Uterine atony

Hayley E. Miller[a] *and Jessica R. Ansari*[b]

Purpose of review
Postpartum hemorrhage (PPH) is the leading preventable cause of maternal morbidity and mortality worldwide. Uterine atony is identified as the underlying etiology in up to 80% of PPH. This serves as a contemporary review of the epidemiology, risk factors, pathophysiology, and treatment of uterine atony.

Recent findings
Rates of postpartum hemorrhage continue to rise worldwide with the largest fraction attributed to uterine atony. A simple 0–10 numerical rating score for uterine tone was recently validated for use during cesarean delivery and may allow for more standardized assessment in clinical and research settings. The optimal prophylactic dose of oxytocin differs depending on the patient population, but less than 5 units and as low as a fraction of one unit is needed for PPH prevention, with an increased requirements within that range for cesarean birth, those on magnesium, and advanced maternal age. Carbetocin is an appropriate alternative to oxytocin. Misoprostol shows limited to no efficacy for uterine atony in recent studies. Several uncontrolled case studies demonstrate novel mechanical and surgical interventions for treating uterine atony.

Summary
There is a critical, unmet need for contemporary, controlled studies to address the increasing threat of atonic PPH.

Keywords
postpartum hemorrhage, surgical interventions for atony, uterine atony, uterotonic treatment

INTRODUCTION

Postpartum hemorrhage (PPH) is the leading preventable cause of maternal morbidity and mortality worldwide. Globally, PPH accounts for 8% of maternal deaths in developed regions, 20% in developing regions, and approximately 11% in the United States [1▪]. Uterine atony is identified as the predominant driver of PPH worldwide, with a prevalence ranging from 30 to 80% depending on study methodology [2▪], followed by obstetric lacerations (∼20%), retained placental tissue (∼10%), and clotting-factor deficiencies (<1%) [1▪]. Uterine atony is loosely defined as the failure of the uterus to contract adequately after delivery of the placenta and is diagnosed by various methods including clinical judgment or scoring, second line uterotonic administration, hemorrhage or transfusion in the absence of other explanatory diagnoses [3]. As the incidence of uterine atony and PPH are rising, dedicated uterine atony randomized controlled trials are essential for assessing pharmacotherapy and surgical interventions.

EPIDEMIOLOGY AND INCIDENCE

The American College of Obstetricians and Gynecologists (ACOG) defines PPH as 1000 ml or more of blood loss or loss of blood accompanied by signs and symptoms of hypovolemia within 24 h of delivery [4]. The incidence of PPH and rates of massive blood transfusions (MBT) are rising despite efforts in reducing the most preventable contributor of maternal morbidity and mortality [5]. Uterine atony is the most common etiology for all PPH, and recent studies demonstrate that atony is also the most common etiology of severe hemorrhage and MBT [1▪,2▪,3–6].

MBT is defined by the WHO multicountry survey as transfusion of $\gtrsim$5 units of red blood cells or $\gtrsim$1000 ml of whole blood [5]. In one large observational study of 11 667 406 women in China, MBT showed an increasing trend year-over-year from

[a]Division of Maternal-Fetal Medicine and Obstetrics, Department of Obstetrics and Gynecology, Stanford University School of Medicine and [b]Division of Obstetric Anesthesia, Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford and Department of Anesthesiology, Stanford, Palo Alto, California, USA

Correspondence to Hayley E. Miller, MD, Center for Academic Medicine, OBGYN, Mail code 5317, Stanford University School of Medicine, 453 Quarry Road, Palo Alto, CA 94304, USA. Tel: +1 831 419 0566; e-mail: Hayleym@stanford.edu

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KEY POINTS

- Uterine atony remains the most common etiology of postpartum hemorrhage, severe maternal hemorrhage, obstetric massive blood transfusion, and hysterectomy.
- Epidemiologic studies have shown that rates of hemorrhage and uterine atony increased year-over-year since 2010.
- A standardized 0–10 numeric rating score has been validated for standardized assessment of uterine tone during cesarean delivery.
- Oxytocin and carbetocin are acceptable first line agents for prevention and treatment of uterine atony. Methylergonovine and carboprost are efficacious second line agents. Recent studies show minimal to absent efficacy of misoprostol for treating uterine atony.
- A more rigorous, randomized and controlled approach to evaluation of the many recent mechanical and surgical treatments proposed in case series literature is needed.

