A meta-analysis on the efficacy of carboprost vs methylergometrine maleate in the active management of third stage of labor for the prevention of postpartum haemorrhage*

Joann C. Vivar, MD and Nelinda Catherine B. Pangilinan, MD, FPOGS, FPSUOG
Department of Obstetrics and Gynecology, Rizal Medical Center

ABSTRACT

Objective: To determine the efficacy of Carboprost versus methylergometrine maleate in the active management of third stage of labor for the prevention of postpartum hemorrhage.

Methods: Entries in electronic databases with references cited in original studies and review articles were used to identify randomized clinical trials of carboprost versus methergin in the active management of third stage of labor. The quality of published clinical trials were evaluated and assessed based on the efficacy of Carboprost versus methylergometrine maleate for the prevention of postpartum hemorrhage.

Results: Six (6) clinical trials were analyzed comprising a total sample pool of 525 women randomized to carboprost group and another 525 women to methergin. The risk ratio for dichotomous outcomes were calculated using a random-effects model while continuous outcomes were pooled using the standard mean difference. Results showed that both carboprost and methergin are both effective in preventing postpartum hemorrhage. But carboprost was found to be more efficacious in reducing the duration and decreasing the amount of blood loss in the third stage of labor and there was less need for an additional drug dose. Risks of side effects were higher in carboprost. Vomiting is the most frequent adverse event followed by diarrhea but are usually self-limiting.

Conclusion: Carboprost is well known for its therapeutic role in the management of postpartum hemorrhage, well-tolerated and with minimal adverse effects. It is therefore recommended to be used in hypertensive patients where methylergometrine maleate is contraindicated and in cases refractory to other uterotonic agents.

Keywords: Carboprost 15, methy prostaglandin $F_2\alpha$, 15 methyl $PGF_2\alpha$, methergin, methylergometrine maleate, metaanalysis, post-partum hemorrhage

INTRODUCTION

Postpartum hemorrhage is defined in several ways. According to the World Health Organization, it is defined as blood loss of more than 500 ml for vaginal delivery and 1000ml for cesarean section (Peters and Duvekot, 2009)[1]. It is further classified as excessive bleeding that occurs in the first 24 hours after delivery (Ottawa, et. al. 2009)[2] for a primary or immediate postpartum hemorrhage and secondary or late postpartum hemorrhage is defined as occurring between 24 hours after delivery of the infant and 6 weeks postpartum (CPG 2012)[3].

It is one of the major causes of maternal morbidity and mortality worldwide with a mortality rate of 140, 000 per year, or 1 maternal death occurs every 4 minutes (Ottawa, et. al 2009)[2]. According to the World Health Organization (WHO), United Nations Populations Fund (UNFPA) and the World Bank (WB) 2005 Joint Report, the Philippines has an estimated of 4,600 annual maternal deaths with postpartum hemorrhage causing 17.2 % of these maternal deaths as reported in the Philippine Health Statistics (DOH 2010)[4] but one report from the WHO cited as high as 53% of maternal mortalities attributed to postpartum hemorrhage (WHO Newsletter April 2007)[5] with roughly over 11 Filipino women die every day (Tulali, 2010)[6].

Risk factors for postpartum hemorrhage include prolonged third stage of labor for more than 30 minutes, severe anemia, eclampsia, antepartum hemorrhage, intrapartum blood loss, history of postpartum hemorrhage or retained placenta, polyhydramnios, multiple gestation and difficult instrumental delivery (Peters, et. al. 2009)[1]. In terms of underlying causes of postpartum hemorrhage, it is usually classified in terms of 4 Ts: Tone for uterine atony or distended bladder, Tissue for retained placenta and clots, Trauma for presence of vaginal, cervical or uterine injury, and Thrombin for preexisting or acquired coagulopathy (Ottawa, et. al. 2009)[2].

To prevent postpartum hemorrhage, active management of the third stage of labor (AMSTL) is

* First Place, 2015 Philippine Obstetrical and Gynecological Society (POGS) Mid-year Residents' Research Paper Contest, April 17, 2015, Lounge, Subic Bay Exhibition & Convention Center

recommended[7]. Whenever possible, it is also recommended to delay cord clamping by at least 60 seconds (Ottawa, et. al. 2009)[2] and delivery of the placenta by controlled cord traction is also helpful. Since uterine atony is the most frequent cause of PPH, prophylactic administration of uterotonic drugs during the third stage of labor have been shown to reduce the occurrence of PPH by about 40% (Peters, et. al. 2009)[1]. Based on the WHO guidelines, it recommended to routinely use oxytocin, which compared to other uterotonics, has lesser side effects, and deemed more effective (WHO 2007)[5]. Oxytocins is a nonapeptide which binds to a G-protein on the surface of the uterine myocite, generating diacylglycerol (DAG) which in turn stimulates prostaglandin synthesis and produces inositol-triphosphate (IP3) which promotes the release of calcium from the sarcoplasmic reticulum leading to muscle contraction.[8]

Second line of uterotonic agents include ergot derivatives, the oxytocin analogue, carbetocin, prostaglandins and syntometrine which is a combination of ergonovine and oxytocin[8] (unavailable in the Philippines).

Ergot alkaloids, which are derived from the fungus *Claviceps purpurea*, was the first effective oxytocic drug. This agent, although banned from intrapartum use remains the second line intervention in the absence of contraindications in cases where uterine atony persists after oxytoxin administration during cesarean delivery. Ergometrine maleate or methylergometrine which acts via a calcium channel or an α-receptor in the inner myometrial layer has a half life of 120 minutes.[9]

Like oxytocin, prostaglandins increase intramyometrial calcium concentration that enhances uterine contraction and causes vasoconstriction[10]. The use of intramyometrial 15-methyl prostaglandin F2α, carboprost is known to have an extended half-life, fewer gastrointestinal and vasopressor side effects and good uterotonic activity and also considered a good second-line uterotonic agent[11].

