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Misoprostol Use in Obstetric Practice: Indications, Efficacy, and Safety

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Abstract:

Background: Misoprostol, a synthetic counterpart of prostaglandin E1, is commonly used in obstetrics and gynecology for its uterotonic and cervical-ripening effects. It increases cervix softening and dilation by activating uterine smooth muscle contraction and allowing collagen to degrade in cervical tissue. Because cervical stenosis and difficult dilatation are prevalent problems during hysteroscopy, pharmacological cervical preparation has received more attention. Misoprostol has been studied as a pre-procedural drug to facilitate hysteroscope insertion, shorten procedure time, and reduce problems associated with mechanical cervical dilation. Before the procedure, various routes of administration, such as oral, vaginal, sublingual, and buccal, were investigated, with variable dosages and timing. Although numerous trials show greater cervical dilatation and simpler hysteroscope entrance, data on the appropriate dose, route, and time of administration are conflicting. Furthermore, misoprostol may cause stomach cramps, nausea, diarrhea, fever, and vaginal bleeding. As a result, assessing the efficacy and safety of misoprostol in cervical preparation before hysteroscopy remains therapeutically important.

Keywords: Misoprostol; Cervical ripening; Hysteroscopy; Cervical dilation; Prostaglandin E1; Gynecology.

Introduction:

Misoprostol is a synthetic counterpart of prostaglandin E1 with stomach antisecretory and mucosal protecting properties. In Canada, the oral form is licensed for the treatment and prevention of nonsteroidal anti-inflammatory medication (NSAID)-induced gastroduodenal ulcers, as well as the treatment of duodenal ulcers caused by peptic ulcer disease. The most common adverse effects of a single oral dose of misoprostol include diarrhea, stomach pain, nausea, flatulence, and dyspepsia (Chatsis and Frey, 2019).

Misoprostol also possesses uterotonic characteristics, which cause smooth muscle fibers in the myometrium to contract and the cervix to relax, so aiding cervical opening. It is approved in Canada for the termination of intrauterine pregnancy with a gestational age of 63 days or less, when combined with mifepristone (L. Yang & Xu, 2025).

Misoprostol tablets, delivered orally and vaginally, are used to induce labor or cervical ripening, but many nations do not officially approve them for this usage. The standard dosage is 50 mcg orally or 25 mcg vaginally, which can be repeated every 4 hours if contractions are absent or not uncomfortable. Misoprostol for cervical ripening and labor induction has serious side effects similar to other prostaglandins, including uterine tachysystole, meconium staining of liquor, and, in rare cases, uterine rupture. Other adverse effects include fever, chills, vomiting, and diarrhea (Hemida, 2022).

Mechanism of Action

Misoprostol directly stimulates prostaglandin E1 receptors on parietal cells in the stomach, hence inhibiting basal and nocturnal gastric acid output. In a dose-dependent manner, this effect lowers the amount of stomach acid secreted in response to food, alcohol, NSAIDs, histamine, and caffeine. Misoprostol causes edema in the mucosa and submucosa and encourages the secretion of mucus and bicarbonate. As a result, the mucosal bilayer

thickens, reducing hydrogen ion leakage and improving mucosal blood flow regulation. In the end, these consequences aid in maintaining the mucosa's capacity to produce new cells (Turner et al., 2016).

The drug's abortifacient qualities, as well as its capacity to induce labor and cervical ripening, are caused by prostaglandins binding to smooth muscle cells in the uterine lining, which results in uterotonic effects.

The breakdown of collagen in the stroma's connective tissue and a decrease in cervical tone brought on by more frequent and intense contractions are the main causes of cervical dilatation. Additionally, postpartum hemorrhage is lessened by the medication's uterotonic qualities (Bakker et al., 2017).

Pharmacokinetics

- Misoprostol is quickly absorbed when taken orally, reaching its maximal plasma concentration in 12 ± 3 minutes. About 30 minutes after oral administration, the suppression of stomach acid output begins to take effect and lasts for roughly three hours.
- **Distribution**: Less than 90% of misoprostol acid is bound to plasma proteins. Breast milk contains misoprostol (Levonorgestrel, 2019).Misoprostol is a prodrug that is converted into the active metabolite misoprostol acid through deesterification (Amini et al., 2020).
- **Misorpostol** is mostly eliminated as an inactive metabolite in the urine (Krugh et al., 2024).
- Misoprostol taken orally is rapidly and entirely absorbed from the digestive system and substantially metabolized by the liver. The plasma level increases quickly, peaks in concentration in 30 minutes, and then declines after 120 minutes. Repeated oral dosages may be necessary to cause regular uterine contractions since oral administration has a quicker onset and rate of metabolism than vaginal administration (Tang et al., 2007).

Indications

Gastric acid production can be inhibited by misoprostol. In order to prevent stomach ulcers, it was initially put on the market in the 1980s. Misoprostol is a synthetic prostaglandin E1 analogue that is frequently used in obstetrical and gynecological conditions, including postpartum hemorrhage, induced labor, abortion, and cervical maturation (Kumar et al., 2021).

