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Clinical Guidelines

Labor induction abortion in the second trimester

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Abstract

Labor induction abortion is effective throughout the second trimester. Patterns of use and gestational age limits vary by locality. Earlier gestations (typically 12 to 20 weeks) have shorter abortion times than later gestational ages, but differences in complication rates within the second trimester according to gestational age have not been demonstrated. The combination of mifepristone and misoprostol is the most effective and fastest regimen. Typically, mifepristone 200 mg is followed by use of misoprostol 24–48 h later. Ninety-five percent of abortions are complete within 24 h of misoprostol administration. Compared with misoprostol alone, the combined regimen results in a clinically significant reduction of 40% to 50% in time to abortion and can be used at all gestational ages. However, mifepristone is not widely available. Accordingly, prostaglandin analogues without mifepristone (most commonly misoprostol or gemeprost) or high-dose oxytocin are used. Misoprostol is more widely used because it is inexpensive and stable at room temperature. Misoprostol alone is best used vaginally or sublingually, and doses of 400 mcg are generally superior to 200 mcg or less. Dosing every 3 h is superior to less frequent dosing, although intervals of up to 12 h are effective when using higher doses (600 or 800 mcg) of misoprostol. Abortion rates at 24 h are approximately 80%–85%. Although gemeprost has similar outcomes as compared to misoprostol, it has higher cost, requires refrigeration, and can only be used vaginally. High-dose oxytocin can be used in circumstances when prostaglandins are not available or are contraindicated. Osmotic dilators do not shorten induction times when inserted at the same time as misoprostol; however, their use prior to induction using misoprostol has not been studied. Preprocedure-induced fetal demise has not been studied systematically for possible effects on time to abortion. While isolated case reports and retrospective reviews document uterine rupture during second-trimester induction with misoprostol, the magnitude of the risk is not known. The relationship of individual uterotonic agents to uterine rupture is not clear. Based on existing evidence, the Society of Family Planning recommends that, when labor induction abortion is performed in the second trimester, combined use of mifepristone and misoprostol is the ideal regimen to effect abortion quickly and completely. The Society of Family Planning further recommends that alternative regimens, primarily misoprostol alone, should only be used when mifepristone is not available.
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Background

These guidelines focus on the technique of labor induction abortion from 13 to 24 weeks of pregnancy. Labor induction abortion affects expulsion of the fetus from the uterus without instrumentation. A failed labor induction abortion occurs when the fetus is not expelled within a specific timeframe, and an additional procedure is necessary. This terminology is not to be confused with medical (or medication) abortion, which involves the use of medications to cause abortion in the first trimester, commonly as an outpatient. Similar techniques may be used for labor induction abortion from the late first trimester into the early third trimester. Uterine instrumentation may be necessary either for removal of the fetus or retained placenta.

These guidelines consider abortion of a living fetus during the second trimester of pregnancy and do not consider labor induction abortion for a pregnancy complicated by fetal demise. Pregnancies with fetal demise may be treated similarly in most cases; however, the dosage necessary to cause fetal expulsion is lower, and the induction process is typically shorter [1–4].

The majority of second-trimester abortions performed in the United States are performed surgically by dilation and evacuation (D&E) [5]. The frequency of labor induction abortion increases as gestational age advances. In the late second trimester and early third trimester, labor induction is the primary method of termination in cases of fetal abnormalities. In many other countries, however, induction is the primary method of abortion throughout the second trimester. Whereas labor induction abortion represents

approximately 2% of second-trimester abortions in the United States, [6] more than 80% of abortions throughout the second trimester in Sweden and other Nordic countries are inductions [7].

Comparing or combining data from studies investigating labor induction abortion is problematic because biologic differences, such as parity or fetal anomaly or demise, may influence outcomes. Additional problems include the following:

- Gestational age: reports may include various gestational age ranges, such as 12–16, 12–20, 12–23 weeks, or be restricted to the latter part of the second trimester, for example, 18–23 weeks.
- Additional interventions: use of additional interventions, such as oxytocin, or induced fetal demise complicates interpretation of the data. Some studies include women both with and without spontaneous fetal demise. All of these factors may impact outcome measures of success.
- Procedure length: comparisons of labor induction abortion methods usually include an assessment of the length of the procedure, for which there is no universally accepted definition. Abortion time, induction time, and time to abortion are used synonymously. These guidelines consider abortion time or induction time as the interval from the start of uterotonic medication to fetal expulsion. Some reports consider the abortion time to be the interval from the start of medication to placental delivery. Since the interval from fetal expulsion to placental delivery is highly dependent on practice patterns regarding management of the placenta, these guidelines consider the interval from fetal expulsion to placental delivery separately from the abortion time. Since these assessments are "time-to-event" measurement, nonparametric techniques are appropriate, and times should be reported as the median value. However, in many studies, the mean time to abortion is reported, which limits the ability to interpret the data.
- Definitions of successful abortion: some studies define success as complete abortion such that no curettage is required. This definition is similar to the definition used for successful medical abortion in the first trimester. Some studies define success as delivery of the fetus within a prespecified time frame, usually 24 or 48 h. The most common definition of success, and the one that is used in these guidelines, is that the fetus is expelled by the medical method intended. We considered instrumental procedures to include any procedure where an instrument was passed into the uterine cavity. Procedures for fetal removal, which are uncommon, are distinguished from procedures for placental removal, which are much more common. Treatment of failure may be surgical or pharmacologic.

Agents used for labor induction abortion

Induction procedures, by definition, are dependent on uterine contractions sufficient to expel the fetus and placenta. The prostaglandin E_1 (PGE_1) analogues misoprostol and gemeprost, either alone or in combination with other agents, have supplanted most other methods because of high efficacy and the relative ease of use.