OBJECTIVES

General Objective:

To determine the efficacy of Carboprost (15-methyl prostaglandin $F_2\alpha$) versus methylergometrine maleate in the active management of third stage of labor for the prevention of postpartum hemorrhage

Specific Objectives:

1. To compare the incidence of postpartum hemorrhage in terms of blood loss > 500cc in Carboprost versus Methergin
2. To determine the duration of the third stage of labor in those who used Carboprost versus methylergometrine
3. To compare the amount of blood loss in the groups who used Carboprost versus methylergometrine
4. To compare the need for additional drug dose in those who used Carboprost versus methylergometrine
5. To compare the side effects of Carboprost versus methylergometrine

MATERIALS AND METHODS

Articles were gathered by searching through PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), the LILACS, MEDLINE (OVID Platform), Excerpta Medica database (EMBASE), Health Services Technology, Administration and Research (HealthSTAR). Hand searching was also done to look for relevant journals which include, The Philippine Journal of Obstetrics and Gynecology, Obstetric Gynecology Journal and other related journals from the different Asian countries accessible. All submitted researches cited at the POGS Annual Report from 2000 to 2013 were searched for the keywords and then copies of full texts of qualified researches were acquired either thru published POGS journal or via personal communication with the institutions and/or authors of the submitted studies. Citations and articles published in any language from January 1990 to January 2014 were included in the search. A lateral search in PubMed was also done using the "related articles" link. A search for reviews, conference proceedings and abstracts was also performed. For articles where abstracts were the only available downloadable data, authors were personally notified via electronic mail for possibilities of acquiring full copies of their research. The search terms include "carboprost" OR "prostaglandin $F_2\alpha$" OR "$PGF_2\alpha$" OR "15-metyl prostaglandin $F_2\alpha$" AND "methylergometrine maleate" OR "methylergometrine" OR "methergin".

Inclusion Criteria

All clinical trials selected met the following criteria:

1. Each study included is a randomized trial
2. Each study required a group of pregnant woman who either were given carboprost or methylergometrine in the active management of the third stage of labor.

Assessment of Qualities of Studies

Quality assessment of chosen studies was assessed on the bases of the methods used for sampling and for allocation or random assignment into the intervention or control arms as recommended by Higgins et.al.[11] The methods of randomization were categorized as (a) adequate, (b) unclear, (c) inadequate and (d) not used; allocation concealment as:(a) adequate, (b) unclear, (c) inadequate and (d) not used. An allocation quality grade of "3" was assigned to the trial with superior randomization technique while a score of "1" or "2" for inferior and a score of zero for its absence.

Abstraction of Study Data

A total of two (2) independent raters critically appraised all the studies using the method of Haynes and Guyatt. Critical appraisal was performed 2 weeks apart with the raters not communicating during the interim periods of data assessment, and data analysis. We emailed the original authors to clarify outcomes and inclusion criteria as well as for other additional information.

Statistical Analysis

Statistically combinable data outcomes were entered into REVMAN 5.1, a freeware of the Cochrane Collaboration. The presence of publication bias was evaluated using the Forest plot technique.[12] To enable us to correctly combine individual and cluster trials, the mean difference and risk ratio were used (with 95% confidence interval) and calculated the heterogeneity of evaluated data measures by the generic inverse variance method.[14,15]

MEASURES OF TREATMENT EFFECT

Dichotomous data

For dichotomous data, the results are presented as summary risk ratio (RR) with 95% confidence intervals (CI). The RR as relative effect measure has consistency, works well with small or big rate of events, and is easier to interpret in clinical practice.

Continuous data

For continuous data, the mean difference was used if outcomes are measured in the same way among trials while the standardized mean difference was used to combine trials that measure the same outcome, but used different methods.

The magnitude of the effect size of the interventions compared was computed at the end of each intervention or observation period since baseline and or change data were not available for all included clinical trials.

Dealing with missing data

For included studies, levels of attrition were noted. We planned to explore the impact of include studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. For all outcomes we carried out analysis, as far as possible, on an intention-to-treat basis; we attempted to include all participants randomized to each group in the analysis, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomized minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. We considered that heterogeneity might not be important if I^2 was less than 40%. If we identify substantial heterogeneity we explored it by prespecified subgroup analysis.

For thoroughness and completeness, we analyzed both random effects and fixed effects model estimates, however, the random effects model was preferred when substantial outcome heterogeneity was observed[16,17]. ($I^2 > 50\%$).

Assessment of reporting biases

If we suspected reporting bias we attempted to contact study authors for missing outcome data. If this was not possible, and the missing data are thought to introduce serious bias, we planned to explore the impact of include such studies in the overall assessment of results by a sensitivity analysis.

RESULTS

The summary of study selection, filtering and final inclusion of studies is summarized in Figure 1. Upon using the keywords, there were 230 potential studies identified and filtered for possible downloading and retrieval. From the 230, 138 were marked as grossly irrelevant, 92 were classified as potentially eligible studies, 85 of which were excluded for the following reasons: 1.) not a controlled trial, 2.) used a different control group (such as misoprostol or oxytocin), 3.) availability in foreign language only, and 4.) absence of full text necessary for critical appraisal. One study was then excluded due to the incomplete data outcome available. (see Figure 1).

Participants

A total of 6 randomized controlled trials (RCTs) reported on Carboprost (15-methyl prostaglandin 2α) versus Methylergometrine maleate in the active management of third stage of labor in the prevention of postpartum hemorrhage which met the inclusion criteria for analysis.

These studies comprised a total sample of 1050 women randomized to being recipients of either Carboprost or methylergometrine. All participants are greater than 18 years of age, pregnant of at least 34 weeks age of gestation and of vertex presentation and longitudinal lie. Those with history of asthma and hypersensitivity to carboprost or methergine were excluded in the studies.

The overall mean age for participants in the Carboprost group was 25.356 years and 25.377 years for the methergin group. Overall average parity was 1.03333