Although vaginal misoprostol caused higher difficulties for mothers and newborns, it was a more successful option for cervical ripening and induced labor. Compared to vaginal misoprostol, oral misoprostol produced less tachysystole and may lower the incidence of cesarean sections (Sheibani & Wing, 2018). Misoprostol used sublingually appeared to be more effective than oral and vaginal methods in reducing delivery time without raising associated problems (Pergialiotis et al., 2023).

Misoprostol may result in cervical relaxation and contraction of uterine smooth muscle fibers. According to a study, misoprostol alone was safe, effective, and acceptable for ending a pregnancy at home (Raymond et al., 2023). The success rate was above 95% even if the pregnancy was prolonged (Podolskyi et al., 2023). For term prelabor rupture of the membranes inducement of labor, oral misoprostol was a safe option. By modifying the dosage and frequency of administration, the incidence of adverse responses could be decreased (Padayachee et al., 2020). Misoprostol is readily accessible around the world because of its low cost, room temperature storage, and extended shelf life (Berghella & Bellussi, 2020). Additionally, misoprostol may be utilized to treat asthma and shield heart tissue from harm caused by some chemotherapy drugs including doxorubicin and paclitaxel (Aktaş et al., 2024).

In high-risk patients, misoprostol is recommended as a pill to lower the risk of NSAID-induced stomach ulcers but not duodenal ulcers. Misoprostol is frequently used with diclofenac to treat rheumatoid arthritis or osteoarthritis symptoms in patients who are at a high risk of developing stomach ulcers. In other nations, misoprostol is used either alone or in conjunction with mifepristone for first-trimester abortions. It is also used to treat miscarriages and prevent postpartum hemorrhage. **(Hobday et al., 2018)**, **(Speer, 2019)**.

Table 1. Misoprostol for cervical ripening **(Rafat & Azhar, 2023)**.

Misoprostol	
Route	Intravaginal/oral/sublingual/buccal
Preparations/form ulations	Available in tablet form: 25 µg, 100 µg, 200 µg
Pharmacodynamics	Half-life depends on route of administration: vaginal—20 min; oral—8 min; sublingual—11 min; peak action is attained by vaginal route in 1–2 h, and by oral route in 30 min
Initial dose	Intravaginal: 25 µg; oral: 25–50 µg; sublingual: 25–50 µg
Maximum dosage	Up to 6 doses
Dosing interval	Every 4–6 h
Use with oxytocin if needed	Oxytocin should be delayed until at least 4 h after last dose when administered vaginally and at least 2 h after the last dose when administered orally
Side effects	Uterine hyperstimulation; tachysystole
Advantages of use	Inexpensive, stable at room temperature
Disadvantages of use	Higher risk of tachysystole and meconium passage, risk of uterine rupture in vaginal birth after caesarean (VBAC)
Contraindications	Any contraindication to vaginal birth; glaucoma; renal or hepatic failure; previous caesarean delivery

Adverse effects and contraindications for using misoprostol

Misoprostol frequently caused nausea, vomiting, diarrhea, headaches, dizziness, and other side effects. Misoprostol may cause uterine rupture, tachysystole, and cervical laceration in pregnant women, according to certain research (Sichitiu et al., 2020). Furthermore, misoprostol's teratogenic hazards must be carefully considered. Numerous studies have demonstrated that it may result with fetal problems as cerebral ischaemia, cleft lip and palete, hydrocephalus, and Holoprosencephaly (L. Yang & Xu, 2025).

Misoprostol is not linked to myocardial infarction or bronchospasm, despite the fact that other prostaglandins can. Cumulative dosages of up to 2,200 mcg in 12 hours are generally tolerated without major side effects, and toxic levels are not clearly defined. After consuming 6,000 mcg of misoprostol, a case of non-lethal overdose was documented, accompanied by heat, rhabdomyolysis, hypoxemia, and metabolic acidosis. A fatal event including gastrointestinal bleeding, esophageal and stomach necrosis, and organ failure was recorded following ingestion of 12,000 mcg (60 pills). Misoprostol's most frequent side effects are fever, chills, shaking, nausea, vomiting, diarrhea, and stomach pain. According to Henriques et al. (2007), each of these effects is dose-dependent.

About 35% of women may experience gastrointestinal side effects, which are more frequent following oral or sublingual delivery. The most frequent side effect is diarrhea, which is often moderate and lasts only one

day. Fever and shivering are additional temporary side effects that can happen to 28% and 7.5% of women who take 600 mcg of misoprostol orally, respectively (Nomura, Nakamura-Pereira, Nomura, et al., 2023).

The occurrence of fever and shivering from misoprostol in the active management of the third stage favors the routine use of oxytocin as the drug of choice for the prevention of hemorrhage. Uterine hyperstimulation is one of the most common side effects of labor induction, however it is dose-dependent. High doses of misoprostol used in the past were associated with a high risk of uterine hyperstimulation. Depending on the method and dosage, the risk is comparable to that of dinoprostone at low doses (≤50 mcg of initial dose), ranging from 4 to 12% (Elati & Weeks, 2012).

