REVIEW

Uterotonics and tocolytics for anesthesiologists

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Purpose of review
Obstetric anesthesiologists are supposed to understand the uterotonics and tocolytics used in the perinatal period to provide a better clinical practice. This review describes current consensus of uterotonics and tocolytics used in the perinatal period that an obstetric anesthesiologist should know.

Recent findings
Rational use of uterotonics for cesarean section has been well studied in the past decades. Oxytocin remained as a first line uterotonics for cesarean section. For continuous infusion, it is reported that ED90 is higher for laboring parturients than for nonlaboring parturients (6.2 vs. 44.2 IU/h) implying that protocol for oxytocin infusion should be different between laboring patients with prior exposure to oxytocin and nonlaboring patients. For bolus administration, 'rule of three' has been proposed and its efficacy has been reported. When oxytocin fails to achieve sufficient uterine contraction, second-line agents must be administered, and it has been reported that methylergonovine is a superior second-line uterotonic to carboprost. On the other hand, the role of tocolytic agents in obstetric anesthesia has not been well studied.

Summary
Anesthesiologists involved in obstetric anesthesia should be able to determine the appropriate uterotonic for cesarean section and know the indication of tocolytics in perinatal period.

Keywords
carbetocin, misoprostol, oxytocin, tocolytics, uterotonics

INTRODUCTION

One attraction of obstetric anesthesia is that anesthesiologists can be actively involved in the selection of therapeutic strategy. In other fields, the indication and timing of surgeries are determined by surgeons, with no opportunities for anesthesiologists to offer their opinions. However, in obstetric anesthesia, anesthesiologists can play an important role in decision-making such as whether to attempt vaginal delivery or to perform cesarean delivery, and the time when cesarean delivery should be performed if selected, by giving their expert opinions. In order to do so, however, obstetric anesthesiologists must have a firm understanding of the physiology of labor and of the clinical practice of obstetrics. Of particular importance is a sufficient understanding of the uterotonics and tocolytics used in the perinatal period. This study will introduce recent findings regarding the use of tocolytics and uterotonics that anesthesiologists involved in obstetric anesthesia should know.

RATIONAL ADMINISTRATION OF UTEROTONICS FOR CESAREAN SECTION

In cesarean delivery, uterotonics have conventionally been administered to achieve sufficient uterine contraction following delivery. In the past 10 years, research has progressed regarding methods for the rational administration of uterotonics. This research was sparked by a 2004 report by Carvalho *et al.* [1] which stated that the minimum effective initial dose of oxytocin in elective cesarean deliveries is 0.35 IU, which is far less than the previous conventional dose (5–10 IU). In 2006, Balki *et al.* [2] (who was also part of the Carvalho study) reported that the minimum effective initial dose of oxytocin in emergency cesarean delivery for labor arrest is 2.99 IU. This finding suggests the occurrence of desensitization to oxytocin during the course of delivery, in which oxytocin is administered to promote uterine contraction; however, this dose is still less than the dose conventionally administered in the past. Also, in 2010, Butwick *et al.* [3]

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Curr Opin Anesthesiol 2016, 29:000–000
DOI:10.1097/ACO.0000000000000332

KEY POINTS

- Obstetric anesthesiologists with a sufficient understanding of the uterotonics and tocolytics used in the perinatal period can be actively involved in the selection of therapeutic strategy.
- Rational use of uterotonics for cesarean section has been studied in the past decades. Anesthesiologists involved in obstetric anesthesia should be able to determine the appropriate uterotonic for a given situation.
- Various kinds of tocolytic agents are used in the various kinds of situation in the peri-partum period. Obstetric anesthesiologists are supposed to know these indications to provide better clinical practice.

demonstrated that 5 IU oxytocin significantly increases the prevalence of hypotension, thus raising awareness of the side-effects of oxytocin overdose. Findings thus far have been summarized well in a review by Dyer *et al.* [4]. Since that review was published, however, further research has begun to determine oxytocin administration methods that minimize side-effects while maximizing efficacy.

