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CLINICAL ARTICLE

Randomized controlled trial comparing 200 μg and 400 μg sublingual misoprostol for prevention of primary postpartum hemorrhage

Innocent A. Ugwu [a], Timothy A. Oluwasola [a,b,*], Obehi O. Enabor [a], Ngozi N. Anayochukwu-Ugwu [c], Abolaji B. Adeyemi [a], Oladapo O. Olayemi [a,b]

[a] Department of Obstetrics and Gynecology, University College Hospital, Ibadan, Nigeria
[b] Department of Obstetrics and Gynecology, College of Medicine, University of Ibadan, Ibadan, Nigeria
[c] Department of Hematology, University College Hospital, Ibadan, Nigeria

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ABSTRACT

Objective: To compare efficacy and adverse effects of 200 μg and 400 μg misoprostol for prevention of postpartum hemorrhage (PPH). *Methods:* In a randomized control trial, women with term singleton pregnancies in active labor attending University College Hospital, Ibadan, Nigeria, were enrolled between July 2011 and February 2012. Participants were randomly assigned using random numbers (block size four) to receive 200 μg or 400 μg sublingual misoprostol after delivery of the anterior shoulder, alongside intravenous oxytocin. Investigators were masked to group assignment, but participants were not. The primary outcomes were blood loss up to 1 h after delivery, PPH (blood loss ≥500 mL), and adverse effects. *Results:* Overall, 62 patients were assigned to each group. No significant differences between the 200-μg and 400-μg groups were recorded in mean peripartum blood loss (307 ± 145 mL vs 296 ± 151 mL; $P = 0.679$) and PPH occurrence (5 [8.1%] vs 6 [9.7%] women; $P = 0.752$). Noticeable adverse effects were reported by 16 (25.8%) women in the 200-μg group and 42 (67.7%) in the 400-μg group ($P < 0.001$). Risk of shivering was significantly lower with 200 μg than 400 μg (relative risk 0.33, 95% confidence interval 0.19–0.58). *Conclusion:* Blood loss and PPH occurrence did not differ by misoprostol dose, but a 200-μg dose was associated with a reduction in adverse effects.

Pan Africa Clinical Trials Registry: PACTR201505001107182

1. Introduction

Postpartum hemorrhage (PPH) affects approximately 2%–5% of all women who give birth, is responsible for nearly one-quarter of all maternal deaths globally, and has remained the leading cause of maternal mortality in many low-income countries [1,2]. Most deaths from PPH (99%) occur in low-resource countries, where the majority of women do not receive prophylaxis because they deliver where there are limited or no facilities for adequate management of PPH [1,3–6]. Approximately two-thirds of women with PPH have no identifiable clinical risk factors [5,7].

The outcome of PPH management is dependent on the early recognition and prompt institution of necessary treatment protocols [7]. Aside from maternal mortality, anemia, prolonged hospital stay, and difficulty establishing breastfeeding can all follow PPH [4,7]. Although blood transfusion can alleviate anemia and reduce the duration of hospital stay, it carries the risk of transfusion reactions and infections; additionally, access to safe blood transfusion remains a challenge in low-resource countries [4,7,8]. The optimal solution to these events is prevention: both prepartum, by ensuring that women are sufficiently healthy to withstand PPH should it occur; and intrapartum, by adopting active management of the third stage of labor (AMTSL). AMTSL is an evidence-based, effective strategy that is dependent on circumstances and the availability of appropriate, effective oxytocics [5–9].

The occurrence of PPH despite use of intravenous oxytocin and other components of AMTSL suggests that oxytocin alone might be inadequate for the prevention of PPH. Several uterotonics have been used for AMTSL, but their effectiveness is limited by either adverse effects or challenges with storage [7,8]. Misoprostol, an analog of prostaglandin E_1, has been suggested as an alternative to oxytocin on the basis of its ability to act as an effective uterotonic agent. It is safe and inexpensive, can be taken orally, has a long shelf-life, and does not require refrigeration [10–14]. Facility-based trials have demonstrated that misoprostol is safe and efficacious for prevention of PPH [8,11,15–17], and oral formulations have been recommended for the third stage of labor when other oxytocics (e.g. oxytocin) are unavailable or ineffective [1]. However, misoprostol has been associated with various adverse effects, such as shivering, fever, nausea, vomiting, and diarrhea—all of which are dose-related [15–19].

