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# Original Article

## Introduction of an algorithm for ROTEM-guided fibrinogen concentrate administration in major obstetric haemorrhage

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### Summary

We compared blood component requirements during major obstetric haemorrhage, following the introduction of fibrinogen concentrate. A prospective study of transfusion requirements and patient outcomes was performed for 12 months to evaluate the major obstetric haemorrhage pathway using shock packs (Shock Pack phase). The study was repeated after the pathway was amended to include fibrinogen concentrate (Fibrinogen phase). The median (IQR [range]) number of blood components given was 8.0 (3.0–14.5 [0–32]) during the Shock Pack phase, and 3.0 (2.0–5.0 [0–26]) during the Fibrinogen phase ($p = 0.0004$). The median (IQR [range]) quantity of fibrinogen administered was significantly greater in the Shock Pack phase, 3.2 (0–7.1 [0–20.4]) g, than in the Fibrinogen phase, 0 (0–3.0 [0–12.4]) g, $p = 0.0005$. Four (9.5%) of 42 patients in the Shock Pack phase developed transfusion associated circulatory overload compared with none of 51 patients in the Fibrinogen phase ($p = 0.038$). Fibrinogen concentrate allows prompt correction of coagulation deficits associated with major obstetric haemorrhage, reducing the requirement for blood component therapy and the attendant risks of complications.

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### Introduction

Despite the decline in mortality due to major obstetric haemorrhage [1], it remains the most frequent cause of major morbidity in the obstetric population [2], leading to postpartum hysterectomies and intensive care admissions. Major obstetric haemorrhage is often associated with coagulopathy of dramatic onset, the severity of which varies depending on the cause, with varying contributions from dilution as well as the consequences of consumption of coagulation factors.

Fibrinogen represents 85–90% of the whole amount by weight of plasma coagulation factors, and is the first to fall below a critical level during bleeding and haemodilution [3]. Fibrinogen depletion in early postpartum haemorrhage (PPH) was the single variable independently associated with progression to a severe PPH [4, 5]. Early detection and aggressive correction of this depletion may be crucial to effective PPH management. At the Liverpool Women's Hospital, we have routinely used ROTEM® (TEM International GmbH, Munich, Germany) for near-patient testing of coagulation since April 2011, alongside our major obstetric haemorrhage pathway. The ExTEM test measures the extrinsic coagulation pathway, by the addition of tissue factor to a citrated sample of blood. The FibTEM test 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) in the third trimester of pregnancy is 15–19 mm, significantly higher

than in the non-pregnant population (10–12 mm) [6]. The MCF result is available 30–40 min after the test has started. In an earlier study, we found that clot firmness results available at 5 min (A5) showed close correlation with the subsequent MCF values [7]. We have used A5 values in our algorithm, so that decisions about the need for fibrinogen-containing products could be made soon after obtaining a blood sample. The rate-limiting step then became the time for blood products to become available from the blood bank.

In the UK, the fibrinogen replenishing products commonly used in acquired hypofibrinogenaemia are fresh frozen plasma (FFP) and cryoprecipitate. The treatment of major haemorrhage with the use of formulaic shock packs is a recent trend based on retrospective studies of military casualties, which suggested that mortality was lowest in those given a 1:1:1 ratio of packed red cells, FFP and platelets [8, 9]. A Consensus Panel of the Canadian National Advisory Committee on Blood and Blood Products examined the evidence for this approach in 2011 [10]. It concluded that the survivorship bias has probably contributed substantially to the observed reduction in mortality seen in retrospective studies, and that there was a lack of evidence to support 1:1:1 blood component ratios as a standard of care. In a civilian setting, the use of these products is associated with a time delay for crossmatch, thawing and transport. They are also associated with serious hazards of transfusion such as infection, transfusion-associated circulatory overload and transfusion-related acute lung injury.

