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REVIEW ARTICLE

Management of postpartum haemorrhage: from research into practice, a narrative review of the literature and the Cardiff experience

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ABSTRACT
Postpartum haemorrhage (PPH) is caused by obstetric complications but may be exacerbated by haemostatic impairment. In a 10-year programme of research we have established that haemostatic impairment is uncommon in moderate PPH and that fibrinogen falls earlier than other coagulation factors. Laboratory Clauss fibrinogen and the point-of-care surrogate measure of fibrinogen (FIBTEM A5 measured on the ROTEM® machine) are predictive biomarkers for progression from early to severe PPH, the need for blood transfusion and invasive procedures to control haemorrhage. Fibrinogen replacement is not required in PPH unless the plasma level falls below 2 g/L or the FIBTEM A5 is below 12 mm. Deficiencies of coagulation factors other than fibrinogen are uncommon even during severe PPH, and ROTEM® monitoring can inform withholding FFP safely in most women. In the absence of placental abruption, clinically significant thrombocytopenia is uncommon unless the platelet count is low before the bleed started, or very large bleeds (>5000 mL) occur. Measuring blood loss is feasible in routine practice during PPH and is more accurate than estimation. These research findings have been collated to design an ongoing quality improvement programme for all maternity units in Wales called OBS Cymru (Wales) (The Obstetric Bleeding Strategy for Wales).

Keywords: Postpartum haemorrhage; Viscoelastometry; Fibrinogen; Coagulopathy; Quality improvement

Aims

The aims of this review are to: summarise the literature relating to the coagulation profile of women with PPH, describe how point-of-care (POC) based algorithms can provide timely information for clinicians with the potential to reduce blood product use and describe how protocols used during research can have a positive impact on all patients, with fewer major complications and massive blood transfusions.

Background

The incidence of postpartum haemorrhage (PPH) is increasing in many countries and is the most common cause of death for women of child-bearing age worldwide.[1–6] Bleeding is caused by obstetric complications but may be exacerbated by haemostatic impairment.[7] It is widely assumed that haemostatic impairment often complicates PPH and consequently, when coagulation test results are unavailable, guidelines endorse the use of formulaic infusion of fresh frozen plasma (FFP) or cryoprecipitate in fixed ratios with red blood cells (RBC),[8–10] based on evidence extrapolated from non-pregnant adult major trauma. It is questionable whether these data should be applied to the management of PPH, given the very different baseline coagulation status of the groups.

High-quality studies describing coagulopathies associated with PPH are limited, however it is probable that they result from complex interactions between dilution, local consumption, disseminated consumption and increased fibrinolysis.[7] The nature of haemostatic impairment varies according to the cause of the bleed and is affected by complications of pregnancy such as preeclampsia, sepsis and impaired liver function. The physiological adaptations of pregnancy result in a pro-thrombotic state at term with increased levels of

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pro-coagulants and decreased anti-coagulants. In particular, at term the fibrinogen level is 4–6 g/L, compared to 2–4 g/L in healthy non-pregnant women.[11,12] Until recently it was not known whether fibrinogen replacement during severe PPH should target 'normal for term' (>4 g/L), 'normal for non-pregnancy' (>2 g/L), or somewhere in between. This is important when considering the role of FFP in treating coagulopathy in PPH.[13]

Fresh frozen plasma contains about 2 g/L of fibrinogen, whereas the average fibrinogen level in a woman with 1000–2000 mL blood loss due to atony or trauma is about 4 g/L.[14] This means that in most cases, infusion of FFP during PPH would reduce fibrinogen by dilution.[15] This implies that unmonitored fixed-ratio infusions of FFP would expose many women to FFP without any prospect of improving haemostasis. Studies exploring the use of fixed-ratio infusions of FFP:RBC during PPH report fewer women developing laboratory evidence of coagulopathy, however, some of these studies describe multiple interventions including early involvement of senior staff.[16–20] When guided by viscoelastometric POC testing (VE-POCT), we have shown that FFP can be withheld safely in women experiencing moderate to severe PPH, without development of clinically significant haemostatic impairment.[21] A recent review suggested that FFP was not the optimal way to replace fibrinogen during PPH.[13]

Postpartum haemorrhage observations and research advancements in Cardiff, Wales

Using fibrinogen concentrate to treat PPH with hypofibrinogenemia

We observed that some women experiencing severe PPH had laboratory fibrinogen levels <1 g/L associated with clinical haemostatic impairment. At this time the Royal College of Obstetrics and Gynaecology (RCOG) guidance was to maintain fibrinogen >1 g/L using cryoprecipitate.[22] Thawing and infusing cryoprecipitate takes time, delaying correction of the coagulopathy. At our centre and others, we addressed this issue by infusing fibrinogen concentrate which rapidly increased the fibrinogen level and was associated with the clinical impression of improvement in haemostasis.[23–26] We infused between 2 and 4 g fibrinogen concentrate to six women over a two-year period (approximately 12 000 deliveries) with clinical improvement, although the data on all women with low fibrinogen was not collected at this time.[24] These early reports reflected a reactive rather than preventative strategy to haemostatic impairment. More recent studies from other groups have reported improvements in haemostasis with the use of fibrinogen concentrate to treat hypofibrinogenaemia.[27,28] These case reports are selective and prone to reporting bias, but were sufficiently encouraging to promote further investigation.