Mifepristone is an antiprogestin that can be used 24–48 h before prostaglandin analogue administration.

Misoprostol is a PGE_1 analogue available in a tablet form that is stable at room temperature and inexpensive. It is formulated for oral use but is effective by vaginal, buccal, or sublingual administration for the purposes of abortion [8]. Both the route of administration and the dose influence the frequency of side effects, which are mostly gastrointestinal and include nausea, vomiting, intestinal cramping, and diarrhea. Transient pyrexia is also seen in 5%–10% of women. Fever may be confused with infection but resolves within several hours of stopping misoprostol. Side effects increase with both increasing higher doses and the cumulative dose of misoprostol [9].

Gemeprost is a PGE_1 analogue that is chemically similar to misoprostol. It is formulated as a vaginal suppository that requires refrigeration and is not as widely available as misoprostol. Gemeprost is not available in the United States.

Oxytocin can be used in doses that are much higher than those used for term induction. Higher doses are needed because of the relative paucity of oxytocin receptors early in gestation. Oxytocin alters the characteristics of uterine contractions by increasing contraction frequency, baseline tone (transiently) and contraction amplitude (strength) [10].

Ethacridine lactate, a nonprostaglandin, is infused slowly into the extra-amniotic space appears to be a very safe agent to use [11,12].

Clinical questions and recommendations

1. At what gestational ages can labor induction abortion techniques be used?

Gestational age parameters for induction abortion services are generally based on facility practices, patient and provider preference, applicable laws, and public policy. The minimum gestational age in individual reports varies from 12 to 18 weeks. The upper gestational age limit is frequently 20 or 22 weeks, but some reports include gestational ages to 24 or 26 weeks, and a few have limits up to 29 weeks.

Su et al. [13], in a series of women receiving misoprostol alone, noted shortened time to abortion in women with gestations up to 19 weeks compared to women with pregnancies over 19 weeks. Increasing gestational age is also correlated with increased induction time when using mifepristone and misoprostol from 12 to 20 weeks [14]. This relationship of gestational age to abortion time may be less

evident as gestational age advances. In two smaller series of women with misoprostol induction at gestational ages 18–23 weeks' gestation, induction time was not related to gestational age [15,16]. In contrast to surgical abortion, complication rates do not appear to increase with advancing gestational age. In a retrospective study of terminations for fetal anomalies using vaginal misoprostol, Lo et al. [17] noted that pregnancies less than 17 weeks had a higher rate of incomplete abortion and operative procedures as compared to pregnancies greater than 20 weeks. Unlike most other studies, these authors had follow-up data through 6 weeks postinduction.

2. How does labor induction abortion compare to surgical abortion?

Where both methods are available, the choice between induction and D&E may be made for either personal or medical reasons. In some instances, the woman may wish to see or hold her fetus. Examination of an intact fetus may improve the chances for accurate diagnosis of anatomic abnormalities. When an intact fetus is necessary for these reasons or others, use of induction techniques is required. However, chromosomal analysis can be performed with specimens obtained by D&E [18]. These procedures do not have an effect on bereavement; women who self-select their technique have similar measures of grief resolution [19].

The choice of labor induction abortion over surgical abortion may be affected by the presence of infection or anemia. Acute cervical infection or pelvic infection is a relative contraindication to performing surgical abortion until antibiotic treatment has been started, whereas labor induction techniques can be started immediately. However, a serious pelvic infection may be associated with impaired uterine contractility, which can limit the effectiveness of induction methods. In the case of severe anemia, or if there is significant vaginal bleeding from placental abruption, a D&E procedure will generally stop bleeding promptly, unless there is an intraoperative injury or placental implantation abnormality. However, the delay to completing a D&E, if pretreatment with osmotic dilators is necessary, may also be a consideration. An induction method may be preferable if the woman has a relative contraindication to anesthesia. If she does need an operative procedure, it is most likely to be a placental removal, which can often be managed under local anesthesia with or without mild to moderate intravenous conscious sedation.

Very few studies compare labor induction and D&E abortion, with only two randomized trials. One older study compared women predominantly at 13–16 weeks' gestation undergoing D&E to women at 17–24 weeks' gestation undergoing labor induction abortion with prostaglandin F_2 (PGF_2) or urea [20]. Major complications were more common in the induction group than in the D&E group

(1.03 vs. 0.49 per 100 abortions). The incidences of coagulopathy or cardiac arrest were rare for D&E (1 to 2 per 10,000) and not reported with labor induction, although the numbers were too small to be significantly different. Overall, an additional technique was necessary to complete the procedure more frequently with labor induction than D&E (1.7% vs. 0.15%, respectively; RR 11.7 [95% confidence interval (CI), 7.3–18.7]).

A second study comparing D&E with mifepristone and misoprostol induction was terminated early secondary to inadequate enrollment [21]. The number of women experiencing adverse events was lower among those who received D&E than with mifepristone and misoprostol (odds ratio, 0.06; 95% CI, 0.01–0.76). Women receiving mifepristone and misoprostol reported significantly more pain than those who underwent D&E; analgesia for labor induction was continuous morphine intravenous infusion with a patient-controlled system, while women having a D&E received light general anesthesia without intubation for D&E procedures. Efficacy and acceptability were similar between the two groups.

Autry and associates [22] retrospectively compared complication rates of the two methods of abortion. Complications were defined as failed induction, transfusion, infection, retained products of conception, organ damage (including uterine perforation) requiring additional surgery, cervical laceration requiring repair, and hospital readmission. Complication rates were 29% for induction versus 4% for D&E (p<.001). The severity of the complications is important to understand as their implications are different. When labor induction abortions were limited to those just using misoprostol, the complication rates were still lower with D&E (22% vs. 4%, respectively; p<.001).

