Curr Obstet Gynecol Rep (2017) 6:100–108
DOI 10.1007/s13669-017-0202-6

FAMILY PLANNING (A BURKE, SECTION EDITOR)

Misoprostol in Abortion Care: Review and Update

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Published online: 29 April 2017

Abstract
Purpose of Review We seek to update readers on misoprostol use in abortion care. We discuss literature on misoprostol use in first trimester medication abortion, second trimester induction abortion, management of early pregnancy loss, and first and second trimester surgical abortion. We review publications investigating efficacy, acceptability, and safety of misoprostol doses, routes of administration, use with mifepristone and osmotic dilators, and timing in relation to mifepristone or surgery.
Recent Findings In 2016, the Food and Drug Administration approved updated labeling for medication abortion: mifepristone 200 mg oral followed in 24–48 h by misoprostol 800 mcg buccal through 70 days gestation. Intervals less than 24 h decrease efficacy. The addition of mifepristone to misoprostol for second trimester induction abortion decreases time from misoprostol to complete uterine evacuation. Misoprostol may be used alone or in combination with osmotic dilators or mifepristone for cervical preparation for surgical abortion. Routine cervical priming with misoprostol is not recommended in the first trimester. Same-day cervical preparation with misoprostol may be used from the late first trimester through 18–20 weeks, although additional mechanical dilation may be required. After 18–20 weeks, misoprostol may be used with overnight osmotic dilators, although mifepristone may be preferred to avoid misoprostol side effects and enhance ease of the surgical procedure.

Summary Misoprostol plays an indispensable role in abortion care and may be administered in doses of 400–800 mcg by oral, buccal, vaginal, and sublingual routes. More studies are needed to assess variations in dose and timing and to determine upper gestational age limits for same-day preparation.

Keywords Misoprostol · Abortion · Mifepristone · Cervical preparation · Cervical ripening

This article is part of the Topical Collection on *Family Planning*

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Introduction

Misoprostol, a prostaglandin E1 analogue, is approved by the Food and Drug Administration (FDA) for gastric ulcer prevention with long-term anti-inflammatory medication use. Misoprostol is widely used off-label in obstetric and gynecologic care and is included in the FDA-approved labeling of mifepristone for medication abortion. Misoprostol promotes increased uterine tone and contractility and causes cervical softening. In abortion care, misoprostol is used alone or in combination with mifepristone or methotrexate for medication abortion and alone or in combination with osmotic dilators to prepare the cervix for surgical abortion. Side effects associated with misoprostol include nausea, vomiting, diarrhea, abdominal cramping, and thermoregulatory effects (chills, low-grade temperature elevations); the intensity of these effects varies by dose and route of administration [1•].

Misoprostol may be administered by a variety of routes, including oral, buccal, sublingual, vaginal, and rectal. Before surgical abortion, misoprostol is administered in doses of 400 and 600 mcg vaginal or buccal for cervical priming. Before medication abortion, the dose varies depending on the route of administration (400 mcg with oral administration, 800 mcg with vaginal and buccal administration). Pharmacokinetic studies show differences by route of administration in amount

and timing of peak serum concentrations, total serum concentrations (measured as area under the curve), and uterine tone and contractility [2–6]. The vaginal route has a slower time to peak serum concentration and a higher area under the curve (AUC) compared with oral administration, as well as more prolonged and enhanced uterine contractility [2, 3]. Sublingual misoprostol exhibits a time to peak serum concentration similar to that of oral and results in the highest peak serum concentration of all routes, with a larger AUC than both vaginal and oral routes [4, 5]. Consistent with the finding of rapid and high absorption, women experience more side effects with sublingual misoprostol and find it less acceptable than buccal administration [5]. Although buccal administration produces lower serum levels than vaginal, uterine tone and contractility are similar. Rectal administration results in lower uterine tone and activity than other routes [6]. Routes of administration associated with prolonged duration of action (buccal and vaginal) are more effective than routes with smaller areas under the curve (oral and rectal) [7, 8].

In 2014, researchers published data from a large retrospective cohort of patients having medication abortion showing a decrease in serious infections and deaths from infection with a protocol change from vaginal to buccal misoprostol. This study demonstrated that medication abortion has a very low risk of serious infection and that buccal administration of misoprostol may reduce the risk of serious infection compared with vaginal [7–9]. However, the link between route of administration and infection is not conclusive, and providers continue to offer misoprostol by vaginal as well as other routes.

