SOCIETY of FAMILY PLANNING
research, education, and leadership

Contraception 88 (2013) 341 – 349

Clinical Guidelines

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

Release date June 2013
SFP Guideline #20133

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.

0010-7824/$ – see front matter
http://dx.doi.org/10.1016/j.contraception.2013.05.001

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