A comparison of D&E and induction mortality rates from 1972 to 1987 showed that D&E had lower death rates under 20 weeks of gestation, while induction had lower rates after 20 weeks [23]. Cowett et al. [24], using decision analysis, reported that D&E is more cost effective than labor induction abortion using misoprostol alone.

Although induction abortion and surgical abortion are dissimilar, intermediate or hybrid procedures have been described. Hern [25] used preprocedure feticide and serial osmotic dilators prior to induction methods. On the day of abortion, he removed the dilators, performed an amniotomy, and administered intravaginal misoprostol. In some women, fetal expulsion was completed medically, while others had surgical completion. Multiple other techniques in use lack any evidence regarding efficacy or safety; examples include starting induction in the morning and completing the abortion by D&E for those women undelivered by late afternoon [26]. This regimen allowed virtually all women to go home without an inpatient admission.

Realistically, comparison of labor induction abortion methods to D&E is difficult because physicians generally

perform one or the other. In many institutions, a choice between surgical and medical methods does not exist; only one method of abortion is available to women for reasons of either technical capability or of facility availability. If well-trained D&E providers are not available, induction is the safer method. Hospital services are usually necessary (or available for backup) for induction procedures. Local or state health policy or statutory restrictions may dictate one procedure or the other. Using the same published safety data, countries have developed policies and practices that are almost opposite from each other, as demonstrated by the predominance of surgical methods in the United States and the predominance of labor induction abortion in many other countries.

3. What is the role for mifepristone prior to labor induction abortion?

Using mifepristone prior to administering a prostaglandin analogue markedly reduced induction times compared to simply using the prostaglandin analogue alone for labor induction abortion. Mifepristone followed 36–48 h later by misoprostol or gemeprost consistently demonstrates mean induction times following prostaglandin administration of 6–8 h [27].

As in first trimester abortion, 200 mg of mifepristone is as effective as 600 mg when used from 13 to 20 weeks [28]. In a randomized controlled trial of 600 mg compared with 200 mg of mifepristone, each followed 36–48 h later by vaginal misoprostol, the two regimens had the same mean induction times, 6.9 h. Similar findings were obtained using gemeprost, with an average time to fetal expulsion of 7.5 h [29]. Addition of mifepristone appears to lower nausea and vomiting rates as compared to prostaglandin alone, possibly because the induction is shorter and fewer doses of prostaglandin are needed [30].

Early studies used 600 mg of mifepristone 36–48 h before misoprostol, similar to initial first trimester abortion studies. The largest published study of this dosage used mifepristone 600 mg followed by gemeprost 1 mg every 3 h. This multicenter trial of 267 women from 12 to 24 weeks of pregnancy reported that the mean induction time was 7 h [31].

Misoprostol regimens vary considerably among all studies using 200 mg of mifepristone. One of the most commonly used regimens is mifepristone 200 mg followed 36–48 h by misoprostol 800 mcg vaginally, then an additional 400 mcg vaginally every 3 h, to a maximum of 5 doses in 12 h. If abortion is not complete at that time, the woman has a 12-h rest before starting the cycle again [14,32–34]. In the largest published series (n =1002, gestational ages 13–21 weeks), 97% of women aborted within 24 h, with mean induction times of 5.9 h for multiparous women and 6.6 h for nulliparous women [14]. This regimen is the basis of recommendations by World Health Organization and Royal College of Obstetricians and Gynaecologists, based on trials that included women predominantly at 20 weeks' gestation or less.

Similar results are found with mifepristone followed by gemeprost [35]. The largest series (n=956, gestational ages 12–24 weeks) used 1 mg gemeprost suppositories every 6 h for 4 doses. If abortion was not complete at 24 h, the dosing frequency was increased to every 3 h. The median induction time was 7.8 h.

A more complex regimen of mifepristone followed 36–48 h later by misoprostol and Dilapan™ osmotic dilators did not result in outcomes different than that reported with the use of misoprostol alone [36]. Investigators administered misoprostol 800 mcg vaginally and place two dilators. Four hours later, the dilators were removed, and a second dose of misoprostol 600 mcg was placed unless amniotomy could be performed. After amniotomy, intravenous oxytocin was initiated, and misoprostol was discontinued. The mean induction time was 6.9 h for both regimens.

Tang et al. [37,38] showed shorter median abortion times — 5.5 h versus 7.5 h — when mifepristone was followed 3 h later by sublingual misoprostol as compared to oral administration at 12–20 weeks. Side effects were similar between groups, except for transient fever that was more likely in the sublingual group. Hamoda et al. [39] compared mifepristone followed 36–48 h later by vaginal misoprostol 800 mcg or sublingual misoprostol 600 mcg, as initial doses, followed by 400 mcg given by the same route every 3 h. Rates of complete abortion, side effects and patient satisfaction were similar between groups.

Recent studies have investigated shorter intervals between the mifepristone and prostaglandin analogue. Kapp et al. [16] randomized women at 18 to 23 weeks gestation to mifepristone 24 h before buccal misoprostol or misoprostol alone. The median abortion time with mifepristone was 10 h, a 45% reduction in time compared to the group without mifepristone. Nilas et al. [40] compared cohorts of women using a 1- or 2-day interval between mifepristone and vaginal misoprostol at 17–22 weeks. The women in the 1-day group had longer induction times, 9.8 versus 7.5 h (p<.01); 98% of the women in each group delivered within 24 h of receiving misoprostol. Heikinheimo et al. [41] reported two cohorts of women with a mean gestational age of 16 weeks who had either 1- or 2-day intervals between mifepristone and vaginal misoprostol. The 1-day group had a higher proportion of multiparous and older women as well as a longer time to delivery, 7.25 h versus 6.2 h. The difference was more marked in multiparous women and at higher gestational ages. In contrast, Urquhart and Templeton [30], using mifepristone and extra-amniotic PGE$_2$, found that induction times did not differ whether given 24, 36, or 48 h apart, despite an increase in measured uterine contractility at 36 and 48 h.

