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Standard Medical Therapy for Postpartum Hemorrhage

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INTRODUCTION

Failure of the uterus to contract and retract following childbirth has for centuries been recognized as the most striking cause of postpartum hemorrhage (PPH) and complicates up to 10% of pregnancies globally. In the developing world, PPH is responsible for one maternal death every 7 minutes[1].

In the 19th century, uterine atony was treated by intrauterine placement of various agents with the aim of achieving a tamponade effect. 'A lemon imperfectly quartered' or 'a large bull's bladder distended with water' were employed for this purpose, with apparent success. Douching with vinegar or iron perchloride was also reported[2,3]. Historically, the first uterotonic drugs were ergot alkaloids, followed by oxytocin and, finally, prostaglandins.

Ergot, the alkaloid-containing product of the fungus *Claviceps purpurea* that grows on rye, was recognized for centuries as having uterotonic properties and is the substance referred to by John Stearns in 1808 as '*pulvis parturiens*' (a powder [for] childbirth), at which time it was used as an agent to accelerate labor[4]. By the end of the 19th century, however, recognition of the potential hazards associated with ergot use in labor, namely its ability to cause uterine hyperstimulation and stillbirth, had tempered enthusiasm for its use. Focus was diverted toward its role in preventing and treating PPH at a time when, according to an 1870 report, maternal mortality in England approached one in 20 births[5].

Attempts to isolate the active alkaloids from ergot were not successful until the early 20th century, when Barber and Dale isolated ergotoxine in 1906[3]. Initially thought to be a pure substance, this agent was subsequently found to comprise four alkaloids, and in 1935 Moir and Dudley were credited with isolating ergometrine, the active aqueous extract 'to which ergot rightly owes its long-established reputation as the pulvis parturiens'[6,7]. Moir reported on its clinical use in 1936, stating[7]:

'. . . the chief use of ergometrine is in the prevention and treatment of postpartum haemorrhage. Here the ergometrine effect is seen at its best. If after the delivery of the placenta the uterus is unduly relaxed, the administration of ergometrine, 1 mg by mouth or 0.5 mg by injection, will quickly cause a firm contraction of the organ. If severe haemorrhage has already set in, it is highly recommended that the drug should be given by the intravenous route. For this purpose one-third of the standard size ampoule may be injected or, for those who wish accurate dosage, a special ampoule containing 0.125 mg is manufactured. An effect may be looked for in less than one minute.'

Another uterotonic agent, oxytocin, the hypothalamic polypeptide hormone released by the posterior pituitary, was discovered in 1909 by Sir Henry Dale[8] and synthesized in 1954 by du Vigneaud[9]. The development of oxytocin constituted the first synthesis of a polypeptide hormone and gained du Vigneaud a Nobel Prize for his work.

The third group of uterotonics comprises the ever-expanding prostaglandin family. The prostaglandins were discovered in 1935 by a group led by Swedish physiologist Ulf von Euler[10] who found that extracts of seminal vesicles or of human semen were capable of causing contraction of uterine tissue and lowering blood pressure. The term 'prostaglandin' evolved from von Euler's belief that the active material came exclusively from the prostate gland. This family of 'eicosanoids', 20-carbon fatty acids, was subsequently found to be produced in a variety of tissues and capable of mediating a myriad of physiologic and pathologic processes. Prostaglandins, by virtue of their ability to cause tetanic myometrial activity, are increasingly used as adjunctive therapy to standard oxytocin and ergometrine to treat PPH resulting from uterine atony (see Section 8).

This chapter is devoted to critical evaluation of the standard pharmacological methods available to treat uterine atony, with particular focus on agent selection based on effectiveness, safety profile, ease of administration, cost and applicability in low resource settings.

UTERINE ATONY

Powerful efficient contractions of the myometrium are essential to arrest blood loss after delivery. The resultant compression of the uterine vasculature serves to halt the 800 ml/min blood flow in the placental bed. Recognition of a soft, boggy uterus in the setting of a postpartum bleed alerts the attendant to uterine atony.