Hyperstimulation (hypersystole or tachysystole with or without hypertonia) can cause fetal distress, meconium in the amniotic fluid, and uterine rupture. The most dreaded side effect of labor induction is uterine rupture, particularly in women who have previously experienced uterine scarring. Case reports of uterine rupture after first-trimester abortion induction exist, notwithstanding their extreme rarity (Gynecologists, 2009). The majority of uterine rupture instances have been linked to prior uterine scarring or other risk factors and have been reported in third-trimester inductions. Women who use misoprostol to induce labor for vaginal delivery following a cesarean surgery have a 6–12% chance of uterine rupture. As a result, using the medication is typically contraindicated in this situation. Since most research indicates a low risk of uterine rupture, it is crucial to stress that misoprostol can be administered in the second trimester in women who have had a prior cesarean section. **(Morris et al., 2017)**.

Toxicity

Sedation, tremor, convulsions, dyspnea, stomach pain, diarrhea, fever, palpitations, hypotension, and bradycardia are all possible symptoms of an overdose. Oral activated charcoal may aid lower absorption, however hemodialysis is not anticipated to be helpful in treating misoprostol overdose. If an overdose occurs, use supportive therapy to manage symptoms. Depending on the symptoms, this could involve removing undissolved pills from the buccal cavity or vagina, replacing fluid intravenously, using acetaminophen, diazepam, haloperidol, or intramuscular diclofenac. **(Barros et al., 2011)**.

Misoprostol Administration Before Hysteroscopy Procedures:

About 200 years ago, the hysteroscopic procedure was developed. It allows for the direct visualization of focal or diffuse uterine abnormalities, the anatomical layout of the uterine cavity and cervical canal, route permeability, access for biopsies, and the direct removal of lesions (Herman et al., 2017). It is regarded as a minimally invasive procedure that is frequently used in clinics or as an outpatient follow-up procedure to diagnose and treat a variety of conditions, including abnormal uterine bleeding, the assessment of infertile patients, surgeries like myomectomy and polypectomy, the diagnosis of endometrial and endocervix hyperplasia and carcinoma, among others. The anatomopathological confirmation of lesions visually observed using guided biopsy is a significant advantage of this technology over other diagnostic procedures (Zhuo et al., 2016).

The cervix must frequently be dilated in order to complete the procedure, particularly in surgical hysteroscopies where the equipment used is larger than the endocervical canal. Cervical stenosis, pain or patient intolerance, bleeding that impairs hysteroscopic view, and technical issues are the most common reasons for inadequate tests. Over the years, a number of cervical dilation techniques, including the use of hydrophilic laminators, bladder catheter balloons, and Hegar dilators, have been created in an effort to lessen these technical issues and the frequency of subpar tests. However, these methods make patients extremely uncomfortable and raise the possibility of problems during the dilation procedure. Depending on the definition employed, the complication rate ranges from 0.3 to 5%, with discomfort, vagal reaction, uterine perforation, false passage creation, and cervical lacerations being the most frequent. Seldom are serious side effects such pelvic infection and organ perforation recorded (Inácio et al., 2023).

As a result, new cervical dilation techniques had to be developed. These techniques should provide cervix preparation for a brief period of time, be patient-acceptable, be simple to administer, act quickly, and provide sufficient cervical ripening to make the surgery easier. One of the most researched medications in this

regard is misoprostol (Moreira, 2018). It has been utilized for cervical preparation before hysteroscopy because it encourages efficient cervical ripening and is a widely accessible, affordable, and simple technique to store and administer. Misoprostol's most frequent side effects, which mostly happen prior to the surgery, are cramping, pelvic and/or stomach pain, nausea, altered intestinal transit, variable degrees of vaginal bleeding, fever, and/or chills.

According to Angioni et al. (2008), these effects are generally considered to be manageable and infrequently lead to the procedure's cancellation or modification.

Misoprostol reduces the time required for cervical dilatation and increases the mean cervical diameter during the preoperative phase of hysteroscopy, according to the scientific literature. However, it is still unclear what the best dosage, how to administer it, and when to administer it before hysteroscopy, as well as whether the medication lowers the rates of pre- and postmenopausal complications. This is why it is crucial to conduct the current study in routine gynecological practice. The study's goals were to evaluate the ease of the operative hysteroscopic technique with the use of misoprostol, as determined by the full execution of the procedure's side effects, and to examine the incidence of hysteroscopic complications with its use (Zhuo et al., 2016).

A research comprised nulliparous women who received misoprostol prior to hysteroscopy. Misoprostol was given orally, vaginally, or sublingually in doses ranging from 100 to 400, and it was taken three to twenty-four hours before to hysteroscopy (Salah et al., 2024).