Overall, induction times are markedly reduced by the addition of mifepristone pretreatment prior to misoprostol or gemeprost administration. Misoprostol is effective with vaginal, buccal, or sublingual routes when used in

combination with mifepristone. Although regimens commonly use a 36- to 48-h interval between the mifepristone and initiation of the prostaglandin analogue, the interval can be decreased substantially to 24 h while maintaining acceptable abortion times. Although a shorter interval may increase the time to delivery slightly, the overall abortion time for the woman is significantly reduced as compared to a prostaglandin analogue alone.

4. How does misoprostol compare to other agents for induction abortion?

Labor induction abortion with the PGE_1 analogue misoprostol either alone or in combination with other agents has supplanted most other methods because of high efficacy, low cost, and relative ease of use. Misoprostol has been compared directly to multiple agents, as summarized in Table 1 [22]. It has not been compared directly to some older agents like urea, which had been replaced with other agents by the time misoprostol became available.

In the available studies comparing misoprostol to either intra- or extra-amniotic $PGF2_{\alpha}$, vaginal PGE_2 (dinoprostone), or intravenous oxytocin, studies that use an adequate dose of misoprostol demonstrate a shorter or equal induction time (Table 2). Ethacridine lactate, a nonprostaglandin compound that is infused slowly into the extra-amniotic space, appears to be a very safe agent to use but, however, has a longer abortion time than misoprostol [11,12].

Early studies evaluated gemeprost as a single suppository (1 mg) every 3 h with abortion rates of approximately 80% at 24 h after initial administration and 95% at 48 h [53–55]. Two prospective randomized studies performed in the UK compared vaginal gemeprost 1 mg every 3 h for a maximum of 5 doses in 24 h to 1 mg every 6 h for a maximum of 4 doses in 24 h [54,56]. The regimens were repeated 24 h after the initial treatment, and intravenous oxytocin

was initiated if the abortion had not occurred within 36–48 h. These two studies found that although more frequent dosing was associated with a somewhat shorter abortion time, the cumulative abortion rates within 24 h, the overall rate of side effects, and the rate of surgical intervention for incomplete abortion were the same in both groups [54,56].

The rates of nausea in these studies, where stated, ranged from 16% to 56%, and the rates of vomiting ranged from 4% to 20%. There is no clear pattern of either superiority or inferiority, in terms of side effects, when misoprostol is compared to the other agents.

When the PGE_1 analogues used alone are compared directly, outcomes are related to the misoprostol dose [57]. In one study, gemeprost was superior to 100 mcg of misoprostol used every 6 h, but comparable to 200 mcg of misoprostol every 12 h [57]. In other studies, misoprostol was equivalent to or more efficacious than gemeprost [57–60]. Two randomized controlled trials compared misoprostol with gemeprost after pretreatment with 600 mg mifepristone [61,62]. Neither showed a faster induction time. Similarly, neither Nuutila et al. [57] nor Ho et al. [63] showed a difference in induction time when 200 mg of mifepristone was used. Bartley and Baird [64] had similar results, with median induction times of 6.0 and 6.1 h for gemeprost and misoprostol, respectively, when pretreatment with mifepristone was included.

A meta-analysis of randomized trials comparing various regimens of misoprostol to gemeprost in midtrimester abortion demonstrated that vaginal misoprostol compared with gemeprost vaginal suppositories was associated with a reduced need for narcotic analgesia and surgical evacuation of the uterus [9]. No other statistically significant differences were observed.

High-dose oxytocin is an option when misoprostol is not available or when there is a desire to avoid prostaglandin use and side effects. However, it requires intravenous access and a relatively complicated regimen to avoid serious complications, and induction times are likely to be prolonged. Several regimens using only oxytocin for induction have been described. Winkler and associates [65], in a small retrospective evaluation of 22 subjects, used a regimen that began with 100 units of oxytocin infused over 3 h followed by 1 h without oxytocin to allow diuresis for prevention of water intoxication. The dose of oxytocin was increased 50 units per 3 h until fetal expulsion was achieved, to a maximum of 300 units over 3 h. Women in the oxytocin group had a gestational range of 17–24 weeks' (mean of 21.3 weeks). The mean induction time was 8.2 h, which was shorter than the induction time compared with PGE_2 group. Owen et al. [66] found similar outcomes for PGE_2 and concentrated oxytocin inductions. Using a regimen of less concentrated oxytocin; 20 units over 3 h, Yapar reported a 24-h cumulative abortion rate of 90% [67] in women with a mean gestational age of 20 weeks.

Table 1
Complication rates among labor induction abortions and D&E (mean± SD)

	Labor induction (n=158)	D&E (n=139)	p
Any complication	45±28.5	5±3.6	<.001
Failed initial method	11±7.0	0±0	<.01
Hemorrhage with transfusion	1±0.6	1±0.7	NS
Infection with intravenous antibiotics	2±1.3	0±0	NS
Retained products of conception[a]	33±20.9	1±0.7	<.001
Cervical laceration with repair	2±1.3	3±2.2	NS
Organ damage (including perforation)	2±1.3	0±0	NS
Hospital readmission	1±0.6	1±0.7	NS

NS, not significant. Adapted from Autry et al. [22].

[a] Requiring dilation and curettage for labor induction abortions or reoperation for surgical abortions.