The role of standard coagulation tests and Clauss fibrinogen for detection of coagulopathy in PPH

To investigate the effect of severity of bleeding on standard coagulation tests, we evaluated a consecutive cohort of 18 501 women who delivered at our unit over three years. Blood test results of women with PPH >1500 mL (n=456, 2.5%) were reviewed. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) usually remained within the normal range until blood loss reached 4000–5000 mL.[29] This reflected sufficient coagulation factors for haemostasis until the bleed volume reached 4000–5000 mL, and infusion of FFP up to that time was unlikely to have improved haemostasis. In contrast, fibrinogen fell rapidly as blood volume loss increased, such that by 2000 mL the majority of cases had a fibrinogen below the normal range for term (4 g/L), and at 4000 mL most women had a fibrinogen <2 g/L.[29] A UK Obstetric Surveillance System (UKOSS) survey of women transfused ≥8 units of RBCs (average blood loss 6000 mL) also found that many more women had a fibrinogen <2 g/L than an abnormal PT or aPTT, both at first presentation and when coagulation was at its worst.[30] The likelihood of hypofibrinogenaemia depended on the cause of bleeding and was most often associated with placental abruption.[14,30] Taken together, these studies indicate that the standard coagulation tests PT and aPTT show that early depletion of coagulation factors is uncommon in obstetric haemorrhage, and that plasma fibrinogen level may be a more important therapeutic target.

Fibrinogen and FIBTEM as biomarkers to predict severity of progression of postpartum haemorrhage

In an influential paper, Charbit et al. measured multiple coagulation factors in women experiencing PPH. Fibrinogen level was the only independent predictor of progression to severe PPH and a fibrinogen <2 g/L had a 100% positive predictive value for progression from moderate to severe PPH.[31] This finding was confirmed by us in retrospective and prospective studies and by other groups investigating PPH in multiple cohorts using diverse methodologies (Table 1).[14,31–35] These studies now show convincingly that plasma Clauss fibrinogen, measured early during PPH, is a biomarker for predicting progression to severe PPH.

Although plasma Clauss fibrinogen levels yield useful information, it takes at least an hour for a result to be available, limiting its utility to direct practice during PPH. Visco-elastomeric POC tests generate a surrogate measure of fibrinogen with results available within 10 minutes of venepuncture.[36–38] We initiated the Obstetric Bleeding Study 1 (OBS-1) to investigate whether a FIBTEM assay, performed on the ROTEM® machine (Werfen, Barcelona, Spain), could predict progression from early to severe PPH. A consecutive cohort of 346 women with PPH >1000 mL was enrolled. At

Table 1 Studies investigating the association between fibrinogen and progression of postpartum haemorrhage

Study	N	Study design			Fibrinogen g/L		
		Time of fibrinogen assay	Outcome defining progression of PPH	Descriptive statistic reported	No progression of PPH	Progression of PPH	ROC AUC (95% CI)
Charbit[31]	129	Infusion of uterotonic after manual exploration of uterus	Invasive procedure to control bleeding, fall in Hb ≥4 g/L or ≥4 units RBC	Median (IQR)	4.4 (3.7–5.1)	3.3 (2.5–4.2)	0.75 (CI NR) p <0.0001
Cortet[32]	738	Diagnosis of PPH	Invasive procedure to control bleeding, fall in Hb ≥4 g/L, ≥4 units RBC or admission to ITU	Mean (SD)	4.2 (1.2)	3.4 (0.9)	0.66 (0.64–0.68)
Poujade[55]	98	Variable time before embolisation	Success of radiological embolisation	Mean (SD)	2.9 (1.3)	1.8 (0.9)	NR
Gayat[34]	257	Variable time before procedure	Invasive procedure to control bleeding	Median (IQR)	2.7 (2.1–3.5)	1.8 (1.1–2.5)	0.83 (±0.03)*
de Lloyd[33]	240	First clinical concern during PPH	≥2500 mL blood loss	Mean (SD)	4.4 (1.1)	3.1 (1.0)	0.85 (0.78–0.93)
Collins[14]	346	1000–1500 mL blood loss	Transfusion of ≥8 units allogeneic blood products	Median (IQR)	3.9 (3.2–4.5)	2.1 (1.8–3.4)	0.82 (0.72–0.92)
Simon[35]	797	Before bleeding started	PPH requiring manual uterine exploration, RBC transfusion or fall in Hb ≥2 g/L	Mean (SD)	4.9 (1.0)	4.3 (1.3)	NR

Studies are shown which investigated the association of Clauss fibrinogen, taken early during a postpartum haemorrhage or before bleeding started, with progression of bleeding. Variable study designs were employed but in all cases a low Clauss fibrinogen was associated with a statistically significantly increased risk of progression. This demonstrates that fibrinogen level is a useful biomarker for predicting progression of postpartum haemorrhage, however, due to the time required to obtain a result, its clinical utility is limited. PPH: postpartum haemorrhage; Hb: haemoglobin concentration; RBC: red blood cells; NR: not reported; ITU: Intensive Care Unit; CI: confidence interval; ROC: receiver operating characteristics; IQR: inter-quartile range; SD: standard deviation; AUC: area-under-the-curve.

