

# Current Status of Prostaglandins for Cervical Ripening

Javine McLaughlin, M.D., and Lawrence D. Devoe, M.D.

**OBJECTIVE:** To review the safety and efficacy of administering various prostaglandin formulations to achieve cervical ripening and spontaneous vaginal delivery in women near or at term.

**STUDY DESIGN:** Peer-reviewed clinical research articles in English and searchable on PubMed.com. A thorough literature search was conducted on PubMed.com using the following terms: [misoprostol], [dinoprostone], [prostaglandin E<sub>1</sub>], [prostaglandin E<sub>2</sub>], [PGE<sub>1</sub>], [PGE<sub>2</sub>], [cervical ripening], [induction of labor].

**RESULTS:** The review shows conflicting opinions concerning the safety and efficacy of current standard-of-care formulations for cervical ripening. A gold standard option for optimal treatment has not been confirmed.

**CONCLUSION:** While the clinical evidence suggests that prostaglandin E<sub>1</sub> (PGE<sub>1</sub>) and E<sub>2</sub> (PGE<sub>2</sub>) both could be used for cervical ripening when no contraindications are present, PGE<sub>2</sub> formulations remain the only commercially available prostaglandin products for cervical ripening approved by the U.S. Food and Drug Administration. We conclude that more research is warranted on the risks of treatment-emergent adverse events and serious complications during induction of labor. (J Reprod Med 2017;62:221–228)

**Keywords:** cervical ripening; dinoprostone; labor induction; misoprostol; prostaglandin; PGE<sub>1</sub>; PGE<sub>2</sub>; receptors, prostaglandin E; review.

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## Overview

### Induction of Labor

Induction of labor is one of the most common obstetric procedures in the United States.<sup>1</sup> The rate rapidly increased from 9–32% between 1989 and

2005<sup>2-4</sup> and decreased from 32–23% between 2005 and 2014.<sup>4-6</sup> While numerous individual factors may affect the outcome of labor induction techniques, cervical ripening is a critical prelude to the onset of labor and normal parturition.<sup>7,8</sup> The procedure has been associated with reduced time to delivery and decreased rates of failed inductions.<sup>8,9</sup>

The Bishop score is the most commonly used index for assessing the likelihood of successful labor induction; a Bishop score  $\geq 9$  indicates a greater likelihood of successful induction, and a score  $\leq 7$  is indicative of an unfavorable cervix.<sup>10</sup> Labor induction is considered successful following the initiation of regular strong uterine contractions, progressive cervical dilation and effacement, and descent of the fetal head during active labor. While there is no generally accepted definition of failed or

From the Department of Obstetrics and Gynecology, Methodist Richardson Medical Center, Richardson, Texas, and the Section of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Medical College of Georgia, Augusta University, Augusta, Georgia.

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Address correspondence to: Javine McLaughlin, M.D., Department of Obstetrics and Gynecology, Methodist Richardson Medical Center, 2831 East President George Bush Highway, Richardson, TX 75082 (jhobgyn@gmail.com).

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unsuccessful induction of labor,<sup>11</sup> it can be defined as when active labor is not achieved or labor does not progress.<sup>10,12</sup> In the case of an unfavorable cervix, as judged by the Bishop score, both mechanical agents (i.e., laminaria insertion or Foley catheter) and pharmacologic agents (i.e., prostaglandins or oxytocin) have been used to enhance cervix favorability and to increase the likelihood of a successful induction of labor. While low-dose synthetic oxytocin (Pitocin [oxytocin injection, USP], Par Pharmaceutical Companies, Inc., Spring Valley, New York) has been the principal pharmacologic agent for labor induction since the 1950s,<sup>13</sup> oxytocin alone often fails to induce labor successfully.<sup>14</sup>

This review will focus specifically on the medical use of various prostaglandin formulations for cervical ripening to initiate the labor and delivery process when no contraindications to vaginal delivery are present.

