

## Obstetric Use of Misoprostol (Cytotec)

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Misoprostol is a synthetic analogue of prostaglandin E<sub>1</sub>. It initially received FDA approval for prevention and treatment of acid peptic disease related to use of non-steroidal anti-inflammatory medications<sup>1</sup> and is marketed by G. D. Searle Co. as *Cytotec* in the United States. Like other prostaglandins of the E and F classes, misoprostol has uterotonic properties and has therefore been investigated as an agent for cervical ripening and induction of labor, as well as other obstetric and gynecologic indications. Its advantages over other presently available prostaglandin preparations include low cost, few side effects, and the ability to be stored at room temperature.<sup>1</sup>

With regard to cervical ripening and induction of labor, misoprostol was studied in a variety of dosing routes and regimens and compared to other prostaglandins such as dinoprostone (prostaglandin E<sub>2</sub>), oxytocin, and other induction methods, as well as placebo.<sup>2,3</sup> Misoprostol was shown to have a higher rate of vaginal delivery within 24 hours (70.3 percent vs. 50.9 percent), shorter induction-to-delivery interval, and lower cesarean-section rates (15.6 percent vs. 21.5 percent) than pooled figures for control methods<sup>4</sup>. Although uterine tachysystole (>12 contractions within 20') and meconium passage are increased with misoprostol, meta-analyses have not shown any increase in overt hyperstimulation, Apgar scores <7 at five minutes, or NICU admissions compared to controls.<sup>2,4</sup> When misoprostol is used for cervical ripening, there is less need for oxytocin augmentation compared to dinoprostone (34 percent vs. 66 percent).<sup>5</sup>

A number of studies examined the route of administration of misoprostol—oral vs. vaginal. Recent studies also looked at buccal and combined oral/vaginal administration.<sup>6,7</sup> An evaluation of the pharmacokinetics of oral vs. vaginal misoprostol shows a higher peak with oral administration and greater bioavailability and more sustained levels for vaginal.<sup>8</sup> Although results of clinical trials varied and the quality of the studies were mixed, head-to-head studies show higher vaginal delivery rates within 24 hours for 25 mcg vaginally vs. 25 or 50 mcg orally.<sup>7,9</sup> When larger oral doses such as 200 mcg were compared to 25 or 50 mcg vaginal doses, the rates of successful vaginal delivery were equivalent, but the oral route resulted in increased uterine tachysystole and hyperstimulation. A recent study showed a dose of 25 mcg vaginally resulted in a 67 percent rate of vaginal delivery

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within 24 hours vs. 36 percent for 25 mcg orally.<sup>7</sup> In certain cases, there might be benefits to the oral route to try to minimize vaginal exams.

Several dosage regimens were also evaluated. A 50 mcg vaginal dose was found to have a shorter induction to delivery interval and less oxytocin use than 25 mcg, although induction success and vaginal delivery rates were similar. Neonatal outcomes were similar, although more uterine hyperstimulation was seen at the 50 mcg dose.<sup>10</sup> Another study found the 25 mcg vaginal dose resulted in less uterine tachysystole (17.4 percent vs. 36.7 percent) and meconium passage (17.4 percent vs. 27.7 percent) than a 50 mcg dose.<sup>11</sup> A recent meta-analysis comparing the two doses concluded the 50 mcg dose was more effective than the 25 mcg dose, but might not be as safe.<sup>21</sup>

There are reports of uterine rupture following use of misoprostol in women with a scarred uterus,<sup>12,13</sup> and one review article states, "the rate of uterine rupture was significantly higher in patients with previous cesarean delivery who had labor induced with misoprostol than in patients with previous cesarean delivery who did not receive misoprostol".<sup>4</sup> Uterine rupture rates in patients undergoing a trial of labor after cesarean section were reported as 5.6 percent for misoprostol, 2.9 percent for prostaglandin E<sub>2</sub>, and 0.7 percent for oxytocin, compared to 0.45 percent for spontaneous labor.<sup>14,15</sup>

In November 1999, the American College of Obstetricians and Gynecologists (ACOG) issued a committee opinion<sup>16</sup> endorsing the efficacy of misoprostol for induction of labor in patients who have unfavorable cervixes. Subsequently, the Searle Co. issued a warning letter to health care practitioners advising that misoprostol was not approved for the induction of labor and reporting on adverse occurrences associated with misoprostol. This letter caused concern in the medical and lay community. In response, ACOG took the unprecedented step of issuing a response to the Searle letter<sup>17</sup> that stated in part: "although the letter correctly points out the potentially serious, but relatively rare, risks of misoprostol when employed for cervical ripening or labor induction, it fails to comment on the extensive clinical experience with the agent and the large body of published reports supporting its safety and efficacy when used appropriately."

We favor the guidelines for use of misoprostol for cervical ripening and labor induction in accordance with ACOG Committee Opinions 228 and 248:

1. An initial intravaginal dose of 25 mcg every four hours should be used; a 50 mcg dose every six hours may be considered. This should be given as one-quarter of a 100 mcg tablet that was divided with a pill-cutter. Gel suspension should not be used, and use of vaginal lubricants should be minimized.
2. Misoprostol is not recommended for women with prior uterine surgery (cesarean section, myomectomy) due to the risk of uterine rupture.
3. Misoprostol should be used in a hospital setting with fetal heart rate and uterine activity monitoring. Limited ambulation is permissible if preliminary fetal monitoring is reassuring.

4. Oxytocin should not be administered less than four hours after the last misoprostol dose.
5. There is insufficient clinical evidence to address the safety or efficacy of misoprostol in patients with multifetal gestation or suspected fetal macrosomia.
6. If a physician elects to use misoprostol for cervical ripening or labor induction, the patient should be informed of the need for induction and the choice of medications available, and the risks, benefits, and alternatives of these choices. Hospital and departmental guidelines should be established for its use.

Misoprostol affords a very significant cost savings over other forms of labor induction. A 100 mcg tablet of misoprostol costs less than \$1, while prostaglandin E<sub>2</sub> vaginal gel costs \$50-75, and prostaglandin vaginal inserts cost greater than \$125. Oxytocin itself is not expensive (approx. \$15 per ampule) but entails added charges due to intravenous administration and more intensive nursing care.

Misoprostol is also used for prevention and treatment of postpartum hemorrhage. Doses of 400-600 mcg are used orally in the third stage of labor with results comparable to standard therapy (oxytocin and/or methylergometrine).<sup>3,18</sup> Rectal doses of 400-1,000 mcg are reported for prevention of postpartum hemorrhage and as second-line treatment of hemorrhage, with good results.<sup>19,20</sup> However, the absorption of misoprostol rectally is not studied and is likely slower than intravenous or intramuscular routes; this should be taken into account in determining its place in management schemes for postpartum hemorrhage.

Misoprostol is used as well for a variety of other gynecologic indications, including ripening the non-pregnant cervix prior to hysteroscopy, treatment of missed or incomplete abortion, and for first- and second-trimester pregnancy termination.<sup>1,3</sup> It is not our purpose to discuss or advocate the use of misoprostol for these indications.

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**Note to physicians and healthcare professionals:** The preceding information is intended to serve as a *guide*. *The obstetric use of misoprostol should be tailored to each patient's clinical situation by the physician in consultation with the patient.*

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