*In this study the ROC refers to a composite predictive tool combining fibrinogen <2 g/L, abnormal placental implantation, prothrombin ratio <50%, heart rate >115 beats per minute, troponin raised.

recruitment baseline FIBTEM was performed concurrently with a plasma Clauss fibrinogen, whilst all other routine PPH management was provided. Clinicians were blinded to the FIBTEM result but did know the laboratory fibrinogen when it became available (Fig. 1).[14]

Despite only a moderate correlation between Clauss fibrinogen and FIBTEM (r=0.59) the two parameters had an almost identical value for predicting progression. As the Clauss fibrinogen or FIBTEM fell the need for any RBC transfusion, ≥4 units RBC, ≥8 units of blood products (RBC + FFP + platelets), use of an invasive procedure or a bleed >2500 mL increased. The lower the fibrinogen or FIBTEM A5 the higher the proportion of women with poor outcomes (Fig. 2). For example, the median (IQR) fibrinogen and FIBTEM A5 of women who received ≥8 units of blood products was 2.1 (1.8–3.4) g/L and 12 (7–17) mm, respectively, compared with 3.9 (3.2–4.5) and 19 (17–23) in those who did not. FIBTEM A5 <10 mm was associated with more prolonged bleeding (median 127 versus 65 min, P=0.02), longer in level 2 care patients needing extended postoperative care with enhanced interventions and monitoring (median 24 versus 11 hours, P <0.001) and shorter time to first RBC transfusion (P <0.001). In addition, the combination of a low fibrinogen/FIBTEM, with the clinical observation that there was on-going PPH at recruitment, was a stronger predictor of these poor outcomes than either alone.[14]

The OBS-1 study confirmed that a low fibrinogen or FIBTEM A5, measured early during a PPH, was associated with progression of PPH, however it remained unknown whether correction of these parameters would improve outcome. Furthermore, the appropriate clinical target for fibrinogen or FIBTEM A5 to maintain haemostasis, and therefore when fibrinogen-containing products should be infused, was unknown.

Appropriate triggers for fibrinogen replacement during PPH

In an audit report comparing a ROTEM®-based algorithm (that infused 3 g of fibrinogen concentrate if the FIBTEM was <7 mm, or <12 mm with severe bleeding, and FFP if the Extem CT was >100 s) with the unit's previous practice of treating major PPH with shock packs (consisting of 4 RBC, 4 FFP and 1 pool of platelets), the ROTEM®-based algorithm was associated with a large reduction in FFP, cryoprecipitate and platelet usage: and fewer women needed >5 units RBCs or had transfusion associated circulatory overload or admission to ITU.[39,40] While these data were retrospective and non-randomised, the outcomes indicate that ROTEM®-guided transfusion management may be superior to an empiric massive transfusion approach for PPH. There is no information in the paper about response times to administration of blood products after adoption of fibrinogen concentrate infusions, although immediate availability of fibrinogen concentrate stored on their delivery suite may have reduced response time and therefore improved clinical outcomes.

A prospective, double-blind, randomised controlled trial led by Wikkelsoe investigated whether infusing 2 g of fibrinogen concentrate after 500–1000 mL blood loss, irrespective of plasma fibrinogen level, reduced the need for RBC transfusion and blood loss. No difference in outcomes was achieved with the empiric administration 2 g of fibrinogen concentrate for PPH showing that early pre-emptive, formulaic fibrinogen replacement was not indicated. Analysis found that the average fibrinogen level when fibrinogen concentrate had been infused was about 4.5 g/L in both arms of the study, demonstrating that this level is adequate for haemostasis during PPH.[41] The results provide good evidence against the use of empiric fibrinogen replacement during

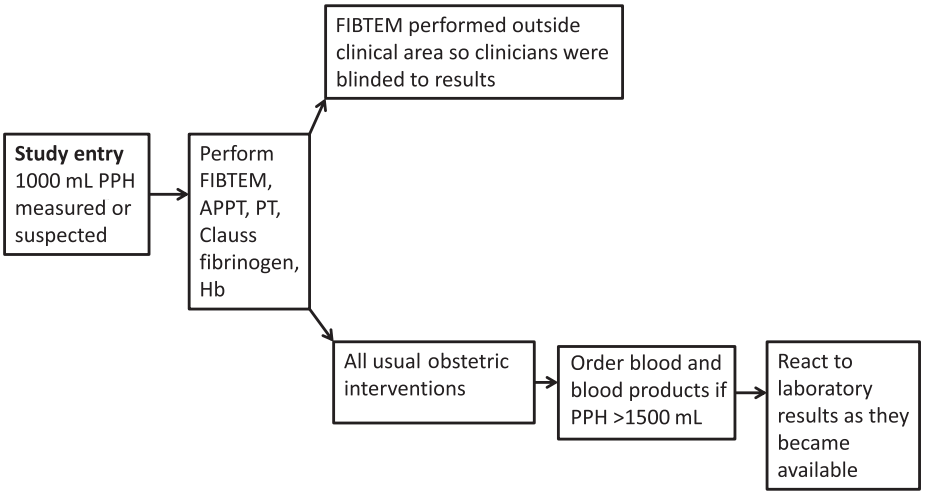

Fig. 1 Study design for OBS-1. PPH: postpartum haemorrhage. APTT: activated partial thromboplastin time. PT: prothrombin time. Hb: haemoglobin

