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Uterotonic Agents

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ABSTRACT

Uterine atony is a common cause of primary postpartum hemorrhage, which remains a major cause of pregnancy-related mortality for women worldwide. Oxytocin, methylergonovine, carboprost, and misoprostol are commonly used to restore uterine tone. Oxytocin is the first-line agent. Methylergonovine and carboprost are both highly effective second-line agents with severe potential side effects. Recent studies have called into question the effectiveness of misoprostol as an adjunct to other uterotonic agents, but it remains a useful therapeutic in resource-limited practice environments. We review the current role these medications play in the prevention and treatment of uterine atony.

Keywords: Carboprost; Methylergonovine; Misoprostol; Oxytocin; Postpartum hemorrhage; Uterine atony; Uterotonic agent.

The mechanisms that regulate the onset of myometrial contractile activity are multiple and complex, involving hormonal mediators such as estrogen and progesterone, as well as other neuroendocrine mediators. Drugs capable of acting at the terminal part of this regulatory chain are called uterotonic agents and belong to three different classes (1, 2) (Figure 1):

- Oxytocin and its analogue carbetocin
- Ergot alkaloids
- Prostaglandins

These classes of drugs have different mechanisms of action, but ultimately, they all lead to an increase in intracellular calcium within the myometrial cell, a crucial event for the contraction of the muscle tissue to occur.

Oxytocin and its analogue are agonists of oxytocin receptors. Oxytocin receptors are transmembrane receptors belonging to the G protein family. This receptor family is characterized by the presence of seven transmembrane domains and two forms: one with low affinity for its ligand and one with high affinity. The latter is characterized by a structural modification (alteration of the orientation of domains 3 and 6) that more easily exposes the binding sites of the G protein (3,4). When the receptor binds to its ligand, the G protein is phosphorylated and induces the activity of phospholipase C-beta.

Through its activity, phospholipase C-beta releases inositol triphosphate (IP3) and diacylglycerol (DAG) into the intracellular space (3,4). IP3 promotes the release of Ca2+ ions from intracellular stores, and the increase in intracellular calcium concentration promotes the formation of the calcium-calmodulin complex and the sliding of actin and myosin filaments, leading to contraction (3,4).

Ergot alkaloids act as partial agonists of alpha receptors. A specific receptor in myometrial cells has not yet been identified; their main effect is vasoconstriction, and through a mechanism that is still not fully understood, they cause an increase in intracellular calcium, presumably by acting on calcium cellular channels, thereby promoting uterine contractile activity (5).

Prostaglandins (PGs) are a group of biologically active hydrated fatty acids derived from arachidonic acid, playing a role in maintaining pregnancy and initiating labor (6). Prostaglandins, similar to oxytocin, have specific receptors on myometrial cells, also belonging to the G protein family. They induce the release of cAMP and inositol triphosphate, leading to the release of Ca2+ into the cytoplasm, thereby triggering contractile activity and inducing the maturation of the uterine cervix. Additionally, they promote the expression of oxytocin receptors and strengthen the gap junctions of myometrial cells (72). The specificity of prostaglandin receptors expressed on the myometrium is for prostaglandins E and F (1).

(IP3: Inositol trisphosphate; Ca2+: Calcium ions; 5-HT: 5-hydroxytryptamine; a1: alpha-1; DAG: Diacylglycerol)

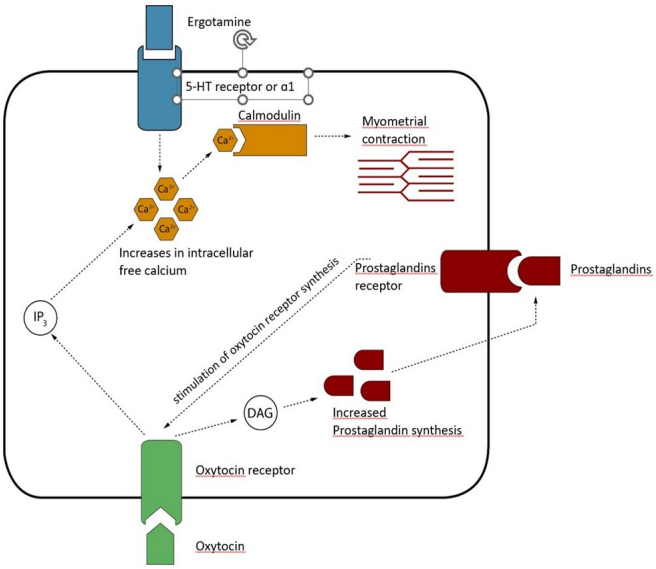

Figure No. 1 Receptor mechanisms of uterotonic drugs (2).

