

Advances in the treatment of fetal demise in the second and third trimester

Treatment of fetal demise is best managed as a 2-step process, beginning with cervical preparation using cervical dilators, cervical balloons, mifepristone and/or misoprostol, and followed by emptying the uterus using surgical evacuation or induction of labor with misoprostol or oxytocin



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Clinical care for fetal demise is complex and multidimensional, including empathetic emotional support for the patient and family members who are experiencing a tragedy, investigation of the cause of the demise, and a plan for emptying the uterus. This editorial narrowly focuses on the options for treatment of fetal demise with the goal of emptying the uterus while minimizing complications.

When planning treatment of fetal demise, focus on fetal size and gestational age

Most guidelines for the treatment of fetal demise use gestational age to guide selection of a treatment.^{1,2} I believe that fetal size is as important as gestational age for selecting a treatment plan. When considering treatment, there are 2 reasons why fetal

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size is as important as gestational age:

- The physiologic processes that caused fetal demise may have caused fetal growth restriction, resulting in a fetal size that is 2 or more weeks below expected fetal size for gestational age.
- Fetal demise may have occurred weeks before the diagnosis was made, resulting in gestational age being greater than fetal size. This editorial will use ultrasonography estimate of fetal size in gestational weeks to guide treatment recommendations. When discussing fetal size, we will use the convention of weeks-days (w-d). Twenty-five weeks and zero days gestation is represented as 25w0d.

Treatment in the second and third trimester is a 2-step process

Step 1: Cervical preparation

In most cases of first trimester fetal demise, no cervical preparation is necessary. Cervical dilation with metal dilators followed by uterine

evacuation with an appropriately sized vacuum catheter is a highly successful treatment.³ However for second and third trimester, fetal demise it is best to use a 2-step process, beginning with cervical preparation followed by emptying the uterus. For example, at a fetal size of 13w0d to 16w0d, cervical preparation can be achieved by administering a single buccal dose of misoprostol 400 µg 3 to 4 hours prior to uterine evacuation or by inserting a Dilapan-S (Medicem Inc) osmotic cervical dilator 3 to 6 hours prior to uterine evacuation.⁴⁻⁷ At a fetal size of 16w0d to 19w6d, cervical preparation can be achieved by placing osmotic cervical dilators 4 to 6 hours before surgical evacuation and administering buccal misoprostol 400 µg 3 hours before surgical evacuation.⁸

Alternatively, from 16w0d to 25w0d osmotic cervical dilators can be placed on day 1 of a 2-day process, and the patient can return on day 2 to have the cervical dilators removed followed by surgical evacuation of the uterus. Mifepristone 200 mg oral

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dose can be administered on day 1 to facilitate cervical preparation. In my practice, I use mifepristone 200 mg on day 1 when the fetal size is ≥ 20 w0d gestation. Options for cervical preparation include use of osmotic dilators, cervical balloons, misoprostol, and/or mifepristone. These options are discussed below. With fetal demise, natural physiologic processes often have caused sufficient cervical softening and dilation that no cervical preparation is necessary and immediate uterine surgical evacuation or induction of labor can be initiated.

Step 2: Emptying the uterus

In the second and third trimesters, the approach to uterine evacuation is based on fetal size. At fetal sizes < 25 w0d, options for emptying the uterus include surgical evacuation with a vacuum catheter and grasping forceps or induction of labor with misoprostol followed by vaginal birth and expulsion of the placenta. At fetal sizes > 25 w0d gestation, following completion of cervical preparation, the most common approaches to uterine evacuation are induction of labor with misoprostol or oxytocin. Rarely, with a stillbirth at term, some clinicians will select hysterectomy to empty the uterus, avoiding uterine rupture during labor induction for patients at the highest risk, including those with a prior classical cesarean birth or more than 2 prior cesarean births with a low-transverse uterine incision.