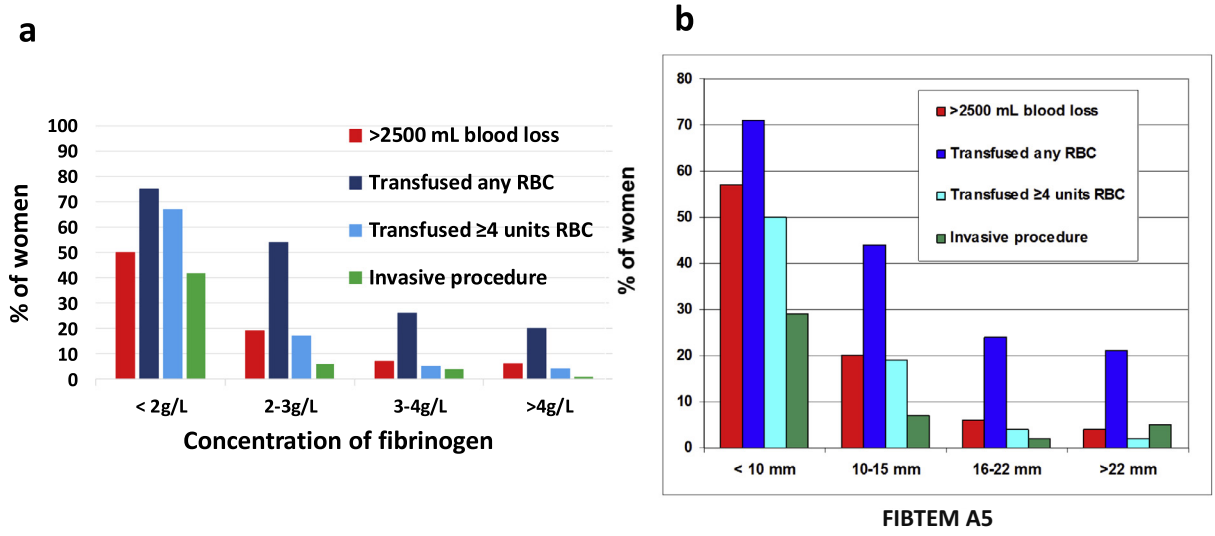

Fig. 2 The proportion of women progressing to >2500 mL blood loss (red), red blood cell transfusion (dark blue), at least 4 units red blood cell transfusion (light blue) or an invasive procedure to control the bleed (green) dependent on Clauss fibrinogen (Fig. 2a) or FIBTEM A5 (Fig. 2b) taken at 1000–1500 mL blood loss is shown. Data are derived from the Obstetric Bleeding Study-1 study. RBC: red blood cells. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

PPH in the absence of a monitored low plasma fibrinogen level, exposing many women to plasma-derived blood products unnecessarily.

In the Obstetric Bleeding Study 2 (OBS-2) we used FIBTEM A5 and observation of ongoing bleeding to guide fibrinogen and FFP replacement. In OBS-1, a FIBTEM A5 <16 mm (fibrinogen about 3 g/L), in a woman with ongoing bleeding, had been associated with progression to multiple poor outomes[14] and this was supported by other observational studies (Table 1). The OBS-2 was a double-blind, placebo controlled RCT which enrolled women with PPH >1000–1500 mL. The study investigated whether infusing fibrinogen concentrate[42] if FIBTEM A5 was <16 mm, and bleeding was ongoing, reduced blood product usage. The OBS-2 also investigated whether it was safe to withhold FFP if FIBTEM A5[43] was ≥15 mm on the assumption that a normal fibrinogen was a surrogate for adequate levels of other coagulation factors (Fig. 3a).[14,29,31]

There was no statistically significant difference in any outcome between the fibrinogen and placebo (Normal saline) groups, demonstrating that a fibrinogen of around 3 g/L is adequate for haemostasis during PPH.[44] Pre-specified subgroup analyses[43] showed that fibrinogen >2 g/L or FIBTEM A5 >12 mm were adequate for haemostasis despite severe PPH. However, if FIBTEM A5 or fibrinogen was <12 mm or <2 g/L at the time of randomisation, women in the fibrinogen group received fewer blood products and had lower blood loss after study medication compared to placebo.[44] These exploratory subgroup analyses did not reach statistical significance possibly due to the small number of women randomised with a fibrinogen <2 g/L. However these results, in conjunction with the data from Mallaiah,[39] suggest that an appropriate intervention point for infusion of fibrinogen is a FIBTEM A5 <12 mm or fibrinogen <2 g/L, and a study investigating this is warranted.

In our experience a fibrinogen level below 2 g/L is uncommon during obstetric haemorrhage. Combining data from consecutive studies and observation from our institution over the last eight years shows a rate of 1–2/1000 deliveries and a similar incidence has been observed across all units in Wales. In OBS-2, irrespective of blood loss, women with a FIBTEM A5 >15 mm or who had stopped bleeding, had FFP withheld (n=605). Median (IQR) blood loss was 1500 mL (1300–2000 mL) and none of the women developed haemostatic impairment,[21] suggesting that haemostatic impairment during PPH can be assessed accurately using VE-POCTs.

Thrombocytopenia and platelet transfusion during postpartum haemorrhage

It has been suggested that a massive transfusion protocol used for PPH should include platelets.[18,20,45,46] Guidelines recommend maintaining the platelet count above 75×10^9/L during PPH.[8,9] There are limited data on the incidence and causes of thrombocytopenia during PPH, therefore we analysed the women recruited to the OBS-1 study. In moderate to severe PPH, thrombocytopenia was uncommon, with 8/347 (2.3%) women having a platelet count $<75 \times 10^9$/L. Twelve women (3.4%) received a platelet transfusion and these fell into two

