Intramyometrial oxytocin in preventing postpartum hemorrhage during cesarean delivery: A systematic review*

Joanna Marie O. Guerra-Calilung, MD and Florante P. Gonzaga, MD, FACOG, FPOGS, FACS
Department of Obstetrics and Gynecology, The Medical City

ABSTRACT

Background: Postpartum hemorrhage from uterine atony, a major global and local health burden, remains to be a leading cause of maternal mortality. Intravenous oxytocin infusion has become the conventional first-line drug in the active management of third stage of labor in most countries. This, however, has been associated with refractory uterine atony and major hemodynamic side effects; hence the need to explore on the possibility of a better alternative such as intramyometrial oxytocin administration.

Objective: The study aims to evaluate the efficacy and safety of intramyometrial oxytocin in preventing postpartum hemorrhage during cesarean deliveries.

Methods: A review was done involving electronic search of databases for randomized clinical trials published since 1980, and a check of all the references according to inclusion and exclusion criteria. Four full articles were retrieved and assessed for methodological quality. Data were extracted and analyzed.

Results: Comparisons involved (1) intramyometrial versus intravenous oxytocin, and (2) intramyometrial oxytocin against intramyometrial carboprost. Limited evidence showed significant reduction of postpartum hemorrhage (RR 0.40; 95% CI 0.19 to 0.82) and maternal adverse drug events (RR 0.10; 95% CI 0.01 to 0.75) with intramyometrial oxytocin compared to intravenous oxytocin. Maternal adverse events were reduced, but not significantly, in intramyometrial oxytocin compared with intramyometrial carboprost.

Conclusion: Guideline changes could not be recommended because there is insufficient information about intramyometrial oxytocin administration from the small number of studies and participants available.

Keywords: intramyometrial/myometrial oxytocin, cesarean section, prophylaxis, postpartum hemorrhage, uterine atony

INTRODUCTION

Postpartum hemorrhage remains to be a major health burden, leading to maternal mortality in the developing and in the developed countries.[1] Defined as blood loss of 500 mL or more and 1000 mL or more within 24 hours of vaginal and cesarean deliveries, respectively, postpartum hemorrhage represents about 25% of all cases of maternal deaths every year worldwide.[1-4] In the Philippines, 2010 Department of Health's latest statistics of maternal mortality ranks postpartum hemorrhage as the third leading cause, with 17.3% prevalence.[5]

Excessive bleeding both in cesarean section and in vaginal delivery can be due to abnormality in any of the four factors (the "4 Ts"): uterine *tone*, retained *tissue*, *trauma* of the genital tract, and *thrombin* disorders or coagulopathy. Among these, uterine atony is the main causative factor of postpartum hemorrhage, occurring about 1 in 20 deliveries, especially in cesarean sections.[2,3] In most cases of uncontrolled uterine atony, complications can develop, namely anemia and hemodynamic shock; need for blood transfusion with accompanying transfusion risks; coagulopathy, infection, hysterectomy with its inherent surgical risks and subsequent loss of fertility; pituitary necrosis and maternal mortality. In our institution alone, among the patients who delivered, 1 out of 2293 parturients in 2011, 1 in 2251 in 2012, and 3 out of 2028 in 2013 eventually had postpartum hysterectomy despite medical efforts. Of the five cases, three were post-cesarean delivery; one eventually required intensive care, but ultimately succumbed to death.

To prevent uterine atony and subsequent postpartum hemorrhage, it is recommended to perform active management of the third stage of labor.[4,6,7] It has been included in numerous guidelines, followed especially by tertiary hospitals such as ours, to administer uterotonic drugs. Uterotonic drugs stimulate contractions of the uterus to facilitate placental separation from the uterine wall after delivery of the fetus and compression of myometrial blood vessels, reducing the amount of blood loss. Several studies have been made reviewing and comparing the different uterotonic agents – oxytocin, prostaglandins, oxytocin agonists like carbetocin, and ergot alkaloids.[8-11]

Among the uterotonic agents, oxytocin has proven to effectively reduce bleeding by about 60%, and is the recommended drug in the prevention as well as treatment of postpartum hemorrhage.[6,12] For prophylaxis, 10 IU intramuscular or 5 IU slow intravenous injection of oxytocin

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can be given. For treatment of postpartum hemorrhage, it can be given at 20 IU in 1 liter as continuous intravenous infusion or 10 IU intramuscularly.[13] In the Philippines, the Clinical Practice Guidelines for Postpartum Hemorrhage revised last November 2012 advise the use of intravenous oxytocin as administration of choice in the active management of the third stage of labor with Level III Grade C recommendation.[14] Oxytocin is a polypeptide hormone produced by the hypothalamus and stored at the posterior lobe of the pituitary gland. It is short-acting with half-life of 3 to 5 minutes.[13,15-16] However, in prolonged oxytocin infusion, water intoxication, hyponatremia, seizures and coma can occur secondary to its anti-diuretic action. Some studies even reported the use of continuous intravenous oxytocin in labor induction and augmentation as a possible risk factor itself for postpartum uterine atony.[15,18] It was suggested to lead to oxytocin receptor desensitization to additional intravenous oxytocin administered as prophylactic uterotonin during cesarean deliveries. On the other hand, when given as intravenous bolus, oxytocin can cause severe hypotension and tachycardia. In fact, major maternal adverse effects of oxytocin are cardiovascular in nature, like myocardial ischemia and arrhythmia. Other side effects include nausea, vomiting, headache and flushing.[11-17]

Some studies have also explored on oxytocin administration via intraumbilical course during cesarean section. A Cochrane study was already able to include nine studies involving 1118 women, reviewing intraumbilical vein injection of oxytocin as an intervention to manage the third stage of labor; however, they were not able to recommend it yet until further researches have been conducted.[19]

Literature and textbooks have mentioned intramyometrial administration of oxytocin as part of the management of the third stage of labor. Possible advantages over the intravenous route are its direct effect and more focused action on the uterine wall during abdominal deliveries, with assumed reduction of adverse side effects even in higher doses since it is not systemically administered. Although already performed in some government institutions, a number of studies has reported conflicting results and disagreements on the effectiveness and safety of intramyometrial injection of oxytocin in preventing uterine atony and postpartum hemorrhage in cesarean deliveries; hence a need for a systematic review to provide a uniform recommendation regarding intramyometrial oxytocin as an alternative prophylactic method, and, if needs be, to call for future researches focusing on this practice in order to fill gaps in information on this facet.