Because the sublingual mucosa absorbs substances quickly and avoids first-pass metabolism in the liver, it has also been observed that the mean concentration peak obtained through the sublingual route is higher than that obtained through the oral and vaginal routes. The drug's absorption curve when given rectally resembles that of the vaginal route. **(Nomura, Nakamura-Pereira, Brizot, et al., 2023)**.

Cervical ripening before hysteroscopy with misoprostol:

Many gynecological conditions, including irregular menstruation, endometrial biopsy, polyp removal, fibroid removal, and infertility, are diagnosed and treated with a procedure termed hysteroscopy (Elsayed et al., 2023).

Compared to other procedures, hysteroscopy has several advantages because it is inexpensive, minimally invasive, simple to conduct, and popular with patients. It is therefore considered the ultimate standard for diagnosis and treatment. To inspect the inside of the uterus, a hysteroscope—a thin telescope-like device with a tiny camera—is introduced through the cervix (Bosteels et al., 2015).

One of the primary problems with operative hysteroscopy is the discomfort caused by the hysteroscope's difficult insertion into the internal cervical os. Particularly during the hysteroscopic procedure, patients may experience pain at different points. There are several pharmaceutical (like paracetamol or NSAIDs) and non-pharmacological (like intracervical block and paracervical block) methods to reduce the discomfort of hysteroscopy (O'Flynn et al., 2011).

Traditionally, Visual Analog Scale scores are used to measure pain. A Visual Analog Scale score of 4 or lower on a scale of 10 is widely accepted in the Netherlands; a score higher than four need extra analgesics. Despite being widely used, the VAS score may induce recollection bias because it reflects pain in retrospect. There are several steps involved in a hysteroscopy, and the level of pain may change during the process. As a result, the Visual Analog Scale score might not be the best method for assessing pain in this regard.

As an alternative, the so-called continuous pain score meter is presented. This device can be utilized throughout the various stages of the treatment since it continuously measures pain electronically. Misoprostol's impact on the cervical canal means that pain should be lessened when the hysteroscope is introduced, but not necessarily during the entire process. The various stages of hysteroscopy can be understood through continuous and real-time pain monitoring (Tasma et al., 2018).

Cervical dilatation is not required for diagnostic minihysteroscopes with modest instrument diameters less than 5 mm, but it is required for larger surgical instruments (Guraslan et al., 2022).

Misoprostol (PG E1) use before surgical hysteroscopy made cervical dilatation easier and less complicated, but it is also expensive and has a long list of side effects, such as fever, diarrhea, nausea, and cramping in the stomach (Zhuo et al., 2016).

According to studies, using misoprostol before to hysteroscopic surgery may shorten the procedure's duration and even reduce the risk of complications by improving visibility of the uterine cavity (Kodama et al., 2013). Techniques for cervical priming and dilatation have been developed. The most studied drug that has demonstrated potential for cervical priming is misoprostol (Bastu et al., 2013).

The most significant disadvantage of hysteroscopy is still its discomfort, even when performed by trained surgeons using an atraumatic technique. Potential pharmacological pain treatment for hysteroscopic procedures has been the subject of numerous investigations. Misoprostol usage reduced self-reported pain and reduced the need for postoperative analgesics (Riemma et al., 2022).

The use of misoprostol (prostaglandin E1) before surgical hysteroscopy has been linked to a speedier process, less operational problems, and simpler cervical dilatation. However, the medication's effectiveness is limited by adverse effects such as fever, nausea, cramping in the stomach, and diarrhea (Inácio et al., 2023).

Misoprostol has also been utilized by surgeons for cervical priming before hysteroscopy due to its impact on cervical ripening in pregnant women. Misoprostol has been shown in multiple trials to be effective in attaining cervical dilatation in individuals undergoing hysteroscopy; nevertheless, some publications concluded that misoprostol usage prior to hysteroscopy did not facilitate cervical dilatation (Hua et al., 2016).

In order to assess cervical width using Hegar dilators and the amount of time required, Fernandez et al. (2004) investigated the use of vaginal misoprostol for cervical ripening prior to operative hysteroscopy in premenopausal women with three dose regimens of misoprostol 200, 400, or 800 mcg administered vaginally 4 hours prior to surgery in comparison to a placebo group. They found no appreciable difference between the administration of a placebo and misoprostol. On the other side, misoprostol administration led to an increase in postoperative discomfort.

Assessing the Efficacy and Safety of Misoprostol Prior to Hysteroscopy in Women with Difficult Cervix:

The number of outpatient surgeries has dramatically increased in recent years due to improvements in surgical methods and the availability of minimally invasive procedures. Hysteroscopy is one of the most important outpatient procedures for women's health care (Moore & Carugno, 2023).

A useful surgical method for identifying and treating intrauterine and cervical lesions is hysteroscopy. To safely and precisely access the uterine cavity with a hysteroscope and ensure a clear view for diagnosis and therapeutic procedures, the cervix must be sufficiently dilated (Amer-Cuenca et al., 2020).

