

## Review Article

# Carbetocin versus Oxytocin for the Prevention of Postpartum Haemorrhage

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### Abstract:

Postpartum haemorrhage is the leading cause of maternal mortality worldwide. Total 67-80% of cases are caused by uterine atony. Preventive measures include prophylactic drug use to aid uterine contraction after delivery, thus avoiding severe blood loss and reducing maternal morbidity and mortality. Carbetocin is a synthetic analogue of oxytocin with a long half-life which ensure more effective contraction and less adverse effects. It can be administered as a single dose injection either intravenously or intramuscularly rather than as an infusion over several hours as is the case with oxytocin. Carbetocin is currently indicated for prevention of uterine atony after delivery by caesarean section in spinal or epidural anaesthesia. A reduced need for additional uterotonic was observed with carbetocin vs. oxytocin in high-risk women and carbetocin was at least as effective as syntometrine in low-risk women. Carbetocin is effective treatment for the prevention of postpartum haemorrhage not only following caesarean delivery but also after vaginal delivery in high-risk women and those who suffer from hypertensive disorders in pregnancy. Further research is required to assess whether prophylactic carbetocin is superior to conventional uterotonic agents following vaginal delivery in low-risk women.

**Key words:** Carbetocin, Postpartum Haemorrhage.

### Introduction:

The risk of postpartum haemorrhage is much higher for women undergoing caesarean section<sup>1,2</sup>. particularly in developing countries where the majority of operations are carried out as an emergency procedure<sup>3</sup>. Postpartum haemorrhage occurs in up to 15% of vaginal deliveries<sup>4</sup> and represents the most important cause of maternal morbidity and mortality worldwide<sup>5,6</sup>. In most cases, uterine atony is responsible for the occurrence of excessive bleeding during or following childbirth<sup>7-9</sup>. Current strategies for preventing postpartum haemorrhage

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include the prophylactic use of uterotonic agents to enhance natural uterine contraction and retraction following caesarean section and in the third stage of labour for vaginal delivery<sup>9,10</sup>. Oxytocin is the most widely used uterotonic agent, but only has a half-life of 4-10 min<sup>9-11</sup>. So must be administered as a continuous intravenous infusion to achieve sustained uterotonic activity. Another uterotonic drug frequently used in vaginal deliveries is syntometrine, which contains 5 IU/ml oxytocin and 0.5mg/ml ergometrine<sup>12,13</sup>. Syntometrine combines the rapid onset of action of oxytocin and the prolonged uterotonic effects of an ergot alkaloid. Intramuscular syntometrine use in active management of the third stage of labour is associated with a significant reduction in the risk of non-severe postpartum haemorrhage (<1000ml of blood loss) compared with intramuscular oxytocin<sup>12,13</sup>. Although intramuscular syntometrine is equally effective as intravenous oxytocin<sup>14</sup>, gastrointestinal and cardiovascular side effects such as maternal nausea, vomiting and raised blood pressure 12-14 are more frequent due to stimulation of smooth muscle contraction and vasoconstriction by ergometrine<sup>15,16</sup>. Oral and rectal administration of misoprostol, a synthetic analogue of prostaglandin E1, have demonstrated lower efficacy than injectable uterotonic agents in preventing excessive bleeding following vaginal delivery<sup>17,18</sup> and are associated with a high incidence of shivering, fever and a possible risk of severe hyperthermia<sup>19,20</sup>. These factors deem misoprostol

unsuitable for routine prevention of excessive postpartum bleeding in developed countries, despite low cost and ease of use<sup>20,21</sup>. Although injectable prostaglandins such as prostaglandin 15-methyl F2 $\alpha$  or sulprostone can prevent excessive bleeding following vaginal delivery, safety concerns and cost limit their suitability for routine use in active management of the third stage of labour. However, they remain useful therapeutic options for postpartum haemorrhage treatment when other interventions prove ineffective<sup>21</sup>. Recent interest has focused on the prophylactic use of the oxytocin receptor agonist carbetocin<sup>22-29</sup>. Here we review the most recent clinical data regarding the efficacy of carbetocin in the prevention of postpartum haemorrhage following caesarean section and vaginal delivery, and provide an update on the safety and tolerability in comparison to conventional uterotonic agents.

