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Clinical Guidelines

Interruption of nonviable pregnancies of 24–28 weeks' gestation using medical methods

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Abstract

The need to interrupt a pregnancy between 24 and 28 weeks of gestation is uncommon and is typically due to fetal demise or lethal anomalies. Nonetheless, treatment options become more limited at these gestations, when access to surgical methods may not be available in many circumstances. The efficacy of misoprostol with or without mifepristone has been well studied in the first and earlier second trimesters of pregnancy, but its use beyond 24 weeks' gestation is less well described. This document attempts to synthesize the existing evidence for the use of misoprostol with or without mifepristone to induce labor for nonviable pregnancies at gestations of 24–28 weeks. The composite evidence suggests that a regimen combining mifepristone and misoprostol may shorten the time to expulsion, though the overall success rates are similar to those seen with misoprostol-only regimens.

Keywords: Abortion; Pregnancy termination; Labor termination; Labor induction; Second-trimester abortion; Third-trimester abortion; Midtrimester; Medical abortion: induced abortion; Misoprostol; Mifepristone; Fetal demise; Intrauterine fetal death; Fetal anomaly

Background

The goal of these guidelines is to provide clinical recommendations for inducing labor at gestations of 24–28 weeks, focusing on regimens that utilize mifepristone and misoprostol. Interruption of pregnancy at this gestational age is usually due to special circumstances, such as fetal demise or lethal fetal anomalies. In recent years, the use of misoprostol, alone or in combination with mifepristone, for these indications has increased due to the availability, safety and efficacy of these medications.

Misoprostol and mifepristone

The prostaglandin E1 analogues have emerged as essential agents in creating uterine contractility in an effort to cause pregnancy expulsion at almost any gestational age. Misoprostol has several advantages over other prostaglandin analogues [1]. Available in tablet form, it is stable at room temperature (20°C) when packaged properly, is inexpensive and can be administered via several mucosal routes (oral, vaginal, buccal and sublingual).

A progesterone receptor antagonist, mifepristone, is often used to prime the uterus and cervix prior to the use of a prostaglandin analogue for pregnancy expulsion in the first and second trimester of pregnancy [2,3]. The addition of mifepristone has been shown to increase the overall success rate of the regimen and may shorten the time to expulsion once uterotonics are initiated. In studies of first- and second-trimester abortion (12–28 weeks), a combination of mifepristone with misoprostol (mifepristone–misoprostol) appears to be the most effective regimen [2–4]. Unfortunately, many of these studies included very few pregnancies with a gestation of more than 20 weeks. Moreover, no standard protocols exist delineating the optimal regimen for inducing labor at 24–28 weeks' gestation.

Limitations of this review

Choice of studies: We intentionally did not limit this review to randomized controlled trials (RCTs) (see Search Strategy). While such studies reliably provide high-quality data, there are few published RCTs appropriate for inclusion in this review. Further, most of the RCTs did not adequately describe their randomization procedures. We included prospective and retrospective studies with acknowledgment of their limitations but also with the recognition that the results of such research can be clinically useful.

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Any review of the evidence on this topic has limitations, as there are very few studies focused specifically on 24–28 weeks of gestational age.

- Indication and gestational age: Most published studies focused on either medication abortion in the second trimester or labor induction in the third trimester. Gestational age range among included studies varied widely, but studies were included only if they contained data on pregnancies of 24–28 weeks.
- Procedure length: No consensus exists regarding how to define procedure length. In keeping with previously published Society of Family Planning (SFP) guidelines [5], this document considers the procedure time to be the interval between initiation of uterotonics (e.g., misoprostol) and fetal expulsion. Although time is typically a nonparametric assessment, we incorporated data from studies that also reported means.
- Outcome success: Studies varied in their definition of success, from complete expulsion by the intended medical regimen (e.g., without the need for surgical intervention) to a specific time frame, most often 24 or 48 h. We chose to focus on the most commonly used definition, expulsion of the fetus by the intended medical regimen, though we included other reported outcomes.

Choice of terminology

This guideline is focused on the management of nonviable fetuses of 24–28 weeks' gestation and will utilize terminology specific to this situation, including interruption of pregnancy, induction and expulsion.

