Received: 27 April 2020 | Revised: 4 August 2020 | Accepted: 13 October 2020 | First published online: 6 November 2020

DOI: 10.1002/ijgo.13426

CLINICAL ARTICLE

Obstetrics

WILEY GYNECOLOGY OBSTETRICS FIGO

A comparative study between preoperative rectal misoprostol and intraoperative intrauterine administration in the reduction of blood loss during and after cesarean delivery: A randomized controlled trial

Moutaz M. El-Sherbini | Ahmed M. Maged | Omneya M. Helal | Mirna O. Awad | Sally A. El-Attar | Jehan A. Sadek | Rasha ElKomy | Mariam A. Dawoud

Department of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, Cairo, Egypt

Correspondence
Ahmed M. Maged, 11 Eid Mostafa Street, Haram, Giza, 12111, Egypt.
Email: prof.ahmedmaged@gmail.com

Abstract

Objective: To compare the efficacy and safety of rectal misoprostol with intrauterine misoprostol in the reduction of blood loss during and after cesarean delivery.

Methods: Ninety-eight pregnant women, all candidates for elective cesarean delivery, were equally randomized into two groups: the rectal group (received preoperative misoprostol rectally) and the intrauterine group (received intrauterine misoprostol after the delivery of the placenta). The primary outcome was the estimated blood loss (EBL) during cesarean delivery. Secondary outcomes included the occurrence of excessive blood loss (>1000 mL) within the first 24 hours postoperatively and the occurrence of any maternal or fetal side effects.

Results: There were no statistically significant differences between the two groups regarding either the EBL (693.12 ± 139.09 vs 692.39 ± 132.83; *P*=0.979) or the occurrence of postpartum hemorrhage (>1000 mL) (6.1% vs 4.1%; *P*=0.99. Apgar scores at 1 and 5 minutes were significantly higher in the intrauterine group compared to the rectal group.

Conclusion: Insertion of intrauterine misoprostol is as effective as rectal insertion in reducing blood loss during and after cesarean delivery; however, it has a safer neonatal outcome and is more convenient when administered during cesarean delivery.

ClinicalTrials.gov: NCT03723031.

KEYWORDS

Cesarean delivery, Intraoperative blood loss, Intrauterine misoprostol, Postpartum hemorrhage, Rectal misoprostol, Third stage of labor

1 | INTRODUCTION

Cesarean delivery is the most common major surgical procedure undergone by women around the world. Over the past two decades, there has been a witnessed increase in rates of cesarean deliveries, which continues to rise, achieving 30% in resource-rich countries and exceeding 60% in resource-limited countries.[1] According to a *Lancet* report from 2014, Egypt is one of the countries with the highest rates of cesarean delivery, in which the rate had reached 55.5%.[2] The rate is almost double to three times the ideal rate of 10%–15%.[3]

In resource-limited countries, postpartum hemorrhage (PPH) remains the leading cause of maternal mortality.[4] The increased rates of cesarean delivery have been incriminated as the primary cause behind the rise in PPH.[5] PPH after a cesarean delivery has been

defined as blood loss over 1000 mL. The estimated prevalence rate of PPH is in the range of 0.6%–6.4%.[6,7]

Oxytocin is the uterotonic of choice in obstetric medicine. Both the Royal College of Obstetricians and Gynaecologists and the American College of Obstetricians and Gynecologists currently recommend the routine use of oxytocin (5 IU bolus dose or infusion, respectively) after the delivery of the infant as a prophylactic measure against PPH.[7,8] Regardless of the mode of administration, the use of oxytocin is not without side effects and it may cause hypotension and tachycardia.[9]

Misoprostol is a prostaglandin E1 analogue that effectively prevents and treats PPH owing to its uterotonic properties. It can be used through different routes: oral; sublingual; buccal; rectal; and intrauterine with similar efficacy to oxytocin in reducing blood loss.[10,11] Misoprostol combined with oxytocin reduces operative and postoperative blood loss in cesarean delivery more effectively than oxytocin alone.[12] Because of its characteristics—such as ready availability, low cost, thermal stability, and ease of administration—misoprostol can be used in resource-limited countries in low-resource settings.[13] Quiroga Díaz et al.[14] reported that intrauterine misoprostol combined with an oxytocin infusion during cesarean delivery reduces intraoperative blood loss, prevents PPH, and minimizes the need for additional uterotonic agents.[14]

The aim of the present study was to evaluate the efficacy and safety of the rectal route of misoprostol (before cesarean delivery) versus its intrauterine insertion in the reduction of blood loss associated with lower segment cesarean delivery.