This article reviews the current evidence and recommendations for misoprostol dosing and routes in surgical and medication abortion care.

Misoprostol in First Trimester Medication Abortion

Updated FDA Labeling

The FDA initially approved mifepristone and misoprostol for outpatient medication abortion in 2000. The initial FDA-approved regimen, for use until 49 days gestation, was comprised of mifepristone 600 mg oral followed in 48 h by misoprostol 400 mcg oral [10] and had success rates of 92 to 97% [11–13]. Researchers have published multiple reports on alternatives to the initial FDA regimen, including a lower dose of mifepristone, different routes of misoprostol administration, increased gestational age, varied timing of misoprostol administration with respect to mifepristone, and home use of misoprostol and mifepristone [14–17, 18•, 19, 20]. Success rates of evidence-based alternative regimens were higher than those of the initial FDA-approved regimen [21]. Prescribing medications off-label is a common and accepted practice when supported by published medical evidence, and use of evidence-based regimens for medication abortion became standard of care [21]. In 2015, retrospective data collected on 13,373 patients in a large urban healthcare network who were prescribed mifepristone 200 mg oral followed in 24–48 h by misoprostol 800 mcg buccal demonstrated the efficacy of this previously published regimen through 63 days gestation with an overall success rate of completed abortion of 97.7% [22]. In 2016, the FDA approved updated labeling for mifepristone, bringing the federally approved regimen into alignment with evidence-based practice. The current FDA-approved regimen, for use through 70 days gestation, consists of mifepristone 200 mg oral followed in 24–48 h by misoprostol 800 mcg buccal [10] (Table 1).

Timing of Misoprostol in Medication Abortion

Current FDA labeling supports the practice used by most healthcare providers of giving misoprostol on the first visit, allowing women to take the medication at their convenience 24–48 h after the mifepristone. In 2015, researchers published a review of 20 medication abortion studies, including a total of 33,846 women through 70 days gestation. When they compared data from the six studies reporting a 24-h interval between mifepristone and buccal misoprostol and the 13 studies reporting a 24- to 48-h interval, the authors found that success rates were slightly lower with a 24-h interval (94.2% compared with 96.8%, $p < .001$). Lower success of the shorter misoprostol interval was found in both the earliest abortions of 49 or less days (96.8% compared with 98.2%, respectively, $p = 0.046$) and in abortions at 50–63 days (92.1% compared

Table 1 Improving access to medication abortion

Old labeling	New labeling
Use through 49 days gestation	Use through 70 days gestation
Day 1: mifepristone 600 mg (3 tablets) orally	Day 1: mifepristone 200 mg (1 tablet) orally
Day 3: misoprostol 400 mcg (2 tablets) orally at healthcare provider facility	Day 3: 24–48 h after mifepristone dose: misoprostol 800 mcg (4 tablets) buccally (placed in the cheek); home administration allowed
Post-treatment examination: patients return to provider 14 days after taking mifepristone	Post-treatment assessment: patients are assessed 7–14 days after taking mifepristone; not necessarily an in-person clinic visit
Prescriber: by or under the supervision of a physician who is authorized to prescribe the drug	Prescriber: by or under the supervision of a healthcare provider who is authorized to prescribe the drug

Chart recreated from information in Jones and Boonstra [23], with permission

with 96.3%, respectively, $p = 0.009$); of note, the authors found insufficient data to draw conclusions regarding misoprostol interval in the 64–70-day range due to less published data on later medication abortion [24••]. Another study of abortions up to 55 days compared misoprostol administration 48 h after mifepristone to 2 h after; 48 h after remained superior. Although a small study, all women in the 48-h arm completed termination within 48 h while only 76% of women in the 2-h arm achieved completion at 48 h ($p = 0.002$) [25]. Thus, while more data are needed regarding optimal timing especially at later gestations, evidence demonstrates that a greater than 24-h interval maximizes effectiveness.