Surgeons encounter difficulties with cervical dilatation during hysteroscopy, especially in nulliparous and menopausal patients, those with cervical stenosis, and while doing procedures like myomectomy, polypectomy, intrauterine septa removal, or mass excision with a resectoscope. Cervical dilation must be adequate and suitable in these situations. Cervical dilatation has been linked to consequences like aspain, vasovagal responses, and infections, according to research on hysteroscopy. Consequently, the cervical dilation procedure may be responsible for some of the hysteroscopy-related problems (S. Rodriguez et al., 2022).

Misoprostol preparation of the cervix before to hysteroscopy may facilitate the hysteroscope's insertion through the cervix, possibly lowering the risk of problems. However, factors like menopausal state, manner of prior births (vaginal or cesarean section), and parity (nulliparous or parous) can influence misoprostol's efficacy. Menstrual cycles terminate after menopause. The period between the onset of menstrual alterations or vasomotor symptoms and one year following the last menstrual cycle is considered the transition to menopause. This shift usually starts at age 47 and lasts for five to eight years. Menopausal women and nulliparous women are susceptible to hysteroscopy problems (Karimzadeh et al., 2024).

Misoprostol is linked to side effects include fever, diarrhea, and vaginal bleeding, even while it helps lessen entry-related problems (Zhuo et al., 2016).

Research on misoprostol's effectiveness in diverse patient populations has produced contradictory findings. In both premenopausal and postmenopausal individuals, Barcaite et al. showed that 400 µg of misoprostol was effective in lowering cervical resistance and promoting cervical dilatation. **(Barcaite et al., 2005)**.

The Effects of Sublingual Misoprostol on Cervical Preparation before Hysteroscopy:

A crucial step in lowering problems during transcervical surgeries is cervical softening. This biological process, which is regulated by hormones, sets off an inflammatory reaction that causes metalloproteinases (MMPs) secreted by neutrophils and macrophages to break down extracellular matrix and collagen fibers (Socha et al., 2023).

Prostaglandins (PGs) are essential for promoting MMP secretion and action, increasing extracellular matrix water content, and promoting fibroblast production of glycosaminoglycans (GAGs). Additionally, by encouraging leukocyte infiltration into cervical tissue, PGs control the activity of inflammatory cells. Furthermore, the secretory leukocyte protease inhibitor (SLPI), which normally suppresses neutrophils, is suppressed by prostaglandins (Flis & Socha, 2024).

The narrow cervical channel, which acts as the anatomical border between the vagina and the uterine corpus, frequently requires the cervix to be dilated before ordinary hysteroscopes can be inserted. This dilatation makes it easier to pass the hysteroscope's outer sheath into the cervix (Zhuo et al., 2019). Pharmacological or mechanical methods can be used to accomplish this. Hegar's dilators, balloon catheters, vaginal osmotic dilators (like laminaria), and prostaglandins (like misoprostol) are common techniques (Falcone et al., 2020).

Complications may arise from challenging cervical dilatation or challenging hysteroscope insertion through the cervix (Nair et al., 2023). Depending on the definition employed, the complication rate ranges from 0.3 to 5%, with discomfort, vagal reaction, uterine perforation, false passage creation, and cervical lacerations being the most frequent. Seldom are serious side effects such pelvic infection and uterine perforation described (Inácio et al., 2023).

The cervix must be prepared and softened in advance to make hysteroscopy easier. For this, misoprostol can be administered sublingually or vaginally. Misoprostol aids in cervix dilatation and uterine smooth muscle contraction. But it could potentially cause adverse effects. When getting ready for a hysteroscopy, it's important to think about using medications that work well and have few negative effects (Mirgaloybayat et al., 2024).

According to a study by Mulayim et al. (2010), misoprostol administered sublingually prior to hysteroscopy caused a shorter duration of cervical dilatation than the misoprostol-treated group (Zhuo et al., 2019). In a study by Hameed and Farhan, it was found that the normal saline infiltration group experienced less problems and a much shorter time to achieve cervical dilatation than the misoprostol group. **(B. H. Hameed & Farhan, 2021)**.

Conclusion:

Misoprostol's uterotonic qualities, convenience of administration, affordability, and stability at room temperature have made it a useful and efficient drug in obstetric and gynecological treatment. It is essential for several clinical procedures, including as cervical ripening, medical abortion, postpartum hemorrhage control, and labor induction.

Although there are hazards associated with its usage, especially when it is administered incorrectly or without sufficient monitoring, current data supports its efficacy and safety when used in therapeutic settings and at suitable doses. The need to follow established clinical guidelines is highlighted by variations in dosage schedules and delivery modalities.

In summary, misoprostol is still a crucial part of contemporary obstetric care, particularly in environments with limited resources. To maximize maternal outcomes while reducing potential problems, more study and regular protocol-based use are advised.

