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Cervical ripening before surgical evacuation of first-trimester pregnancy: a comparison between misoprostol and trinitroglycerin

Fatemeh Hosseinzadeh [1], Mandana Mansour Ghanaie [1]*, Roya Faraji [2], Ghazaleh Ghorbani [1], Seyedeh Maryam Asgari Galebin [3], Sedigheh Pakseresht [4], Saman Marofizadeh [5], Seyed Mohammad Asgari Galebin [3]

[1] Reproductive Health Research Center, Department of Obstetrics & Gynecology, Alzahra Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

[2] Reproductive Health Research Center, Guilan University of Medical Sciences, Rasht, Iran

[3] Guilan University of Medical Sciences, Rasht, Iran

[4] Department of Obstetrics, Community Health, Women Health Promotion, Social Determinants of Health Research Center, Reproductive Health Research Center, Shahid Beheshti Nursing and Midwifery School, Guilan University of Medical Sciences, Rasht, Iran

[5] Department of Biostatistics, School of Nursing and Midwifery, Guilan University of Medical Sciences, Rasht, Iran

Abstract

Introduction: Termination of pregnancy through curettage in the first trimester requires cervical ripening (CR) which can be induced by medicinal or mechanical methods. In the pharmaceutical method, vaginal administration of misoprostol as well as vaginal trinitroglycerin (TNG) has been shown to induce effective CR. This study was conducted with the aim of comparing vaginal misoprostol and vaginal TNG in the CR of women candidates for the first-trimester curettage.

Materials and Methods: This double-blind clinical trial study was conducted on 168 pregnant women with a gestational age of less than 14 weeks who were candidates for curettage. Participants were randomly divided into two groups receiving vaginally either TNG (400 µgr) (n=87) or misoprostol (400 µgr) (n=81). Then, the state of CR and the need for mechanical dilatation were compared between the two groups. Also, the presence of any side effects caused by drug use was determined.

Results: The percentage of CR in the misoprostol group (67.9%) was significantly higher than the TNG group (32.2%) (P<0.001). Therefore, the need for mechanical dilatation in the TNG group (66.7%) was significantly higher compared with the misoprostol group (32.1%) (P<0.001). Also, the rate of complications like diarrhea (9.9%) and abdominal pain (7.4%) in the misoprostol group was significantly higher than in the TNG group (0%). However, headache in the TNG group (34.5%) was significantly higher than the misoprostol group (0%) (P>0.001). Generally, the rate of complications in the TNG group (35.6%) was significantly higher compared with the misoprostol group (13.6%) (P>0.001).

Conclusion: Vaginally Misoprostol is more effective than vaginally TNG on CR of first-trimester curettage as well as it significantly reduces the need for mechanical dilatation of the cervix.

Keywords: Misoprostol, Trinitroglycerin, Cervical ripening

*Corresponding Author: Mandana Mansour Ghanaie

✉ Email: m_m_ghanaie@yahoo.com

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Introduction

With a prevalence of 15%, abortion is one of the most common complications of pregnancy that occurs during the first and second trimesters. However, regarding the excretion of pregnancy products due to an unfavorable cervix or insufficient uterine contractions, evacuation of the residues with medicinal or surgical methods is also possible (1).

According to the definition of the World Health Organization (WHO), abortion is defined as "termination of pregnancy before the 20th week of gestational age or a fetus weighing less than 500 g (2). Induced abortion, as one of the types of abortion, means the termination of pregnancy by medical or surgical methods before the 20th week of pregnancy, which can be due to maternal or fetal medical indications or spontaneous loss of the products of conception (3).In general, induced abortion is one of the most common problems of pregnancy. More than 200,000 abortions are performed in England every year, and about 90% of them occur in the first trimester of pregnancy (4).

Some maternal medical disorders such as cardiovascular diseases, hypertension, diabetes, and malignancies, as well as fetal defects such as encephalitis, trisomy, and myelomeningocele, lead to the termination of pregnancy (3). Today, medical termination of pregnancy is more common due to surgical complications (5).

Although curettage in the first trimester of pregnancy is associated with relatively few complications, there is a possibility of damage to the cervix, uterine rupture, and vaginal bleeding, especially in the adolescent age group and also in primigravid women. In order to reduce these side effects, the cervix should be softened to the desired extent. On the other hand, CR leads to a reduction in the length of the operation and also greater patient satisfaction (6,7) .Common methods used for CR include both mechanical (for example, Foley catheters) and pharmacological (for example, prostaglandins) methods (8–11).