2 | MATERIALS AND METHODS

A prospective single-blind randomized study was conducted on 98 pregnant women, aged 20–40 years, with a full-term singleton healthy living fetus (gestational age >37 weeks confirmed by the first day of the last menstrual period or first-trimester ultrasound scan) and candidates for elective cesarean delivery. They were recruited from the Obstetrics and Gynecology Department, Kasr Al-ainy Hospital – Faculty of Medicine, Cairo University, between November 2018 and April 2020. The present study was approved by the Hospital Ethical Committee and was registered at ClinicalTrials.gov (NCT03723031).

Patients with a preoperative level of hemoglobin of less than 9 gm/dL or experiencing concomitant medical disorders (e.g. cardiac, renal, and hepatic diseases or coagulopathies) and those known to be allergic to prostaglandins were excluded. Women attending for emergency cesarean delivery, who had more than two previous cesarean deliveries, or who were at increased risk for obstetric hemorrhage (e.g. peripartum hemorrhage, abnormal placentation, previous history of uterine atony or PPH, polyhydramnios, and uterine fibroids) were also excluded.

Informed written consent was obtained for all participants (after discussing the nature and aim of the study as well as the potential maternal or fetal adverse effects). All eligible candidates were subjected to a full history taking together with a thorough clinical and obstetric examination (including the first day of the last menstrual period, maternal body weight, and vital signs) followed by obstetric ultrasonography to confirm gestational age and the eligibility of the current pregnancy for participation in the study. Preoperative laboratory tests (including complete blood count, prothrombin time and concentration, and liver and kidney function tests) were also performed. On the day of the cesarean delivery, patients who met the eligibility criteria and agreed to participate in the study were randomly assigned in a 1:1 ratio into two groups: the rectal misoprostol group (n=49) and the intrauterine misoprostol group (n=49). The women in the rectal misoprostol group received preoperative misoprostol 400 μg (Cytotec, Pfizer, G.D. Searle LLC) rectally by insertion of a urinary catheter,[15] while the women in intrauterine misoprostol group received intrauterine misoprostol 400 μg (200 μg at each cornu; Cytotec, Pfizer, G.D. Searle LLC) inserted intraoperatively after delivery of the placenta. Randomization was performed using computer-generated random numbers and only the participants were masked to the group allocation.

All cesarean deliveries were carried out under spinal anesthesia by one of the senior obstetrics and gynecology residents in the hospital using the following operative steps: Pfannenstiel incision, transverse lower uterine segment incision, immediate cord clamping (<30 seconds), removal of the placenta by controlled cord traction after its spontaneous separation, closure of the uterus in two layers, and closure of the anterior abdominal wall using an anatomical manner (adequate hemostasis was ensured in all operative steps). If the duration of the cesarean delivery exceeded 90 minutes (from skin incision to skin closure), the patient was excluded from the study.

After delivery of the infant, patients in both groups received an intravenous bolus of 5 IU oxytocin (Syntocinon, Novartis, Basel, Switzerland) and 20 IU oxytocin in 500 mL of lactated Ringer's solution (infused at a rate of 125 mL/hour).

The number and the difference in weight of the operative towels (before and after cesarean delivery) and the amount of blood in the suction unit were recorded (it was calculated that a difference of 1 g of weight was equal to blood loss of 1 mL). The estimated blood loss (EBL) for each patient was measured using the following formula[16]:

$$\text{EBL} = \text{EBV} \times \frac{(\text{Preoperative hematocrit} - \text{Postoperative hematocrit})}{\text{Preoperative hematocrit}}$$

where EBV is the estimated blood volume in mL and equals weight in kg × 85.

The time interval between insertion of the urinary catheter (and insertion of rectal misoprostol for the rectal misoprostol group) and delivery of the fetus was recorded together with the neonatal outcome (Apgar score at 1 and 5 minutes, admission to the neonatal intensive care unit [NICU], and neonatal death). Monitoring of fluid was also performed through rate of infusion and urine output. A complete blood count test was performed 12 hours after delivery. All patients were followed up for 24 hours after the delivery regarding the occurrence of excessive blood loss (>1000 mL), the need for a blood transfusion, or the use of

additional ecbolics denoting uterine atony (i.e. additional intravenous bolus oxytocin of 5 IU and 1 mL [0.2 mg] intramuscular ergometrine with or without 600 μg rectal misoprostol postoperatively), misoprostol-related side effects in the first 6 hours (i.e. shivering, pyrexia >38°C, headache, nausea, vomiting with or without the need for anti-emetic drugs). The data of both groups were collected, analyzed, and compared.