Clinical questions and recommendations

What is the evidence for indicated interruption of pregnancy at 24–28 weeks using a misoprostol-only regimen?

Eleven studies of misoprostol-only regimens were identified that included pregnancies with a gestational age of 24–28 weeks (Table 1). Seven of these were reported to be RCTs, but the randomization schemes were not well characterized. Five studies included only pregnancies complicated by intrauterine fetal demise (IUFD) [6–10]. Misoprostol doses and routes varied, ranging from 50 to 400 mcg, dosed orally or vaginally, every 3–12 h [6–12]. Comparison groups generally were made up of women who received other prostaglandins or uterotonic medications [7,9–12]. Oxytocin was sometimes used as an adjunct to other methods [8–11].

The remaining four misoprostol-only studies were retrospective and focused on interruption of an "abnormal" pregnancy [13,14] or in pregnancies complicated by IUFD [13–16]. Comparison groups included laminaria tents [14], other prostaglandins [13,15] and mifepristone–misoprostol [15,16]. Misoprostol doses varied from 25 to 600 mcg, and three of the four studies used vaginal routes and a 12–h dosing regimen [13–15] (Table 1).

The heterogeneity of these studies does not allow for a meta-analysis. A summary of the main outcomes is shown in Table 1. These include a mean or median time to expulsion of 10–20 h and a 24-h success rate of 62–100%. All doses of misoprostol were effective; the highest doses did not appear to confer a clear benefit, either in time to expulsion or in success of the regimen at 24 or 48 h.

The more important factor for expulsion time and success rate was the dosing interval. Longer times to expulsion and lower expulsion rates were associated with the longest misoprostol dosing intervals [6,13–15]. Studies with dosing intervals of every 12 h reported 24-h completion rates of about 70%, and expulsion times of 16–20 h (Table 1). In contrast, misoprostol dosing every 4 h conferred expulsion times of 10–15 h. The type of case may also be important, with data from some studies suggesting more rapid expulsion for demised fetuses.

Route of dosing may also be important, but conclusions are limited by lack of data, as most studies used vaginal dosing. One study did directly compare oral and vaginal regimens at similar doses [8] and found a slightly longer time to expulsion in women receiving oral misoprostol. No studies utilizing sublingual or buccal administration of misoprostol were found, although at least one study using buccal misoprostol is ongoing.

Based on the study outcomes summarized in Table 1, a dosing regimen of vaginal misoprostol 100 mcg or 200 mcg given every 4 h is associated with a 24-h expulsion rate of 84–100%, with mean or median expulsion times of 10–14 h [6–8,10,11]. Few study subjects required additional uterotonic agents (addressed later in the review). Higher doses (400 mcg every 4 h) were similarly effective, and thus, a higher dose appears unnecessary. More data are needed to conclusively determine whether a difference in success rate exists between "low" (less than 400 mcg) and "high" (400 mcg or greater) doses.

The summarized studies had several limitations. Notably, there was broad heterogeneity in regimens including dosage, route and dosing interval of misoprostol and the use of adjunctive agents like oxytocin. Finally, as discussed earlier, most studies did not limit the gestational age to 24–28 weeks but, instead, incorporated these within a larger gestational age range.

What is the evidence for indicated interruption of pregnancy at 24–28 weeks using a mifepristone–misoprostol regimen?

Seven studies used a mifepristone–misoprostol regimen and included pregnancies at 24–28 weeks' gestational age (Table 2). There were no RCTs; three of these studies were prospective [17–19], and four were retrospective [15,16,20,21]. The mifepristone dose was either 200 mg or 600 mg. The interval between mifepristone and misoprostol

