Uses of Misoprostol in Obstetrics and Gynecology

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Misoprostol is a synthetic prostaglandin E_1 analogue that is used off-label for a variety of indications in the practice of obstetrics and gynecology, including medication abortion, medical management of miscarriage, induction of labor, cervical ripening before surgical procedures, and the treatment of postpartum hemorrhage. Due to its wide-ranging applications in reproductive health, misoprostol is on the World Health Organization Model List of Essential Medicines. This article briefly reviews the varied uses of misoprostol in obstetrics and gynecology.
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Misoprostol is a synthetic prostaglandin E_1 analogue marketed as an oral preparation used to prevent and treat gastroduodenal damage induced by nonsteroidal anti-inflammatory drugs (NSAIDs). However, misoprostol is used off-label for a variety of indications in the practice of obstetrics and gynecology, including medication abortion, medical management of miscarriage, induction of labor, cervical ripening before surgical procedures, and the treatment of postpartum hemorrhage. Misoprostol's effects are dose dependent and include cervical softening and dilation, uterine contractions, nausea, vomiting, diarrhea, fever, and chills.[1] Although misoprostol is not approved by the US Food

and Drug Administration (FDA) for these indications, in 2002, pregnancy was removed from the label as an absolute contraindication to misoprostol use.[2] Misoprostol's advantages over other synthetic prostaglandin analogues are its low cost, long shelf life, lack of need for refrigeration, and worldwide availability (Figure 1).[3]

Pharmacokinetics

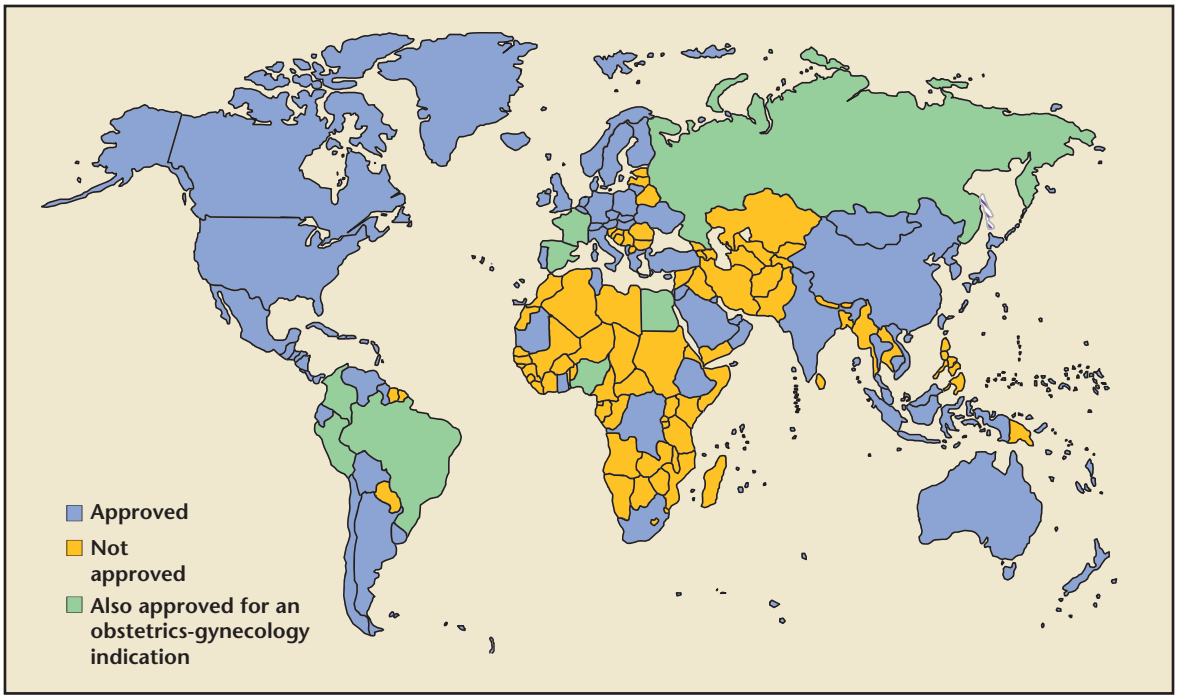
Routes of misoprostol administration include oral, vaginal, sublingual, buccal, or rectal. Pharmacokinetics studies (Figure 2) comparing oral and vaginal administration have shown that vaginal misoprostol is associated with slower absorption, lower peak plasma levels, and slower clearance, similar to an extended-release preparation.[4-6] Vaginal misoprostol is also associated with a greater overall exposure to the drug (area under the curve [AUC]) and greater effects on the cervix and uterus.[5] There is, however, a wide variation in the absorption of misoprostol through the vaginal epithelium among different women.[3] There is no clinically significant difference between vaginal misoprostol that is administered dry and vaginal misoprostol moistened with water, saline, or acetic acid.[7-9]

