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ORIGINAL ARTICLE

Evaluation of isosorbide dinitrate versus misoprostol in management of second trimester missed abortion

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ABSTRACT:

Background: Cervical ripening prior to fetal expulsion may be induced by the metabolic activity of endogenous nitric oxide (NO) and the medical use of nitro vasodilatory medications such as isosorbide dinitrate. In order to manage second trimester missed abortions, we set out to compare the therapeutic efficacy and safety of isosorbide dinitrate versus misoprostol.

Methods: This prospective, double-blind, clinical trial was conducted at the department of obstetrics & gynecology at Zagazig university hospitals, Sharkia, Egypt, on 70 women having missed abortion between the 14-20 weeks of gestation. Patients were divided into two groups: Group (1): 35 women with missed abortion gestational age (GA) (14-20) received isosorbide dinitrate 80 mg = 4 tab., n = 35) and Group (2): 35 women with missed abortion GA (14-20) received misoprostol (100 mcg = ½ tab, n = 35).

Results: Both groups showed accepted success rate; Dinitrate success rate was 74.3% and Misoprostol success rate was 85.7% without any statistically significant difference between both groups. The symptoms of post-induction complications were comparable in both groups. Headache was the most frequent complication in dinitrate group 20% while abdominal pain was the most frequent complication in Misoprostol 8.6 %.

Conclusion: The findings of this study can offer a valuable insight aimed to enhancing counselling and support for isosorbide dinitrate compared to misoprostol in management of second trimester abortion. However, Isosorbide dinitrate is associated with significant side effects more than misoprostol as tachycardia, hypotension.

Keywords: Isosorbide dinitrate, Misoprostol, second trimester, Missed abortion.

INTRODUCTION

Women often have abortions at some point in their lives. An abortion occurs in around 20% of clinically identifiable pregnancies. The majority of abortions take place before 12 weeks, and just 2-3% of pregnancies are thought to terminate spontaneously in the second trimester [1].

The prevalence of missed abortions in the second trimester varies according to a number of circumstances, including maternal age, health, and access to healthcare. In general, second trimester missed abortions are less frequent than first trimester missed abortions. Research indicates that the prevalence of abortion, encompassing missed abortions as well, varies between 1 and 5% following the first trimester. [2].

Abortion is a medical issue that disturbs the patient and, if addressed, may result in a coagulation abnormality. A successful pregnancy termination in the second trimester depends heavily on cervical ripening and dilatation [3].

Cervical ripening refers to the cervix becoming softer. There are numerous pharmacological and non-pharmacological techniques for cervical ripening, each with pros and cons of their own. For example It has long been believed that prostaglandins, and particularly PGE2, are important mediators of cervical ripening [4].

Isosorbide dinitrate, a nitric oxide donor, has been used clinically as a cervical ripening agent and has been shown to enhance cervical smooth muscle relaxation in both early and term pregnancy [5].

When organic nitrates are broken down, NO is released, which prompts soluble guanylyl cyclase (GC) to activate. The second messenger implicated in NO mediation, cyclic guanosine monophosphate (cGMP), is produced as a result of this activation from guanosine triphosphate (GTP). The smooth muscles loosen up as a result of the elevated cGMP level. Furthermore, in order to maintain vascular tone, organic nitrates take part in the endothelial cells' endogenous NO generation pathway [6].

Misoprostol is a synthetic form of prostaglandin E1, which binds to smooth muscle cells in the uterus lining to produce uterotonic effects. This process also gives rise to the drug's abortifacient qualities and helps to induce labor and cervical ripening [7].

The breakdown of collagen in the stroma's connective tissue due to edema and a decrease in cervical tone as a result of more frequent and amplitude contractions are the main causes of cervical ripening. Additionally helpful in reducing postpartum hemorrhage are its uterotonic qualities [8].