### **Pharmacologic Agents for Cervical Ripening** *Prostaglandins*

The prostaglandins belong to a group of bioactive lipid compounds with hormone-like activity which, together with relaxin, estrogen, nitric oxide, and various inflammatory mediators, are involved in the process of cervical ripening.<sup>7</sup> Produced endogenously by almost every tissue in the body, including the myometrium, the prostaglandins are important for spontaneous vaginal delivery. During the third trimester of pregnancy, the estrogen concentration will gradually increase, resulting in a decreased progesterone/estrogen ratio. With an action opposing progesterone, estrogen stimulates increased production of prostaglandins and oxytocin receptors<sup>15,16</sup> and enhances the sensitivity of the myometrium to stimulatory agonists.<sup>17</sup> Due to the positive effects of estrogen on uterine activity, it has recently been suggested that a progesterone/estrogen ratio of <0.45 could be a prognostic factor for delivery rate.<sup>18</sup>

Prostaglandins have become one of the most commonly utilized agents for cervical ripening and may serve as important messengers in a wide variety of functions, including cervical softening in the absence of uterine contractility.<sup>8,19-22</sup> Prostaglandins may also have a uterotonic effect on the pregnant uterus, with the result that simultaneous administration with oxytocin is strictly contraindicated.<sup>8,23</sup> Commonly associated with the use of prostaglandins are increased collagenase activity in the cervix and increased levels of elastase,

glycosaminoglycan, dermatan sulfate, hyaluronic acid, and intracellular calcium in cervical smooth muscle.<sup>23</sup> Further advancing the labor induction process are contraction of myometrial fibers and relaxation of cervical smooth muscle and dilation.<sup>23,24</sup>

The prostaglandins E<sub>1</sub> (PGE<sub>1</sub>) and E<sub>2</sub> (PGE<sub>2</sub>) are ligands for the PGE<sub>2</sub> receptor (EP) family, expressed in the myometrium, endometrium, trophoblast cells, amnion, cervix, and decidua.<sup>25,26</sup> The receptor subtypes EP<sub>1</sub> and EP<sub>3</sub> are primarily contractile, whereas EP<sub>2</sub> and EP<sub>4</sub> are predominantly relaxatory.<sup>26</sup> Interestingly, PGE<sub>1</sub> is a potent EP<sub>3</sub> receptor agonist and has been shown to cause increased cervical contractility,<sup>26</sup> whereas PGE<sub>2</sub> appears to have a wide-ranging affinity that modifies specific functions during labor, such as cervical consistency, dilation, and effacement.<sup>27-29</sup> Highlighting the relationship between gene expression and successful outcome, individual variations in the regulation of the receptors may cause the induction to fail in as many as one-third of the procedures.<sup>30</sup>

Examining the association between labor induction and cesarean delivery rates, we find the evidence to be somewhat controversial. On the one hand, the 2009 American College of Obstetricians and Gynecologists (ACOG) guidelines state that the risk of cesarean delivery is unaffected by the use of prostaglandins.<sup>8</sup> On the other hand, the ACOG guidelines also conclude that induction of labor in nulliparous women with an unfavorable cervix is associated with a twofold increased risk of cesarean delivery,<sup>8</sup> although contradictory evidence has been reported.<sup>31</sup> A meta-analysis of 27 randomized controlled trials indicates that induction of labor in women with intact membranes may, in fact, be associated with a reduced risk of cesarean delivery.<sup>24</sup>

High body mass index (BMI) and premature rupture of membranes (PROM) are considered to be independent risk factors for cesarean section and failed labor induction.<sup>8,29,32-35</sup> Interestingly, severe obesity has been associated with lower prostaglandin sensitivity,<sup>36</sup> which could be explained by compartment distribution effects. In a recent clinical study evaluating PGE<sub>1</sub> formulations, it was found that BMI and time to delivery from first administration was positively correlated in both nulliparous and multiparous women.<sup>37</sup> While the clinical evidence suggests that the cesarean section rates in women with PROM are largely unaffected by a PGE<sub>2</sub> vaginal insert,<sup>8,38,39</sup> caution is generally

advised when using prostaglandins in the presence of obstetric complications, such as nonvertex presentation or multiple pregnancy.