2012 to 2019 (P for trend <0.0001), with an overall incidence of 23.68 per 10 000 births. Uterine atony caused a population attributable fraction of MBT of 43%, more than three times the next-leading etiology [5]. A similar large population-based study from Ireland revealed that from 2011 to 2018, there was a 54% increase in major hemorrhage, a 60% increase in PPH, and a 54% increase in blood transfusion. Uterine atony was the most common cause (single causative agent for 40% of cases) of major hemorrhage [6].

DEFINING AND QUANTIFYING UTERINE ATONY

One of the challenges in both clinical care and in clinical research is consistency in the definition, communication, and assessment of uterine contraction tone. Clinical trials assessing uterotonic agents have historically used a variety of nonstandardized uterine tone assessment tools including satisfactory/nonsatisfactory, grades from A to F, and numeric scores on 0–10, 10–0, and 0–100 scales [7▪▪] (Fig. 1).

Cole *et al.* recently obtained serial uterine tone assessments on a 0–10 uterine tone numeric rating score (NRS) from 84 cesarean deliveries. The operating obstetricians palpated the uterine fundus, assigned a score at 3 and 10 min after fetal delivery, and were blinded to the score assigned by the other. The uterine tone NRS demonstrated good to excellent interrater reliability and good interrater agreement. The scale was also responsive to change in tone over time [7▪▪].

The relationship of uterine tone scores to clinical outcomes of blood loss, hemorrhage, and transfusion remains unknown. However, widespread adoption of a standardized quantitative scale may improve clinical communication between obstetricians and anesthesiologists and improve patient care. In addition, if strong correlation between uterine tone NRS and clinical outcome can be established, uterine tone scores may prove an acceptable intermediate outcome and asset for needed clinical research.

RISK FACTORS

Several studies have investigated risk factors of uterine atony across different populations. Risk stratification for PPH is commonly performed using an assessment tool from one of several organizations including ACOG and California Maternal Quality Care Collaborative (CMQCC) [8▪▪]. Among the most commonly accepted risk factors are induced or augmented labor, intraamniotic infection, cesarean birth, Hispanic ethnicity, prolonged labor and second stage of labor, preeclampsia, magnesium sulfate therapy, extremes of maternal age and parity (0 and >4), and uterine distension as a result of polyhydramnios, multiple gestation, or fetal macrosomia [1▪,2▪,5,8▪▪]. In a recent systematic review and meta-analysis of 1239 patients, additional identified risk factors included uterine rupture, predelivery oxytocin exposure, and instrumented vaginal delivery [8▪▪]. In this same review, several commonly cited risk factors were not found to confer an increased risk for PPH including polyhydramnios, maternal obesity, leiomyomas, prolonged second stage of labor, and magnesium sulfate exposure [8▪▪].

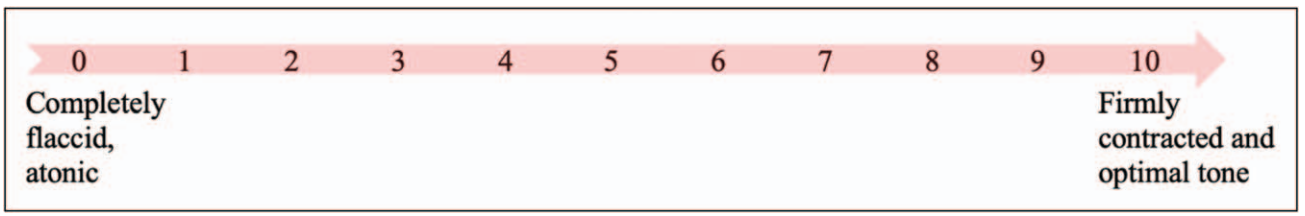

FIGURE 1. Palpation of the uterine fundus during cesarean delivery.

It has been well established that cesarean birth is a common risk factor for atonic PPH, and this risk also appears increased after trial of labor after cesarean birth (TOLAC) [9]. A recent large retrospective cohort study assessed risk of atonic PPH among people attempting TOLAC compared to people attempting labor with an unscarred uterus. This study of 1455 pregnant patients showed a significantly higher incidence of uterine atony, PPH, and blood transfusion after TOLAC. This risk was highest for patients whose indication for prior cesarean was second stage arrest [9].