### Pharmacology:

Carbetocin is a long-acting synthetic analogue of oxytocin<sup>30,31</sup> that can be administered as a single-dose injection, either intravenously or intramuscularly<sup>32</sup>. Intravenously administered carbetocin has a half-life of approximately 40 min, around 4-10 times longer than that reported for oxytocin. Following intramuscular injection, carbetocin reaches peak plasma concentrations in less than 30 min and has 80% bioavailability<sup>32</sup>. The effect of various intravenous and intramuscular doses of carbetocin on the postpartum uterus has been evaluated by tocographic recordings of uterine contractions 24-48h after vaginal delivery at term in 40 women<sup>33</sup>. A single intravenous bolus of 8-30  $\mu$ g carbetocin or a single intramuscular injection of 10-70  $\mu$ g carbetocin produced a tetanic uterine contraction within 2 min of drug administration<sup>33</sup>. Uterine activity persisted for an average of 120 min following intramuscular injection and an average of 60 min following intravenous injection<sup>33</sup>. Thus, these data show that carbetocin onset of action is rapid irrespective of administration route, but duration of action is longer following intramuscular injection. The optimal carbetocin dose (intravenous or intramuscular) is 100  $\mu$ g<sup>34</sup>.

### Carbetocin at Caesarean Delivery:

Carbetocin is currently approved in 23 countries for prevention of uterine atony and excessive bleeding following caesarean delivery in spinal or epidural anaesthesia. This therapeutic indication is supported by the results of two published controlled clinical trials<sup>35,36</sup>. The first study from Montreal (Canada) was a parallel-group, randomised, double-blind, double-dummy trial, comparing uterotonic efficacy and safety of carbetocin and oxytocin in 57 women undergoing elective caesarean section<sup>35</sup>. A single 100  $\mu$ g intravenous

injection of carbetocin following placental delivery was at least as effective as a 16-h intravenous infusion of 32.5 IU oxytocin in controlling intraoperative blood loss. No significant differences in mean blood loss were observed between treatment groups (Table I). However, significantly fewer women in the carbetocin group (53%) than in the oxytocin group (79%) had blood loss of  $\geq 200$  ml ( $p = 0.041$ ) (Table I). The second study was a larger parallel-group, randomised, double-blind, double-dummy, Canadian multi-centre trial, comparing the efficacy and safety of carbetocin and oxytocin in 694 women undergoing elective caesarean section<sup>36</sup>. A single 100  $\mu$ g intravenous injection of carbetocin was more effective at preventing uterine atony than a 5 IU intravenous bolus of oxytocin followed by intravenous infusion of 20 IU over 8h; a significantly lower incidence of additional oxytocic interventions for treatment failure was observed in the carbetocin arm (Table I). Data from these two studies were pooled to determine overall treatment effect in a recent meta-analysis<sup>29</sup>. The risk of postpartum haemorrhage, defined as a blood loss  $\geq 500$  ml, was not significantly decreased with carbetocin compared with oxytocin (relative risk [RR] = 0.71 and 95% confidence interval [CI] = 0.14-3.53). However, carbetocin significantly reduced the need for subsequent interventions with uterotonic drugs (RR = 0.44, 95% CI = 0.25-0.78) or uterine massage (RR = 0.38, 95% CI = 0.18-0.80) compared with oxytocin. The authors<sup>29</sup> also evaluated a randomised controlled trial published in abstract form<sup>37</sup>, comparing a single 100  $\mu$ g intravenous injection of carbetocin ( $n = 62$ ) vs. placebo ( $n = 57$ ) following elective caesarean section. Postpartum haemorrhage incidence was not reported as an outcome measure and could not be assessed, but the requirement for additional oxytocic therapy to prevent haemorrhage was significantly lower with carbetocin vs. placebo (RR = 0.18, 95% CI = 0.09-0.35). Moreover, women in the carbetocin group demonstrated a significant increase in uterine tone for 20 min following administration of study medication compared with placebo ( $p < 0.05$ ). Another study, published in abstract form<sup>36</sup>, investigated the efficacy of carbetocin vs. oxytocin for prevention of uterine atony in high-risk women undergoing delivery by caesarean section in Mexico (Table I). Risk factors included fetal macrosomia, polyhydramnios, low placental insertion, multiple gestation, prolonged labour, uterine myomas and chorioamnionitis. The main efficacy outcome measure was uterine atony incidence. A total of 77 women received carbetocin and 75 received oxytocin following caesarean delivery. Significantly fewer women experienced uterine atony after caesarean delivery with carbetocin (8%) vs. oxytocin (19%) ( $p < 0.0001$ ). Blood loss  $\geq 500$  ml was only observed in women who received oxytocin.