* Corresponding author at: Department of Obstetrics and Gynecology, University College Hospital, PMB 5116, Ibadan, Nigeria. Tel.: +234 8033384064.
E-mail address: sesanoluwasola@yahoo.com (T.A. Oluwasola).

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In terms of PPH prevention, studies have suggested that 200 μg misoprostol could have a similar effectiveness as 400 μg or 600 μg doses, but with a reduced frequency of adverse effects [12,18]. Therefore, the aim of the present study was to compare efficacy and adverse effects between women given 200 μg and those given 400 μg sublingual misoprostol alongside intravenous oxytocin for PPH prevention in the third stage of labor.

2. Materials and methods

A randomized controlled trial was conducted between July 1, 2011, and February 29, 2012, among women in the active stage of labor attending the Obstetrics Unit of the University College Hospital, a tertiary care teaching hospital in Ibadan, Oyo state, Nigeria. Women with term singleton pregnancies with anticipated vaginal delivery were eligible for the study. The exclusion criteria were contraindications to misoprostol, coagulation disorders, and need for cesarean delivery. Patients with hypertensive diseases in pregnancy, anemia, prepartum hemorrhage, or conditions requiring prophylactic oxytocin infusion after delivery (e.g. multiple pregnancy, coexisting uterine fibroids, previous history of PPH, polyhydramnios, or grand-multiparity) were also excluded. The Institutional Review Committee of the University of Ibadan/University College Hospital Ibadan approved the study. All patients were adequately counseled and voluntary informed consent was obtained before recruitment to the study.

After providing informed consent and reaching the second stage of labor, the participants were randomly assigned (1:1) to receive either 200 μg or 400 μg misoprostol tablets (Beijing Zizhu Pharmaceuticals, distributed by Emzor Pharmaceuticals, Lagos, Nigeria). Randomization was done via the blocked randomization method. An independent statistician generated sets of four random numbers in blocks of four and prepared boxes of four opaque, sealed envelopes containing details of allocation. Placebo tablets with a similar appearance to that of the misoprostol tablets used were not available, which meant that patients in the 200-μg group received only one tablet whereas those in the 400-μg group received two. Although masking of patients was therefore not possible, the tablets were given to the patients by an independent nurse; investigators and data analysts were masked to group assignment.

Misoprostol was given to patients after delivery of the anterior shoulder by an independent person who was neither involved in allocation concealment nor in measurement of blood loss. AMTSL—including oxytocin—was ensured for all women in accordance with the unit protocol. To minimize performance bias, strict adherence to a standardized care protocol was ensured through display in labor rooms. Indications for, and receipt of, additional uterotonics was recorded for every women. Oxytocin infusion solely for augmentation of labor was discontinued after delivery, and the total dose of oxytocin used, in addition to the duration of the first, second, and third stages of labor, was recorded.

To ensure accurate measurement of blood loss, a combination of direct measurement and gravimetric methods was adopted (Supplementary Material S1). The attending midwives emptied the blood within the delivered placenta into a plastic bedpan, which was then placed under the buttocks to collect subsequent blood loss for up to 1 h after delivery of the placenta. The blood was subsequently measured in a graduated measuring cup and the volume was noted. The pads used to clean blood stains in the linen during delivery were also weighed and the known dry weight was subtracted. Differences in packed cell volume (PCV) levels before and after delivery were also determined and recorded.

All women were evaluated for 24 h after delivery, and specific adverse effects associated with sublingual misoprostol were recorded, including shivering, fever (temperature > 38 °C within 12 h of delivery), nausea, vomiting, diarrhea, headache, fatigue, dizziness, chills, flatulence, abdominal pain, and any other adverse effects mentioned by the patient.

