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The Effect of the Combined Use of Methylergonovine and Oxytocin during Caesarean Section in the Prevention of Post-partum Haemorrhage

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Abstract: We aimed to show to patients the benefit of post-partum haemorrhage prophylaxis treatment and the effectiveness as a uterotonic agent of the combined use of methylergonovine and oxytocin infusion in the prevention of haemorrhage during and after Caesarean section, by comparison with a control group which received oxytocin infusion only. Two groups of patients undergoing Caesarean section at the same clinic were included in the study. A combination of methylergonovine and oxytocin was administered to the first group during the intra-operative and post-operative periods. The second group did not receive methylergonovine and was administered only with oxytocin infusion in the intra-operative and post-operative periods. Pre-operative and post-operative haemogram readings were taken for all patients in each of the groups for comparison. No difference was found between the two groups with regard to mean ages and pre-operative haemogram values. The decrease in post-operative haemoglobin values for the group administered with methylergonovine maleate and oxytocin was found to be significantly greater than for the group administered with oxytocin only. Results indicated that prophylactic methylergonovine treatment was clearly successful for the patients and no adverse side effects were found. The routine use of methylergonovine and oxytocin infusion in combination during the intra-operative period of Caesarean section reduced the level of post-partum haemorrhage considerably. We believe that this procedure will also reduce the risk of uterine atony, but clearly, prospective studies will be necessary in future to confirm this assumption.

In recent years, there has been a marked increase in the number of Caesarean sections carried out. This can be attributed largely to the rise in the rate of primary elective Caesarean section. In turn, this has led to a higher frequency of placenta previa, uterine atony and post-partum haemorrhage.

The increased prevalence of post-partum haemorrhage across the world is of particular concern as it is widely recognized as a major contributor to maternal mortality. Studies have estimated that post-partum haemorrhage might account for as much as 30% of maternal mortality and its incidence all over the world ranged from 2 to 11% of all childbirths [1,2]. The frequency of post-partum haemorrhage was found to be higher in underdeveloped regions such as Africa, Asia and Latin America [3]. The currently accepted definition is to consider post-partum haemorrhage as blood loss of more than 500 mL whatever the type of delivery and severity as blood loss beyond 1000 mL [4]. The American College of Obstetricians and Gynaecologists adjudged that a decrease in haematocrit at a rate of 10% or more constituted post-partum haemorrhage [5].

Although haemoglobin and haematocrit levels are valuable diagnostic tools in identifying haemorrhage, they can be misleading in the determination of acute bleeding. Therefore, follow-up of a patient's vital signs, together with checks of haemoglobin and haematocrit levels, are necessary diagnostic tools in establishing the presence of bleeding [6,7].

The aim of the treatment for post-partum haemorrhage is to restore myometrial contraction. For this purpose, the following therapeutic options can be used, alone or in combination: stimulation of uterine contractions with manual massage of the uterus; administration of oxytocin, misoprostol, methylergonovine and ergonovine with ergot derivatives. Note also that the increased sensitivity of the pregnant uterus to these drugs contributes to their therapeutic efficacy.

The preferred therapy for the treatment and prevention of post-partum haemorrhage varies from clinic to clinic. Currently, there is no consensus on treatment strategies or the superiority of one treatment over another, particularly with regard to the prevention of post-partum haemorrhage [8].

The increase in post-partum haemorrhage frequency all over the world has led to an increase in published studies on its prevention. In a meta-analysis of 29 studies comparing the administration of misoprostol with intravenous injections of oxytocin to prevent post-partum haemorrhage, the haemorrhage frequency for patients who were given prophylaxis was found to be similar or less than that for those who were not. Additionally, it was indicated that the infusion of oxytocin could be more effective than the administration of intramuscular misoprostol [9]. From the wide range of studies of post-partum haemorrhage prophylaxis, a variety of results have been obtained on treatments and their efficacies.

