appears to be a physiological buffer rather than required for haemostasis.
OBS 2 trial – FFP restrictive arm: (FFP withheld if A5 > 15mm) [17]
Results. The study recruited 605 women and 98% had FFP withheld. The median (25th –75 th centile) total blood loss was 1500 (1300–2000)mL with 300 (50–545)mL occurring after enrolment. Total blood loss was >2500mL in 40/605 (6.6%) women. RBCs were transfused in 141/605 (23.3%) patients and 11 (1.8%) received ! 4 units. At least one invasive procedure was performed in 283/605 (46.8%) women. Level 3 care was required for 10/605 (1.7%) women. No women developed clinically significant haemostatic impairment.

OBS Cymru program 2018 [18]*: Point of care targeted management of postpartum haemorrhage:*

- *Risk Assessment for PPH is now becoming a routine part of the admission process in obstetric led birth settings, leading to increased awareness of and early planning for PPH detection, prevention and management.*
- *Early identification by means of Measuring Blood Loss is quickly becoming embedded in practice, with over 90% of women having their postnatal blood loss measured.*
- *Multidisciplinary Team Working is improving as a result of the training provided by OBS Cymru teams. Clinicians including Midwives, HCAs, anaesthetists, obstetricians, ODPs, and students working in maternity settings have received OBS Cymru training, and have embraced the 4 stage approach to PPH management.*
- *ROTEM point of care testing machines have been installed in every labour ward in Wales to allow access to rapid coagulation results and guide blood product management. Early data suggests this is leading to a decrease in the administration of blood products for the reason of PPH.*

Quantitative bloods loss during PPH [19]*: 2019*
Gravimetric techniques vs visual estimation
https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2019/12/quantitative-blood-loss-in-obstetric-hemorrhage

METHODS AND DESIGN

Overview

The study took place at a single obstetric centre in New Zealand. Per annum, there are a minimum of 6000 deliveries at the centre and over on average 600 PPH's greater than 1000mls. For 2016 we had 6974 deliveries recorded, with 300 PPH bleeds greater than 1500mls, and 63 women bled more than 2500mls.

This randomised-control double blind trial aimed to assess the feasibility to recruit to the pilot and whether the early administration of fibrinogen concentrate can reduce overall blood loss and decrease the requirement for blood and blood product administration in severe PPH. We hoped that this pilot study would allow us to plan for a larger multi-centre trial of fibrinogen concentrate in major obstetric haemorrhage but in view of difficulties around recruitment the pilot was terminated after one year with only three patients enrolled. We screened twenty-eight patients but recorded that three hundred women had PPH > 1500mls during the period of our pilot.

The investigators included obstetric anaesthetists, an obstetric haematologist and research nurses.

Primary Aim

The primary aim of this study was to investigate whether it was feasible to use the FIBTEM A5 test to guide the administration of fibrinogen concentrate in women with severe and persistent PPH.

Secondary Aims

1. To assess the impact of early supplementation of fibrinogen concentrate in women with severe and persistent PPH on the overall level of blood loss and allogeneic blood product requirement.
2. To assess the correlation between fibrinogen using the Clauss method and point of care testing during severe and persistent PPH.

We can not with confidence make any conclusions from our data due to the very small numbers.

Outcomes

The primary outcome of this study is the total number of women who met the inclusion criteria and go on to receive treatment following randomisation based on the results of their FIBTEM A5 tests.

Secondary outcomes included: *(but was not analysed due to small numbers recruited)*

- Estimated blood loss post randomisation
- Overall requirement for blood and blood products
- Total estimated blood loss
- Fibrinogen level as per Clauss method at baseline, 30 min, 2 hours and 4 hours post intervention
- Need for additional haemostatic interventions including balloon tamponade, uterine artery embolisation, surgical arterial ligation and hysterectomy
- Admission to the high-dependency or intensive care units
- Mortality
- Overall length of hospital stay
- The incidence of adverse events, including thromboembolic, up till 6 weeks post randomisation.
- The incidence of transfusion related adverse outcomes including Transfusion Associated Cardiac Overload (TACO) and Transfusion Related Acute Lung Injury (TRALI).
- Safety outcomes:
    - Adverse events from randomization until discharge
    - All serious adverse events
    - Rate of thromboembolic events at 3 months (including deep vein thrombosis, pulmonary embolism, cerebral sinus vein thrombosis, pelvic vein thrombosis, myocardial infarction

- Other adverse drug reactions (anaphylaxis or allergic reaction, fever, headache, nausea or vomiting).