### *Dinoprostone*

Dinoprostone (11 $\alpha$ ,15S-dihydroxy-9-oxo-prosta-5Z,13E-dien-1-oic acid) is a synthetic PGE<sub>2</sub> analog that induces cervical ripening with a half-life of approximately 2.5–5 minutes in tissue.<sup>29</sup> Used by obstetric practitioners since the 1970s to augment uterine smooth muscle contractility, dinoprostone was initially administered orally at 0.5 mg or intravenously at 1.5  $\mu$ g/mL to achieve successful labor induction.<sup>40,41</sup> More recent formulations are used intracervically or vaginally at doses equivalent to (or lower than) previous oral administrations, thus avoiding common systemic side effects, mainly from the gastrointestinal tract, while demonstrating a more predictable onset of labor.<sup>29,42,43</sup>

There are currently 2 commercially available dinoprostone formulations approved by the U.S. Food and Drug Administration (FDA) for cervical ripening and vaginal delivery in women at or near term. The dinoprostone 10-mg vaginal insert releases the drug at a controlled rate of 0.3 mg/h over 12 hours through a retrievable hydrogel delivery system (Cervidil, Propess, Ferring Pharmaceuticals, Parsippany, New Jersey),<sup>29</sup> which allows for continuous exposure to the drug over time. Using a different delivery platform, the dinoprostone intracervical gel is administered directly to the cervix in the form of a single dose suspension, which is rapidly absorbed and metabolized in the local tissues (Prepidil, 0.5 mg, 2.5 mL syringe, Pharmacia & Upjohn Company, Pfizer, New York, NY).<sup>43</sup> The safety and efficacy of using the dinoprostone gel to induce cervical ripening has been investigated using doses ranging from 0.5–6 mg, either as a single dose or in intervals ranging from 6–9 hours with a maximum of 3–4 doses (Table I).

The controlled-release functionality and ready removability at the onset of active labor is a major advantage of the dinoprostone 10-mg vaginal insert, allowing increased control over the procedure and reduced dose variations.<sup>22,44–55</sup> While both formulations have demonstrated their efficacy in achieving cervical ripening, the intracervical gel is intrinsically more difficult to remove in case of adverse events or at the onset of active labor.<sup>56</sup> The use of the dinoprostone intracervical gel has also declined due to other challenges, such as patient discomfort during administration, even when han-

dled by an experienced clinician,<sup>57</sup> and the need for repeat administrations. The intracervical gel may also increase the risk of uterine tachysystole if the drug passes into the extraamniotic space through diffusion.<sup>56</sup>

The dinoprostone 10-mg vaginal insert has been associated with shorter induction-to-delivery time intervals,<sup>45,46</sup> increased rates of successful vaginal delivery within 24 hours in women at or near term without increasing obstetric risk,<sup>46,47,50,57</sup> and decreased cesarean section rates<sup>21,22,46,50,58–61</sup> as compared with the intracervical gel. Other studies have demonstrated that the dinoprostone 10-mg vaginal insert results in a higher degree of spontaneous vaginal delivery in both nulliparous and multiparous women,<sup>45,50,61–64</sup> a shorter interval from induction to delivery, and fewer maternal complications as compared with dinoprostone 1 mg intracervical gel (incremental dosing after 6 hours, up to a combined maximum dose of 4 mg)<sup>49</sup> or oxytocin alone.<sup>51</sup> From a health-economics perspective, administration of the dinoprostone vaginal insert has been associated with shorter and more cost-effective hospital stays for women near or at term than has the intracervical gel.<sup>45,46,50</sup>