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The aim of our study was to show the efficacy of the additional use of prophylactic methylergonovine maleate and to discuss cardiovascular risk as an adverse effect in patients routinely given oxytocin infusion when undergoing Caesarean section. For this purpose, one group of patients was administered a combined treatment comprising methylergonovine maleate and oxytocin infusion, while the other group was given oxytocin infusion only. The two groups were then compared by performing pre-operative and post-operative haemogram follow-up. We aimed to determine the importance of prophylactic treatment for post-partum haemorrhage by comparing the reduction rates of haemoglobin levels in the post-partum period. A further aim was to evaluate the efficacy of methylergonovine maleate treatment in the prevention of post-partum haemorrhage.

Material and Methods

This study was carried out in the Department of Obstetrics and Gynecology of the Medical School Hospital at Recep Tayyip Erdogan University between 1 June 2012 and 31 May 2014. It was approved by the Ethics Committee of the School of Medicine of Recep Tayyip Erdogan University. All the patients included were informed of the purpose of the study. Our study was a randomized, prospective study. Also, each patient who was to be administered with methylergonovine maleate was informed about possible adverse effects, and written informed consent was obtained.

A total of 1210 patients undergoing Caesarean section were included in the study. The inclusion criteria were as follows: age, 18–40 years; gestation ≥34 weeks, gravida 1–3; and all with indications for Caesarean. Patients with certain conditions were excluded from the study: those with known pre-eclampsia, eclampsia and hypertensive disease; patients with coagulation disorder; patients who had been given blood transfusion; those diagnosed with severe anaemia (Hb<7 gr/dL) and polycythemia vera (Hb>16 gr/dL), as they might increase the risk of haemorrhage and cause ischaemia; and patients with known ischaemic heart disease, cerebrovascular disease or peripheral vascular disease, and with no post-partum uterine atony which would require additional medical therapy or blood transfusion due to change in haemoglobin levels. Combined treatment (methylergonovine maleate and oxytocin infusion) was administered during the intra-operative and post-operative period to the first group of 295 women undergoing Caesarean section, while no methylergonovine maleate was given to the second group of 915 women; they received oxytocin infusion only.

Oxytocin intravenous infusion was given as 20 units in 500 mL of lactated Ringer's at 333 cc per hour in the operating room after delivery of the placenta and 30 units in 1000 mL of lactated Ringer's at 333 cc per hour in the post-operative periods, respectively, to both patient groups. Additionally, for the second group (the 295 patients), 0.2 mg of methylergonovine was also administered intramuscularly in the first minute after delivery and post-operatively after 3 hr due to its effect duration. The effect duration of methylergonovine is approximately 3 hr when used intramuscularly. Haemogram readings were taken for all patients included in the study. These were noted during the pre-operative period and in the post-operative fourth hour, and haemoglobin readings were taken in the fourth hour. To determine the presence of acute haemorrhage in all of the patients, hourly follow-up checks of blood pressure and pulse rate, urine output and vaginal bleeding were carried out during the post-operative period. In the absence of haemorrhage symptoms, a haemogram measurement was taken once in the first 24-hr post-operative period of clinical follow-up. To detect any adverse effects of the drug in the patients administered with methylergonovine maleate, hourly follow-up checks were carried out by assistant doctors on the patients for the presence of nausea, vomitus, tinnitus, bradycardia, tachycardia, hypertension, allergic reaction, diarrhoea and chest pain, in addition to the follow-up for post-partum haemorrhage and vital signs.

Haemogram readings of all patients included in the study were carried out using the same equipment and by the same biochemistry specialist. The Beckman method was used to evaluate blood haemoglobin levels, and the readings were taken using a Beckman Coulter analyser.