CONTINUOUS INFUSION OF OXYTOCIN FOR CESAREAN SECTION

Oxytocin has conventionally been used as a first line uterotonics for cesarean section either by continuous infusion or bolus administration. Northwestern Medical Hospital in Chicago had, by convention, been performing continuous infusion of oxytocin [10 IU in normal saline (0.9% NaCl) 500 ml], although there was no established protocol regarding the rate of infusion. Thus, in 2008, a protocol was adopted in which continuous infusion of oxytocin (30 IU in 0.9% saline 500 ml) is begun at 18 IU/h and is increased to 36 IU/h if sufficient uterine contraction is not achieved. In 2014, preprotocol to postprotocol adoption changes were reported [5]. According to this report, following protocol adoption, the average intraoperative dose of oxytocin decreased to 8.4 IU. Despite a slight increase in estimated blood loss, no significant differences were observed in the percentage of patients demonstrating blood loss higher than 1000 ml or in the percentage of patients who required additional uterotonics in addition to oxytocin. This group further revised the protocol; in an examination of the rate of continuous infusion necessary to achieve sufficient uterine contraction 4 min after delivery, they reported that the effective dose of oxytocin (ED90) was higher for laboring parturients than for nonlaboring parturients (6.2 vs. 44.2 IU/h) [6▪▪]. It is, therefore, suggested that protocol for oxytocin infusion should be different between laboring patients with prior exposure to oxytocin and nonlaboring patients.

BOLUS ADMINISTRATION OF OXYTOCIN FOR CESAREAN SECTION

Bolus administration of oxytocin has been another popular method for cesarean section, in spite of its possible risk of hypotension. In 2010, Tsen and Balki [7] proposed an oxytocin administration protocol called the 'rule of threes' (Table 1). In 2015, results from a study investigating the efficacy of this rule were reported from Brigham and Women's Hospital in Boston [8▪▪]. The rule group (i.e. those patients to whom the rule of threes was applied) received slow intravenous administration of 3 IU oxytocin immediately after delivery, followed by intravenous administration of 3 IU oxytocin every 3 min until sufficient contraction was achieved (maximum 3 administrations). The control group, on the other hand, began with continuous wide-open infusion of oxytocin (30 IU/500 ml) immediately after delivery, with infusion continued until sufficient contraction was achieved. If sufficient contraction was not achieved 9 min after delivery, additional uterotonics were administered, starting with methylergonovine and followed by carboprost and then misoprostol. In both groups, once sufficient uterine contraction was confirmed, oxytocin administration was changed to continuous infusion of 3 IU/h and was continued until the woman left the operating room. The rule group required less than half the dose of oxytocin used by the control group (mean, 4.0 vs. 8.4 IU; point estimate of the difference, 4.4 ± 1.0 IU; 95% CI, 2.60–6.15; $P < 0.0001$), while no significant differences were observed in hemodynamics or blood loss. Another challenge to prevent maternal hypotension following bolus administration of oxytocin has been reported. Farber *et al.* [9] examined whether co-administration of calcium chloride

Table 1. Oxytocin protocol for cesarean delivery: 'rule of threes'

3 IU oxytocin IV loading dose (administered no faster than 15 s)
3 min assessment intervals. If inadequate uterine tone, give 3 IU oxytocin IV rescue dose
3 total doses of oxytocin (initial load + 2 rescue doses)
3 IU/h oxytocin IV maintenance dose (30 IU/l at 100 ml/h)
3 pharmacologic options (e.g. ergonovine, carboprost, and misoprostol) if inadequate uterine tone persists

Source: Tsen and Balki [7]. IV, intravenous.

(200 mg or 500 mg) with bolus administration of oxytocin (5 IU) could prevent changes in maternal hemodynamics, and reported that no significant differences were observed in blood pressure reduction, vasopressor use, or uterine tone.

CARBETOCIN FOR CESAREAN SECTION

Carbetocin is a newly developed uterotonic with a longer half-life than that of oxytocin, thus giving rise to investigation of its utility as a uterotonic following delivery (cesarean or vaginal) [10]. A group at Mount Sinai Hospital in Toronto has continuously reported the results of a series of studies on the optimal dose of carbetocin. They have reported that 100 μg of carbetocin recommended by the Society of Obstetricians and Gynecologist of Canada yields favorable uterine contraction, but the prevalence of hypotension and other side-effects is high [11,12]. More recently sequential allocation trials to determine the ED90 of carbetocin for achieving sufficient uterine tone have reported that the ED90 at elective cesarean delivery (nonlaboring) was 14.8 μg [13▪], while the ED90 at emergency cesarean delivery (laboring) was 121 μg [14▪]. However, the effects of high-dose carbetocin are not guaranteed, and caution is necessary because of the high prevalence of arrhythmias and other side-effects.