Inclusion Criteria

- Women aged 18 years and over
- Estimated blood loss greater than 1500 ml <4 hours postpartum, not responsive to first line uterotonic therapy and/or manual uterine rubbing/compression and evidence of ongoing haemorrhage at the time of randomisation.
- FIBTEM A5 ≤15 mm on ROTEM POC testing

Exclusion Criteria

- Pre-existing coagulation disorders (e.g. liver disease)
- Women with confirmed venous thromboembolism occurring in the last 12 weeks of pregnancy
- Documented allergy to any of the study medications or their constituents
- Women refusing traditional blood products
- Administration of anti-coagulant therapy in the previous 12-24 hours
- Women who have had a documented fibrinogen level (Clauss) of <2 g/L prior to randomisation.
- Women whose FIBTEM A5 level is <8mm at randomization – (these women and those with a fibrinogen level < 2 g/L should receive immediate replacement of fibrinogen and cannot be included in the study).
- Women who wish not to participate in any research trials or who have expressed that they do not wish to participate in this trial.

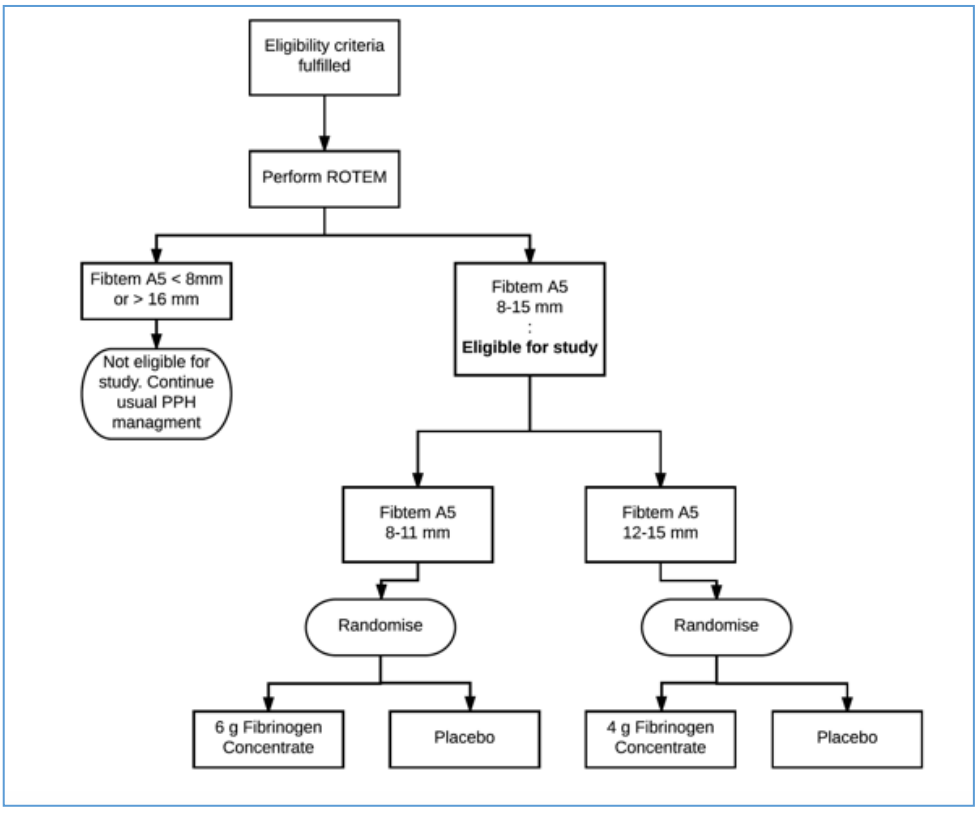

Figure 1: Randomisation process based on FIBTEM A5 result

Standard of care is in accordance with Ministry of Health National Consensus Guideline for Treatment of Postpartum Haemorrhage (figure) and the National Women's Health Guideline on Postpartum Haemorrhage Prevention and Management. Treatment of PPH is otherwise left at the discretion of the attending anaesthetists and obstetricians, in accordance with their usual practice.

Results (limited interpretability due to very small numbers)

Our Ethics committee consented due to the nature and unpredictability and allowed for enrolment with Ethical approval for this study with two physician consent at time of enrollment. Ethics has been obtained from the Auckland District Health Board Research Review Committee (approval reference: 16/NTB/35). The study was conducted in compliance with the Declaration of Helsinki.

Postpartum haemorrhage is a sudden and unanticipated complication of delivery. Obtaining consent for research purposes in the emergency setting is difficult given the often stressful and time-pressured nature of the situation. Therefore, eligible women were enrolled into the study by a two-physician decision at the time of the PPH. Consent for data collection and analysis was obtained from the women at a later date, after the initial management of the PPH. All three patients consented to the continued use of their data for the study.