Statistical analysis. The NCSS (Number Cruncher Statistical System) 2007 & PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) program was used for the statistical analysis. For the evaluation of study data, including the comparisons of descriptive statistical methods (Mean, Standard Deviation, Median, Frequency, Ratio, Minimum, and Maximum) as well as quantitative data, a Student's *t*-test was used for intergroup comparisons of the parameters with normal distribution, and a Mann–Whitney *U*-test was used for intergroup comparisons of the parameters without normal distribution. A paired samples *t*-test was used for pre-operative and post-operative comparisons of the parameters with normal distribution. Significance was evaluated at the level of $p < 0.01$ and $p < 0.05$.

Results

This study was carried out on 1264 patients undergoing Caesarean section in the Department of Obstetrics and Gynecology of the Medical School Hospital at Recep Tayyip Erdogan University between 1 June 2012 and 31 May 2014. Fifty-four patients were excluded from the study because some of them (n = 18) refused and others (n = 36) had coronary artery diseases or the increasing risk factors for coronary artery diseases. Thus, 1,210 patients were included. Patients complaining of chest pain and palpitations were evaluated for changes of blood pressure by electrocardiogram test, during the operative and post-operative period. Neither ST elevation nor depression was found in symptomatic patients. Pulse rate and blood pressure were measured at 80–100/min. and <140/90 mm/Hg in symptomatic patients, respectively. A control group without treatment was not included in this study. Each patient with Caesarean section received prophylactic treatment in the clinic. Therefore, a control group without treatment was not approved by the Ethics Committee of the School of Medicine of Recep Tayyip Erdogan University.

The combined treatment of methylergonovine maleate and oxytocin was administered during the intra-operative and post-operative periods, to the first group of patients, comprising 24.4% of the women (n = 295) undergoing Caesarean section. The second group, 75.6% of the patients (n = 915), received oxytocin treatment but no methylergonovine maleate.

When the mean ages of the two groups of patients were compared, no statistically significant difference was found between them ($p > 0.05$).

The ages of the women treated with the combined drugs ranged between 18 and 44 years, with a mean of 31.07 ± 5.30 years. Those not administered with methylergonovine maleate but with oxytocin only ranged in age from 17 to 48 years, while the mean was determined to be 31.36 ± 5.68 years.

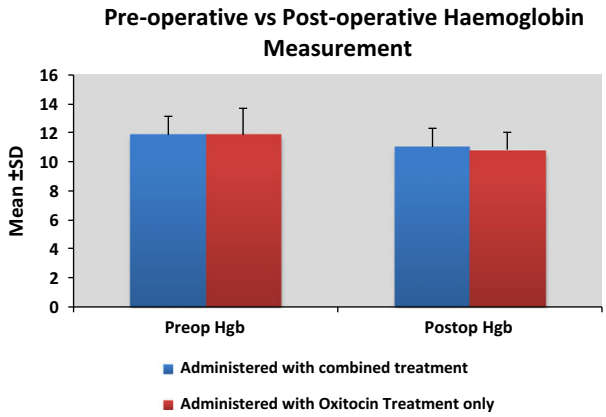

Fig. 1. Measurements of haemoglobin values in patients administered with combined treatment (methylergonovine and oxytocin) and patients administered with oxytocin only during pre-operative and post-operative periods.

When pre-operative and post-operative Hb (haemoglobin) values of the patients administered and not administered with methylergonovine maleate were compared, no significant difference was found between the mean pre-operative Hb values of both groups ($p = 0.687$; $p > 0.05$). However, the mean post-operative Hb values of the group which received methylergonovine maleate were found to be statistically significantly higher ($p = 0.005$; $p < 0.01$) (Fig. 1).

In the group administered with methylergonovine maleate, the mean reduction in Hb level of 0.85 ± 097 units, between the pre-operative and post-operative readings, was determined to be statistically significant ($p = 0.001$; $p < 0.01$).

In the group not administered with methylergonovine maleate, the mean reduction in Hb level of 1.05 ± 0.95 units, between the pre-operative and post-operative readings, was also found to be statistically significant ($p = 0.001$; $p < 0.01$).