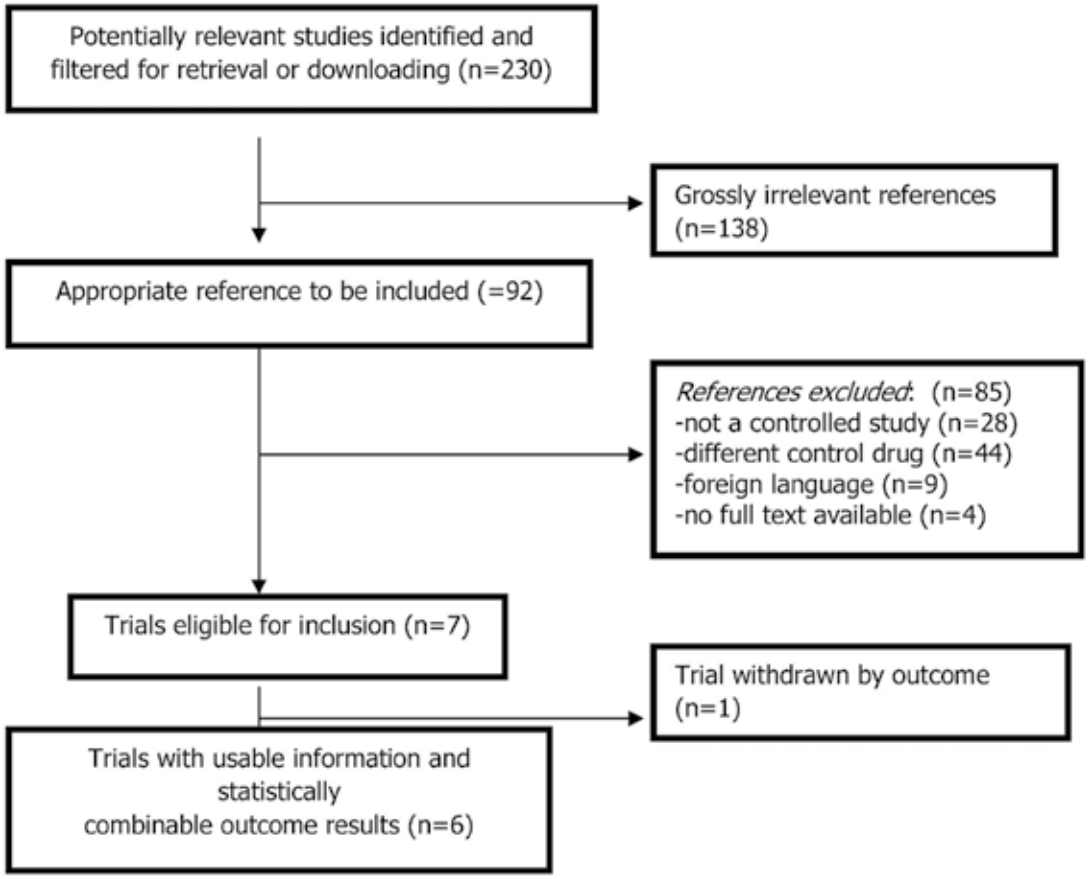

Figure 1. Study Selection of Randomized Studies of Carboprost versus Methergin for Active Management of Third Stage of Labor

± 0.56003 for carboprost group while for the methergin group, the mean parity was 0.903333 ± 0.50807.

Interventions and Comparisons

All six studies compared carboprost injected via the intramuscular route from methergin IM/IV but 2 studies utilized a third arm for comparison. Lamba, et. al. added oxytocin in the comparison while Shrestha, et. al. used a third arm wherein carboprost was administered via the intramyometrial route, however all outcomes were similar across studies.

Outcomes

All six studies measured the efficacy of carboprost versus methylergometrine based on the mean duration of the third stage of labor in minutes. Five studies compared the mean amount of blood loss during the third stage of labor.

In terms of other determinants for postpartum hemorrhage, five studies mentioned that none of their participants had retained placental tissues. Incidence of postpartum hemorrhage was cited in four studies and the need for additional dose of the drug was identified in four studies. All six studies specified the side effects noted.

Incidence of Postpartum Hemorrhage (Blood Loss > 500cc)

Overall, the incidence of postpartum hemorrhage with a minimal blood loss of at least 500cc was noted to be reduced and is in favor of the carboprost group but is not statistically significant (Risk Ratio 0.55 [0.11,2.64], 95% CI, P=0.45) (Table 1) as shown in four studies using the random effects model.

Duration of the Third Stage of Labor

Using the random effects model, there was a statistically significant difference between those who were given carboprostversus methergin in the mean difference on the effects on the duration of the third stage of labor (Standard Mean Difference -0.86, 95% CI [-1.16, -0.56], P value < 0.00001) (Table 2) which shows to be shorter in the carboprost group.

Amount of Blood Loss in the Third Stage of Labor

Five studies reported on the mean amount of blood loss during the third stage of labor with a significant difference between the two groups which seems to be lesser in the carboprost group. (Standard Mean Difference -0.60, 95% CI [-1.12, -0.07], P value = 0.03) (Table 3).

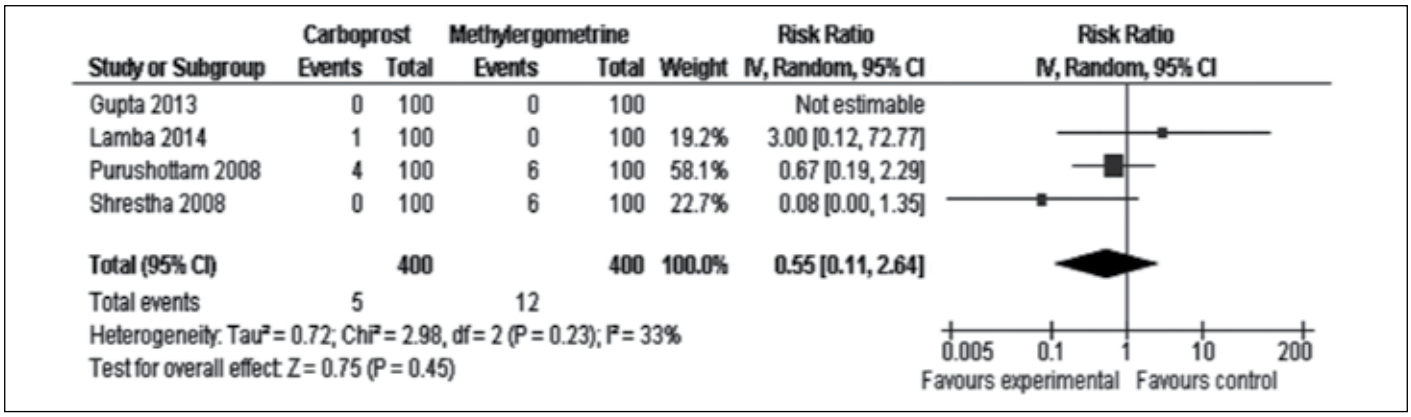

Table 1. Incidence of Postpartum Hemorrhage with Blood Loss > 500cc in Carboprost Versus Methylergometrine. Analysis of Six RCTs, 2014