The primary outcome measures were amount of blood loss during delivery and up to 1 h after delivery, occurrence of primary PPH (blood loss of ≥500 mL), and adverse effects. Secondary outcomes were change in PCV and need for additional uterotonics. Data were collected on maternal characteristics such as age, parity, length of pregnancy at delivery, and relevant obstetric history. Other information obtained included the details of the labor process, mode of delivery, need for episiotomy, birth weight, length of the third stage of labor, need for additional oxytocics, and need for manual removal of placenta.

It was calculated that a minimum of 62 patients in each group would be required to detect a difference of 83 mL in blood loss and with a power of 90%. Data were coded, cleaned, and analyzed via SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Analyses were planned to be by intention to treat. Results were presented as appropriate tables, and charts of relevant variables were generated. Differences between the groups were assessed by χ^2 and Student t tests. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated as appropriate. $P < 0.05$ was considered to be statistically significant.

3. Results

A total of 124 patients underwent randomization, and 62 individuals were assigned to both groups (Fig. 1). All individuals completed the study. The two groups were similar in terms of sociodemographic characteristics, booking status, parity, length of pregnancy at delivery, and mean prepartum PCV (Table 1). Additionally, the mean duration of the stages of labor and the mean birth weight did not differ significantly between the groups (Table 2). Among the 124 participants, labor onset was spontaneous for 111 (89.5%) women, and 57 (46.0%) women required oxytocin augmentation. The two groups did not differ in labor onset, oxytocin augmentation, or incidence of episiotomy (Table 2).

In terms of the primary outcomes, the mean total blood loss by 1 h after delivery and the frequency of PPH did not differ between groups (Table 3). As would be expected, blood loss was higher among women who underwent episiotomy than among those who did not, but the difference was similar in the two groups (Table 3). Among all participants, episiotomy increased the mean blood loss by 77 ± 5 mL.

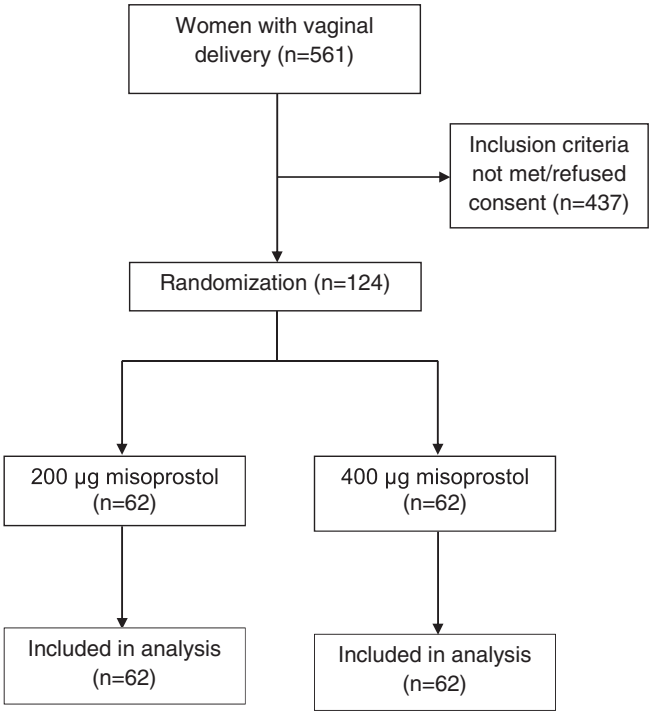

Fig. 1. Flow of participants through the study.

Table 1
Sociodemographic and prepartum characteristics of the study women.[a]