Oxytocin and its analogues

Oxytocin

Oxytocin is a synthetic product analogous to the nanopeptide produced by the magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus and secreted by the neurohypophysis in response to certain stimuli such as childbirth and nipple suction. To a lesser extent, it is synthesized by peripheral tissues such as the placenta, amnion, corpus luteum, and heart (4). Oxytocin is secreted in a pulsatile manner throughout pregnancy and the peripartum period. At the onset of labor, hormonal secretion peaks occur every 25-30 minutes, characterized by low amplitude and short duration. As the latent phase of labor progresses, the frequency, amplitude, and duration of pulsatile secretion progressively increase, reaching secretory peaks every 2.2 minutes during the expulsion period (7).

Oxytocin plays a central role in trophism, cellular differentiation, and proliferation, and the cascade of second messengers it induces by binding to its

receptor is complex and not perfectly understood. Among the identified pathways are:

- activation of Rho proteins, whose biological function is to regulate the activation of myosin light chain phosphorilation, providing greater tension in muscle fibers (3).
- activation of MAP kinases ERK1 and ERK2, which, at the cytoplasmic level, promote prostaglandin production and, at the nuclear level, induce a proliferative response (8).
- activation of EF2 (elongation factor 2), a protein involved in protein synthesis mechanisms (8).
- activation of MAP kinase 1, namely ERK5, whose biological function is to regulate the expression of the gene for myosin light chains and plays a crucial role in cellular development and differentiation (8).

The primary biological role of oxytocin is to induce uterine contractions during childbirth and lactation for breastfeeding. It is universally recognized as the first-choice drug in the treatment of uterine atony (9-11).

Oxytocin receptors are not equally expressed in the uterus throughout gestation. They are poorly expressed during pregnancy and before the onset of labor, while there is an increase in myometrial sensitivity to oxytocin due to an up-regulation of receptors, resulting from a hormonal change with a reduction in progesterone (4). Progesterone indeed plays a negative modulatory role in the affinity of oxytocin receptors. Some authors suggest that this is due to its binding with the receptors themselves (12), while others report that this function is mediated by its ability to interfere with cholesterol transport and thus interfere with the stabilization of the receptor in its high-affinity form for its ligand (13). Oxytocin receptors are also widely expressed peripherally, especially in the central nervous system, with variable expression depending on age (4).

Synthetic oxytocin must be stored protected from light at a temperature of 2-8°C. Its plasma half-life is very short (approximately 1-6 minutes), and consequently, continuous infusion is necessary to achieve a constant effect on uterine contractility. Intravenous administration has an almost immediate effect on contractility and reaches maximum efficacy after 30 minutes. On the other hand, intramuscular administration has a slower onset of contractile action (3-7 minutes), but its effectiveness lasts longer, up to an hour (10, 14). Generally, its administration is well-tolerated; however, some side effects have been reported in the literature (Table n.1), mostly involving the cardiovascular system (15). These adverse effects are more likely to occur if oxytocin is administered as a bolus; therefore, infusion is preferable when possible (16).

Common	Headache, bradycardia, tachycardia, nausea, vomiting
Uncommon	Cardiac arrhythmias
Rare	Skin rash
Very rare	Anaphylactic reaction, anaphylactic shock
Frequency unknown	Myocardial ischemia, prolonged QT interval, hypotension, uterine hypertonus, tetanic contractions, uterine rupture, hyponatremia, water intoxication, acute pulmonary edema, and DIC.

Table no. 1 Adverse effects of oxytocin reported in the literature.

Oxytocin desensitization

An important phenomenon related to prolonged exposure to oxytocin is called desensitization, which reduces the contractile response of the my-

ometrium to oxytocin; this process is typical of G protein-coupled receptors, and oxytocin receptors are no exception. This process, resulting from an overexposure between the ligand and its receptor, involves several steps, such as phosphorylation and uncoupling (which make the receptor functionally inactive) and removal from the cell membrane, with sequestration and degradation (17). Literature reports prolonged exposure to oxytocin results in reduced expression and synthesis of oxytocin receptors, reducing myometrial contractile activity (18-20). An in vitro study reports that pre-treatment with oxytocin results in a 50% reduction in receptors after 4.2 hours of exposure, with almost complete inhibition after 6 hours of exposure, demonstrating a time-dependent relationship between oxytocin exposure and desensitization; even increasing oxytocin doses are ineffective as receptor alterations are both functional and structural (19). In the in vitro model, a reduction in contractility with pre-treatment at different oxytocin concentrations was quantified, observing a greater reduction in contractile activity with pre-treatment at high doses compared to low doses (21). The phenomenon of desensitization is closely related to oxytocin receptor expression, thus signaling pathways activated by second messengers and the efficacy of uterotonic drugs with different mechanisms of action are preserved (19). Considering this phenomenon's understanding, it is advisable in patients with prolonged labor and undergoing oxytocin administration for induction or acceleration to administer drugs with different mechanisms of action for postpartum hemorrhage treatment.