Table 2
Selected comparisons of vaginal misoprostol to other agents

Agent	Sample size	Gestational ages (weeks)	Agent abortion time (median or mean) (h)	Rate (%) of nausea and vomiting[a]	Misoprostol comparator dose (vaginal)	Misoprostol abortion time (h)	Rates (%) of nausea and vomiting	Comments	References
Ethacridine lactate extra-amniotic	388	13–20	29	–[b]	400 mcg every 8 h, 800 mcg every 8 h after 24 h	20	29/20	Retrospective cohort, ethacridine lactate group had higher gestational ages 93% of misoprostol group vs. 76% of ethacridine group delivered within 24 h	[8]
	388	13–20	14.2 13.2*	–	400 mcg every 6–12 for gestational ages <16 weeks 200 mcg every 6–12 for 16–20 weeks; doses doubles after 24 h	10.8 9.9*	–	Side effects "similar in all of the groups"; 10% had vomiting overall	[9]
PGF2α intra-amniotic	100	16–22	10.7	–	200 mcg every 6 × 4 doses	13.6	–	Used laminaria 18 h before induction Misoprostol group was more likely to complete abortion within 24 h (88% vs. 72%) Misoprostol group used less analgesia	[42]
	217	15–24	21.1	–[c]	400 mcg every 4 h	18.3	–	Vaginal misoprostol had fewer side effects and was more acceptable Misoprostol had fewer episodes of nausea and vomiting	[43]
	117	16–22	21		400 mcg oral misoprostol 4 h			Similar rates of abortion at 24 h. PGF group more likely to have retained placenta	[44]
	132	12–24	20.8	28/23	400 mcg every 3 h	16.2	16/16	Difference more marked for multiparous women Shivering and fever more common among misoprostol users	[13]

PGF2α extra-amniotic	51	17–24	17.5	35/8	200 mcg every 12 h	22	32/12	Side effects similar	[45]
	40	16–24	16	–/45	200 mcg every 8 h	10.3	–/5	PGF2α group had more vomiting, diarrhea and pyrexia	[46]
Intravenous D-cloprostenol (PGF analogue 2.5 mg) with intra-amniotic hypertonic saline	233	14–23	29	–/8	400 mcg every 3 h	13.1	–/5	Retained placenta and hemorrhage less common in misoprostol group Misoprostol more acceptable to patients and staff	[47]
PGE2 vaginally	80	13–28	25	–/27	100 mcg every 4 h	10.6	–/34	Included some women with fetal demise	[48]
	55	12–22	10.6	–/33	200 mcg every 12 h	12.0	–/4	PGE2 more likely to result in pyrexia, nausea, vomiting or diarrhea	[1]
PGE2 vaginally combined with high-dose intravenous oxytocin	30	16–24	18	47/–	100 mcg every 12 h	22	47/–	Vomiting more common in misoprostol group	[49]
	126	16–24	17	42^d	600 mcg and 400 mcg every 4 h	12	25^d	The misoprostol group had fewer gastrointestinal side effects	[50]
High-dose intravenous oxytocin	47	13–32	21.7	–/0	400 mcg every 4 h	15.2	–/17	Cohort study. Some women had fetal demise. Side effects not significantly different; small size of study	[51]
High-dose intravenous oxytocin plus low-dose misoprostol	38	14–24	18	25/15	400 mcg every 4 h	12	56/11	Study stopped early as misoprostol was more effective. Side effects were similar	[52]

Studies reported are randomized trials unless otherwise indicated. Misoprostol was used vaginally unless otherwise indicated.

[a] Nausea/vomiting.

[b] – indicates not stated.

[c] Nausea and vomiting were expressed as number of episodes.

[d] Nausea and/or vomiting.

* Treated with oxytocin in addition.

Owen et al. [49] compared vaginal misoprostol to a combination of intravenous oxytocin and low-dose PGE_2 and concluded that misoprostol was inferior; however, an inadequate misoprostol dose of 100 mcg every 12 h was used. When compared to oral misoprostol 400 mcg every 4 h, high-dose oxytocin use is associated with longer induction times [51]. Nuthalapaty et al. [52] compared women at 14–24 weeks undergoing induction, using either escalating high-dose oxytocin combined with low-dose misoprostol (starting at 400 mcg vaginally and decreasing to 100 mcg for repeat doses), or misoprostol alone (600 mcg of misoprostol initially followed by 400 mcg every 4 h). The median induction times were 18 and 12 h, respectively (p<.01). The success rate for misoprostol compared with oxytocin at 12 h, 60% versus 12%, was also strikingly different.

Overall, misoprostol appears to be more effective than $PGF_{2\alpha}$, PGE_2, high-dose oxytocin, and ethacridine lactate when adequate doses are used. Both PGE_2 and $PGF_{2\alpha}$ analogues are expensive and require refrigeration, in contrast to misoprostol, which is inexpensive and stable at room temperature. Compared to the agents presented in this section, misoprostol is the preferred agent. There is no overwhelming argument for use of either misoprostol or gemeprost based on clinical outcome. However, the restriction of gemeprost to vaginal use, and storage and availability issues, make it less attractive than misoprostol.

5. What is the optimal dose and dosing schedule for misoprostol?

There is a large range of effective misoprostol dosing, ranging from 100 to 800 mcg for an individual dose and using various schedules, including regimens with loading doses.

Most early studies used low doses of misoprostol, such as 200 mcg vaginally every 6–12 h [2,3,45,49,57]. Induction times varied from 14 to 22 h. Although a regimen using 100 mcg vaginally was less effective than the one using 200 mg [57], a more recent randomized trial comparing 100 and 200 mcg of misoprostol sublingually every 2 h showed similar efficacy, with mean abortion times of 14.75 and 15.2 h, respectively, [58].