Unfortunately, identification of risk factors has limited utility for predicting uterine atony. A substantial proportion of PPH occurs in the absence of risk factors, and current risk-assessment tools fail to include risks that appear to be well established. Two large studies suggest only 39–50% of people with uterine atony had an identified risk factor [2▪]. Therefore, vigilance after all deliveries is critical in preventing a PPH secondary to uterine atony.

PATHOPHYSIOLOGY

Because uterine blood flow at term pregnancy can reach as high as 1300 ml/min, failure of the uterus to contract after delivery of the placenta can lead to rapid hemorrhage from the placental bed [10]. Under normal conditions, strong, sustained myometrial contraction compresses the spiral arteries supplying the placental bed. Tissue factor type-1 plasminogen activator inhibitor in addition to coagulation factors promote blood clotting and hemostasis [11].

The detailed cellular-level physiology of myometrial contraction is beyond the scope of this review; however, at its most basic, sodium ion influx followed by increased intracellular calcium from both intracellular and extracellular sources results in myosin light-chain kinase activity and smooth muscle contraction [12]. Uterotonic agents work via different mechanisms to increase intracellular calcium and promote myometrial contractility [12].

TREATMENT

Pharmacologic agents

Management of the third stage of labor includes uterine massage, umbilical cord traction, and prophylactic treatment with oxytocin or carbetocin. Additional dosing of oxytocin or carbetocin, as well as second-line uterotonic agents methylergonovine, 15-methyl-PGF2-alpha (carboprost), and misoprostol, and are used to intervene when uterine atony is recognized. These uterotonic therapies, detailed in Fig. 2, reduce PPH from uterine atony by 40–50% [1▪,2▪,12].

Pharmacologic prophylaxis

Oxytocin is the first-line therapy for prevention of uterine atony. Oxytocin stimulates rhythmic myometrial contractility in low doses and sustained, tetanic uterine contraction in higher doses. Oxytocin infusions and dosing vary among different populations based upon mode of delivery and risk factors. Several small studies have assessed appropriate oxytocin dosing among these populations [1▪,2▪,13].

In a 2021 systematic review assessing oxytocin dosing regimens following cesarean birth, an oxytocin bolus 0.5–3 IU was considered an effective prophylactic dose, and adverse hemodynamic effects were observed when >5 IU oxytocin bolus was used [13]. These findings were confirmed by a 2021 meta-analysis, showing that oxytocin bolus plus infusion regimens may lead to minor reductions in mean blood loss, and doses >5 IU may lead to increased side effects [14▪▪].

Multiple recent small RCTs have assessed oxytocin bolus dose requirements in specific high-risk patient populations. Of note, all studies found an oxytocin bolus dose requirement well under 5 units (and generally under 1 unit). A randomized controlled trial of oxytocin bolus dosing at the time of cesarean delivery showed that patients with a history of prior cesarean birth required a higher oxytocin dose (0.95 units [95% confidence interval (CI) 0.82–1.08] vs. 0.55 units [95% CI 0.38–0.73], $P < 0.001$) [15]. Similarly, when patients with preeclampsia receiving magnesium sulfate were compared to nonhypertensive patients (not on magnesium) at the time of cesarean, patients on magnesium required significantly higher oxytocin doses and suffered significantly more side effects and hypotension as a result [16]. Women >35 years of age required more oxytocin to achieve adequate uterine tone compared to their younger counterparts (1.41 IU; 95% CI, 0.63– 2.19) vs. 0.66 IU (0.04–1.29), $P < 0.001$), with a higher prevalence of adverse effects [17]. Finally, one small study found that obese women required higher oxytocin bolus dosing at cesarean than historic controls (ED90 still < 1 unit) [18].

Carbetocin, a long-acting synthetic analogue of oxytocin, has been shown to reduce the incidence of PPH and the need for additional uterotonics when compared to oxytocin [19]. However, carbetocin is unavailable for use in the United States. Carbetocin has a different structure and a longer half-life compared to oxytocin. Its pharmacokinetic profile