Clinical studies report findings similar to those observed in vitro. A randomized study on 30 patients undergoing accelerated or induced labor with oxytocin and subjected to cesarean section due to labor arrest showed that patients previously exposed to oxytocin required a dosage 9 times higher than patients without oxytocin use during labor (22). In another randomized study of 40 patients, it was observed that in patients undergoing elective cesarean section, thus not exposed to oxytocin, uterine contractility was achieved with lower doses compared to patients who had labored (23). A case-control cohort study conducted in France between 2004 and 2006 collected data from 1483 patients whose delivery was complicated by postpartum hemorrhage, with the control group consisting of 1758 women who had delivered without complications. Results show that women who received oxytocin during labor had a significantly higher risk of developing postpartum hemorrhage compared to patients not exposed to oxytocin during labor. These results refer to patients not undergoing prophylactic oxytocin administration at delivery, while in those subjected to prophylaxis, the risk increase remains only in patients exposed to high doses of oxytocin; oxytocin exposure can be considered an independent factor for postpartum hemorrhage (24).

In light of these findings, attempts were made to investigate whether protocols involving oxytocin use for labor induction or acceleration showed a statistically significant difference between the use of high or low doses of oxytocin. A recent Cochrane review comparing outcomes of high and low-dose oxytocin protocols for labor induction reports no significant differences in maternal and neonatal outcomes between the two protocols, including the incidence of postpartum hemorrhage (25).

Several studies have sought to investigate the role time plays in desensitization. An in vitro study at-

tempted to define the time necessary for oxytocin receptors to re-sensitize, but the reported data showed no improvement in uterine contractility until 90 minutes of rest period after oxytocin suspension (21). In this case, the in vitro model shows limitations compared to the in vivo model, where the phenomenon of re-sensitization has been observed. A retrospective cohort study of 490 patients undergoing cesarean section after labor arrest reports that the longer the time without oxytocin administration, the less blood loss; another finding from this study is that the higher the dose of oxytocin used during labor, the higher the likelihood that further measures are needed to stop bleeding (26).

Despite desensitization, oxytocin is the drug of choice for postpartum hemorrhage prophylaxis, at a dosage of 10 IU intravenously or intramuscularly, even in patients whose labor has been exposed to oxytocin for induction or acceleration (27). In current practice, up to 40 IU of oxytocin can be administered in 500 or 1000 milliliters (ml) of intravenous fluids or 10 IU intramuscularly (9, 11).

Carbetocin

Carbetocin is a synthetic analogue of oxytocin with a longer half-life (42-50 minutes). Its action appears within 2 minutes of intravenous or intramuscular administration, and its side effects are minimal and comparable to those of oxytocin (28, 29). Its effectiveness in uterine contractions lasts longer compared to oxytocin. In vitro studies suggest that this is due to its longer half-life rather than a higher affinity for the receptor (30). A double-blind study investigating the efficacy of different doses of carbetocin in inducing satisfactory uterine contractions in patients undergoing elective cesarean section reported that a dose of 14.8 micrograms of carbetocin was sufficient to achieve effective uterine contractions in 90% of cases (31). Literature reports conflicting data when comparing oxytocin and carbetocin. In vitro studies suggest that carbetocin may be less effective, while clinical studies indicate that carbetocin is as effective as oxytocin, if not superior in certain circumstances. For instance, when used in the prophylaxis of postpartum hemorrhage in the case of cesarean section, some societies recommend it as a prophylaxis instead of oxytocin (29, 32). A double-blind randomized study comparing the efficacy of 100 micrograms of carbetocin with oxytocin in continuous infusion for controlling postpartum bleeding in 57 women demonstrated that carbetocin was as effective as oxytocin. Moreover, patients administered carbetocin required fewer additional interventions to stop bleeding (33). A large double-blind randomized study conducted in 23 countries involving 29,645 women compared the efficacy of 100 micrograms of carbetocin with 10 IU of oxytocin administered after vaginal delivery. The results show that carbetocin is not inferior to oxytocin for blood loss > 500 ml, the need for using other uterotonics, or other measures for controlling bleeding and for adverse effects (34). Considering the known phenomenon of desensitization affecting oxytocin receptors, it's not surprising that the effects of carbetocin are also influenced by prior exposure to oxytocin. An in vitro study investigated the effectiveness of oxytocin and carbetocin on myometrium pre-treated with oxytocin, reporting results that highlight the superiority of oxytocin over its analogue in inducing contractions in myometrium pre-treated with oxytocin (35).

World Health Organization guidelines consistently recommend oxytocin, in a dose of 10 IU intravenously or intramuscularly, for the prevention of postpartum hemorrhage, even in the presence of

other available oxytocics, including carbetocin (10).

The use of carbetocin, in a dose of 100 micrograms intravenously or intramuscularly, is indicated for the prevention of postpartum hemorrhage in settings where oxytocin is not available or its quality cannot be ensured. An important aspect to consider is that carbetocin is a more stable drug, being thermostable at room temperature and unaffected by light or freezing (purity > 95% for a minimum of 3 years at 30°C, 6 months at 40°C, 3 months at 50°C, and 1 month at 60°C). This characteristic makes it suitable for conditions where drug storage might be challenging, such as in low-income or developing countries (36).