MISOPROSTOL FOR CESAREAN SECTION

Misoprostol is a relatively inexpensive prostaglandin E 1 formulation which can be administered orally, sublingually, vaginally, or anally; thus, in countries lacking medical resources, it has garnered attention as a means of preventing postpartum hemorrhage [15]. Previous studies have reported that compared with oxytocin alone, the combined use of oxytocin and misoprostol significantly reduces blood loss during cesarean delivery as well as the minimum effective doses of other uterotonics [16–18].

FIRST-LINE UTEROTONICS FOR CESAREAN SECTION

Balki *et al.* [19▪▪] recently reported results from a fascinating study in which human myometrial sections isolated during cesarean deliveries were used to compare the efficacy of various uterotonics. These comparisons revealed that the most effective uterotonic was oxytocin, followed by ergonovine, prostaglandin $F_{2\alpha}$, and misoprostol (Fig. 1). Oxytocin was also found to be more effective for nonlaboring women than for laboring women, and more effective in nonoxytocin augmented labor than in oxytocin-augmented labor. These results support the use of oxytocin as a first-line uterotonic in cesarean deliveries. However, in oxytocin-pretreated myometrial strips, the combination of oxytocin with ergonovine or carboprost yielded more powerful uterine contractions than did oxytocin alone [20▪]; thus, in emergency cesarean delivery for labor arrest, the combination of these uterotonics should be considered from the outset. Also, in oxytocin-pretreated myometria, desensitization reportedly attenuates the efficacy of both carbetocin and oxytocin, thus requiring caution [21].

SECOND-LINE UTEROTONICS FOR CESAREAN SECTION

When administration of oxytocin fails to achieve sufficient uterine contraction during cesarean

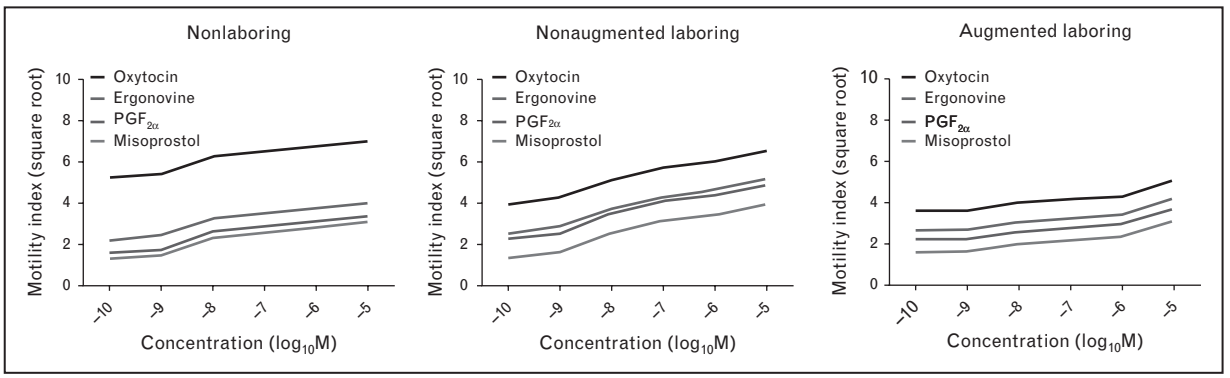

FIGURE 1. Motility index of various drugs in nonlaboring, nonaugmented laboring, and augmented laboring women. The dose–response curves for the motility index of contractions for oxytocin, ergonovine, $PGF_{2\alpha}$, and misoprostol in myometrial samples obtained from nonlaboring, nonaugmented laboring, and augmented laboring women based on modelized data. Source: Balki *et al.* [19▪▪]. PGF, prostaglandin F

section, second-line agents must be administered. However, frequencies of second-line uterotonic use during cesarean delivery vary greatly from hospital to hospital. Bateman *et al.* [22▪] examined the frequencies of second-line uterotonic use during cesarean deliveries at 367 American hospitals. They found that the median frequency of second-line uterotonic use was 7.1% [Interquartile Range (IQR): 5.2–10.8%]; while the median frequencies of methylergonovine, carboprost, and misoprostol use were 5.2% (IQR: 3.1–7.5%), 1.0% (IQR: 0.5–1.6%), and 1.2% (IQR: 0.4–3.0%), respectively. A recent retrospective cohort study by Butwick *et al.* [23▪▪] found that among parturients who were administered either methylergonovine or carboprost as a second-line uterotonic, the percentage of women who required some form of treatment for hemorrhage was significantly lower in the methylergonovine group; thus, they reported methylergonovine to be a superior second-line uterotonic to carboprost. Going forward, anesthesiologists involved in obstetric anesthesia will need to not only rely on protocols, but also be able to determine the appropriate uterotonic for a given situation.