**Table-I :** Prevention of postpartum haemorrhage: summary of carbetocin vs. oxytocin in caesarean delivery.

Study	Population	Main Outcome	Carbetocin	Oxytocin
RCT (29)	n=57 elective	-Mean intraoperative		
delivery.	blood loss.		158 ml	188 ml
		-Blood loss $\geq$ 200 ml	53%	79%
RCT (30)	n=694 elective	Additional oxytocic		
delivery.	delivery.	Intervention for		
		uterine atony	4.7%	10.1%
Randomised	n=152 at high	-Uterine atony	8%	19%
pragmatic	risk of PPH	-Intraoperative		
clinical trial		blood loss	--	500ml
(32)				

RCT, Randomized Controlled Trial, PPH, Post Partum Haemorrhage

**Table-II:** Prevention of postpartum haemorrhage: summary of carbetocin vs. oxytocin in vaginal delivery.

Study	Population	Main Outcome	Carbetocin	Oxytocin
RCT (20)	n=160 at risk	-Uterine massage	43.4%	62.3%
	of PPH required	-Uterotonic intervention		
		Clinically indicated	44.6%	63.6%
RCT (21)	n=329	-Mean reduction in Hb		
	Singleton	concentration in 48 hrs	1.4gm/dl	1.5gm/dl
	Pregnancy	-Need for additional		
	Low PPH risk oxytocin injection		8.7%	6.7%
Retrospective	n=118 delivery	-Mean blood loss	388 ml	551 ml
Study (22)	at term in routine	-Blood loss $\geq$ 500 ml	21.4%	43.5%
	clinical setting	-Blood loss $\geq$ 1000 ml	1.8%	14.5%

RCT, Randomized Controlled Trial, PPH, Post Partum Haemorrhage

### Carbetocin in Vaginal Delivery:

The efficacy of prophylactic carbetocin has also been investigated in prevention of postpartum haemorrhage following vaginal delivery. A randomised, double-blind, placebo-controlled study has compared the efficacy of a single 100 µg intramuscular dose of carbetocin with a 2-h intravenous infusion of 10 IU oxytocin<sup>26</sup> (Table II). The study was conducted in two hospital centres in Canada and enrolled 160 women (83 in the carbetocin arm and 77 in the oxytocin arm) with ≥1 known risk factor including: history of previous postpartum haemorrhage or retained placenta, grand multiparity, uterine overdistension related to multiple gestation, fetal macrosomia or polyhydramnios, chorioamnionitis, antepartum haemorrhage, induction or augmentation of labour with oxytocin for at least 4h, prolonged labour or rapid excessive labour. Treatment began immediately following placental delivery. The primary outcome measure was the need for additional uterotonic medications to prevent postpartum haemorrhage. Other efficacy variables included the need for uterine massage, change in haemoglobin and haematocrit over the initial 24 h postpartum, estimated blood loss following study drug administration to the end of delivery, uterine tone and amount/type of lochia. The number of women requiring additional uterotonic medication was comparable between treatment groups but significantly fewer women required at least one uterine massage following treatment with carbetocin (43.4%) vs. oxytocin (62.3%) ( $p < 0.025$ ). Overall, uterotonic intervention (either additional uterotonic agents or uterine massage) was required in 44.6% of women who received carbetocin and in 63.6% of women who received oxytocin, a statistically significant difference ( $p < 0.025$ ).