Nine amino acyl residues make up the peptide hormone oxytocin, which is also a nonapeptide hormone. It is one of the two hormones produced in the hypothalamus and stored and released by the posterior pituitary gland. It is specifically released into the posterior pituitary gland for usage at a later time from the paraventricular nucleus of the hypothalamus. The neural or posterior lobe, or pars nervosa, is the specific region of the posterior pituitary gland that accumulates oxytocin. After being released, most hormones cause negative feedback loops. One of the few hormones with positive feedback loops is oxytocin; that is, when oxytocin is released, other hormones are stimulated to release even more oxytocin. The second and only other hormone stored and released by the posterior pituitary, antidiuretic hormone (ADH), also referred to as vasopressin, shows a negative feedback loop following release in contrast to this feedback. After this hormone starts to affect the body, less of it will be released [9].

Endogenous and exogenous oxytocin both trigger the same reaction in the female reproductive system. G-protein coupled receptors in the myometrium trigger an increase in intracellular calcium in uterine myofibrils, which in turn triggers uterine contractions. Positive feedback is activated by oxytocin receptor activation, which results in several signals that increase intracellular calcium levels and drive uterine contraction [10].

The release of oxytocin provokes contractions in the uterus, which in turn trigger the production of further oxytocin. This process increases the frequency and strength of contractions and permits a mother to deliver her baby vaginally. When the fetus's head presses on the cervix, the mother's brain receives nerve impulses that cause the posterior pituitary to release oxytocin. The cycle continues until parturition as oxytocin is subsequently transported to the uterus via the circulation, intensifying uterine contractions even more [11].

METHODS:

This prospective, double-blind, clinical trial was conducted at the department of obstetrics & gynecology at Zagazig university hospitals, Sharkia, Egypt, from June 2023 to July 2024 on 70 women having missed abortion between the 14-20 weeks of gestation. Approval was taken from the research ethical committee and the institutional review board (IRB number 10984-15-8-2023) of Faculty of Medicine, Zagazig University. The work was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria:

Women between the ages of 18 and 35 who were pregnant, singleton pregnancies, primigravida and multigravida, and gestation ages between 14 and 20 weeks determined by fetometry or the first day of the last menstrual cycle; ultrasound confirmed the missed abortion [3].

Exclusion criteria:

Several pregnancies, individuals with a history of ischemic heart disease, hypertension, contraindications to isosorbide dinitrate, and a history of myomectomy, ruptured uterus, or uterine scarring [3].

Patients who met the requirements for inclusion were split into two groups: Group 1: Isosorbide dinitrate 80 mg = 4 tabs was given to 35 women who had missed their abortions GA (14–20).(Trade name: EPICO_SANOFI_CO, Dinitra tab) and Group (2): Misoprostol (100 mcg = ½ tab, n = 35) was given to 35 women who had missed their abortions GA (14–20).(Brand name: SIGMA _CO, Misotac tab)

The drugs were administrated into the posterior fornix, and cervical changes were assessed at baseline and every three hours to track any alterations. In order to promote cervical softening, the participants received an additional dose (up to a maximum of four doses) if their cervical circumstances did not improve following therapy administration. Regardless of the type of treatment, oxytocin was administered in a balanced electrolyte solution once the cervix was soft. oxytocin **(**syntocinon, NOVARTIS_MYLAN_CO**)** was administered at a rate of 2 mIU/min for the first 15 minutes, then doubled in a balanced electrolyte solution. The duration of the abortion induction from the start of medicine administration until the fetus's evacuation was measured. Each woman's vital signs were checked to make sure she was in stable condition and showed hemodynamic stability before the next dose was administered. Data and medical information were gathered on paper during this time and subsequently input into a computational database. Adverse effects, such as headache, nausea, dizziness, vomiting, pelvic discomfort, lower back pain, and abdominal pain, were evaluated for the participants. After four dosages, the absence of cervical activity was deemed a treatment failure.