Prostaglandins are effective drugs for inducing abortion, which have different types and include misoprostol (PGE1), tromethamine carboprost (PGF2α) and dinoprostone (E2). Among these drugs, misoprostol is more favorable because of its low risk, cheapness, and availability compared to the other two drugs. By increasing the contractile power of the uterus through direct stimulation of the myometrium, misoprostol prepares the cervix and expels the remnants of pregnancy (12,13). According to the FIGO protocol, misoprostol with a medicinal dose of 400 µgr is used for CR and for performing surgical curettage in the first trimester of pregnancy (14,15). However, it has side effects such as nausea, vomiting, diarrhea, and fever, which of course are reduced with anti-nausea and anti-diarrhea drugs (16).

It is sometimes difficult to tolerate these side effects, especially since CR takes more than three hours (17). On the other hand, pregnant women with a history of previous cesarean section and with the presence of uterine scar, require more clinical care because of the possibility of uterine perforation. In the study conducted by Ayati et al., misoprostol by both rectal and vaginal methods with a dose of 800 µgr was effective for medical abortion in the first trimester of pregnancy in women who had a history of cesarean delivery. The remarkable thing in this study was that patients responded to the treatment with different doses of medicine (18). Meanwhile, in the study of Roudsari et al., who examined the use of vaginal misoprostol to terminate pregnancy in the first trimester, more than one-third of the participants had positive results with the second dose (19). Currently, in addition to prostaglandins, including misoprostol, nitrite oxide (NO) compounds are also recommended for CR before curettage (8,20,21). The advantage of using TNG compared to misoprostol is CR without causing contraction in the uterus, also it can be easily and safely used on an outpatient basis (8,20). But prostaglandins still remain the best compounds in this regard; for their fewer side effects. They are easier to accept and seemingly safer than prostaglandins like misoprostol in cases such as women with a history of cesarean section or uterine scars (8,20). The results of a study by Sharifzadeh et al. showed that there was no statistically significant difference in CR after using misoprostol with a dose of 400 µgr and TNG with a dose of 1200 µgr, therefore, they introduced TNG as a suitable substitute for misoprostol in CR (22). The present study was conducted with the aim of comparing misoprostol and TNG in the CR of women candidates for curettage because limited research has been done on effective

drugs for CR in women candidates for first trimester curettage. Also, few studies have compared the effect of TNG and misoprostol and other related issues like the contradictory results obtained regarding the comparison of the two drugs as well as their effective dose for curettage; and how to reduce the drug complications in pregnant women.

Materials and Methods

The study protocol was a double-blind randomized study conducted according to the recommendations in the CONSORT statement (23). The study was approved by the research ethics committee of Guilan university of science with an ethical code of IR.GUMS.REC.1400.044 and an IRCT clinical trial code of IRCT20210510051247N1. One hundred sixty-eight women with gestation age of less than 14 weeks and Bishop score $\leq$ 4, scheduled for surgical termination of pregnancy by suction curettage, agree to participate in this study from June 2021 to September 2022.

Inclusion criteria were healthy women candidates for curettage with a gestational age of less than 14 weeks, body temperature of less than 38 ^{0}c, a normal heart rate ranging 70-100 bmp and a systolic blood pressure between 100-130 mm Hg, no narcotic consumption, no coagulation disorder, no chronic diseases (such as active liver disease, cardiovascular disease, uncontrolled seizures, history of glaucoma, suffering from adrenal disease), no previous cervical surgery, and no more than one uterine scar. Exclusion criteria included the patient's unwillingness to continue participating in the study as well as ongoing bleeding, and allergy to either IMN or misoprostlol.

The sample size was calculated using G*Power statistical software, version 3.1. Considering that the main purpose of the plan was to compare the ratio of CR between the two groups of TNG and misoprostol, the sample size method was used to compare the two ratios. To determine the sample size, a type I error of 0.05 and a type II error of 0.2 (power 0.8) were set. Also, according to the study of Dabiri et al. (24), the ratio of CR in the two groups was considered to be 0.5 and 0.7 respectively. According to the above mentioned, the sample size was equal to 74 people in each group (total sample size: 148 people), but because of the possible loss of samples (15%) and in order to increase the accuracy of the study, 88 people were placed in each group, eventually.