The rectal route of administration shows a similar pattern to vaginal administration, but has a lower AUC, including a significantly lower maximum peak concentration.[6] The sublingual route of administration has an AUC similar to vaginal administration, but more rapid absorption and higher peak levels than either vaginal or oral administration (Figure 2).[7] This translates into higher rates of gastrointestinal side effects. Nevertheless, the sublingual route also causes uterine contractions at a rate equivalent to vaginal administration and has less variation in absorption.[10] The buccal route of administration shows a lower AUC, a lower peak concentration, and fewer side effects than sublingual administration.[11] The buccal route has a pattern of absorption similar to the vaginal route, but produces lower serum levels overall. Nonetheless, the buccal and vaginal routes of administration have similar effects on uterine tone and activity.[12] The buccal route of administration is also thought to be the least variable in terms of drug exposure and peak levels. The administration of NSAIDs for pain relief does not alter the efficacy of misoprostol.[13,14] There are no known drug interactions with misoprostol.[1]

Teratogenicity

Misoprostol is considered a teratogen. Congenital defects following prenatal exposure in early pregnancy to misoprostol include skull defects, bladder exstrophy, arthrogryposis, cranial nerve palsies, facial malformations, terminal transverse limb defects, and Moebius sequence.[1,15,16] This constellation of congenital malformations is thought to be due to a vascular

Figure 1. *World map of misoprostol approval. Produced by Gynuity Health Projects. Reproduced with permission from Gynuity Health Projects. Copyright © 2008. Access at www.gynuity.org.*



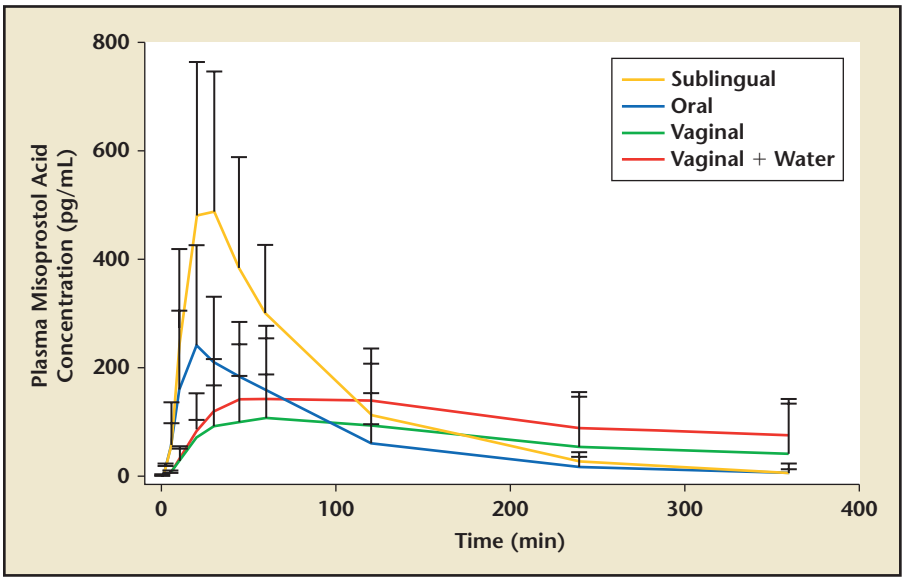


Figure 2. *Mean plasma concentrations of misoprostol acid over time (arrow bars = 1 SD). Reprinted from Tang OS et al, "Pharmacokinetics of different routes of administration of misoprostol,"* Hum Reprod. *2002;17:332-336. Copyright © 2002 with permission from Oxford University Press.*[7]

disruption secondary to uterine contractions caused by misoprostol. The incidence of these abnormalities does not appear to be high when population registries have been studied, especially given that exposure to misoprostol is quite common among some populations of patients.[17,18] The absolute risk of congenital malformations after prenatal exposure to misoprostol is estimated to be approximately 1%.