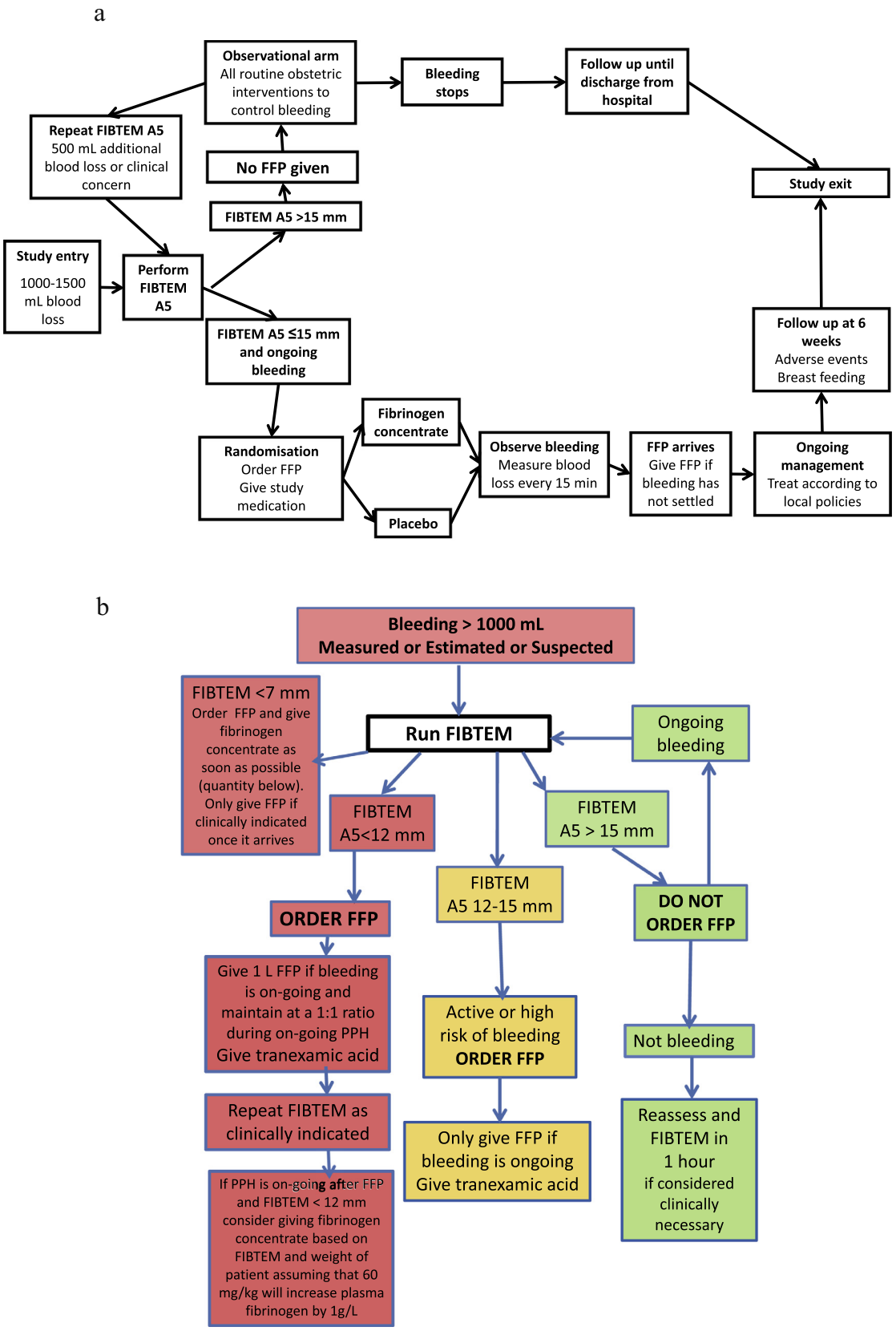

Fig. 3 ROTEM® guided blood product algorithms. Fig. 3a shows the study design and blood product algorithm used for women recruited into the Obstetric Bleeding Study-2. Fig. 3b shows the blood product algorithm used for women who were not enrolled. FFP: fresh frozen plasma.

groups. Firstly, women who were thrombocytopenic before delivery due to preeclampsia or pre-existing diseases such as immune or inherited thrombocytopenia and secondly, women with initially normal platelet counts who either had a placental abruption or bleeds >5000 mL.[47] These findings were supported by the UKOSS survey of women who received ≥8 units of RBC (median blood loss 6000 mL) where the median first platelet count taken during the bleed was 131×10^9/L and lowest was 68×10^9/L; 77% of these women received a platelet transfusion. Placental abruption was associated with the largest fall in platelet count (137 to 54×10^9/L).[30] These reports suggest that the platelet count is adequate during PPH in the vast majority of cases, and inclusion of platelets in shock packs would result in many women receiving unnecessary platelet infusions.

Measurement of blood loss after delivery and during PPH

Early recognition of PPH with measured rather than estimated blood loss is critical because clinicians often underestimate the volume of bleeding.[48] Measurement of blood loss is more accurate and is feasible in routine practice, should be started after every delivery even if the initial loss seems normal[49] and is a key recommendation in RCOG guidance.[8] We adopted the practice of gravimetric measurement of blood loss on swabs and pads with the addition of measured blood loss in conical under-buttock drapes and suction bottles during our studies to standardise patient recruitment and ensure timely escalation of care. Measurement of blood loss alone does not lead to improved outcomes during PPH,[50] but when integrated into a pathway can aid escalation of care.[20] In addition, escalation of care also needs to take into account other factors such as maternal vital signs, as bleeding can be concealed and the apparent rate of blood loss misleading, although specific guidance is not available.

Impact of obstetric bleeding studies on practice and evolving quality improvement

Between 2013 and 2015 women recruited to OBS-2 followed the study blood product algorithm (Fig. 3a) and those not recruited were treated using the local major obstetric haemorrhage ROTEM® algorithm (Fig. 3b). Since 2010 PPH outcome data has been collected at our institution as part of a quality improvement initiative. During OBS-2, RBC usage decreased by 32%, FFP usage by 86% and the number of women receiving five or more units RBC fell by 86% (Fig. 4). In addition, bleeds ≥2500 mL fell by 83% and level 3 ITU admissions (women requiring advanced respiratory support) due to PPH decreased from about four per year to none in three years. Although temporally related, it is unlikely that the intervention of fibrinogen administration was solely responsible for these improved outcomes as only seven women treated in the interventional arm had a fibrinogen <2 g/L. This implies that other factors associated with running the study and complying with protocols were influencing maternal outcomes. In order to standardise recruitment to the study, women were risk assessed, blood loss was measured rather than estimated and obstetricians and anaesthetists attended the mother's bedside to obtain consent and take study bloods as specified in the study protocol.