It was determined that the extent of the reduction in post-operative Hb values compared to pre-operative Hb values demonstrated a highly significant difference between the two groups ($p = 0.002$; $p < 0.01$). The extent of the reduction in post-operative Hb values compared to pre-operative Hb values was found to be significantly greater in the group receiving oxytocin only, as compared with the group receiving the combined treatment (Table 1).

Table 1.
Comparison of haemoglobin values in patients administered with combined treatment (methylergonovine and oxytocin) and patients administered with oxytocin only during pre-operative and post-operative periods.

	Patients with combined treatment (methylergonovine and oxytocin) (n = 295) Mean ± SD	Patients administered with oxytocin only (n = 915) Mean ± SD	*p*
Pre-operative haemoglobin	11.89 ± 1.23	11.86 ± 1.86	0.687[1]
Post-operative haemoglobin	11.04 ± 1.24	10.81 ± 1.20	0.005[1]
p[2]	0.001**	0.001**	
Difference	0.85 ± 0.97	1.05 ± 0.95	0.002[3]

[1]Student's *t*-test. [2]Paired samples *t*-test. [3]Mann–Whitney *U*-test. **$p < 0.01$.

Discussion

Post-partum haemorrhage is one of the most important causes of maternal mortality, and it is an important health problem especially in underdeveloped countries. Previous studies have shown that life-threatening post-partum haemorrhage occurs in approximately 1 of 1000 deliveries [10]. Uterine atony is the most important cause of post-partum haemorrhage, and it accounts for approximately 85%–90% of cases [7].

In the physiology of childbirth, post-partum haemorrhage is prevented by myometrial contractions beginning with the separation of the placenta and participation of hormones [11]. For this reason, the promotion of myometrial contractions has become the main aim of treatments for post-partum haemorrhage.

Recently, more attention has been given to post-partum haemorrhage and more studies have been focused on its prevention, but there is still no consensus on the effectiveness of treatment options.

By comparing the two groups, one receiving the combined treatment of methylergonovine maleate and oxytocin and the other receiving oxytocin only, our aim was to demonstrate the efficacy of methylergonovine maleate treatment in post-partum haemorrhage prophylaxis. We also sought to determine the importance of prophylactic combination treatment for post-partum haemorrhage by comparing the reduction rates of haemoglobin levels in the post-partum period.

Methylergonovine (methylergometrine) is a semi-synthetic derivative of ergot alkaloid which causes vasoconstriction of the uterine vascular smooth muscles. Methylergonovine is a partial agonist of α-adrenergic (α1) and serotonergic (5-HT2) receptors. As α1 receptors increase in the uterus during pregnancy, the pregnant uterus becomes more sensitive to methylergonovine [12]. But due to the adverse effects of methylergonovine, it is usually not preferred in prevention of post-partum haemorrhage. Methylergonovine may cause an increase in morbidity–mortality due to increasing vasospasm; therefore, its use is limited to patients with ischaemic heart disease or who are at risk of ischaemic heart disease, with peripheral vascular disease and diabetes mellitus. Many studies have shown that methylergonovine may lead to an increase in the risk of acute coronary syndrome or acute myocardial infarction in patients with chronic ischaemic heart disease or risk factors including pre-existing hypertension, pre-existing diabetes, tobacco use, obesity, chronic renal disease and dyslipidaemia [13]. However, the relationship between maternal demographic features (age, race, etc.) with ischaemic heart disease risk was not directly found. But we think that an increase in maternal age can cause an elevated risk of developing of pre-existing hypertension, pre-existing diabetes and dyslipidaemia. Therefore, an increase in maternal age can lead to elevated adverse effects of methylergonovine.

The World Health Organization recommends intramuscular oxytocin infusion in post-partum haemorrhage prophylaxis. However, due to fewer side effects such as hypertensive attack and ischaemia, and also for practical reasons such as avoiding the need of injection, the use of sublingual or rectal misoprostol is usually preferred at most centres [14].