Drug	Dose and Route	Frequency	Onset of action	Contraindications	Adverse Effects
Oxytocin	IV: 10-40 units per 500-1,000 mL IM: 10 units	Continuous	3-5 min	Rare, hypersensitivity to medication	Usually none. Depending on dose and route: Nausea, vomiting, headache, flushing Hyponatremia with prolonged dosing. Risk of hypotension, tachycardia, ST-segment depression, myocardial ischemia, arrhythmias with high doses
Carbetocin	IV or IM 100 micrograms	Once	2 min	Use with caution in patients with asthma, epilepsy, migraine, cardiovascular disease	Same as above
Methylergonovine	IM: 200 micrograms	Every 2-4 hours	2-5 min	Hypertension, preeclampsia, peripheral vascular disease (Raynaud phenomenon, ischemic heart disease.	Nausea, vomiting, severe hypertension, headache
15-methyl-PGF2-alpha	IM: 250 micrograms Intramyometrial: 0.25 mg	Every 15-90 min, eight doses maximum (2 gm)	2-5 min	Asthma. Relative contraindication for hypertension, active hepatic pulmonary or cardiac disease.	Nausea, vomiting, diarrhea, fever (transient), headache, chills, shivering, hypertension, bronchospasm, hypoxemia
Misoprostol	600-1,000 micrograms oral, sublingual, or rectal	One time	Variable based on administration	Rare, hypersensitivity to medication or prostaglandins.	Nausea, vomiting, diarrhea, shivering, fever (transient), headache

FIGURE 2. Pharmacologic agents and properties in treatment for atonic PPH. PPH, postpartum hemorrhage.

allows for a reduction in infusion after the initial bolus [1▪,2▪,19]. However, the major pitfall of carbetocin is the cost. No cost-effectiveness studies have shown a benefit to using carbetocin compared to oxytocin [19]. A recent retrospective cohort study comparing outcomes among patients who received carbetocin compared to oxytocin showed similar overall outcomes between groups. In the subgroups of patients with placenta previa and multiple gestation, investigators noted a decrease in the need for second line uterotonics, blood transfusion, and PPH [19].

The adverse effects of these prophylactic medications depend on the dose and route of administration. Adverse effects include hypotension, tachycardia, ST-segment depression, myocardial

ischemia, arrhythmias, and less severe side effects include flushing, headache, nausea, and vomiting. A double-blind study comparing IV bolus doses of carbetocin 100 μg and oxytocin 5 IU found no significant differences in hemodynamic parameters between groups [20].

Pharmacologic treatment

Medications used for treatment of uterine atony have limited recent studies; however, it is important to review mechanism of action, dose, route of administration, frequency of dosing, and common side effects and contraindications [1▪,2▪,4].

Methylergonovine is an ergot alkaloid and is indicated for the prevention and treatment for uterine atony. Methylergonovine is administered at a dose of 200 μg intramuscularly, with rapid onset of action within 2–5 min, peak plasma levels in 20–40 min, and a long half-life of approximately 2 h. Because oxytocin bolus and rapid hemorrhage can mask hypertensive side effects of methylergonovine, repeat dosing is not recommended until 2–4 h after initial dose. Nausea and vomiting are cited as the most common side effects, however, hypertension, myocardial ischemia and infarction, cerebrovascular accidents, seizures, or death have been documented. Relative contraindications include hypertensive disorders, peripheral vascular disease, and ischemic heart disease [1▪,2▪,4].

Carboprost is a synthetic analog of prostaglandin F2α, which works to increase myometrial intracellular free calcium concentration. Carboprost is administered at a dose of 250 μg intramuscularly, with similar pharmacokinetic profile to methylergonovine: onset in 2–5 min, plasma level peak after 20–30 min, and a half-life of approximately 2 h. Dosing can be repeated every 15–20 min up to a maximum of 2 mg. Common adverse effects include fever, chills, diarrhea, nausea, and vomiting, with a clinically insignificant increase in blood pressure. Carboprost also impacts bronchial smooth muscle and thus has respiratory side effects most often seen after multiple doses, including bronchospasm, abnormal ventilation-perfusion ratio, increased pulmonary shunt fraction, and hypoxemia. As carboprost-induced bronchospasm may be life-threatening, asthma is considered a relative contraindication [1▪,2▪,4].

Misoprostol (15-deoxy-16- hydroxy-16-methyl PGE1) is a synthetic prostaglandin E1 analog [1▪,2▪,4]. Misoprostol is inexpensive and easily accessible, however, is not as effective as other pharmacological treatments in the management of uterine atony due at least in part to very slow onset. Two randomized controlled trials have demonstrated that misoprostol is ineffective as a second line uterotonic agent (no better than placebo or additional oxytocin); however, these trials did demonstrate a high incidence of fever and shivering as misoprostol side effects [21▪▪,22▪▪]. A first-line uterotonic medication meta-analysis in 2020 concluded that misoprostol makes little or no difference in uterine atony but produces more side effects [23▪▪]. As such, misoprostol may only have a role in treatment of uterine atony when other agents are contraindicated or unavailable. There are no contraindications to misoprostol other than an allergy to prostaglandins.