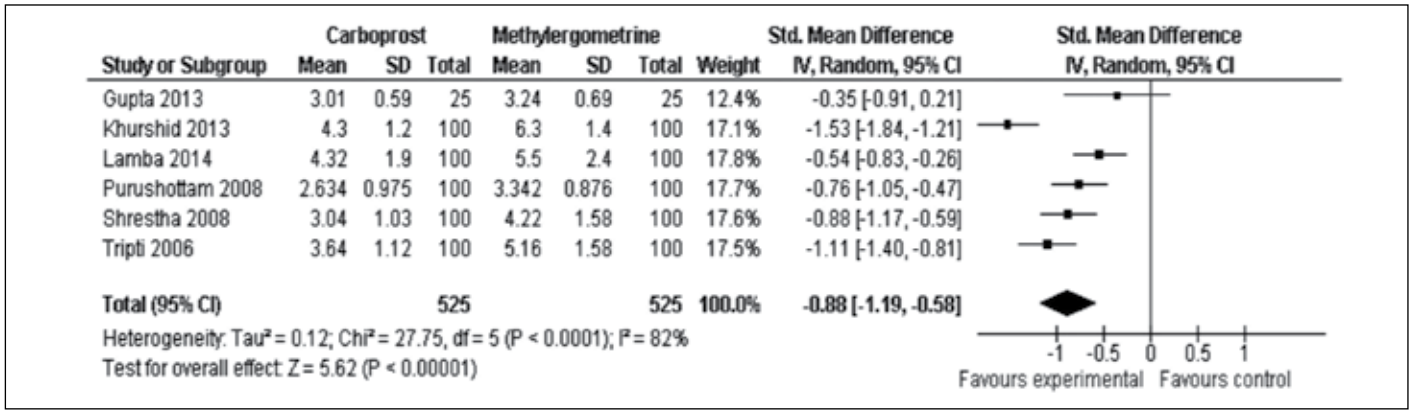

Table 2. Duration of the Third Stage of Labor with Carboprost Versus Methylergometrine Maleate. Analysis of Six RCTs, 2014

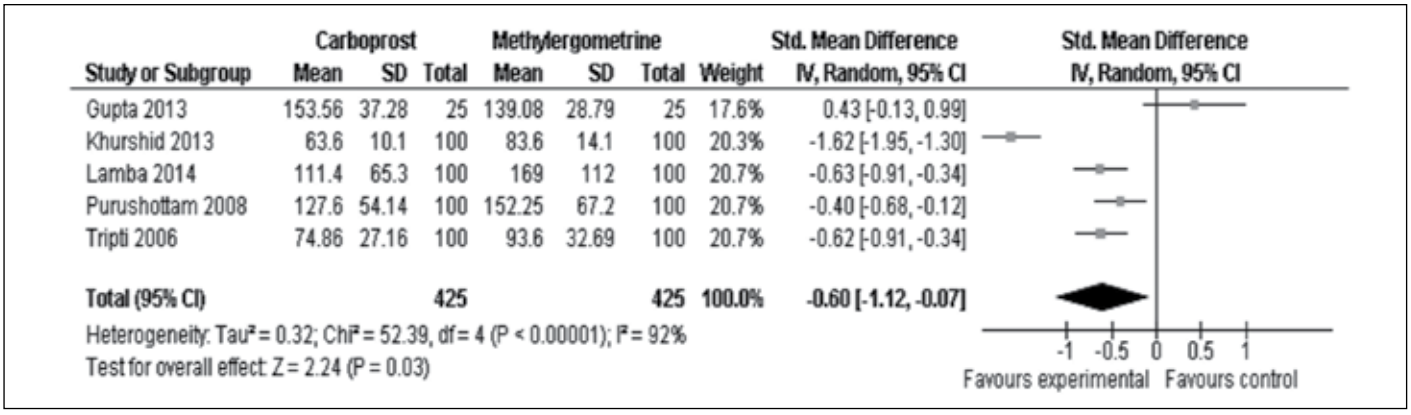

Table 3. Amount of Blood Loss in the Third Stage of Labor Using Carboprost Versus Methylergometrine. Analysis of Six RCTs, 2014

Need for Additional Drug Dose

Four studies reported the need for an additional drug dose after the giving the interventions in both groups. There was a fewer need for an additional dose in the carboprost group with an only case reported which is considerably statistically significant (Risk Ratio 0.21 [0.05, 0.85], P=0.03) (Table 4).

Side Effects

All six studies reported the side effects encountered in both groups. Four studies stated that the adverse effects were mild, transient and not severe enough to need energetic management. One study described occurrence of headache in one case in the carboprost group (Shrestha 2008). On the other hand, one study (Lamba 2014) reported on encountering an increase in the diastolic blood pressure in 65 of cases in the methergin group and 2% of the same group developed shivering.

Vomiting

All six studies reported on encountering cases of vomiting as a side effect which occurs less in the methergin

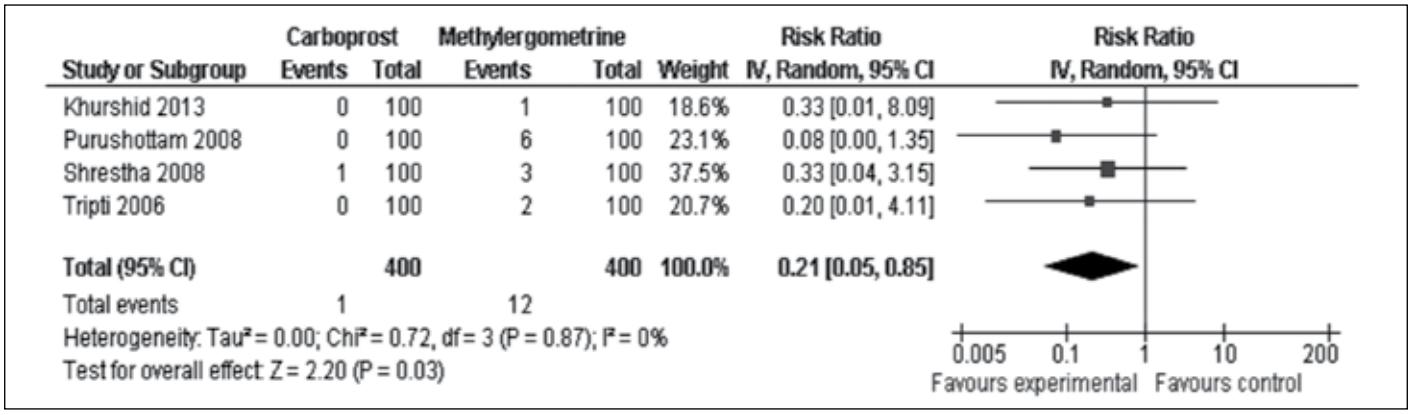

Table 4. Need for Additional Drug Dose Using Carboprost Versus Methylergometrine. Analysis of Six RCTs, 2014