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Pharmacokinetic studies reveal that misoprostol is excreted into breast milk with drug levels that rise and fall very quickly. Levels become undetectable within 5 hours of maternal ingestion.[19] However, breastfeeding women should be advised that misoprostol may cause infant diarrhea.[20]

Medication Abortion

In 2000, the FDA approved medication abortion using 600 mg of oral mifepristone, a progesterone antagonist, with 400 μg of oral misoprostol 48 hours later for pregnancies up to 49 days of gestation.[21] However, there is excellent evidence of efficacy up to 63 days of gestation using the regimens of 200 mg of mifepristone orally followed by home administration of either 800 μg of buccal misoprostol in 24 to 36 hours or 800 μg of vaginal misoprostol in 6 to 48 hours.[22,23] Women then return 4 to 14 days later for a clinical evaluation to document complete abortion. Success rates for these regimens range from 95% to 98%, with failure due to ongoing pregnancy in approximately 1%.[21] In the United States, most women undergo ultrasound for pregnancy dating and confirmation of complete abortion. However, serial serum β-human chorionic gonadotropin (βhCG) levels can also be used to confirm complete abortion.[24,25]

Candidates for medication abortion must be able to adhere to the treatment regimen as well as have access to a telephone and transportation to a medical facility in case of emergency. Multiple gestation is not a contraindication to medication abortion provided that the pregnancy is no more than 49 to 63 days, depending on the regimen being used.[22] Contraindications to mifepristone medication abortion include hemorrhagic disorder; concurrent anticoagulant therapy; inherited porphyrias; chronic adrenal failure; concurrent long-term systemic corticosteroid use; confirmed or suspected ectopic or molar pregnancy; allergy to mifepristone, misoprostol, or other prostaglandin; and unwillingness to undergo a vacuum aspiration if needed.[26] If the woman has an intrauterine device in place, it must be removed before treatment. Women with serious systemic illnesses (eg, severe cardiac, renal, or liver disease or severe anemia) should be evaluated individually to determine which method of abortion is safest. Rhesus (Rh)-negative women typically receive Rh immune globulin on the day of mifepristone administration.[22]

Medication abortion necessarily involves heavy bleeding and cramping as the pregnancy is expelled. Other transient side effects from misoprostol include nausea, vomiting, diarrhea, fever, and chills.[21] At the follow-up visit, ongoing pregnancies are most commonly treated with suction curettage because of the risk of congenital anomalies. Women with persistent nonviable pregnancies may opt for expectant management, a repeat dose of misoprostol, or suction curettage.[27] Mifepristone medication abortion is safe with an estimated complication rate of 2.2 per 1000 women.[28] The most frequent complications are heavy bleeding requiring curettage and/or transfusion and

infection. The estimated mortality rate for mifepristone abortion is 1 per 100,000 women, most commonly due to fatal sepsis.[28] Where mifepristone is not available, medication abortion can be accomplished with methotrexate and misoprostol or misoprostol alone.[29]

Cervical Ripening Before Surgical Abortion

First Trimester

First-trimester surgical abortion is a common, safe procedure with a major complication rate of less than 1%.[30] Risk factors for major complications in the first trimester, such as cervical laceration and uterine perforation, are provider inexperience, patient age less than 18 years, and increasing gestational age.[31,32] Studies have shown that the use of laminaria for cervical ripening reduces the risk of cervical laceration and, to a lesser extent, uterine perforation.[33,34] Although pharmacologic priming agents, such as misoprostol, may potentially have the same effects, no published studies to date have been large enough to assess these outcomes. The risk of these injuries during first-trimester suction curettage is very small, given an experienced provider. Nevertheless, the Society of Family Planning recommends that providers consider cervical ripening for women late in the first trimester (12-14 weeks of gestation), adolescents, and for women in whom cervical dilation is expected to be difficult either due to patient factors or provider inexperience.[35]