Variable	200 μg misoprostol (n = 62)	400 μg misoprostol (n = 62)	χ^2 value	*P* value
Age group, y			3.122	0.373
<25	7 (11)	6 (10)		
25–29	19 (31)	12 (19)		
30–34	24 (39)	33 (53)		
≥35	12 (19)	11 (18)		
Mean age, y	30.52 ± 5.3	30.45 ± 4.0	0.114[b]	0.910
Marital status			–	>0.99[c]
Single/separated	1 (2)	1 (2)		
Married	61 (98)	61 (98)		
Ethnic origin			–	0.126[c]
Non-Yoruba	9 (15)	3 (5)		
Yoruba	53 (85)	59 (95)		
Religion				
Christianity	42 (68)	43 (69)	0.037	0.847
Islam	20 (32)	19 (31)		
Occupation				
Unskilled	15 (24)	12 (19)	1.730	0.421
Skilled	28 (45)	24 (39)		
Highly skilled	19 (31)	26 (42)		
Educational level			0.832	0.660
Primary/none	5 (8)	3 (5)		
Secondary	14 (23)	12 (19)		
Tertiary	43 (69)	47 (76)		
Booking status			0.162	0.687
Booked	46 (74.2)	44 (71.0)		
Unbooked	16 (25.8)	18 (29.0)		
Parity			0.033	0.857
Primiparous	28 (45.2)	27 (43.5)		
Multiparous	34 (54.8)	35 (56.5)		
Length of pregnancy at delivery, wk			0.036	0.850
37–39	40 (54.5)	41 (66.1)		
40–42	22 (35.5)	21 (33.9)		
Mean length of pregnancy at delivery, wk	39.0 ± 1.4	38.8 ± 1.5	0.799[b]	0.426
Mean admission packed cell volume, %	34.5 ± 3.2	34.2 ± 2.8	0.484[b]	0.629

[a] Values are given as number (percentage) or mean ± SD, unless indicated otherwise.
[b] By Student *t* test.
[c] By Fisher exact test.

The mean postpartum PCV, and mean difference in prepartum and postpartum PCV were similar in the two groups (Table 3). The need for additional uterotonics was also similar in the two groups.

However, the frequency of noticeable adverse effects was significantly lower among women who received 200 μg misoprostol than among those who received 400 μg ($P < 0.001$) (Table 3). The adverse effects profile differed between the two groups (Fig. 2, Table 4). A significant difference was recorded in the occurrence of shivering, but no significant differences were noted for other adverse effects such as nausea, abdominal pain, dizziness, fatigue, headache, or vomiting. One woman in the 400-μg group reported all adverse effects except diarrhea and flatulence, which were not reported by any participants.

In terms of risk estimates for the most common adverse effects, women in the 200-μg group had a 62% lower risk of reporting any adverse effect than did women who received 400 μg ($P < 0.001$) (Table 4). They also had a 67% lower risk of shivering ($P < 0.001$) (Table 4). Similarly, although not significant, the risk of fever was lower in the 200-μg group than in the 400-μg group ($P = 0.121$).

Table 2
Intrapartum variables.[a]

Variable	200 μg misoprostol (n = 62)	400 μg misoprostol (n = 62)	*t* test/χ^2 value	*P* value
Duration of labor				
First stage, h	9.0 ± 3.7	10.1 ± 3.3	1.874[b]	0.063
Second stage, min	21.0 ± 16.0	24.8 ± 14.3	1.445[b]	0.151
Third stage, min	6.5 ± 4.3	8.1 ± 7.0	1.460[b]	0.147
Birth weight, kg	3.1 ± 0.5	3.1 ± 0.4	0.577[b]	0.565
Type of labor			0.773[c]	0.379
Spontaneous	54 (87.1)	57 (91.9)		
Induced	8 (12.9)	5 (8.1)		
Oxytocin augmentation			0.292[c]	0.589
Yes	27 (43.5)	30 (48.4)		
No	35 (56.5)	32 (51.6)		
Episiotomy			0.033[c]	0.856
Yes	27 (43.5)	26 (41.9)		
No	35 (56.5)	36 (58.1)		

[a] Values are given as mean ± SD or number (percentage), unless indicated otherwise.
[b] *t* test statistic.
[c] χ^2 value.