The primary outcome measure was the estimated blood loss (EBL) during cesarean delivery. Secondary outcome measures were the occurrence of excessive blood loss (>1000 mL) and the need for a blood transfusion within the first 24 hours postoperatively, the use of additional uterotonics, and the occurrence of any maternal side effects or fetal and neonatal effects.

The calculation of the sample size was done using the comparison of amount of intraoperative blood loss between women undergoing lower section cesarean delivery treated with intrauterine misoprostol and those treated with rectal misoprostol, as this was the primary outcome of the present study. As reported in previous publications,[1,7,11,14] the mean ± SD of intraoperative blood loss in the rectal misoprostol group was approximately 429 ± 234 mL and it was assumed that for the intrauterine misoprostol to be clinically effective, it should minimize blood loss by at least 20%. Accordingly, it was calculated that the minimum proper sample size was 49 women in each arm to be able to reject the null hypothesis with 80% power at an α level of 0.05 using the Student *t*-test for independent samples. The calculation of the sample size was done using Stats Direct statistical software version 2.7.2 for MS Windows (Stats Direct Ltd., Cheshire, UK).

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data were summarized using mean ± SD for quantitative variables and number (percentage) for categorical variables. Comparisons between groups were done using the unpaired *t*-test.[17] For the comparisons of categorical data, the χ^2 test was performed. The Fisher exact test was used when the expected frequency was less than 5.[18] $P<0.05$ was considered statistically significant.

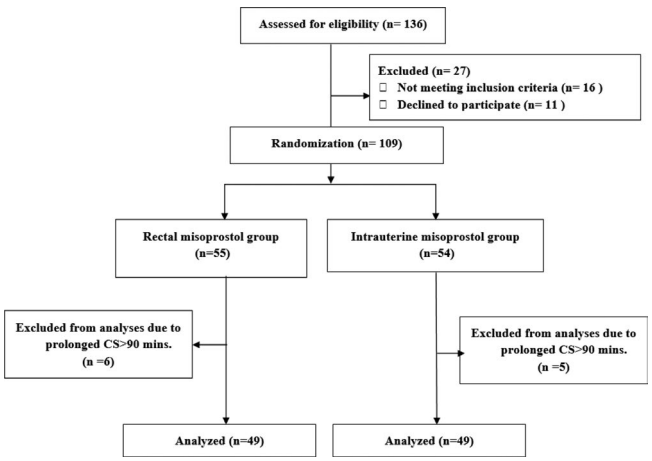

FIGURE 1 Flowchart of patients through the study

3 | RESULTS

A total of 98 patients scheduled for elective cesarean delivery were enrolled in the study (a flow chart of patients is shown in Fig. 1). There was proper matching between both groups regarding different patient and pregnancy characteristics such as age, body mass index, parity, gestational age, previous cesarean deliveries, and neonatal weight (Table 1). With regard to the hematological parameters, the preoperative level of hemoglobin, preoperative and postoperative levels of hematocrit, and postoperative level of hemoglobin were not significantly different between the two groups (Table 2). The difference in intraoperative blood loss was not statistically significant between the two groups (Table 2 and Fig. 2).

There was no statistically significant difference between the two studied groups regarding the occurrence of excessive blood loss (>1000 mL in the first 24 hours) or the use of extra uterotonics (Table 2). None of the patients needed a blood transfusion. With regard to

TABLE 1 Patients and pregnancy characteristics.[a]

