If the results of haemostatic tests are not available and haemorrhage is continuing then, after 4 units of RBCs have been transfused, FFP should be infused at a dose of 12–15 ml/kg and 6:4 RBC:FFP transfusion maintained until tests of haemostasis are available. Such empirical use of FFP is in line with published guidance.[67,68,71,105] FFP transfusion earlier than this could be considered for placental abruption or amniotic fluid embolism, because these situations are associated with early coagulopathy[106,107] or if diagnosis of PPH has been delayed.

Evidence level 4

In rare cases of massive bleeding where women have been given 8 or more units of RBCs and they continue to bleed, and still no coagulation results or platelet counts are available, then 2 pools of cryoprecipitate and 1 pool of platelets should be infused.[108]

Evidence level 3

***Fibrinogen***

**A plasma fibrinogen level of greater than 2 g/l should be maintained during ongoing PPH.**

C

**Cryoprecipitate should be used for fibrinogen replacement.**

D

Observational studies show that a fibrinogen level of 1.0–1.5 g/l is likely to be too low for adequate haemostasis during ongoing PPH.[97,98,109–111] Fibrinogen below 3 g/l and especially below 2 g/l is associated with progression of bleeding, increased RBC and blood component requirements, and the need for invasive procedures.[109]

Evidence level 2+

A double-blind RCT[112] has shown that pre-emptive infusion of 2 g fibrinogen concentrate in women with 500–1000 ml PPH has no benefit; however, the fibrinogen level at the time of randomisation was greater than 4 g/l in most women.

Evidence level 1

The appropriate fibrinogen intervention trigger or target level is unknown. A pragmatic view based on available evidence is that, during continuing PPH, cryoprecipitate or fibrinogen concentrate should be used to maintain a fibrinogen level of at least 2 g/l, even if PT/APTT are normal. Fibrinogen loss can be replaced by cryoprecipitate or fibrinogen concentrate, although fibrinogen concentrate is not licensed for acquired hypofibrinogenaemia in the UK. Similar clinical outcomes and increments in fibrinogen have been reported for cryoprecipitate and fibrinogen concentrate, but these are based on limited data.[113] It is expected that 2 pools of cryoprecipitate (1 pool is taken from five donors) would increase the fibrinogen level by about 1 g/l. Increasing the fibrinogen level by 1 g/l requires about 60 mg/kg fibrinogen concentrate.[114] Observational studies report improved clinical haemostasis and possible reduced use of FFP and post-transfusion-related events, such as TACO,[94,115] associated with infusion of fibrinogen, but RCTs are required.[93,113,114,116,117]

Evidence level 3

***Transfusion of platelets***

**During PPH, platelets should be transfused when the platelet count is less than $75 \times 10^9$/l based on laboratory monitoring.**

D

There is general consensus that platelets should be transfused at a trigger of $75 \times 10^9$/l to maintain a level greater than $50 \times 10^9$/l during ongoing PPH.[68,71]

Evidence level 4

### 5.3.6 Is there a role for antifibrinolytic drugs?

**Consideration should be given to the use of tranexamic acid in the management of PPH.** B

A large RCT[118] found that early administration of tranexamic acid in the management of trauma in nonpregnant patients resulted in a significant reduction in death from haemorrhage. The dose employed in this study was 1 g intravenously over 10 minutes followed by an infusion of 1 g over 8 hours. One RCT[119] assessed the role of high-dose tranexamic acid in PPH. Women with PPH greater than 800 ml following vaginal delivery were randomly assigned to receive tranexamic acid (loading dose 4 g over 1 hour, then infusion of 1 g/hour over 6 hours) or not; the study concluded that high-dose tranexamic acid can reduce blood loss, fall in Hb and the need for blood transfusion. The study was not powered to address safety issues and specifically, the risk of the treatment causing deep vein thrombosis.

Evidence level 1+

A Cochrane review[2] on treatments for PPH found that trials testing the effectiveness of tranexamic acid were too small to draw meaningful conclusions. A large trial[120] is currently in progress aiming to determine the effect of early administration of tranexamic acid on mortality, hysterectomy and other morbidities in women with PPH. The dose of tranexamic acid employed in this trial is 1 g by intravenous injection; a second dose may be given after 30 minutes.