Table 3
Outcomes.[a]

Variable	200 μg misoprostol (n = 62)	400 μg misoprostol (n = 62)	*t* test/χ^2 value	*P* value
Total 1-h postpartum blood loss, mL	307 ± 145	296 ± 151	0.415[b]	0.679
Episiotomy	353 ± 171	338 ± 161	0.334[b]	0.740
No episiotomy	271 ± 110	266 ± 137	0.192[b]	0.848
Packed cell volume 24 h after delivery, %	31.6 ± 3.5	31.5 ± 2.8	0.224[b]	0.823
Change in packed cell volume, %	2.8 ± 1.7	2.7 ± 1.5	0.566[b]	0.572
Postpartum hemorrhage [c]			0.100[d]	0.752
Yes	5 (8.1)	6 (9.7)		
No	57 (91.9)	56 (90.3)		
Additional uterotonics			0.062[d]	0.803
Yes	10 (16.1)	9 (14.5)		
No	52 (83.9)	53 (85.5)		
Noticeable adverse effects			21.898[d]	<0.001
Yes	16 (25.8)	42 (67.7)		
No	46 (74.2)	20 (32.3)		

Abbreviations: PCV, packed cell volume; PPH, postpartum hemorrhage (defined as).
[a] Values are given as mean ± SD or number (percentage) unless stated otherwise.
[b] *t* test statistic.
[c] Blood loss ≥500 mL.
[d] χ^2 value.

4. Discussion

In the present study, the total postpartum blood loss and occurrence of PPH among women who received 200 μg or 400 μg were similar. However, the occurrence of adverse effects was significantly lower in the 200-μg group.

The present results are similar to reports by earlier investigators [11–23]. For example, Diab et al. [19] reported no significant difference in postpartum blood loss, change in hemoglobin, or need for therapeutic uterotonics when 200 μg of misoprostol was compared with 400 μg, and Elati et al. [21] found no difference in postpartum intrauterine pressure or blood loss in a comparison of 200 μg, 400 μg, and 600 μg of sublingual misoprostol. Similarly, Danielson et al. [22] reported that there was no significant difference in uterine contractility after receipt of 200 μg and 400 μg of misoprostol when administered via the same route.

The most common maternal adverse effects in the present study were shivering and fever (body temperature ≥ 38 °C), both of which were dose-related. Shivering was more commonly reported than fever, and the incidence of shivering and fever was higher in the 400-μg group than in the 200-μg group. The frequency of shivering with 400 μg misoprostol was similar to the 60% previously reported by El-Refaey et al. [23], but higher than the 42% reported by Musa et al. [16] and 21.2% reported by Chaudri et al. [15]. Similarly, Elati et al. [21] reported a dose-related rise in body temperature and chills, with 8% of women experiencing a fever (temperature > 39 °C) after 200 μg 400 μg, compared with 45% after 600 μg. The similar incidence of fever in the 200-μg and 400-μg groups in their study might be due to the higher cutoff of 39 °C for fever. In the brain, fever is mainly mediated

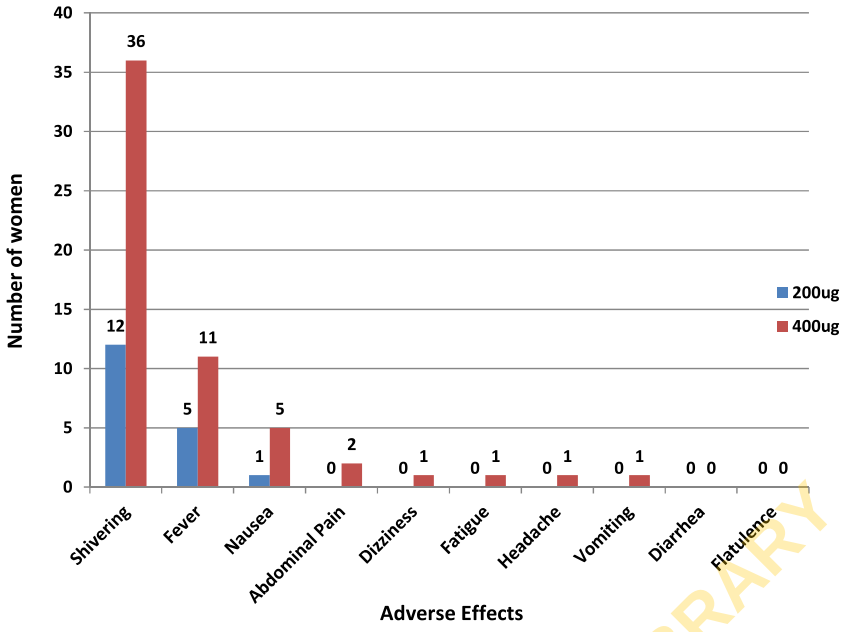

Fig. 2. Adverse effects profiles.

by prostaglandins, which can cross the blood–brain barrier to the thermoregulation centers in the hypothalamus, leading to an increase in the thermoregulatory set point. To raise the body temperature to this new set point, corresponding increases in heart rate, muscle tone, and shivering occur [21,24,25].