The particular contribution that uterine atony makes toward PPH is so well known that a universal reflex action when faced with excessive postpartum bleeding is to induce uterine contraction using bimanual massage. Prompt recognition of this condition and institution of uterotonic therapy will effectively terminate the majority of cases of hemorrhage. Once effective uterine contractility is established, persistent bleeding should prompt the search for retained placental fragments, genital tract trauma or a bleeding diathesis.

Astute risk assessment is crucial in identifying women at increased risk of uterine atony, thereby allowing preventive measures to be instituted and for delivery to take place where transfusion and anesthetic facilities are available. That having been said, one must remember that the majority of parturients with one or more risk factors do not bleed excessively and, conversely, large numbers of women with no risk factors experience true hemorrhage.

The established risk factors associated with uterine atony are outlined in Table 1. It is worth noting that multiparity, hitherto believed to be a significant risk factor, has not emerged as having an association with uterine atony in recent studies[11–13]. Whereas previous PPH confers a 2–4-fold increased risk of hemorrhage compared to that in women without such a history[13,14]. The presence of leiomyomata may result in more than a two-fold increase in the risk for PPH[15].

It is appropriate that women with these predisposing risk factors should deliver in a hospital with adequate facilities to manage PPH. Prophylactic measures include appropriate hospital booking for women at risk and correction of anemia before delivery, active management of the third stage of labor, ensuring the availability of cross-matched blood and access to interventional radiology services and critical care.

Table 1 Risk factors for uterine atony

Factors associated with uterine overdistension
Multiple pregnancy
Polyhydramnios
Fetal macrosomia

Labor-related factors
Induction of labor
Prolonged labor
Precipitate labor
Augmented labor
Instrumental delivery
Manual removal of placenta

Use of uterine relaxants
Deep anesthesia (especially halogenated anesthetic agents)
Magnesium sulfate
Nitroglycerin

Intrinsic factors
Previous postpartum hemorrhage
Previous cesarean section
Antepartum hemorrhage (abruptio or previa)
Chorioamnionitis
Obesity
Uterine fibroids
Age > 35 years

Recognizing the risks of pulmonary embolus and alloimmunization associated with blood transfusion, intraoperative cell salvage has recently been introduced into obstetric practice in cases where massive obstetric hemorrhage is anticipated or in the management of patients who decline blood transfusion (see Chapter 72). The fact that uterine atony occurs unpredictably in women with no identifiable predisposing risk factors underpins the need for strict protocols for PPH management to be in place in every unit that provides obstetric care (see Chapters 40 and 41).

OXYTOCIN

With timely and appropriate use of uterotonic therapy, the majority of women with uterine atony can avoid surgical intervention. Stimulation of uterine contraction is usually achieved in the first instance by bimanual uterine massage and the injection of oxytocin (either intramuscularly or intravenously), with or without ergometrine. The mode of action of oxytocin involves stimulation of the upper uterine segment to contract in a rhythmical fashion. Owing to its short plasma half-life (mean 3 min), a continuous intravenous infusion is required in order to maintain the uterus in a contracted state[16]. The usual dose is 40 IU in 500 ml of saline, with the dosage rate adjusted according to response (typical infusion rate 10 IU/h or 2 ml/min). When administered intravenously, the onset of action is almost instantaneous and plateau concentration is achieved after 30 minutes. By contrast, intramuscular administration results in a slower onset of action (3–7 min) but a longer lasting clinical effect (up to 60 min).

Metabolism of oxytocin is via the renal and hepatic routes. Its antidiuretic effect, amounting to 5% of the antidiuretic effect of the endogenous peptide hormone vasopressin, can result in water toxicity, especially if administered in large volumes of electrolyte-free solutions. This degree of water overload can manifest itself with headache, vomiting, drowsiness and convulsions. On the other hand, rapid intravenous bolus administration of undiluted oxytocin results in relaxation of vascular smooth muscle, which can lead to hypotension. The intravenous route is contraindicated in known hypersensitivity or profound hypotension. It is therefore best given intramuscularly or by dilute intravenous infusion. Oxytocin is stable at temperatures up to 25°C, but refrigeration is recommended if stored for extended periods to prolong its shelf-life.