Osmotic cervical dilators

The 2 most used cervical dilators are Dilapan-S, a polyacrylate-based hydrogel rod, and laminaria, dried compressed seaweed stipe (stalk) from *Laminaria japonica* or *Laminaria digitata*. Dilapan-S rods are avail-

able in diameters of 3 mm and 4 mm and rod lengths of 55 mm and 65 mm. Laminaria dilators are available in diameters of 2, 3, 4, 5, 6, 8 and 10 mm and rod length of 60 and 70 mm. Dilapan-S dilators reach near-maximal dilation in approximately 4 to 6 hours but continue to expand over the following 18 hours to achieve a maximum dilation of 3.3 to 3.6 times their dry diameter.⁹ Laminaria dilators expand to 2.7 to 2.9 times their dry diameter over 24 hours.⁹

A general rule is that as many dilators as possible should be placed until significant resistance to the placement of additional dilators is encountered.¹⁰ In my practice, for fetal size ≥ 20 weeks' gestation, I place 2 Dilapan-S rods, 4 mm in diameter, 55 mm in length, and then encircle the Dilapan-S with laminaria rods that are 4 mm in diameter and 60 mm in length. Once cervical resistance to the placement of the 4 mm laminaria rods is observed, I encircle those laminaria with laminaria 2 mm in diameter, filling in the interstices between the 4 mm laminaria. The next day, cervical dilation is routinely ≥ 3 cm.

In a retrospective study of 491 patients undergoing pregnancy termination after 14 weeks' gestation, with a mean gestational age of 24 weeks, compared with no osmotic cervical dilators, inserting osmotic cervical dilators the day before initiating misoprostol for induction of labor resulted in a decrease in time to delivery (428 min vs 640 min; $P < .001$) and a decrease in total misoprostol dose (990 μ g vs 1,449 μ g; $P < .0001$).¹¹

Cervical balloons

All clinicians know that a Foley catheter or a Cook cervical ripening balloon can be used for cervical

preparation in the third trimester.^{12,13} The Foley catheter also has been reported to be useful for cervical preparation in the second trimester. In one study of 43 patients 17 to 24 weeks' gestation scheduled for a second-trimester dilation and evacuation, an intracervical Foley catheter was placed the evening before evacuation, and the balloon was inflated with 30 mL to 50 mL of saline. At the same time, mifepristone 200 mg was administered to the patients.¹⁴ The following day, dilation and evacuation was performed. In 72% of cases no additional cervical dilation was required on the day of evacuation. The investigators concluded that if osmotic cervical dilators are not available, the placement of an intracervical Foley catheter plus administration of mifepristone facilitates performance of an evacuation on the following day. If the patient prefers a 1-day procedure, the Foley can be inserted in the morning to facilitate cervical preparation, and the uterus can be evacuated in the afternoon.

Misoprostol

Misoprostol, a derivative of prostaglandin E1, is useful for both cervical preparation and induction of labor. The dose of misoprostol and the route of administration are major determinants of uterine response.¹⁵⁻¹⁹ When administered by an oral route, misoprostol has fast onset and offset of action and often does not cause sustained uterine contractions. Hence, oral misoprostol, at a low dose is useful for cervical ripening, but not as useful for stimulation of sustained uterine contractions for induction of labor. When administered by a buccal or vaginal route, misoprostol has prolonged activity and often

results in sustained uterine contractions. At any given dose of misoprostol, buccal and vaginal misoprostol administration are more effective than oral administration in inducing sustained uterine contractions sufficient to empty the uterus.¹⁵⁻¹⁹

Mifepristone

Mifepristone, an anti-progestin, is useful for cervical preparation and sensitizing myocytes to the action of uterotonics. Progesterone reduces cell-to-cell communication among uterine myocytes, facilitating uterine quiescence by suppressing connexin 43 and other proteins. Mifepristone blocks the effect of progesterone, inducing the production of myocyte connexin 43, enhancing efficient cell-to-cell communication, permitting uterine myocytes to contract in unison, creating the potential for powerful and sustained contractions.²⁰⁻²³ Randomized clinical trials report that administration of mifepristone 200 mg prior to misoprostol induced labor results in more rapid emptying of the uterus.²⁴⁻²⁷