In obstetric practice, many studies have shown that instituting AMTSL (by early cord clamping, controlled cord traction, and administration of oxytocics prophylactically) remains an important tool for prevention of PPH. This approach alone contributes to a reduction of approximately 66% in the incidence of PPH and 81% in the need for therapeutic oxytocics, whereas the duration of the third stage of labor is reduced from 15 min to 5 min [6,8,9,20]. These markedly improved outcomes are accomplished when accompanied by effective labor supervision, prompt intervention in the labor process when necessary, and improved delivery room facilities. All patients in the present study had AMTSL both to ensure a common platform and for ethical reasons.

The present study had some limitations. First, true allocation concealment was not possible because no similar looking placebo tablets were available; however, an independent assistant gave the drugs to the patients without revealing the dosage to any of the researchers. Second, the direct measurement of blood and weighing of pads contaminated with feces, urine, and amniotic fluid might have influenced the data, but the blood loss in both groups was assessed in the same way such that the between-group differences would not have been affected substantially. Third, we recruited only low-risk women whose chance of PPH from atony was minimal. Because the main focus of the study was to compare the efficacy of the two dosage regimens and the adverse effects profile, it was imperative to have a homogenous study population, which was provided by patients in low-risk groups.

Table 4
Risk estimates for adverse effects.

Adverse effect	200 μg misoprostol (n = 62)[a]	400 μg misoprostol (n = 62)[a]	*P* value	Relative risk (95% confidence interval)
Any	16 (25.8)	42 (67.7)	<0.001	0.38 (0.24–0.60)
Shivering	12 (19.4)	36 (58.1)	<0.001	0.33 (0.19–0.58)
Fever	5 (8.1)	11 (17.7)	0.121	0.46 (0.17–1.23)
Nausea	1 (1.6)	5 (8.1)	0.136	0.20 (0.02–1.66)

[a] Values are given as number (percentage).

In summary, it has been established that 200 μg misoprostol taken sublingually is well tolerated and safe, and is as efficacious as 400 μg in routine management of the third stage of labor. The incidence of adverse effects was lower with a dose of 200 μg. Further comparison of oxytocin with 200 μg of misoprostol for management of the third stage of labor would be worth consideration.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijgo.2015.09.026.

Conflict of interest

The authors have no conflicts of interest.

References

[1] World Health Organization. WHO recommendations for the prevention and treatment of postpartum haemorrhage. http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9789241548502/en/. [Published 2012. Accessed August 27, 2015].
[2] World Health Organization, UNICEF, UNFPA and The World Bank. Trends in maternal mortality:1990–2010. http://www.who.int/reproductivehealth/publications/monitoring/9789241503631/en [Published 2012. Accessed August 27, 2015].
[3] Ajenifuja KO, Adepiti CA, Ogunniyi SO. Postpartum haemorrhage in a teaching hospital in Nigeria: a 5-year experience. Afr Health Sci 2010;10(1):71–4.
[4] Ujah IA, Aisien OA, Mutihir JT, Vanderjagt DJ, Glew RH, Uguru VE. Factors contributing to maternal mortality in North-Central Nigeria: a seventeen-year review. Afr J Reprod Health 2005;9(3):27–40.
[5] Oyelese Y, Ananth CV. Postpartum hemorrhage: epidemiology, risk factors, and causes. Clin Obstet Gynaecol 2010;53(1):147–56.
[6] Westhoff G, Cotter AM, Tolosa JE. Prophylactic oxytocin for the third stage of labour to prevent postpartum haemorrhage. Cochrane Database Syst Rev 2013;10, CD001808.
[7] Anderson JM, Etches D. Prevention and management of postpartum hemorrhage. Am Fam Physician 2007;75(6):875–82.
[8] Afolabi EO, Kuti O, Orji EO, Ogunniyi SO. Oral misoprostol versus intramuscular oxytocin in the active management of the third stage of labour. Singapore Med J 2010;51(3):207.
[9] Begley CM, Gyte GM, Devane D, McGuire W, Weeks A. Active versus expectant management for women in the third stage of labour. Cochrane Database Syst Rev 2015;3, CD007412.
[10] Hofmeyr GJ, Gülmezoglu AM, Novikova N, Linder V, Ferreira S, Piaggio G. Misoprostol to prevent and treat postpartum haemorrhage: a systematic review and meta-analysis of maternal deaths and dose-related effects. Bull World Health Organ 2009;87(9):666–77.
[11] 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(9543):1248–53.