The aim of this study is to determine via systematic review whether intramyometrial oxytocin administration is a better prophylactic practice than the standard method and other available agents in preventing postpartum hemorrhage in cesarean deliveries.

OBJECTIVES

A. General Objective

To evaluate the efficacy and safety of intramyometrial injection of oxytocin as a method in the prevention of postpartum hemorrhage during cesarean deliveries

B. Specific Objectives

(1) To identify randomized controlled trials testing intramyometrial oxytocin in the prevention of postpartum hemorrhage during cesarean deliveries
(2) To assess the methodological quality of obtained trials
(3) To evaluate the effectiveness of intramyometrial oxytocin in promoting uterine contractility and preventing excessive blood loss during cesarean delivery
(4) To evaluate for adverse side effects and hemodynamic changes resulting from intramyometrial oxytocin
(5) To identify gaps in information on the use of oxytocin via intramyometrial route as prophylactic uterotonic method

METHODS

The study protocol was submitted to the Institutional Review Board. A systematic review without meta-analysis of all randomized controlled trials published since 1980 was done comparing intramyometrial oxytocin with intravenous oxytocin and other available uterotonic methods in preventing postpartum hemorrhage during cesarean delivery. An intervention review was preferred over an experimental study design due to the ethical issues involved in performing actual experiments on obstetric patients with critical outcome measures such as hemorrhage, hemodynamic changes and adverse drug effects.

A. Criteria for Considering Studies for this Review

A.1. Types of studies

All published clinical trials with the following criteria were included: (1) studies which made use of randomization and quantitative methods of data collection and analysis; (2) original articles and review articles; and (3) articles published since 1980 to widen the search.

Exclusion criteria were as follows: (1) animal researches, (2) articles not published in or without translation to English; and (3) citations without an abstract.

A.2. Types of participants

Study participants were pregnant women who

underwent cesarean delivery regardless of the maternal age, age of gestation, type of anesthesia used, indication for and timing of cesarean section, presence of risk factors for postpartum hemorrhage, and timing of administration and dosage of uterotonic agent.

A.3. Types of interventions

From the available research articles collected, this study was able to compare the intervention of interest (intramyometrial oxytocin) with the following interventions: (1) intravenous oxytocin, and (2) intramyometrial carboprost, an analogue of prostaglandin $F_{2\alpha}$. There were no subgroups available for comparison.

A.4. Types of outcome measures

The primary outcome measured was postpartum hemorrhage (estimated blood loss more than 500 mL).

Secondary outcomes measured in the study were (1) mean difference in pre- and post-delivery hemoglobin level, (2) occurrence of decrease in hematocrit level, (3) maternal hemodynamic change in terms of decrease in blood pressure, and (4) maternal adverse drug events such as nausea, vomiting, fever, diarrhea, headache and hypertension.

B. Search Methods for Identification of Studies

The search methodology design initially accessed both published and unpublished studies using the following databases: PubMed, Unbound MEDLINE, Cochrane Library, ScienceDirect, Green Journal, Herdin for local articles, HighWire, ClinicalKey and Google Scholar, utilizing all and combinations of the keywords *intramyometrial* or *myometrial oxytocin*, *cesarean section, postpartum hemorrhage, uterine atony*, and *prophylaxis*. Standardized methodological filters for identifying trials were used in applicable search engines. All hits were then screened based on their title, abstract and full text if possible. By using the inclusion and exclusion criteria, published primary studies were identified. Full copies of such articles were obtained for data synthesis and analysis. For unpublished studies, they were separately described but not included in the synthesis and analysis.

Subsequently, references/bibliographies and citations of each primary journal collected were screened; those found relevant based on their title and/or abstract were also included in the review. Language restriction was applied, including only those written in English or with translation to English.

C. Data Collection and Analysis

C.1. Selection of trials and Assessment of methodological quality

The abstracts of studies identified by the search strategy were examined. Full articles were retrieved and assessed for methodological quality.

Information on participants, interventions, outcomes and results of each included study were extracted and tabulated (Appendix 3). Trial quality was assessed according to methods set out by Cochrane Handbook for Systematic Reviews of Interventions available in the Review Manager 5 software.20 The following features were considered:

(a) adequacy of sequence generation;
(b) method of randomization;
(c) method of allocation concealment;
(d) method of blinding;
(e) handling of attrition bias and intention-to-treat analysis; and
(f) equality of treatment of groups aside from the main treatment.

The critical appraisal process was applied to all identified primary journals prior to synthesis; it was also utilized to provide a context for the interpretation of compiled findings. Trials that were explicitly clear that there were randomization, blinding, and concealment of allocation were considered to be of high quality.

C.2. Data extraction

Data were extracted from the included studies using methods and pointers for dichotomous and continuous data set out in section 7 of the Cochrane Handbook for Systematic Reviews of Interventions.20 Most of the data were explicitly reported in the primary journals but when not readily available, dichotomous data were derived from percentages available in the figures and text of included studies. For continuous data, mean value and standard deviation of the outcome measured and the number of participants on whom the outcome was measured per intervention were determined.

C.3. Data analysis

Statistical analysis was carried out using the Review Manager 5 software (RevMan 2008). Data from the four included studies were all quantitative. The analysis was set to fixed-effect model with 95% confidence interval (CI). For dichotomous data, risk ratio (RR) under Mantel-Haenszel (M-H) statistical method was computed for applicable outcomes as follows: postpartum hemorrhage, occurrence of hematocrit decrease and maternal drug adverse events. For continuous data, mean difference (MD) was computed under Inverse Variance (IV) statistical method. Outcome measures included mean hemoglobin difference and maternal hemodynamic change in terms of blood pressure difference.