### 5.3.7 Is there a role for recombinant factor VIIa (rFVIIa) therapy?

**The routine use of rFVIIa is not recommended in the management of major PPH unless as part of a clinical trial.** ✓

rFVIIa (NovoSeven®, Novo Nordisk, Bagsværd, Denmark) is an expensive product that is licensed in the UK for the treatment of bleeding episodes in patients with specific inherited bleeding disorders. Outwith its licence, it has been used primarily in the management of uncontrolled haemorrhage in the trauma setting. It reduces blood loss through enhancement of tissue factor-dependent coagulation. Its effectiveness is markedly diminished by hypothermia, acidosis and low platelets, so effective resuscitation towards normal physiology is a prerequisite of its use.[121]

Evidence level 3

There are only poor quality data from anecdotal reports or patient registries to support its use.[122] Systematic reviews of case series and observational studies have examined the use of rFVIIa in PPH.[123,124] In a review of the literature regarding the use of rFVIIa in the treatment of PPH, Ahonen[122] concluded that rFVIIa should not be used to compensate for inadequate blood transfusion therapy; administration of blood and blood products, as well as management of uterine atony, are essential in the treatment of PPH before considering administration of rFVIIa. A 2015 open-label RCT[125] (n = 84) found that administration of rFVIIa lowered the risk of requiring second-line therapies by 44% (RR 0.56, 95% CI 0.42–0.76) compared with controls (no rFVIIa) in women with PPH in whom uterotonics had failed to arrest the bleeding. All 84 women survived, but two women in the intervention group experienced a venous thromboembolism (2/42).

Evidence level 1+

A study[126] investigating the safety of rFVIIa when employed on an off-label basis to treat life-threatening haemorrhage found a significant increase in the risk of arterial, but not venous, thromboembolic events when compared with placebo (5.5% versus 3.2%).

The use of rFVIIa may be considered as a treatment for life-threatening PPH, but should not delay or be considered a substitute for a life-saving procedure, such as embolisation or surgery, or transfer to a referral centre.

### 5.4 *Monitoring and investigation in major PPH: what investigations should be performed and how should women be monitored?*

**Full protocol for monitoring and investigation in major PPH (blood loss greater than 1000 ml) and ongoing haemorrhage or clinical shock:** D

- **immediate venepuncture (20 ml) for:**
  - **cross-match (4 units minimum)**
  - **full blood count**
  - **coagulation screen, including fibrinogen**
  - **renal and liver function for baseline**
- **monitor temperature every 15 minutes**
- **continuous pulse, blood pressure recording and respiratory rate (using oximeter, electrocardiogram and automated blood pressure recording)**
- **Foley catheter to monitor urine output**
- **two peripheral cannulae, 14 gauge**
- **consider arterial line monitoring (once appropriately experienced staff available for insertion)**
- **consider transfer to intensive therapy unit once the bleeding is controlled or monitoring at high dependency unit on delivery suite, if appropriate**
- **recording of parameters on a modified early obstetric warning score (MEOWS) chart (see Appendix IV)**
- **acting and escalating promptly when abnormal scores from a MEOWS chart are observed**
- **documentation of fluid balance, blood, blood products and procedures.**

Continuous physiological monitoring is necessary and the recording of parameters over time on a flow chart that will give the reader good visual cues on the clinical progress of the patient (Appendix IV). The need to continually re-evaluate the woman's physiological condition, even when bleeding appears to have stopped, is essential to recognise continuing bleeding.

The presence of a central line not only provides a means of accurate central venous pressure monitoring, but also a route for rapid fluid replacement. Nevertheless, the threshold for instituting invasive monitoring has been controversial, with some authorities advising early recourse to central venous pressure monitoring[127–129] and others advocating caution.[76,130] The 2000–02 report of the UK Confidential Enquiries into Maternal Deaths (CEMD)[29] included the recommendation: 'Central venous and direct arterial pressure monitoring should be used when the cardiovascular system is compromised by haemorrhage or disease'. Central venous pressure monitoring requires early involvement of a senior skilled anaesthetist, who will usually take responsibility for this aspect of management. The use of ultrasound is more likely to make the procedure safer,[29] as this procedure carries significant morbidity and mortality.[131] Once bleeding is under control, transfer to an intensive care or high dependency unit on delivery suite should be considered, depending on the severity of the blood loss (see section 5.6.3).

Evidence level 4

It is also important that once the bleeding is arrested and any coagulopathy is corrected, chemical thromboprophylaxis is administered, as there is a high risk of thrombosis. Alternatively, anti-embolism stockings, foot impulse devices or intermittent pneumatic compression devices can be used if chemical thromboprophylaxis is contraindicated, for example, in cases of thrombocytopenia.[132]

Evidence level 4

### 5.5 *What is the role of the anaesthetist in the management of PPH?*

**The management of PPH requires a multidisciplinary approach: the anaesthetist plays a crucial role in maintaining haemodynamic stability and, if necessary, in determining and administering the most appropriate method of anaesthesia.**

D

Anaesthetists play an important role in the multidisciplinary team involved in the management of patients with PPH. A senior anaesthetist should be consulted early to help assess, initiate and continue prompt resuscitation of these patients, using their expertise in fluid and transfusion therapy as well as their experience in managing critically ill patients.[10]