Disadvantages of oxytocin are its short half-life, the requirement for parenteral administration, and the need for refrigeration for storage. The use and re-use of syringes in low resource settings carry the risk of spreading infectious diseases such as HIV and hepatitis. Uniject injection devices have been proposed for some clinical circumstances, whereby 10 IU of oxytocin is administered in prefilled, disposable and non-reusable vials[17]. The long-acting oxytocin analog carbetocin with a more sustained action, similar to that of ergometrine but without its associated side-effects,

may offer advantages over standard oxytocic therapy[18]. Comparative studies of carbetocin for the prevention of PPH have identified enhanced effectiveness of this analog when compared with an oxytocin infusion[19,20] (see Chapter 44).

Whether the administration of oxytocin infusion (40 IU/h over 4 hours) after cesarean delivery is beneficial was the subject of the Elective Caesarean Section Syntocinon Infusion Trial (ECSSIT), a multicenter randomized trial. Over 2000 patients, who underwent elective cesarean delivery at term, were randomized to either oxytocin bolus or oxytocin bolus and infusion. Results showed no difference in the occurrence of major hemorrhage between the groups (bolus and infusion 15.7% versus bolus only 16.0%). However, oxytocin infusion was found to be beneficial in patients who were delivered by a junior obstetrician[22].

ERGOMETRINE

In contrast to oxytocin, the administration of ergometrine results in a sustained tonic uterine contraction via stimulation of myometrial α-adrenergic receptors. Both upper and lower uterine segments are stimulated to contract in a tetanic manner[16]. Intramuscular injection of the standard 0.25 mg dose results in an onset of action of 2–5 min. Metabolism is via the hepatic route, and the mean plasma half-life is 30 min. Nonetheless, the clinical effect of ergometrine persists for approximately 3 h. The co-administration of ergometrine and oxytocin results in a complementary effect, with oxytocin achieving an immediate response and ergometrine a more sustained action.

Common side-effects of ergometrine include nausea, vomiting and dizziness; all are more striking when the intravenous route is used. As a result of its vasoconstrictive effect via stimulation of α-adrenergic receptors, hypertension can occur. Contraindications to the use of ergometrine therefore include hypertension (including pre-eclampsia), heart disease and peripheral vascular disease. If given intravenously, where its effect is almost immediate, it should be administered over 60 s with careful monitoring of pulse and blood pressure. Its heat lability is relevant to the developing world in particular. Ergometrine is both heat and light sensitive, and should be stored at temperatures below 8°C and away from light.

The product Syntometrine® (5 units oxytocin and 0.5 mg ergometrine) combines the rapid onset of oxytocin with the prolonged effect of ergometrine. The mild vasodilatory property of oxytocin may counterbalance the vasopressor effect of ergometrine.

First-line treatment of uterine atony, along with bimanual massage, therefore involves administration of oxytocin or ergometrine as an intramuscular or diluted intravenous bolus, followed by repeat dosage if no effect is observed after 5 min and complemented by continuous intravenous oxytocin infusion. Atony that is refractory to these first-line oxytocics warrants prostaglandin (PG) therapy from a medical point of view, the institution of bimanual massage at the bare minimum, inspection of the vulva, vagina and cervix, assessment of the presence of retained tissues, and other modalities mentioned in this text.