Table 1
Summary of misoprostol-only regimen studies

Author and year	n[a]	Mean or median* EGA (weeks)	Indication	Misoprostol			Outcomes			Other
				Dose (mcg)	Route	Interval	Time to expulsion (h) (mean±SD or *median, range)	Success rate (%)		
								24 h	48 h	
Prospective studies										
Chittacharoen, 2003 [6]	80	23.8	IUFD	400	Oral	4 h	13.9±5.6	92.5	100	For GA 23–28 weeks:, expulsion times were:
		22.7		200	Vaginal	12 h	18.9±10.4	67.5	100	Oral route: 14.3 h; vaginal route: 20.5 h (p=.027)
Eng, 1997 [7]	25	18.6	IUFD	200	Vaginal	3 h	Not given	84	–	Success rate at 24 h for GA 17–26 weeks: 100% The majority aborted within 12 h
Fadalla, 2004 [8]	70	21.6	IUFD	100	Oral	4 h	14.9±3.4	Not given	–	More women in the oral group received oxytocin
		25.5		100	Vaginal	4 h	10.8±2.8	Not given	–	(31% vs. 11%, p=.04) and required surgical intervention for the placenta (26% vs. 6%, p=.02)
Makhlouf, 2003 [11]	50	23.3	IUFD and anomalies	100	Vaginal	4 h	10.6	100	–	14% of women received oxytocin (based on contraction frequency)
Nakintu, 2001 [9]	60	18–40 (range)	IUFD	50+	Vaginal	6 h	12.4	Not given	–	Escalating misoprostol dosing (first dose 50 mcg, doubled every 6 h) versus "titrated" oxytocin. Success rate for GA 23–28 weeks: misoprostol group:~15 h; oxytocin group: 25 h
Van Mensel, 2009 [10]	70	20*	IUFD	400	Vaginal	4 h	10.4* (4.5–22.0)	91.4	98.6	Misoprostol doses dependent on GA: 400 mcg before 26 weeks and 100 mcg after 26 weeks.
				100	Vaginal	4 h				Only 10 pregnancies were between 23- and 28-week GA
Yapar, 1996 [12]	49	20	IUFD and anomalies	200	Vaginal	12 h	24±22.2	74.3	74.6	Misoprostol given up to 3 doses then followed by oxytocin if needed (used in 40% of misoprostol group)
Retrospective studies										
de Heus, 2003 [15]	47	24	IUFD	100	Vaginal	12 h	16.5*	70	90	Authors reported GA <20 weeks versus >20 weeks had no effect on time to expulsion
Mendilcioglu, 2002 [13]	41	23.1	IUFD and anomalies	400/600	Oral/ Vaginal	12 h	20.3±10.3	83 (12 h)	–	The 600-mcg dosing regimen was sometimes combined with a 400-mcg oral loading dose. Most subjects also received oxytocin.
		23.5	IUFD and anomalies	600	Vaginal	12 h	17.3±10.9	73 (12 h)	–	
Thornburg, 2009 [14]	43	22.9	IUFD and anomalies	200	Vaginal	12 h	16.4* (6.8–40) 20.6*(4.3–69)	62.5 63.2	100	Authors reported median 16.4 h to expulsion for group without laminaria, and 20.6h in group with laminaria
Vayrynen, 2007 [16]	130	30.4	IUFD	25–400	Vaginal	4 h	13.3* (2.1–97)	Not given	–	Combined varied regimens of misoprostol dosing to report composite outcomes

GA = gestational age. Induction-to-expulsion time refers to time after first dose of misoprostol. When not listed in table, SD or range was not reported.

Signifies that the number represented below is a median and not a mean.

[a] n=number of women in study who received misoprostol (not necessarily 24 weeks).