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Misoprostol is a proven cervical ripening agent prior to first-trimester surgical abortion.[36] Studies have shown that the optimal dose in terms of balancing effectiveness and side effects is 400 μg.[37] There are data evaluating oral, vaginal, and sublingual routes of administration. Effective regimens are 400 μg of misoprostol vaginally 3 to 4 hours, 400 μg orally 8 to 12 hours, or 400 μg sublingually 2 to 4 hours prior to suction curettage.[35] Compared with the oral route, vaginal administration is equally or more effective and is associated with fewer side effects.[36,38,39] The sublingual route is more effective than oral, equivalent to or better than vaginal administration, but is associated with more side effects than either oral or vaginal administration.[40] Although not yet studied for first-trimester surgical abortion, buccal administration is widely used. Buccal misoprostol offers the effectiveness and decreased side effects of vaginal administration combined with high acceptability for both patient and staff. These regimens significantly increase baseline cervical dilatation and facilitate further mechanical dilation compared with placebo.[41] Some studies have also reported decreased procedure time and estimated blood loss. These differences are statistically, but not clinically, significant.[42,43] There is no clear evidence to date that misoprostol reduces pain during the procedure compared with placebo.[35] It is important to note that if misoprostol is used for cervical ripening, and the woman is unable to undergo surgical abortion as planned, she is at some risk for expelling the pregnancy. Therefore, before receiving misoprostol, all women should give informed consent for the abortion procedure and be adequately screened by appropriately trained personnel.

Second Trimester

Cervical preparation prior to second-trimester surgical abortion (dilation and evacuation, D&E) is critical to prevent complications from forceful dilation of the cervix.[33,34] Providers have traditionally used osmotic dilators such as laminaria to slowly dilate the cervix over several hours to days before the procedure.[44] Although there are fewer studies than in the first trimester, misoprostol has been evaluated in the second trimester as a substitute for laminaria and as an adjunct to laminaria. The regimens studied for second-trimester D&E vary widely and include 400 μg of vaginal misoprostol for 3 to 4 hours, 400 μg and 600 μg of buccal misoprostol for at least 90 minutes, 600 μg of buccal misoprostol for 2 to 4 hours, and 800 μg of buccal misoprostol for at least 20 minutes but not more than 90 minutes preoperatively.[45-48] As a substitute for laminaria, misoprostol does not achieve the same degree of preoperative cervical dilation and frequently additional mechanical dilation is required.[47] Although this additional mechanical dilation may be easily achieved in most patients, especially those under 16 weeks of gestation and multiparous women, there is a higher rate of difficult or inadequate dilation when using misoprostol instead of laminaria.[46]

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The ideal dosing regimen for second-trimester procedures is unknown. In terms of safety, a review of more than 6000 surgical abortions between 12 and 16 weeks using 400 μg of vaginal or buccal misoprostol 90 minutes preprocedure showed a uterine perforation rate of 0.45 per 1000, comparable to historical reports for laminaria use.[49] Cervical lacerations, however, were not reported. The Society of Family Planning does not recommend the use of misoprostol as an alternative to laminaria except by experienced clinicians in the early second trimester (before 16 weeks) in women at low risk for cervical or uterine injury.[44]

Misoprostol use as an adjunct to laminaria has been evaluated in a randomized, controlled trial using 400 μg of misoprostol at least 90 minutes preoperatively in 125 women between 13 and 20 6/7 weeks of gestation.[48] Misoprostol improved preoperative dilation in women only at 19 weeks of gestation and above. However, if women needed subsequent mechanical dilation after laminaria had been removed, misoprostol significantly improved the subjective ease of dilation in women at 16 weeks of gestation and above. Given this, the Society of Family Planning does not recommend routine use of misoprostol as an adjunct to laminaria under 16 weeks, but it may be considered at later gestational ages.[44] In general, misoprostol may be used for cervical ripening prior to surgical abortion in women with prior cesarean deliveries in the first and second trimesters because uterine rupture rarely occurs in this setting.[44]

Cervical Ripening Before Other Procedures

Researchers have studied cervical ripening prior to other gynecologic procedures in nonpregnant women, including hysteroscopy, endometrial biopsy, and intrauterine device (IUD) insertion. Similar to cervical ripening prior to surgical abortion, the aim of misoprostol use in hysteroscopy is to prevent complications of mechanical dilation such as cervical laceration, uterine perforation, and the creation of a false passage.[50] One meta-analysis of 10 studies concluded that misoprostol leads to greater preoperative dilation, decreased need for additional dilation, and reduced rates of cervical laceration in premenopausal women.[51] The greatest benefits were seen in nulliparous women and with operative hysteroscopy. However, women treated with misoprostol had higher rates of transient vaginal bleeding, cramping, and fever preoperatively. There may also be potential concerns regarding loss of distension from excessive cervical dilation caused by misoprostol.[52] More research is needed to determine the ideal candidate for misoprostol use before hysteroscopy.