When OBS-2 ended in November 2015, it was expected that improved outcomes would continue. However, it rapidly became apparent that this was not the case and the end of the study coincided with an increase in large haemorrhages to rates similar to before

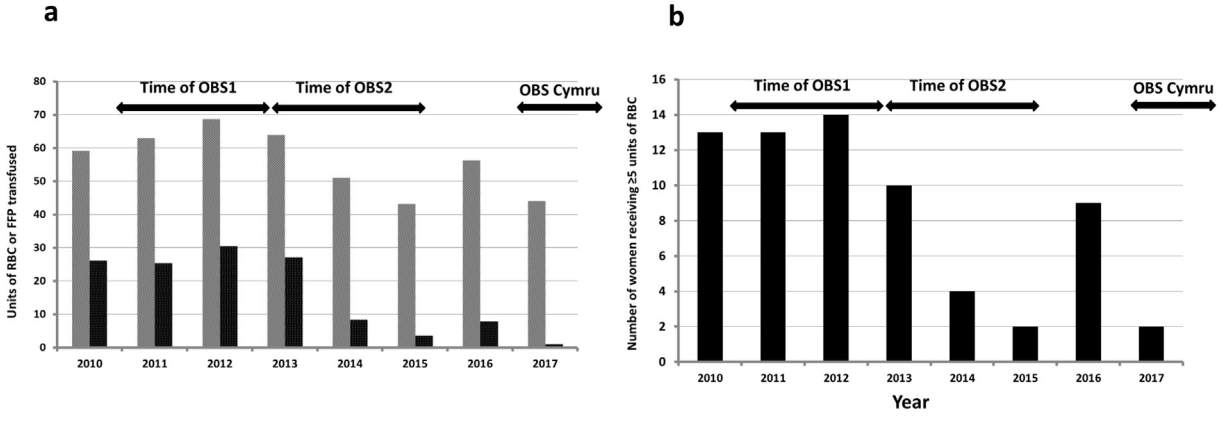

Fig. 4 Changes in transfusion practice across time in Cardiff. Fig. 4a shows the number of units of red blood cells (RBC) (grey) and fresh frozen plasma (FFP) (black) transfused for each year between 2010 and 2017. The Obstetric Bleeding Study-2 study was associated with a reduction in RBC and FFP transfusion which increased after the study finished and fell again once the Obstetric Bleeding Study for Wales Cymru was initiated. Fig. 4b shows data for the number of women who received at least 5 units of RBC, representing a subgroup of very severe postpartum haemorrhage. A similar temporal trend was observed

the study (Fig. 4). A systematic review of 16 large bleeds over a six-month period identified common themes including a return to estimating blood loss, the multidisciplinary team not attending the mother's bedside in a timely fashion and POCTs not being performed early in the course of the haemorrhage. This resulted in delayed recognition of a deteriorating patient and delayed escalation of obstetric intervention.

Quality improvement initiatives in postpartum haemorrhage

In 2011 Shields described a quality improvement programme that standardised care during PPH. This included risk assessment followed by an escalating three-stage approach based on 500, 1000 and 1500 mL blood loss and/or clinical signs. This stepwise, prescriptive approach required accurate contemporaneous measurement rather than estimation of blood loss and was initiated after every delivery. The protocol stipulated that a senior midwife, obstetrician and anaesthetist should attend the mother's bedside when blood loss reached 1000 mL. At 1500 mL blood loss, empirical fixed-ratio blood product transfusion was started based on data derived from trauma studies. The group noted that PPH progressed in fewer women, the number of blood products used fell and fewer women developed coagulopathy.[19] The protocol was rolled out across a region by the California Maternal Quality Care Collaborative (CMQCC) with similar results.[20] A similar quality improvement programme was initiated by The Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). Both CMQCC and AWHONN have extensive information available on their websites (http://www.awhonn.org/?page=PPH and https://www. cmqcc.org/resources-tool-kits/toolkits/ob-hemorrhage-toolkit).

These initiatives overlapped with our experiences in terms of risk assessment, measured blood loss and early escalation of obstetric care by senior clinicians. The main difference was the approach to blood product replacement, liberal fixed-ratio infusion of blood products based on data derived from trauma[19,20] versus VE-POCTs to target haemostatic therapy based on our programme of research. It is not known which of these approaches results in better outcomes and clinical trials specifically addressing the value of VE-POCTs are required to address this.

Understanding the impact of point-of-care tests of coagulation in postpartum haemorrhage

During OBS-2 ROTEM®-guided blood product replacement was introduced into routine practice at our centre for all patients. As experience increased and clinicians accepted the results as clinically reliable, management of PPH changed. If early in the bleed the ROTEM® results were normal, the bleeding must be due to a physical cause (atony, trauma or retained placental tissue) and not coagulopathy. This knowledge facilitated early targeted escalation of obstetric care and, if necessary, involvement of a more experienced colleague. If coagulation was abnormal early in the bleed the mother was immediately identified as high risk. Early coagulopathy in such cases raises suspicion of delayed resuscitation, placental abruption or amniotic fluid embolus. The mother required urgent treatment for coagulopathy, almost always with fibrinogen replacement, and escalation of obstetric management to address the underlying cause of bleeding. This binary classification helped the team focus on the most important clinical problem and our impression was that VE-POCTs facilitated behavioural change of the multidisciplinary team.