Alternative Misoprostol Doses and Routes in Medication Abortion

Regimens of medication abortion outside of the USA demonstrate efficacy of protocols using misoprostol 400 mcg sublingual 24–48 h after mifepristone. The sublingual route has a higher peak plasma concentration and greater bioavailability. It thus allows for lower doses compared to the buccal route. The goal of reducing the misoprostol dose is to reduce price and side effects such as vomiting, fevers, and chills. While misoprostol is often inexpensive, prices vary and increase where availability is scarce [26]. Researchers conducted a prospective comparative open-label trial in six centers across four countries to determine effectiveness when extending the regimen using sublingual misoprostol to 70 days. A total of 703 cases between 57 and 70 days gestation were analyzed. Success rates did not differ significantly for the 57–63-day and the 64–70-day cohorts (94.8 and 91.9%, RR 0.79, 95% CI 0.61–1.04), nor did ongoing pregnancy rates (1.8 and 2.2%, RR 1.10, 95% CI 0.64–1.87) [27]. Using mifepristone 200 mg oral followed in 24 to 48 h by misoprostol 400 mcg sublingual is an acceptable alternative to the current FDA regimen for medication abortion up to 70 days gestation.

Doses and Routes of Misoprostol for Medication Abortion with Mifepristone Alternatives

Health Canada, Canada's analogue of the US FDA, approved the use of mifepristone in July 2015. Prior to approval, providers used methotrexate in conjunction with misoprostol as well as misoprostol alone for medication abortion. The standard dose of methotrexate for medication abortion is 50 mg oral or IM followed in 3 to 5 days by misoprostol 800 mcg administered vaginally or sublingually every 3 to 12 h until completion of the abortion. In a meta-analysis out of Canada, researchers found the efficacy of sublingual and vaginal misoprostol alone for medication abortion up to 63-day ranges from 78 to 84% and 83 to 85%, respectively [28]. The addition of methotrexate increases success rates to 82–98% [28]. Where available, the current FDA-approved regimen should be used in place of misoprostol alone or misoprostol and methotrexate.

Misoprostol for Early Pregnancy Loss

Misoprostol is used in a variety of doses and routes for management of early pregnancy loss (EPL). A recent randomized, prospective trial compared efficacy of vaginal and oral routes of administration among 100 women presenting with first trimester missed abortion. Participants were randomly assigned to receive misoprostol 400 mcg vaginally or orally every 6 h for a maximum of three doses. Success rates were higher with vaginal administration (92 versus 74%, $p = 0.03$), and mean time to expulsion was shorter (10.87 versus 13.24 h, $p = 0.003$) [29]. In addition to the vaginal route, many providers use misoprostol 800 mcg buccal in a single, or repeated as needed, dose for EPL management. Buccal administration can be useful if there is concern that vaginal misoprostol will be displaced by heavy bleeding. Further study is needed of various doses and routes of misoprostol for EPL management.

Misoprostol in Second Trimester Induction Abortion

Approximately 9% of pregnancy terminations take place in the second trimester, and most are performed surgically [30]. However, some women choose medication abortion in the second trimester to obtain an intact specimen for pathologic evaluation or to hold the fetus after expulsion, to avoid surgery, or due to a lack of local providers skilled in later surgical abortion.

Mifepristone in Combination with Misoprostol for Induction Abortion

Healthcare providers increasingly are using mifepristone for second trimester labor induction. As an anti-progesterone, mifepristone acts as a cervical priming agent. In a recent randomized, double-blinded trial of misoprostol 400 mcg buccal administration 24 h after placebo or mifepristone 200 mg oral, complete uterine evacuation at 48 h was achieved in 91.7% of women in the mifepristone group and 71.7% of women in the placebo group (RR 1.28, 95% CI 1.07–1.53). Mean time to completion was also significantly shorter in the combined group [31].

The ideal window for misoprostol administration after mifepristone for induction abortion may be 24 to 48 h. A randomized, double-blinded, placebo-controlled trial compared administration of mifepristone 200 mg oral simultaneously with or 24 h before initiating misoprostol 400 mcg buccal every 3 h. Women in the 24-h arm were more likely to complete abortion within 24 h of misoprostol administration (94.4 versus 85.0%, RR 1.11, 95% CI 1.05–1.18). Simultaneous dosing

resulted in less total time from initial clinical contact to complete abortion while the 24-h interval resulted in less total time from misoprostol administration [32•]. Since mifepristone may be administered in an outpatient setting 24 h before admission for misoprostol dosing, hospital admission time may be reduced with the 24-h interval between the two medications.