Variables	Group		*P* value
	Intrauterine (n=49)	Rectal (n=49)	
Maternal age (years)	27.98 ± 4.49	29.02 ± 4.67	0.264
BMI (kg/m^2)	35.16 ± 5.21	34.73 ± 5.12	0.682
Primigravidas	7 (14.3)	4 (8.2)	0.337
Multigravidas	42 (85.7)	45 (91.8)	
Gestational age at termination (weeks)	38.16 ± 0.87	38.45 ± 0.87	0.108
Previous 1 CD	17 (34.7)	26 (53.1)	0.126
Previous 2 CDs	17 (34.7)	15 (30.6)	
Fresh abdomen	15 (30.6)	8 (16.3)	
Neonatal weight (g)	3290.1 ± 133.29	3291.12 ± 102.47	0.966
Indications for CD			
Previous 1 CD	17 (34.7)	26 (53.1)	0.374
Previous 2 CD	17 (34.7)	15 (30.6)	
Pregnancy on top of ICSI	7 (14.2)	4 (8.2)	
Malpresentation	5 (10.2)	3 (6.1)	
Cephalopelvic disproportion	3 (6.1)	1 (2)	
Duration of CD (min)	80.34 ± 3.77	81.64 ± 2.78	0.055
Interval between urinary catheter insertion and fetal delivery (min)	15.45 ± 1.03	15.32 ± 1.10	0.552

Abbreviations: BMI, body mass index; CD, cesarean delivery; ICSI, intracytoplasmic sperm injection.

[a]Values are given as number (percentage) or mean ± SD.

TABLE 2 Hematologic parameters, EBL, and neonatal outcome in the studied groups.[a]

Variables	Group		*P* value
	Intrauterine (n=49)	Rectal (n=49)	
Hb concentration (gm/dL)			
Preoperative Hb	11.22 ± 1.14	11.71 ± 0.97	0.023
Postoperative Hb	10.47 ± 1.06	10.71 ± 1.07	0.252
Drop in Hb	0.75 ± 0.5	1 ± 0.59	0.028
Hematocrit (%)			
Preoperative Hct	32.73 ± 3.66	34.16 ± 3.28	0.45
Postoperative Hct	29.39 ± 3.49	30.84 ± 3.01	0.30
Drop in Hct	3.35 ± 1.83	3.32 ± 0.74	0.925
EBL			
EBL by the formula (mL)	692.39 ± 132.83	692.39 ± 132.83	0.979
Weight difference of soaked towels (gm)	397.96 ± 85.37	403.67 ± 95.28	0.755
Blood loss in suction (mL)	571.43 ± 94.1	531.63 ± 104.43	0.050
No. of soaked towels	4.73 ± 2.03	4.49 ± 1.86	0.535
Excessive blood loss> 1000 mL in first 24 h	3 (6.1)	2 (4.1)	0.867
The need for use of extra ecbolics	8 (16.3)	4 (8.2)	1
Apgar score at 1 min	7.45 ± 0.65	7.02 ± 0.90	0.008
Apgar score at 5 min	9.55 ± 0.50	9.18 ± 0.73	0.004

Abbreviations: EBL, estimated blood loss.

Values are given as number (percentage) or mean ± SD.

neonatal outcome, Apgar scores at 1 and 5 minutes were significantly higher in the intrauterine group compared to the rectal group (*P*=0.008 and *P*=0.004, respectively), taking into consideration that the mean time interval from insertion of the catheter to delivery of the fetus was almost the same in both groups (15.5 minutes in the intrauterine group vs 15.3 minutes in the rectal group) (Table 2). No neonatal deaths or admissions to the NICU were recorded. No side effects related to misoprostol were reported in either group. However, postoperative shivering was noticed in both groups and was not significantly different.

4 | DISCUSSION

Excessive blood loss during and after delivery represents a main cause of maternal morbidity and mortality, especially in countries with limited medical resources. It accounts for almost 25% of maternal deaths worldwide.[19] The use of misoprostol has been established as an effective uterotonic agent in resource-limited countries to decrease blood loss, whether used alone or in combination with oxytocin. Several studies evaluated the role of misoprostol in minimizing the intraoperative and postpartum blood loss during cesarian deliveries, and several routes of administration have been proposed (e.g. oral, sublingual, buccal, vaginal, uterine, or rectal routes). They all agreed that the administration of misoprostol significantly reduces blood loss during cesarean delivery, and hence PPH, but there are some conflicts regarding the side effects of misoprostol and the effect on the neonatal outcome that can differ according to the route of administration. Moreover, no mode of administration was shown to be superior to the other.[11,12,14,20,21]

It was found that intrauterine misoprostol was as effective as preoperative rectal misoprostol in minimizing the intraoperative and postoperative blood loss during cesarean delivery.