It takes time for mifepristone to have its full effect on uterine myocytes. Hence, most protocols recommend waiting 24 hours following mifepristone administration before initiating treatment with an agent to stimulate uterine contractions such as misoprostol or oxytocin. However, preliminary data suggest that partial benefit of mifepristone can be obtained when initiating misoprostol 3 to 5 hours after mifepristone administration.²⁸ In a study of 481 patients undergoing induction of labor in the second or third trimester, the time from initiation of misoprostol to vaginal birth was 15 hours with no mifepristone pretreatment, 13.2 hours if mifepristone was administered 3 to 5 hours before

initiating misoprostol, 9.3 hours if mifepristone was administered 24 hours before initiating misoprostol, and 10.5 hours if mifepristone was administered 48 hours before initiating misoprostol.²⁸

Fetal size <25w0d gestation: Cervical preparation and surgical evacuation

For fetal demise at a fetal size less than 25w0d, if clinical experts are available, the best treatment option is cervical preparation followed by surgical evacuation of the uterus using a vacuum catheter and grasping forceps to empty the uterus.^{29,30} A disadvantage of surgical evacuation of the uterus is that an intact fetus is not available for the patient to hold and mourn, and pathologic examination of an intact fetus is not possible. An alternative approach is cervical preparation followed by induction of labor using misoprostol with the goal of delivering an intact fetus. Although no prospective clinical trials are available comparing these 2 options, retrospective studies have reported that, at fetal size <25w0d gestation, compared with induction of labor, surgical evacuation of the uterus results in fewer complications,³⁰ including fewer cases of retained placenta requiring an unplanned procedure and fewer presumed uterine infections.²⁹

For surgical evacuation of fetal demise with a fetal size of <25w0d gestation, the first step on day 1 is placement of osmotic cervical dilators. In addition to osmotic cervical dilators, if the gestational age or fetal size is ≥ 19 weeks' gestation an oral dose of mifepristone 200 mg to facilitate cervical preparation may be considered. On day 2, the osmotic dilators are removed and surgical evacuation is

performed. In one randomized study, for pregnancies at 19 to 24 weeks' gestation, compared with osmotic dilators alone, administration of mifepristone 200 mg at the time of placement of osmotic dilators resulted in fewer procedures that were difficult to complete.³¹ In some cases, 2 consecutive days of cervical preparation with osmotic dilators may be needed to properly prepare the cervix for uterine evacuation. For example, the cervix of a nulliparous teenage patient may require 2 days of cervical preparation with osmotic dilators to facilitate uterine evacuation. In some cases of fetal demise, the cervix is already dilated to ≥ 3 cm and surgical evacuation of the uterus or induction of labor can be initiated without the need for cervical preparation.

Fetal size 14w0d to 28w6d gestation: Cervical preparation and induction of labor

Treatment of fetal demise at 14w0d to 28w6d gestation with the goal of the vaginal birth of an intact fetus is optimized by the administration of mifepristone for cervical preparation followed by induction of labor with misoprostol.^{26,27}

In one clinical trial, 66 patients with fetal demise between 14w0d and 28w6d gestation were randomly assigned to receive mifepristone 200 mg or placebo followed 24 to 48 hours later with initiation of misoprostol induction of labor.²⁶ Among the patients from 14w0d to 24 weeks' gestation, the misoprostol dose was 400 μ g vaginally every 6 hours. For patients from 24w0d to 28 weeks' gestation, the misoprostol dose was 200 μ g vaginally every 4 hours. At 24 hours, a consultant obstetrician determined if additional misoprostol should be given. The median time

from initiation of misoprostol to birth for the patients in the mifepristone and placebo groups was 6.8 hours and 10.5 hours ($P=.002$).

