**Beyond MBRRACE : new developments to stem the tide of postpartum haemorrhage**

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Running Title: New developments for postpartum haemorrhage

Postpartum haemorrhage (PPH) continues to be a major killer globally. The latest UK confidential enquiry report produced by the excellent MBRRACE collaboration(1) shows that the death rate per 100,000 maternities was slightly up at 0.49 in 2009-12 compared to 0.39 in the previous report. Massive obstetric haemorrhage (blood loss ≥2500 ml) is responsible for 80% of major morbidity in young women, having nearly doubled in incidence from 0.3% in 2003 to 0.58% in 2012.(2) It is the commonest reason for a recently pregnant woman to require ICU admission.

What ways can be found to address this seemingly perennial problem? Apart from the brace sutures and balloon tamponade (which have helped to reduce the need for hysterectomy), PPH management has remained largely unchanged for many decades. But there are exciting innovations on the horizon that have the potential to improve care. The areas of inadequacy highlighted in the MBRRACE report fall into three themes – and there are important recent developments in each area:

**1. Communication, ownership and team work; attention to detail regarding maternal observations; maintaining a high index of suspicion; and human factors such as situation awareness.**

Before a PPH can be treated, it is critical to accurately assess the problem. We are all familiar with the scenario of a recently delivered woman continuing to ‘trickle’ who is mistakenly treated with relative complacency. Visual estimation of blood loss is still commonly practised even though widely acknowledged to be inaccurate. The gravimetric method of weighing all blood soiled materials and subtracting dry weights improves accuracy and has the advantage of being simple, practical, objective and readily available even in the most remote situations. However, where resources allow, placing a calibrated drape under a woman immediately after delivery has been shown to be more precise.(3)

Surprisingly, a large, well-conducted randomised trial showed that accurately measuring blood loss had no effect on outcomes (4). This suggests that knowing the exact volume of blood loss may not be as important as recognition of *clinically important* blood loss. And this is where the shock index (SI) (maternal pulse divided by the systolic blood pressure) is proving useful. The old teaching maxim to *‘beware of the pulse that rises above the systolic blood pressure’* has recently been further evaluated and refined. In the first hour after delivery, an SI of >0.9 has 100% sensitivity, and an SI of >1.7 has 98% specificity for adverse outcomes of PPH (5). These cut-offs have been incorporated into a 3-level simple traffic light device (the CRADLE device) to triage women postnatally, and is being tested throughout the world. If effective, this device could assist with many of the MBRRACE recommendations – not only improving the clinical evaluation of blood loss, but improving communication and teamwork between practitioners by helping escalate problems appropriately.

**2. Resuscitation**

A major issue in resuscitation is rapid recognition and appropriate treatment of PPH related coagulopathy. Fibrinogen represents 85– 90% of the total amount of coagulation factors in the plasma and is the first to fall below a critical level, with varying contributions from haemodilution and consumption. This variability is more pronounced in obstetric haemorrhage and depends on the cause. When bleeding is due to genital tract trauma, dilution plays a major role, and the smaller fall in fibrinogen level may require no replenishment, as fibrinogen levels are raised at 4-6 g/L in pregnancy, as opposed to the population normal range of 2-4 g/L. This contrasts with cases of abruption and amniotic fluid embolism where catastrophic and rapid defibrination can occur, requiring aggressive correction.

Several studies have found that fibrinogen depletion in early PPH is highly predictive of progression to a severe PPH [6] especially if levels fell close to or below 2g/l. The utility of this fact has been severely limited by the length of time taken for laboratory assessment of fibrinogen levels. However, bedside viscoelastometric point-of-care coagulation tests such as ROTEM® (TEM International GmbH, Munich, Germany) or TEG® 5000 (Haemonetics, Braintree MA, USA) are proving a game-changer. These tests are able to identify patients with low fibrinogen levels within 10 minutes, and thus help to individualize fibrinogen replacement strategies. This focuses care on those most in need, whilst preventing women with high levels of fibrinogen being given potentially thrombogenic supplements. Both manufacturers are currently releasing cartridge based systems (the ROTEM Sigma & TEG 6) that require very little technical expertise to perform the tests making them easier to use by members of the theatre team.