After obtaining a written consent form eligible women in the study, demographic information of the participants was recorded through a checklist which included age, gravidity, parity, gestational age, height, weight, body mass index (BMI), education level, employment status, history of cesarean, hypertension, diabetes, blood disorders or other diseases, drug sensitivity, and the cause of curettage.

Primary cervical examination was performed by a resident of gynecologist, and if the cervix was closed, the case was selected randomly using the Sealed Envelope Ltd. 2019 and placed with online randomization service in one of the two groups (A, B). The participants in group A were given 400 µgr of TNG vaginally and in group B they received 400 µgr of misoprostol, which is equivalent to two 200 µgr of misoprostol, as the same way.

Since the drugs were given to the patient by list, by another resident of gynecology, neither parcipating women nor the surgeon who performed the surgical abortions , were aware of wheater IMN or misoprostol had been administered. In case of no response to the drug, 4 hours after drug taking, the patients in both groups were examined again by another resident of gynecology, completely unaware of the condition of the groups. If the cervix was completely closed and consistently firm, the result was considered negative, so the patient was not transferred to the operating room for the bougie dilatation. If the cervix was relatively soft or had dilatation, the patient was transferred to the operating room for curettage and was examined with a bougie dilator Under general anesthesia. The bougie is a device that is used to mechanically dilate and prepare the cervix in the operating room. This device is available in different sizes with a diameter of 1-26 mm and numbers 1-8, which is used to open the cervix. Passing a bougie with a size equal or up to 8 mm through the cervix indicates a positive successful response to the drug, therefore the patient can undergo curettage without the need for mechanical dilatation. If an 8 mm Hegar bougie didn’t pass, it was considered a negative and unsuccessful failure treatment method.

Curettage was performed after gentle mechanical dilatation with a Hegar bougie.

The questionnaire concerned symptoms such as: abdominal pain, diarrhea, hypotension (BP ≤ 90 mmHg), headache, vaginal bleeding and palptations.

Statistical analysis

The values of quantitative variables are shown as "standard deviation ± mean" and the values of qualitative variables are shown as "% frequency". In order to compare individual and clinical variables between the two groups of TNG and misoprostol, the independent t-test was used for quantitative variables and the chi-square test (or Fisher's exact test) was used for qualitative variables. For statistical comparison of CR between the two groups, the chi-square test was used and for statistical comparison of the frequency of side effects, fishers exact test and chi-square test were used.

The data was analyzed using SPSS version 16 software and a significance level of 0.05 was set. P–value <0.05 was considered statically significant.

Results

Of the 174 women recruited to the study; 2 women decided to discontinue their participation in the study and 4 people were omitted due to excessive bleeding.

A total of 40 people from the TNG group and 62 people from the misoprostol group were transferred to the operating room for curettage.

28 people from the TNG group and 55 people from the misoprostol group had positive results, it implies that the Hegar bougie no.8 was removed gently without any pressure, through the cervix.

The personal, social, and clinical characteristics of the 168 participants are shown in Table 1. The average age of women was 30.76 ± 6.59 years. The average gestational age of women was 38.15 ± 2.16 weeks. Of the 168 cases studied, 66 (39.3%) had a university education and 58 (34.5%) were employed. The pregnancy of 59 people (35.1%) was G1, 57 people (33.9%) were G2, and 52 people (31.0%) were G3 or more. 63 cases (37.5%) had no children, 77 cases (45.8%) had one child, and 28 cases (16.7%) had two or more children. 7 cases (4.2%) had hypertension, 14 cases (8.3%) had diabetes, 37 cases (22.0%) had other diseases, and 4 cases (2.5%) had drug sensitivity. The reason for curettage was residual pregnancy in 110 people (65.5%), 50 people (29.8%) had other reasons for abortion, including missed-abortion, blighted ovum as well as lack of fetal heart formation, and 8 people (4.8%) were under forensic medicine justification.

There was no statistically significant difference between the two groups of TNG and misoprostol in terms of all individual, social and clinical variables (P>0.005); In other words, the women candidates for curettage in the two investigated drug groups were homogenous (similar) in terms of all individual, social and clinical variables (Table 1).

Table 1. Baseline characteristics of study population.