For the particular outcome measuring maternal

blood pressure change which combined data from two journal articles, assessment of heterogeneity was also done. Chi^2 statistics, df, I^2 statistics and funnel plot were presented. For significant heterogeneity, random-effects meta-analysis was used as an overall summary since the average treatment effect across trials was considered clinically meaningful. Under the random-effects analysis, the results were presented as the average treatment effect with 95% confidence intervals and the estimates of T^2 and I^2.

RESULTS

A. Description of Studies

The search identified four international randomized controlled trials meeting the inclusion criteria, involving 258 parturients via cesarean delivery. The full text of all included papers were retrieved then examined by three reviewers. Two trials compared intramyometrial oxytocin with intravenous oxytocin; the other two compared intramyometrial oxytocin with intramyometrial carboprost (Table 1). No other systematic reviews or meta-analyses were found during the search. For other details of the included studies, Characteristics of Included Studies. No local trials were identified by the search.

Excluded studies were two unpublished trials – one was not approved by Ethics Board due to large doses of oxytocin both in the intervention and in the control group, hence it did not proceed to the experiment level. The other one was a thesis paper required for a master's degree and printed only for university records.

The first excluded study made by Campbell in 2012 planned to perform a double-blind interventional randomized trial comparing intramyometrial route versus oxytocin infusion in improving outcomes in cesarean delivery in terms of uterine tone, estimated blood loss, pre- and post-operative hematocrit changes, need for additional uterotonics and need for blood pressure support. The unpublished thesis paper by El-Shorbagy in 2013 made use of a double-blind randomized trial comparing intramyometrial versus intravenous oxytocin in assessing uterine tone/contractility, blood pressure, heart rates, hemoglobin concentration and need for crystalloid solution infusion in patients undergoing cesarean section.

B. Risk of Bias of Included Studies

Overall, the methodological quality of the four primary trials was moderate to high.

B.1. Randomization and selection bias

All four studies were randomized. One made use of computer-generated numbers[21] while the three did not specify randomization method. Allocation concealment was described in two of the four journals, making use of unmarked indistinguishable pre-prepared syringes containing study solutions.[21,23]

B.2. Blinding of outcome

Two out of the four trials were appropriately blinded.[21,23] In the study of Dennehy, et. al., the obstetricians, participants and anesthesiologists were blinded to the intervention. Only the operating surgeon and participants were blinded in the study made by

Table 1. Specific characteristics and data of trials included in the review analysis

Study	Sample Size (A/B)	Interventions	Clinical Outcomes
Dennehy (1998)	39 (20/19)	A - 5 IU oxytocin IV + 2 mL NSS IMy B - 20 IU oxytocin IMy + 0.5 mL NSS IV	Mean hemoglobin difference Maternal BP change
Mangla (2012)	100 (50/50)	A – 20 IU oxytocin IV B – 5 IU oxytocin IMy	Postpartum hemorrhage Maternal BP change Maternal drug adverse events
Catanzarite (1990)	46 (25/21)	A – 125 mcg carboprost IMy vs B – 20 IU oxytocin IMy	Change in hematocrit level
Bai (2013)	73 (37/36) Total=258	A – 20 IU oxytocin IMy + 20 IU oxytocin IV B – 250 mcg carboprost IMy	Postpartum hemorrhage Mean hemoglobin difference Maternal drug adverse events

IMy = intramyometrial, IV = intravenous, NSS = normal saline solution, BP = blood pressure

Catanzarite. The other two journals did not mention blinding methods.

B.3. Handling of attrition bias and Intention-to-treat analysis

For the study of Dennehy, *et. al.,* intention-to-treat analysis was not done. Only one patient under the intramyometrial oxytocin group did not complete the study protocol since she received general anesthesia instead of spinal anesthesia. She was not included in the statistical data, however this was unlikely to affect the results. Upon analysis of the demographic data of the remaining participants, there was no statistical difference noted between groups.[21] The three remaining studies had no losses hence no risk of attrition bias; all participants were included in the analysis therefore intention-to-treat analysis was not done.[22-24]

C. Effects of Interventions

Four included trials were analyzed in this review.[21-24] The first analysis compared intramyometrial oxytocin and intravenous oxytocin administration, involving two journals and a total of 139 parturients.[21,22] The second analysis which included two journals reviewed intramyometrial oxytocin against intramyometrial carboprost, with total of 119 participants.[23,24] Table 2 summarizes the results of data and analytical methods performed.

C.1. Postpartum Hemorrhage

Data were derived from two studies to determine the treatment effect in reducing postpartum hemorrhage in women who underwent cesarean delivery.[22,25] The results showed that the intramyometrial route of oxytocin administration at 5 IU, when compared with the intravenous route at 20 IU, significantly reduced risk of postpartum hemorrhage based on blood loss during cesarean section (RR 0.40; 95% CI 0.19 to 0.82) (Figure 1). The RR of less than 1 indicated that treatment – in this case, the intramyometrial route of oxytocin administration – reduced risk of outcome, which is postpartum hemorrhage. Since the null value equivalent to RR of 1 was not within the narrow confidence interval of 0.19 to 0.82, then it could be said that the observed relationship was statistically significant.

When compared with intramyometrial carboprost, intramyometrial oxytocin was less effective in reducing postpartum hemorrhage; the difference between the two was statistically significant (RR 3.16; 95% CI 1.14 to 8.79). However, the confidence interval has a very wide range, increasing the uncertainty of this finding (Figure 2).

Postpartum hemorrhage was not measured in the remaining trials, which could be one pitfall in the evaluation of this outcome. Different journals also used different methods of quantifying blood loss, hence a difficulty in estimating the effect of interventions – one estimated volume of blood loss mixed with amniotic fluid in the graduated suction jar and the number of soaked sponges, together with amount of vaginal bleeding within the first hour after operation,[22] while the other did not specify how blood loss was measured during the 2-hour post-operative observation period.[24]

C.2. Change in hemoglobin and hematocrit levels

Two studies reported mean hemoglobin difference,[21,24] and only one reported hematocrit decrease.[23] Even with higher intramyometrial oxytocin dose than in the intravenous route, mean hemoglobin difference between these two groups showed no significant difference pre- and post-cesarean delivery (MD 0.40; 95% CI -6.96 to 7.76) (Figure 3), since the null value of MD equivalent to 0 was within the very wide range of confidence interval.