Fibrinogen concentrate (Haemocomplettan® P; CSL Behring GmBH, Marburg, Germany) has been extensively and exclusively used in place of cryoprecipitate in major obstetric haemorrhage protocols in various countries across Europe for many years, because of its improved safety profile [11–13]. It is a pasteurised, freeze-dried product that is readily and quickly available for treatment, without the need for thawing or crossmatch. The pasteurisation process minimises the risk of viral pathogen transmission [14]. In the UK, fibrinogen concentrate is available as Riastap® (CSL Behring), which is only licensed for the treatment of congenital hypofibrinogenaemia. Riastap and Haemocomplettan P are identical in both form and preparation. We obtained local approval to use Riastap on a named-patient basis to treat haemorrhage-associated hypofibrinogenaemia within our Trust.

The initial dose of fibrinogen concentrate recommended by the manufacturers is 2–4 g for a 70-kg patient [15, 16]. We incorporated a dose of 3 g in our algorithm, which allowed further doses to be titrated according to the patient's individual response to treatment.

The aim of this study was to compare blood component requirements, complications associated with blood transfusion and patient outcomes following the introduction of fibrinogen concentrate for the management of coagulopathy associated with major obstetric haemorrhage.

## Methods

The local Ethics Committee and the Hospital Transfusion Committee approved this prospective two-phase study. All anaesthetists within the Trust received training in the use of ROTEM and major haemorrhage pathway.

Patients were included in the study if they had a major obstetric haemorrhage (estimated blood loss > 1500 ml) associated with coagulopathy (FIBTEM A5 < 12 mm, indicative of a plasma fibrinogen level of 2 $g.l^{-1}$). Patients receiving anticoagulant therapy were excluded.

Data were collected during the initial ('Shock Pack') phase of the study from April 2011 to March 2012, when major haemorrhage packs containing four units of red cells, four units of FFP and one adult dose of platelets were used to correct coagulation deficits (Appendix 1).

In July 2012, the major obstetric haemorrhage algorithm was updated, removing the blind administration of FFP from the start of the pathway. A Flowchart was added to guide interpretation of FibTEM A5 values, and assist the clinical decision to use fibrinogen concentrate (Appendix 2). Data were collected during the second ('Fibrinogen') phase of the study from July 2012 to June 2013.

Table 1 shows the outcomes that were measured during each phase of the study. The total quantity of fibrinogen was calculated by adding the average fibrinogen content of each of the blood components administered. A pooled bag of cryoprecipitate from five donors contains 1.552 g in a mean volume of 189 ml [16]. The fibrinogen

 

**Table 1** Outcomes measured during each phase of the study.

| | |
|---|---|
| Blood component requirements | Total number of blood components |
| | Proportion of patients receiving fibrinogen replenishing products |
| | Units of fresh frozen plasma |
| | Pooled bags of cryoprecipitate |
| | Total quantity of fibrinogen |
| | Number of units of red blood cells |
| | Number requiring ≥ 6 units of red blood cells |
| Patient outcomes and complications of blood component transfusion | ICU admission |
| | Transfusion-associated circulatory overload |
| | Transfusion-related acute lung injury |
| | Postpartum hysterectomy |
| | Death |

content of FFP is more variable; a typical unit contains 0.8 g in a volume of 300 ml [17].

Statistical comparison was with Mann–Whitney U-tests and Fisher's exact tests, using GraphPad Prism version 6.0d for Windows, GraphPad Software, La Jolla, CA, USA, www.graphpad.com. A value of $p < 0.05$ indicated statistical significance.

## Results

Data were collected from 42 patients in the Shock Pack phase of the study and from 51 patients in the Fibrinogen phase. There were no changes in overall patient population, surgical/anaesthetic experience, proficiency in use of the ROTEM or use of cell-salvage between the two phases.

Table 2 shows the estimated blood loss, diagnosis and surgical management of the study population. The use of blood components is shown in Figs. 1 and 2. There were significant differences between the Shock Pack and Fibrinogen phases in the total number of blood components units of FFP pooled bags of cryoprecipitate total quantity of fibrinogen and doses of platelets. A higher proportion of patients in the Shock Pack phase received fibrinogen-containing products (30/42; 71%) than in the Fibrinogen phase (21/51; 41%, $p = 0.0062$).