CARBOPROST

Carboprost (15-methyl PGF2α) acts as a smooth muscle stimulant and is a recognized second-line agent for use in the management of postpartum uterine atony unresponsive to oxytocin or ergometrine. It is an analog of PGF2α (dinoprost) with a longer duration of action than its parent compound, which is attributed to its resistance to inactivation by oxidation at the 15-position. Available in single-dose vials of 0.25 mg, it may be administered by deep intramuscular injection or, alternatively, by direct intramyometrial injection. The latter route of administration is achieved either under direct vision at cesarean section or transabdominally or transvaginally following vaginal delivery and has the advantage of a significantly quicker onset of action[23,24]. Peripheral intramuscular injection yields peak plasma concentrations at 15 min in contrast to less than 5 min for the intramyometrial route. Using a 20-gauge spinal needle, intravascular injection can be avoided by pre-injection aspiration, and intramyometrial rather than intracavitary placement of the needle can be confirmed by observing resistance on injection, as described by Bigrigg and colleagues[25]. The dose may be repeated every 15 min up to a maximum cumulative dose of 2 mg (eight doses), although, in reported case series, the majority of patients require no more than one dose.

Reported efficacy is high. Successful arrest of atonic hemorrhage was reported in 13/14 patients by Bigrigg and colleagues[25]. The largest case series to date[24], by Oleen and Mariano, involved a multicenter surveillance study of 237 cases of PPH refractory to standard oxytocics and reported an efficacy of 88%. The majority of women in this study required a single dose only.

Owing to its vasoconstrictive and bronchoconstrictive effects, carboprost can result in nausea, vomiting, diarrhea, pyrexia and bronchospasm. Contraindications therefore include cardiac and pulmonary disease. The cost of carboprost makes it unsuitable for consideration in low resource settings. Furthermore, it is both light and heat sensitive and must be kept refrigerated at 4°C.

MISOPROSTOL

Misoprostol is a synthetic analog of prostaglandin E1 which selectively binds to myometrial EP-2/EP-3 prostanoid receptors, thereby promoting uterine contractility. (Its use and clinical efficacy are discussed in Section 6) It is metabolized via the hepatic route. It may be given orally, sublingually, vaginally, rectally or via direct intrauterine placement. The rectal route of administration is associated with a longer onset of action, lower peak levels and a more favorable side-effect profile when compared with the oral or sublingual route. The results of an international

multicenter, randomized trial of oral misoprostol as a prophylactic agent for the third stage of labor showed it to be less effective at preventing PPH than parenteral oxytocin[26]. Fifteen per cent of women in the misoprostol arm required additional uterotonics compared with 11% in the oxytocin group. This may be due to its longer onset of action (20–30 min to achieve peak serum levels compared to 3 min for oxytocin). However, owing to the fact that its more prolonged time interval required to achieve peak serum levels may make it a more suitable agent for protracted uterine bleeding, there is mounting interest in its role as a therapeutic rather than a prophylactic agent.

The use of rectal misoprostol for the treatment of PPH unresponsive to oxytocin and ergometrine was first reported by O'Brien and colleagues[27] in a descriptive study of 14 patients. Sustained uterine contraction was reported in almost all women within 3 min of its administration. However, no control group was included for comparison. A single-blinded, randomized trial of misoprostol 800 µg rectally versus Syntometrine intramuscularly plus oxytocin by intravenous infusion found that misoprostol resulted in cessation of bleeding within 20 min in 30/32 cases (94%) compared to 21/32 (66%) for the comparative agents[28]. A Cochrane review supports these findings, suggesting that rectal misoprostol in a dose of 800 µg could be a useful 'first-line' drug for the PPH[29].

Although oxytocin is the drug of choice in the management of obstetric hemorrhage, misoprostol is an excellent and widely used alternative when the use of oxytocin is not possible. The latter has the significant advantage of low cost (US$ 0.10/ tablet), thermostability, long shelf life, light stability and lack of requirement for sterile needles and syringes for administration. The optimal dosage of misoprostol is the subject of ongoing debate (see Chapter 34). Physiological studies have shown uterotonic effects with doses as low as 200 µg. In their systematic review, Hofmeyr et al. state that 400 µg misoprostol may be safer than and just as effective as 600 µg for PPH prophylaxis[30]. For treatment, doses lower than 800 µg may be as effective. The same review describes that 8/11 maternal deaths occurred in women receiving more than 600 µg misoprostol which raises concern over its safety or the accuracy in ascribing the cause of hemorrhage to atony. Further research needs to address the smallest dose of the drug that is effective and safe.