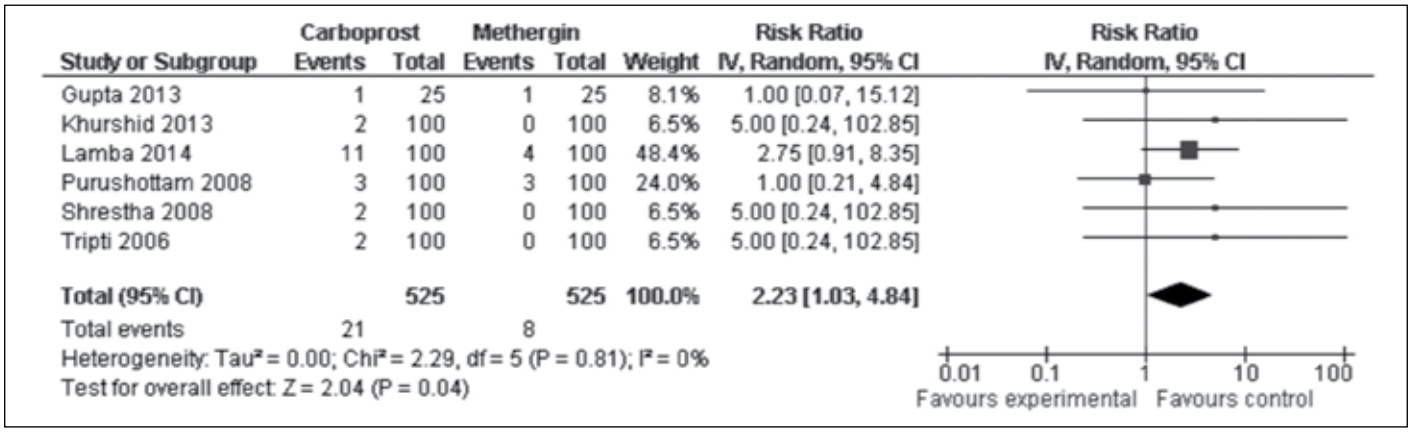

Table 5. Risk of Vomiting as a Side Effect, Comparison Between Carboprost Versus Methylergometrine. Analysis of Six RCTs, 2014

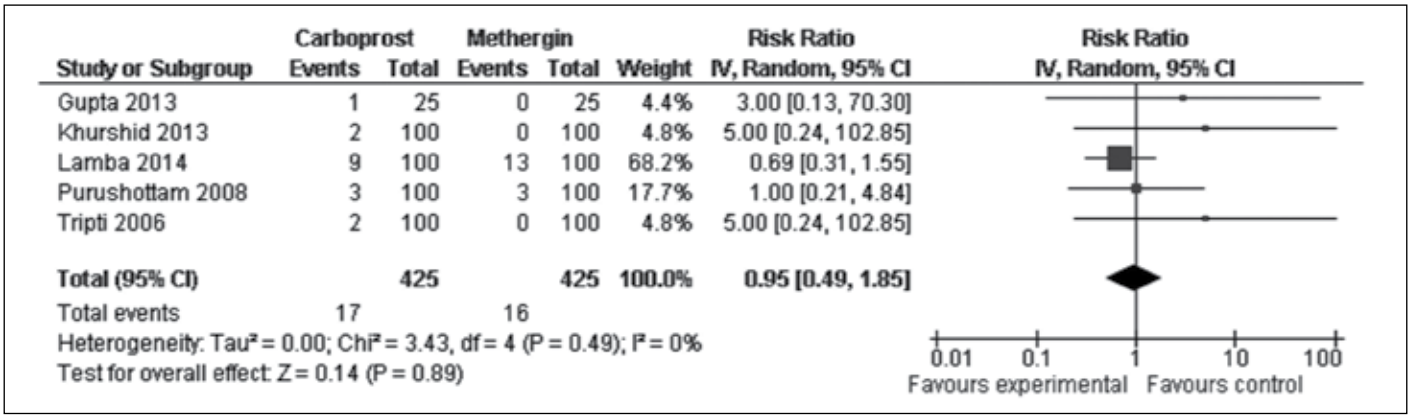

Table 6. Risk of Developing Nausea as a Side Effect, Comparison Between Carboprost Versus Methylergometrine. Analysis of Six RCTs, 2014

group and is statistically significant (RR 2.23, 95% CI, [1.03, 4.84], P=0.04 (Table 5).

Nausea

Five studies reported encountering nausea as a side effect which has comparable results (RR 0.95, 95% CI, [0.49, 1.85], P=0.89) (Table 6).

Diarrhea

Diarrhea was the most frequently reported statistically significant side effect on the carboprost group (RR 21.79, 95% CI, [5.22, 90.90], P<0.0001) (Table 7) as shown in three studies.

Fever

Fever was reported in 2 studies favoring the methergin group but did not reach considerable statistical significance (RR 2.19, 95% CI, [0.50, 9.60], P=0.30) (Table 8).

Risk of Bias

Figure 2 summarizes the risk of bias among the six clinical trials and was seen in six key areas during

Study or Subgroup	Carboprost Events	Carboprost Total	Methergin Events	Methergin Total	Weight	Risk Ratio IV, Random, 95% CI
Gupta 2013	2	25	0	25	22.9%	5.00 [0.25, 99.16]
Lamba 2014	16	100	0	100	26.0%	33.00 [2.01, 542.64]
Purushottam 2008	5	100	0	100	24.6%	11.00 [0.62, 196.33]
Shrestha 2008	48	100	0	100	26.5%	97.00 [6.06, 1551.67]
Total (95% CI)		**325**		**325**	**100.0%**	**21.79 [5.22, 90.90]**
Total events	71		0			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.35$, df = 3 (P = 0.50); $I^2 = 0\%$

Test for overall effect: Z = 4.23 (P < 0.0001)

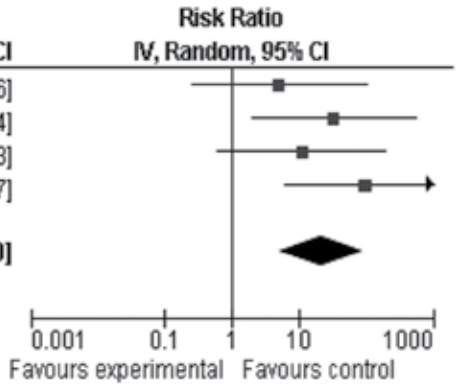

Table 7. Risk of Diarrhea with Caboprost Versus Methylergometrine Maleate. Analysis of Six RCTs, 2014