TOCOLYTICS FOR PRETERM LABOR

Preterm labor, defined as parturition between 20 and 36 weeks of pregnancy, is the biggest factor in perinatal death. Thus far, vaginal progesterone and cervical pessary have been confirmed as useful measures for preventing preterm labor in pregnancies with threatened preterm labor [24]. Although the preventive effects of long-term administration of tocolytics against threatened preterm labor remain controversial, they are still used to buy time for steroid-induced maturation of the fetal lungs and for transport of the mother to a high-order medical institution [25]. The tocolytics often used for this purpose are β-mimetics (including ritodrine and terbutaline), but these can result in tachycardia and other side-effects [26]; thus, the most commonly used tocolytic agents are calcium channel blockers (such as nifedipine), which possess few side-effects [27]. There has also been a recent examination into the efficacy of oxytocin receptor antagonists (such as atosiban) [28], as well as a discussion of the pros and cons of magnesium [29]. Magnesium has been reported to improve neurologic prognosis in neonates; however, if a pregnant woman who has been administered magnesium requires emergency cesarean delivery with general anesthesia, the anesthesiologist must be careful about interactions between magnesium and muscle relaxants.

TOCOLYTICS FOR EXTERNAL CEPHALIC VERSION

External cephalic version (ECV) is the application of external force to the abdominal wall to turn a fetus from a breech position to a cephalic position. Due to the reported risk to the baby in vaginal delivery in a breech presentation, cesarean delivery has been recommended, although ECV is also sometimes attempted in order to avoid cesarean delivery. General anesthesia via neuraxial block has been reported to improve the success rate of ECV [30]. There has also been an investigation into whether the use of tocolytics improves the success rate of ECV. In a meta-analysis of such results, the use of β-stimulants was reported to improve the success rate of ECV; however, the effects of calcium channel blockers and nitroglycerin have not been demonstrated sufficiently [31].

TOCOLYTICS FOR RAPID UTERINE RELAXATION

Fetal heart rate is monitored to evaluate the fetus during delivery. In a diagnosis of nonreassuring fetal status (NRFS), intrauterine fetal resuscitation must be performed. Representative methods of intrauterine fetal resuscitation include maternal oxygen administration, maternal postural change, and rapid fluid loading. In addition, the utility of tocolytic administration has also been examined [32,33]. Although β-mimetics (ritodrine [34,35], hexoprenaline [36], orciprenaline [37]) and nitroglycerin [38,39] have been reported to be effective for NRFS, these reports all used small sample sizes and vague methods for assessing efficacy. A relatively recent study comparing nitroglycerin and the β-mimetic terbutaline demonstrated that while the β-mimetic yielded a significantly greater tocolytic effect, there was no significant difference in the success rate of intrauterine fetal resuscitation [40]. Furthermore, based on the significant reduction in maternal blood pressure in the nitroglycerin group, the use of nitroglycerin for NRFS should be considered carefully. At present, there is no sufficient evidence to declare that tocolytics for NRFS reduce the rate of cesarean delivery; rather, further study is needed.

TOCOLYTICS FOR UTERINE INVERSION

Uterine inversion refers to the uterus turning inside out and coming out of the vagina. It can result in fatal postpartum hemorrhage, thus requiring correction of the uterus as quickly as possible, which in turn requires sufficient uterine relaxation. In the past, β-agonists have been useful in this context [41]. Although nitroglycerin has also been reported

as useful for uterine inversion, some believe that the placenta must be present for nitroglycerin to exert a tocolytic effect [42,43]. Although one study has reported that nitroglycerin yielded uterine relaxation in the absence of the placenta [44], there is not yet sufficient evidence that nitroglycerin is effective for uterine inversion. In uterine inversion, blood loss increases over time, and hemodynamics become unstable; therefore, when reduction is difficult to achieve with uterotonics, the anesthesiologist should make preparations to enable immediate conversion to general anesthesia. While the risks of general anesthesia of course require sufficient caution, relaxing the smooth muscle with an inhalational anesthetic while also relaxing the skeletal muscle with a muscle relaxant is anticipated to contribute to a successful reduction.