Complete history taking, personal history (name, age, marital status, address), menstrual history (particularly last menstrual period), history of hypertension, diabetes, and ischemic heart disease (IHD), history of allergy to any medication, surgical history of the procedure and laparoscopic interference, general examination with emphasis on vital signs (blood pressure, temperature, heart rate, and respiratory rate), and abdominal examination (inspection for abdominal distension and scar detection) were all performed on all patients. Additionally, we performed a local examination to evaluate cervical dilatation and effacement and to look for any cervical lacerations or discharges. We then palpated the abdomen to determine fundal level, guarding, and rigidity. Complete blood count (CBC), liver, renal, and coagulation profile (PT, PTT, and INR) tests were among the laboratory examinations. Random blood sugar (RBS) was also performed.

In order to determine gestational age, placental site, amniotic fluid index, confirm missed abortion, rule out congenital abnormalities, and rule out multiple pregnancies, ultrasound was performed. The absence of heartbeats in a fetus with FL, which corresponds to 14–20 weeks gestation, was one of the ultrasound criteria used to diagnose a second trimester missed abortion (By utilizing LOGIQP7, VR25, copyright 2016).

Outcomes:

The fetus and placenta were expelled as the primary outcomes, and complications, the time from induction to expulsion, and the retained placental product and requirement for (E&C) evacuation and curettage were the secondary outcomes.

STATISTICAL ANALYSIS

The Statistical program for Social Science (IBM Corp., Released 2021) was used to edit, code, and tabulate the gathered data. Armonk, NY: IBM Corp.; IBM SPSS Statistics for Windows, Version 27.0. To check if the data distribution was normal, the Shapiro-Wilk test was used. The difference between the means of data that were normally distributed was examined using the independent t-test. To investigate the association between non-numerical variables, the chi square test was employed. Data before and after induction were compared using a paired t-test. Mann-Whitney To investigate the variation in the mean of data that is not normally distributed, use the U test. If a p-value is less than 0.05 at the 95% confidence interval, it is deemed significant.

RESULTS

The current study registered 70 women who had missed abortions and divided them into two groups. We found that there was no statistically significant difference between the two groups, with the mean age in the Dinitrate group (n = 35) ranging from 20 to 32 years and the Misoprostol group (n = 35) ranging from 19 to 34 years. Based on our study, there were no statistically significant variations in the obstetric histories of the two groups. (Table 1).

According to induction related data, the median gestational age at induction in both groups was almost the same. And median dose for induction and expulsion time, were statistically insignificant between both groups (Table 2).

Both groups showed accepted success rate; Dinitrate success rate was 74.3% and Misoprostol success rate was 85.7% without any statistically significant difference between both groups (p=0.23) (Table 3, figure 1).

There was no significant difference between both groups regarding number of doses needed to achieve successful induction, vital data before and after induction and post-induction complication (Table 4-6).

Table 1: Mean age and Obstetric Data of studied groups:

	Dinitrate		Misoprostol		P value
	Mean	Range	Mean	Range	
Age (years)	24.9	20-32	24.2	19-34	0.43
BMI	28.6	23.3-33.9	28.9	23.7-34.1	0.8
Gravidity	3	2-4	3	2-4	0.8
Parity	2	1-3	2	1-3	0.98
Gestational age	16	15-18	17	15-18	0.8
Previous abortion	2.7	1-7	2.6	1-6	0.87

Mann-Whitney U test

Table 2: Induction related data of studied groups:

	Dinitrate		Misoprostol		P value
	Median	Range	Median	Range	
Gestation at Induction (weeks)	16	15-18	17	15-18	0.8
Dose	3	2-4	3	2-4	0.9
Expulsion Time (Hr)	9	6-12	10	8-12	0.1

Table 3: Comparison of Success rate between studied groups and frequency of evacuation and curettage

	Dinitrate		Misoprostol		P value
	N	%	N	%	
Fail	9	25.7	5	14.3	0.23
Success	26	74.3	30	85.7	
No of E&C	7	20	2	5	0.07

Chi square test

Table 4: Comparison of number of doses needed to achieve successful induction:

	Dinitrate		Misoprostol		P value
	N	%	N	%	
1	3	8.6	3	8.6	0.9
2	7	28	8	31	
3	21	60	21	60	
4	26	74.3	30	85.7	

Chi square test

Table 5: Comparison of vital data before and after induction by dinitrate and misoprostol.

