Post-partum haemorrhage: definitions, medical and surgical management. 
A time for change

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Any woman who gives birth can have post-partum haemorrhage which may threaten her life. PPH is one of the leading causes of maternal mortality and an important cause for serious morbidity in the developing and developed world. We are at the threshold of major developments in its prevention and treatment due to changing ideas about its definition and medical and surgical management. The implementation of these changes is an essential part of a wider commitment towards saving mothers from complications of childbirth.

Introduction, definitions and classification

Post-partum haemorrhage (PPH) is a clinical problem of indisputable importance to patients, clinicians and to those interested in achieving equity in reproductive health. As a condition it is almost always associated with meaningful implications to patients. Even the mild self-limiting cases have consequences for the patient’s puerperium in the form of fatigue, tiredness, failure to breast-feed and possible need for haematinics or blood transfusion. All are symptoms and consequences of anaemia and acute blood loss. The cascade associated with intractable PPH is an entirely different matter however. It is a spiral of events that challenges the acumen of the attending clinicians and their ability to implement the prepared drills of action to handle such a clinical emergency. PPH can transform a normal woman in labour to a critically ill patient within minutes. The management of such a patient is a real test for the thought processes, resources, organizational effort and the education of a labour ward and its staff.

Historically, PPH was one of the leading causes of maternal death in industrialized nations up to the Second World War. It is still a leading cause of maternal death in the rest of the world today. The classification, definition and treatment of PPH have seen almost no change over the
last 50 years. Defined by the World Health Organization (WHO) as post-partum blood loss in excess of 500 ml, it is a clinical diagnosis that encompasses excessive blood loss after delivery of the baby from a variety of sites: uterus, cervix, vagina and perineum. Blood loss during the first 24 h after delivery is known as primary PPH, whereas blood loss from 24 h up to 6 weeks after delivery is termed late or secondary PPH. The bleeding is also classified according to its site. Hence primary PPH is also classified as either placental or extra-placental bleeding.

The definition and classification of PPH have stood the test of time but they are not without problems. For example a cut-off point of 500 ml implies that any loss smaller than this is within normal limits and can therefore be tolerated without risk. This is certainly not the case in countries where severe anaemia is common and where blood loss of as little as 250 ml may constitute a clinical problem. Furthermore, not all placental site bleeding is the same. There is a difference in bleeding from the upper segment to that from the lower segment of the uterus. The bleeding from the former usually if not always responds to uterotonic agents, whereas the latter does not. It is useful to embed this distinction in the literature and in training as it impacts on management options and pathways and on the speed with which they are adopted.

One could argue that the initial administration of uterotonic agents in cases of PPH is nothing more than a clinical test. The outcome of a such test could be positive with cessation of the bleeding. In such a case a retrospective diagnosis of upper segment PPH is made. Continuation of bleeding, on the other hand, would indicate that ‘Examination under anaesthesia’ to exclude trauma is necessary. If this is excluded and the bleeding continues then this patient might have lower segment bleeding that will require laparotomy to deal with it. B-Lynch sutures or hysterectomy for example might provide the appropriate and curative intervention for cases of lower segment PPH. Wasting time in anticipation of a response to uterotonic agents in these cases will be futile.

The incidence of PPH ranges between 5% and 8% in places where some form of prophylaxis is practised, but may be as high as 18% when a physiological approach is the norm. Physiological control of post-partum bleeding occurs by contraction and retraction of the interlacing myometrial fibres surrounding maternal spiral arteries in the placental bed. Myometrial contraction compresses the spiral arteries and veins, thereby obliterating their lumina. Haemostasis following placental separation is thereby initially a mechanical process not primarily dependent upon an intact coagulation system. Development of this mechanism was a crucial aspect of viviparity without which mammals would not have evolved. However it is flawed: Primary PPH due to uterine atony occurs when the relaxed myometrium fails to constrict these blood vessels, thereby allowing
haemorrhage. Since up to one-fifth of maternal cardiac output, which is in excess of 600 ml/min, enters the uteroplacental circulation at term, it is understandable that primary atonic PPH can be catastrophic—capable of exsanguinating the mother within minutes. Whilst uterine atony is responsible for the majority of primary PPH, the surgical obstetrical causes such as injury of the cervix, vagina, paravaginal spaces, perineum and episiotomy comprise about 20% of all primary PPH.