Oxytocin remains the first-line drug for treating postpartum hemorrhage, with up to 40 IU of oxytocin administered in 500 or 1000 cc intravenous fluids or 10 IU intramuscularly (9, 11).

Ergot Alkaloids

Ergotamine Maleate and Methylergometrine

Ergot alkaloids were the first known uterotonic drugs, with their first mention dating back to a medical text in 1582. They were used from the late 1700s to the 1800s to induce labor. However, their use for this indication was abandoned in the early 1900s due to a high number of uterine ruptures. Instead, they were utilized in the third stage of labor to reduce bleeding (37). Among this class of drugs, ergotamine and methylergometrine are used in obstetrics for their greater uterotonic effects compared to their vasoconstrictive effects (5).

Due to their alpha-adrenergic stimulation, these drugs can cause significant side effects such as hypertension, severe nausea, and vomiting (38). Other rarer events described in literature include myocardial infarction, coronary artery spasm (39), the onset of eclamptic seizures (40), and intracranial hemorrhage (5). Because of their vasoconstrictive action, hypertension, preeclampsia, and cardiovascular diseases are contraindications to their administration (11). The vasoconstrictive action also affects arterioles, where it is a partial agonist on dopamine receptors (5).

A recent Cochrane review, updated in 2019, investigated the effectiveness of ergot alkaloids in postpartum hemorrhage prophylaxis compared to oxytocin. It failed to demonstrate the superiority of one over the other in preventing postpartum hemorrhage of more than 500 ml, in the need for transfusions, or in the further use of uterotonics. Moreover, ergot alkaloids were reported to have more side effects (41). The review reports, with low-quality evidence, that the combined use of oxytocin and ergotamine results in a reduction in postpartum blood loss but with an increase in side effects (41).

Currently, ergot alkaloids are used as second-line drugs for treating postpartum hemorrhage, administered in doses of 0.2 mg of methylergometrine intramuscularly or intravenously every 2-4 hours (11), or 0.5 mg of ergometrine intramuscularly or intravenously (9).

Prostaglandins

Prostaglandins (PGs) are part of the class of compounds called prostanoids, which are the end products of one of the pathways that arachidonic acid metabolism can undergo through cyclooxygenation (6). They perform various biological functions, have paracrine and autocrine activity, a short half-life, and mostly play a role as inflammatory media-

tors. Some of them, specifically prostaglandins E (PGE1 and PGE2) and F (PGF2a), play an important role in initiating contractile activity and cervical maturation (6). Prostaglandins are produced by fetal membranes and decidua. During pregnancy, fatty acids are stored in the cellular membranes of these tissues to be released towards term when the action of estrogen and other biochemical mediators (inflammatory cytokines, CRH) induces, on one hand, fetal lipase activity, releasing the precursor of prostaglandins from its storage, and on the other hand, cyclooxygenase activity, the enzymes catalyzing prostaglandin synthesis (1). At the end of pregnancy and the onset of labor, there is a progressive increase in prostaglandins, especially if labor has occurred spontaneously; contrary to oxytocin receptors, receptor expression does not vary in myometrial cells between pregnant and non-pregnant women (6). Studying the profile of prostaglandins in maternal circulation and in amniotic fluid suggests that prostaglandin E2 is mainly of fetal origin, while PGF2alpha is predominantly of maternal origin (42). Among prostaglandin receptors, EP1, EP2, and EP3 are found on myometrial cells, binding to prostaglandin E2, while FP and EP4 bind to prostaglandin PGF2alpha (1). Prostaglandin E2 has been shown to be more effective than F2alpha in inducing contractions and cervical maturation, probably due to greater receptor expression for PGE2 at the myometrial level (43). Literature reports that prostaglandins E and F have similar contractile activity, but F more frequently causes gastrointestinal symptoms, while E more frequently causes hyperthermia (6).

In vitro studies report oxytocin remains superior to prostaglandins in contractile effectiveness (44). In myometrium not pre-exposed to oxytocin, oxytocin is demonstrated to be superior to ergotamines and prostaglandins in inducing contractile activity, while in myometrium pre-treated with oxytocin, the combination with ergotamines and prostaglandins is more effective than oxytocin alone (45). For this reason, in various guidelines, prostaglandins are also indicated as second-line treatment, as an alternative to ergot alkaloids.

Prostaglandins are not exempt from side effects. Besides gastrointestinal disorders and hyperthermia, they can cause severe hypotension and pulmonary edema (46, 47).

Dinoprost and Carboprost

Dinoprost is an analog of prostaglandin F2a, whose use has been investigated both intravenously (48) and intrauterine, proving effective in stopping uterine atony bleeding after the administration of oxytocin and ergot alkaloids (49).

Carboprost (15-methyl-PGF2a) is a synthetic prostaglandin analogous to PGF2a. Methylation has increased its half-life and thus its effectiveness over time compared to the natural peptide (6).