The aim of misoprostol use in hysteroscopy is to prevent complications of mechanical dilation such as cervical laceration, uterine perforation, and the creation of a false passage.

The optimal dosing regimen for cervical ripening before hysteroscopy is unclear. In premenopausal women, studies have found either 200, 400, or 1000 μg of vaginal misoprostol or 400 μg of oral misoprostol given at least 9 to 12 hours preoperatively to be superior to placebo.[53-57] Most of these studies focused on nulliparous women. There are few trials comparing routes of administration, doses, and interval to procedure prior to hysteroscopy. One study that compared 400 μg of oral and vaginal misoprostol given 10 to 12 hours before operative hysteroscopy found vaginal misoprostol to be superior in baseline cervical dilation and time required for cervical dilation.[52] Trials evaluating vaginal misoprostol for shorter intervals, 4 to 6 hours preoperatively, have not shown evidence of an effect.[58,59] Therefore, it may be that time to adequate cervical ripening is different for pregnant and nonpregnant women. For peri- and postmenopausal women and women treated with gonadotropin-releasing hormone agonists, data are conflicting and most studies do not show a benefit from misoprostol.[53,60-63] Misoprostol's actions on the cervix may require endogenous estrogen. It is not known if more intensive dosing regimens would affect the postmenopausal cervix.[51]

Only a single study has evaluated misoprostol for endometrial biopsy. This trial randomized a mixed population of 42 premenopausal, perimenopausal, and postmenopausal women to either 400 μg of oral misoprostol or placebo 3 hours prior to endometrial biopsy.[64] This study found no evidence of an effect on cervical resistance, success rate for obtaining the biopsy, and the ease of performing the biopsy. However, the study was underpowered for these endpoints. The study did note significantly more pain with the biopsy and uterine cramping in the misoprostol group.

Based on a single, small study, IUD insertion in nulliparous women may be facilitated by misoprostol use. A Swedish trial randomized 80 women to 400 μg of sublingual misoprostol plus 100 mg of diclofenac or 100 mg of diclofenac alone 1 hour before Nova-T IUD insertion.[65] Although baseline cervical dilation was similar in both groups, providers rated the insertion procedure as "easy" in 74% of the misoprostol group compared with

55% in the control group ($P = .04$). However, the majority of the IUD insertions were uncomplicated in both groups. There was no difference between the groups in terms of pain scores during IUD insertion or overall side effects.

Medical Management of Miscarriage

Misoprostol is an option for the medical management of early pregnancy failure, including anembryonic pregnancies and embryonic demise, and incomplete abortion for women at 12 weeks or less of gestation.[66,67] Contraindications include pelvic infection or sepsis, hemodynamic instability or shock, allergy to misoprostol, known bleeding disorder, concurrent anticoagulant therapy, and confirmed or suspected ectopic or molar pregnancy.[68] If the woman has an IUD in place, it must be removed before treatment. Similar to medication abortion, cramping and bleeding will occur with pregnancy passage and side effects such as nausea, vomiting, diarrhea, fever, and chills may be experienced.[68] Studies have shown, however, that misoprostol is acceptable to most women for this indication.[69,70]

For early pregnancy failure, the most commonly used regimen is a single dose of 800 μg of vaginal misoprostol.[68] The success rate is approximately 85% as long as at least 7 to 14 days is allowed for completion of expulsion and a second dose of misoprostol is considered for initial failures.[69] Ultrasound is typically used to confirm complete abortion. As long as the gestational sac is absent and the woman is asymptomatic, there is no endometrial stripe thickness that requires intervention.[71] Compared with surgical evacuation, there is no significant difference in the rates of infection or hemorrhage.[69] For incomplete abortion, effective misoprostol regimens include a single dose of 600 μg orally, a single dose of 800 μg vaginally, or a single dose of 400 μg sublingually.[68,69] Depending on the study, success rates range from 66% to 100% using these doses.