References:

1. Aktaş, İ., Gur, F. M., & Bilgiç, S. (2024). Protective effect of misoprostol against paclitaxel-induced cardiac damage in rats. Prostaglandins & Other Lipid Mediators, 171, 106813.
2. Amer-Cuenca, J. J., Marín-Buck, A., Vitale, S. G., La Rosa, V. L., Caruso, S., Cianci, A., & Lisón, J. F. (2020). Non-pharmacological pain control in outpatient hysteroscopies. Minimally Invasive Therapy & Allied Technologies, 29(1), 10–9.
3. Amini, M., Reis, M., & Wide-Swensson, D. (2020). A relative bioavailability study of two misoprostol formulations following a single oral or sublingual administration. Frontiers in Pharmacology, 11, 50.
4. Angioni, S., Loddo, A., Milano, F., Piras, B., Minerba, L., & Melis, G. B. (2008). Detection of benign intracavitary lesions in postmenopausal women with abnormal uterine bleeding: a prospective comparative study on outpatient hysteroscopy and blind biopsy. Journal of Minimally Invasive Gynecology, 15(1), 87–91.
5. Bakker, R., Pierce, S., & Myers, D. (2017). The role of prostaglandins E1 and E2, dinoprostone, and misoprostol in cervical ripening and the induction of labor: a mechanistic approach. Archives of Gynecology and Obstetrics, 296, 167–79.
6. Barcaite, E., Bartusevicius, A., Railaite, D. R., & Nadisauskiene, R. (2005). Vaginal misoprostol for cervical priming before hysteroscopy in perimenopausal and postmenopausal women. International Journal of Gynecology & Obstetrics, 91(2), 141–145.
7. Barros, J. G., Reis, I., & Graça, L. M. (2011). Acute misoprostol toxicity during the first trimester of pregnancy. International Journal of Gynecology & Obstetrics, 113(2), 157–8.
8. Bastu, E., Celik, C., Nehir, A., Dogan, M., Yuksel, B., & Ergun, B. (2013). Cervical priming before diagnostic operative hysteroscopy in infertile women: a randomized, double-blind, controlled comparison of 2 vaginal misoprostol doses. International Surgery, 98(2), 140–4.
9. Berghella, V., & Bellussi, F. (2020). Misoprostol before surgical abortion: evidence-based and ready to be incorporated in clinical guidelines to change practice. American Journal of Obstetrics & Gynecology MFM, 2(4).
10. Bosteels, J., Kasius, J., Weyers, S., Broekmans, F. J., Mol, B. W. J., & D'Hooghe, T. M. (2015). Hysteroscopy for treating subfertility associated with suspected major uterine cavity abnormalities. Cochrane Database of Systematic Reviews, 2.
11. Chatsis, V., & Frey, N. (2019). Misoprostol for cervical ripening and induction of labour: a review of clinical effectiveness, cost- effectiveness and guidelines.
12. Elati, A., & Weeks, A. (2012). Risk of fever after misoprostol for the prevention of postpartum hemorrhage: a meta-analysis. Obstetrics & Gynecology, 120(5), 1140–8.
13. Elsayed, M. A., Abd Elfatah, A. T., Mohamed, A. I., & Elsayed, H. S. (2023). Administration of Misoprostol versus Hyoscine Butylbromide Prior to Hysteroscopy as a Cervical Priming Agent. The Egyptian Journal of Hospital Medicine, 92(1), 5640–6.
14. Falcone, F., Raimondo, G., Stark, M., Dessole, S., Torella, M., & Raimondo, I. (2020). Balloon catheter for cervical priming before operative hysteroscopy in young women: a pilot study. Journal of Investigative Surgery.
15. Fernandez, H., Alby, J. D., Tournoux, C., Chauveaud□ Lambling, A., DeTayrac, R., Frydman, R., & Porcher, R. (2004). Vaginal misoprostol for cervical ripening before operative hysteroscopy in pre□ menopausal women: a double□ blind, placebo□ controlled trial with three dose regimens. Human Reproduction, 19(7), 1618–21.
16. Flis, W., & Socha, M. W. (2024). The Role of the Nlrp3 Inflammasome in the Molecular and Biochemical Mechanisms of Cervical Ripening: A Comprehensive Review. Cells, 13(7), 600.
17. Guraslan, H., Senturk, M. B., Dogan, K., Yuksel, B., Kaya, C., Karacan, T., Karabay Akgul, O., & Ceylan, Y. (2022). Diagnostic office hysteroscopy; why is it still painful procedure despite the surgical experience and mini□ hysteroscope? Journal of Obstetrics and Gynaecology Research, 48(6), 1418–5.
18. Gynecologists, A. C. of O. and. (2009). ACOG practice bulletin no. 107: induction of labor. Obstet Gynecol, 114, 386–97.