It is administered at a dose of 0.25 mg, intramuscularly or intramyometrially, for a maximum of 8 administrations (total of 2 g); side effects are mostly of the gastrointestinal type, nausea, vomiting, and diarrhea due to the smooth muscle stimulation it exerts. It can cause a modest rise in blood pressure and bronchospasm, so it is contraindicated in patients with reactive respiratory diseases such as asthma; relative contraindications include cardiopulmonary or hepatic pathologies (50).

Misoprostol

Misoprostol is a synthetic analog of prostaglandin E1. FIGO guidelines indicate it as a second-line

therapy (after oxytocin or its analog) in low-resource settings in developing countries due to its low cost and storage at room temperature. It can be administered orally, sublingually, rectally, or vaginally, with dosages ranging from 600 to 1000 micrograms (51). Adverse effects depend on the route of administration and dose, and it is not yet clear which is the minimum dosage and the best route of administration (52). The uterotonic effects of misoprostol have long been known. In a systematic review that collected data on women treated with misoprostol for postpartum hemorrhage, an attempt was made to define the dosage and administration mode that offer the greatest efficacy at the expense of acceptable side effects. The results suggest that oral administration of 200 micrograms and 200-400 sublingual or rectal doses, or 200-400 sublingual or rectal doses, are adequate. It also suggests not exceeding the dose of 600 micrograms orally to reduce the risk of hyperthermia. There is not enough data to make conclusions about intrauterine administration (53).

Literature reports that misoprostol is effective compared to placebo in controlling bleeding but remains inferior to oxytocin in efficacy and does not replace it even in active management of the third stage of labor (52, 53).

Alprostadil (PGE1) is a natural prostaglandin with a vasodilatory effect mainly used as a second-line treatment for erectile dysfunction (54). It has also been investigated for female sexual dysfunctions (55) and can be used as a labor induction method (85-87). Currently, it is not a drug indicated for the treatment of uterine atony.

Sulprostone

Sulprostone is a synthetic analog of prostaglandin E2, more uterine-selective than natural prostaglandin E2 (6). It is indicated for the treatment of postpartum hemorrhage, administered intravenously. The vials contain 0.5 mg to be diluted in 250 or 500 ml. In both cases, it is recommended to start with a dose of 1.7 mcg per minute up to a maximum of 8.3 mcg per minute. It should not be administered for more than 10 hours, and the total dose should not exceed 1500 mcg in 24 hours (56).

The effectiveness of sulprostone in controlling postpartum hemorrhage was investigated in a large population study involving 4,038 patients with postpartum hemorrhage due to uterine atony and 1227 patients with severe postpartum hemorrhage due to uterine atony. Of these women, 33.9% of those with uterine atony and 53.5% of those with severe atony were treated with sulprostone. The results show that 83.4% of the women treated with sulprostone did not require further treatment to control hemorrhage. An interesting finding from the study is the lower use of sulprostone after vaginal delivery compared to cesarean delivery, especially in centers with a low number of deliveries (57). The effectiveness results of sulprostone from this study are in line with those reported in the literature (58-60). Due to its effectiveness and low incidence of serious adverse effects, it is indicated as a second-line therapy in the treatment of postpartum hemorrhage in Italian guidelines (61).

Dinoprostone

Another prostaglandin E2 analog is dinoprostone, which, like other prostaglandins, has efficacy in inducing uterine contractions. Its main indication is labor induction due to its effectiveness in cervical ripening. It is available in the form of a slow-release device (Propess) (62) and intravaginal gel

(Prepidil) (63).

The Italian national guidelines recommend sulprostone as the prostaglandin to be used as second-line therapy. However, due to its national shortage (AIFA note of 5/7/2019), the use of carboprost has been authorized as a replacement for sulprostone.

The following tables summarize the indications of the main guidelines on the use of first- and second-line uterotonic drugs in the prophylaxis and treatment of postpartum hemorrhage (9, 11, 61) (Table n. 2-4).

Prophylaxis	10 IU IM of Oxytocin in vaginal delivery 5 IU in a bolus and 30-40 IU in slow infusion over 4 hours in cesarean delivery
First-line therapy Strong recommendation, low-quality evidence	Oxytocin 5 IU IM or in a bolus over 1-2 minutes (at least 5 minutes if the patient has cardiovascular disease) Or Ergometrine 2 ampoules of 0.2 mg IM Or Oxytocin 5 IU IM or in a bolus over 1-2 minutes (at least 5 minutes if the patient has CV pathology) + Ergometrine 2 ampoules of 0.2 mg IM + 10 IU of oxytocin in 500 ml over 2 hours of maintenance
Second-line therapy Weak recommendation, very low-quality evidence	Ergometrine 2 ampoules of 0.2 mg IM Or Sulprostone (1 ampoule of 0.50 mg intravenously in 250 cc) (from 0.1 to 0.4 mg/h up to a maximum of 1.5 mg in 24 hours)

Table No. 2 Summary of ISS SNLG 2016 Recommendations updated to 2018 (61).