	Dinitrate group		P value	Misoprostol group		P value
	Pre Mean +SD	Post Mean +SD		Pre Mean +SD	Post Mean +SD	
SBP	113.7+9.5	106.9+11	0.001	112.1+7.8	112.1+9.6	1
DBP	74+6.5	67.7+7.7	0.001	73.7+4.9	73.7+5.5	1
HR	77.4+7.8	87.9+9.9	0.001	80+6	79.5+6.2	0.06

SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate

Table 6: Comparison of post-induction complication between studied groups:

	Dinitrate		Misoprostol		P value
	N	%	N	%	
Headache	7	20	3	8.6	0.17
Nausea	3	8.6	2	5.7	0.64
Vomiting	2	5.7	1	2.9	0.55
Abdominal Pain	0	0	3	8.6	0.07
Hemorrhage	0	0	2	5.7	0.15

Chi square test

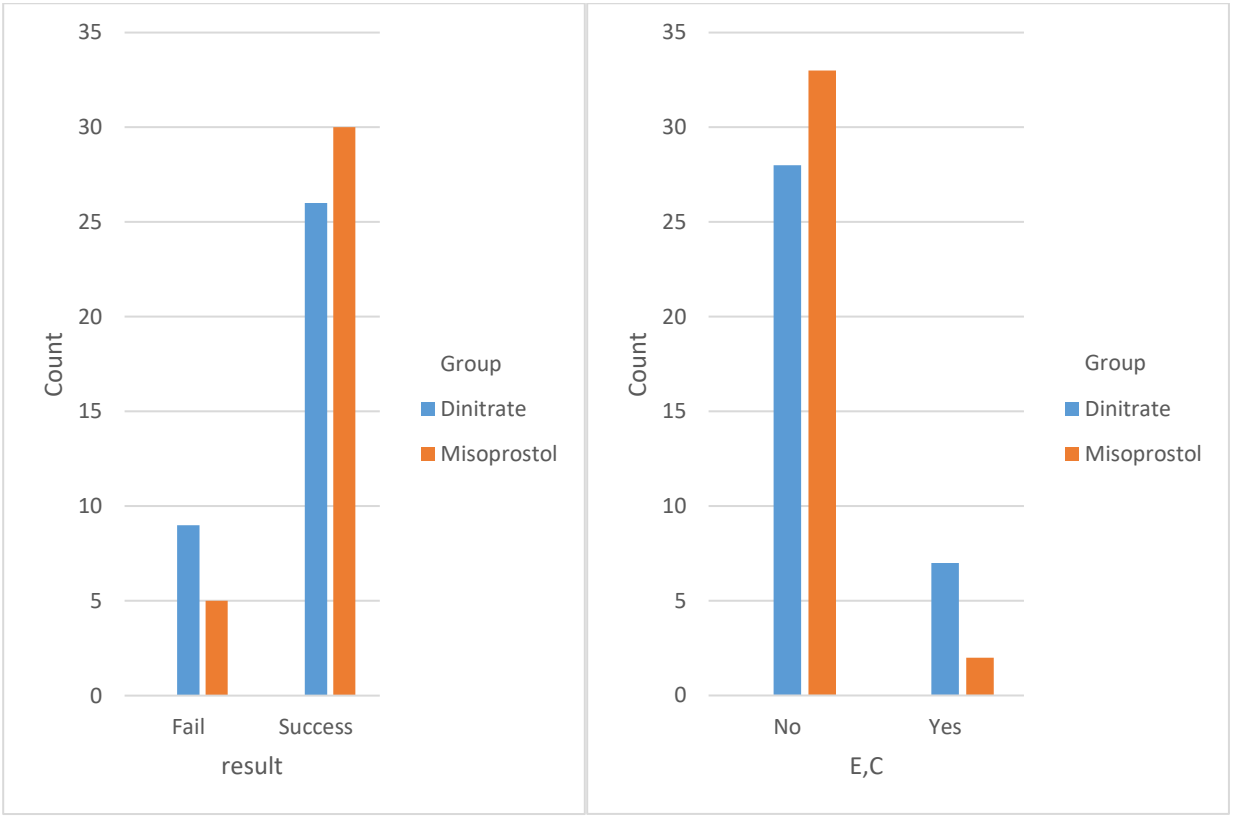

Figure 1: Comparison of Success rate between studied groups and Frequency of E&C.

DISCUSSION

One of the most tragic events in obstetrics is a missed abortion, which causes a severe emotional crisis for the mother, father, and family. [12]. The prevalence of missed abortions in the second trimester varies according to a number of circumstances, including maternal age, health, and access to healthcare. In general, second trimester missed abortions are less frequent than first trimester missed abortions. Research indicates that the prevalence of abortion, encompassing missed abortions as well, varies between 1 and 5% following the first trimester. [2].

A successful pregnancy termination depends critically on cervical ripening and dilatation [3]. Cervical ripening refers to the cervix becoming softer. There are numerous pharmacological and non-pharmacological techniques for cervical ripening, each with pros and cons of their own. For example, prostaglandins, isosorbide mononitrate, and isosorbide dinitrate have long been recognized as important mediators of cervical ripening [4].

Isosorbide dinitrate, a nitric oxide donor, has been used clinically as a cervical ripening agent and has been shown to enhance cervical smooth muscle relaxation in both early and term pregnancy [5]. The most popular is misoprostol because to its ease administration, affordability, and relative stability at room temperature [13].