Table 2
Summary of mifepristone–misoprostol regimen studies

Author and year	n[a]	Mean or median* (EGA (weeks)	Indication	Dose regimen				Induction-to-expulsion time in hours (mean or *median)	Expulsion rate (%, 24 h)	Other
				Mifepristone dose and (pre-misoprostol timing)	Misoprostol					
					Dose (mcg)	Route	Interval			
Prospective studies										
Fairley, 2004 [17]	49	28*	IUFD	200 mg (36–48 h)	400	Oral then vaginal	4 h	7* (1.5–29.5)	–	Authors noted higher incidence of
		31*			50	Vaginal	3 h	10.2* (1.5–20)	–	Gastrointestinal side effects in first group
Jannet, 1996 [18]	106	22.1	IUFD and anomalies	600 mg (24 h)	400	Oral	6 h	12.5±7.5	–	Mean time to expulsion: IUFD: 9.6h, and 13.6 h for live fetuses ($p<.05$)
Wagaarachchi, 2002 [19]	96	32.4*	IUFD and anomalies	200 mg (24–48 h)	200 (24–34 weeks) 100 (>34 weeks)	Vaginal Oral	3 h	8.5* (0.5–75.9)	87.5	Definition of success included expulsion of both fetus and placenta
Retrospective studies										
de Heus, 2004 [14]	95	20.6	IUFD and anomalies	200 mg (2 days)	600 then 400	Vaginal	3 h	13.0*	88	Comparator group received sulprostone (regimen determined by date of hospital protocol change)
Mazouni, 2006 [20]	252	21.1	IUFD and anomalies	600 mg (36 h)	200	Vaginal	3 h	8.5* (3–114)	–	All patients had prior uterine scar.
		23.3			400	Vaginal	3 h	9* (1.3–124)	–	
Mazouni, 2009 [21]	174	24	Multiple indications	600 mg (36 h)	400	Vaginal	3 h	12.7 (No laminaria) 9* (laminaria)	91.2	In laminaria group, laminaria were placed 24 h after mifepristone
Vayrynen, 2007 [16]	130	32.2*	IUFD	200 mg (Variable timing, median: 19 h)	25–400	Vaginal	4 h	12.8* (3.2–126)		When stratified by 5-week GA intervals, induction time decreased with advancing GA

Induction-to-expulsion time refers to time after first dose of misoprostol. When not listed in table, SD or range was not reported.

Signifies that the number represented below is a median and not a mean.

[a] n=number of women in study who received misoprostol (not necessarily 24–28 weeks).

was usually 24 to 48 h with the one exception reporting varying intervals between mifepristone and the first misoprostol dose [16]. The amount of misoprostol was even more varied in these studies than in the misoprostol-only studies with doses as low as 25 mcg. Misoprostol was given orally [19], vaginally [15,16,20,21] or through both routes [17,19]. No published studies were found that utilized a sublingual or buccal route of misoprostol administration.

With the large variation in misoprostol doses following mifepristone, it is difficult to identify a single optimal misoprostol dosing regimen. Mean or median expulsion times ranged from 7 to 13 h, with 24-h completion rates of >85% (Table 2). Results appear similar whether 200 mg or 600 mg of mifepristone was used. The highest misoprostol doses did not always correlate with shorter expulsion times. One study that compared different misoprostol doses found similar results with doses of 200 mcg and 400 mcg [20]. Other studies also suggest that misoprostol doses of 200 mcg or 400 mcg every 3 to 4 h are associated with similar expulsion times (Table 2). Again, dosing interval may be at least as important as dose.

Does mifepristone shorten expulsion times when added to misoprostol?

Generally, mean and median expulsion times in studies of mifepristone–misoprostol seem shorter than those reported for misoprostol-only regimens. However, only two retrospective studies directly compare these regimens, and they differ in when mifepristone was used [15,16]. One used mifepristone only for live anomalous fetuses, not for IUFDs [15], whereas the other reported routine use of mifepristone after 2001, when institutional practice patterns changed [16]. In a letter to the editor, a group of authors recently reported that they often use mifepristone 36 h before misoprostol (200 mcg every 3 or 6 h) to induce expulsion in nonviable pregnancies in the second and third trimester [22]. They found that the time to expulsion with this regimen was significantly shorter (p=.04) than with misoprostol alone. No definitive RCTs exist to guide us in this gestational age range, but data suggest that mifepristone shortens expulsion time and increases success rates for pregnancy interruption at earlier gestational ages.

What are the reported complications of these regimens?

Regimens using misoprostol alone or in combination with mifepristone appear quite safe, with few reported serious complications.

Hemorrhage

Hemorrhage necessitating intervention was rare, but most studies were either underpowered for this outcome or did not report any data. One prospective study reported that about 20% of women who received misoprostol had blood loss >500 cc, with one woman requiring transfusion [10]. Two mifepristone–misoprostol studies, one of which was retrospective, reported a hemorrhage (>1000 cc) rate greater than 10%, though the gestational ages at which these cases occurred were not specified [16,17]. Other studies reported a much lower incidence or even absence of bleeding complications [6,7,9,11,12].