In 2019, Maged et al[15] proved the safety and efficacy of misoprostol administered rectally before elective cesarean delivery to decrease blood loss intraoperatively and postoperatively. They claimed that the rectal route is associated with a slower rate of absorption than the oral and buccal routes, with a delayed peak level of more than 60 minutes after its administration so that its peak bioavailability is usually reached by the end of the operation.[15]

However, it is believed that the preoperative route may have an adverse effect on the fetus, especially with the delay while extracting the fetus that may accompany operative difficulties as marked adhesions from repeated previous surgeries. This was the reason for choosing the intrauterine route, nullifying any effects of the drug on the fetus.

It is also believed that the large surface area of the decidua, with its large feeding vessels, allows for good absorption and is almost similar to the mucosal absorption of the sublingual, vaginal, and rectal routes. This suspected theory was proven after a similar decrease of blood loss during and after the cesarean delivery was found in both the rectal and intrauterine routes.

Quiroga Díaz et al.[14] compared the use of intrauterine misoprostol combined with oxytocin to the use of oxytocin alone in reducing blood loss during and after cesarean delivery. They reported that

adding intrauterine misoprostol reduced the drop in hemoglobin and the need for additional uterotonics by 39.6% and 50%, respectively. Furthermore, a major drop in hemoglobin (>3 g%) was noted in 13% of patients receiving oxytocin only versus 3% of those who received extra intrauterine misoprostol. Therefore, they recommended the combination of intrauterine misoprostol and oxytocin to reduce blood loss during and after cesarean delivery.

The same was done by Al Alfy et al.[21] who reported that EBL was significantly lower among patients who had intrauterine misoprostol added to the oxytocin protocol (442.6 mL vs 591 mL for patients receiving oxytocin alone). Moreover, the number of patients who experienced excessive blood loss (>1000 mL) was significantly lower in the combined intrauterine misoprostol–oxytocin regimen (2 vs 10 cases when oxytocin was used alone). Similarly, Bahadur et al.[22] concluded that the combined use of the intrauterine misoprostol and oxytocin infusion significantly reduces intraoperative and postoperative blood loss during cesarean delivery.

The present study agrees with all the aforementioned studies on the extra benefit achieved by using intrauterine misoprostol to reduce blood loss during and after cesarean delivery and hence PPH. However, all those studies used the drop in hemoglobin, the difference in weight of soaked towels, and the amount of blood collected in suction to evaluate the blood loss during cesarean delivery, but in the present study the EBL formula was added to calculate the intraoperative blood loss more accurately (by using this formula, the error in calculation caused by the addition of the amount of liquor can be avoided).

According to the present findings, Apgar scores at both 1 and 5 minutes were lower in women who received preoperative rectal misoprostol when compared to those who received the intrauterine drug.

It is believed that the present study is the first to compare the efficacy and safety of the rectal and intrauterine routes among low-risk pregnant women, and the results demonstrated that both routes reduce blood loss during and after cesarean delivery and are both equally effective. Moreover, newborns that were born to mothers who had misoprostol via the intrauterine route had significantly higher Apgar scores at 1 and 5 minutes. Other strengths include the randomized controlled nature of the study and the considerations of the effects of the drug on the fetus.

The limitations of the present study are the small sample size and the exclusion of women with higher order cesarean deliveries (more than two previous cesarean deliveries) and those with a higher risk for obstetric hemorrhage. A greater number of candidates, including higher-risk patients, together with an assessment of the neonatal cord blood pH might help to emphasize the results.

In conclusion, the combined use of intrauterine misoprostol or rectal misoprostol with oxytocin reduces intraoperative blood loss and PPH with the same efficacy. Apart from shivering, misoprostol has no side effects whether it is administered via the intrauterine or rectal route. However, the intrauterine route is preferred as it is safer than the rectal route on the fetus, especially in cases of a prolonged interval between administration of misoprostol and delivery of the fetus. In addition, the potential of contamination in the case of rectal administration is avoided.

AUTHOR CONTRIBUTIONS

MME, MOA, SAE, and MAD were responsible for data collection and manuscript writing. AMM was responsible for project development and manuscript writing. OMH contributed to data analysis and manuscript writing. JAS was responsible for data analysis and manuscript revision. RE contributed to statistical analysis and manuscript revision.