Between intramyometrial oxytocin and intramyometrial carboprost, the reduction in hemoglobin level was statistically smaller in the carboprost group, but the confidence interval was wide (MD 6.00; 95% CI 2.78 to 9.22), indicating greater uncertainty with regards to this result (Figure 4).

Severe reduction in hematocrit levels occurred less frequently in the intramyometrial oxytocin group than in the intramyometrial carboprost, but there was no statistical significance on the observed difference between the two groups (RR 0.53; 95% CI 0.19 to 1.47) (Figure 5).

C.3. Maternal hemodynamic change (blood pressure change)

Main hemodynamic effect of intramyometrial oxytocin against intravenous oxytocin in terms of blood pressure decrease was reported by two journals.[21,22] Data were pooled and risk ratio under fixed effect analysis model was computed (MD -2.77; 95% CI -3.47 to -2.07) (Figure 6). Upon inspection of the funnel plot, significant heterogeneity was noted (Figure 7). On assessment of heterogeneity, the two studies being compared and pooled were significantly heterogenous (Chi^2 test 155.40, df 1, I^2 99%).

Since the average treatment effect across trials was clinically meaningful, re-analysis had to be done using the random-effects analysis. This method checked for the best estimate to produce the average effect, thus re-computing the Inverse Variance to be 0.56, favoring the intravenous oxytocin intervention (from -2.77, formerly favoring the intramyometrial oxytocin group). It also confirmed heterogeneity expressed as T^2 statistics of > 1, *i.e.* there is presence of substantial between-study variance (T^2 61.87, I^2 99%). Z test was calculated by the software to show overall treatment effect (Z=0.10), interpreted as

Table 2. Data and Analyses

Comparison 1. Intramyometrial oxytocin versus intravenous oxytocin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effects size
1.1 Postpartum hemorrhage	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.19, 0.82]
1.2 Mean hemoglobin difference (g/L)	1	39	Mean Difference (IV, Fixed, 95% CI)	0.40 [-6.96, 7.76]
1.3.a. Maternal hemodynamic change (BP in mmHg)	2	139	Mean Difference (IV, Fixed, 95% CI)	-2.77 [-3.47, -2.07]
1.3.b. Maternal hemodynamic change (BP in mmHg)	2	139	Mean Difference (IV, Random, 95% CI)	0.56 [-10.38, -11.49]
1.4 Maternal drug adverse events (nausea and vomiting)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 0.75]

Comparison 2. Intramyometrial oxytocin versus intramyometrial carboprost

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effects size
2.1 Postpartum hemorrhage	1	73	Risk Ratio (M-H, Fixed, 95% CI)	3.16 [1.14, 8.79]
2.2 Mean hemoglobin difference (g/L)	1	73	Mean Difference (IV, Fixed, 95% CI)	6.00 [2.78, 9.22]
2.3 Hematocrit decrease	1	46	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.19, 1.47]
2.4 Maternal drug adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.4.1. Nausea	1	73	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.07, 1.50]
2.4.2. Vomiting	1	73	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.06, 1.07]
2.4.3. Fever	1	73	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.12, 3.66]
2.4.4. Diarrhea	1	73	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.71]
2.4.5. Headache	1	73	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.71]
2.4.6. Hypertension	1	73	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 1.94]

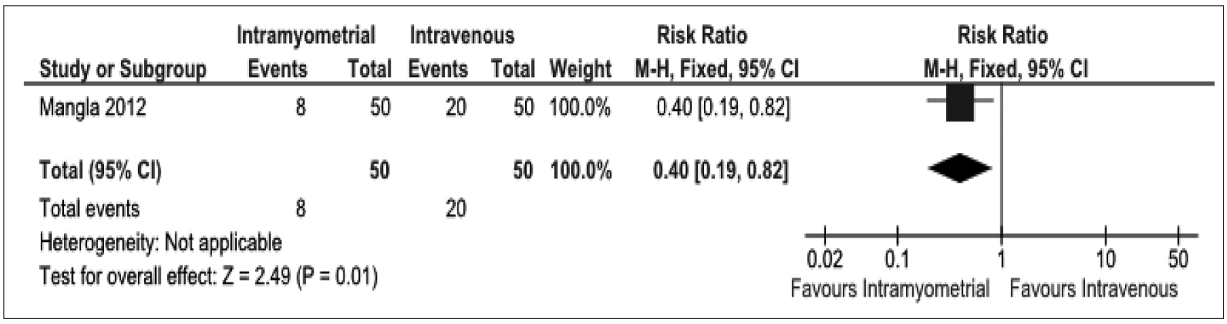

Figure 1. Intramyometrial oxytocin vs Intravenous oxytocin, Outcome: Postpartum hemorrhage

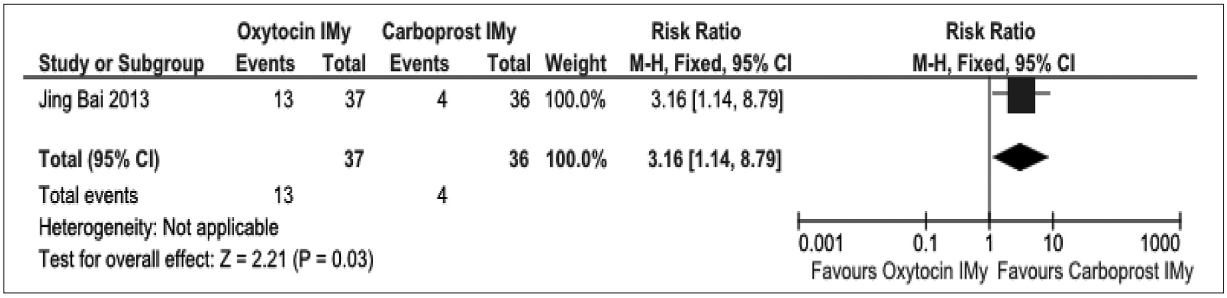

Figure 2. Intramyometrial oxytocin vs Intramyometrial carboprost, Outcome: Postpartum hemorrhage