There was no difference in the number of units of red blood cells given in each phase. However, significantly more patients received six or more units of red blood cells in the Shock Pack (12/42; 29%) than the Fibrinogen group (5/51; 10%, $p = 0.0299$). Table 3 shows patient outcomes and complications as a result of blood component transfusion.

**Table 2** Estimated blood loss, diagnosis and surgical management of massive obstetric haemorrhage before (Shock Pack phase) and after (Fibrinogen phase) introduction of fibrinogen concentrate. Values are number, with multiple diagnoses and surgical managements.

| | Shock Pack (n = 42) | Fibrinogen (n = 51) |
|---|---|---|
| Estimated blood loss; ml | | |
| < 1499 | 10 | 12 |
| 1500–2999 | 12 | 19 |
| 3000–4999 | 8 | 7 |
| > 5000 | 3 | 3 |
| Not recorded | 9 | 10 |
| Obstetric diagnoses | | |
| Abruption | 3 | 7 |
| Placenta praevia | 5 | 1 |
| Trauma | 11 | 19 |
| Atony | 7 | 5 |
| Uterine inversion | 0 | 2 |
| Other | 15 | 18 |
| Surgical management | | |
| Hysterectomy | 6 | 3 |
| Balloon tamponade | 9 | 6 |
| Brace suture | 8 | 7 |
| Repair of trauma | 10 | 18 |
| Exploratory laparotomy | 2 | 1 |
| Other | 6 | 17 |

## Discussion

The incidence of massive obstetric haemorrhage is rising, having doubled from three per 1000 live births in Scotland in 2004, to six per 1000 live births in 2011 [2]. It is the leading cause of admission to intensive care units in women of childbearing age [18], with an emergency postpartum hysterectomy required as a life-saving measure in the most severe patients. When this procedure is performed under these circumstances, it is associated with considerable morbidity, and a patient fatality rate of 0.6% has been reported [19]. The youngest patient ever to have had a postpartum hysterectomy in our institution was 19 years of age.

We introduced an updated major haemorrhage pathway into our clinical practice, following recommendations by the North West Regional Transfusion Committee in April 2011. The aim of this pathway was to standardise investigations and treatment at the

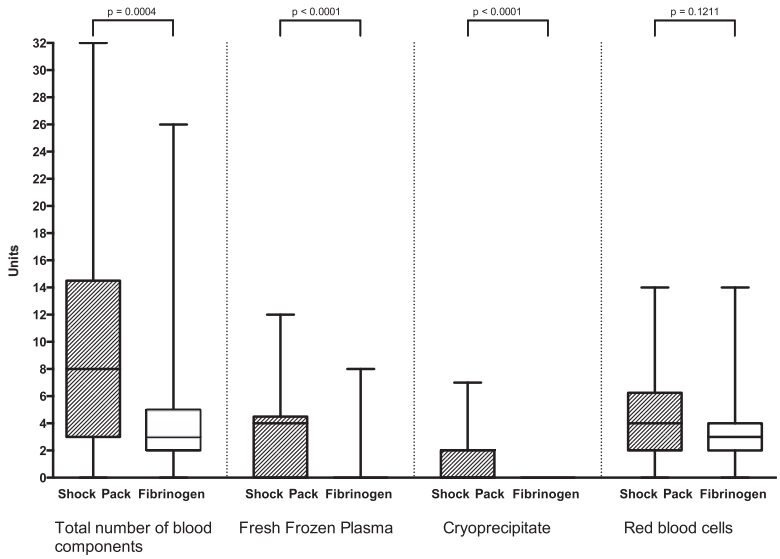


**Figure 1** Total number of blood components, units of fresh frozen plasma, pooled bags of cryoprecipitate and units of red blood cells before (Shock Pack phase) and after (Fibrinogen phase) introduction of fibrinogen concentrate. Horizontal line, median; box, IQR; whiskers, range.