No significant differences were observed between treatment groups for other efficacy variables. The investigators concluded that a single intramuscular injection of carbetocin is more likely to prevent postpartum haemorrhage in high-risk women than a continuous intravenous infusion of oxytocin. Another randomised, double-blind, controlled trial has compared efficacy and safety of intramuscular carbetocin with intramuscular syntometrine in preventing primary postpartum haemorrhage in low-risk women with singleton pregnancy achieving vaginal delivery from 34 weeks<sup>27</sup> (Table II). The setting was the delivery suite of a university-based obstetric unit in Hong Kong. A total of 329 women were randomised to receive either a single intramuscular injection of 100 µg carbetocin ( $n = 165$ ) or a single intramuscular injection of 1 ml syntometrine (5 IU oxytocin and 0.5 mg ergometrine) ( $n = 164$ ) after the second stage of labour (following anterior shoulder delivery). The primary efficacy outcome was reduction in haemoglobin levels from admission to the labour ward

until 48h after delivery. Secondary efficacy outcomes included the need for additional oxytocin injections, the incidence of ≥500 ml blood loss and the incidence of retained placenta. The study did not demonstrate significant differences between treatment arms for any of the efficacy outcomes. Thus, intramuscular carbetocin was considered as effective as intramuscular syntometrine in preventing primary postpartum haemorrhage following vaginal delivery in low-risk women. A recent retrospective study has also compared carbetocin efficacy with combined use of oxytocin and ergometrine following routine vaginal delivery in Macau, China<sup>28</sup> (Table II). Women ( $n = 118$ ) received either a single intramuscular injection of 100 µg carbetocin or a single intramuscular injection of 5 IU oxytocin and 0.2 mg ergometrine immediately following delivery. Significantly less blood loss was observed with carbetocin compared with oxytocin and ergometrine ( $p = 0.01$ ), with a mean difference between treatment groups of 163 ml. Postpartum haemorrhage incidence, defined as blood loss ≥500 ml, was significantly lower in the carbetocin group (21.4%) than in the combination group (43.5%) ( $p = 0.01$ ). Notably, nine patients (14.5%) in the combination group experienced ≥1000 ml blood loss compared with one patient (1.8%) in the carbetocin group ( $p = 0.02$ ), and a significantly greater reduction in haematocrit was observed with oxytocin and ergometrine compared with carbetocin. The authors concluded that carbetocin should be considered a good alternative to conventional uterotonics in preventing postpartum haemorrhage after vaginal delivery. In this retrospective study, carbetocin displayed significantly better uterotonic activity than an oxytocin/ergometrine combination containing less than half the ergometrine dose contained in syntometrine<sup>27</sup>. However, these findings are still of interest as these retrospective data more closely reflect everyday clinical practice.

### Pharmacological Studies in Volunteers:

In pharmacokinetic and dose-tolerance studies, up to 400 µg of intravenous or intramuscular carbetocin was associated with the occurrence of minimal adverse effects (mainly facial flushing and feeling of warmth) in non-pregnant women<sup>32</sup>. After intramuscular administration of 400 and 800 µg, a significant increase in pulse rate was observed<sup>32</sup>. A study assessing uterotonic effects of various doses of intramuscular or intravenous carbetocin on the postpartum uterus 24–48 h following vaginal delivery at term<sup>33</sup> revealed that carbetocin produced mild abdominal cramping in most women. Severe abdominal pain was reported by three women who received doses of 50 or 100 µg intravenously or 70 µg intramuscularly. Less frequently reported adverse events were back pain, facial flushing and feeling of warmth. Similar to the study previously mentioned<sup>32</sup> a transient increase in pulse rate occurred