Many misoprostol regimens have also been used successfully to treat missed abortions; however, despite prior findings of isosorbide dinitrate's strong impact on cervical ripening, there are few reports of its usage for missed abortion patients [14].

Non-pharmacological techniques consist of: Laminaria (Osmotic Dilators): Laminaria is a naturally occurring seaweed that takes in moisture and swells over time, opening up the cervix. It is usually put into the cervix, where it grows over a few hours after absorbing fluid to enable dilation. It can be used either on its own or in combination with medication, such as misoprostol. Additionally, Foley Catheter Cervical dilatation can be achieved mechanically by inserting a balloon catheter into the cervix and inflating it with saline. Although less frequently employed, this technique can be utilized to gradually dilate while taking medicine in the event of a missed abortion [2].

Approximately 50% of women who go through labor and delivery following a missed abortion have an unfavorable cervix that needs to mature with the help of a pharmacological drug, like isosorbide dinitrate applied into the cervix or through posterior vaginal fornix. Reduced cervical collagen and a rise in moisture and active ingredients are the hallmarks of cervical ripening. Cervical cylindrical-epithelial cells may be directly or indirectly affected by isosorbide dinitrate's effects [3].

In this study, we examine the effectiveness of misoprostol and isosorbide dinitrate in inducing second trimester abortions in seventy women.

Seventy women who had missed their second trimester abortions were included in the study. Thirty-five of the patients received misoprostol, while the remaining thirty-five patients received dinitrate.

Age, parity, and gestational age were matched between the two groups ($p < 0.05$). The doses required to produce inductions in both groups did not differ significantly from one another ($p=0.9$). Unlike our findings , in study of **Mohamed & Atalla [15]** Compared to misoprostol, dinitrate successfully produced abortions using a notably smaller number of doses.