A common practice in the UK is to use ‘major haemorrhage packs’ to provide blood and fresh frozen plasma (FFP) in a 1:1 ratio. This minimizes the coagulopathy that develops as a part of massive haemorrhage. The evidence for this from trauma and military medicine has been questioned on the basis that ‘survivorship bias’ at least partly accounted for the better survival reported in casualties that received early resuscitation with FFP alongside red cells. Moreover, the concentration of fibrinogen within a unit of FFP (2.6 g/L) makes it unsuitable for replenishing fibrinogen levels in bleeding pregnant women. Indeed it might actually lower her fibrinogen levels through dilution, and the large volumes needed to provide adequate fibrinogen might push her into Transfusion Associated Circulatory Overload.

Cryoprecipitate or fibrinogen concentrate may be better for treating PPH associated hypofibrinogenaemia. To date there are no RCTs to suggest that either of these products is better than the other, but an adult dose of cryoprecipitate is pooled from 10 patients (approximately equivalent to 2g fibrinogen concentrate) thereby increasing the risks of immune modulation and infections, and being a frozen product requires thawing and matching against the patients blood group. Fibrinogen concentrate on the other hand is a lyophilized pasteurized product that can be quickly reconstituted with water and injected within minutes. Rapid and targeted correction of coagulopathy using fibrinogen concentrate guided by ROTEM® has been shown to significantly reduce the need for blood and blood products,(7) and hence the overall cost of treating these patients despite the product itself being expensive. Besides, in cases with severe defibrination and an ongoing consumptive element, repeated doses sometimes up to a total of 15 g of fibrinogen may be required. An equivalent dose of cryoprecipitate would hence expose the patient to plasma from 70 patients with potential sequelae. A randomized controlled trial of fibrinogen concentrate vs placebo in obstetric bleeding is under way (8)

**3. “Turning off the tap”**

The MBRRACE report rightly speaks of the importance of ‘turning off the tap’ of PPH. Each minute of ongoing bleeding during a PPH increases maternal hypovolaemia as well as coagulopathy, and stopping the bleeding has to be the main priority. The focus has always been on the delivery of repeated uterotonics, or the removal of a retained placenta. But the postpartum uterus can be very insensitive to uterotonics, probably due to intrapartum oxytocics occupying the myometrial oxytocin receptors. (9) It is in this situation that mechanical methods are becoming increasingly important for managing PPH. The two options are to reduce blood flow to the pelvis, and to compress the myometrial vessels. Arterial embolisation is increasingly available, but aortic compression is an underused alternative that is low cost, simple to perform, and can be carried out early in a PPH. The fist or heel of the hand is pressed into the abdomen just above the umbilicus with two fingers on the femoral pulse to ensure that the pelvic blood flow has ceased. It is well tolerated and has the great benefit that it can be used whilst the placenta is still retained.

An alternative, to be used only when the placenta has been delivered, is bimanual uterine compression. Traditionally the uterus is compressed between a hand on the abdomen and a fist placed in the vagina. Although effective, this technique is very invasive, painful for the woman, tiring for the doctor and has overtones of sexual violence. An alternative may be to compress the uterus manually through the lax postnatal abdominal wall. Two small, randomised trials have shown this to be effective for both prophylaxis and treatment (10, 11). These deserve to be replicated, and maybe extended to explore whether a similar effect can be obtained by compression of the uterus against the sacrum. An alternative is the PPH Butterfly, a device currently undergoing initial clinical testing in the UK. This is a device the size of a speculum that is inserted into the postnatal vagina and then opened up to provide a transverse platform against which the uterus can be compressed. Mannequin tests show it to be as effective as bimanual compression as well as being less invasive.

All these uterine compression techniques have the potential to ‘turn off the tap’ of PPH – but it remains to be seen which is the most effective and acceptable to women. The more acceptable the technique, the earlier it can be used in the PPH process and the lower will be the total blood loss.

**Conclusion**

Mortality figures for PPH have shown considerable improvements worldwide. Nevertheless, optimising PPH care is very important - not only because of the immense family impact of a maternal death, particularly on the vulnerable newborn, but because PPH is an absolutely recoverable condition that generally affects young, fit women. Effective management therefore has the potential for massive societal benefits – and the above innovative approaches may well have an important role in achieving this.

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