A National Institute for Health and Care Excellence review of VE-POCT during PPH focused only on blood and blood product usage (https://www.nice.org.uk/guidance/dg13). Our experience is that VE-POCTs can act as a trigger around which care can be structured by encouraging clinicians to attend the bedside early. The VE-POCT results influence decision making and, if normal, allow the obstetrician to focus on managing the obstetric cause of bleeding while the anaesthetist concentrates on appropriate resuscitation and blood product replacement. Our observation, supported by the findings from OBS-2 and other retrospective observational studies,[27,28,39,40,44] is that in the small number of women who are identified as having a fibrinogen <2 g/L or FIBTEM A5 <12 mm, rapid correction of hypofibrinogenaemia with fibrinogen concentrate improves haemostasis and is advantageous, although large prospective trials are needed to verify these findings.

Local quality improvement initiatives

Improved local clinical outcomes may be a consequence of multiple inter-related factors. These included risk assessment of all women, cumulative measurement of blood loss and ensuring that an experienced midwife, obstetrician and anaesthetist attend the mother at 1000 mL blood loss with ROTEM® assessment of coagulation for all women whether they were enrolled into the OBS-2 study or not. We do not know which one of these interventions improves outcomes and it is likely to be a combination of all of these factors. Over a one year period (2017, 18 months after finishing the OBS-2 trial) in our tertiary referral centre, 2.8/1000 women had a PPH >2500 mL, a blood transfusion of ≥ 5 units RBC or received FFP. When compared with the published data from Healthcare Improvement Scotland, where an overall rate of 6/1000 was reported, our results fall below three standard deviations from the mean.[2] We are currently seeking to replicate these improvements across Wales.

All Wales quality improvement programme: OBS Cymru (Obstetric Bleeding Strategy for Wales (Cymru))

The OBS Cymru (http://www.1000livesplus.wales.nhs.uk/OBS-cymru) is a registered quality improvement initiative that aims to reduce maternal morbidity due to PPH across Wales. Wales has a population of 3.1 million and delivers 30 000 women per year in 12 consultant led units (CLU), with between 500 and 6000 deliveries per annum in each CLU. The project aims to reduce rates of major PPH and blood transfusion, level 3 ICU care and hysterectomy due to PPH.

The OBS Cymru intervention

The key to OBS Cymru is to limit the number of moderate bleeds that progress to severe haemorrhage and so reduce maternal morbidity. The project focused on four key elements which draw on the quality improvement work from other groups[19,20] and the lessons learnt from our research programme.

1. Risk assessment of all women: potential risk factors for PPH are flagged on admission to delivery suite and with on-going risk assessment during labour.
2. Cumulative gravimetric measurement of blood loss after every delivery: to facilitate escalation of care with specific actions required at 500, 1000 and 1500 mL blood loss.
3. Multidisciplinary care with a senior midwife, obstetrician and anaesthetist attending the bedside at 1000 mL blood loss.
4. ROTEM®-guided blood product replacement using an algorithm derived from the results of OBS-2.

These themes are embedded into clinical practice using a number of interventions and tools (available at http://www.1000livesplus.wales.nhs.uk/OBS-cymru). A PPH proforma describing an escalating four-stage approach was developed and is placed in all mothers' notes on admission to delivery suite. (Specific paperwork which describes all actions and interventions which should occur as PPH progresses and also acts as a template for scribing the events).

- Stage 0: risk assessment for all women in labour (on admission and as labour progresses).
- Stage 1: at >500 mL after a vaginal birth a senior midwife is informed, the cause of bleeding assessed and initial treatment instituted.
- Stage 2: at >1000 mL a senior midwife, obstetrician and anaesthetist attend the bedside to assess and escalate management as appropriate. Samples for ROTEM®, bedside lactate and haemoglobin, FBC and coagulation screen are taken and tranexamic acid is given.
- Stage 3: at >1500 mL with on-going bleeding the consultant obstetrician and anaesthetist are informed. The major obstetric haemorrhage protocol is activated and ROTEM®-guided blood product replacement instituted whilst medical and surgical treatments are continued.

This is a complex intervention and so its impact is being assessed according to Medical Research Council guidance.[51] The step-wise interventions have been incorporated into an all Wales PPH guideline (http://www.wisdom.wales.nhs.uk/sitesplus/documents/1183/Post%20Partum%20Haemorrhage_Maternity%20Network%20Wales%20All%20Wales%20Guidelines_2017.pdf) and are based on the Royal College of Obstetrics and Gynaecology (RCOG) green-top guidance[8] and incorporate the OBS Cymru approach.

Data are collected prospectively on all PPHs >1000 mL in Wales, to be compared with retrospective data collected from the units. It is too early to assess whether key markers of severe PPH are changing; this information will be reported at the completion of the project in 2019.

OBS Cymru ROTEM® guided algorithm

The OBS Cymru ROTEM®-guided blood product algorithm is shown in Fig. 5 (http://www.oaa-anaes.ac.uk/assets/_managed/cms/files/Guidelines/ROTEM%20Protocol.pdf). At 1000 mL blood loss with ongoing bleeding FIBTEM A5 and EXTEM CT, bedside venous lactate and haemoglobin are performed and FBC and coagulation sent to the laboratory. Intravenous tranexamic acid is given. The WOMAN trial showed that tranexamic acid, given within three hours of delivery, reduced death due to bleeding without an increase in thrombotic or other adverse events,[52] so our algorithm infuses tranexamic acid as soon as PPH is recognised or at the latest 1000 mL. The rationale for early ROTEM® testing is not only to rapidly identify the small number of women who need haemostatic support, but to reassure the obstetrician that coagulation is normal and focus treatment on obstetric causes of bleeding. Haemostatic blood product replacement initially focuses on fibrinogen. If FIBTEM A5 is ≤12 mm or Clauss fibrinogen <2 g/L, fibrinogen concentrate is given. Fibrinogen concentrate is not licensed for this indication in the UK and an alternative, as recommended by RCOG, is to infuse cryoprecipitate.[8] The recommendations on fibrinogen replacement are based on data from OBS-2 and the Liverpool PPH algorithm.[39,40,44] The target is to maintain the fibrinogen >2 g/L which is supported in the 2016 RCOG guideline.[8,9] If the EXTEM CT is prolonged above the normal range (75 s based on local validation) or the PT/aPTT is above the normal range, after fibrinogen replacement, 15 mL/kg FFP is infused based on RCOG guidance and OBS-2 data.[8,44] Platelets