Prophylaxis	10 IU IM of Oxytocin as an IV bolus or intramuscular administration
First-line teraphy $ Second-line teraphy	Oxytocin 5 IU slow IV, possibly to be repeated $ Ergometrine 0.5 mg slow IV or intramuscular administration (if not contraindicated for hypertension) $ Oxytocin in continuous infusion 40 IU in 500 cc of isotonic crystalloid solution at 125ml/hour (if no need for fluid restriction) $ Carboprost 0.25 mg intramuscular, to be repeated at intervals not less than 15 minutes $ Misoprostol 800 micrograms sublingual administration

Table No. 3 Summary of recommendations on uterotonics from the Royal College of Obstetricians and Gynaecologists (9).

Prophylaxis	10 IU IM of Oxytocin intramuscular administration 5 IU of Oxytocin slow IV during cesarean section (possibly also Tranexamic Acid 0.5-1 gr)
First-line teraphy $ Second-line teraphy	Oxytocin 10-40 IU in IV infusion in 500 or 1000 ml or 10 IU intramuscular administration $ Methylergometrine 0.2 mg every 2-4 hours $ Carboprost 0.2 mg intramuscular or 0.25 mg intramyometrial administration every 15-90 minutes, up to a maximum of 8 administrations $ Misoprostol 600-1000 mg oral, sublingual or rectal administration

Table No. 4 Summary of recommendations on uterotonics from the American College of Obstetricians and Gynecologists (11).

REFERENCES

1. Vannuccini S, Bocchi C, Severi FM, Challis JR, Petraglia F. Endocrinology of human parturition. Ann Endocrinol (Paris). 2016;77(2):105-13.

2. Drew T, Balki M. What does basic science tell us about the use of uterotonics? Best Practice & Research Clinical Obstetrics & Gynaecology. Vol 61, Nov 2019, Pages 3-14.

3. Arrowsmith S, Wray S. Oxytocin: its mechanism of action and receptor signalling in the myometrium. J Neuroendocrinol. 2014;26(6):356-69.

4. Gimpl G, Fahrenholz F. The oxytocin receptor system: structure, function, and regulation. Physiol Rev. 2001;81(2):629-83.

5. de Groot AN, van Dongen PW, Vree TB, Hekster YA, van Roosmalen J. Ergot alkaloids. Current status and review of clinical pharmacology and therapeutic use compared with other oxytocics in obstetrics and gynaecology. Drugs. 1998;56(4):523-35.

6. O'Brien WF. The role of prostaglandins in labor and delivery. Clin Perinatol. 1995;22 (4):973-84.

7. Fuchs AR, Romero R, Keefe D, Parra M, Oyarzun E, Behnke E. Oxytocin secretion and human parturition: pulse frequency and duration increase during spontaneous labor in women. Am J Obstet Gynecol. 1991;165(5 Pt 1):1515-23.

8. Devost D, Wrzal P, Zingg HH. Oxytocin receptor signalling. Prog Brain Res. 2008;170:167-76.

9. Prevention and Management of Postpartum Haemorrhage: Green-top Guideline No. 52. BJOG. 2017;124(5):e106-e49.

10. WHO recommendations: Uterotonics for the prevention of postpartum haemorrhage. WHO Guidelines Approved by the Guidelines Review Committee. Geneva2018.

11. Committee on Practice B-O. Practice Bulletin No. 183: Postpartum Hemorrhage. Obstet Gynecol. 2017;130(4):e168-e86.

12. Burger K, Fahrenholz F, Gimpl G. Non-genomic effects of progesterone on the signaling function of G protein-coupled receptors. FEBS Lett. 1999;464(1-2):25-9.

13. Qian XD, Beck WT. Progesterone photoaffinity labels P-glycoprotein in multidrug-resistant human leukemic lymphoblasts. J Biol Chem. 1990;265(31):18753-6.

14. Gonser M. Labor induction and augmentation with oxytocin: pharmacokinetic considerations. Arch Gynecol Obstet. 1995;256(2):63-6.

15. Rousseau A, Burguet A. Oxytocin administration during spontaneous labor: Guidelines for clinical practice. Chapter 5: Maternal risk and adverse effects of using oxytocin augmentation during spontaneous labor. J Gynecol Obstet Hum Reprod. 2017;46(6):509-21.

16. Thomas JS, Koh SH, Cooper GM. Haemodynamic effects of oxytocin given as i.v. bolus or infusion on women undergoing Caesarean section. Br J Anaesth. 2007;98(1):116-9.

17. Smith MP, Ayad VJ, Mundell SJ, McArdle CA, Kelly E, Lopez Bernal A. Internalization and desensitization of the oxytocin receptor is inhibited by Dynamin and clathrin mutants in human embryonic kidney 293 cells. Mol Endocrinol. 2006;20(2):379-88.