Practitioners use a variety of routes of misoprostol administration for second trimester medication abortion [33]. A recent placebo-controlled study of 268 women at 12–24 weeks gestation examined the efficacy of misoprostol 400 mcg sublingual and 400 mcg vaginal. Success rates did not differ significantly at 24 and 48 h nor did mean time to expulsion. Most patients preferred the sublingual route for convenience and comfort [34]. Another recent study randomized women, after they received mifepristone followed in 24 to 48 h by misoprostol 800 mcg vaginal, to receive subsequent doses of misoprostol 400 mcg by sublingual, vaginal, and oral routes. The vaginal and sublingual routes did not differ in time to completed abortion, and both were superior to the oral route [35].

In 2012, the International Federation of Gynecology and Obstetrics (FIGO) set forth recommendations for misoprostol for second trimester labor induction. The FIGO-recommended regimen is misoprostol 400 mcg sublingual every 3 h for a maximum of five doses, with a rest period of 12 h then restart after the fifth dose. A recent small retrospective study compared misoprostol 200 mcg vaginally every 4 h to the FIGO regimen and found no significant difference in time to abortion completion or total dose required ($p = 0.24$) [36]. Adding mifepristone when available to the FIGO regimen can expedite delivery. While the FIGO guidelines are useful, alternative regimens may be equally effective. One recent study of 120 women having second trimester labor induction terminations added mifepristone 24 to 48 h before misoprostol to the FIGO regimen, changed sublingual to buccal administration, and did not limit the number of misoprostol doses. The success rate for uterine evacuation was 99.2% within 18 h [37].

Mifepristone in combination with misoprostol increases the efficiency of second trimester abortion. More data are needed on the optimal route of administration. More data are needed as well regarding the risk of uterine rupture with misoprostol use for induction abortion in women with prior cesarean section. The risk of rupture in women with one cesarean section appears low and adjustments to dosing are not required, although some providers administer misoprostol in 200 mcg doses following an initial 400 mcg dose [33].

Misoprostol in Surgical Abortion

Preparation of the cervix before surgical abortion is recommended in the late first trimester and second trimester in order to reduce complications [38–40]. Misoprostol is the most commonly used pharmacologic agent for cervical priming [38, 41] and can be used either alone or as an adjunct to cervical dilators or mifepristone. In published studies, the dose, route, and interval of misoprostol vary; the most commonly reported regimen is 400 mcg vaginal over 3 to 4 h; the buccal route is also commonly mentioned [42]. Buccal administration may be as effective as vaginal, has similarly low side effects, and is more acceptable to patients and staff [38, 43]. The benefits of misoprostol for cervical priming must be weighed against the delay in timing of surgery and side effects experienced by patients, which include pain, chills, and gastrointestinal effects. Recent publications focus on use of misoprostol to promote same-day procedures in second trimester abortion (Table 2).

Misoprostol in First Trimester Surgical Abortion

In 2016, the Society of Family Planning (SFP) published updated guidelines on cervical dilation before first trimester abortion at less than 14 weeks. Based on level A (good and consistent) scientific evidence, the authors concluded that priming with misoprostol may decrease cervical lacerations and uterine perforations, both rare complications, as well as incomplete abortion; however, SFP does not recommend routine cervical priming for first trimester surgical abortion due to associated side effects and procedure delays in the absence of proven benefit. SFP recommends providers consider misoprostol for patients at increased risk of complications from mechanical cervical dilation, such as those at 12 to 14 weeks gestation, adolescents, and others with anticipated difficult dilation. When misoprostol is used for priming, SFP recommends one of the following approaches to route and timing: 400 mcg vaginally 3 to 4 h, orally 8 to 12 h, buccally 3 to 4 h, or sublingually 2 to 4 h preoperatively. Based on level B (limited or inconsistent) scientific evidence, SFP found that all routes of misoprostol administration are acceptable to women, although side effect severity is less with vaginal compared with oral and sublingual administration [38].