5 min after intramuscular administration of  $\geq 70$   $\mu\text{g}$  carbetocin ( $78.5 \pm 0.7$  to  $81.7 \pm 0.07$  beats/min), not reaching the level of tachycardia. A significant decrease in blood pressure was not observed. A mild increase in blood pressure (max. 140/80 mmHg) that produced distressing abdominal pain was found in only two patients following intravenous injection doses (50 and 100  $\mu\text{g}$ ). In an ascending dose-tolerance study with intramuscular carbetocin<sup>36</sup>, a single injection of carbetocin (range 15-200  $\mu\text{g}$ ) was administered immediately after birth to healthy women who delivered vaginally at term. There was no dose dependent effect on blood pressure, heart rate and respiratory rate and no cases of nausea, vomiting or pruritus were reported. Incidence of abdominal pain and tremor were 27% and 40%, respectively. Abdominal pain was only severe enough to suggest a possible link with carbetocin in one case (2%)<sup>34</sup>. There were six cases of  $\geq 1000$  ml blood loss and four cases of retained placenta<sup>34</sup>. Most of these serious adverse events occurred in women who had received the highest dose of intramuscular carbetocin (200  $\mu\text{g}$ ) and only the retained placenta cases were considered to be possibly linked to carbetocin use by the investigators<sup>34,36</sup>. Lowest blood loss was recorded with 75-125  $\mu\text{g}$  carbetocin and drug-related serious adverse events were not evident until at least 125  $\mu\text{g}$  was administered. These findings confirm that the intramuscular dose of 100  $\mu\text{g}$  carbetocin, effectively used for prevention of uterine atony following vaginal delivery in all recently published studies<sup>26-28</sup>, is the optimal dose with respect to safety and tolerability. Another study evaluated drug transfer to breast milk following intramuscular injection of 70  $\mu\text{g}$  carbetocin in five healthy women (7-14 weeks postpartum)<sup>40</sup>. The mean AUC of carbetocin concentration in breast milk over 240 min following drug administration was 50 times lower than plasma concentration (18.6 and 29.0 pg/ml for the right and left breast, respectively, compared with 1119.3 pg/ml in plasma). The small amounts transferred from plasma into colostrum or breast milk following a single injection of carbetocin presents little risk to breast-fed infants<sup>40</sup>. Since carbetocin is a peptide, a small amount of drug ingested by an infant is assumed to be rapidly degraded by gut enzymes<sup>39,40</sup>.

**Effectiveness in Caesarean Delivery:**

Adverse events reported by  $\geq 10\%$  of women who received prophylactic intravenous carbetocin following caesarean delivery were headache, tremor, hypotension, flushing, nausea, abdominal pain, pruritus and feeling of warmth (Table III)<sup>39</sup>. In the trial comparing carbetocin with placebo, flushing, abdominal pain and pruritus were more frequently observed with carbetocin and the drug was associated with decreased blood

pressure and transient tachycardia<sup>31,37</sup>. Adverse events observed in the carbetocin vs. oxytocin trials were similar in type and frequency between treatment arms<sup>35-36,39</sup> and the meta-analysis from these trials confirmed that the risk of experiencing headache, tremor, dizziness, flushing, shortness of breath, premature ventricular contractions/tachycardia, abdominal pain, nausea, vomiting, metallic taste, pruritus, back pain, feeling of warmth, chills or sweating was similar with carbetocin or oxytocin<sup>29</sup>.

**Table-III:** Adverse effects observed in clinical trials with carbetocin following caesarean section after administration under spinal or epidural anaesthesia<sup>39</sup>.

System	Very Common	Common	Uncommon or Sporadic
Blood and lymphatic system			Anaemia
Nervous system	Headache, tremor		
Vascular	Hypotension, flushing	Dizziness	
Respiratory, thoracic and mediastinal		Chest pain, Tachycardia	dyspnoea
Gastrointestinal	Abdominal pain, Nausea	Metallic taste, vomiting	
Skin and subcutaneous tissue			
General and administration site conditions		Feeling of warmth	Chills, Sweating pain

### Effectiveness in Vaginal Delivery:

Use of carbetocin in vaginal delivery also revealed a similar safety profile to oxytocin<sup>26</sup>. The incidence of dizziness, tremor and vasodilation were comparable between treatment arms. However, the incidence of headache was 2-fold lower with carbetocin (7.2%) vs. oxytocin (14.3%), and vomiting (7.8%) and pruritus (5.2%) were only reported in the oxytocin arm. Conversely, abdominal pain was only reported in women who received carbetocin (6%). Other adverse events previously reported (e.g. increased pulse, decreased diastolic blood pressure and feeling of warmth) were not observed in this trial<sup>26</sup>. Comparison of adverse events with carbetocin and syntometrine revealed that nausea and vomiting were significantly reduced with carbetocin<sup>27</sup>. Facial flushing and pain at the injection site were only reported in the syntometrine arm (2% and 0.7%, respectively). Hypertension (defined as blood pressure  $\geq 140/90$  mmHg) at 30 and 60 min following delivery was 5.3% and 4% in the syntometrine group, respectively, whereas hypertension was not observed in the carbetocin group at either time point. However, 21.3% experienced tachycardia (defined as maternal pulse  $\geq 100$  beats/min) within 60 min of delivery with carbetocin, compared with 12.7% in the syntometrine group. The duration of tachycardia was not reported in this study. Only one out of 150 women (0.7%) in the carbetocin group required manual removal of retained placenta compared with three out of 150 women (2%) in the syntometrine group. The retrospective study comparing carbetocin with the combination of oxytocin and ergometrine did not report any safety and tolerability data<sup>26</sup>.