Nevertheless, it was observed that oxytocin infusion was more effective in post-partum haemorrhage prophylaxis and in the presence of active haemorrhage. In some studies comparing the efficacy of oxytocin and misoprostol, it was considered that this condition could be due to the later achievement of peak plasma concentration of misoprostol [15]. The efficacy of sublingual misoprostol and oxytocin infusion was found to be similar in previous studies [16]. In a study investigating the efficacy of methylergonovine (which was less commonly used in the prevention of post-partum haemorrhage due to its side effects) in the control of bleeding, patients administered methylergonovine were compared with patients receiving 15-methyl PGF2α. While 15-methyl PGF2α was effective in the control of bleeding during the post-partum first hours, the performances of each of the drugs by the post-partum 3rd day showed both to be successful, with similar rates [9].

In summary, the results of post-partum haemorrhage prophylaxis vary across the range of the studies. In a meta-analysis of 17 studies, while the rate of post-partum haemorrhage varied between 4% and 51% without uterotonic treatment, it was shown that the rate of post-partum haemorrhage regressed to the following values with prophylactic oxytocin infusion, misoprostol treatment and ergometrine treatment, respectively: 0–32%, 1–45% and 0–37%. In the same study, the blood loss occurring with the administration of prophylactic uterotonic treatment was compared [9,17–33]. It was found that this was reduced by an average of 151–499 mL in the patients administered with oxytocin, 155–433 mL in the patients administered with misoprostol and 149–476 mL in the patients administered with ergometrine. In a meta-analysis of 12 studies, severe post-partum haemorrhage was observed at a rate of 0.5–17% in the patients not administered with prophylactic treatment [9,15,34–44]. This rate regressed to 0.4–9% in the patients who received prophylactic treatment. Given these results, it was concluded that prophylaxis treatment was important in post-partum haemorrhage.

In our study, we administered methylergonovine treatment during the intra-operative and post-operative periods to patients undergoing Caesarean section who had similar mean haemoglobin values in the pre-operative period. It was found that the reduction level in post-operative haemoglobin values, compared to the pre-operative period, in patients who were administered with the combined treatment, was significantly lower than for the group which did not receive methylergonovine maleate. Also, no adverse effects were observed in the patients administered with methylergonovine prophylaxis during our study. Similarly, the results of clinical studies showed that oxytocin and ergot derivatives were successful in the treatment of post-partum haemorrhage, especially in resistant haemorrhage. It was demonstrated that a 70–80% success rate could be obtained with the use of oxytocin in combination with ergot derivatives [45].

Although the use of methylergonovine is not recommended for post-partum haemorrhage prophylaxis in many centres due to side effects, it has been shown that the adverse effects of methylergonovine did not cause unfavourable results for the patients in the studies comparing methylergonovine with other uterotonic treatments. In one study, the side effects of oxytocin and methylergonovine uterotonic treatments were compared. The patients undergoing Caesarean section were divided into two groups and administered oxytocin and methylergonovine uterotonic treatments, respectively, for post-partum haemorrhage prophylaxis. The patients were then compared for changes in pulse and blood pressure, development of chest pain, ST elevation and depression in the electrocardiogram. While tachycardia, hypotension and ST changes in the electrocardiogram, indicating myocardial ischaemia, were found in the patients administered with oxytocin infusion, and moderate hypertension was observed in the group which received methylergonovine, no evidence supporting ischaemia was determined from the electrocardiogram [46].

In summary, in accordance with many other studies, the results of our study indicate that prophylactic uterotonic treatment plays an important role in post-partum haemorrhage. Furthermore, we found that prophylactic methylergonovine treatments with oxytocin combination treatments were more successful than treatments with oxytocin only for the patients in our study and significantly without any evidence of adverse side effects. It is suggested that methylergonovine induces vasospasm; therefore, it can cause elevated myocardial ischaemia and infarction risk [47].