However, higher doses are generally more effective when misoprostol is used alone. Accordingly, lower doses should be abandoned. A prospective randomized, double-blinded controlled trial found that misoprostol 400 mcg every 6 h was more effective than 200 mcg used every 6 h [4]. Misoprostol doses of 400 and 600 mcg appear to have similar efficacy regardless of a 4- or 6-h dosing interval time (time to abortion, 11–12 h) [68]. With a dosing interval of 12 h, 600- and 800-mcg doses also showed similar abortion times (15.2 h) [69], although a noncomparative cohort study in women receiving 800 mcg every 12 h found a slightly shorter average time of 12 h [70].

Multiple dosing frequency regimens have been studied. Although initial studies considered dosing intervals of 6 to

12 h with vaginal misoprostol, randomized trials have demonstrated shorter abortion times with vaginal administration every 3 h [71,72]. In general, it appears that increased time to abortion is related more to the dosing interval than the dose itself.

Lower doses of misoprostol are effective, however, when they are preceded by a "loading dose" (a higher initial dose) or mifepristone. One of the earliest larger studies (*n*=128) in the early second trimester used 800 mcg misoprostol vaginally, followed by 400 mcg at 18 and 24 h, if needed [73]. Abortion occurred at a mean of 11.8 h, with 102 women (80%) aborting within the first 18 h. All patients had routine curettage after expulsion of the fetus, so the rate of retained placenta was not evaluated.

A misoprostol-only regimen using a loading dose of 600 mcg vaginally followed by 200 mcg vaginally every 3 h resulted in similar mean abortion times and success rates at 24 and 48 h as compared to a regimen of 400 mcg of misoprostol vaginally every 3 h [4]. Ngai et al. [74] showed similar outcomes using mifepristone 200 mg followed 36–48 h later by misoprostol 200 mcg vaginally or 400 mcg orally every 3 h.

Overall, when misoprostol is used alone, 400 mcg appears to be the minimum effective dose. Although many regimens in the past used longer dosing intervals, repeating the dose approximately every 3 h has the same efficacy but will shorten the abortion time. Most ideally, a loading dose of 600 to 800 mcg should be administered, which will allow for lower dose of misoprostol to be used (200 mcg vaginally) every 3 h.

6. What is the optimal route of administration of misoprostol?

Although misoprostol is labeled for oral ingestion, it is also effective for induced abortion when administered by vaginal, sublingual, and buccal routes. Vaginal administration is associated with shorter induction times compared to oral administration [32,47,75–77]. The incidence of side effects is also lower for vaginal use except for transient fever [77]. The abortion rate is not improved by moistening the misoprostol tablets [78,79]. Sublingual administration appears to be similar to vaginal and also is superior to oral. von Hertzen et al. [80] found that vaginal administration of 400 mcg every 3 h was associated with higher rates of abortion by 24 h (86% vs. 80%) than using the same schedule with sublingual administration. Outcomes were very similar for multiparous women, but significantly different for nulliparous women. In this study, side effects were similar in the two groups, but 72% of women preferred the sublingual route. A single recent study is the only published report of buccal misoprostol alone for labor induction abortion at 18–22 weeks. Ellis et al. [81] administered misoprostol 400 mcg vaginally to 64 women then randomized the women to receive subsequent doses of 200 mcg misoprostol every 6 h either buccally or

vaginally. The median abortion times in the buccal and vaginal groups were 15 and 12 h, respectively (p=.44).

Ho et al. [75] found oral administration to be more acceptable to women than vaginal administration for labor induction abortion. The most common reasons cited for not liking vaginal administration were pain and inconvenience with insertion. The authors, however, did not describe how the tablets were administered vaginally. Ellis et al. [81] found no difference in acceptability in a group of women randomized to buccal or vaginal misoprostol.

Combined oral and vaginal regimens may be as effective as vaginal alone regimens. el-Rafaey et al. [61] randomized women to receive an initial dose of vaginal misoprostol with repeat doses by oral or vaginal routes. Abortion times and side effects were the same for both groups. Feldman et al. [82] compared women who received 400 mcg of misoprostol every 8 h, either orally or vaginally, after a loading dose of 800 mcg vaginally. No significant differences either in abortion time or in side effects were found. Similar results are found when mifepristone is used before misoprostol.

Overall, misoprostol, when used alone for labor induction abortion, should be administered vaginally or sublingually. However, when a vaginal loading dose is administered, outcomes following subsequent oral and vaginal administration are similar. Only a single small study has evaluated buccal misoprostol; more research would be needed before recommending this route when using misoprostol alone.

7. Does the use of osmotic dilators affect the abortion time?

Labor induction abortion studies using natural prosta-glandins found that placing osmotic dilators 4–24 h before induction decreased abortion time [30,83–88]. However, this adjunctive benefit does not occur when modern prostaglan-din analogues are used.

Two randomized studies examined the use of cervical preparation with laminaria at the time of misoprostol induction [2,15]. One study used feticide with hypertonic saline prior to misoprostol administration [15]. Both studies demonstrated that laminaria placement actually increased the abortion interval, and this difference was statistically different in one of the trials [2,15]. Additionally, women who received laminaria had increased analgesic needs during the induction procedure [15].

Laminaria use has also been compared to mifepristone, which has cervical ripening properties [86]. Ho et al. [89] compared mifepristone given 36 h and laminaria placed 12 h prior to gemeprost induction. Mifepristone was more effective than laminaria at shortening the induction interval. Prairie et al. [90] compared mifepristone to laminaria 24 h prior to misoprostol induction, also finding that mifepristone resulted in significantly shorter induction intervals. Dilapan has also proven to be of no benefit in regimens with gemeprost [91].