18. Phaneuf S, Rodriguez Linares B, TambyRaja RL, MacKenzie IZ, Lopez Bernal A. Loss of myometrial oxytocin receptors during oxytocin -induced and oxytocin-augmented labour. J Reprod Fertil. 2000;120(1):91-7.

19. Robinson C, Schumann R, Zhang P, Young RC. Oxytocin-induced desensitization of the oxytocin receptor. Am J Obstet Gynecol. 2003;188(2):497-502.

20. Balki M, Erik-Soussi M, Kingdom J, Carvalho JC. Oxytocin pretreatment attenuates oxytocin-

induced contractions in human myometrium in vitro. Anesthesiology. 2013;119(3):552-61.

21. Balki M, Ramachandran N, Lee S, Talati C. The Recovery Time of Myometrial Responsiveness After Oxytocin-Induced Desensitization in Human Myometrium In Vitro. Anesth Analg. 2016;122(5):1508-15.

22. Balki M, Ronayne M, Davies S, Fallah S, Kingdom J, Windrim R, et al. Minimum oxytocin dose requirement after cesarean delivery for labor arrest. Obstet Gynecol. 2006;107(1):45-50.

23. Carvalho JC, Balki M, Kingdom J, Windrim R. Oxytocin requirements at elective cesarean delivery: a dose-finding study. Obstet Gynecol. 2004;104(5 Pt 1):1005-10.

24. Belghiti J, Kayem G, Dupont C, Rudigoz RC, Bouvier-Colle MH, Deneux-Tharaux C. Oxytocin during labour and risk of severe postpartum haemorrhage: a population-based, cohort-nested case-control study. BMJ Open. 2011;1 (2):e000514.

25. Budden A, Chen LJ, Henry A. High-dose versus low-dose oxytocin infusion regimens for induction of labour at term. Cochrane Database Syst Rev. 2014(10):CD009701.

26. Tran G, Kanczuk M, Balki M. The association between the time from oxytocin cessation during labour to Cesarean delivery and postpartum blood loss: a retrospective cohort study. Can J Anaesth. 2017;64(8):820-7.

27. Westhoff G, Cotter AM, Tolosa JE. Prophylactic oxytocin for the third stage of labour to prevent postpartum haemorrhage. Cochrane Database Syst Rev. 2013(10):CD001808.

28. Hunter DJ, Schulz P, Wassenaar W. Effect of carbetocin, a long-acting oxytocin analog on the postpartum uterus. Clin Pharmacol Ther. 1992;52(1):60-7.

29. Rath W. Prevention of postpartum haemorrhage with the oxytocin analogue carbetocin. Eur J Obstet Gynecol Reprod Biol. 2009;147(1):15-20.

30. Atke A, Vilhardt H. Uterotonic activity and myometrial receptor affinity of 1-deamino-1-carba-2-tyrosine(O-methyl)-oxytocin. Acta Endocrinol (Copenh). 1987;115(1):155-60.

31. Khan M, Balki M, Ahmed I, Farine D, Seaward G, Carvalho JC. Carbetocin at elective Cesarean delivery: a sequential allocation trial to determine the minimum effective dose. Can J Anaesth. 2014;61(3):242-8.

32. Su LL, Chong YS, Samuel M. Carbetocin for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2012(2):CD005457.

33. Boucher M, Horbay GL, Griffin P, Deschamps Y, Desjardins C, Schulz M, et al. Double-blind, randomized comparison of the effect of carbetocin and oxytocin on intraoperative blood loss and uterine tone of patients undergoing cesarean section. J Perinatol. 1998;18(3):202-7.

34. Widmer M, Piaggio G, Nguyen TMH, Osoti A, Owa OO, Misra S, et al. Heat-Stable Carbetocin versus Oxytocin to Prevent Hemorrhage after Vaginal Birth. N Engl J Med. 2018;379(8):743-52.

35. Cole NM, Carvalho JC, Erik-Soussi M, Ramachandran N, Balki M. In Vitro Comparative Effect of Carbetocin and Oxytocin in Pregnant Human Myometrium with and without Oxyto-

cin Pretreatment. Anesthesiology. 2016;124 (2):378-86.

36. Malm M, Madsen I, Kjellstrom J. Development and stability of a heat-stable formulation of carbetocin for the prevention of postpartum haemorrhage for use in low and middle-income countries. J Pept Sci. 2018;24(6):e3082.

37. van Dongen PW, de Groot AN. History of ergot alkaloids from ergotism to ergometrine. Eur J Obstet Gynecol Reprod Biol. 1995;60(2):109-16.

38. McDonald S, Abbott JM, Higgins SP. Prophylactic ergometrine-oxytocin versus oxytocin for the third stage of labour. Cochrane Database Syst Rev. 2004(1):CD000201.

39. Taylor GJ, Cohen B. Ergonovine-induced coronary artery spasm and myocardial infarction after normal delivery. Obstet Gynecol. 1985;66 (6):821-2.