Clinical studies conducted in the United States and the European Union have reported that treatment-emergent adverse events (TEAEs) are rare ( $\leq 5\%$ ) when the dinoprostone 10-mg vaginal insert is used for cervical ripening.<sup>61–63</sup> The most common TEAEs are uterine tachysystole with fetal heart rate (FHR) involvement associated with fetal distress, uterine tachysystole not associated with fetal distress, and fetal distress in the absence of uterine tachysystole. Less frequently reported TEAEs ( $\leq 1\%$ ) are nausea, vomiting, diarrhea, abdominal pain, and fever.<sup>29</sup>

### *Misoprostol*

Misoprostol ([ $\pm$ ] methyl 11- $\alpha$ , 16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate) is a synthetic PGE<sub>1</sub> analog that has been altered from an original compound, with approximately equal amounts of 2 diastereomers. Following absorption and selective binding, misoprostol undergoes rapid deesterification to an active metabolite with a terminal half-life of 20–40 minutes.<sup>65</sup>

Misoprostol 100/200  $\mu$ g tablets have been approved in the United States since 1985 for reducing the risk of gastric ulcers caused by nonsteroidal antiinflammatory drugs, including aspirin, in patients at high risk for complications (Cytotec, GD

**Table I** Comparative Studies Examining the Safety and Efficacy of Dinoprostone Versus Misoprostol<sup>67-72,77-80</sup>

Protocol	No. of patients	Route of administration	Significant findings	Study
Dinoprostone 10 mg Misoprostol ~50 µg	89 97	Vaginal insert Intravaginal	<ul style="list-style-type: none"> <li>Both formulations deemed safe and efficient for cervical ripening</li> <li>Dinoprostone demonstrated increased median time from induction to delivery</li> <li>Dinoprostone demonstrated decreased CS rates for non-reassuring FHR changes</li> </ul>	Garry et al, 2003 <sup>69</sup>
Dinoprostone 0.5 mg Dinoprostone 10 mg Misoprostol ~50 µg	35 38 38	Intracervical Vaginal insert Intravaginal	<ul style="list-style-type: none"> <li>Dinoprostone demonstrated fewer cardiotocographic abnormalities</li> <li>Concerns raised when using misoprostol in outpatient settings for cervical ripening</li> </ul>	Ramsey et al, 2005 <sup>70</sup>
Dinoprostone 10 mg Misoprostol ~50 µg Misoprostol 100 µg	436 443 428	Vaginal insert Vaginal insert Vaginal insert	<ul style="list-style-type: none"> <li>The 3 protocols demonstrated similar profiles in terms of CS rates</li> <li>Dinoprostone vs. misoprostol 100 µg demonstrated similar median times from induction to delivery</li> <li>Misoprostol ~50 µg demonstrated significantly increased median time from induction to delivery</li> </ul>	Wing, 2008 <sup>77</sup>
Dinoprostone 10 mg Misoprostol ~50 µg	276 55	Vaginal insert Intravaginal	<ul style="list-style-type: none"> <li>Misoprostol deemed to be cost-efficient</li> </ul>	Nadia Bennett et al, 2016 <sup>79</sup>
Dinoprostone 10 mg Misoprostol 200 µg	215 228	Intravaginal Titrated oral	<ul style="list-style-type: none"> <li>Misoprostol (200 µg; 1 µg/mL) deemed to be as effective as dinoprostone in women at term, with lower rates of AEs</li> </ul>	Wang et al, 2016 <sup>80</sup>
Dinoprostone 3 mg Misoprostol ~50 µg	71 72	Intravaginal Intravaginal	<ul style="list-style-type: none"> <li>Both formulations demonstrated similar profiles in terms of neonatal outcomes and median times from induction to delivery</li> <li>Misoprostol demonstrated increased frequency of uterine tachysystole with FHR involvement</li> </ul>	Charoenkul et al, 2000 <sup>67</sup>
Dinoprostone 1 mg <sup>a</sup> Misoprostol ~50 µg <sup>b</sup> Misoprostol ~50 µg <sup>b</sup>	240 120 120	Intracervical Intravaginal Oral	<ul style="list-style-type: none"> <li>Dinoprostone and vaginal misoprostol demonstrated similar profiles in terms of median times from induction to delivery</li> <li>Vaginal misoprostol demonstrated increased incidence of tachysystole and greater rates of CS for fetal distress</li> <li>Oral misoprostol demonstrated significantly decreased efficacy and fewer vaginal deliveries at 24 h</li> </ul>	le Roux et al, 2002 <sup>68</sup>
Dinoprostone 3 mg <sup>c</sup> Misoprostol ~50 µg <sup>c</sup>	83 80	Intravaginal Intravaginal	<ul style="list-style-type: none"> <li>Misoprostol deemed efficient for induction of labor beyond 40 weeks' gestation</li> <li>Misoprostol demonstrated increased incidence of abnormal FHR tracings and NICU admissions</li> </ul>	Papanikolaou et al, 2004 <sup>72</sup>
Dinoprostone 3 mg <sup>d</sup> Misoprostol ~50 µg <sup>d</sup>	60 60	Intravaginal Intravaginal	<ul style="list-style-type: none"> <li>Misoprostol deemed efficient for induction of labor beyond 40 weeks' gestation</li> <li>Misoprostol demonstrated increased incidence of uterine tachysystole with FHR involvement, tachysystole, and NICU admissions</li> </ul>	Ayaz et al, 2010 <sup>71</sup>
Dinoprostone 3–6 mg Misoprostol ~25 µg	635 633	Intravaginal Intravaginal	<ul style="list-style-type: none"> <li>Both formulations demonstrated similar profiles in terms of CS rates and fetal outcomes</li> <li>Misoprostol demonstrated increased median time from induction to labor</li> </ul>	Petersen et al, 2013 <sup>78</sup>