Study or Subgroup	Carboprost Events	Carboprost Total	Methergin Events	Methergin Total	Weight	Risk Ratio IV, Random, 95% CI
Gupta 2013	1	25	0	25	22.0%	3.00 [0.13, 70.30]
Lamba 2014	4	100	2	100	78.0%	2.00 [0.37, 10.67]
Total (95% CI)		**125**		**125**	**100.0%**	**2.19 [0.50, 9.60]**
Total events	5		2			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.05$, df = 1 (P = 0.82); $I^2 = 0\%$

Test for overall effect: Z = 1.04 (P = 0.30)

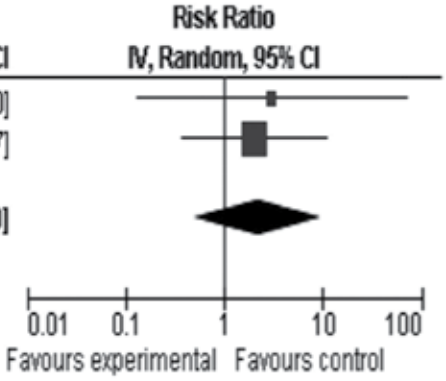

Table 8. Risk of Fever with Carboprost Versus Methylergometrine Maleate. Analysis of Six RCTs, 2014

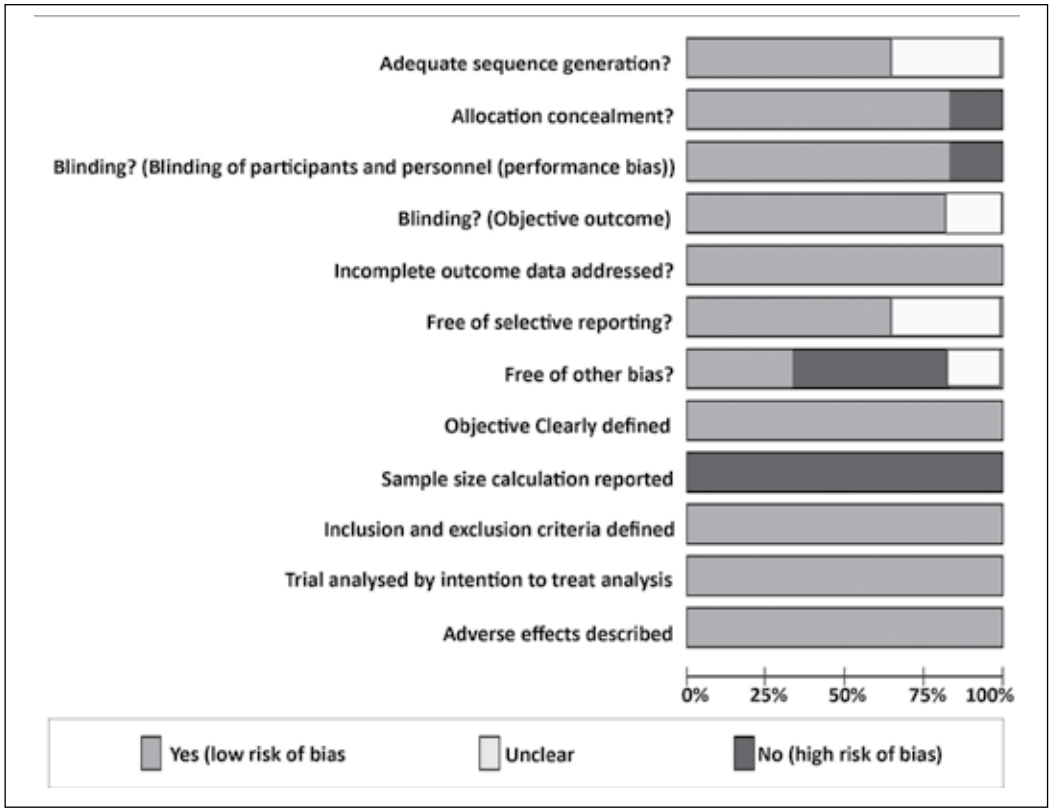

Figure 2. Risk of Bias Graph: Review Author's Judgements on Each Risk of Bias Item in Percentages Across All Included Studies on the Efficacy of Carboprost Versus Methergin in the Active Management of the Third Stage of Labor for the Prevention of Postpartum Hemorrhage, 2014

critical appraisal[13]. Sample size calculation and its bias was a common problem for all studies since it was not discussed how it was arrived at. Other issues encountered were selection bias (random sequence generation and allocation concealment), performance bias (on blinding of personnel and participants), detection bias) on objective assessment of the outcome), and selective reporting bias.

DISCUSSION

Active management of the third stage of labor lowers maternal blood loss and reduces the risk of postpartum hemorrhage[24,36]. Cochrane Database Review of many studies has revealed that active management is associated with significantly lesser blood loss during the third stage of labor[25]. Prophylactic oxytocics should be offered routinely in the management of the third stage of labor in all women as they reduce the risk of PPH by about 61%[26].

Prostaglandins have been extensively used in the treatment of atonic postpartum hemorrhage due to its potent uterotonic action[37]. Prostaglandin analogue, 15-methyl $PGF_2\alpha$ is 10 times more potent than its natural form and is able to resist enzymatic degradation. Single intramuscular injection of 15 methyl $PGF_2\alpha$ is absorbed rapidly and produces increased tone of uterus which is sustained for a period of 5 to 7 hours. Cyclical contractile uterine activity resulted in rapid separation and expulsion of placenta and sustained contraction of uterus resulted in significant control of blood loss[21].

This study was conducted to determine the efficacy of second-line uterotonics in the prevention of postpartum hemorrhage. The findings reveal that both drugs are equally effective in preventing postpartum hemorrhage but one drug (carboprost) has an advantage over the other (methylergometrine maleate) in the active management of the third stage of labor in terms of the major outcome considered such as the duration of the third stage of labor, the amount of blood loss in the third stage of labor and need for additional drug dose. There is a statistically significantly shorter duration of the third stage of labor, lesser amount of blood loss shown in the carboprost group and there was lesser need for an additional drug dose with carboprost, but the incidence of postpartum hemorrhage which was defined as blood loss of more than 500cc was noted to be equivalent in both groups. In terms of side effect, there was a greater risk for side effects to develop in the carboprost group.