### Cost- Effectiveness of Carbetocin Vs Oxytocin:

One study from Mexico has compared cost-effectiveness of prophylactic carbetocin and oxytocin following caesarean section<sup>36</sup>. Cost-effectiveness was modeled from the perspective of the third party payer (Mexican Institute of Social Security) and resource use was obtained from the clinical trial data (Table I). Costs were estimated using the financial information provided by the Mexican Institute of Social Security and were reported in USD. Univariate and probabilistic sensitivity analyses were performed using probability distribution data from the clinical trial and the Monte Carlo Simulation technique<sup>41</sup>. The mean cost per woman was significantly lower following carbetocin treatment (3525 USD) compared with oxytocin treatment (4054 USD) ( $p < 0.0001$ ). The mean cost-effectiveness ratio was 3874 USD for carbetocin and 4944 USD for oxytocin. The incremental cost-effectiveness ratio revealed that carbetocin was dominant and the cost-effectiveness acceptability curve and net health benefits demonstrated that carbetocin was superior to oxytocin independently of the willingness- to-pay threshold.

### Conclusion:

Carbetocin is a long-acting synthetic analogue of oxytocin that combines the safety and tolerability profile of oxytocin with the sustained uterotonic activity of ergometrine and is currently indicated for the prevention of uterine atony following caesarean delivery. Evidence from three randomized controlled trials indicates that a single intravenous injection of 100  $\mu\text{g}$  carbetocin significantly reduces the need for additional uterotonic interventions to maintain adequate uterine tone and prevent/treat excessive bleeding following caesarean delivery vs. placebo or intravenous oxytocin. Furthermore, the administration of a single injection of carbetocin is more convenient than an oxytocin infusion, which requires an intravenous line and is time consuming. In high-risk women, carbetocin is superior to oxytocin in preventing  $\geq 500$  ml of blood loss following caesarean section and may represent the most cost-effective uterotonic drug in developing countries with low resources, as suggested by the results of the clinical trial conducted in Mexico. Two recent randomized controlled clinical trials and one retrospective study have indicated that carbetocin may also represent a good alternative to conventional uterotonic agents for prevention of postpartum haemorrhage after vaginal delivery. When administered as a single 100  $\mu\text{g}$  dose, carbetocin has demonstrated longer duration of action compared with intravenous oxytocin, as indicated by the reduced need for additional uterotonic interventions in high-risk women with carbetocin. Carbetocin is also at least as effective as syntometrine for management of the third stage of labour in low-risk women. Carbetocin has been associated with a low incidence of adverse effects, with a similar tolerability profile to intravenous oxytocin. It has also been associated with a lower incidence of gastrointestinal side effects compared with the combination of oxytocin and ergometrine. A higher rate of tachycardia has been reported with carbetocin vs. syntometrine. Tachycardia duration was not reported, but based on available data from other trial, a transitory and slight increase of no clinical relevance would be expected. In this context it must be taken into account that the definition of physiological tachycardia in pregnancy ranges from 100 to 120 beats/min. Carbetocin appears to have a better cardiovascular side-effect profile than oxytocin or syntometrine. However, data from the hitherto published literature are limited. The effect of carbetocin on blood pressure needs further investigation, and preeclampsia remains a contraindication to the use of carbetocin. Available data are encouraging to suggest carbetocin could become useful for prevention of postpartum haemorrhage even in preeclamptic pregnant women. Nevertheless, the careful assessment of the patient's history and close blood pressure monitoring are mandatory in each patient treated with carbetocin, in particular in those with suspected preexisting cardiovascular disease. The

promising findings from these studies suggest that carbetocin may become the drug of choice for prevention of postpartum haemorrhage after vaginal delivery in high-risk women. More trials in low-risk women who undergo vaginal delivery are needed to assess whether carbetocin is superior to conventional uterotonic drugs for the majority of pregnant women. Also, further studies could be conducted to determine if single intramuscular administration of carbetocin is advantageous in settings where prophylactic use of intravenous uterotonics is unsafe or impracticable, like in domiciliary practice or in third stage of labour management in developing countries.

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