27

STANDARD MEDICAL THERAPY

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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. Uterine atony is a condition which, in spite of the presence of effective medical interventions, still claims thousands of maternal lives. In the developing world, lack of access to uterotonic therapies that have been available for almost a century represents one of the most glaring disparities in obstetric care today.

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[1,2]. 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[3]. 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 postpartum hemorrhage at a time when, according to an 1870 report, maternal mortality in England approached one in 20 births[4]. Attempts to isolate the active alkaloids from ergot were not successful until the early 20th century, when Barber and Dale isolated ergotoxine in 1906[2]. Initially thought to be a pure substance, this agent was subsequently found to comprise four alkaloids and in 1935 Moir and Dudley were credited for isolating ergometrine, the active aqueous extract 'to which ergot rightly owes its long-established reputation as the pulvis parturiens'[5,6]. Moir reported on its clinical use in 1936, stating[6]:

> '. . . 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.'

Oxytocin, the hypothalamic polypeptide hormone released by the posterior pituitary, was discovered in 1909 by Sir Henry Dale[7] and synthesized in 1954 by du Vigneaud[8]. 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[9] 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 strong myometrial tetanic activity, are increasingly being employed as adjunctive therapy to standard oxytocin and ergometrine to treat postpartum hemorrhage resulting from uterine atony (see Chapter 12).

This chapter is devoted to critical evaluation of the standard pharmacological methods available to overcome 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 contribution that uterine atony makes toward postpartum hemorrhage is so well-known that a universal reflex action when faced with excessive postpartum bleeding is to massage a uterine contraction. Prompt recognition of this condition and institution of uterotonic therapy will effectively terminate the majority of cases of hemorrhage. Once effective uterine contractility is assured, persistent bleeding should prompt the search for retained placental fragments, genital tract trauma or a bleeding diathesis (see Chapters 9 and 25).

Astute risk assessment is crucial in identifying women at increased risk of uterine atony, thereby allowing for preventive measures to be instituted and for delivery to take place where transfusion and anesthetic facilities are available. 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[10-12]. Previous postpartum hemorrhage confers a 2–4-fold increased risk of hemorrhage compared to women without such a history[12,13].

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
Oxytocin augmentation
Manual removal of placenta
Use of uterine relaxants
Deep anesthesia (especially halogenated anesthetic agents)
Magnesium sulfate
Intrinsic factors
Previous postpartum hemorrhage
Antepartum hemorrhage (abruptio or previa)
Obesity
Age > 35 years

It is appropriate that women with these predisposing risk factors should deliver in a hospital with adequate facilities to manage postpartum hemorrhage. Prophylactic measures adopted include appropriate hospital booking for women at risk, active management of the third stage of labor, intravenous access during labor and ensuring the availability of cross-matched blood. However, it is noteworthy that uterine atony occurs unpredictably in women with no identifiable predisposing risk factors. This underpins the need for strict protocols for the management of postpartum hemorrhage to be in place in every unit that provides obstetric care.

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[14]. The usual dose is 20 IU in 500 ml of crystalloid solution, with the dosage rate adjusted according to response (typical infusion rate 250 ml/h). When administered intravenously, the onset of action is almost instantaneous and plateau concentration is achieved after 30 min. 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, which amounts to 5% of the antidiuretic effect of vasopressin, can result in water toxicity if given in large volumes of electrolyte-free solutions. This degree of water overload can manifest itself with headache, vomiting, drowsiness and convulsions. Furthermore, rapid intravenous bolus administration of undiluted oxytocin results in relaxation of vascular smooth muscle, which can lead to hypotension. It is therefore best given intramuscularly or by dilute intravenous infusion. Oxytocin is stable at temperatures up to 25°C but refrigeration may prolong its shelf-life.

A disadvantage of oxytocin is its short half-life. The long-acting oxytocin analog carbetocin has been studied in this context as its more sustained action, similar to that of ergometrine but without its associated side-effects, may offer advantages over standard oxytocic therapy[15]. Comparative studies of carbetocin for the prevention of postpartum hemorrhage have identified enhanced effectiveness of this analog when compared with an oxytocin infusion[16,17].

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 thus stimulated to contract in a tetanic manner[14]. 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 therefore results in a complementary effect, with oxytocin achieving an immediate response and ergometrine a more sustained action.

Common side-effects include nausea, vomiting and dizziness and these are more striking when given via the intravenous route. As a result of its vasoconstrictive effect via stimulation of α-adrenergic receptors, hypertension can occur. Contraindications to use of ergometrine therefore include hypertension (including pre-eclampsia), heart disease and peripheral vascular disease. If given intravenously, where its effect is seen as being almost immediate, it should be given over 60 s with careful monitoring of pulse and blood pressure. Relevant to the developing world in particular is its heat lability. It 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, 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 will warrant prostaglandin therapy.

CARBOPROST

Carboprost (15-methyl $PGF_{2\alpha}$) 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/ergometrine. It is an analog of $PGF_{2\alpha}$ (dinoprost) with a longer duration of action than its parent compound, 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[18,19]. 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[20]. 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 is reported in 13/14 patients by Bigrigg and colleagues[20]. The largest case series to date[19] involved a multicenter surveillance study of 237 cases of postpartum hemorrhage 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 E_1 which selectively binds to myometrial EP-2/EP-3 prostanoid receptors, thereby promoting uterine contractility. 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 postpartum hemorrhage than parenteral oxytocin[21]. Fifteen percent 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 postpartum hemorrhage unresponsive to oxytocin and ergometrine was first reported by O'Brien and colleagues[22] in a descriptive study of 14 patients. Sustained uterine contraction was reported in almost all women within 3 min of its administration. However, there was no control group 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 (93%) compared to 21/32 (66%) for the comparative agents[23]. 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 treatment of primary postpartum hemorrhage[24].