Patients with coronary artery disease or risk factors for coronary artery disease (e.g. smoking, obesity, diabetes, high cholesterol) were excluded from our study. Additionally, electrocardiogram and arterial tension were evaluated in the presence of symptoms and found to be without any evidence of adverse side effects (ST changes in the electrocardiogram, the existence of hypertension) in our patients.

We believe that the administration of methylergonovine with oxytocin as a combined uterotonic treatment for post-partum haemorrhage prophylaxis can be as safe and efficient as the other uterotonic treatments, and may also reduce the risk of uterine atony in selected patients [patients with no coronary artery disease or no risk factors for coronary artery disease (e.g. smoking, obesity, diabetes, high cholesterol).

Conclusion

In order to demonstrate the superiority of one treatment over another in post-partum haemorrhage prophylaxis, and to arrive at a consensus on the best approach to treatment, we believe that large-scale studies, considering the various risks of haemorrhage (presence of anaemia, multiple foetuses, the size of foetus, previous Caesarean section, presence of hydramnios, etc.) and including a much larger sample of patients, are necessary prospective studies in future.

Conflict of Interest

The authors declare no conflict of interest.

References

1 Khan KS, Wojdyla D, Say L, Gu¨ lmezoglu AM, Van Look PFA. WHO analysis of causes of maternal death: a systematic review. Lancet 2006;**367**:1066–74.

2 WHO, UNICEF, UNFPA. The World Bank. Maternal mortality in 2005: estimates developed by WHO, UNICEF, UNFPA, and the World Bank. In: World Health Organization (ed.). WHO Press, World Health Organization. World Health Organization: Geneva, Switzerland, 2005;16–17, 23–27, 29–38.

3 Anderson FWJ. Maternal mortality: an enduring epidemic. Clin Obstet Gynecol 2009;**52**:214–223.

4 Sentilhes L, Vayssière C, Mercier F, Aya AG, Bayoumeu F, Bonnet MP *et al.* Postpartum hemorrhage: Guidelines for clinical practice – Text of the Guidelines (short text). Journal de Gyne´cologie, Obste´trique et Biologie de la Reproduction 2014;**43**:1170–1179.

5 ACOG. By Reviewing Only Articles of Measured American College Obstetricians and Gynecologists Task Force on Quality Assurance. Quality Assurance in Obstetrics and Gynecology. Washington, DC: ACOG, 1989.

6 Karoshi M, Keith L. Challenges in managing postpartum hemorrhage in resource-poor countries. Clin Obstet Gynecol 2009;**52**:285–298.

7 Driessen M, Bouvier-Colle M-H, Dupont C, Khoshnood B, Rudigoz R-C, Deneux-Tharaux C. Postpartum hemorrhage resulting from uterine atony after vaginal delivery: factors associated with severity. Obstet Gynecol 2011;**117**:21–31.

8 Montufar-Rueda C, Rodriguez L, Jarquin JD, Barboza A, Bustillo MC, Marin F *et al.* Severe postpartum hemorrhage from uterine atony: a multicentric study. J Pregnancy 2013;**29**:525914.

9 Sloan NL, Durocher J, Aldrich T, Blum J, Winikoff B. What measured blood loss tells us about postpartum bleeding: a systematic review. BJOG 2010;**117**:788–800.

10 Gupta A. A comparative study of methylergonovine and 15-methyl prostaglandin F2α in active management of third stage of labor. Obstet Gynecol Sci 2013;**56**:301–306.

11 Bose P, Regan F, Paterson-Brown S. Improving the accuracy of estimated blood loss at obstetric haemorrhage using clinical reconstructions. BJOG 2006;**113**:919–24.

12 Tripathi KD. 5-Hydroxytryptamine, its antagonists and drug therapy of migraine. In: Tripathi KD, (ed.). Essential of Medical Pharmacology, 6th edn. Jaypee brothers, New Delhi, India, 2008; 162–72.