Prior to the publication of the SFP guidelines, researchers reported the results of a double-blinded trial in which women in the first trimester were randomized to four arms, vaginal or sublingual misoprostol administered at 1 or 3 h before abortion. The authors found greater baseline cervical dilation with the sublingual route at 1 h and comparable cervical dilation at 3 h for both routes. Although this demonstrates that cervical preparation may be enhanced with sublingual administration, the vaginal route was preferred by patients because of taste. Moreover, surgical duration did not differ by route or timing [44], which may be due to the fact that priming does not improve procedure duration in the first trimester. Also prior to the SFP updated guidelines, a WHO research group published the results of a multi-country trial in which participants at 12 weeks or less were randomized to misoprostol 400 mcg

Table 2 Recommendations for cervical preparation before surgical abortion

Gestational age (weeks)	Management recommendations
<12	No routine cervical preparation. Decision to prepare the cervix should be tailored to patient and provider risk factors.
12–14	Consider same-day cervical preparation with misoprostol alone or synthetic osmotic dilators alone for adolescents or when difficult cervical dilation is anticipated.
14–16	Same-day cervical preparation with misoprostol alone or synthetic osmotic dilators alone.
16–20	Cervical preparation with osmotic dilators alone, misoprostol alone, or in combination when difficult cervical dilation is anticipated. Overnight or same-day preparation at 16–18 weeks. Experienced D&E providers may consider same-day preparation at 18–20 weeks.
20–24	Cervical preparation with at least 1 day of overnight osmotic dilators. Adjuvant medication (either mifepristone at time of dilator placement or misoprostol on day of D&E) may be beneficial.

vaginal or placebo 3 h before dilation and aspiration. The incidence of all complications was low for both groups (2% in the misoprostol group versus 3% in the placebo group, RR 0.68, 95% CI 0.47–0.96); the difference in complications was due to the difference in incidence of incomplete abortion, most of which required reaspiration [<1% (misoprostol) versus 2% (placebo), RR 0.29, 95% CI 0.16–0.53]. Participants who received misoprostol had significantly more pain and bleeding [45]. The authors of the SFP guidelines published a letter to the editor noting that the small reduction in the risk of uterine reaspirations in the WHO study did not justify routine use of misoprostol because of added wait time and symptoms; they argued that the decision to use misoprostol should be tailored to individual patient and provider risk factors [1•].

Misoprostol in Late First and Early Second Trimester (<15 Weeks) Surgical Abortion

Researchers have examined various approaches to cervical preparation before abortion in the late first and early second trimester. In 2013, investigators published results of a trial in which participants were randomized to misoprostol 400 mcg buccal or synthetic osmotic cervical dilators for same-day cervical priming 3 to 4 h before surgical abortion at 12 to 15 weeks. They found no significant difference in preoperative dilation, procedure time, procedure pain, complications, and participants' satisfaction, although misoprostol patients had more pain during priming [46]. For late first trimester and early second trimester surgical abortion, misoprostol may be preferred to osmotic dilators because administration eliminates the need for a preoperative pelvic procedure.

A recent study measured blood loss and other operative outcomes in patients at 12 to 14 weeks randomized to mifepristone alone 36 h before abortion, misoprostol 400 mcg oral alone 3 h before abortion, or both combined. The researchers found significantly less blood loss, shorter procedure duration (5 ± 2 min in the combination group, 7 ± 5 min misoprostol group, and 7 ± 3 min mifepristone group, $p = 0.001$), and fewer cases of moderate hemorrhage (managed with uterotonics or reaspiration) in the combination group [47]. However, the absolute differences in these outcomes were small, and benefits must be weighed against the cost of mifepristone and the additional time spent preparing the patient for the procedure.

Cervical priming is recommended in the second trimester and should be considered at 12 to 14 weeks gestation for adolescents and others with anticipated difficult dilation [38]. Same-day priming with misoprostol is an acceptable and effective alternative to more time-consuming approaches to cervical preparation such as placement of osmotic dilators and mifepristone, which is administered at least 24 h preoperatively.