19. Hameed, B. H., & Farhan, F. S. (2021). A comparative clinical trial of vaginal misoprostol versus intracervical normal saline infiltration as a cervical ripening agent at time of hysteroscopy. Journal of Obstetrics and Gynaecology Research, 47(3), 978–83.
20. Hemida, R. (2022). Misoprostol for Cervical Ripening Prior to Molar Evacuation: A letter to the editor. Journal of Obstetrics, Gynecology and Cancer Research, 7(4), 356–357.
21. Henriques, A., Lourenço, A. V, Ribeirinho, A., Ferreira, H., & Graça, L. M. (2007). Maternal death related to misoprostol overdose. Obstetrics & Gynecology, 109(2 Part 2), 489–90.
22. Herman, H. G., Kerner, R., Gluck, O., Feit, H., Keidar, R., Bar, J., & Sagiv, R. (2017). Different routes of misoprostol for same-day cervical priming prior to operative hysteroscopy: a randomized blinded trial. Journal of Minimally Invasive Gynecology, 24(3), 455–60.
23. Hobday, K., Hulme, J., Homer, C., Zualo Wate, P., Belton, S., & Prata, N. (2018). ―My job is to get pregnant women to the hospital‖: a qualitative study of the role of traditional birth attendants in the distribution of misoprostol to prevent post-partum haemorrhage in two provinces in Mozambique. Reproductive Health, 15, 1–12.
24. Hua, Y., Zhang, W., Hu, X., Yang, A., & Zhu, X. (2016). The use of misoprostol for cervical priming prior to hysteroscopy: a systematic review and analysis. Drug Design, Development and Therapy, 2789–801.
25. Inácio, Q. A. S., Troncon, J. K., Valério, F. P., Herren, H., Nogueira, A. A., & Poli Neto, O. B. (2023). misoprostol administration before hysteroscopy procedures–a retrospective analysis. Revista Brasileira de Ginecologia e Obstetrícia, 44, 1102–9.
26. Karimzadeh, A., Allahqoli, L., Salehiniya, H., Hanjani, S., Namavari, G., Fazel Anvari-Yazdi, A., Tahermanesh, K., & Alkatout, I. (2024). Assessing the efficacy and safety of misoprostol prior to hysteroscopy in women with difficult cervix: a systematic review and meta-analysis. Journal of Clinical Medicine, 13(18), 5494.
27. Kodama, M., Onoue, M., Otsuka, H., Yada-Hashimoto, N., Saeki, N., Kodama, T., Wakasa, T., & Funato, T. (2013). Efficacy of dienogest in thinning the endometrium before hysteroscopic surgery. Journal of Minimally Invasive Gynecology, 20(6), 790–5.
28. Krugh, M., Patel, P., & Maani, C. V. (2024). Misoprostol. In StatPearls [Internet]. StatPearls Publishing.
29. Kumar, N., Haas, D. M., & Weeks, A. D. (2021). Misoprostol for labour induction. Best Practice & Research Clinical Obstetrics & Gynaecology, 77, 53–63.
30. Levonorgestrel, I. (2019). Drugs and Lactation Database (LactMed)[Internet]. Bethesda (MD): National Library of Medicine (US), 63–7.
31. Mirgaloybayat, S., Madadian, M., Tahermanesh, K., Derakhshan, R., Sarhadi, S., & Rokhgireh, S. (2024). Comparative study of the effects of sublingual trinitroglycerin and sublingual misoprostol on cervical preparation before hysteroscopy: a randomized controlled trial. *Clinical and Experimental Obstetrics & Gynecology*, *51*(7), 167.
32. Moore, J. F., & Carugno, J. (2023). Hysteroscopy [Internet]. Treasure Island (FL): StatPearls Publishing.
33. Moreira, A. R. R. (2018). Uso de Misoprostol em Histeroscopia: Revisão do Seu Papel em Contexto diagnóstico e cirúrgico. PQDT-Global.
34. Morris, J. L., Winikoff, B., Dabash, R., Weeks, A., Faundes, A., Gemzell□ Danielsson, K., Kapp, N., Castleman, L., Kim, C., & Ho, P. C. (2017). FIGO‘s updated recommendations for misoprostol used alone in gynecology and obstetrics.
35. Mulayim, B., Celik, N. Y., Onalan, G., Bagis, T., & Zeyneloglu, H. B. (2010). Sublingual misoprostol for cervical ripening before diagnostic hysteroscopy in premenopausal women: a randomized, double blind, placebo-controlled trial. Fertility and Sterility, 93(7), 2400–4.
36. Nair, A. K., Subbaiah, M., & Maurya, D. K. (2023). Comparison of efficacy of vaginal misoprostol versus a synthetic osmotic dilator (Dilapan-S) for cervical preparation before operative hysteroscopy: a randomized controlled study. Gynecology and Minimally Invasive Therapy, 12(4), 225–9.
37. Nomura, R. M. Y., Nakamura-Pereira, M., Brizot, M. de L., Trapani Júnior, A., Paro, H. B. M. da S., Rosas, C. F., Medeiros, R. D. de, Surita, F. G., Luz, A. G., & Mattar, R. (2023). Uso de misoprostol em obstetrícia. Femina, 350–60.