There are few studies on the use of osmotic dilators in advance of starting induction with misoprostol alone. Hern [25], using a combination of medical techniques and assisted delivery or D&E, reported no failed procedures and rare complications in a large observational series. A series of women treated with mifepristone 48 h prior to misoprostol, combined with laminaria 12 h before misoprostol, had a mean abortion time of 4 h [92].

Overall, there appears to be no benefit to inserting osmotic dilators at the same time as misoprostol or gemeprost, as induction times may be prolonged and side effects may be increased. Whether prior insertion of dilators is of benefit for labor induction abortion is not clear.

8. How should expulsion of the placenta be managed with labor induction abortion?

There have been a variety of approaches to management of the placenta with labor induction abortion. Some practitioners perform curettage routinely after delivery of the placenta, whether the placenta is delivered spontaneously or not. Recommendations for active placental removal (manually or with curettage) are often based on policy rather than medical necessity. Historically, placental extraction rates vary from 15% to 50% with various agents [62,93–96]. These rates do not seem to vary with agents used today including gemeprost [54] and misoprostol [97,98].

Some investigators recommend placental removal 30 min after fetal expulsion when prostaglandin E_2 is used [99] or after 2 h when saline infusion is used [20], based on an increase in bleeding after the recommended time period. Such recommendations may not be applicable for agents more commonly used today.

Few studies follow the natural time course of placental expulsion without intervention for placental delivery. In women receiving misoprostol alone for labor induction abortion, Leader et al. [97] found that about half of women deliver the placenta within an hour, and there was no increase in bleeding when women were observed past 2 h. This study also showed that routine misoprostol administration after fetal expulsion did not decrease the time to placental delivery. Green et al. [98] in a retrospective series of 233 women using misoprostol alone concluded that there was no increase in bleeding for at least 4 h; 59% of women delivered the placenta within an hour, and the rate of operative removal was 6%. Dickinson and Evans [47] randomized women to receive intramuscular oxytocin, oral misoprostol, or no medication after fetal delivery. After oxytocin, 90% of women expelled the placenta within an hour, compared to 71% and 69% after misoprostol or no medication.

Low rates of intervention for placental delivery are also reported for regimens using mifepristone and misoprostol [39,74,100]. It is not clear whether these low rates reflect a pharmacologic effect or practice patterns. In a small study that noted the time to placental delivery after mifepristone

abortion and buccal misoprostol, only 1 (3%) of 32 women required placental removal [16].

Overall, routine surgical intervention for removal of the placenta after an arbitrary time period is not required following labor induction abortion using prostaglandin analogues alone or in combination with mifepristone.

9. What is the relationship of prior cesarean delivery to outcome of induction abortion?

Although prior hysterotomy is suspected to be a risk factor for uterine rupture during labor induction abortion, most published literature consists of case reports or small series and include rupture in both scarred and unscarred uteri. Uterine rupture is a catastrophic complication that often results in hysterectomy and can occur in a scarred or an unscarred uterus during induction. Uterine rupture during labor induction abortion has been reported with almost all agents including high-dose oxytocin [67,101], ethacridine lactate [102], urea/$PGF_{2\alpha}$ [103], saline/$PGF_{2\alpha}$ [47] and misoprostol [101,104–108]. Approximately half have been in unscarred uteri, and most have occurred in women with pregnancies of 18–25 weeks gestational age. The lowest total misoprostol dose administered prior to uterine rupture was a single dose of 200 mcg [108], but several women received multiple doses prior to uterine rupture. Rupture has been reported when mifepristone was used in combination with misoprostol [100,109] and gemeprost [31,55].

In addition to case reports and series, retrospective cohort studies have contrasted uterine rupture rates in women with scarred and unscarred uteri. Goyal [50] reviewed multiple labor induction publications in which misoprostol was used alone or with other agents, such as oxytocin. The risk of uterine rupture for women with a prior cesarean delivery was 0.28% (95% CI, 0.08–1.0) compared with the rate for unscarred uteri, 0.04% (95% CI, 0.02–0.20).

Labor induction abortion outcomes, including abortion time, do not differ between women with and without a prior cesarean delivery [110]. Mazouni et al. [111] and Herabutya et al. [112] also found similar outcomes but did report slightly higher rates of retained placenta for women with prior cesarean delivery.

Overall, there is no clear evidence of an increased risk of uterine rupture with labor induction abortion in women with one prior cesarean delivery. Retained placenta may be slightly higher with labor induction abortion in women with a prior cesarean delivery as compared to women without such a history. There is insufficient information to make evidence-based recommendations for women who have had multiple cesarean deliveries.

10. What is the effect of feticide on labor induction abortion outcome?

Deliberately causing demise of the fetus before labor induction abortion is performed primarily to avoid transient fetal survival after expulsion; this approach may be for the comfort of both the woman and the staff, to avoid futile resuscitation efforts. Some providers allege that feticide also facilitates delivery, although little data support this claim.

Transient fetal survival is very unlikely after intra-amniotic installation of saline or urea, which are directly feticidal. Transient survival with misoprostol for labor induction abortion at greater than 18 weeks ranges from 0% to 50% [51] and has been observed in up to 13% of abortions performed with high-dose oxytocin [52]. Factors associated with a higher likelihood of transient fetal survival with labor induction abortion include increasing gestational age, decreasing abortion interval and the use of nonfeticidal inductive agents such as the PGE_1 analogues [113].

Fetal demise may be induced using a variety of medications. Fetal intracardiac potassium chloride (KCl) injection is highly effective but requires expertise and time for observation after injection to ensure cardiac cessation [103,114]. Very rare serious complications, including maternal cardiac arrest, have occurred from injection into the maternal circulation [115]. Fetal intracardiac injection of lidocaine, with similar technical considerations as KCl, has also been used, although the risk to the woman may be less [116].