Misoprostol in Second Trimester Surgical Abortion

Misoprostol, mifepristone, and osmotic dilators may be used alone or in combination for cervical priming before second trimester surgical abortion by dilation and evacuation (D&E) to reduce the risk of complications such as cervical lacerations and uterine perforations with the passage of instruments and tissue during surgery. SFP guidelines published in 2008 on cervical preparation for abortion from 20 to 24 weeks recommend at least 1 day of cervical preparation and, based on level B evidence, recommend misoprostol 400 mcg buccal as an adjuvant to osmotic dilators to augment cervical dilation and decrease the need for additional mechanical dilation before D&E [48]. In 2014, SFP published guidelines on cervical preparation for second trimester abortion before 20 weeks gestation. Based on level A evidence, the authors concluded that cervical preparation decreases the risk of cervical injury. Misoprostol results in less preoperative cervical dilation than osmotic dilators; however, based on level B evidence, the increased risk of inadequate dilation with misoprostol does not increase the risk of uterine perforation or cervical laceration. SFP recommends against the routine use of misoprostol in combination with osmotic dilators at less than 16 weeks and advises that misoprostol may be used for priming in women with past cesarean section. Combined use of misoprostol and mifepristone may increase the risk of spontaneous abortion before D&E. Based on level C (consensus and expert opinion) evidence, SFP advises that only experienced providers should

consider same-day procedures with either serial misoprostol or misoprostol plus osmotic dilators for abortion after 18 weeks [39••].

Misoprostol for Same-Day Cervical Preparation Before Second Trimester Abortion

Several new publications support the use of same-day cervical preparation with misoprostol, either alone or in combination with synthetic osmotic dilators, for D&E through 18–20 weeks gestation [39••, 49, 50]. Most patients with same-day priming will require mechanical cervical dilation at the start of D&E [51]. Women prefer same-day cervical preparation [49]. The benefits to patients, in particular the shortened preparation time, must be weighed against the greater level of skill required to perform D&E with same-day priming, especially at later gestations. For physicians with experience in mechanical dilation, same-day cervical preparation with misoprostol may be used through 18–20 weeks.

A recent study randomized 156 women at 13–19 weeks gestation to overnight laminaria or misoprostol 400 mcg buccal in one to two doses at least 3 h before D&E. Procedure time, pain, patient satisfaction, and complication rates did not differ significantly between groups. Women in the misoprostol group were more likely to require mechanical dilation [51]. In 2016, researchers published results of a randomized placebo-controlled study in which 29 patients at 16–21 weeks received synthetic osmotic cervical dilators 4 h before D&E either alone or with adjuvant misoprostol 400 mcg buccal for 3 h. The study was halted early due to adverse events in the placebo group, primarily with gestational age over 19 weeks. Although the study was underpowered for complications, the findings warrant caution with use of same-day synthetic osmotic dilators alone for cervical preparation before D&E at greater than 19 weeks [49]. Adjunctive misoprostol is recommended for these cases. In 2016, investigators published results of a study in which 96 women at 14 to 19 weeks were randomized to mifepristone 200 mg oral or placebo, immediately followed by misoprostol 400 mcg vaginally 4 to 6 h before D&E. They found no statistically significant difference in initial cervical dilation or procedure time and no complications in either group [52].

Misoprostol for Adjuvant Cervical Preparation Before Later Second Trimester Abortion

Adequate cervical preparation is particularly important at later gestations in order to reduce the risk of complications. Recent publications on later abortion focus on the use of adjuvant mifepristone and misoprostol with overnight osmotic dilators. Because complications in abortion are rare and thus difficult to study prospectively, publications focus on operative time, cervical dilation, procedural difficulty, and patient satisfaction to assess the benefits of various regimens for cervical preparation.

A recent double-blinded, placebo-controlled trial randomized 196 patients at 21–23 weeks gestation to overnight laminaria and either misoprostol 400 mcg buccal or placebo 3–4 h before D&E. Mean procedure duration was slightly less and cervical dilation slightly greater with the addition of misoprostol. However, patients experienced significantly more pain with misoprostol, and physicians did not feel it enhanced ease of the procedure [53].

In 2015, researchers published the results of a multi-center double-blinded randomized placebo-controlled trial comparing three regimens for cervical preparation before D&E at 16–23 6/7 weeks. Three hundred participants were randomized to overnight osmotic dilators alone, overnight dilators plus misoprostol 400 mcg buccal 3 h preoperatively, and overnight dilators plus mifepristone 200 mg oral administered with dilator placement. Outcomes were compared for two separate cohorts: 16–18 6/7 weeks and 19–23 6/7 weeks. The primary outcome of operative time (first instrument in to last out of the uterus) did not differ by treatment group for either cohort; however, other findings support the use of adjuvant medications, in particular mifepristone, especially for later gestations. With mifepristone, total procedure time (speculum placement to last operative intervention) was shorter and physicians rated procedures easier than with dilators alone. Misoprostol resulted in greater initial cervical dilation in the earlier cohort compared with dilators alone but was associated with significantly more pain, fever, and chills. The study, which was not powered to compare incidence of complications, found 10% complications with dilators alone (95% CI 4.2–16.0), 2% with adjuvant misoprostol (95% CI 0–4.7), and 2% with adjuvant mifepristone (95% CI 0–4.8) [54•].