This study demonstrates comparable efficacy of carboprost and methylergometrine for preventing incidence of postpartum hemorrhage. This finding is congruent with the most recent Cochrane Review of 17 misoprostol and 8 intramuscular prostaglandin trials that concluded that neither intramuscular prostaglandin nor misoprostol are preferable to conventional injectable uterotonics as part of the active management of the third stage of labor[27]. There was also no difference observed in the risk of blood transfusion between two treatments as reviewed in the WHO guidelines[28].

These results are comparable in the systematic review done by Chelmow in 2010 which revealed that carboprost injection compared with ergot alkaloids seemed to be equally effective in reducing the proportion of postpartum hemorrhage although carboprost seemed more effective at reducing blood loss in the third stage of labor. In his review, both carboprost and methylergometrine are equally effective at improving other measures of blood loss such as volume of blood loss and levels of hemoglobin and hematocrit with moderate-quality of evidence presented[29].

Retained placenta was also not encountered in five studies reviewed here. This is in agreement with the findings with the systematic review of Fernando, revealing that prostaglandins were superior to placebo or oxytocin in achieving the expulsion of the placenta without manual removal (3 RCTs, 132 participants; RR 2.53, 95% CI 1.66 to 3.86; I2 0%)[30].

In a study by Kerkes and Domokos, they recorded changes in the infraumbilical artery pressure using an open catheter and Hewlett Packard 8020 after treating the cases with $PGF_2\alpha$, (n=6), ergometrine (n=3), and physiological saline (n=4). They found a marked rise of 60 mmHG in the pressure and a sustained contracture response of the myometrium with $PGF_2\alpha$ as compared to minimal response with ergometrine. They observed similar results after intramyometrial injection of $PGF_2\alpha$ during cesarean section when a wave of contractions was seen starting from the site of injection and spreading to the distal segment of the uterus. The sustained contracture superimposed with cyclical contractile uterine activity resulted in rapid separation and expulsion of the placenta, and the sustained contraction resulted in significant control of blood loss[31].

This capability of 15-methyl prostaglandin (PG) $F_2\alpha$ to enhance uterine contractility makes it a very effective medication in reducing the duration and in active management of the third stage of labor[24].

Part of the recommendation of ACOG in the appropriate management of excessive postpartum bleeding is to give additional uterotonics as the first-line treatment for hemorrhage. This include the administration of methyergonovine maleate and 15-methyl prostaglandin (PG) $F_2\alpha$[32]. Carboprost has been reported to be 81% effective in treatment of persistent hemorrhage due to uterine atony, and may avoid the need for surgical intervention[33]. In a study by Bai et. al., he compared the

median blood loss in women given carboprost versus oxytocin and results showed that the blood loss was significantly lower than that in the oxytocin group[11].

In this study, there was a statistically significant advantage of carboprost versus methergin in terms of lesser need for an additional drug dose. This finding was in contradiction with the findings and recommendations in the WHO guidelines for the management of postpartum hemorrhage and retained placenta wherein results showed no statistically significant difference between the prostaglandin group (4 out of 106) and the injectable uterotonic group (2 out of 116) (RR 2.05, 95% CI, 0.39-2.86) in terms of use of additional uterotonics[27].

In terms of side effects, most studies mentioned an increase in the adverse events encountered more often in the carboprost group[34]. But according to the review by Fernando, adverse events were not different between groups[30]. The natural prostaglandins are rapidly metabolized in the circulation and therefore require higher dose for desired action, which causes more side effects[21]. Hypersensitivity is the only absolute contraindication but carboprost should be used with caution in asthma since prostaglandins causes contraction of smooth muscles which may lead to transient bronchoconstriction[34]. Carboprost tromethamine also stimulates the smooth muscle of the gastrointestinal tract[35]. The most commonly encountered side effect is vomiting (RR 10.74, 95% CI, 2.06 to 56.02)[33]. This is similar with the results findings in this review wherein all six studies has a statistically significant increased risk of vomiting in the carboprost group. Diarrhea is also a commonly encountered side effect[11] as was revealed in our own review. Despite the aforementioned potential side effects, most trials and reviews concluded that serious side effects are rare and self-limited. Another factor for consideration is the cost of carboprost which is more expensive in most of the other available uterotonics[34].

SUMMARY AND CONCLUSION

The result of this study showed that both 15-methyl prostaglandin $F_2\alpha$ (carboprost) and methylergometrine maleate are both effective in preventing postpartum hemorrhage. Furthermore, it was noted that carboprost was found to be more efficacious in reducing the duration of the third stage of labor and decreasing the amount of blood loss in the third stage of labor. Moreover, there was less need for an additional dose in the carboprost group. However, in terms of side effects, it was seen to be of higher risk to occur in the carboprost group as compared with methergin. Vomiting is the most frequently reported adverse event, followed by diarrhea. Although most studies stated that most of the side effects are not severe enough to warrant active management and are usually self-limiting.

Carboprost or 15-methyl prostaglandin $F_2\alpha$ is well known for its therapeutic role in the management of postpartum hemorrhage, which is well-tolerated and with minimal adverse effects. It is therefore recommended to be used for prophylactic purpose in hypertensive patients where methylergometrine maleate is contraindicated and in cases refractory to other uterotonic agents.

REFERENCES

1. Peters, Nina C.J., Duvekot, Johannes J., Carbetocin for the Prevention of Postpartum Hemorrhage, A Systemic Review., CME Review Article. Volume 64, Number 2. Obstetrical and Gynecological Survey. Lippincott Williams & Wilkins 2009.

2. Ottawa, Dean Leduc., et. al., Active Management of the Third Stage of Labour: Prevention and Treatment of Postpartum Hemorrhage. Society of Obstetrics and Gynecology Canada Clinical Practive Guideline. Journal of Obstetrics and Gynecology of Canada. No. 235 October 2009. *J Obstet Gynaecol Can* 2009;31(10):980-993

3. Clinical Practice Guidelines on Third Trimester Bleeding and Postpartum Hemorrhage, Philippine Obstetrical and Gynecological Society. Second Edition. November 2012.

4. Administration of Life-Saving Drugs and Medicine by Midwives to Rapidly Reduce Maternal and Neonatal Morbidity and Mortality. Administrative Order No. 2010-0014. Department of Health. http://www.doh.gov.ph

5. Reducing the Global Burden: Postpartum Hemorrhage. Department of Making Pregnancy Safer, World Health Organization. Issue 4: April 2007.