		Miso (n= 81)	TNG (n=87)	Total (n= 168)	T/x^2	P- value*
Maternal, y, mean (±SD)		31.44±6.47	30.11±6.67	30.76±6.59	1.31	0.192†
height, cm, mean (±SD)		158.70±4.38	158.26±4.05	158.48±4.21	0.67	0.500 †
Weight,kg, mean (±SD)		68.56±11.80	70.01±12.27	69.31±12.03	0.78	0.435†
BMI, kg/m2, mean (±SD)		27.28±4.93	27.97±4.87	27.97±4.84	0.91	0.361 †
GA, wk, mean (±SD)		8.03±2.40	8.24±1.97	8.15±2.16	0.36	0.563 †
Gravidity, mean (±SD)		2.00±0.96	2.21±1.29	2.11±1.14	1.19	0.237 †
Parity, mean (±SD)		0.79±0.74	0.86±0.84	0.83±0.79	0.59	0.556 †
Cause of curettage	ROP	54 (66.7)	56 (64.4)	110 (65.5)	0.10	0.754 ††
	others	27 (33.3)	31 (35.6)	58 (34.5)		
Education, n (%)	Academic	27 (33.3)	39 (44.8)	66 (39.3)	2.60	0.107 ††
	N-	54 (66.7)	48 (55.2)	102 (60.7)		
Employment	employed	58 (34.5)	35 (40.2)	23 (28.4)	1.61	0.447 ††

housekeeper	58 (71.6)	52 (59.8)	110 (65.5)		
c/s history, n (%)	26 (32.1)	26 (29.9)	52 (31.0)	0.08	0.756 ††
HTN, n (%)	4 (4.9)	3 (3.4)	7 (4.2)	-	0.712 **
Diabet, n (%)	6 (7.4)	8 (9.2)	14 (8.3)	0.18	0.675 ††
Other diseases, n (%)	20 (24.7)	17 (19.5)	37 (22.0)	0.65	0.421 ††
Drug allergy, n (%)	3 (3.8)	1 (1.2)	4 (2.5)	-	0.350 **

Data are mean (SD) or n(%)

Miso, misoprostol; TNG, trinitroglycerin; BMI,body mass index; C/S, cesarean section; HTN, hypertension; ROP, retain product of conception.

*p> 0.05 significant statistical difference between groups (student t test or x2 test)

†Independent t test

††x2 test

** Exact fisher test

So, the CR rate in the misoprostol group (67.9%) was significantly higher than the TNG group (32.2%) but this difference was not statistically significant (P<0.001) (Table 2).

Table 2. cervical ripening, mechanical dilatation & causes of curettage.

			Miso (n= 81)	TNG (n=87)	x^2	P-value*
Result	CR	Yes	55 (67.9)	28 (32.2)	21.41	<0.001 ††
		No	26 (32.1)	59 (67.8)		
	MD	Yes	26(32.1)	58(66.7)	20.05	<0.001 ††
		No	55(67.9)	29(33.3)		
Cause	ROP	Yes	40 (74.1)	15 (26.8)	24.59	<0.001 ††
		No	14 (25.9)	41 (73.2)		
	other	Yes	15 (55.6)	13 (41.9)	1.07	0.300 ††
		No	12 (44.4)	18 (58.1)		

Data are n (%)

CR, Cervical Ripening; MD, Mechanical Dilatation; Miso, Misoprostal; TNG, Trinitroglycerin

ROP, Residue of pregnancy

*P<0.05 Significant Statistical difference between groups

†† x^2 test

Diarrhea was a common side effect in women treated with misoprostol. The rate of diarrhea in the misoprostol group (9.9%) was significantly higher than the TNG group (0%) (P=0.002); also, the rate of abdominal pain in the misoprostol group (7.4%) was significantly higher than the TNG group (0%) (P=0.011). The most common side effect after TNG was headache. The rate of headache in the TNG group (34.5%) was significantly higher than the misoprostol group (0%) (P<0.001). According to the findings, there was no statistically significant difference between women receiving TNG and misoprostol in terms of palpitations (P=0.683) and hypotension (P=0.498). Generally, the rate of complications in the TNG group (35.6%) was significantly higher than the misoprostol group (13.6%) (P<0.001) (Table3).

Table 3. Side effects in groups.