Induction of Labor in the Second Trimester

Misoprostol is an effective drug for labor induction in the second trimester for fetal death or termination of pregnancy.[67] The optimal dose, schedule, and route of administration have not been determined. Several randomized, controlled trials exist examining the different doses and schedules.[72-75] The doses used in these randomized trials range from 200 μg to 800 μg administered vaginally, and the interval between dosing ranged from every 3 to every 12 hours. No conclusive evidence of superiority of one dose or schedule over another can be clearly drawn from these studies. An important study aimed at answering the question of dose optimization was performed by Dickinson and Evans,[76] who administered vaginal misoprostol either 200 μg every 6 hours, 400 μg every 6 hours, or a 600 μg loading dose followed by 200 μg every 6 hours. Both the 400 μg and 600/200 μg regimens were superior to the 200 μg regimen in terms of median time to delivery. The 600/200 μg regimen caused more side effects than the other 2 dosing schedules. Side effects of misoprostol noted in several studies include maternal fever, chills, and gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal pain.[1] Therefore, it makes sense to administer the lowest dose of misoprostol that is most effective, thereby decreasing the side effects. Although the optimal dose for fetal death or termination of pregnancy in the second trimester has not been established, a reasonable approach may be to start with 400 μg vaginally every 6 hours for a 48-hour period. There is also evidence that the addition of 200 mg of mifepristone to the induction protocol decreases the interval to delivery for termination of pregnancy.[77]

Induction of labor with misoprostol in the setting of a previous cesarean delivery scar, although contraindicated in the third trimester, can be safely performed in the second trimester. The data on the absolute risk of induction of labor in this setting are lacking. Many studies on second-trimester induction with misoprostol have excluded patients with a previous cesarean delivery due to the fear of uterine rupture. Importantly, however, several randomized studies did include patients with a previous cesarean delivery.[73,74,78] No adverse effects occurred in these patients. Furthermore, several retrospective studies have specifically addressed the safety of misoprostol use for second-trimester induction in the case of a prior cesarean delivery. In one of the largest retrospective studies on the subject, 188 women with a previous cesarean delivery underwent induction of labor between 17 and 24 weeks of gestation.[79] The dose of misoprostol was 400 μg orally together with 400 μg vaginally for the first dose followed by 400 μg vaginally every 6 hours for a maximum of 5 doses. The main outcomes included

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hemorrhage requiring transfusion, postabortal infection, retained placenta, and uterine rupture. There was no evidence that a previous cesarean delivery affected the incidence of complications. Similar results were found in another study of 80 women undergoing termination of pregnancy between 13 and 26 weeks of gestation for a variety of reasons with 1 or more cesarean section scars.[80] Misoprostol, 400 μg, was administered to women up to 20 weeks of gestation and 200 μg for women greater than 20 weeks of gestation, vaginally or sublingually, every 6 hours up to 24 hours. The mean induction to abortion interval was 16.4 hours and was not statistically different between women with and without a prior cesarean delivery scar. There was no case of uterine rupture or scar dehiscence. No statistically significant differences were found in rates of incomplete abortion, blood loss, or sepsis.

Cervical Ripening and Induction of Labor With a Viable Fetus

Compared with placebo, misoprostol causes cervical ripening before induction with oxytocin.[81,82] When used for cervical ripening, misoprostol can be administered orally, sublingually, or vaginally, although there is more evidence for vaginal regimens.[83,84] A commonly used dose is 25 μg administered vaginally every 4 hours as needed, with a maximum dose of 150 μg.[85] Doses are withheld if contractions are more frequent than every 4 minutes. Electronic fetal heart rate monitoring is used to evaluate fetal status 20 minutes before administration and continued for 4 hours after each dose.