6. Tulali, Carlos., Philippine Policies on Maternal, Newborn and Child Health and Nutrition: Towards Achieving MDGs 4 and 5. PLCPD Policy Brief. March 2010.

7. Clinical Practice Guideline: Prevention and Management of Primary Postpartum Hemorrhage. Institute of Obstetricians and Gynecologists. Royal College of Physicians of Ireland and Directorate of Strategy and Clinical Programmes Health Service Executive. Version 1.1. Guideline No. 17. October 2012.

8. Maughan, K.L. et. al. Preventing Postpartum Hemorrhage: Managing the Third Stage of Labor. *American family Physician*, 2006;73(6):1025-1028.

9. Dyer, R.A. et. al. The Use of Uterotonic Drugs During Cesarean Section. *International Journal of Obstetric Anesthesia*, 2010; 19:313-319.

10. Anderson, Janice M., Prevention and Management of Postpartum Hemorrhage. *American Family Physician*. 2007;75(6):875-882. www.aafp.org/afp

11. Bai, Jing, et. al. A Comparison of Oxytocin and Carboprost Tromethamine in the Prevention of Postpartum Hemorrhage in High Risk Patients Undergoing Cesarean delivery. *Experimental and Therapeutic Medicine*, 2014;7:46-50.

12. Higgins JPT, Green S, editors. Assessment of study quality. Cochrane handbook for systematic reviews of interventions 5.1.0 [updated March 2011], Section 6. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

13. Higgins JPT, Altman DG, Sterne, JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

14. Steichen TJ, Egger M, Sterne JAC. Tests For Publication Bias In Meta-Analysis. *Stata Technical Bulletin* 1998;44:3-4.

15. Sterne JAC, Bradburn MJ, Egger M. Meta-Analysis In STATA TM. In: Systematic Reviews In Health Care: Meta-Analysis In Context. Egger M, Smith GD, Altman DG, editors. London: BMJ Books; 2001. pp. 347-69.

16. Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, Guyatt GH. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

17. Li and Ghosh. Meta-analysis based on weighted ordered P-values for genomic data with heterogeneity. BMC Bioinformatics. 2014, 15:226. http://www.biomedcentral.com/1471-2105/15/226

18. Gupta, Anshu. A Comparative Study of Methylergovine and 15-methyl Prostaglandin F2 α in Active Management of Third Stage of Labor. *Obstetrics & Gynecology Science*, 2013;56(5):301-306.*

19. Kuhrshid, R. et. al. A comparison Between Intramuscular PGF2 at 125µg and Intravenous Methylergometrine 0.2mg in the Active Management of Third Stage of Labor.*

20. Lamba, A. et. al. Comparison of Oxytocin, Methergin and Carboprost in Active Management of Third Stage of Labour. *Scientific Journal of Medical Science*, 2014;3(3):301-306.*

21. Purushotam, B.J. and Roopa, P. et. al. Prophylactic Intramuscular PGF2α Versus Intravenous Methylergometrine for Prevention of Atonic PPH in High Risk Women. *The Journal of Obstetrics and Gynecology of India*, 2008;58(5):417-420.*

22. Shrestha, A. et. al. Comparison of Intramyometrial and Intramuscular 15-methyl PGF2α Against Traditional Prophylactic Intramuscular Methergin for the Active Management of Third Stage of Labor. *Nepal Journal of Obstetrics and Gynecology*, 2008 Nov-Dec;3(2):35-39.*

23. Tripti, Nagaria and Manju, Ekka. Intramuscular PGF2α 125µg Versus Intravenous Methylergometrine 0.2mg in the Active Management of Third Stage of Labor. *Journal of Obstetrics and Gynecology of India*, 2006 September/October;56(5):396-398.*

24. FIGO Guidelines: Prevention and Treatment of Postpartum Hemorrhage in Low-Resource Settings. FIGO Safe Motherhood and Newborn Health (SMNH) Committee. *International Journal of Gynecology and Obstetrics*, 117;(2012):108-118

25. Prendiville, WJ, Elbourne, D, McDonald, S. Active versus Expectant Management in the Third Stage of Labor. Cochrane Database Syst Rev 2000;(3): CD000007.

26. RCOG. Prevention and Management of Postpartum Haemorrhage. Green-top Guideline 52. London: RCOG, 2009.

27. Gulmezoglu, A.M>, Forna, F., Villar, J., et. al. Prostaglandins for Prevention of Postpartum Hemorrhage (Cochrane Review). In: The Cochrane Library, Issue 1, 2003; Oxford: Update software.

28. WHO Guidelines for the Management of Postpartum Haemorrhage and Retained Placenta. World Health Organization. WHO Library. 2009.

29. Chelmow, david. Postpartum Hemorrhage: Prevention. BMJ Publishing. *Clinical Evidence* 2011;04:1410.

30. Fernando, Grille-Ardila Carlos. Prostaglandins for Management of retained Placenta (A Systematic Review of Randomized Trials). Universidad Nacional de Colombia. Faculty of Medicine. Colombia. 2012.

31. Kerkes, L., Domokos, N. The effect of Prostaglandin F2α on Third Stage Labor. *Prostaglandin* 1979;18:161-166.

32. ACOG. Optimizing Protocols in Obstetrics. Management of Obstetric Hemorrhage. Series 2. The American Congress of Obstetricians and Gynecologists District II. October 2012.

33. Bhau, Usha and Koul, Indu. Recent Advances in the Management of Postpartum Hemorrhage. JK Science. October-December 2008, 10(4):163-165.

34. Nisha, Shingh and Uma, Shingh. Methylergometrine and Carboprost Tromethamine Prophylaxis for Postpartum Hemorrhage. *The Journal of Obstetrics and Gynecology of India*, 2005;55(4):325-328.

35. Robinson, R., Mujumdar, M., Griffith, J., Casavant, M., Baker, S., Therapeutic Error: Carboprost Tromethamne Given to a Newborn Intramuscularly. The Internet Journal of Pediatrics and Neonatology. *Internet Scientific Publications*, 2006;6(2).

36. Queensland Maternity and Neonatal Clinical Guideline. Primary postpartum haemorrhage. Queensland Government, 2012

37. Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Management of Postpartum haemorrhage (PPH). C-OBs 43. RANZCOG, 2011.

38. Smith JR. Postpartum Hemorrhage Treatment & Management. eMedicine, 2012.

39. World Health Organization. WHO recommendations for the prevention and treatment of postpartum haemorrhage. Geneva: WHO, 2012.

* Included studies