For the period 02/04/2017 until 12/11/2017 we had 300 women with bleeds of more than 1500mls, of those only 28 was screened for eligibility for enrollment to the trial. Of the 300 women presenting with bleeds more than 1500mls, 63 had bleeds of more than 2500mls. None of the women screened had an A5 measured by ROTEM of < 12mm and therefore did not qualify for the 6g Fibrinogen arm (Fig 1).

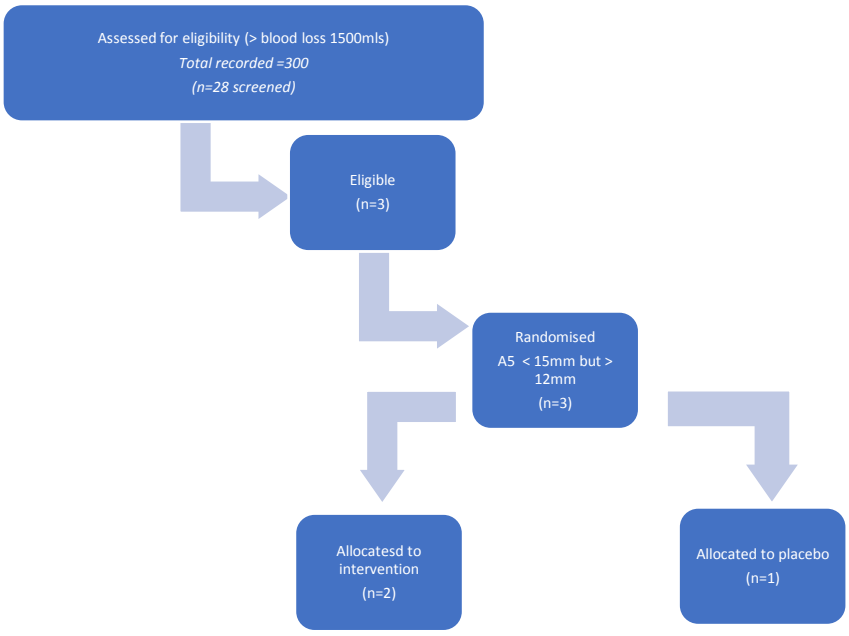

Fig 2. Screening and Recruitment for FibUpFront PPH.

Issues with recruitment was research staffing issues, quickly developing PPH as well as fast resolving PPH (bleeding stopped), technical issues with ROTEM, initially time taken to mix and administer the study drug (definitive learning curve regarding quick mixing and administration) or preference by procedural anaesthetist to give earlier blood products or cryoprecipitate.

We present the results as case type reports for each individual case and only report observed findings, unfortunately no conclusion can be made in terms of our secondary outcomes. We did however demonstrate that this is a very difficult situation to recruit to, our primary aim was to review whether it was feasible to use the FIBTEM A5 test to guide the administration of fibrinogen concentrate in women with severe and persistent PPH.
Similar findings for the Danish study FibPPH by Wikkelsoe et al in 2015[8] where consent was an issues and they were unable to recruit those women with bigger bleeds, the average Fibrinogen level for the group was 4.2 g/dl and therefore demonstrated that pre-emptive treatment with fibrinogen in women with normal fibrinogen does not reduce bleeding in PPH. The OBS 2 Trial group[16] commented that further studies are required to investigate the subgroup of women who presents with A5 < 12mm with ongoing PPH. They however found recruitment difficult and suggested they will not be running such a trial in the future due to resource limitations and consent restraints.

Please note Fibrinogen referred to below as per Clauss laboratory technique.

Case no. 1: Total PPH 2500mls.

29-year-old G3P1 BMI 55kg/m^2 (152cm and 128kg) with history of anaemia during pregnancy, intra-venous iron administered one month prior to delivery date and diagnosed with Gestational DM.
Her Hb on day of delivery was 115g/dl with normal platelet count.
Trend of Hb recorded during and post PPH bleed:
11:30 am 115g/dl
22:10 pm presenting to theatre with 1400ml PPH for EUA, 2nd tear vaginal tear repair and Bakri balloon insertion.
Labour ward blood loss mostly determined by visual estimation, in theatre it is measured and all swabs weighed (gravimetric technique).
A general anaesthesia was performed with rapid sequence induction, rapid FBC and coagulation screen was sent at 22:10 pm.
The ROTEM A5 available at 22:15pm with A5 = 14mm meeting criteria for enrolment.
Surgery started at 22:25 after general anaesthesia ready by 22:20pm
Study drug was administered at 22:55pm (placebo)
One unit of RBC was administered at 23:00pm , total crystalloid Plasmalyte 148: 2000mls.
Case completed at 23:08pm. Bleeding stopped shortly after study drug administered.
Fibrinogen was checked prior to arrival in theatre at 21:40pm presumably when booked for theatre after PPH declared.
Fibrinogen 4.2 g/dl and Hb 107 at this stage.