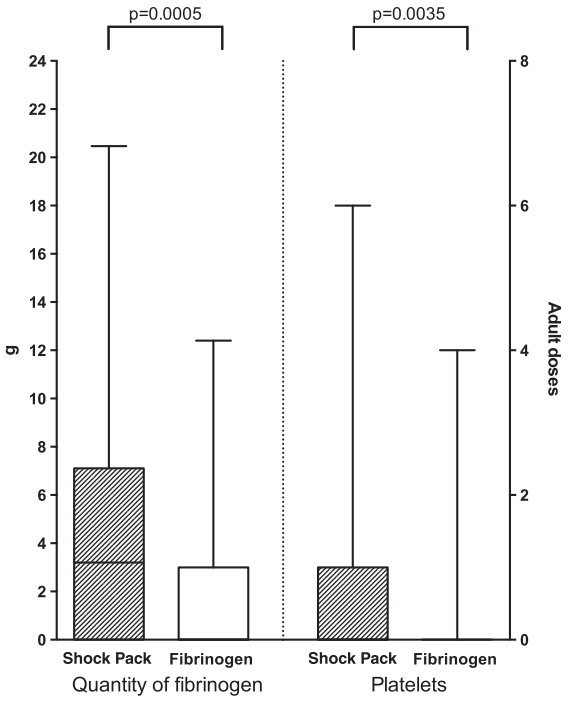


**Figure 2** Total quantity of fibrinogen and adult doses of platelets before (Shock Pack phase) and after (Fibrinogen phase) introduction of fibrinogen concentrate. Horizontal line, median; box, IQR; whiskers, range.

declaration of a major obstetric haemorrhage, clarifying dialogue and teamwork between clinicians and laboratory staff. The pathway also highlights the need to correct coagulopathy at the outset, and to measure fibrinogen concentration, which was often omitted when coagulation tests were requested. However, there remained significant delays in obtaining both FFP and the results of laboratory fibrinogen measurements. We also introduced ROTEM at this time, which was used alongside laboratory measurements in an observational capacity. The ROTEM machine was installed in the obstetric theatre recovery area, with remote viewing available in all obstetric theatres. All anaesthetists were trained to use ROTEM for any patient with major haemorrhage or suspected coagulopathy.

**Table 3** Patient outcomes and complications as a result of blood component transfusion before (Shock Pack phase) and after (Fibrinogen phase) introduction of fibrinogen concentrate. Values are number (proportion).

| | Shock Pack (n = 42) | Fibrinogen (n = 51) | p value |
|---|---|---|---|
| ICU admission | 4 (9%) | 1 (2%) | NS |
| TACO | 4 (9%) | 0 | 0.0367 |
| TRALI | 0 | 0 | NS |
| Postpartum hysterectomy | 6 (14%) | 3 (6%) | NS |
| Death | 0 | 0 | NS |

TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury.

A pilot study showed that 30 of 64 (47%) patients had a normal FibTEM MCF result at entry into the major obstetric haemorrhage pathway. These patients required significantly fewer units of packed red blood cells than those whose first FibTEM MCF was less than 15 mm (mean number of units transfused 0.8 vs 3.7, $p < 0.001$; unpublished observation from internal audit). We also found a robust correlation between FibTEM MCF and A5 [7], which was confirmed in subsequent studies [20, 21]. There is also a strong reported correlation between FibTEM A5 measurements and fibrinogen levels [22–28].

We considered targeting fibrinogen-containing products on the basis of FibTEM A5 results, but there was concern that delays in treatment could occur if we did not order FFP for all patients at the initiation of the pathway, due to the time required for crossmatch, defrosting and transportation.