Compared with the patients in the placebo-misoprostol group, the patients in the mifepristone-misoprostol group required fewer doses of misoprostol (2.1 vs 3.4; $P=.002$) and a lower total dose of misoprostol (768 μg vs 1,182 μg ; $P=.003$). All patients in the mifepristone group delivered within 24 hours. By contrast, 13% of the patients in the placebo group delivered more than 24 hours after the initiation of misoprostol treatment. Five patients were readmitted with retained products of conception needing suction curettage, 4 in the placebo group and 1 in the mifepristone group.²⁶

In a second clinical trial, 105 patients with fetal demise after 20 weeks of gestation were randomly assigned to receive mifepristone 200 mg or placebo.²⁷ In this study, 86% of the patients were $\geq 26\text{w}0\text{d}$ gestation, with a mean gestational age of approximately 32w2d. Thirty-six to 48 hours later, misoprostol induction of labor was initiated. Among the patients from 20 to 25 completed weeks of gestation, the misoprostol dose was 100 μg vaginally every 6 hours for a maximum of 4 doses. For patients from ≥ 26 weeks' gestation, the misoprostol dose was 50 μg vaginally every 4 hours for a maximum of 6 doses. The median times from initiation of misoprostol to birth for the patients in the mifepristone and placebo groups were 9.8 hours and 16.3 hours, respectively ($P=.001$). Compared with the patients in the placebo-misoprostol group, the patients in the mifepristone-misoprostol group required a lower total dose of misoprostol (110 μg vs 198 μg ; $P<.001$). Delivery within 24 hours following initiation of

misoprostol occurred in 93% and 73% of the patients in the mifepristone and placebo groups, respectively ($P<.001$). Compared with patients in the mifepristone group, shivering occurred more frequently among patients in the placebo group (7.5% vs 19.2%; $P=.09$), likely because they received greater doses of misoprostol.²⁷

Fetal size $\geq 29\text{w}0\text{d}$ gestation

At a fetal size $\geq 29\text{w}0\text{d}$ gestation, if the cervix is ripe with a Bishop score

of ≥ 7 , oxytocin induction of labor is often used as a first-line treatment. If the cervix is not ripe, misoprostol induction of labor may be considered at doses less than those used in the second trimester of pregnancy.³² TABLES 1,^{1, 26, 33-36} 2,³⁷ and 3³⁷ summarize regimens proposed for fetal size $\geq 29\text{w}0\text{d}$. One regimen begins with an initial misoprostol dose of 50 μg . If adequate uterine contractions occur, the 50 μg dose is repeated every 4 hours up to 6 total doses. If contractions are inadequate, the dose can be increased to 100 μg

TABLE 1 Misoprostol dosing protocols for medication management of fetal demise^{1, 26, 33-36}

Gestational age	Reference	Vaginal dose of misoprostol used to empty the uterus
Up to 13w6d	33, 34	800 μg single dose. A second dose of misoprostol may be considered if ultrasonography shows the gestational sac was not expelled, ³¹ or if there was no bleeding 48 hours after the first dose of misoprostol. ³²
14w0d to 24 weeks	26	400 μg every 6 hours for 4 doses
24w0d to 28 weeks	26	200 μg every 4 hours for 6 doses
$\geq 29\text{w}0\text{d}$	35	If the cervix is unripe: <ul style="list-style-type: none"> • 50 μg every 4 hrs up to 6 doses • If the first dose does not stimulate contractions (2 in 10 minutes) increase dose to 100 μg every 4 hrs for up to 5 doses • If the cervix is ripe: consider oxytocin induction of labor
ACOG Practice Bulletin No. 10. Management of stillbirth	1	400 to 600 μg every 3 to 6 hours
20w0d to 27w6d		
ACOG Practice Bulletin No. 135. Second-trimester abortion	36	800 μg followed by 400 μg every 3 hrs up to a maximum of 5 doses
13w0d to 26 weeks		"If the abortion is not complete after five doses, the woman may be allowed to rest for 12 hours before starting the cycle again."

Following completion of the cervical preparation step, misoprostol can be used to stimulate uterine contractions to empty the uterus. References 1, 26, and, 33-36 refer to administering mifepristone 24 to 48 hours prior to initiation of misoprostol. Based on multiple clinical trials, mifepristone (200 mg) administration for cervical preparation 24 to 48 hours prior to misoprostol administration improves clinical outcomes (References 26, 33, and 34).