After induction of Anaesthesia in theatre recorded laboratory Hb 90g/dl and Fibrinogen 3.2g/dl (A5 was 14mm at this time which roughly correlates with OBS 2 trial estimation that A5 14mm = 2.8 g/dl)
The next Hb available at 05:00 am the next day 89g/dl with Hb at discharge 79g/dl, she received another one unit of RBC during her post-partum stay. Unfortunately no other ROTEM POC tests or coagulations screens were recorded for this patient. .
No other complications after discharge and no VTE recorded.

Case no.2 : Total PPH 3200 mls

37 year old G6P1 (height 160cm and weight 76kg BMI 29.7 kg/m^2) diagnosed with placenta accrete for elective midline laparotomy, caesarean delivery followed by caesarean hysterectomy.
This patient had a previous morbidly adherent placenta with PPH 5230mls two years prior. Her ferritin was 28mcg/L and Hb 98g/dl at the start of the case, initially under combined spinal epidural but then induction of general anaesthesia as PPH evolved.

Three units RBC was administered shortly after delivery at 09:21am and 2grams of tranexamic Acid given intra-venously – prior to study drug administration.
0945am: Hb 97g/L , Platelets 207 and Fibrinogen 2.9 g/dl
10am : Study drug given (intervention drug)
10:10am Fib 2.7g/dl, Hb 104 g/L and Platelets 162
10: 15am Blood loss recorded as 3200mls
10:15am Cell saver blood 760mls administered to patient as well as one further unit of RBC.
10:45am Fibrinogen 3.9g/ dl, Hb 115g/L and Platelets 165.

Transfer to Intensive care unit stable and uneventful recovery with discharge Hb 120g/dl.
No recorded VTE post operatively.

Rotem data A5 :

09:45am 15mm (at time of enrolment)/ laboratory Fibrinogen recorded as 2.9g/dl.
10:15am 14mm (shortly after study drug administered)
10:50am 20mm/ laboratory fibrinogen recoded as 3.9g/dl – bleeding stopped.
14:19pm 19mm (in recovery post operatively)
Next day 10:36am 19mm

Case no 3: Total PPH 3000mls

28yr G1P0 , uncomplicated pregnancy had Intra-venous Iron replacement prior to delivery for low ferritin and anaemia.

Presented for:

Examination under anaesthetic for on-going postpartum haemorrhage requiring suturing of vaginal tears - 1600mls PPH in labour ward.

11:20am Hb 125g/L, platelets 215 (blood loss 1600mls)

12pm General anaesthesia, tranexamic acid 500mg intra-venously administered prior to induction.

12:41 pm *Study drug administered (Intervention drug)*

12:50pm Hb 93g/dl, platelets 218

13:30 Fibrinogen 4.1g/dl (bleeding stopped)

18:45pm Hb 82g/L

No blood products given intra-operatively

Next day 05:45am Hb 75g/L

13:45 Hb 72g/L – one unit RBC administered.

Developed sepsis with positive blood cultures and elevated CRP during next fer days post-partum.

Her Hb dropped to 63g/dl two days later and required further RBC administration, on discharge Hb 92g/dl.

No VTE recorded post-operatively.

Conclusion and updates / Evolution of management of PPH to targeted management.
Refer to publication : Prevention and treatment of postpartum haemorrhage: focus on haematological aspects of management
Claire McLintock
Hematology 2020, p542
ASH Education Program

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WOMAN Trial Collaborators
PMID: 28456509 , PMCID: PMC5446563, DOI: 10.1016/S0140-6736(17)30638-4
Free PMC article

16. Viscoelastometric-guided early fibrinogen concentrate replacement during postpartum haemorrhage: OBS2, a double-blind randomized controlled trial
P. W. Collins1, *, R. Cannings-John2 , D. Bruynseels3 , S. Mallaiah4 , J. Dick5 , C. Elton6 , A. D. Weeks7 , J. Sanders8 , N. Aawar2 , J. Townson2 , K. Hood2 , J. E. Hall 9and R. E. Collis 3on behalf the OBS2 study team†
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