MECHANICAL AND SURGICAL APPROACHES TO TREATING UTERINE ATONY

In cases of failed pharmacologic management, mechanical and surgical intervention offers an attempt to treat uterine atony. Several uncontrolled case series on surgical techniques have been published in recent years that offer various techniques using compression sutures, balloon tamponade, and vacuum systems [24–27,28▪,29,30▪▪]. Although these techniques offer alternatives to pharmacologic therapy, the studies did not use randomized design, so their efficacy should be interpreted with caution.

Intrauterine balloon tamponade including Bakri balloon placement has been shown to have an overall success rate of 85.9% in the treatment for PPH [28▪]. Intrauterine balloon tamponade has been accepted as an effective intervention for uterine atony among low-resource settings with a low complication rate. However, a recent large meta-analysis suggests that independent use of intrauterine balloon tamponade effectiveness from randomized and nonrandomized studies has no beneficial effect [28▪]. A recent small, randomized control trial showed dual intervention of intrauterine balloon compression with ascending uterine artery ligation resulted in longer surgical time, but significantly improved hemorrhage control, blood loss after Bakri removal, and postpartum quality of life scores when compared to Bakri balloon use alone [29].

The most frequent approach to uterine compression sutures is the B-Lynch suture, however, modifications to the technique have been proposed due to complications including pyometra, endometritis, uterine synechiae, and necrosis. Several small studies have described the following alternatives:

(1) Isthmic circumferential suture requires a suture at the level of the incision line, through the avascular windows of the broad ligament, with simultaneous Bakri balloon use [24];

(2) Alternative pull-on compress and pull-on release approach requires the surgeon to tighten the suture continuously during the assistants alternative compression and release of the uterus [25];
(3) The 'uterine sandwich' technique has demonstrated hysterectomy sparing in cases of severe uterine atony through the simultaneous use of B-Lynch suture and intrauterine balloon tamponade [26];
(4) Vertical compression sutures, similar to the Hayman technique which is classically described after vaginal delivery (without a hysterotomy), includes bilateral sutures placed 2 cm from the lateral edge of the uterus and 4 cm from the cornual border, and a third placed in the midline at the same level [27].

New vacuum control devices offer novel alternatives for treating PPH. The Jada System is a recently FDA-approved device that uses low-level vacuum to encourage the natural force of uterine contraction to control PPH. After birth, the device is placed transvaginally, a balloon is used to create a cervical seal, and the device is connected to evacuate blood and facilitate uterine contractions. The device cannot be used with a cervix <3 cm dilated, concurrent intrauterine infection, uterine anomaly, uterine rupture, or current cervical cancer [30▪▪]. However, as blinded and controlled studies are lacking, evidence to date only provides proof of principle and feasibility of placement of this new device.

New strategies to manage PPH and uterine atony are needed, and although these approaches include small studies, they should be considered when medical management fails.

Embolization

Embolization of pelvic blood vessels including the uterine arteries is an alternative approach to atonic PPH utilized when pharmacologic and surgical methods have failed and the patient desires future fertility. Embolization is generally reserved for hemodynamically-stable patients without suspicion for uncontrolled coagulopathy. Patient selection should be determined by a multidisciplinary team including interventional radiology. Angiography is usually performed through femoral arterial access with embolization of the internal iliac, uterine, pudendal, and/or obturator arteries depending on the visualized site of bleeding. A variety of agents including gelatin, polyvinyl alcohol, cyanoacrylate, micro-coil, or glue particles, are injected to occlude the vessel proximal to the site of extravasation [31,32]. In a 2020 systematic review and meta-analysis including 43 studies, pelvic artery embolization showed a clinical success rate of 90.5% for PPH and a technical success rate of 99.3%. Major adverse effects included postembolization syndrome generally characterized by transient low-grade fever, pain, fatigue, nausea, and vomiting that peaks 48 h after the procedure, as well as menstrual abnormality and PPH in subsequent pregnancy. This review showed that gelatin sponge granules were the safest and most effective as embolic agents for PPH. Clinical failure was related to placenta accreta spectrum, low hemoglobin level, coagulation factors, and number of transfusions [32].