Although it was statistically insignificant ($p=0.23$), misoprostol had a clinically greater success rate than dinitrate in our data (85.7% vs. 74.3%). The short sample size may account for the discrepancy between clinical and statistical significance. This is not in agreement with study of **Mohamed & Atalla [15]** since the group receiving isosorbide treatment had a noticeably higher success rate for abortions.

Hidar et al., [16] concurred with our findings that there was no discernible difference in the two groups' success rates (90 vs. 93%) for dinitrate and misoprostol, respectively. This variety could be explained with different sample size **Hidar et al., [16]** was similar to our sample (30 for each group) while **Mohamed & Atalla [15]** had a large sample (80 for each group).

Unlike our study **Arteaga-Troncoso et al., [3]** demonstrated that, at any given time, the

fetal expulsion rate with the misoprostol-oxytocin regimen was at least 2.1 times higher than the fetal expulsion rate utilizing the isosorbide dinitrate-oxytocin combination, at a rate of about 4.4 times.

In study of **Moustafa et al.**, **[17]** After four doses, misoprostol had a significantly higher success rate than dinitrate (92% vs. 48%, respectively). **Arteaga-Troncoso et al.**, **[3]** claimed that in the isosorbide dinitrate-oxytocin group, the success rates for uterine expulsion within 7, 10, and 15 hours were 42%, 83.3%, and 100%, respectively. On the other hand, among women who received the misoprostol-oxytocin regimen at the same times, the effective expulsion rates were 10%, 66.7%, and 86.7%, respectively.

In contrast, the success rates for uterine expulsion with dinitrate within 6, 9 and 12 hours were 28.6, 60 and 74.3%, and with misoprostol within 31.5, 60.1 and 85.7% of the research.

Radulovic et al., **[18]** found that whereas nitrate causes a more pronounced cervical ripening than misoprostol, both groups experienced a significant rate of adverse effects. Also, **Hofmeyr et al.**, **[19]**, revealed that there are good induction success rates when misoprostol is given either by alone or in conjunction with mifepristone. **Kumar et al. [20]** concurred with our conclusion that misoprostol, as opposed to isosorbide, seems to have a greater efficacy as a cervical ripening agent in primigravid women. Though misoprostol did not significantly outperform isosorbide in this trial, isosorbide can be utilized for the same purpose in multigravida women.

Mousiolis et al. [21] concurred with our research that the administration of isosorbide is believed to accelerate the cervical ripening process. They had a better success rate than our trial, which can be attributed to the combination of misoprostol and isosorbide.

Vital data revealed that following administration, dinitrate is linked to a considerable drop in SBP and DBP as well as an increase in heart rate. Study of **Arteaga-Troncoso et al.**, **[3]** discovered that patients using dinitrate had a rise in heart rate and a non-significant drop in mean diastolic blood pressure. But, **Moustafa et al.**, **[17]** confirm our findings that dinitrate is linked to an increase in heart rate and a reduction in mean arterial blood pressure (MAP).

Nicoll et al., **[22]** revealed that after receiving isosorbide (20 or 40 mg in tablets), the mother's pulse was higher than they were for the group that had only vaginal examinations. The primary drawback of the misoprostol regimen is its potential for side effects, which affect up to 30% of patients **[23].**

The most dangerous side effects are severe vaginal hemorrhage, fast placental separation, and anomalies in uterine contractibility. Additional unfavorable gastrointestinal side effects include nausea, vomiting, dyspepsia, flatulence, diarrhea, and abdominal pain **[24].**

In the current study, headaches accounted for 20% of the most common complications in the dinitrate group, while abdominal pain accounted for 8.6% of the most common complication in the Misoprostol group.

However **Mohamed & Atalla**, **[15]** show that the most common adverse effect in both groups was abdominal colic, while headaches were more common in the nitrate group. They also observed a higher rate of complications in the nitrate group compared to the misoprostol group.