<sup>a</sup>Repeated every 6 h (maximum 4 doses).<sup>b</sup>Repeated every 6 h (maximum 2 doses).<sup>c</sup>Repeated every 9 h (maximum 3 doses).<sup>d</sup>Repeated every 6 h (maximum 3 doses).

AE = adverse event, BMI = body mass index, CS = cesarean section, FHR = fetal heart rate, NICU = neonatal intensive care unit.

Searle, Pfizer, New York, NY).<sup>65</sup> Outside the United States misoprostol is also available as a single-dose retrievable 200- $\mu\text{g}$  vaginal insert (dose-release rate, 7  $\mu\text{g}/\text{h}$  over 24 hours; Misodel, Mysodelle, Myspess, Ferring Pharmaceuticals, Pymble NSW, Australia).<sup>66</sup> Misoprostol has been used off-label with various routes of administration, including buccal, sublingual, oral, vaginal, and rectal, in obstetric practices. In vitro studies show that misoprostol may increase myometrial contractions, decrease total collagen content, and decrease the area covered by connective tissue.<sup>26</sup> While misoprostol has never received FDA approval for cervical ripening and labor induction, its relative ease of use combined with low costs has led to this drug becoming one of the most commonly used treatments for this indication. However, the labeling contains a warning to pregnant women about serious side effects, such as uterine rupture,<sup>65</sup> and close uterofetal monitoring is recommended.<sup>67</sup> The misoprostol labeling does not contain data on safety and efficacy, nor does it recommend uniform dosage or dose intervals,<sup>65</sup> although the majority of all maternal or neonatal complications associated with misoprostol have occurred at doses  $>25 \mu\text{g}$ .<sup>67</sup>