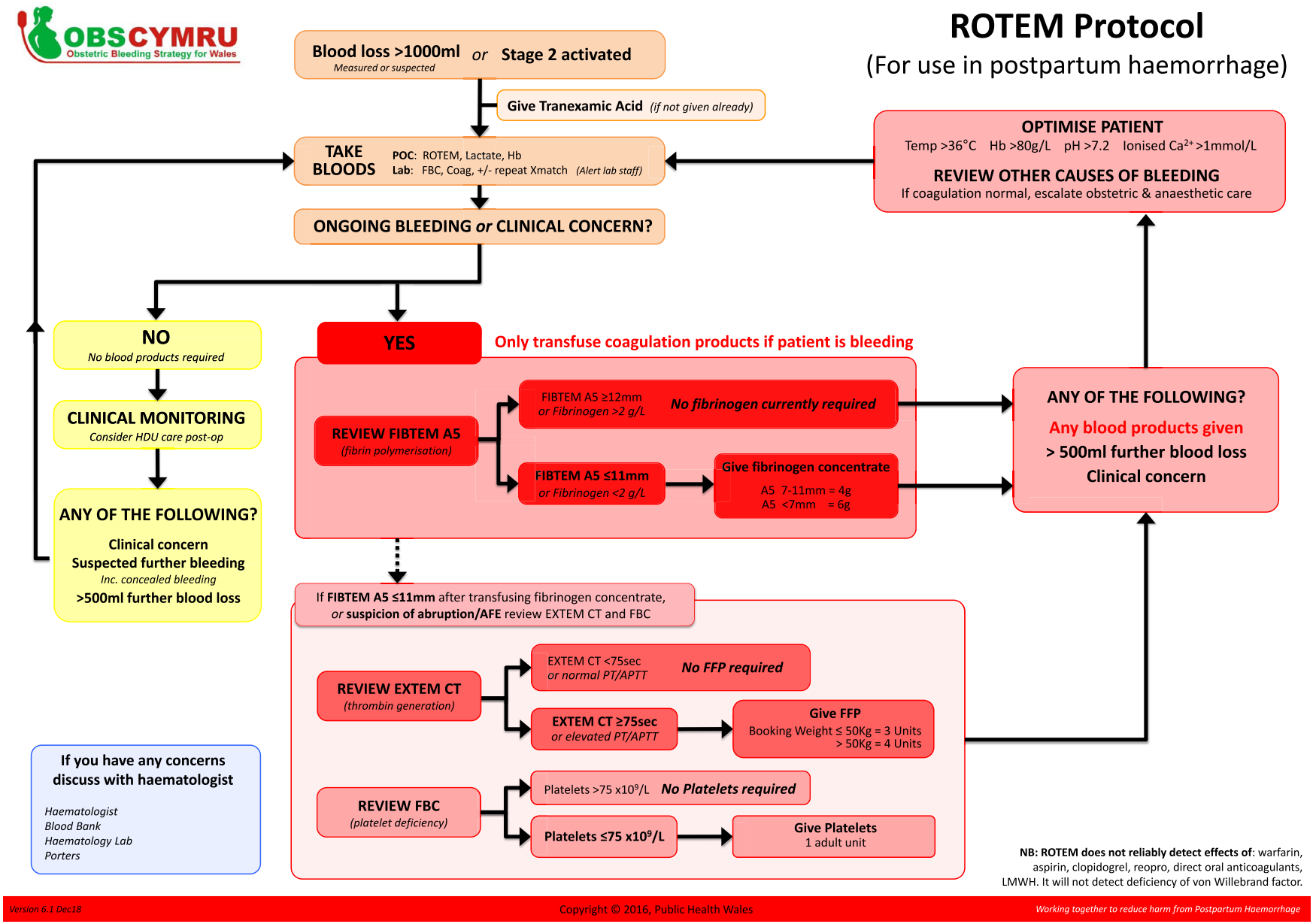

Fig. 5 OBS Cymru blood product algorithm

are transfused if $<75 \times 10^9$/L based on RCOG guidance.[8] Because coagulopathy can evolve rapidly during PPH we repeat ROTEM® and laboratory testing every 500 mL or every 30 min during ongoing bleeding, or at any time for clinical concern. Tests are repeated after blood products are given to assess response.

The future – questions to be addressed

The role of VE-POCTs in the management of PPH remains debated[53,54] and definitive evidence is lacking. We hypothesise that it is the combined effect of the early recognition of bleeding, triggering timely interventions incorporating VE-POCTs and a management strategy involving the whole multidisciplinary team, that is the key to preventing progression of PPH and minimising morbidity. A study comparing such an approach utilising early VE-POCT, with accepted standard care based on laboratory tests of coagulation, is now necessary although this would necessitate large multi-centre studies. It may also be possible to partially address some of these questions by specifically studying high risk surgical procedures such as women having a caesarean section for placenta previa or women who present with abruption.

Data on the cost effectiveness of such an approach is important if this is to be used more generally within a variety of health care settings. We suggest that qualitative assessment of the impact of the intervention on team dynamics and behaviour should also be studied. A multinational group of interested researchers may be required to address these issues.

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Declarations of interest

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