Because of the vasodilator effect of NO, headaches are one of the most common side effects of dinitrate treatment **[25]. Arteaga-Troncoso et al.**, **[3]** concurred with our findings that the most common side effect of dinitrate is headache, while the most common side effect of misoprostol is pelvic and abdominal pain. Results of **Moustafa et al.**, **[17]** They discovered that the most common side effect of dinitrate was headache, whereas the most common side effect of misoprostol was abdominal pain, which confirms our findings.

Also, **Srivastava et al.**, **[26]** claimed that misoprostol was linked to pelvic and abdominal pain in their study. Also, **Radulovic et al., [27]** validate our findings, which show that isosorbide is linked to a higher incidence of headaches and misoprostol is connected with a higher incidence of abdominal pain and hemorrhage.

CONCLUSION

In comparison to misoprostol, the results of this study can provide insightful information that can improve counseling and support for isosorbide dinitrate in the management of second trimester abortions. But compared to misoprostol, isosorbide dinitrate is more likely to cause serious adverse effects such tachycardia and hypotension.

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Consent for publication
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Competing interests
The authors declare that they have no competing interest.

REFERENCES:

1. McNamee KM, Dawood F, Farquharson RG. Mid-trimester pregnancy loss. Obstet Gynecol Clin North Am, 2014; 41(1):87–102
2. American College of Obstetricians and Gynecologists. Early pregnancy loss: ACOG practice bulletin, number 200. Obstet Gynecol, 2018; 132(5), e197-e207
3. Arteaga-Troncoso G, Chacon-Calderon AE, Martinez-Herrera FJ, Cruz-Nuñez SG, Lopez-Hurtado M, Belmont-Gomez A, et al. A randomized controlled trial comparing isosorbide dinitrate-oxytocin versus misoprostol-oxytocin at management of foetal intrauterine death. *Plos one*, 2019; *14*(11), e0215718.
4. Pierce S, Bakker R, Myers A, Edwards K. Clinical Insights for Cervical Ripening and Labor Induction Using Prostaglandins. *AJP Rep.*, 2018; *8*(4), e307.
5. Ghosh A, Lattey R, Kelly J. Nitric oxide donors for cervical ripening and induction of labour. *Cochrane Database Syst Rev*, *2016;* (12).
6. Pirahanchi Y, Dimri M. Biochemistry, Guanylate Cyclase. *StatPearls*. 2023.
7. Socha W, Flis W, Pietrus M, Wartęga M. Results of Induction of Labor with Prostaglandins E1 and E2 (The RIPE Study): A Real-World Data Analysis of Obstetrical Effectiveness and Clinical Outcomes of Pharmacological Induction of Labor with Vaginal Inserts. *Pharm., 2023; Vol. 16, Page 982*, *16*(7), 982.
8. Socha W, Flis W, Pietrus M, Wartęga M, Stankiewicz M. Signaling Pathways Regulating Human Cervical Ripening in Preterm and Term Delivery. *Cells, 2022, Vol. 11, Page 3690*, *11*(22), 3690.
9. Baribeau A, Anagnostou E. Oxytocin and vasopressin: Linking pituitary neuropeptides and their receptors to social neurocircuits. *Front. Neurosci.*, 2015; *9*(SEP), 160850.
10. Marcet-Rius M, Bienboire-Frosini C, Lezama-García K, Domínguez-Oliva A, Olmos-Hernández A, Mora-Medina P, et al. Clinical experiences and mechanism of action with the use of oxytocin injection at parturition in domestic animals: Effect on the myometrium and fetuses. *J. Anim.*, 2023; *13*(4), 768.
11. Uvnäs-Moberg K. The physiology and pharmacology of oxytocin in labor and in the peripartum period. *Am J Obstet Gynecol*, 2024; *230*(3), S740–S58.
12. Tokoro S, Koshida S, Tsuji S, Katsura D, Ono T, Murakami T, et al. Insufficient antenatal identification of fetal growth restriction leading to intrauterine fetal death: a regional population-based study in Japan. *J. Matern. -Fetal Neonatal Med.*, 2023; *36*(1), 2167075.
13. Alfirevic Z, Aflaifel N, Weeks A. Oral misoprostol for induction of labour. *Cochrane Database Syst Rev*, 2014; *2014*(6).
14. Haghighi L, Moukhah S, Goshtasbi A. Comparing the effect of oral and vaginal isosorbide dinitrate in pre-induction cervical ripening in term pregnancy: A controlled clinical trial. *Adv. Biomed. Res.*, 2015; *4*(1), 129.
15. Mohamed E, Atalla M. Second trimester a abortion induction with misoprostol only versus misoprostol plus isosorbide mononitrate: a randomized controlled study. *Al-Azhar Intern. Med. J.* 2022; *3*(4), 92–6.
16. Hidar S, Bouddebous M, Chaïeb A, Jerbi M, Bibi M, Khaïri H. Randomized controlled trial of vaginal misoprostol versus vaginal misoprostol and isosorbide dinitrate for termination of pregnancy at 13-29 weeks. *Arch. Gynecol. Obstet.*, 2005; *273*(3), 157–60.
17. MOUSTAFA ZM, MUHAMMED IL, NAGLAA AH, HESHAM MB. Isosorbide Mononitrate versus Misoprostol for Cervical Ripening in Early Missed Abortion. *Med J Cairo Uni*, 2019; *87*(December), 4699-705.
18. Radulovic V, Ekerhovd E, Abrahamsson G, Norström A. Cervical priming in the first trimester: morphological and biochemical effects of misoprostol and isosorbide mononitrate. *Acta Obstet Gynecol Scand*, 2009; *88*(1), 43–51.
19. Hofmeyr J, Gülmezoglu M, Pileggi C. Vaginal misoprostol for cervical ripening and induction of labour. *Cochrane Database Syst Rev*, *2010;* (10).
20. Kumar, B. S., Chakraborty, A., & Samanta, A. Evaluation of isosorbide as a cervical ripening agent prior to induced abortion in contrast to misoprostol- a randomized controlled trial. Obstet Gynecol Sci, 2019, 62(5), 313–21.
21. International Journal of Reproduction, Contraception, Obstetrics and Gynecology,