Our interest in fibrinogen concentrate was triggered by the publication of a case series showing its benefits in major obstetric haemorrhage [29]. We discussed this with our haematologists and the Hospital Transfusion Committee. The Liverpool Women's Hospital is a stand-alone tertiary referral centre that does not have 24-h on-site transfusion laboratories. We requested that a supply of fibrinogen concentrate be available on the delivery suite for use on a named-patient basis, guided by FibTEM A5 results. This was accepted by our Clinical Governance Committee to address the risks inherent in delivering parturients at high risk of major haemorrhage in our Trust. The second phase of the study was then conducted to provide assurance to the same committee that this approach would result in improved outcomes.

We chose a conservative threshold for treating haemorrhage-induced coagulopathy, giving fibrinogen concentrate to all patients with a FibTEM A5 below 7 mm, indicative of a fibrinogen level of 1.5–2 $g.l^{-1}$, a conventional level at which fibrinogen replacement therapy has been widely recommended [28, 30, 31]. Our algorithm allowed us to reassess the response to its administration promptly, and administer more fibrinogen rapidly if the FibTEM value still indicated abnormality.

Our results show that there was a significant reduction in the total usage of allogeneic blood products, similar to evidence from cardiac [32], vascular [24, 30, 33] and trauma [34] studies, as well as a systematic Cochrane review [35]. We did not find any adverse events associated with fibrinogen concentrate, in line with other studies [36]. Volume overload with FFP is a significant clinical problem [16], even in relatively young fit patients. Following the change in our clinical practice from large volume infusions of FFP to targeted small volumes of fibrinogen concentrate, we have not had any further cases of transfusion-associated circulatory overload.

This audit demonstrates a key change in the role of obstetric anaesthetists when dealing with massive obstetric haemorrhage. In the past, obstetricians dealt with the diagnosis and management of the four Ts (tone, tissue, trauma and thrombin), while anaesthetists faced the challenge of maintaining normovolaemia in a patient with ongoing rapid blood loss, guided by information from appropriate monitors of haemodynamic parameters. Now that we have experience of using real-time monitoring of coagulation, the obstetric anaesthetist can diagnose and treat haemorrhage-associated coagulopathy at the earliest possible stage.

Fresh frozen plasma is an inappropriate fluid for volume resuscitation due the high risk of allergic reactions [16]. Furthermore, the concentration of fibrinogen within a typical unit of FFP (2.6 $g.l^{-1}$) [17] is around half that of the median (IQR) concentration of 5 $g.l^{-1}$ (4.4–5.8) seen in the third trimester of pregnancy [26]. Administration of FFP to a pregnant patient at term may thus result in a reduction in fibrinogen levels. Our study suggests that early correction of low fibrinogen levels with fibrinogen concentrate results in fewer patients who require massive transfusion of red cells, additional doses of fibrinogen-containing products, or platelets.

The choice of sample size for this single centre study was pragmatic, and based on the number of parturients who met our inclusion criteria at each phase of our study. This was sufficient to detect differences in blood component usage, but the study was not sufficiently powered to determine whether the observed reduction in the number of hysterectomies was attributable to chance, or represented a major benefit arising from effective correction of coagulopathy.

As a sequential phased study, we cannot exclude the effects of increased experience with ROTEM and improved teamwork as contributory factors to the improved outcomes. However, we feel that these are minor, when compared with the ease and speed with which we have been able to correct and monitor observed coagulopathy, using our bespoke algorithm to guide fibrinogen concentrate administration. These findings from our study need to be confirmed by a randomised controlled trial. In November 2013, we commenced recruitment as one of four centres in the Obstetrics Bleeding Study 2, which compares fibrinogen concentrate with placebo for the treatment of post-partum haemorrhage. Recruitment for this study will end in December 2014 [37].

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## Competing interests

No external funding or competing interests declared.