13 Bateman BT, Huybrechts KF, Hernandez-Diaz S, Liu J, Ecker JL, Avorn J. Methylergonovine maleate and the risk of myocardial ischemia and infarction. Am J Obstet Gynecol 2013;**209**:459.

14 World Health Organization. WHO Recommendations for the Prevention and Treatment of Postpartum Haemorrhage. World Health Organization, Geneva, Switzerland, 2012.

15 Gu¨lmezoglu AM, Villar J, Ngoc NT, Piaggio G, Carroli G, Adetoro L *et al.* WHO multicentre randomised study of misoprostol in the management of the third stage of labour. Lancet 2001;**358**:689–95.

16 Schellenberg JC. Primary Postpartum Haemorrhage (PPH) [Internet]. Geneva Foundation for Medical Education and Research, Versoix, Switzerland, 2013. [cited 2008 May 24].

17 Derman RJ, Kodkany BS, Goudar SS, Geller SE, Naik VA, Bellad MB *et al.* Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial. Lancet 2006;**368**:1248–53.

18 Nordström L, Fogelstam K, Fridman G, Larsson A, Rydhstroem H. Routine oxytocin in the third stage of labor: a placebo-controlled study randomised trial. Br J Obstet Gynaecol 1997;**104**:781–6.

19 Strand RT, Da Silva F, Jangsten E, Bergstrom S. Postpartum hemorrhage: a prospective, comparative study in Angola using a new disposable injection device for oxytocin administration. Acta Obstet Gynecol Scand 2005;**84**:260–5.

20 Phillip H, Fletcher H, Reid M. The impact of induced labour on postpartum blood loss. J Obstet Gynaecol 2004;**24**:12–5.

21 Bamigboye AA, Hofmeyr GJ, Merrell DA. Rectal misoprostol in the prevention of postpartum hemorrhage: a placebo-controlled trial. Am J Obstet Gynecol 1998;**179**:1043–6.

22 Zachariah ES, Naidu M, Seshadri L. Oral misoprostol in the third stage of labor. Int J Gynecol Obstet 2006;**92**:23–6.

23 Yuen PM, Chan NS, Yim SF, Chang AM. A randomised double blind comparison of Syntometrine and Syntocinon in the management of the third stage of labour. Br J Obstet Gynaecol 1995;**102**:377–80.

24 Verma P, Aggarwal N, Jain V, Suri V. A double-blind randomized controlled trial to compare sublingual misoprostol with methylergometrine for prevention of postpartum hemorrhage. Int J Gynecol Obstet 2006;**94**(Suppl 2):137–8.

25 Tsu VD, Mai TT, Nguyen YH, Luu HT. Reducing postpartum hemorrhage in Vietnam: assessing the effectiveness of active management of third-stage labor. J Obstet Gynaecol Res 2006;**32**:489–96.

26 Soriano D, Dulitzki M, Schiff E, Barkai G, Mashiach S, Seidman DS. A prospective cohort study of oxytocin plus ergometrine compared with oxytocin alone for prevention of postpartum hemorrhage. Br J Obstet Gynaecol 1996;**103**:1068–73.

27 Prata N, Hamza S, Gypson R, Nada K, Vahidnia F, Potts M. Misoprostol and active management of the third stage of labor. Int J Gynecol Obstet 2006;**94**:149–55.

28 Poeschmann RP, Doesburg WH, Eskes TK. A randomized comparison of oxytocin, sulprostone and placebo in the management of the third stage of labour. Br J Obstet Gynaecol 1991;**98**:528–30.

29 Ozkaya O, Sezik M, Kaya H, Desdicioglu R, Dittrich R. Placebo-controlled randomized comparison of vaginal with rectal misoprostol in the prevention of postpartum hemorrhage. J Obstet Gynaecol Res 2005;**31**:389–93.

30 Nellore V, Mittal S, Dadhwal V. Rectal misoprostol vs. 15-methyl prostaglandin F2alpha for the prevention of postpartum hemorrhage. Int J Gynecol Obstet 2006;**94**:45–6.