Complication	Miso (n=81)	TNG (n=82)	x^2	P-Value
Diarrhea	8 (9.9)	-	-	0.002 †
Abdominal Pain	6 (7.4)	-	-	0.011 †
Palpitations	2 (2.5)	4 (4.6)	-	0.683 †
Hypotension	-	2 (2.3)	-	0.498 †
Headache	-	30 (34.5)	34.0	<0.001 ††
General	11 (13.6)	31 (35.6)	10.88	>0.001††

Data are n (%)

** Exact fisher test

††: x^2 test

In women whose curettage was due to retained products of conception, the rate of diarrhea in the misoprostol group (13.0%) was significantly higher than the TNG group (0%) (P=0.006); also, the rate of abdominal pain in the misoprostol group (9.3%) was significantly higher than the TNG group (0%) (P=0.026), while the rate of headache in the TNG group (32.1%) was significantly higher compared with the misoprostol group (0%) (P<0.001). According to the findings, there was no statistically significant difference between women receiving TNG and misoprostol in terms of palpitations (P=0.615) and hypotention (P=1.000). Generally, the rate of complications in the TNG group (32.1%) was higher than the misoprostol group (16.7%), but this difference was not statistically significant (P=0.059).

In women whose curettage was caused by other reasons, the rate of headache in the TNG group (38.7%) was significantly higher than the misoprostol group (0%) (P<0.001).

According to our findings, there is a statistically significant difference between women receiving TNG and misoprostol in terms of diarrhea (P=0.466), abdominal pain (P=0.466), palpitations (P=0.240) and hypotention (p=0.0001). Generally, the rate of complications in the TNG group (41.9%) was significantly higher than in the misoprostol group (7.4%) (P=0.003) (Figure1).

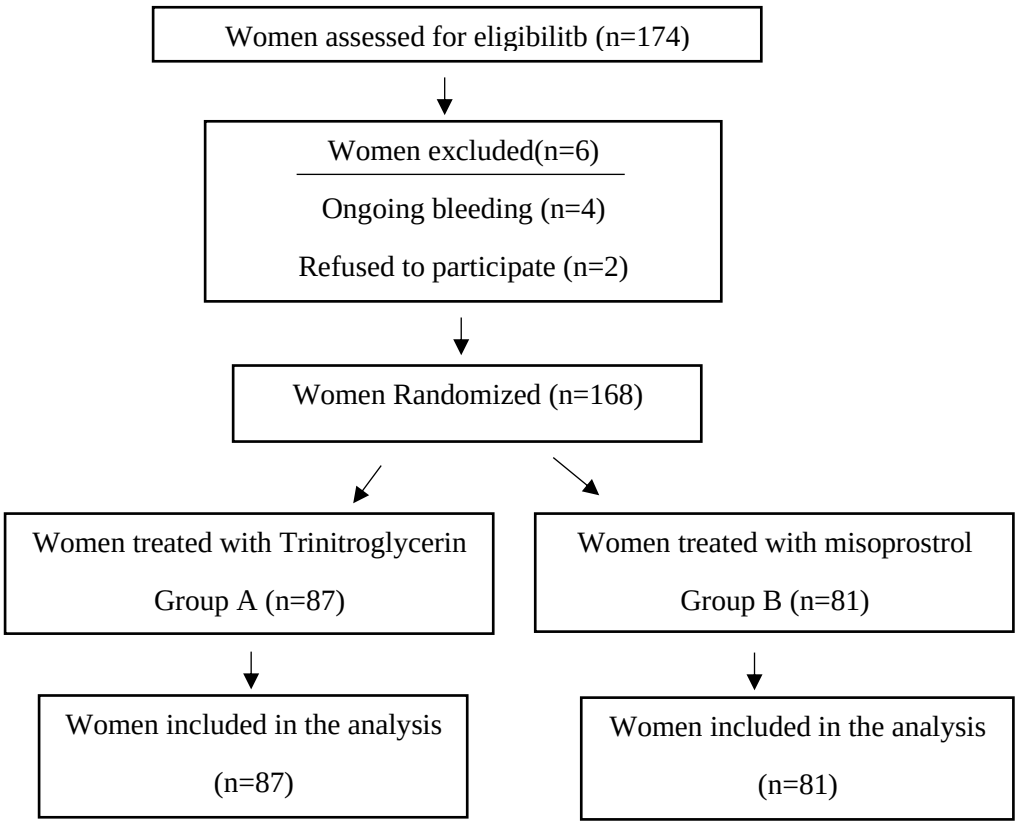

Figure 1. Flow diagram of the clinical trial.

