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Induction of labor

Use of specific agents

Prostaglandin E1 (misoprostol) — Misoprostol (Cytotec) is a prostaglandin E1 analog available as 100 and 200 mcg tablets, which can be broken to provide 25 or 50 mcg doses. It is rapidly absorbed from both the oral and vaginal routes [47]. Either route is reasonable; one route of administration is not clearly better than another in terms of important health outcomes, although available data are difficult to interpret because of differences in dosing [43]. The 25 mcg dose is generally preferred because adverse effects are mostly seen at higher doses [3]. The existence of a toxic dose of misoprostol has not been determined and cumulative total daily doses of 1600 mcg have been tolerated, with only symptoms of gastrointestinal discomfort [48].

The approved indication for misoprostol is treatment and prevention of gastric ulcer disease related to chronic nonsteroidal anti-inflammatory drug use. Administration of this drug for cervical ripening and labor induction is considered an off-label use in the United States. However, there is good evidence that it is an effective alternative to PGE2 preparations for cervical ripening and labor induction [18,44-46,49]. The American College of Obstetricians and Gynecologists (ACOG) has stated that use of misoprostol appears as safe and efficacious as other prostaglandin agents when used as a cervical ripening and/or labor induction agent as described below [3].

Vaginal administration — The optimal dose and timing interval of intravaginally applied misoprostol have not been determined [44,50-53].

- Misoprostol 25 mcg vaginally, with redosing intervals of three to six hours is a common dose [3,44,54-57]. Oxytocin may be initiated, if necessary, four hours after the final misoprostol dose.
- In some situations, such as inadequate uterine activity at lower doses, misoprostol 50 mcg vaginally at six-hour intervals may be appropriate; however, this dose has been associated with a higher risk of tachysystole [3].

●A misoprostol vaginal insert consisting of a controlled-release, retrievable polymer chip for gradual delivery of 200 mcg over 24 hours is available in some countries but not in the United States. In a large randomized trial comparing patients who received the misoprostol vaginal insert with those receiving a dinoprostone vaginal insert, use of the misoprostol vaginal insert resulted in a significantly shorter median time to vaginal birth (21.5 versus 32.8 hours) but also resulted in a higher chance of uterine tachysystole requiring intervention (13.3 versus 4 percent) and did not change the chance of cesarean birth [58].

A meta-analysis reported that the 50 mcg dose vaginally was more effective than the 25 mcg dose (eg, resulted in a higher chance of birth after a single dose and of delivery within 24 hours, and a lower chance of oxytocin use), but the 25 mcg dose resulted in lower rates of tachysystole, cesarean birth for nonreassuring FHR, neonatal intensive care units admission, and meconium passage [59].

Oral administration — When administered orally, the concentration peaks sooner and declines more rapidly than with vaginal administration (figure 2) [47]. The dose recommended by the World Health Organization is 25 mcg orally, with two-hour redosing intervals [57]. Oxytocin may be initiated, if necessary, four hours after the final misoprostol dose.

Randomized trials have used a wide variety of oral doses (20 to 200 mcg) and intervals of administration (1 to 6 hours) [60]. Despite many trials, there is no clear consensus as to the optimum oral dose or dosing interval, and whether the patient should swallow a tablet versus a titrated oral misoprostol solution.

A 2021 meta-analysis supported the use of low-dose oral misoprostol for induction of labor and suggested that a starting dose of 25 mcg may offer a good balance of efficacy and safety [46]. It should be noted, however, that the authors considered the recommendation to have only moderate-to-low certainty given imprecision, inconsistency, and study limitations. Included trials compared oral misoprostol protocols of one- to two-hourly versus four- to six-hourly dosing; doses of 20 to 25 mcg versus 50 mcg; and 20 mcg hourly titrated versus 25 mcg two-hourly static.

Buccal or sublingual administration — Other approaches to use of misoprostol, including buccal and sublingual administration, have been described, but are less well studied and should be considered

investigational [61-64]. These routes of administration may avoid first-pass hepatic metabolism associated with oral ingestion and thus increase bioavailability similar to that achieved with vaginal administration. Pharmacokinetic data support the hypothesis that buccal and sublingual routes of administration are associated with more rapid onset of action and greater bioavailability than other routes [61]. Additionally, it is hypothesized that administration using these routes may reduce the risk of tachysystole by avoiding direct uterine effects.

However, a meta-analysis of five small trials (n = 740 patients) of sublingual versus vaginal administration found no statistically significant differences in rate of vaginal birth not achieved within 24 hours (OR 1.27, 95% CI 0.87-1.84), uterine hyperstimulation syndrome (OR 1.20, 95% CI 0.61-2.33), or cesarean birth (OR 1.33, 95% CI 0.96-1.85), but uterine tachysystole was increased in the sublingual misoprostol group (OR 1.70, 95% CI 1.02-2.83) [65]. A subsequent well-designed trial (IMPROVE) including 300 patients suggested vaginal misoprostol may be superior to the buccal route: time to vaginal birth was reduced by eight hours, and fewer emergency cesareans were performed for FHR abnormalities [66].