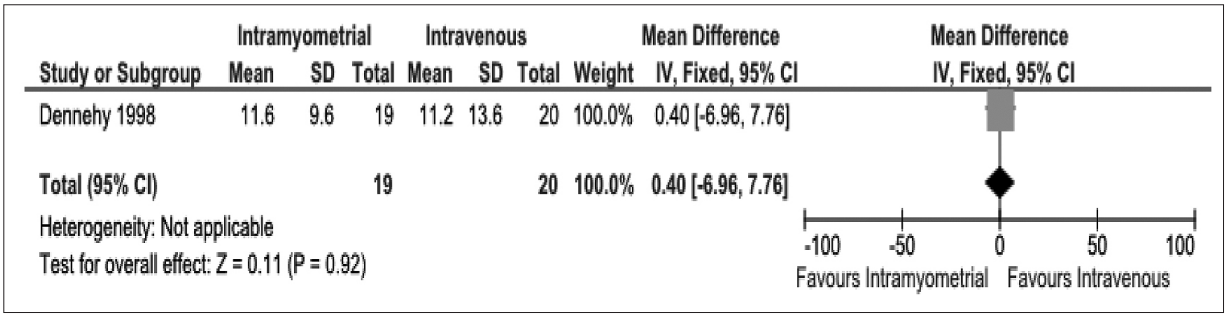

Figure 3. Intramyometrial oxytocin vs Intravenous oxytocin, Outcome: Mean hemoglobin difference

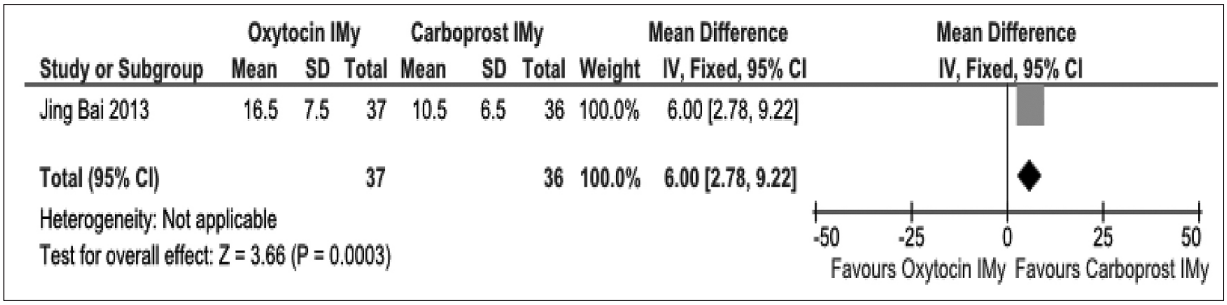

Figure 4. Intramyometrial oxytocin vs Intramyometrial carboprost, Outcome: Mean hemoglobin difference

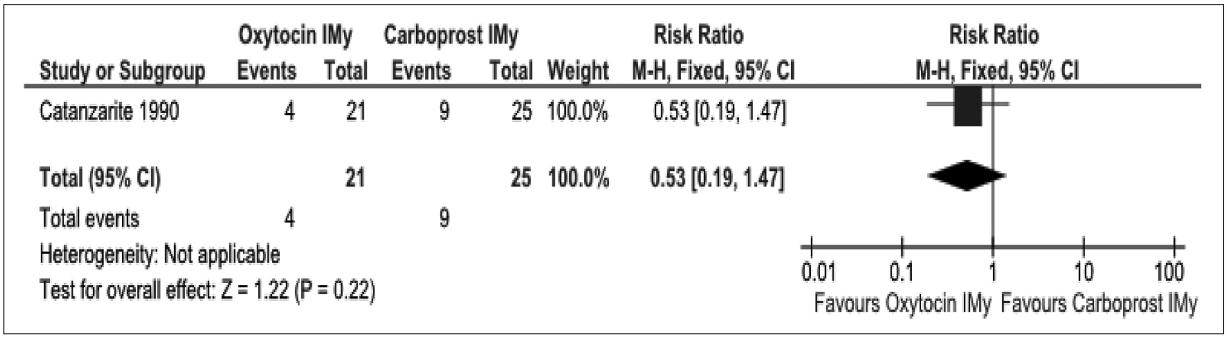

Figure 5. Intramyometrial oxytocin vs Intramyometrial carboprost, Outcome: Change in hematocrit

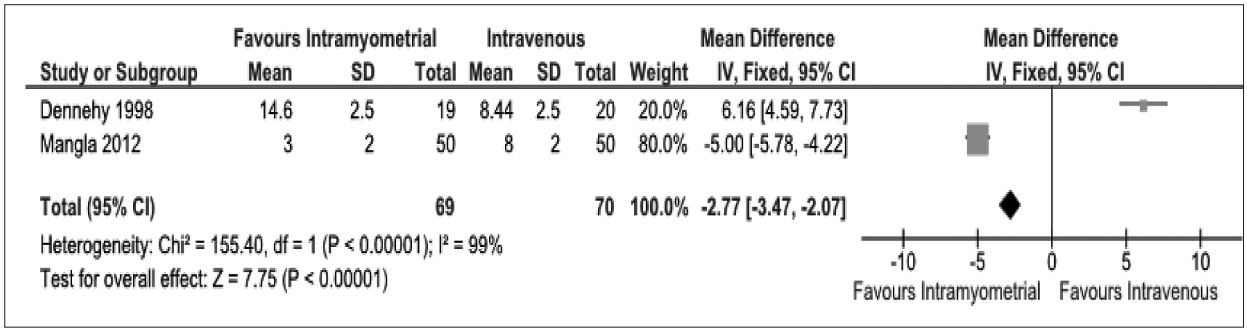

Figure 6. Intramyometrial oxytocin vs Intravenous oxytocin, Outcome: Maternal hemodynamic (BP) change