A strong need exists for high-dose misoprostol to be evaluated in randomized control trials. As an alternative to the aforementioned uterotonics, misoprostol has the significant advantage of low cost, thermostability, light stability and lack of requirement for sterile needles and syringes for administration, making it an attractive option for use in the developing world. It has a shelf-life of several years.

Side-effects of misoprostol are mainly gastrointestinal and are dose-dependent. A frequently reported side-effect of misoprostol is the occurrence of shivering and pyrexia. Side-effects are less marked when the rectal route of administration is used.

OTHER PROSTAGLANDINS

Dinoprost (prostaglandin $F_{2\alpha}$) has been used via intramyometrial injection at doses of 0.5–1.0 mg with good effect[25]. 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. The 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 reasons.

Prostaglandin E_2 (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[26]. 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 E_1 analog, in pessary formulation delivered directly into the uterine cavity or placed in the posterior vaginal fornix, is again largely anecdotal[27-29]. Its mode of action resembles that of $PGF_{2\alpha}$. Rectal administration has also been reported. A retrospective series of 14 cases in which rectal gemeprost 1 mg was used for postpartum hemorrhage unresponsive to oxytocin and ergometrine reported prompt cessation of bleeding in all cases, with no apparent maternal adverse sequelae[30].

HEMOSTATICS: TRANEXAMIC ACID AND RECOMBINANT ACTIVATED FACTOR VII

The antifibrinolytic agent tranexamic acid, which prevents binding of plasminogen and plasmin to fibrin, may well have a role in the control of intractable postpartum hemorrhage, particularly where coagulation is compromised. However, to date there is only one case report in the literature of the use of this agent in the setting of postpartum hemorrhage; that particular case involved a placenta accreta where the source of the persistent bleeding was the lower uterine segment and the uterine body was described as being well contracted[31]. The dose employed was 1 g given intravenously 4-hourly to a cumulative dose of 3 g.

The use of recombinant activated factor VII (rFVIIa) as a hemostatic agent for refractory postpartum hemorrhage has recently been described in a number of case reports[32,33]. 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. Reported cases involve hemorrhage unresponsive to a myriad of conventional treatments including hysterectomy and pelvic vessel ligation, where use of this agent was remarkably successful at arresting seemingly intractable bleeding within a matter of minutes. Doses of 60–120 μg/kg intravenously were used. A more complete discussion of this agent is found in Chapter 26.

CONCLUSIONS

The identification of 'substandard care' in 71% of maternal deaths attributed to hemorrhage in the 2000–2002 Confidential Report (UK)[34] underscores the need for a standard of care to be established in every unit where childbirth takes place and for all relevant health-care workers to be keenly familiar with that standard (see Chapter 22). Integral to any protocol on management of postpartum hemorrhage will be a stepwise approach to achieving effective uterine contractility. The successful management of uterine atony will depend on staff being familiar with the pharmacologic agents available to them with respect to dosage, route of administration and safety profile (Table 2). Application of such protocols has been shown to achieve successful reduction in the morbidity associated with postpartum hemorrhage[35].

It is tempting to credit the second- or third-line agent with successfully controlling a postpartum hemorrhage; however, it is certainly plausible that a synergistic effect is observed where a combination of uterotonics is used.

Table 2 Medical uterotonic therapy

Agent	*Dose*	*Cautions*
Oxytocin (Pitocin®, Syntocinon®)	10 IU i.m./i.v. followed by i.v. infusion of 20 IU in 500 ml crystalloid titrated versus response (e.g. 250 ml/h)	Hypotension if given by rapid i.v. bolus. Water intoxication with large volumes
Ergometrine (Ergonovine®)	0.25 mg i.m./i.v.	Contraindicated in hypertensive patients. Can cause nausea/vomiting/dizziness
Carboprost (15-methyl $PGF_{2\alpha}$) (Hemabate®)	0.25 mg i.m./myometrial. Can be repeated every 15 min. Max. 2 mg	Bronchospasm (caution in patients with asthma, hypertension, cardiorespiratory disease)
Dinoprost ($PGF_{2\alpha}$) (Prostin $F_{2\alpha}$®)	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 p.r. 2-hourly	Hypotension
Gemeprost (Cervagem®)	1–2 mg intrauterine placement/ 1 mg p.r.	Gastrointestinal disturbance
Misoprostol (Cytotec®)	600–1000 μg p.r./intracavitary	Gastrointestinal disturbance, shivering, pyrexia
Tranexamic acid (Cyclokapron®)	1 g 8-hourly i.v.	Can increase risk of thrombosis
rFVIIa (Novoseven®)	60–120 μg/kg i.v.	Fever, hypertension

i.m., intramuscularly; i.v., intravenously; p.r., per rectum

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. This is particularly true of the need to study the potential of a low-cost agent such as misoprostol for use in the developing world. The cost and instability of standard oxytocic drugs are prohibitive in many low-resource settings. Safety and parallel efficacy should therefore suffice as parameters whereby an agent such as misoprostol is judged rather than demonstration of clinical superiority over established uterotonics.

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