40. Soltan AS, Read MD. Postpartum eclampsia associated with ergometrine maleate administration. Br J Obstet Gynaecol. 1994;101 (10):926-7.

41. Salati JA, Leathersich SJ, Williams MJ, Cuthbert A, Tolosa JE. Prophylactic oxytocin for the third stage of labour to prevent postpartum haemorrhage. Cochrane Database Syst Rev. 2019;4:CD001808.

42. Challis JR, Lye SJ, Gibb W. Prostaglandins and parturition. Ann N Y Acad Sci. 1997;828:254-67.

43. Palliser HK, Hirst JJ, Ooi GT, Rice GE, Dellios NL, Escalona RM, et al. Prostaglandin e and f receptor expression and myometrial sensitivity at labor onset in the sheep. Biol Reprod. 2005;72(4):937-43.

44. Balki M, Kanwal N, Erik-Soussi M, Kingdom J, Carvalho JC. Contractile efficacy of various prostaglandins in pregnant rat myometrium pretreated with oxytocin. Reprod Sci. 2012;19 (9):968-75.

45. Balki M, Erik-Soussi M, Ramachandran N, Kingdom J, Carvalho JC. The Contractile Effects of Oxytocin, Ergonovine, and Carboprost and Their Combinations: an In Vitro Study on Human Myometrial Strips. Anesth Analg. 2015;120(5):1074-84.

46. Douglas MJ, Farquharson DF, Ross PL, Renwick JE. Cardiovascular collapse following an overdose of prostaglandin F2 alpha: a case report. Can J Anaesth. 1989;36(4):466-9.

47. Kilpatrick AW, Thorburn J. Severe hypotension due to intramyometrial injection of prostaglandin E2. Anaesthesia. 1990;45(10):848-9.

48. Jelinek J, Roztocil A, Pilka L. [Treatment of post-partum atonic hemorrhage with prostaglandin F2 alpha analogs]. Ceska Gynekol. 1995;60(6):290-2.

49. Kupferminc MJ, Gull I, Bar-Am A, Daniel Y, Jaffa A, Shenhav M, et al. Intrauterine irrigation with prostaglandin F2-alpha for management of severe postpartum hemorrhage. Acta Obstet Gynecol Scand. 1998;77(5):548-50.

50. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/017989s019lbl.pdf.

51. Lalonde A, International Federation of G, Obstetrics. Prevention and treatment of postpartum hemorrhage in low-resource settings. Int J Gynaecol Obstet. 2012;117(2):108-18.

52. Tuncalp O, Hofmeyr GJ, Gulmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2012(8):CD000494.

53. Hofmeyr GJ, Walraven G, Gulmezoglu AM, Maholwana B, Alfirevic Z, Villar J. Misoprostol to treat postpartum haemorrhage: a systematic review. BJOG. 2005;112(5):547-53.

54. Hanchanale V, Eardley I. Alprostadil for the treatment of impotence. Expert Opin Pharmacother. 2014;15(3):421-8.

55. Kielbasa LA, Daniel KL. Topical alprostadil treatment of female sexual arousal disorder. Ann Pharmacother. 2006;40(7-8):1369-76.

56. [Available from: https://www.codifa.it/farmaci/n/nalador-sulprostone-prostaglandine.

57. Schmitz T, Tararbit K, Dupont C, Rudigoz RC, Bouvier-Colle MH, Deneux-Tharaux C, et al. Prostaglandin E2 analogue sulprostone for treatment of atonic postpartum hemorrhage. Obstet Gynecol. 2011;118(2 Pt 1):257-65.

58. Goffinet F, Haddad B, Carbonne B, Sebban E, Papiernik E, Cabrol D. [Practical use of sulprostone in the treatment of hemorrhages during delivery]. J Gynecol Obstet Biol Reprod (Paris). 1995;24(2):209-16.

59. Phuapradit W, Saropala N, Rangsipragarn R. Treatment of atonic postpartum hemorrhage with a prostaglandin E2 analogue. J Med Assoc Thai. 1993;76(6):303-7.

60. Vavala V, Torello-Viera M, Brustia R, Giana M, Monaco A, Scribanti A. [Sulprostone in the prevention and therapy of hemorrhage due to postpartal uterine atony]. Minerva Med. 1990;81(3 Suppl):105-6.

61. SNLG. Emorragia post partum: come prevenirla, come curarla. 2016.

62. Daykan Y, Biron-Shental T, Navve D, Miller N, Bustan M, Sukenik-Halevy R. Prediction of the efficacy of dinoprostone slow release vaginal insert (Propess) for cervical ripening: A prospective cohort study. J Obstet Gynaecol Res. 2018;44(9):1739-46.

63. Vollebregt A, van't Hof DB, Exalto N. Prepidil compared to Propess for cervical ripening. Eur J Obstet Gynecol Reprod Biol. 2002;104(2):116-9.