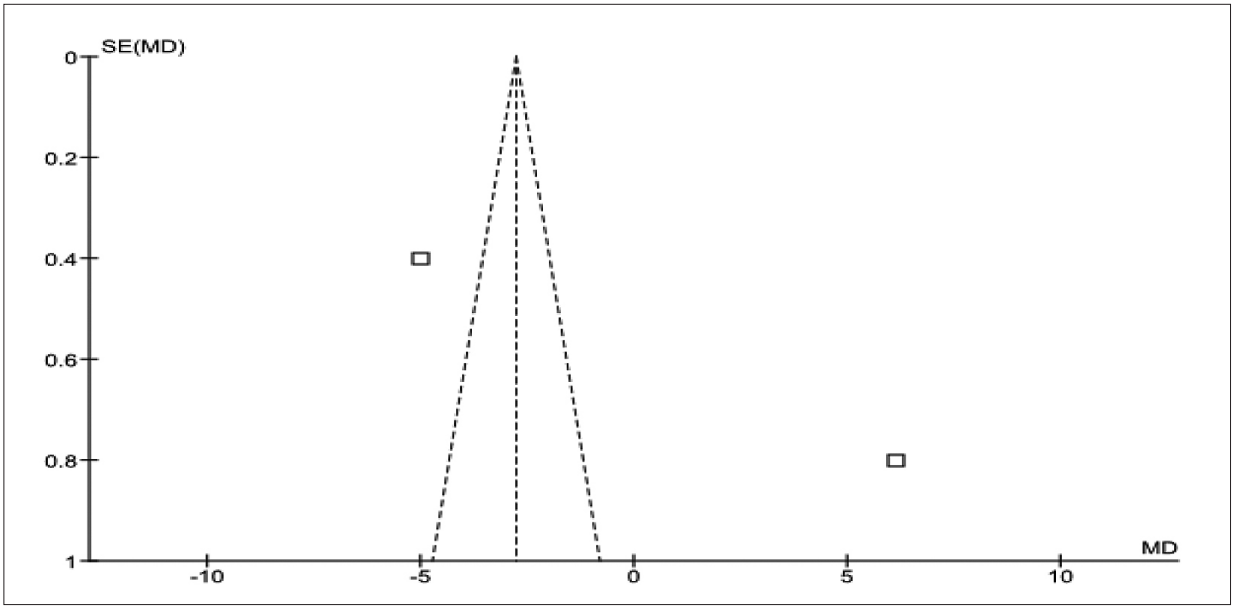

Figure 7. Funnel plot of studies comparing intramyometrial oxytocin vs intravenous oxytocin

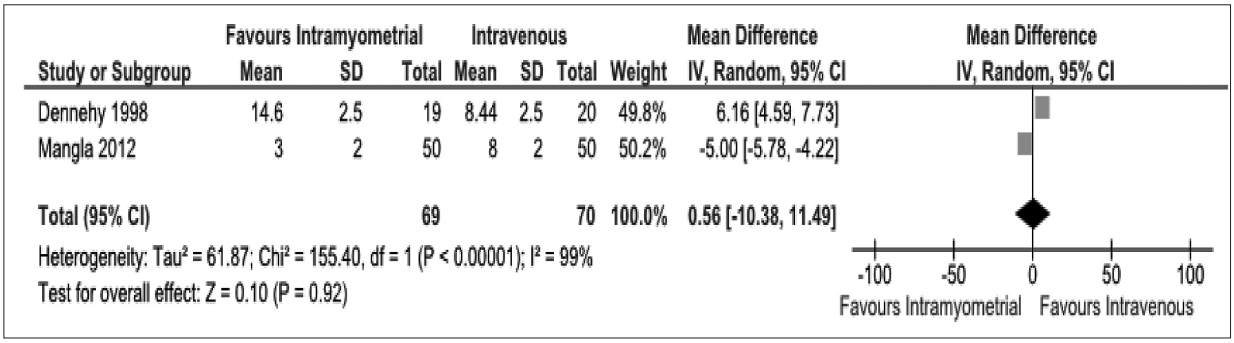

Figure 8. Re-analysis of Intramyometrial oxytocin vs Intravenous oxytocin: Maternal hemodynamic (BP) change

marginal statistical effect since it was within 0 to 0.5 range (Figure 8). Hence, it is suggested that maternal hemodynamic change in terms of change in blood pressure level was less in intravenous oxytocin group but to a marginal extent over the intramyometrial group.

C.4. Adverse effects

Data about the incidence of nausea and vomiting among parturients were reported in two of the available trials – one journal compared intramyometrial versus intravenous oxtocin[22] while the other compared intramyometrial oxytocin with intramyometrial carboprost.[24] Intramyometrial oxytocin was noted to significantly reduce the risk of nausea and vomiting in women undergoing cesarean delivery when compared with intravenous oxytocin (RR 0.10; 95% CI 0.01 to 0.75) (Figure 9).

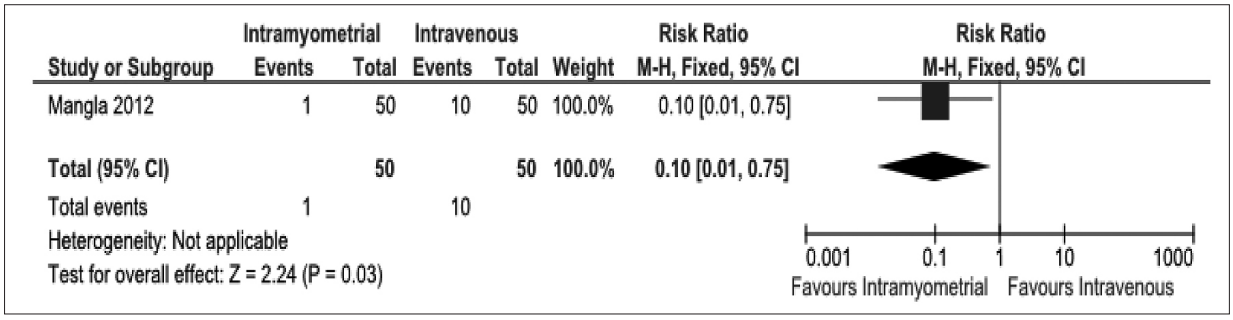

Figure 9. Intramyometrial oxytocin vs Intravenous oxytocin, Outcome: Maternal nausea and vomiting