[12] Hofmeyr GJ, Gülmezoglu AM, Novikova N, Lawrie TA. Postpartum misoprostol for preventing maternal mortality and morbidity. Cochrane Database Syst Rev 2013;7, CD008982.
[13] Mirteimouri M, Tara F, Teimouri B, Sakhavar N, Vaezi A. Efficacy of rectal misoprostol for prevention of postpartum hemorrhage. Iran J Pharm Res 2013;12(2):469–74.
[14] Tunçalp Ö, Hofmeyr GJ, Gülmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database Syst Rev 2012;8, CD000494.
[15] Chaudhuri P, Majumdar A. Sublingual misoprostol as an adjunct to oxytocin during cesarean delivery in women at risk of postpartum hemorrhage. Int J Gynecol Obstet 2015;128(1):48–52.
[16] Musa AO, Ijaiya MA, Saidu R, Aboyeji AP, Jimoh AA, Adesina KT, et al. Double-blind randomized controlled trial comparing misoprostol and oxytocin for management of the third stage of labor in a Nigerian hospital. Int J Gynecol Obstet 2015;129(3):227–30.
[17] Bellad MB, Tara D, Ganachari MS, Mallapur MD, Goudar SS, Kodkany BS, et al. Prevention of postpartum haemorrhage with sublingual misoprostol or oxytocin: a double-blind randomised controlled trial. BJOG 2012;119(8):975–82.
[18] Alfirevic Z, Blum J, Walraven G, Weeks A, Winikoff B. Prevention of postpartum hemorrhage with misoprostol. Int J Gynecol Obstet 2007;99:S198–201.
[19] Diab KM, Ramy AR, Yehia MA. The use of rectal misoprostol as active pharmacological management of third stage of labour. J Obstet Gynaecol Res 1999;25(5):327–32.
[20] Enakpene CA, Morhason-Bello IO, Enakpene EO, Arowojolu AO, Omigbodun AO. Oral misoprostol for the prevention of primary postpartum haemorrhage during third stage of labour. J Obstet Gynaecol Res 2007;33:810–7.
[21] Elati A, Elmahaishi MS, Elmahaishi MO, Elsraiti OA, Weeks AD. The effect of misoprostol on postpartum contractions: a randomised comparison of three sublingual doses. BJOG 2011;118(4):466–73.
[22] Danielsson KG, Marions L, Rodriguez A, Spur BW, Wong PY, Bygdeman M. Comparison between oral and vaginal administration of misoprostol on uterine contractility. Obstet Gynecol 1999;93(2):275–80.
[23] El-Refaey H, O'Brien P, Morafa W, Walder J, Rodeck C. Use of oral misoprostol in the prevention of postpartum haemorrhage. Br J Obstet Gynaecol 1997;104(3):336–9.
[24] Boulant JA. Role of the preoptic-anterior hypothalamus in thermoregulation and fever. Clin Infect Dis 2000;31(Suppl5):S157–61.
[25] Kanosue K, Zhang YH, Yanase-Fujiwara M, Hosono T. Hypothalamic network for thermoregulatory shivering. Am J Physiol 1994;267(1Pt2):R275–82.