Saxena Pet al. Int J Reprod Contracept Obstet Gynecol. 2021;10(3):971-4
22. Nicoll E, Mackenzie F, Greer A, Norman E. Vaginal application of the nitric oxide donor isosorbide mononitrate for preinduction cervical ripening: a randomized controlled trial to determine effects on maternal and fetal hemodynamics. *Am J Obstet Gynecol*, 2001; *184*(5), 958–64.
23. Tang S, Gemzell-Danielsson K, Ho C. Misoprostol: pharmacokinetic profiles, effects on the uterus and side-effects. *BJOG*, 2007; *99 Suppl 2*(SUPPL. 2).
24. Jha, Rani, Manoj Rungta, and Shailesh Kumar Jha. "Missed abortion in a tertiary hospital of Eastern Nepal: Efficacy of sublingual versus vaginal misoprostol." *J. Coll. Med. Sci. Nepal - Nepal* 17.4 2021: 347-51.
25. Cao HY, Song ZK, Tang ML, Yang S, Liu Y, Qin L. Higher than recommend dosage of sublingual isosorbide dinitrate for treating angina pectoris: a case report and review of the literature. *Pan Afr Med J*, 2021; *39*(1).
26. Srivastava S, Kumari K. Comparative study of mifepristone plus misoprostol and misoprostol alone for second trimester termination of pregnancy. *Int J Gynaecol Obstet*, 2021; *5*(2), 06–09.
27. Dhillon APK, Shergill HK, Yadav P. Comparative study between vaginal isosorbide and misoprostol for induction of cervical ripening prior to surgical evacuation of first trimester embryonic demise. Int J Reprod Contracept Obstet Gynecol 2015; 4:398-401.

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