ACKNOWLEDGMENTS

The study was self-funded.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

REFERENCES

1. Gibbons L, Belizan JM, Lauer JA, et al. Inequities in the use of cesarean section deliveries in the world. *Am J Obstet Gynecol*. 2012;206:331.e1–331.e19.
2. The Lancet. Caesarean section use has almost doubled globally since 2000. ScienceDaily. www.sciencedaily.com/releases/2018/10/181011190654.htm. Accessed October 11, 2018.
3. Betrán AP, Merialdi M, Lauer JA, et al. Rates of caesarean section: Analysis of global, regional and national estimates. *Paediatr Perinat Epidemiol*. 2007;21:98–113.
4. Khan KS, Wojdyla D, Say L, et al. WHO analysis of causes of maternal death: a systematic review. *The Lancet*. 2006;367:1066–1074.
5. Joseph KS, Rouleau J, Kramer MS, et al. Investigation of an increase in postpartum hemorrhage in Canada. BJOG: An International Journal of. *Obstet Gynecol*. 2007;114:751–759.
6. Magann EF, Evans S, Hutchinson M, et al. Postpartum hemorrhage after cesarean delivery: An analysis of risk factors. *South Med J*. 2005;98:681–685.
7. American college of obstetrics and gynecology (ACOG). Postpartum Hemorrhage. Practice Bulletin No. 183. *Obstet Gynecol*. 2017;130:e168–e186.
8. Royal College of Obstetricians and Gynecologists (RCOG). Prevention and Management of Postpartum Hemorrhage: Green-top Guideline No. 52. *BJOG*. 2016;124:e106–e149.
9. Begley CM, Gyte GM, Devane D, et al. Active versus expectant management for women in the third stage of labour. *Cochrane Database Syst Rev*. 2019;(2):CD007412.
10. Prata N, Weidert K. Efficacy of misoprostol for the treatment of postpartum hemorrhage: Current knowledge and implications for health care planning. *Int J Womens Health*. 2016;8:341–349.
11. Sood AK, Singh S. Sublingual misoprostol to reduce blood loss at cesarean delivery. *J Obstet Gynecol India*. 2012;62:162–167.
12. Conde-Agudelo A, Nieto A, Rosas-Bermudez A, et al. Misoprostol to reduce intraoperative and postoperative hemorrhage during cesarean delivery: A systematic review and meta-analysis. *Am J Obstet Gynecol*. 2013;209:40.e1–40.e17.
13. Lokugamage A, Paine M, Bassaw-Balroop K, et al. Active management of the third stage at caesarean section: A randomized controlled trial of misoprostol versus Syntocinon. *Aust N Z J Obstet Gynecol*. 2001;41:411–414.
14. Quiroga Díaz R, Cantú Mata R, Tello Gutiérrez HE, et al. Intrauterine misoprostol for the prevention of bleeding cesarean. *Ginecol Obstet Mex*. 2009;77:469–474.

15. Maged AM, Fawzi T, Shalaby MA, et al. A randomized controlled trial of the safety and efficacy of preoperative rectal misoprostol for prevention of intraoperative and postoperative blood loss at elective cesarean delivery. *Int J Gynecol Obstet*. 2019;147:102–107.
16. Maged AM, Helal OM, Elsherbini MM, et al. A randomized placebo-controlled trial of preoperative tranexamic acid among women undergoing elective cesarean delivery. *Int J Gynaecol Obstet*. 2015;131:265–268.
17. Chan YH. Biostatistics102: Quantitative data – parametric & non-parametric Tests. *Singapore Med*. 2003a;J44:391–396.
18. Chan YH. Biostatistics 103: Qualitative data –tests of independence. *Singapore Med J*. 2003b;44:498–503.
19. World Health Organization. *WHO Recommendations for the Prevention and Treatment of Postpartum Hemorrhage*. Geneva, Switzerland: World Health Organization; 2012.
20. Elsedeek MS. Impact of preoperative rectal misoprostol on blood loss during and after elective cesarean delivery. *Int J Gynaecol Obstet*. 2012;118:149–152.
21. Alalfy M, Lasheen Y, Elshenoufy H, et al. The efficacy of intrauterine misoprostol during cesarean section in prevention of primary PPH, a randomized controlled trial. *J Matern Fetal Neonatal Med*. 2018;1–7.
22. Bahadur A, Khoiwal K, Bhattacharya N, et al. The effect of intrauterine misoprostol on blood loss during caesarean section. *J Obstet Gynaecol*. 2019;39:753–756.

How to cite this article: El-Sherbini MM, Maged AM, Helal OM, et al. A comparative study between preoperative rectal misoprostol and intraoperative intrauterine administration in the reduction of blood loss during and after cesarean delivery: A randomized controlled trial. *Int J Gynecol Obstet*. 2021;153:113–118. https://doi.org/10.1002/ijgo.13426