TOCOLYTICS FOR RETAINED PLACENTA

Retained placenta refers to a condition in which the placenta, whether detached from the uterus or not, has not been expelled within 30 min of delivery. If untreated, this condition results in postpartum hemorrhage and potentially the death of the mother. Radical treatment of retained placenta consists of manual removal of the placenta within the uterus; however, this poses the risks of hemorrhage and infection. In addition, when general or local anesthesia is required, there are risks associated with anesthesia. A 2005 report found that intravenous administration of a uterotonic (oxytocin 10 IU) and a tocolytic (nitroglycerin 1 mg) for retained placenta significantly reduced the frequency of manual removal of the placenta [45]; however, a recent meta-analysis was unable to confirm these findings [46]. Another recent meta-analysis was also unable to confirm the efficacy of uterotonics (oxytocin and prostaglandin) for retained placenta [47]. Manual removal of the placenta should be considered the first-line therapy for retained placenta without insisting on the use of tocolytics.

CONCLUSION

Rational use of uterotonics for cesarean section has been well studied in the past decades. Anesthesiologists involved in obstetric anesthesia should be able to determine the appropriate uterotonic for a given situation. On the other hand, the role of tocolytic agents in obstetric anesthesia has not been well studied and further studies are needed.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Carvalho JC, Balki M, Kingdom J, Windrim R. Oxytocin requirements at elective cesarean delivery: a dose-finding study. Obstet Gynecol 2004; 104:1005–1010.
2. Balki M, Ronayne M, Davies S, *et al.* Minimum oxytocin dose requirement after cesarean delivery for labor arrest. Obstet Gynecol 2006; 107:45–50.
3. Butwick AJ, Coleman L, Cohen SE, *et al.* Minimum effective bolus dose of oxytocin during elective caesarean delivery. Br J Anaesth 2010; 104:338–343.
4. Dyer RA, Butwick AJ, Carvalho B. Oxytocin for labour and caesarean delivery: implications for the anaesthesiologist. Curr Opin Anaesthesiol 2011; 24:255–261.
5. Lee AI, Wong CA, Healy L, Toledo P. Impact of a third stage of labor oxytocin protocol on cesarean delivery outcomes. Int J Obstet Anesth 2014; 23:18–22.
6. ■■ Lavoie A, McCarthy RJ, Wong CA. The ED90 of prophylactic oxytocin infusion after delivery of the placenta during cesarean delivery in laboring compared with nonlaboring women: an up-down sequential allocation dose-response study. Anesth Analg 2015; 121:159–164.

This study provides an identical protocol of bolus administration of oxytocin for cesarean section either for laboring and nonlaboring women.

7. Tsen LC, Balki M. Oxytocin protocols during cesarean delivery: time to acknowledge the risk/benefit ratio? Int J Obstet Anesth 2010; 19:243–245.
8. ■■ Kovacheva VP, Soens MA, Tsen LC, Randomized A. Double-blinded trial of a ''rule of threes'' algorithm versus continuous infusion of oxytocin during elective cesarean delivery. Anesthesiology 2015; 123:92–100.

This study demonstrated that a bolus administration of 3 IU of oxytocin following 'rule of threes' can achieve sufficient uterine contraction without increasing a risk of hypotension in comparison with continuous infusion.

9. Farber MK, Schultz R, Lugo L, *et al.* The effect of co-administration of intravenous calcium chloride and oxytocin on maternal hemodynamics and uterine tone following cesarean delivery: a double-blinded, randomized, placebo-controlled trial. Int J Obstet Anesth 2015; 24:217–224.
10. Su LL, Chong YS, Samuel M. Carbetocin for preventing postpartum haemorrhage. Cochrane Database Syst Rev 2012; 4:CD005457.
11. Cordovani D, Balki M, Farine D, *et al.* Carbetocin at elective cesarean delivery: a randomized controlled trial to determine the effective dose. Can J Anaesth 2012; 59:751–757.
12. Anandakrishnan S, Balki M, Farine D, *et al.* Carbetocin at elective cesarean delivery: a randomized controlled trial to determine the effective dose, part 2. Can J Anaesth 2013; 60:1054–1060.
13. ■ Khan M, Balki M, Ahmed I, *et al.* Carbetocin at elective cesarean delivery: a sequential allocation trial to determine the minimum effective dose. Can J Anaesth 2014; 61:242–248.