The scale of the problem

The last two decades have witnessed an increasing awareness of gender-related medical problems in the world. Maternal mortality figures have increasingly become an emotive political issue. The lack of improvement in these figures in the developing world reflects the complex nature of the problems these societies face. In some cases calls were made to exert political pressure on governments to tackle the problems. Linking certain aspects of foreign aid to advances in reproductive health was portrayed as an effective leverage to implement change. In some of the cases where improvement was reported it is difficult to ascertain how much of this improvement is a political dressing and how much is a real improvement. The fact remains however that the figures are far too high, reflecting in their distribution the socio-economic divisions around the globe. The exact contribution of PPH to maternal mortality figures is not known precisely because haemorrhage in labour or afterward is usually presented as one group. It is however one of the leading causes of maternal mortality—especially in less developed countries where multiparity, fibroid uterus and anaemia are common. World-wide it is the most common reason for blood transfusion after delivery and it is estimated that at least 150,000 women per annum bleed to death during or immediately after labour. This figure is almost certainly an underestimate. Death due to PPH is reported to represent between 17% and 40% of maternal mortality in some parts of the world. Even in developed countries, for example The Netherlands, PPH causes 13% of all recorded maternal deaths. In the USA, it has been reported that obstetric haemorrhage is responsible for 13% of maternal death with PPH the lethal event in over one-third of these cases. In those parts of the world where blood replacement is not possible due to lack of resources, post-partum severe hypotensive shock leads to considerable morbidity including acute renal failure, partial or total necrosis of the anterior pituitary gland and other organ system injury such as pancreatitis and adult respiratory distress syndrome (ARDS).

To prevent serious morbidity or death from PPH many systems need to be functioning: trained birth attendants, emergency transport systems.
(the window of time needed to save life is short), availability of blood transfusion and other essential obstetric functions at the first referral level. It is recognized that routine pharmacological use of uterotonic agents is an important prophylactic measure against PPH. Strategies to reduce post-partum bleeding include the use of uterotonic drugs such as oxytocin, Syntometrine (combination of oxytocin and ergometrine) or ergometrine. Other measures include early clamping of the cord and delivery of the placenta by cord traction. These are collectively termed ‘active’ management of the third stage. With ‘passive’ (expectant, physiologic, conservative) management, oxytocics are used only if there is excessive bleeding, the cord is clamped relatively late and the placenta delivered with the help of gravity and maternal effort. However, many variations of third stage management exist in which a mixture of active and passive management is used.

Systematic reviews of interventions during the third stage of labour suggest that there are advantages to using active management strategies7,8. Prophylactic oxytocics reduce the risk of PPH by about 60% and the need for extra oxytocics by about 70%. Passive management could be practised in low risk women delivering at hospitals or those delivering at home or in clinics who can be transferred to the hospital within a very short time in case of an emergency. This is a likely scenario in industrialized countries. In developing countries, however, there are different factors to consider. In rural areas, access to a skilled birth attendant might not be possible. Transfer to a clinic or hospital in case of an emergency might be slow and complicated. The high incidence of pregnancy anaemia in most developing countries makes it more important to prevent any avoidable blood loss.

The use of Syntometrine however is associated with several problems. Syntometrine possesses hypertensive properties and has been known to produce a rise in blood pressure in women previously known to be normotensive. It is therefore contraindicated in women with hypertension in pregnancy, which may affect about one in seven women9. Syntometrine frequently causes nausea and vomiting7. Syntometrine and oxytocin have to be given by intramuscular injection requiring a sterile needle and syringe, an important consideration in the developing world in view of the rising incidence of HIV, hepatitis B and C and other blood-borne diseases in many parts of the world. Finally, because oxytocic agents are not stable at high ambient temperatures, they require special storage conditions. When Syntometrine is stored for prolonged periods the temperature must be maintained between 2 and 8°C and it must be protected from light. Studies designed to simulate the storage conditions commonly found in tropical countries found that a variety of brands of ergometrine lost 21–27% of their active ingredients after 1 month, and over 90% after 1 year of storage exposed to light and at 21–25°C10,11.
These storage requirements are an important barrier to the effective use of oxytocics in the developing world. Oxytocin alone is not without problems although they are not as widely known as those of ergometrine\textsuperscript{12-14}. The main preservative used in syntocinon ampoules is chlorobutanol which has a negative effect on cardiac muscle\textsuperscript{15,16}. Obstetricians in general are not familiar with its side-effects whilst anaesthetists can easily visualize it on their monitors\textsuperscript{17}. Since syntocinon has a direct effect on the heart, it is not allowed to be used intravenously without an infusion in North America. The parenteral nature of syntocinon however is the main obstacle to its wide use around the world.