Retained placenta

Rates of retained placenta were not universally reported but when listed were 0–8% [11,14]. The threshold to intervene for a placenta varied across studies and was often dependent on institutional practice patterns.

Uterine rupture or dehiscence

Addressed separately (section 2.6).

What are the reported side effects of these regimens?

The side effects reported in studies are consistent with what we have come to expect from the use of misoprostol, including pain, gastrointestinal symptoms and fever. Studies differed greatly in the reporting of and definitions of side effects. Gastrointestinal side effects may have been reported as a composite event or as the individual symptoms of nausea, vomiting and diarrhea. Combined regimens had rates of side effects fairly similar to those of misoprostol-only regimens:

- Incidence of nausea and vomiting ranged from 2.5% to 34% [6,7,10,11].
- Frequency of diarrhea was 10% or lower, if it occurred [6,10,11]. Oral misoprostol regimens at higher doses were associated with higher incidence of diarrhea [6].
- Noninfectious fever/hyperthermia was reported at frequencies of 10–30% [6,7,10,11].

Should the dosing regimen or interval vary in cases in which there is a prior uterine incision?

Many providers express concern about whether it is safe to provide misoprostol to a woman with a uterine scar. While its use is contraindicated in term labor induction, studies have documented its safe use for first- and second-trimester abortion [23,24]. In our review, some studies excluded women with prior uterine surgery, while others included women with scarred uteri in proportions of up to 14% of the study population [9,10,12,17,18,20]. No cases of uterine rupture in women with prior uterine incision were reported in studies of misoprostol-only regimens [9,10,15,16]. In addition, success of the regimen and overall morbidity were similar for women with and without prior uterine incision.

Single cases of uterine rupture or dehiscence were reported in two of the mifepristone–misoprostol studies [15,20]; one, at 24 weeks, used a misoprostol regimen of 200 mcg every 3 h [20], and the other (unclear gestational age) used a regimen of 600 mcg orally/400 mcg vaginally every 3 h [15]. Each case occurred in a woman with a prior uterine scar. Other studies using a combined regimen reported no incidence of uterine rupture in scarred or unscarred uteri [13,14,16–19,21,25].

Existing data are limited by small sample sizes, variability in regimens and, often, a retrospective study design. Based on what results are available, use of misoprostol with or without mifepristone for women with prior uterine scar appears to be safe at 24–28 weeks of gestational age. Prior cesarean section or uterine scar need not be a contraindication for interruption of pregnancy at this gestational age.

One study directly compared expulsion outcomes in women with and without a prior uterine scar [20]. In this study, women presenting for termination between 15 and 34 weeks' gestation were enrolled. Women with a prior uterine scar received 600 mg of mifepristone, followed 36–48 h later by 200 mcg of misoprostol vaginally every 3 h. Women with an unscarred uterus received the same mifepristone treatment but received 400 mcg of misoprostol vaginally every 3 h. Expulsion outcomes were similar in the two groups, with median expulsion times of 8.5 and 9 h, and 12-h completion rates of 66% and 68%, respectively [20].

Is the outcome/success of the induction affected by fetal status?

Seven misoprostol-only studies restricted enrollment to cases of IUFD [6–10,15,16], and an additional four included pregnancies with live anomalous fetuses as well [11–14]. While mean expulsion times seemed slightly shorter for demised fetuses, the confidence intervals overlapped heavily. Only one study reported group-specific results for demised and live fetuses, but authors did not perform statistical comparisons [14].

One prospective mifepristone–misoprostol study included both live anomalous fetuses and IUFD [18]. The authors found that time to expulsion was significantly shorter in the IUFD group (9.6 h vs. 13.6 h, $p<.05$).

A review article published in 2007 evaluated the use of misoprostol for IUFD [26]. Authors cited two case series that suggest that expulsion times are shorter and cumulative misoprostol doses lower for IUFD in the second and third trimesters [27,28]. Currently, there are insufficient data to conclude that IUFD decreases time to expulsion or should be managed with a different misoprostol regimen.