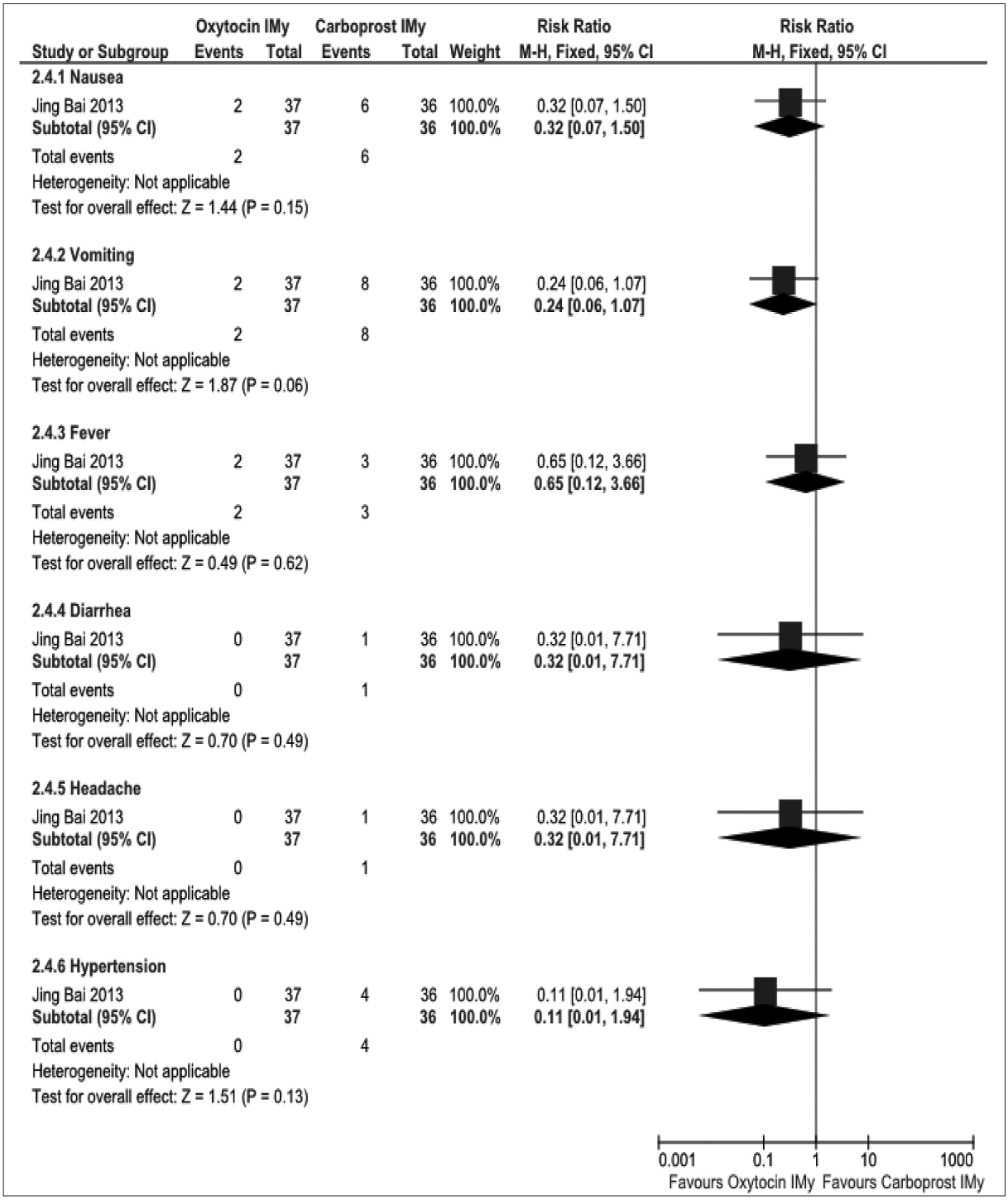

Figure 10. Intramyometrial oxytocin vs Intramyometrial carboprost, Outcome: Maternal adverse events

Subcategorical analysis of nausea (RR 0.32; 95% CI 0.07 to 1.50), vomiting (RR 0.24; 95% CI 0.06 to 1.07), fever (RR 0.65; 95% CI 0.12 to 3.66), diarrhea (RR 0.32; 95% CI 0.01 to 7.71), headache (RR 0.32; 95% CI 0.01 to 7.71), and hypertension (RR 0.11; 95% CI 0.01 to 1.94) among women who received intramyometrial oxytocin also showed reduction in the risk of maternal adverse events when compared with recipients of intramyometrial carboprost; however, the differences for each subcategory were not statistically significant and with wide ranges of confidence intervals (Figure 10).

DISCUSSION

From the four randomized clinical trials available comparing the efficacy and safety as a prophylactic agent of intramyometrial oxyctocin with other conventional uterotonins against postpartum hemorrhage, there was only limited evidence that could be derived. Although these articles published in a span of 20 years (1990 to 2013) had similar measurable outcomes, there was relative diversity in their study participants, intervention dosages and combinations thereof, and data analysis. The inclusion and exclusion criteria set to define the population in one journal were understandably not exactly the same as in the others; furthermore, they differ in the demographic data across the four studies. All of these prevented head-to-head data pooling, comparison, and strict meta-analysis.