Misoprostol has also been shown to be effective for induction of labor with a viable fetus.[86,87] The Cochrane Pregnancy and Childbirth Group reviewed randomized trials comparing vaginal misoprostol with placebo, oxytocin, or prostaglandin E_2 for cervical ripening or induction of a viable fetus in the third trimester.[85] Primary outcomes included rate of vaginal delivery within 24 hours, incidence of uterine hyperstimulation with associated fetal heart rate changes, rate of cesarean delivery, and risk of serious adverse event in mother or fetus. Vaginal misoprostol was found to be

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Main Points

- Misoprostol is a prostaglandin E_1 analogue that causes cervical softening and dilation and uterine contractions. Routes of administration include oral, vaginal, rectal, buccal, and sublingual.
- Medication abortion with 200 mg of mifepristone and 800 μg of buccal or vaginal misoprostol is 95% to 98% effective with evidence-based regimens.
- Misoprostol is an effective cervical ripening agent prior to first-trimester surgical abortion. It is recommended especially for women between 12 and 14 weeks of gestation, adolescents, and for women in whom cervical dilation is expected to be difficult either due to patient factors or provider inexperience.
- Misoprostol for cervical ripening as a substitute for laminaria prior to second trimester dilation and evacuation is only recommended under 16 weeks of gestation.
- Misoprostol is an effective cervical ripening agent in premenopausal women prior to hysteroscopy. The greatest benefit is seen in nulliparous women and for operative hysteroscopy. Whether the routine use of misoprostol prior to hysteroscopy is beneficial is still unknown.
- Misoprostol for cervical ripening prior to gynecologic procedures in postmenopausal women has not been found to be effective.
- Misoprostol is an option for the management of early pregnancy failure and incomplete abortion in women who are hemodynamically stable without signs of infection. A single dose of 800 μg vaginally is typically used.
- Misoprostol is a proven induction agent in the second trimester for termination of pregnancy or fetal death. One regimen is 400 μg vaginally every 6 hours up to 48 hours.
- For cervical ripening and induction of labor for a viable fetus, 25 μg of vaginal misoprostol every 4 to 6 hours is recommended.
- Misoprostol has not been shown to be as effective as injectable uterotonics (oxytocin and methylergotomine) for the prevention and treatment of postpartum hemorrhage. However, it is a valid option when these are not available or fail.

more effective than prostaglandin E_2 or oxytocin for inducing vaginal delivery within 24 hours. However, uterine stimulation with associated fetal heart rate changes was more common in the group of women receiving misoprostol than in women receiving either oxytocin or prostaglandin E_2. Cesarean delivery rate data were conflicting with a trend toward decreased cesareans for failure to progress in labor and increased cesarean deliveries for fetal distress in the misoprostol group. There was no difference in serious neonatal or maternal mortality between women receiving misoprostol and women who received prostaglandin E_2 or oxytocin; however, most studies were underpowered for this assessment. Optimal dosing of misoprostol that will achieve effective induction without uterine hyperstimulation and resultant fetal heart rate changes has been the topic of many studies. As with cervical ripening, an effective dose of misoprostol without high rates of uterine hyperstimulation is 25 μg administered every 4 to 6 hours.[1,85]

Postpartum Hemorrhage

Misoprostol has been used both as prevention and treatment of postpartum hemorrhage secondary to its uterotonic properties. Several randomized, controlled trials[88-90] and a large, prospective, observational study[91] have examined the use of misoprostol as an agent for the prevention of postpartum hemorrhage. There are insufficient data to support the use of misoprostol as a primary preventive measure for postpartum hemorrhage when conventional injectable uterotonics (such as oxytocin and/or methylergotomine) are available as part of the management of the third stage of labor.[1,92] Misoprostol has also not yet been found to be better than oxytocin or ergotamine in well-controlled, randomized trials for the treatment of postpartum hemorrhage.[93] However, it remains an important option for treating postpartum hemorrhage when other agents are not available or fail. A descriptive study showed that 1000 μg of rectally administered misoprostol, when given to patients who failed to respond to oxytocin and ergotamine, controlled postpartum hemorrhage within 3 minutes.[94] However, further studies, with randomized designs, are needed.

Conclusions

Misoprostol has many applications in the practice of obstetrics and gynecology. Off-label use of approved medications is supported by the FDA as long as it is based on sound medical evidence. Researchers and providers must continue to work to further refine the indications for misoprostol in many areas. However, several indications are already supported by high-quality evidence. Given its low cost and ease of use, misoprostol has the potential to improve women's health worldwide. ■

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