With one exception [20], studies that included anomalous fetuses did not report their protocols for induced fetal demise (i.e., feticidal agents). Many institutions and jurisdictions have laws or policies requiring these procedures prior to pregnancy termination at specified gestational ages. SFP Guideline #20101, "Induction of fetal demise before abortion," provides further guidance on this topic [29].

Is the outcome affected by rupture of membranes?

Data are too scant to determine whether premature rupture of membranes (PROM) affects the outcome of induction for nonviable pregnancy between 24 and 28 weeks' gestational age. Of the studies we reviewed, four explicitly included women with PROM [9,10,12,15]. Only one misoprostol-only study reported outcomes by group. While the authors found a mean time to expulsion of 14.7 h (intact membranes) versus 8.5 h (PROM), they did not perform a statistical comparison [9]. Other studies grouped intact membranes and PROM when reporting outcomes, as numbers of PROM were too small to report separately.

Is there any role for mechanical dilators?

One retrospective study addressed the question of whether the addition of mechanical dilators (laminaria) shortens the time to expulsion when added to a mifepristone–misoprostol regimen [21]. Mean gestational age was 30 weeks, and indications were mostly fetal anomalies or preterm membrane rupture. Women received 600 mg of mifepristone 36 h prior to 400 mcg of misoprostol administered vaginally every 3 h (up to 3 doses). At 24 h following the mifepristone dosing, but before initiation of misoprostol, one group received laminaria, and the other received nothing. Median time to expulsion after the first misoprostol dose was 6.4 h in the laminaria group and 9.0 h in the no-laminaria group ($p=.01$). Another study found no decrease in time to expulsion when laminaria were added to a misoprostol-only regimen [14].

Is there any role for additional uterotonics after misoprostol administration?

Successful expulsion was often accomplished without the need for adjunctive medications [6,7,9,15,17]. However, the use of additional agents was difficult to interpret, since reasons for use were varied or not explained. Oxytocin/Syntocinon was the most commonly used adjunctive uterotonic (Table 3). One study reported that three women who did not deliver after 24 h of misoprostol received sulprostone rather than oxytocin [18].

How many times can you repeat the regimen to achieve success?

Although success rates are extremely high with both misoprostol-only and mifepristone–misoprostol regimens, failures can occur. There are no published studies that address the issue of how long to continue the regimen, but many studies arbitrarily choose a 24- or 48-h end point. These end points were not chosen on the basis of patient safety issues. Unpublished international experience has demonstrated that for the rare refractory cases at 48 h, successful expulsion can be achieved by continuing the regimen up to 72 h (personal communication, Ipas). Anecdotally, some clinicians recommend a medication "holiday," artificial rupture of membranes or a change in the type of uterotonic

Table 3
Studies reporting use of oxytocin after misoprostol

Author	Misoprostol regimen	% of women in misoprostol group who received additional augmentation
Fadalla, 2004 [8]	100 mcg every 4 h (oral or vaginal)	31% (oral); 11.4% (vaginal)
Mendilcioglu, 2002 [13]	400 mcg oral initial dose, then 600 mcg vaginal every 12 h	Used equally among all comparison groups but frequency not detailed
Makhlouf, 2003 [11]	100 mcg vaginal every 4 h	14%
Van Mensel, 2009 [10]	400 mcg vaginal every 4 h 100 mcg vaginal every 4 h (>26 weeks)	27%
Vayrynen, 2007 [16]	Varied	46%
Yapar, 1996 [12]	200 mcg vaginal every 12 h	40%

being utilized. More important, success rates and time to expulsion appear to be linked to timely dosing of the misoprostol. Thus, if expulsion is not occurring, greater attention should be paid to dosing intervals.

Other issues

Placenta previa

No published studies evaluate the impact of placenta previa for indicated inductions at gestational ages of 24–28 weeks, and thus, insufficient evidence exists with which to make a recommendation. At less than 24 weeks of gestational age, Thomas et al. found an increased estimated blood loss but no increase in infection, hysterectomy, requirement of postoperative transfusion or other complications in women undergoing pregnancy termination [30]. Clinical experience suggests that advanced gestational age may be associated with an increased likelihood of bleeding complications.