This systematic review shows that intramyometrial route of oxytocin administration could significantly reduce excessive bleeding after cesarean delivery compared to intravenous oxytocin, the current standard method of active management of the third stage of labor. The intramyometrial route also significantly reduced the occurrence of inherent drug adverse effects such as nausea and vomiting when evaluated against the intravenous route of oxytocin administration. These were noted despite the greater dose of oxytocin used in the intravenous route than the intramyometrial group (20 IU versus 5 IU, respectively). This could be supported by the previously mentioned theory on oxytocin receptor desensitization in which continuous exposure to oxytocin and stimulation of oxytocin receptors – as what happens in intravenous infusions in these pregnant women – can lead to reduction in myometrial binding sites and reduction in production of oxytocin receptors secondary to decreased receptor mRNA levels.[25] A great clinical significance of this is that prolonged oxytocin infusion may fail to augment labor or it can cause postpartum uterine atony refractory to additional prophylactic or therapeutic oxytocin infusions. Furthermore, human studies have also reported that locally produced oxytocin in the placenta seems to play a bigger role in labor and promotion of uterine contractions than the circulating oxytocin.[25,26] With these observations, the findings would be in synchrony with the intramyometrial route's advantage of local and direct action on the myometrial cells with less systemic side effects. However, the small number of sample size in the studies, and the wide range of confidence intervals of the results, may further limit the evidence.

When compared against carboprost given through the same route (intramyometrially), oxytocin led to statistically higher risk of hemorrhage and to significant reduction in hemoglobin level, but insignificant reduction of maternal adverse drug events such as nausea, vomiting, and others. Carboprost is a prostaglandin $F_{2\alpha}$ derivative which promotes smooth muscle contractility by increasing intramyometrial calcium concentrations mediated via G-proteins and calcium channel activation. It has a longer half-life which can explain the enhanced action and side effects of this drug over oxytocin. Also, based on the study by Phaneuf, *et. al*., receptor desensitization seems to be homologous in nature, hence administration of a non-oxytocin-derived agent such as carboprost will still produce the expected action and effect.[10,25] Again, increased number of trials and larger sample size of trials on these may be required to show any difference in the adverse effects of the two interventions.

With postpartum hemorrhage as the primary clinical outcome measured in this review, evidence can be summarized as follows: intramyometrial oxytocin significantly reduced postpartum hemorrhage when compared with intravenous oxytocin, but intramyometrial carboprost also showed significant reduction of outcome versus intramyometrial oxytocin. There is suggestion on the benefit of using intramyometrial oxytocin in the prevention of excessive bleeding in women delivering via cesarean section, but this can only be accurate with larger randomized controlled trials of high methodological quality. To point out, not all four trials measured postpartum hemorrhage as mean blood loss in the methodology. In addition, there was actual difficulty in standardizing mean blood loss definitions and in providing accurate blood loss measurements.

The other outcome measures such as change in hematocrit levels and maternal blood pressure changes did not significantly discriminate between the compared groups – most likely requiring large numbers of study participants to further show statistically significant differences among the different interventions. Furthermore, a play of several compensatory mechanisms in the human body could mask the actual hemodynamic effects of each drug and intervention in the corresponding studies.

Based on the critical appraisal of the methodological quality, all four studies performed randomization, but only two were considered of high quality (studies done by Catanzarite, and Dennehy *et. al*.). Blinding was performed only in the same trials. Intention-to-treat analysis was not done by any of these journals, but it did not seem critical since only one out of the initial 259 participants was eventually excluded and not made part of the data extraction and analysis, giving a dropout rate of less than 20%, which is the significant cut-off. General rating by two independent authors was moderate to high quality.

It was part of the review's objectives to identify areas of information that are still vague with respect to prophylactic intramyometrial oxytocin in the management of the third stage of labor. The limited number of available studies restricted this review's capacity to better assess the intervention and compare it with others in terms of cost, need for blood transfusion, need for additional uterotonic agents, need for symptomatic relief from systemic side effects, incidence of retained placenta, mean length of third stage of labor, possibility of maternal deaths, effect on breastfeeding, and possible effects on neonatal outcomes, especially in the Philippine setting.

SUMMARY / CONCLUSIONS AND RECOMMENDATIONS

A. Implications for Practice

Limited and conflicting evidences from the studies suggest that intramyometrial route of oxytocin administration could significantly reduce postpartum hemorrhage after cesarean delivery compared to intravenous oxytocin, the current standard uterotonic method, at a minimum of 5 IU oxytocin as was used in the primary journals.

With the same limitations, there is suggestion on the benefit of intramyometrial oxytocin over intravenous oxytocin and intramyometrial carboprost in the development of maternal drug adverse events such as nausea and vomiting.

Up to date, as mentioned above, published primary journals per se show the inconsistent effect of intramyometrial oxytocin in promoting uterine contractility and reducing risk of uterine atony and postpartum hemorrhage. There is no standard report on different adverse effects. Intramyometrial administration of oxytocin has been observed to increase in some, and decrease in others, the risk of hypotension, nausea, vomiting, flushing and headache. No study has reported severe adverse effect such as myocardial ischemia, arrhythmia, water retention, hyponatremia, seizures, coma and death.

Based on all of these, clinicians should still have an open mind to consider intramyometrial administration of oxytocin as an alternative method of managing the third stage of labor, especially if more common medical methods have failed. This should be kept in mind particularly in cesarean section patients who have been on induced or augmented labor for more than 6 hours and for those patients with high risk for postpartum hemorrhage.

At this point, changes to current practice guidelines could still not be recommended because there is insufficient information on intramyometrial route of oxytocin administration, especially on the exact dosage and specific uterine site of injection, from the small number of studies and study participants used in this review.

B. Implications for Research

The number of trials on intramyometrial oxytocin is still limited. Thus far, there are no local trials and data yet based on the search performed. With this review, knowledge on possible benefits of intramyometrial route of oxytocin administration has been explored from the different randomized clinical trials available. However, larger well-designed trials preferably of parallel characteristics are needed to better establish the efficacy of this intervention in preventing postpartum hemorrhage. The optimal dosing of oxytocin given via the intramyometrial route still needs to be determined in addition to important and concomitant side effects. Furthermore, the best uterine site for myometrial injection has to be established. The cost-effectiveness of intramyometrial oxytocin versus other agents; and the possible benefits of intramyometrial oxytocin over other drugs in terms of need for blood transfusion, need for additional uterotonic agents, incidence of retained placenta, mean length of third stage of labor, possibility of maternal deaths, effect on breastfeeding, and possible effects on neonatal outcome also require further research development. These are significant for clinical decision-making since such decisions should be based on balance between the advantages and disadvantages of intervention used.

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