WHO has what is termed an essential drug list. No uterotonic agent is on this list. The aforementioned problems meant that there is not a suitable one. This omission could only be filled by an agent that, as well as being safe and effective, is also enterally administered, normotensive and thermostable.

**Misoprostol and the third stage of labour**

Other than oxytocin and ergot preparations, prostaglandins are the only group of drugs that have a potential for routine use in the third stage. Prostaglandin agents are known to possess strong uterotonic features that have been utilized in obstetric practice for three decades. They are widely used for cervical ripening, induction of labour and induction of abortion. They are also known to be useful as a last resort in the management of intractable PPH.

Unlike ergometrine-related agents, prostaglandins are not hypertensive\textsuperscript{18}. This, combined with their strong uterotonic effect and apparent superiority in the management of PPH, suggests that they may be the ideal agents for routine prophylactic use in the third stage of labour. To date relatively small controlled trials indicate that injectable prostaglandin analogues seem as effective as Syntometrine\textsuperscript{19-22}.

The use of misoprostol in Obstetrics and Gynaecology has been nothing short of a revolution in reproductive health care. The therapeutic uses of prostaglandins have become more equitable and new indications and ways of treatment have been pioneered. The wide availability of misoprostol to clinicians and the controversial attitude of the pharmaceutical industry have meant that clinicians have had to take the leadership in its development\textsuperscript{23-26}. New regimens and routes of administration were identified and the drug was soon shown to be effective by the oral, vaginal and rectal routes\textsuperscript{27,28}. A small study by El-Refaey in 1993 identified the very rapid change in uterine contractility in response to oral and vaginal misoprostol. The study showed that misoprostol administered by these routes is not only absorbed promptly but can also have a considerable
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impact on uterine contractility in minutes. Figure 1 shows the change in intrauterine pressures in three patients who were pre-treated with mifepristone 36 h earlier. The vertical arrows highlight the point of administering misoprostol whilst the transverse arrows highlight the length of time taken to achieve a change in uterine contractility. This confirmed uterotonic action of misoprostol in early and late pregnancy, led El-Refaey et al\textsuperscript{29} later to consider its use in the third stage of labour. The initial report showed promising efficacy and identified shivering as a potential side-effect.

The proposal to use misoprostol to prevent and treat PPH has been investigated in the last 5 years. El-Refaey \textit{et al} compared misoprostol 500 µg administered before delivery of the placenta to women receiving other standard uterotonic agents in the third stage in a randomized trial of 1000 patients. The rates of PPH and the need for blood transfusion were similar\textsuperscript{30}. Surbek \textit{et al}\textsuperscript{31} also conducted a double-blind randomized controlled trial comparing a single oral dose of misoprostol (600 µg) with placebo in the third stage of labour. The ‘obstetrician estimated the blood loss’ and the difference in haematocrit before and after delivery were measured. The mean estimated blood loss and haematocrit difference were significantly lower in women who received misoprostol than those who received the placebo. Whereas the need for additional oxytocin was lower in the misoprostol group, shivering was more common in the misoprostol arm.

The uterotonic efficacy of misoprostol in the third stage of labour has also been demonstrated by an objective reproducible method, which uses a catheter-tip intrauterine pressure transducer. This tool was used by Chong \textit{et al}\textsuperscript{32} to examine the effect of oral misoprostol in varying doses (200–800 µg) on the post-partum uterus and to compare its uterine contractility pattern to that following intramuscular Syntometrine. The study confirmed that the cumulative uterine activity with all doses of misoprostol and Syntometrine were similar.

The potential of misoprostol as a therapeutic agent for this phase of labour was also recognized by WHO, who went on to conduct an ambitious multi-centre, randomized controlled trial involving nine countries\textsuperscript{33}. This trial is probably the largest in the field of third stage of labour and was designed to compare the use of oral misoprostol (600 µg) to 10 IU of oxytocin.