Digoxin has been administered by intra-amniotic, intra-fetal and intracardiac routes. Currently, there is limited documentation about its effectiveness. In one report, intra-amniotic injection had a failure rate (cardiac activity on ultrasound 24 h after injection) of 5 (8%) of 62 [117]. In a retrospective study, intra-amniotic injection of 0.5 mg had a failure rate of 3 (8%) of 36, while intrafetal injection had a failure rate of 36 (4%) of 993 [118]. In the same series, intrafetal injection of 1 mg had a failure rate of 0 (0%) of 107; intra-amniotic injection of 1 mg was not assessed. Feticidal digoxin doses of 1 mg produce maternal serum levels at or below one therapeutic level; higher doses have not been evaluated systematically [119], and toxicity has not been reported.

There is limited documentation of the effect of feticide on abortion outcome. Elimian et al. [120], in a retrospective study of women having PGE_2 abortion, reported shorter abortion times in women who had undergone feticide by intracardiac KCl injection. An intriguing small retrospective study of 15 women with placenta previa undergoing induction noted a significant decrease in blood loss and need for transfusion in the nine women in whom feticide had been performed [121].

Overall, multiple agents are effective for feticide. Fetal intracardiac KCl is technically more difficult to perform but provides verification of demise. More information about the effectiveness of various doses and routes of digoxin is needed. Although many practitioners have historically felt that labor induction abortion is aided by feticide, there is limited medical literature to support this claim.

Conclusions and recommendations

The following recommendations are based on good and consistent scientific evidence (Grade A):

- Mifepristone followed in 24–48 h by initiation of repeated doses of misoprostol or gemeprost is the most effective regimen available for labor induction abortion.
- Misoprostol as a single agent is effective for labor induction abortion when administered vaginally or sublingually. Gemeprost has similar efficacy to misoprostol; however, it does not demonstrate superiority and has other drawbacks related to cost, route of administration and storage.
- When misoprostol treatment is used alone, the optimal dosing is 400 mcg vaginally or sublingually every 3 h. A vaginal "loading" dose of 600–800 mcg of misoprostol followed by 400 mcg vaginally or sublingually every 3 h may be more effective.

The following recommendations are based on limited or inconsistent scientific information (Evidence Grade B):

- After mifepristone, repeat doses of misoprostol dose may be decreased to 200 mcg.
- Misoprostol may be used by buccal administration.
- Repeat doses of misoprostol may be given by vaginal, sublingual, buccal or oral routes.
- When misoprostol treatment is being used alone, vaginal dosing is superior to sublingual dosing for nulliparous women.
- High-dose oxytocin is an alternative to misoprostol for labor induction abortion.
- Routine placental removal is not warranted.

The following recommendations are based primarily on consensus or expert opinion (Grade C).

- Women with one prior cesarean delivery may be at increased risk of uterine rupture during labor induction abortion; however, the magnitude of the risk, if any, is small.
- Preprocedure feticide may facilitate the time to expulsion with labor induction abortion.

In addition, SFP recognized that other organization have guidelines or recommendation for labor induction abortion, including the World Health Organization, the Royal College of Obstetricians and Gynaecologists, and the Federación Latino American de Sociedades de Obstetrica y Ginecología.

Important questions to be answered

There are multiple effective labor induction abortion regimens, including using a higher dose of misoprostol at 12-h intervals. Few direct comparisons have been performed. Sublingual and vaginal routes of administration have similar outcomes in most circumstances; however, oral administra-tion is convenient and preferable to some women. Oral ingestion may be equally effective to other routes when used for repeat doses or as the primary route after mifepristone pretreatment. Relative effectiveness and acceptability of all routes of administration, including buccal, need to be better evaluated.

The management of women who fail to abort in 24 h has not been studied systematically. More data are needed to inform whether such women would benefit from a period of rest, a change in dose or schedule, or another agent and when D&E should be considered.

Mechanical preparation prior to induction may decrease abortion time. Although simultaneous laminaria use is not helpful with PGE_1 analogue regimens, use of osmotic dilators the day prior to induction with misoprostol has not been systematically studied.

Preprocedure feticide prior to labor induction abortion may be widely practiced, but there is little literature to support its use. Demonstration of the effect of feticide on labor induction abortion outcome, as distinct from avoiding transient fetal survival or legal restrictions, would be useful.

There are several important questions regarding the safety of induction techniques compared to D&E. Randomized trials comparing induction abortion with D&E are unlikely to be done: blinding is impossible, and it may be difficult to find facilities and providers willing to participate. A well-designed ongoing system of monitoring outcomes of both D&E and induction abortion might yield useful comparative information.

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Authorship

These guidelines were prepared by Lynn Borgatta, M.D., M.P.H., and Nathalie Kapp, M.D., M.P.H., and were reviewed and approved by the Board of Directors of the Society of Family Planning.

Conflict Of Interest

Lynn Borgatta, M.D., M.P.H., is a consultant for Merck. Nathalie Kapp, M.D., M.P.H., reports no significant relationships with industry. The Society of Family Planning receives no direct support from pharmaceutical companies or other industries.

Intended Audience

This guideline has been developed under the auspices of the Society of Family Planning for its members and for any physicians and other clinicians who perform surgical abortions or who care for women undergoing these procedures. This guideline may be of interest to other professional groups that set practice standards for family planning services. The purpose of this document is to review the medical literature evaluating common means and goals of inducing fetal demise before pregnancy termination. This evidence-based review should guide clinicians, though it is not intended to dictate clinical care.