This well conducted study determined the ED90 of carbetocin for elective cesarean section to be 14.8 μg. This dose is less than one-fifth of the recommended dose of 100 μg by The Society of Obstetricians and Gynecologist's of Canada guidelines.

14. ■ Nguyen-Lu N, Carvalho JC, Farine D, *et al.* Carbetocin at cesarean delivery for labour arrest: a sequential allocation trial to determine the effective dose. Can J Anaesth 2015; 62:866–874.

This study determined the ED90 of carbetocin for cesarean section due to labor arrest to be 121 μg. This dose is higher than the recommended dose by SOGC guidelines, and should be used carefully because of possible risk of arrhythmias.

15. Hua J, Chen G, Xing F, *et al.* Effect of misoprostol versus oxytocin during caesarean section: a systematic review and meta-analysis. BJOG 2013; 120:531–540.
16. Conde-Agudelo A, Nieto A, Rosas-Bermudez A, Romero R. Misoprostol to reduce intraoperative and postoperative hemorrhage during cesarean delivery: a systematic review and meta-analysis. Am J Obstet Gynecol 2013; 209:40.e1–40.e17.
17. Hernandez-Castro F, Lopez-Serna N, Trevino-Salinas EM, *et al.* Randomized double-blind placebo-controlled trial of buccal misoprostol to reduce the need for additional uterotonic drugs during cesarean delivery. Int J Gynaecol Obstet 2016; 132:184–187.

18. Chaudhuri P, Majumdar A. Sublingual misoprostol as an adjunct to oxytocin during cesarean delivery in women at risk of postpartum hemorrhage. Int J Gynaecol Obstet 2015; 128:48–52.

19. ■■ Balki M, Erik-Soussi M, Kingdom J, Carvalho JC. Comparative efficacy of uterotonic agents: in vitro contractions in isolated myometrial strips of labouring and nonlabouring women. Can J Anaesth 2014; 61:808–818.

This is a novel study which provides the in-vitro dose–response patterns of myometrial contractions of most of the commercially available uterotonic agents and lays a scientific foundation for future studies in this area. Furthermore, this study validates the oxytocin desensitization phenomenon.

20. ■ Balki M, Erik-Soussi M, Ramachandran N, *et al.* The contractile effects of oxytocin, ergonovine, and carboprost and their combinations: an in vitro study on human myometrial strips. Anesth Analg 2015; 120:1074–1084.

This study confirmed that oxytocin pretreatment attenuates contractility induced by oxytocin, but not by ergonovine and carboprost and suggest the choice of uterotonic drug for prevention of postpartum hemorrhage should be based on labor type.

21. Cole NM, Carvalho JC, Erik-Soussi M, *et al.* In vitro comparative effect of carbetocin and oxytocin in pregnant human myometrium with and without oxytocin pretreatment. Anesthesiology 2016; 124:378–386.

22. ■ Bateman BT, Tsen LC, Liu J, *et al.* Patterns of second-line uterotonic use in a large sample of hospitalizations for childbirth in the United States: 2007–2011. Anesth Analg 2014; 119:1344–1349.

This interesting analysis revealed wide inter-hospital variation in second-line uterotonic use that was not explained by patient-level or hospital-level characteristics. Greater emphasis should be placed on defining optimal pharmacologic strategies for the management of uterine atony, including the use of second-line uterotonic.

23. ■■ Butwick AJ, Carvalho B, Blumenfeld YJ, *et al.* Second-line uterotonics and the risk of hemorrhage-related morbidity. Am J Obstet Gynecol 2015; 212:642.e1–642.e7.

This propensity score-matched analysis demonstrated that methylergonovine was associated with reduced risk of hemorrhage-related morbidity during cesarean delivery compared to carboprost. Based on these results, methylergonovine may be a more effective second-line uterotonic.

24. Mackeen AD, Seibel-Seamon J, Muhammad J, *et al.* Tocolytics for preterm premature rupture of membranes. Cochrane Database Syst Rev 2014; 2:CD007062.