The trial was statistically powered for two primary outcomes: the measured blood loss of 1000 ml or more and the use of additional uterotonic agents, and 20,000 women were recruited. Unfortunately the trial had several problems\textsuperscript{34–37}. At the time of data analysis, it was recognized that information on the route of oxytocin administration was not collected. The authors were therefore unable to quantify the proportion of patients who received the oxytocin intravenously or intramuscularly. Furthermore, there was an unexplained statistical heterogeneity between
Fig. 1 The three graphs show the onset of change in uterine contractility after administering oral and vaginal misoprostol in three patients who were undergoing medical termination of pregnancy at 9 weeks gestation and were pre-treated with mifepristone 36 h earlier. The top graph is from a patient who received 400 µg misoprostol orally. The middle graph is from a patient who received 800 µg misoprostol orally. The bottom graph is from a patient who received 800 µg misoprostol vaginally. The vertical axis shows the intra-uterine pressure in mmHg. The horizontal axis shows the time in minutes (1 small box = 0.5 min). The vertical arrow indicates the time of the oral administration of misoprostol. The horizontal arrow shows the time interval taken to achieve tetanic uterine contraction after administering misoprostol.
the individual centres for the primary outcome of measured blood loss. Whilst this large trial is often quoted to have shown that there is a 1% difference in PPH between oral misoprostol and oxytocin, the subtle but profound effect of administration of oxytocin by the intravenous route on the results is often overlooked or ignored. This trial also highlighted the limitation of an outcome measure such as measured blood loss in the third stage of labour when it did not correlate with a clinical morbidity marker like ‘the need for blood transfusion’. The blood transfusion rate was lower in women in the misoprostol group. However, the WHO trial proved the safety of misoprostol administered orally at doses up to 600 µg.

### Pharmacological treatment of post-partum haemorrhage

Ergometrine, and subsequently oxytocin were introduced in the treatment of PPH on the basis of biological and pharmacological principles. The identification of their uterotonic features and the recognition that uterine atony plays a major role in PPH led to their wide adoption as first line drugs in its management. Their prophylactic usage in the third stage of labour was therefore an extension of their role in treatment. It is interesting however that more trial data exist in support of their use in prophylaxis compared to treatment. When the uterotonic features of prostaglandins were later identified they were similarly used in the treatment of PPH. The use of carboprost as an intramyometrial injection, its long list of contraindications and possible side-effects were however prohibitive for the wider use of this prostaglandin analogue. Misoprostol is the most recent drug to be identified as a useful agent in the treatment of PPH and some supporting trial data exist for its use. However, there is a debate about dosage and route of administration.

Misoprostol has been widely investigated by the oral and then the vaginal route for induction of abortion. It soon became clear that the vaginal route is optimal however because the resulting uterine contractility was more potent and side-effects were lower compared to the oral route. Administering misoprostol vaginally however was thought, at least initially, to be unsuitable for management of PPH because of bleeding. The rectal use of misoprostol came as an answer to this problem. The administration of the drug by the rectal or vaginal route might be more practical and effective than the oral route. Inserting the drug vaginally or rectally by the attending clinician is more practical than handling it to a patient who has just given birth to swallow with a glass of water! There are several studies to indicate misoprostol can be used effectively as a preventive measure by the rectal and most recently vaginal routes.
O’Brien et al\textsuperscript{39} reported in a pilot study that misoprostol 1000 µg given rectally is an effective intervention in women with severe PPH, unresponsive to standard uterotonic agents. Subsequent observational studies and a recent randomized study support the use of rectal misoprostol (800 µg) in the treatment of PPH\textsuperscript{40}. The latter trial also concluded that misoprostol is more effective than a combination of intramuscular Syntometrine injection and oxytocin infusion. Interestingly, although the oxytocin bolus and infusion is a standard practice in treatment of PPH, there is little research to support the use of this regime\textsuperscript{41}. The addition of misoprostol to this therapeutic drill seems to be more supported by scientific data than the use of any of the other uterotonic agents.

The rectal use of misoprostol spread quite quickly based on these clinical studies. Hospital management protocols are changing to include the drug in the guidelines of post-partum management. A recent survey from Norway has shown that 20\% of obstetricians now use misoprostol in the treatment of PPH\textsuperscript{42}. This is despite the fact that, until recently, no pharmacokinetic study had shown that misoprostol is absorbed from the rectum\textsuperscript{43}.