The need to evaluate the effectiveness of misoprostol is ongoing in settings where other standard uterotonic agents are not available. Recently the community-based distribution of misoprostol has been proposed as a means of reducing maternal mortality rates in regions where home births are prevalent. In many countries, women are currently empowered to self-administer 600 µg misoprostol orally to prevent PPH (see Chapter 42). WHO initially welcomed this approach[31], but more recently due to the unresolved concern regarding a possible increase in the risk of maternal mortality concluded that its use should not be extended to distribution on a community level[32]. There is an urgent need for FIGO and WHO to release a joint statement for the use of misoprostol in developing countries and the circumstances under which it is best used.

Side-effects of misoprostol are mainly gastrointestinal and are dose and route dependent. The commonly reported side-effects of shivering and pyrexia are usually self-regulating and certainly not life threatening. Moreover, shivering occurs commonly even when misoprostol has not been administered. Oral and sublingual routes of administration achieve a higher and quicker maximum plasma concentration than vaginal or rectal administration, which results in higher rates of shivering and high grade fever[33].

OTHER PROSTAGLANDINS

Dinoprost (prostaglandin F2α) is used via intramyometrial injection at doses of 0.5–1.0 mg with good effect[34]. Low-dose intrauterine infusion via a Foley catheter has also been described, consisting of 20 mg dinoprost in 500 ml saline at 3–4 ml/min for 10 min, then 1 ml/min. Bleeding was arrested in all but one of 18 patients and no adverse outcome was reported. As mentioned earlier, however, this agent has a shorter duration of activity than carboprost and indeed has been unavailable in the US since the 1980s where its withdrawal was attributed to financial considerations.

Prostaglandin E2 (dinoprostone), in spite of its vasodilatory properties, causes smooth muscle contraction in the pregnant uterus, thus making it a potentially suitable uterotonic agent. Its principal indication is in pre-induction cervical priming, but intrauterine placement of dinoprostone has been successfully employed as a treatment for uterine atony[35]. The vasodilatory effect of dinoprostone, however, renders it unsuitable for use in the hypotensive or hypovolemic patient. It may, however, be of use in women with cardiorespiratory disease in whom carboprost is contraindicated.

Experience with gemeprost, a prostaglandin E1 analog, in pessary formulation delivered directly into the uterine cavity or placed in the posterior vaginal fornix, is largely anecdotal[36–38]. Its mode of action resembles that of PGF2α. Rectal administration has also been reported. A retrospective series of 14 cases in which rectal gemeprost 1 mg was used for PPH unresponsive to oxytocin and ergometrine reported prompt cessation of bleeding in all cases, with no apparent maternal adverse sequelae[39].

HEMOSTATICS: TRANEXAMIC ACID AND RECOMBINANT ACTIVATED FACTOR VII

The antifibrinolytic agent, tranexamic acid, prevents binding of plasminogen and plasmin to fibrin; as such, it may well have a role in the control of intractable PPH, particularly where coagulation is compromised. A recent review[40] suggests that tranexamic acid reduces the amount of blood loss at cesarean and

Table 2 Medical uterotonic therapy

Agent	Dose	Cautions
Oxytocin (Pitocin®, Syntocinon®)	5 or 10 IU im/iv followed by iv infusion of 40 IU in 500 ml crystalloid titrated versus response (e.g. 10 IU/h)	Hypotension if given by rapid iv bolus. Water intoxication with large volume
Ergometrine (Ergonovine®)	0.25 mg im/iv	Contraindicated in hypertensive patients. Can cause nausea/vomiting/dizziness
Carboprost (15-methyl PGF2α) (Hemabate®)	0.25 mg im repeat every 15 min to maximum dose of 2 mg (8 doses)	Bronchospasm (caution in patients with asthma, hypertension, cardiorespiratory disease)
Dinoprost (PGF2α) (Prostin F2α®)	0.5–1 mg intramyometrial or 20 mg in 500 ml N/saline infused via Foley catheter into uterine cavity	Bronchospasm, nausea, vomiting and diarrhea can occur
Dinoprostone (Prostin®/Prepidil®)	2 mg pr 2-hourly	Hypotension
Gemeprost (Cervagem®)	1–2 mg intrauterine placement/1 mg pr	Gastrointestinal disturbance
Misoprostol (Cytotec®)	0.6–1 mg pr/intracavitary 0.6–0.8 mg orally/sublingually	Gastrointestinal disturbance, shivering, pyrexia
Tranexamic acid (Cyclokapron®)	1 g 8-hourly iv	May increase risk of thrombosis
rFVIIa (Novoseven®)	60–90 μg/kg iv	Fever, hypertension

