Is the vaginal or buccal route more effective when administering prostaglandins for cervical ripening at term?

Vaginal administration of misoprostol (25 µg initial dose, 50 µg subsequent doses) **may be superior to the buccal route,** according to results of the IMPROVE trial, a prospective randomized placebo-controlled study of 300 women with a singleton vertex fetus requiring cervical ripening for induction of labor at term. Women treated with vaginal misoprostol (VM) had more rapid vaginal delivery, more vaginal deliveries within 24 hours, and fewer urgent cesarean deliveries for nonreassuring fetal testing (although the overall cesarean delivery rate was not significantly different) compared with those treated with buccal misoprostol (BM).

Haas DM, Daggy J, Flannery KM, et al. A comparison of vaginal versus buccal misoprostol for cervical ripening in women for labor induction at term (the IMPROVE trial): a triple masked randomized controlled trial. Am J Obstet Gynecol. 2019. doi:10.1016/j.ajog.2019.04.037.

EXPERT COMMENTARY

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Cervical ripening is routine practice in women undergoing induction of labor who have an unfavorable cervical examination.[1] This is because generating contractions against a long thick cervix is more likely to lead to failed induction and cesarean delivery. Cervical ripening can be achieved using mechanical or pharmacologic methods.

Misoprostol (a prostaglandin E_1 [PGE_1] analog) is approved by the US Food and Drug Administration for the treatment of peptic ulcer disease, but it also is widely used off-label for cervical ripening, partly due to its low cost. Misoprostol's optimal dosing regimen and route of administration are not known. The IMPROVE trial was designed to address this knowledge gap, specifically to compare the efficacy and safety of VM versus BM in women undergoing labor induction at term.

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FAST TRACK

The IMPROVE trial was designed to address a knowledge gap: comparing the efficacy and safety of vaginal misoprostol versus buccal misoprostol for cervical ripening in women undergoing labor induction at term

Details of the study

The IMPROVE trial was a prospective, randomized, noninferiority, triple-masked,

Cervical ripening and risk of cesarean delivery among overweight patients

While a number of studies have evaluated the risk of cesarean delivery (CD) with the use of cervical ripening agents by different routes of administration, Handal-Orefice and colleagues studied this outcome specifically in a predominantly overweight population at a tertiary care center.[1]

The retrospective study included 276 women, of whom 91% had a body mass index (BMI) of 25 kg/m^2 or more and 61% had a BMI of 30 kg/m^2 or more at the time of delivery.

For cervical ripening, 138 women received vaginal misoprostol (25 µg) and 138 received oral misoprostol (50 µg). The frequency of CD (the primary study outcome) was significantly higher with oral compared with vaginal misoprostol use (32% vs 21%; *P* = .04). When the analysis was adjusted for age, BMI, parity, indication for induction, and Foley catheter use, the risk of CD remained significantly higher for the oral misoprostol group (adjusted odds ratio [aOR], 2.01; 95% confidence interval [CI], 1.07–3.76).

Other key findings:

- frequency of CD among nulliparous women: 41% in the oral misoprostol group, 28% in the vaginal misoprostol group (aOR, 2.79; 95% CI, 1.26–6.19)
- time to vaginal delivery: 41 hours for the oral misoprostol group, 31 hours for the vaginal misoprostol group (*P* = .01)
- uterine tachysystole: 11% in the oral misoprostol group, 20% in the vaginal misoprostol group (*P* = .04).

The authors noted that the strengths of the study, including the racial and ethnic diversity of the population (72% of women were of either black or Hispanic race or ethnicity), the commonly used doses of misoprostol, and the performance of inductions outside a research protocol, add to the generalizability of the results.

Reference

1. 1. Handal-Orefice R, Friedman AM, Chouinard SM, et al. Oral or vaginal misoprostol for labor induction and cesarean delivery risk. *Obstet Gynecol*. 2019. doi:10.1097/AOG.0000000000003274.

FAST TRACK

The time to vaginal delivery from first dose was reduced in the VM versus BM group (20.1 vs 28.1 hours; P = .006); urgent CD for nonreassuring fetal testing was similarly reduced in the VM patients (3.3% vs 9.5%; P = .33)

placebo-controlled trial of 300 women with a singleton vertex fetus requiring cervical ripening for induction of labor at term.[2] Enrolled women were randomly assigned to VM or BM (same dosing regimen) and to a matching placebo administered via the opposite route.

Primary outcomes included time-to-vaginal-delivery from first dose, which was reduced in VM vs BM (20.1 vs 28.1 hours; *P* = .006), and urgent cesarean delivery for nonreassuring fetal testing, which was similarly reduced in VM (3.3% vs 9.5%; *P* = .33). These differences persisted after controlling for covariates. There was also a greater difference seen in multiparous versus nulliparous women.

Secondary outcomes also favored VM over BM, including more vaginal deliveries within 24 hours, fewer doses to achieve active labor, and a lower maximum dose of oxytocin.

Overall cesarean delivery rates were similar in the 2 groups (VM, 15.8%; BM, 22.3%; *P* = .15). There were no significant differences in other delivery characteristics or in maternal or fetal adverse events.

Study strengths and limitations

The IMPROVE trial had a triple-blinded study design with an intention-to-treat paradigm and good follow-up. There was also standardization of PGE_1 administration criteria, which was consistent with the American College of Obstetricians and Gynecologists standards of care. Results were similar to those of prior studies regarding rates of tachysystole, urgent cesarean delivery, and vaginal delivery.

The study has good generalizability as it included both elective and medically indicated inductions; however, patients with ruptured membranes were excluded. Although there was no difference in the overall cesarean delivery rates, the study was underpowered to look at this outcome. The authors included a patient satisfaction survey, but this is hard to interpret since study participants all received tablets orally and vaginally. The study did not address efficacy of VM versus BM administration at different doses or time intervals.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Labor induction has doubled over the past 2 decades, with almost 25% of parturients currently undergoing induction in the United States.[3] This number is likely to increase given recent data suggesting that routine induction at 39 weeks may significantly decrease cesarean delivery rates.[4] It is critical, therefore, that we identify the optimal technique for cervical ripening, including the ideal dosing regimen and route of administration. Results of the IMPROVE trial suggest that vaginal administration of misoprostol (25 µg initial dose, 50 µg subsequent doses) may be superior to the buccal route, with more rapid vaginal delivery, more vaginal deliveries within 24 hours, and fewer urgent cesareans for nonreassuring fetal testing (although the overall cesarean delivery rate was not significantly different).

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