At later gestations, adjuvant medications may increase the ease of D&E and thus may decrease complications. Decisions about routine use of adjuvant medications should be tailored to the provider, patient, and setting and should take into account provider skill and experience, and anticipated difficulty of D&E due to gestational age, patient age, and other patient factors. Mifepristone may be preferred by providers and more acceptable to patients than misoprostol.

Conclusions

Misoprostol is an indispensable medication for both medication and surgical abortion care. In recent years, we have seen several important new developments in the use of misoprostol in abortion.

The FDA approved updated labeling for mifepristone, aligning the federally approved regimen for medication abortion with evidence-based practice. The current FDA-approved regimen is less expensive, more acceptable to patients, and

more effective than the previously approved regimen and thus can be used to a higher gestation. The current regimen, for use through 70 days gestation, includes a lower dose of mifepristone, decreased number of health center visits, use of a more effective and well-tolerated misoprostol dose and route of administration, and flexible timing and setting of follow-up [10].

The Society of Family Planning (SFP) published guidelines on the utility of osmotic dilators, misoprostol, and other agents for cervical preparation before first and second trimester surgical abortion [39••, 55]. The guidelines recommend against routine use of cervical priming in the first trimester and advise tailoring priming to patient and provider risk factors. The guidelines support same-day cervical preparation, including regimens with misoprostol alone or as an adjunct to synthetic osmotic cervical dilators, from the late first trimester, when indicated, through 18 weeks [39••]. In recent years, investigators published several studies investigating same-day cervical preparation [49, 50]. Same-day preparation is preferred by patients and may decrease barriers to abortion care. Same-day preparation may be accomplished with misoprostol alone or in combination with synthetic dilators from the late second trimester through 18–20 weeks gestation. Because mechanical dilation is usually necessary with same-day preparation, the surgical proficiency of providers is increasingly important with same-day preparation at advanced gestations [39••]. More studies are needed to determine the upper gestational age limit for same-day preparation.

In published regimens, there is significant variation in dose and route of administration of misoprostol for use in induction abortion and for cervical preparation before surgical abortion. Buccal and vaginal administration balance high efficacy with a lower incidence and severity of side effects [6, 38]. The buccal route may be more acceptable to both patients and staff when compared to vaginal [6, 43]. More studies are needed to assess variations in dose and timing of misoprostol administration. The current recommendation by SFP is to administer 400 mcg 3 to 4 h prior to surgical abortion [39••]. However, some providers use higher misoprostol doses for shorter durations, which may improve preoperative wait times and workflow.

Misoprostol enhances uterine tone and contractility, which may displace fetal parts into the lower uterine segment. Moreover, the increased tone may lead to less blood loss with abortion. The effect of misoprostol on blood loss with surgical abortion has not been well studied. Additionally, the increase in uterine tone and cervical displacement of parts may affect the surgical approach to uterine evacuation, especially in cases of suboptimal cervical dilation; the effect on ease of procedure has not been well studied.

Researchers published studies in recent years on the use of mifepristone in combination with misoprostol or compared to misoprostol for abortion care. Recent publications support using mifepristone with misoprostol to increase the efficiency of second trimester medication abortion [39••, 48]. In surgical abortion in the late second trimester, mifepristone administered at the time of placement of overnight dilators was found to decrease procedure time and increase ease of procedure and was not associated with unpleasant misoprostol side effects such as nausea, pain, and chills [1•]. More studies are needed on the combined use of mifepristone and misoprostol for cervical preparation before surgical abortion at advanced gestations and in patients with risk factors for difficult cervical dilation (Table 2).

Compliance with Ethical Standards

Conflict of Interest Geetha Fink, Sharon Gerber, and Gillian Dean declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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