31 Mitchell GG, Elbourne DR. Oxytocin plus ergometrine versus oxytocin alone in the active management of the third stage of labor. Online J Curr Clin Trials 1993. Doc No. 83.

32 Lam H, Tang O, Lee CP, Ho PC. A pilot-randomized comparison of sublingual misoprostol with syntometrine on the blood loss in third stage of labor. Acta Obstet Gynecol Scand 2004;**83**:647–50.

33 Kundodyiwa TW, Mojoko F, Rusakaniko S. Misoprostol versus oxytocin in the third stage of labor. Int J Gynecol Obstet 2001;**75**:235–41.

34 Høj L, Cardoso P, Nielsen BB, Hvidman L, Nielsen J, Aaby P. Effect of sublingual misoprostol on severe postpartum hemorrhage in a primary health centre in Guinea-Bissau: randomized double blind clinical trial. Br Med J 2005;**331**:723–7.

35 Hofmeyr GJ, Nikodem VC, de Jager M, Drakely A. Side-effects of oral misoprostol in the third stage of labour–a randomised placebo-controlled trial. S Afr Med J 2001;**91**:432–5.

36 Gupta B, Jain V, Aggarwal N. Rectal misoprostol versus oxytocin in the prevention of postpartum hemorrhage—A pilot study. Int J Gynecol Obstet 2006;**94**:139–40.

37 Bugalho A, Daniel A, Faúndes A, Cunha M. Misoprostol for prevention of postpartum hemorrhage. Int J Gynecol Obstet 2001;**73**:1–6.

38 Benchimol M, Gondry J, Mention J-E, Gagneur O, Boulanger JC. Place du misoprostol dans la direction de la deliverance. J Gynecol Obstet Biol Reprod 2001;**30**:576–83.

39 Abdel-Aleem H, Hofmeyr G, Shokry M, El-Sonoosy E. Uterine massage and postpartum blood loss. Int J Gynecol Obstet 2006;**93**:238–9.
40 Begley C. A comparison of 'active' and 'physiological' management of the third stage of labour. Midwifery 1990;**6**:3–17.
41 De Groot ANJ, van Roosmalen J, van Dongen PW, Borm GF. A placebo-controlled study of oral ergometrine to reduce postpartum hemorrhage. Acta Obstet Gynecol Scand 1996;**75**:464–8.
42 Fujimoto M, Takeuchi K, Sugimoto M, Maruo T. Prevention of postpartum hemorrhage by uterotonic agents: comparison of oxytocin and methylergometrine in the management of the third stage of labor. Acta Obstet Gynecol Scand 2006;**85**:1310–4.
43 Vimala N, Mittal S, Kumar S, Dadhwal V, Mehta S. Sublingual misoprostol versus methylergometrine for active management of the third stage of labor. Int J Gynaecol Obstet 2004;**87**:1–5.
44 Walraven G, Blum J, Dampha Y, Sowe M, Morison L, Winikoff B *et al.* Misoprostol in the management of the third stage of labour in the home delivery setting in rural Gambia: a randomised controlled trial. BJOG 2005;**112**:1277–83.
45 Bjørnerem A, Acharya G, Øian P, Maltau JM. [Postpartum hemorrhage–prophylaxis and treatment in Norway]. 2002;**122**: 2536–7.
46 Svanstro¨m M. C., Biber B., Hanes M., Johansson G., Na¨slund U., Balfors E. M. Signs of myocardial ischaemia after injection of oxytocin: a randomized double-blind comparison of oxytocin and methylergometrine during Caesarean section. Br J Anaesth 2008;**100**:683–9.
47 De Labriolle A, Genee O, Heggs LM, Fauchier L. Acute myocardial infarction following oral methyl-ergometrine intake. Cardiovasc Toxicol 2009;**9**:46–8.