TABLE 2 Misoprostol dosing protocols for medication management of fetal demise in patients with no prior history of cesarean birth or major uterine incision^{37,a}

Gestational age	Buccal dose of misoprostol used to empty the uterus
24w0d to 31w6d	400 µg misoprostol every 2 hours
32w0d to 32w6d	200 µg at induction initiation. Thereafter, if no contractions at initiation: <ul style="list-style-type: none"> • 400 µg every 2 hours If contractions are present: <ul style="list-style-type: none"> • 200 µg every 2 hours
≥33w0d	100 to 200 µg misoprostol every 2 hours based on clinician's judgment

^aFollowing completion of the cervical preparation step, misoprostol can be used to stimulate uterine contractions to empty the uterus. For cervical preparation, patients in this study received osmotic cervical dilators 18 to 24 hours prior to initiation of misoprostol. Most patients also received mifepristone 200 mg 24 to 28 hours prior to initiation of misoprostol.

every 4 hours for 5 additional doses.

For fetal demise after 28w0d gestation, the American College of Obstetricians and Gynecologists (ACOG)¹ recommends standard obstetric protocols for induction of labor, including standard protocols for induction of labor following a previous cesarean birth. For a patient with a history of a prior cesarean birth or major uterine surgery, ACOG recommends that management of fetal demise should prioritize the use of mechanical

cervical ripening, for example with a balloon catheter, and induction of uterine contractions with oxytocin.³⁸ ACOG recommends against the use of misoprostol for cervical ripening or labor induction for patients with a stillbirth at term with a history of a cesarean birth.³⁸ Preliminary experience suggests that stillbirth protocols using misoprostol doses modestly greater than those used in the management of a pregnancy with a viable fetus may be safe.⁹ See TABLES 2 and 3.

TABLE 3 Misoprostol dosing protocols for medication management of fetal demise in patients with a prior history of cesarean birth^{37,a,b}

Gestational age	Buccal dose of misoprostol used to empty the uterus
24w0d to 26w6d	One dose of 400 µg at induction initiation followed by 200 µg every 4 hours
27w0d to 31w6d	One dose of 100 µg at induction initiation followed by 50 µg every 4 hours
≥32w0d	Misoprostol not recommended because of the increased risk of uterine rupture

^aFollowing completion of the cervical preparation step, misoprostol can be used to stimulate uterine contractions to empty the uterus. The dose regimens suggested below are designed for patients with a history of a prior cesarean birth or major uterine incision who are at increased risk for uterine rupture during labor. For cervical preparation, patients in this study received osmotic cervical dilators 18 to 24 hours prior to initiation of misoprostol. Most patients also received mifepristone 200 mg 24 to 28 hours prior to initiation of misoprostol.

^bPatients with a prior cesarean birth should be aware that induction of labor is associated with a risk of uterine rupture.

A multidisciplinary approach can optimize compassionate care

There are many gaps in the holistic care of patients and partners experiencing fetal demise. Patients with fetal demise often report that they did not receive sufficient information about the cause of the demise and wanted more opportunity to be involved in decision making about their care.³⁹ The patient's partner often reports feeling unacknowledged as a grieving parent.⁴⁰ Fetal demise is experienced by many patients as a tragedy, triggering feelings of grief, anger, denial, anxiety and depression, sometimes resulting in isolation and substance misuse.

Using a 5-round Delphi process, experts identified 8 core goals in the care of patients with fetal demise:

1. reduce stigma
2. provide respectful care
3. involve patients in care planning
4. attempt to provide an explanation for the demise¹
5. acknowledge the depth of the grief response and provide emotional support
6. offer information about ongoing psychological support
7. provide information about future pregnancy planning
8. provide opportunities for specialized training and support for care providers.⁴¹

Management of stillbirth is optimized by a multidisciplinary approach that includes the expert care of obstetrician-gynecologists, obstetric nurses, anesthesiologists, and expert consultation from social work, chaplaincy, and pathology. A heart-to-heart connection between clinician and patient is a key component of stillbirth care. ●

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