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REVIEW ARTICLE

Misoprostol for intrauterine fetal death

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Recommended Dosages
13–17 weeks: vaginal misoprostol 200 μg 6–hourly (×4)
18–26 weeks: vaginal misoprostol 100 μg 6–hourly (×4)
27–43 weeks: vaginal misoprostol 25–50 μg 4–hourly (×6)
Reduce the dose in women with a previous cesarean section.

KEYWORDS
Intrauterine fetal death;
Misoprostol;
Medical management;
Fetal demise;
Second and third trimester

Abstract

The frequency of intrauterine fetal death (IUFD) with retained fetus varies, but is estimated to occur in 1% of all pregnancies. The vast majority of women will spontaneously labor and deliver within three weeks of the intrauterine death. The complexity in medical management increases significantly when the cervix is unripe or unfavorable, or when the woman develops disseminated intravascular coagulation. Misoprostol regimens for the induction of labor for second and third trimester IUFDs, range from 50 to 400 μg every 3 to 12 h, and are all clinically effective. Nevertheless, the current scientific evidence supports vaginal misoprostol dosages, which are adjusted to gestational age: between 13–17 weeks, 200 μg 6-hourly; between 18–26 weeks, 100 μg 6-hourly; and more than 27 weeks, 25–50 μg 4-hourly. In women with a previous cesarean, lower doses should be used and doubling of doses should not occur. Clinical monitoring should continue after delivery or expulsion because of the risk of postpartum atony and/or placenta retention.

1. Introduction

The frequency of intrauterine fetal death with a retained fetus varies, but is estimated to occur in 1% of all pregnancies. This clinical situation is psychologically stressful for the woman and her family members, and for the health professionals providing care.

When a fetus dies in the uterus, the options for health care are either to await onset of spontaneous labor or to induce labor [1].

The vast majority (over 90%) of women will spontaneously labor and deliver within three weeks of the intrauterine death. Expectant management therefore remains an acceptable option in some settings.

In cases where expectant management is chosen, the clinical concern will be the development of disseminated

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intravascular coagulation with its inherent risks of hemorrhage, blood product transfusion and maternal death.

Induction of labor is a common and evidence-based practice of obstetrics. In cases of intrauterine fetal death (IUFD), therefore, the decision to induce labor in a patient with a ripe cervix is straightforward and the procedure often uncomplicated.

The complexity in medical management increases significantly when the cervix is unripe or unfavorable (Bishop score <6). Inducing labor in a pregnant woman with an unripe cervix is associated with failed induction of labor and a higher risk of cesarean delivery.

This problem has been dramatically reduced with the local or systemic use of prostaglandins and other mechanical methods of cervical ripening prior to intravenous oxytocin administration for labor induction. There is no gold standard, either medical or surgical, for the treatment of late IUFD.

Oral misoprostol administration for labor induction with an IUFD was first described in Sao Paulo, Brazil in 1987 [2]. Since that time, the use of misoprostol for obstetrical purposes has grown widely. There are dozens of reports, many policy statements, reviews, and meta-analyses describing its use for induction with live fetuses. Unfortunately, there is a lack of uniformity in the dose and frequency of misoprostol dosing when used for induction of labor in the second and third trimester, and very few good quality randomized controlled trials for its use in IUFD.

The issues related to proper use of misoprostol are somewhat different for women who need labor induction in the face of IUFD compared to those with live fetuses. This is because although the concerns regarding fetal wellbeing are eliminated, there is the possibility of disseminated intravascular coagulation complicating IUFD and jeopardizing the woman's life. Other concerns are present for all inductions, irrespective of whether there is an IUFD or live fetus. These are the systemic side effects (nausea, vomiting, diarrhea, and shivering), and uterine overactivity (hyperstimulation, hypertonus and tachysystole).

For IUFD induction, vaginal misoprostol is as effective as dinoprostone [3] and gemeprost [4], and less costly. The additional use of cervical laminaria with misoprostol does not increase its efficacy [5], but pre-induction administration of oral mifepristone shortens the time needed for labor induction [6,7]. Mifepristone is, however, not widely available. The spectrum of misoprostol dosing regimens described in the literature for cervical ripening and induction of labor in second and third trimester IUFDs ranges from 50 to 400 μg given every 3 to 12 h by various routes. All have been shown to be clinically effective. Nevertheless, the current evidence base supports the conclusion that the most appropriate route of administration is vaginal [3,8–18].

There is a limited evidence base in peer-reviewed journals for misoprostol use for labor induction with IUFD [19,20]. The vast majority of reports are descriptive series or non-randomized prospective comparisons. Cases series report a shorter time until delivery and lower required doses of misoprostol to obtain successful deliveries in cases of IUFD compared with live fetuses [17,21]. There is a wealth of data for second trimester pregnancy termination which are useful and can be applied to IUFD in the second trimester [20]. Similarly, data for labor induction with live fetuses can be applied to IUFD in the third trimester [13]. Further research specifically on second and third trimester labor induction with IUFD is needed.

For the purposes of this article we have considered an intrauterine fetal death as any intrauterine pregnancy beyond 12 weeks with a dead fetus, which has not been expelled. For fetal death at 12 weeks or less please see the article on missed abortion elsewhere in this issue [22].