25. Manuck TA, Herrera CA, Korgenski EK, *et al.* Tocolysis for women with early spontaneous preterm labor and advanced cervical dilation. Obstet Gynecol 2015; 126:954–961.

26. Anotayanonth S, Subhedar NV, Garner P, *et al.* Betamimetics for inhibiting preterm labour. Cochrane Database Syst Rev 2004; CD004352.

27. Flenady V, Wojcieszek AM, Papatsonis DN, *et al.* Calcium channel blockers for inhibiting preterm labour and birth. Cochrane Database Syst Rev 2014; 6:CD002255.

28. Flenady V, Reinebrant HE, Liley HG, *et al.* Oxytocin receptor antagonists for inhibiting preterm labour. Cochrane Database Syst Rev 2014; 6:CD004452.

29. Crowther CA, Brown J, McKinlay CJ, Middleton P. Magnesium sulphate for preventing preterm birth in threatened preterm labour. Cochrane Database Syst Rev 2014; 8:CD001060.

30. Khaw KS, Lee SW, Ngan Kee WD, *et al.* Randomized trial of anaesthetic interventions in external cephalic version for breech presentation. Br J Anaesth 2015; 114:944–950.

31. Cluver C, Gyte GM, Sinclair M, *et al.* Interventions for helping to turn term breech babies to head first presentation when using external cephalic version. Cochrane Database Syst Rev 2015; 2:CD000184.

32. De Heus R, Mulder EJ, Derks JB, Visser GH. Acute tocolysis for uterine activity reduction in term labor: a review. Obstet Gynecol Surv 2008; 63:383–388.

33. Bullens LM, van Runnard Heimel PJ, van der Hout-van der Jagt MB, Oei SG. Interventions for intrauterine resuscitation in suspected fetal distress during term labor: a systematic review. Obstet Gynecol Surv 2015; 70:524–539.

34. Hutchon DJ. Management of severe fetal bradycardia with ritodrine. Br J Obstet Gynaecol 1982; 89:671–674.

35. Sheybany S, Murphy JF, Evans D, *et al.* Ritodrine in the management of fetal distress. Br J Obstet Gynaecol 1982; 89:723–726.

36. Lipshitz J. Use of a beta 2-sympathomimetic drug as a temporizing measure in the treatment of acute fetal distress. Am J Obstet Gynecol 1977; 129:31–36.

37. Caldeyro-Barcia R. Intrauterine fetal reanimation in acute intrapartum fetal distress. Early Hum Dev 1992; 29:27–33.

38. Mercier FJ, Dounas M, Bouaziz H, *et al.* Intravenous nitroglycerin to relieve intrapartum fetal distress related to uterine hyperactivity: a prospective observational study. Anesth Analg 1997; 84:1117–1120.

39. O'Grady JP, Parker RK, Patel SS. Nitroglycerin for rapid tocolysis: development of a protocol and a literature review. J Perinatol 2000; 20:27–33.

40. Pullen KM, Riley ET, Waller SA, *et al.* Randomized comparison of intravenous terbutaline vs. nitroglycerin for acute intrapartum fetal resuscitation. Am J Obstet Gynecol 2007; 197:414; e411–e416.

41. Abouleish E, Ali V, Joumaa B, *et al.* Anaesthetic management of acute puerperal uterine inversion. Br J Anaesth 1995; 75:486–487.

42. Segal S, Csavoy AN, Datta S. Placental tissue enhances uterine relaxation by nitroglycerin. Anesth Analg 1998; 86:304–309.

43. Harnett MJ, Segal S. Presence of placental tissue is necessary for TNG to provide uterine relaxation. Anesth Analg 2000; 91:1043–1044.

44. Hong RW, Greenfield ML, Polley LS. Nitroglycerin for uterine inversion in the absence of placental fragments. Anesth Analg 2006; 103:511–512.

45. Bullarbo M, Tjugum J, Ekerhovd E. Sublingual nitroglycerin for management of retained placenta. Int J Gynaecol Obstet 2005; 91:228–232.

46. Abdel-Aleem H, Abdel-Aleem MA, Shaaban OM. Nitroglycerin for management of retained placenta. Cochrane Database Syst Rev 2015; 11:CD007708.

47. Duffy JM, Mylan S, Showell M, *et al.* Pharmacologic intervention for retained placenta: a systematic review and meta-analysis. Obstet Gynecol 2015; 125:711–718.