Discussion

In this clinical trial, the therapeutic effect of TNG and misoprostol on CR was compared in women candidates for curettage in Rasht, Iran. The results of our research showed a significant difference regarding the effectiveness of TNG and misoprostol for CR among women candidates for curettage. Therefore, the need for the procedure reduces the need for mechanical dilatation. As the research continued, frequency of side effects caused by the use of drugs was compared between the two groups. Our results showed that diarrhea and abdominal pain were the most common side effects of misoprostol with 9.9% and 7.4% respectively, while general side effects and headache were 35.6% and 35.6% respectively. Headache with a rate of 34.5% was the most common side effect caused by the use of TNG. However, TNG did not have severe side effects for patients. Several studies compared the effectiveness of these two drugs on CR of women candidates for curettage. In a double-blind randomized clinical trial by Sharifzadeh et al., the effect of TNG and misoprostol on CR for curettage was compared in 60 pregnant women in their first trimester. The results of their research showed that the level of effectiveness of misoprostol and TNG on CR in the two groups of study had no statistically significant difference. These researchers concluded that TNG can be used as a suitable substitute for misoprostol in CR. The results of our research are inconsistent with the findings of this research. In our research, which had a larger sample size, misoprostol was not only more effective in CR, but also led to a significant reduction in the need for mechanical dilatation compared to TNG (22).

In another study, Zhuo et al., compared the efficacy and safety of vaginal and oral administration of misoprostol in CR compared with the placebo group. The results of their research showed that the width of the cervix in women receiving vaginal and oral misoprostol was 7.2 and 7.5 mm, respectively, which was significantly more compared with the placebo group. The time needed for CR in both groups receiving vaginal (75 seconds) and oral (82 seconds) misoprostol was significantly less than the placebo group (148 seconds) (25).

In a study, Dabaghi et al., investigated the effect of vaginal misoprostol on CR in 60 pregnant women candidates for D&C compared with the placebo group. The results of their research showed that the vaginal misoprostol can be a suitable drug for CR before performing D&C, and it also led to an easier dilatation of the cervix (26). The results of our research are somewhat comparable with their study. However, in our study, TNG was used instead of the placebo group, and the results presented showed that misoprostol is a better option compared to TNG in CR.

In another clinical trial research, Francis et al. compared the effectiveness of two doses of 25 and 50 µgr of misoprostol on CR at the termination of pregnancy. The results of their research did not report any statistically significant difference in the effectiveness and safety of each dosage regimen compared to the other one (27).

Also, Radulovic et al. in a study compared the effectiveness of misoprostol and isosorbide mononitrate (IMN) before curettage in the first trimester of pregnancy on CR of 120 women with a gestational age of fewer than 14 weeks, who were candidates for curettage (20).

The results of this research showed that misoprostol is more effective than IMN in preparing and CR, but it had more side effects such as abdominal pain, nausea, and bleeding, while the most common side effect of IMN was headache.

In our research, misoprostol had much better effectiveness compared to TNG. On the other hand, the most common side effects of misoprostol were diarrhea and abdominal pain.

In another clinical trial study, Teimouri et al. compared the effect of two drugs; vaginal misoprostol and vaginal TNG on CR in 148 primigravida patients with full-term pregnancies. The results of their research showed that compared to TNG, misoprostol causes faster and more effective CR and is associated with fewer side effects(28). Our results are completely consistent with the findings of their research. Therefore, according to the results of this research and previous studies, vaginal misoprostol had a stronger effect on CR of women who were candidates for curettage compared to vaginal nitroglycerin.

Conclusions

The results of this study showed that vaginal misoprostol has stronger effect on CR in participants and reduced the need for mechanical dilatation, compared to vaginal TNG with the usual dosage.

Although vaginal TNG with a dose of 400 µgr, is less effective than vaginal misoprosterol. It does not have any dangerous side effects, and it can be a substitute for misoprostol, if misoprostol is not available or in case of limitation, such as patient's sensitivity.

Author contribution

FH, MMGh. Conceptualization: **RF**. Data collection: **GhGh, SMAG**. Formal Analysis: **SM**. Writing, review and editing: **SMAG**. Writing, original draft: **MMGh, GhG**.

Conflict of interest

The authors report no conflict of interest regarding the publication of this paper.

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