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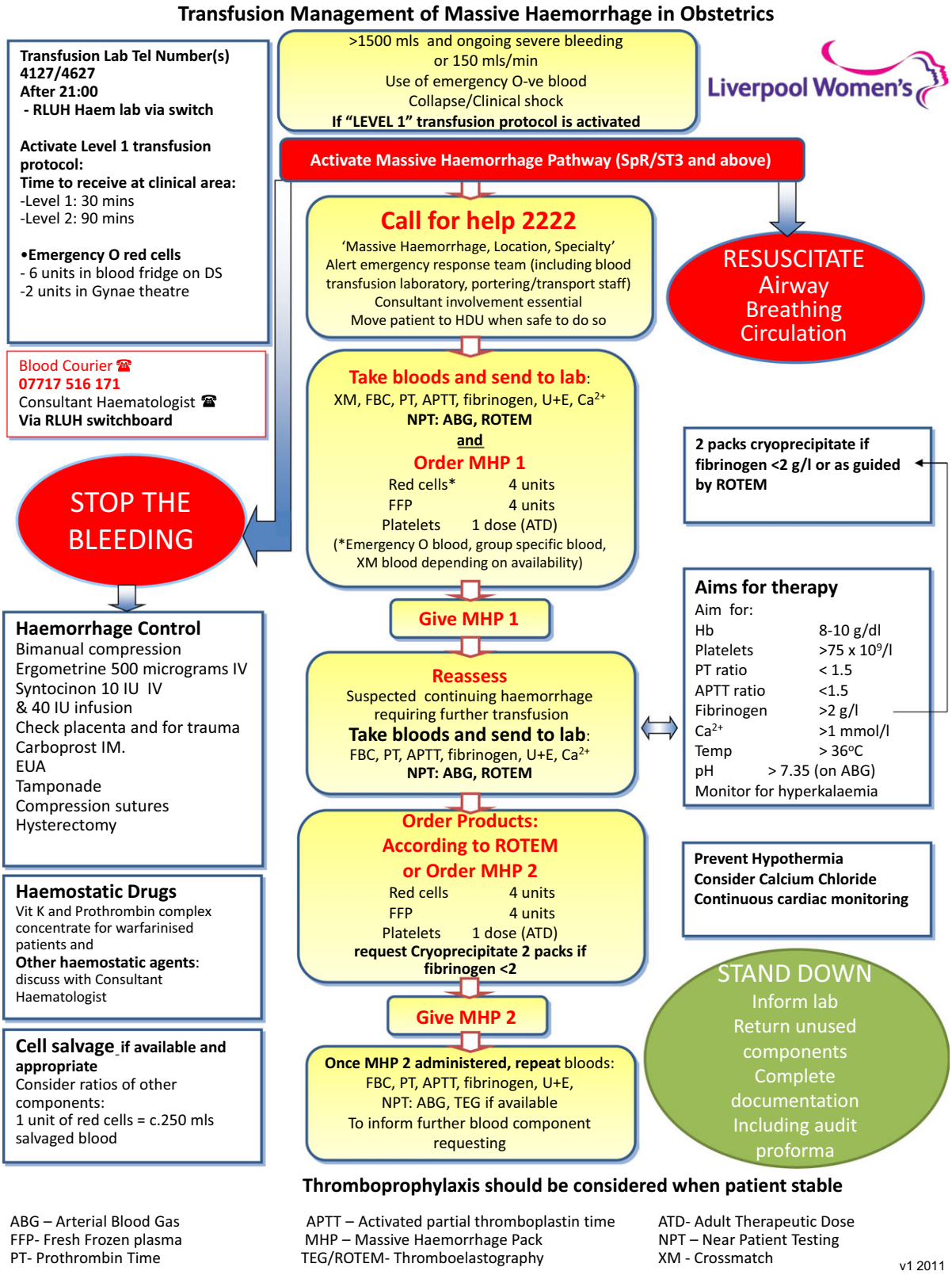
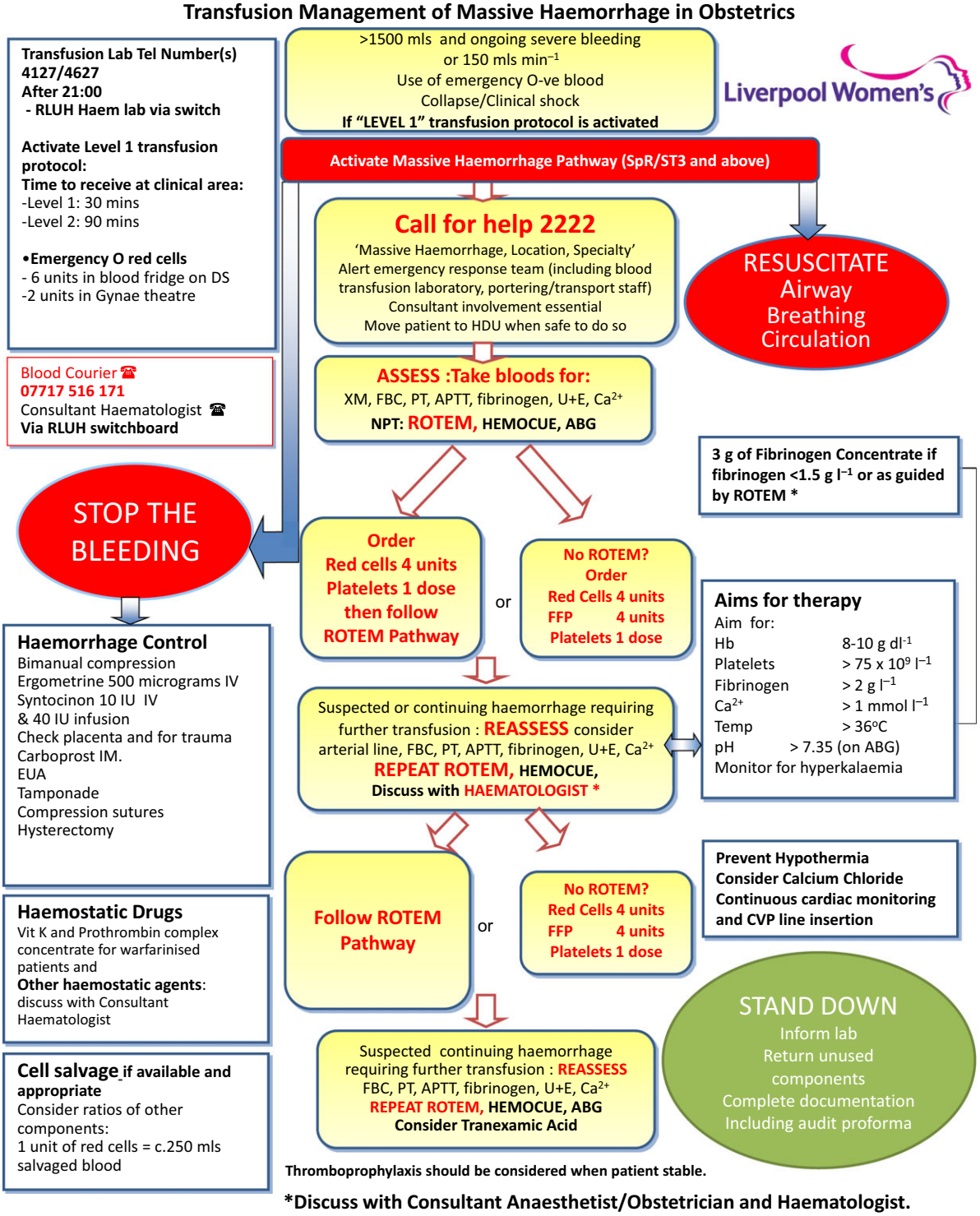
# Appendix 1

## Massive Obstetric Haemorrhage Algorithm April 2011 to March 2012



# Appendix 2

## Major Obstetric Haemorrhage Algorithm incorporating ROTEM-guided Fibrinogen Concentrate, July 2012 to June 2013



## Appendix 2. (Continued)