2. Contraindications

Contraindications of misoprostol induction are allergy to prostaglandins, and contraindications to vaginal delivery. The latter includes placenta previa and transverse lie, although in those circumstances where placenta previa and malpresentation complicate IUFDs up to 24 weeks, it may be appropriate to use misoprostol, depending on the setting and the skills of the health care providers.

3. Precautions

When vaginal misoprostol is used for induction in a woman with a live fetus and a history of prior cesarean or uterine surgery, there is an increased risk of uterine rupture. The majority of studies of induction using misoprostol for second and third trimester IUFD, however, did not include women with previous uterine scars from cesareans [3,5,18,21,23–25]. However, in the studies in which they were included there were no cases of uterine rupture, including during early second trimester [10,16,17,26–30].

In women with previous cesarean births, lower doses should be used and doubling should not occur.

Surveillance for disseminated intravascular coagulation should occur, although the consumption of coagulation factors is a gradual process that usually occurs over weeks after the fetal death. If the patient has disseminated intravascular coagulation, blood transfusion should be given to correct the coagulopathy prior to the induction as part of the comprehensive approach to this complication.

4. Regimen

4.1. IUFD from 13 to 17 weeks

Vaginal misoprostol 200 μg every 6 to 12 h for a total of 4 doses [3,13,18,25,29,31,32]. If the *first dose* does not lead to effective contractions the subsequent dose could be doubled to 400 μg. The maximum daily dosing should not exceed 1600 μg.

4.2. IUFD from 18 to 26 weeks

Vaginal misoprostol 100 μg every 6 to 12 h for a total of 4 doses [3,13,18,25,29,31,32]. If the *first dose* does not lead to effective contractions the subsequent dose could be doubled to 200 μg. The maximum daily dosing should not exceed 800 μg.

4.3. IUFD beyond 26 weeks [10,12–15,33]

If the cervix is unripe (Bishop score <6), vaginal misoprostol 25–50 μg is given every 4 h (up to 6 doses). If the cervix is already ripe (Bishop score ≥6) providers will need to evaluate and decide between oxytocin or misoprostol based on the setting and availability of the drugs. The gold standard, however, remains oxytocin. If the *first dose* does not lead to effective contractions the subsequent dose could be doubled to 50 or 100 μg. The maximum daily dosing should not exceed 600 μg. If expulsion has not occurred after 24 h, the same treatment course can be repeated a second time. Oxytocin administration, if necessary, may begin 4 h following administration of the last dose of misoprostol.

5. Course of treatment

5.1. Repeated dosing

Before administering a repeated dose for IUFD beyond 26 weeks, uterine activity should be evaluated. If the patient has 2 or more contractions in 10 min, the dose should not be repeated, because of the risk of uterine hyperstimulation. If the uterine contraction frequency diminishes, a repeat dose may be given. If, however, the uterine contraction frequency persists or the patient has demonstrated sufficient progress in cervical dilatation, intravenous oxytocin can be administered. We recommend that oxytocin should not be initiated until 4 h following administration of the last dose of misoprostol.

5.2. Monitoring

Clinical monitoring of the women should continue after delivery or expulsion because of the risk of postpartum atony and/or placenta retention. Both may cause postpartum hemorrhage.

Etiologies for IUFD should be sought as appropriate for the institution [1]. Similarly, bereavement and psychological support services should also be provided to women before, during and after delivery of an IUFD.

5.3. Effectiveness

Regardless of the route of misoprostol administration, the vast majority of women (67%–83%) with late IUFD will deliver vaginally within 24 hours [3,10,12,15,17,34]. The remainder will deliver within the ensuing additional 24 hours [2,3,15,17,34,35]. If delivery or abortion has not occurred after this time, options include surgical termination, expectant management, or repeating the induction attempt 24 hours after the first failed attempt. These options should be weighed in the context of the urgency in evacuation of the uterus and the patient's desires for expediency. Variables that influence success (defined as vaginal delivery within 24 hours are favorability of the cervix (Bishop score >6), parity and gestational age [12–14].

Approximately 25% of women will have retained placental fragments; this is a complication that is seen more frequently with second trimester inductions for IUFD than those in the third trimester [25,35].

5.4. Risks and side effects

The most serious complications associated with intra-vaginal misoprostol use for IUFD are premature separation of placenta, postpartum hemorrhage, and rare events such as uterine rupture and amniotic fluid embolism [13]. In women induced with a previous cesarean section scar the risk for uterine rupture may be increased, especially in the third trimester. For these women, therefore, it is advisable to use lower doses of misoprostol under close clinical monitoring [2,3,10,26,28,30,36,37].

There are no reports of maternal mortality and only a few reports of added morbidities such as chorioamnionitis or excessive blood loss. In the few reported cases in which a blood transfusion was needed, many of the women had underlying malarial parasitemia which predisposed to this need [33].

The most commonly reported side effects include [13,19]:

- Cramping: Uterine contractions are frequently painful. Pain treatment such as NSAIDs and opioids may be used. Prophylactic administration should also be considered.
- Gastrointestinal side effects: up to 35% of women will experience nausea, vomiting, or diarrhea
- Pyrexia and shivering: this may occur in up to 7% of women.

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Conflict of interest

The authors do not have any conflict of interest.

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