If the patient needs to go to theatre for a surgical intervention, an experienced anaesthetist should promptly assess the patient in order to decide on the most suitable mode of anaesthesia, depending on the patient's haemodynamic status. Central neuraxial anaesthesia has become the anaesthetic technique of choice in the obstetric population and this has resulted in a reduction in maternal mortality.[133]

Evidence level 4

While general anaesthesia in obstetric patients is associated with increased morbidity and mortality when compared with regional anaesthesia due to the physiological changes that occur in pregnancy,[9] it may be preferable in patients who are haemodynamically unstable or who have a coagulopathy.

The patient may need high dependency or intensive care in the postoperative period. An obstetric early warning score system would help in the early identification of continuous bleeding, especially in cases which are not apparent, as recommended by CMACE (see Appendix IV).[131]

### 5.6 *What methods should be employed to arrest the bleeding?*

**Clinicians should be prepared to use a combination of pharmacological, mechanical and surgical methods to arrest PPH. These methods should be directed towards the causative factor.**

D

Careful clinical examination is required to determine the cause of PPH (see Table 1 and Appendix II for the risk factors and causes of PPH). A 2014 Cochrane review[2] addressing the treatment of primary PPH found no trials evaluating surgical techniques or radiological interventions for women with primary PPH that were unresponsive to pharmacological methods. Thus, recommendations on treatment strategies are based on observational data and consensus only.

Evidence level 4

#### 5.6.1 What pharmacological and mechanical strategies can be used?

**When uterine atony is perceived to be a cause of the bleeding, then a sequence of mechanical and pharmacological measures should be instituted in turn until the bleeding stops.**

✓

The most common cause of primary PPH is uterine atony.[27] The initial management of PPH should, therefore, involve measures to stimulate myometrial contractions. The following mechanical and pharmacological measures should be instituted/administered in turn:[2]

- palpate the uterine fundus and rub it to stimulate contractions ('rubbing up the fundus')
- ensure that the bladder is empty (Foley catheter, leave in place)
- oxytocin 5 iu by slow intravenous injection (may have repeat dose)
- ergometrine 0.5 mg by slow intravenous or intramuscular injection (contraindicated in women with hypertension)
- oxytocin infusion (40 iu in 500 ml isotonic crystalloids at 125 ml/hour) unless fluid restriction is necessary
- carboprost 0.25 mg by intramuscular injection repeated at intervals of not less than 15 minutes to a maximum of eight doses (use with caution in women with asthma)
- misoprostol 800 micrograms sublingually.

The simple mechanical and physiological measures of 'rubbing up the fundus' and emptying the bladder to stimulate uterine contraction represent first-line management of PPH. No published studies have been identified to provide an evidence base for these interventions; nevertheless, professional consensus supports their continued use.[134]

Evidence level 4

Despite decades of empirical use in clinical practice, there are no trials comparing ergometrine with oxytocin as first-line agents for the treatment of PPH. It seems appropriate to use both agents, although oxytocin is to be preferred initially, especially in women with hypertension or pre-eclampsia. Previous guidance[1] advocated an initial dose of 10 iu oxytocin by slow intravenous injection for treatment (rather than prophylaxis) of PPH. The British National Formulary recommends a dose of 5 iu 'by slow intravenous injection (dose may be repeated)'.[135] The 1997–99 report of the UK CEMD highlighted the risk of profound hypotension that may be associated with oxytocin injection.[136] This guideline has adopted the CEMD recommendation that 'When given as an intravenous bolus the drug should be given slowly in a dose of not more than 5 iu'. This dosage is in line with guidance from other authorities.[30,135]

There are no trials comparing the prostaglandin carboprost (15-methyl prostaglandin $F_{2\alpha}$) with other uterotonic agents. Two case series from the USA,[137,138] comprising 26 and 237 cases, respectively, have reported on the use of carboprost in the successful management of PPH, without resort to surgical interventions in 85% and 95% of cases. Two of the four failures in the smaller series were associated with placenta accreta. If bleeding occurs at the time of caesarean section, intramyometrial injection of carboprost may be used (although not licensed). It is also possible to inject intramyometrial carboprost through the abdominal wall in the absence of laparotomy. The recommended dose is 250 micrograms intramuscularly. This may be repeated every 15 minutes to a total dose of 2 mg (eight doses). However, if significant atonic haemorrhage continues after a third dose of carboprost, without significant improvement (i.e. 30 minutes or more after the first dose was given), the team should consider transfer to the operating theatre for examination under anaesthesia, with an awareness of the impending need for laparotomy and/or hysterectomy.

Evidence level 3