Conclusions and recommendations

Findings and recommendations are limited by the small numbers of studies, poor study design and small numbers of included pregnancies at 24–28 weeks' gestational age. Further limitations include the heterogeneity of regimens, which are varied by dose, route and timing of administration of both misoprostol and mifepristone. Nonetheless, the studies we identified did offer some consistency. Therefore, given the fact that clinical guidance is needed, we present the following recommendations.

Level B: Recommendations are based on limited or inconsistent scientific evidence. Indicated interruption of pregnancies at 24–28 weeks' gestational age is safe using either a misoprostol-only or mifepristone–misoprostol regimen. The addition of mifepristone seems to shorten expulsion time.

- Misoprostol-only regimen: Misoprostol 100 mcg or 200 mcg vaginally every 4 h is associated with 24-h expulsion rates of 84–100%, with mean expulsion times of 10–11 h.
  - o Shorter misoprostol dosing intervals (every 4 h) appear to decrease time to expulsion and increase 24-h completion rates.
  - o Higher doses of misoprostol (400 mcg) appear safe but do not clearly decrease the time to expulsion and, thus, may not be necessary.
- Mifepristone–Misoprostol regimens: Mifepristone 200 mg or 600 mg can be followed by misoprostol 36 to 48 h later. Misoprostol 200 mcg or 400 mcg every 4 h is associated with 24-h expulsion rates of 80–97%, with mean expulsion times ranging from 8.5 to 13.6 h.
  - o Consideration may be given to a shorter interval between mifepristone and misoprostol, such as 24 h.
  - o Higher doses of misoprostol (up to 600 mcg) seem safe but do not confer a clear clinical advantage over lower doses and, thus, appear unnecessary.
- Prior uterine scar: Consideration may be given to using 200 mcg or less per dose of misoprostol for women with a prior uterine scar. Data are insufficient to advise a change in dosing interval.

Important questions to be answered

While experience with misoprostol continues to increase, the evidence to guide clinicians in its use for expulsion of pregnancy beyond 24 weeks is limited. Worldwide experience with mifepristone and misoprostol indicate their overall safety. There is a need for larger, well-designed, prospective studies to determine optimal dosing routes and regimens, and use in special patient populations, such as women with IUFD, PROM, prior uterine scar and placenta previa.

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Sources

We searched PubMed and EMBase for all relevant articles. We searched for randomized and nonrandomized prospective studies, as well as retrospective studies, meta-analyses and review articles whose reference lists were searched in turn. Search terms included *abortion*, *pregnancy termination*, *midtrimester*, *second trimester*, *third trimester*, *labor induction*, *second-trimester abortion*, *third-trimester abortion*, *medical abortion*, *induced abortion*, *misoprostol*, *mifepristone*, *fetal demise*, *intrauterine fetal death*, *anomaly* and *genetic anomaly*. These terms were used singly and in combination to achieve maximal results. We identified three reviews [26,31,32] whose reference lists were searched to identify additional studies. We also searched the reference list of a systematic review [4]. We then reviewed inclusion criteria to determine whether the study population included gestations of 24 to 28 weeks. We identified 16 original research studies that included pregnancies within this gestational age range. We did not apply a time limit to the search, but most of the retrieved articles were

published within the last 17 years. We reviewed studies that included at least one misoprostol regimen, with or without mifepristone. Some of these studies compared misoprostol regimens with other prostaglandins (e.g., sulprostone) or oxytocin. While these alternative medications are not the focus of this review, misoprostol was equivalent or superior in efficacy and safety to these other uterotonics in comparative studies.

Authorship

These guidelines were prepared by Jamila B. Perritt, MD, MPH; Anne Burke, MD, MPH; and Alison B. Edelman, MD, MPH, and reviewed and approved by the board of directors of the SFP.

Conflict of interest

The authors have no significant financial relationships or conflicts of interest to declare. The SFP receives no direct support from the pharmaceutical industries.

Intended audience

This guideline is for the SFP fellows and other clinicians who provide interruption of pregnancies between 24 and 28 weeks' gestation. This guideline may be particularly useful to providers who perform these procedures in low-resource settings where alternative medications or procedures may not be available. This guideline is not intended to dictate clinical care but is designed to draw from the available medical literature to guide clinicians.