Hysterectomy

Many of these interventions are not possible in developing countries with the given infrastructure and access to massive blood transfusions and interventional radiology services [1▪]. In developing countries and when all interventions have failed, emergent hysterectomy may be the best management option for people with unremitting uterine atony. The emergent nature of this procedure poses surgical risks, as well as other complications including hypovolemic shock, disseminated intravascular coagulopathy, and adult respiratory distress syndrome. In a 2-year retrospective descriptive cross-sectional study, 146 emergent hysterectomies were documented, and the main indication was PPH (73.3%), with uterine atony cited as the most common etiology (54.2%) [33]. Emergent hysterectomies are life-saving procedures, and complication rates can be minimized with experienced and skilled surgical teams.

CONCLUSION

Uterine atony remains the leading cause of maternal PPH, severe hemorrhage, and massive blood transfusion worldwide [1▪,2▪]. Concerningly, the incidence of uterine atony and maternal PPH continues to increase year over year [1▪,2▪,3,4]. As such, improved modalities for assessment, prevention, and treatment of uterine atony are essential. A recently validated uterine tone numeric rating system may improve and standardize assessment of uterine tone during cesarean deliveries [7▪▪]. Rigorous, randomized controlled assessment of novel pharmacologic therapies and surgical interventions are needed to effectively decrease obstetric morbidity and mortality from uterine atony.

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Conflicts of interest

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- ■ of special interest
- ■■ of outstanding interest

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This prospective study provides guidance on an objective assessment of uterine tone. The study compared obstetrician ratings of uterine tone during cesarean delivery using an 11-point, 0 to 10 numeric rating scale (NRS) to estimate the interrater reliability and agreement of the most commonly reported scoring system in the obstetric literature. This showed that the 0 to 10 NRS for uterine tone is a reliable tool to communicate the degree of uterine tone during cesarean delivery. This study offers an approach to scale uterine atony, particularly in a multidisciplinary team setting.

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A systematic review and meta-analysis using 27 studies, including 1239 records to better understand risk factors for atonic hemorrhage. This study highlights more definite risk factors and historical risk factors that showed no association with atonic hemorrhage. This study identifies novel risk factors to be included in risk-assessment tools.

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A systematic review performed to compare the available evidence on intravenous oxytocin dosing regimens for the prevention of postpartum hemorrhage following cesarean delivery. The study included peer reviewed articles that compared 2 different dosing regimens of intravenous oxytocin for postpartum hemorrhage prevention. 35 studies, 7333 people, were included and showed that bolus plus infusion regimens may lead to minor reductions in mean blood loss and initial bolus doses of <5 IU may minimize nausea. This provides oxytocin dosing guidance for physicians managing uterine atony.

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This was a large, randomized control trial (RCT) assessing the effectiveness of misoprostol as an adjunct to standard uterotonics compared with standard uterotonics alone for treatment of postpartum hemorrhage. This is a quality RCT that does not support the clinical use of sublingual misoprostol 600 micrograms used in conjunction with standard injectable uterotonics for treatment of postpartum hemorrhage. This is an RCT that contributes to contemporary literature and can influence pharmacotherapy management for uterine atony.

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A large, randomized control trial that can offer an alternative to standard dosing of intravenous oxytocin. Researchers and policy makers have been enthusiastic about misoprostol as treatment for postpartum hemorrhage, but evidence to support a particular regimen has been limited. This study provides evidence that sublingual misoprostol 800 micrograms is a reasonable alternative to 40 IU intravenous oxytocin for treatment of primary postpartum hemorrhage after oxytocin prophylaxis.

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A large Cochrane review included 3738 people in 10 countries from randomized controlled trials to identify the most effective uterotonic agents with the least side-effects for PPH. This review showed that adding misoprostol to the treatment of oxytocin likely makes little or no difference to outcomes. This is a large, heterogenous meta-analysis that provides guidance on pharmacotherapy management in PPH.

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This meta-analysis was conducted to evaluate the efficacy, effectiveness, and safety of uterine balloon tamponade for the management of postpartum hemorrhage. Their findings suggest that balloon tamponade systems seem safe and have >85% success in treating postpartum hemorrhage. The evidence on uterine balloon tamponade efficacy and effectiveness is conflicting, and this suggests uterine balloon tamponade should be considered for uterine atony.

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