\section*{Surgical management of intractable post-partum haemorrhage}

A patient who fails to respond to uterotonic agents and continues to bleed will quickly become haemodynamically unstable and develop a cascade of clotting abnormalities. The spectre of maternal mortality can then only be prevented by initiating surgical haemostasis sooner rather than later. The nature, timing and extent of these invasive interventions will depend on the sophistication of the health facility which handles this medical crisis. The fate of such a woman will therefore vary widely, depending not only on where she lives in the world but also on where she lives in her own country.

Traditionally, total abdominal hysterectomy provided the ultimate cure. The procedure is technically different from hysterectomy for gynaecological reasons. The main difference is identifying and removing the lower uterine segment. This might be the curative part of the procedure and has to be handled with care. The bladder has to be reflected, dissected and pushed inferiorly and laterally to minimize the chances of bladder injury and ureteric injury. The boundaries of the lower uterine segment are ill-defined and it can be difficult to identify the cervix. Often it can only be partially removed.

Delaying the decision to carry out post-partum hysterectomy can be catastrophic because the patient may deteriorate much further and faster than anticipated so that it becomes impossible later to carry out what could have been a life-saving intervention. Hysterectomy should not be
delayed until the patient is in extremes or while less definitive procedures of which the surgeon has little experience are attempted. Performing hysterectomy in a timely fashion is therefore a sign of maturity of the team looking after the patient. The pressures to preserve fertility and avoid a hysterectomy can also be equally great and several techniques have evolved in recent decades. Interventions to occlude the blood supply to the uterus or to tamponade the uterine cavity are options to avoid inevitable hysterectomy.

Ligation of the internal iliac arteries has been used but requires complex dissection of the lateral pelvic wall. Vascular embolization procedures have become established and are less invasive interventions with well documented curative effect. The technique involves inserting a catheter in the femoral artery going into the large circulation and then to the uterine vessels. Embolization at this point will at least lower the blood pressure around the uterus. These techniques require a multidisciplinary approach and trained personnel who might not be available in many district hospitals even in industrialized nations.

Within the last decade there has been renewed interest in new uterine tamponade procedures such as balloon compression and other procedures, e.g. the B-Lynch suture. The oldest form of tamponade, uterine packing, has a long history in obstetrics and was widely used in the management of PPH before prostaglandin agents were an option or because of their expense. A 20-m-long gauze pack has to be tightly inserted inside the uterus. For it to work, it must start at the fundus of the uterus otherwise bleeding will continue above the pack. The success of the procedure is dependent on these points and this may become apparent some hours later. Anxieties about the efficacy of the technique and its potential to act as a focus of infection and to cause pressure necrosis on adjacent organs have led to alternative approaches such as the Sengstaken balloon compression. Arulkumaran and others described 14 cases of intratable PPH who avoided surgery by the use of this balloon.

The B-Lynch technique is a suture that envelops and compresses the uterus and was first described in 1997. Compared to hysterectomy or to vascular embolization, the B-Lynch suture is a much simpler procedure and its technique can be easily mastered. It does not require special training and is illustrated in Figure 2a and b. Experience with this technique is promising but the evidence is limited to case reports.

**Conclusion**

PPH is an important cause of maternal morbidity. We now have new pharmacological and technical developments for prevention and treatment which can greatly reduce its incidence and sequelae. Wider use
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of thermostable prostaglandins like misoprostol and dissemination of knowledge about new tamponade procedures can minimize its incidence and limit its serious sequelae. The safety of the third stage of labour, and the incidence of PPH and its complications will remain linked however to the wider issues of reproductive health in general and more specifically to the funding and training needed to raise the standard of care offered to women in labour in many parts of the world.

Fig. 2 (a) The anterior view of the uterus showing the application of the B-Lynch suture. (b) The posterior view of the uterus showing the application of the B-Lynch suture.

References

13 Maycock EJ, Russell WC. Anaphylactoid reaction to Syntocinon. *Anaesth Intens Care* 1993; 21: 211–2
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38 Quiroga DR, Esparza AM, Batiza RV, Coronado LO, Hernandez AS, Martinez CJ. [In Process Citation]. *Ginecol Obstet Mex* 2002; 70: 572–5