im, intramuscularly; iv, intravenously; pr, per rectum

vaginal deliveries, and reduces the requirement for blood transfusion. Tranexamic acid (1 g) is cheap and appears to be safe and effective in the prevention and management of bleeding during pregnancy. The currently ongoing World Maternal Antifibrinolytic Trial (WOMAN)[41], a randomized double-blind placebo-controlled trial, aims to determine the effect of early administration of tranexamic acid on mortality, hysterectomy and other morbidities (surgical interventions, blood transfusion, risk of non-fatal vascular events) in 15,000 women with clinically diagnosed PPH.

The use of recombinant activated factor VII (rFVIIa, Novoseven®) as a hemostatic agent for refractory PPH is described elsewhere in this volume. The mode of action of this agent involves enhancement of the rate of thrombin generation, leading to formation of a fully stabilized fibrin plug that is resistant to premature lysis. Currently, recombinant factor VIIa (60–90 μg/kg) is advocated only after failure of other conventional therapies including embolization or conservative surgery, but prior to peripartum hysterectomy[42]. A recent review of 272 published cases showed that Novoseven arrested or reduced bleeding in 85% of cases[43]. Prospective randomized controlled trials are highly desirable, but may not be forthcoming because of the reluctance of clinicians to enter their patients in such trials. A full discussion can be found in Chapter 50 of this textbook.

CONCLUSIONS

Although the decline in the number of deaths from obstetric hemorrhage in the developed world is impressive, the developing world has benefited little from the many medical advances of the past two decades, especially when one considers deaths directly related to PPH. Even in the UK, the 2006–2008 triennial report[44] recorded five maternal deaths from PPH. In 60% of these deaths, there was a concern over substandard care; in particular, routine observation in the postpartum period was lacking, or it was not appreciated that bleeding was occurring. Regular observations of pulse and blood pressure should be made postdelivery. The use of modified early obstetric warning score (MEOWS) charts should alert caregivers to abnormal trends in hemodynamic measurements that require further action. Obstetricians, midwives and hospital management staff need to be vigilant and ensure that care is optimized through use of regular drills and skills (see Chapter 36) and adherence to national guidelines to further reduce hemorrhage-related maternal deaths[44]. Integral to any protocol on management of PPH will be a stepwise approach to achieving effective uterine contractility.

The successful management of uterine atony depends on staff being thoroughly familiar with the pharmacologic agents available to them with respect to dosage, route of administration and safety profile (Table 2). Application of such protocols achieves a successful reduction in the morbidity associated with PPH[45]. It is tempting to credit the second- or third-line agent with successfully controlling a PPH; however, it is certainly plausible that a synergistic effect is observed where a combination of uterotonics is used.

The global quest for an 'ideal' uterotonic agent must take into account the fact that what is applicable in one setting may have no relevance in another. The cost and instability of standard oxytocic drugs are prohibitive in many low resource settings. *Safety and parallel efficacy should therefore suffice as parameters by which an agent such as misoprostol is judged rather than demonstration of clinical superiority over established uterotonics*. There is an urgent need for a consensus statement to be issued by FIGO and WHO to make misoprostol available in communities where home births are prevalent. The self-administration of misoprostol is practiced in many developing countries and may be the single most efficient way to reduce maternal mortality.

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