38. O'Flynn, H., Murphy, L. L., Ahmad, G., & Watson, A. J. S. (2011). Pain relief in outpatient hysteroscopy: a survey of current UK clinical practice. European Journal of Obstetrics & Gynecology and Reproductive Biology, 154(1), 9–15.
39. Padayachee, L., Kale, M., Mannerfeldt, J., & Metcalfe, A. (2020). Oral misoprostol for induction of labour in Term PROM: a systematic review. Journal of Obstetrics and Gynaecology Canada, 42(12), 1525– 31.
40. Pergialiotis, V., Panagiotopoulos, M., Constantinou, T., Vogiatzi Vokotopoulou, L., Koumenis, A., Stavros, S., Voskos, A., & Daskalakis, G. (2023). Efficacy and safety of oral and sublingual versus vaginal misoprostol for induction of labour: a systematic review and meta-analysis. Archives of Gynecology and Obstetrics, 308(3), 727–75.
41. Podolskyi, V., Gemzell□ Danielsson, K., Maltzman, L. L., & Marions, L. (2023). Effectiveness and acceptability of home use of misoprostol for medical abortion up to 10 weeks of pregnancy. Acta Obstetricia et Gynecologica Scandinavica, 102(5), 541–8.
42. Rafat, D., & Azhar, F. (2023). Induction of Labour. In Labour and Delivery: An Updated Guide (pp. 599–620). Springer.
43. Raymond, E. G., Weaver, M. A., & Shochet, T. (2023). Effectiveness and safety of misoprostol-only for first-trimester medication abortion: An updated systematic review and meta-analysis. Contraception, 127, 110132.
44. Riemma, G., Vitale, S. G., Manchanda, R., Rathore, A., Török, P., De Angelis, C., Urman, B., Sareri, M. I., La Verde, M., & Carugno, J. (2022). The role of hysteroscopy in reproductive surgery: Today and tomorrow. Journal of Gynecology Obstetrics and Human Reproduction, 51(4), 102350.
45. Rodriguez, S., Haimovich, S., Vitale, S. G., Alonso, L., & Carugno, J. (2022). Vasovagal syncope during office hysteroscopy—a frequently overlooked unpleasant complication. Medicina, 58(11), 1626.
46. Salah, N., Maged, A. M., Mahmoud, S. I., Bassiouny, N., Mohsen, R. A., AbdelAziz, S., & Ragab, W. S. (2024). The use of misoprostol before hysteroscopy in Nulliparous women: a systematic review and meta- analysis of randomized controlled trials. BMC Pregnancy and Childbirth, 24(1), 796.
47. Sheibani, L., & Wing, D. A. (2018). A safety review of medications used for labour induction. Expert Opinion on Drug Safety, 17(2), 161–7.
48. Sichitiu, J., Vial, Y., Panchaud, A., Baud, D., & Desseauve, D. (2020). Tachysystole and risk of cesarean section after labor induction using misoprostol: a cohort study. European Journal of Obstetrics & Gynecology and Reproductive Biology, 249, 54–58.
49. Socha, M. W., Flis, W., Wartęga, M., Kunicka, A., & Stankiewicz, M. (2023). A review of the mechanism of action and clinical applications of osmotic dilators for cervical ripening in the induction of labor and in gynecology procedures. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research, 29, e940127- 1.
50. Speer, L. (2019). Misoprostol Alone Is Associated with a High Rate of Successful First-Trimester Abortion. American Family Physician, 100(2), 119.
51. Tang, O. S., Gemzell-Danielsson, K., & Ho, P. C. (2007). Misoprostol: pharmacokinetic profiles, effects on the uterus and side-effects. International Journal of Gynecology & Obstetrics, 99, S160–S167.
52. Tasma, M. L., Louwerse, M. D., Hehenkamp, W. J., Geomini, P. M., Bongers, M. Y., Veersema, S., van Kesteren, P. J., Tromp, E., Huirne, J. A., & Graziosi, G. C. (2018). Misoprostol for cervical priming prior to hysteroscopy in postmenopausal and premenopausal nulliparous women; a multicentre randomised placebo controlled trial. BJOG: An International Journal of Obstetrics & Gynaecology, 125(1), 81–9.
53. Turner, J. V, Agatonovic-Kustrn, S., & WArd, H. (2016). Off-label use of misoprostol in gynaecology. Facts, Views & Vision in Obgyn, 7(4), 261.
54. Zhuo, Z., Yu, H., & Jiang, X. (2016). A systematic review and meta-analysis of randomized controlled trials on the effectiveness of cervical ripening with misoprostol administration before hysteroscopy. International Journal of Gynecology & Obstetrics, 132(3), 272–7.
55. Zhuo, Z., Yu, H., Gao, L., & Jiang, X. (2019). Effectiveness of misoprostol administration for cervical ripening in women before operative hysteroscopy: a randomized, double-blinded controlled trial. Minimally Invasive Therapy & Allied Technologies, 28(6), 344–50.