In the ACOG guidelines, dinoprostone and misoprostol have both been described as acceptable pharmacologic treatments for cervical ripening. The guidelines recommend an initial dose of misoprostol  $\sim 25 \mu\text{g}$  (defined as one-quarter of an unscored 100- $\mu\text{g}$  tablet), administered every 3–6 hours, with oxytocin withheld for a minimum of 4 hours after the last dose.<sup>8</sup> Administration of medium to high doses of vaginal misoprostol, defined as  $\geq 50 \mu\text{g}$  (repeated every 3–6 hours), have been associated with an increased risk of various TEAEs,<sup>8</sup> including tachysystole and cesarean section for fetal distress,<sup>8,68–70</sup> increased rate of uterine tachysystole with FHR changes and neonatal intensive care unit (NICU) admission,<sup>67,71,72</sup> increased rate of cardiocographic abnormalities such as tachysystole and hypertonus,<sup>70</sup> and poor predictability of outcome.<sup>56</sup>

The use of sublingual misoprostol  $\sim 25\text{-}\mu\text{g}$  tablets has been found in a recent clinical study to be effective and safe for induction of labor at term, although time from induction to delivery appeared to be significantly affected by parity, status of membranes, and BMI.<sup>37</sup> The safety and efficacy of a protocol using vaginal misoprostol  $\sim 25 \mu\text{g}$  (up to 3 doses repeated every  $\geq 4$  hours) has been compared with a protocol using oral misoprostol  $\sim 50 \mu\text{g}$  (followed by 2 doses of oral misoprostol 100  $\mu\text{g}$ ).<sup>73</sup>

In this study, vaginal misoprostol was associated with the need for more oxytocin augmentation and more frequent use of the third dose of the drug than with oral misoprostol, with similar rates of uterine tachysystole and other maternal and neonatal complications.<sup>73</sup> As the dosage of titrated oral solutions can be adjusted according to individual responses, it has been suggested that this route of administration demonstrates increased safety and efficacy.<sup>74</sup>

To investigate the effect of different misoprostol protocols for cervical ripening in post-term pregnancies, oral misoprostol doses of  $\sim 50$  and 100  $\mu\text{g}$  were compared with vaginal misoprostol  $\sim 25 \mu\text{g}$ .<sup>75</sup> The researchers found no statistically significant differences between the 3 groups in terms of interval time from the administration of misoprostol to the start of uterine contractions, interval time from the start of uterine contractions to delivery, or median time from induction to labor.<sup>75</sup> However, after the initial dose, oral misoprostol 100  $\mu\text{g}$  appeared to require fewer additional doses of the medication and was associated with reduced meconium passage and increased rate of vaginal delivery, whereas fetal distress was similar to that reported in the other groups.<sup>75</sup> Furthermore, multiple administrations of oral misoprostol (incremental dosing; dose 1–2:  $\sim 20 \mu\text{g}$ ; dose  $\geq 3$ :  $\sim 40 \mu\text{g}$  repeated every 2 hours for 14 hours) have been demonstrated to have only low marginal benefits.<sup>76</sup> Because misoprostol acts on smooth muscles and increases contractions, close maternal uterine activity and fetal monitoring is advised.

#### *Comparative Studies of Dinoprostone and Misoprostol*

Numerous studies on cervical ripening, summarized in Table I, have compared the safety and efficacy of dinoprostone (0.5–3-mg gels or 10-mg controlled-release hydrogel vaginal inserts) with those of misoprostol ( $\sim 25\text{--}100\text{-}\mu\text{g}$  tablets). The average patient cohort size in these studies was  $<200$  women enrolled (range, 35–635) per treatment arm and route of administration (Table I).<sup>67–72,77–80</sup>

In a meta-analysis of 10 controlled trials (N=1,061 women) comparing 2 generalized protocols with dinoprostone (0.5 mg intracervical; repeated every 6 hours; maximum total dose 1.0–2.0 mg) or misoprostol ( $\sim 25\text{--}50 \mu\text{g}$  intravaginal; repeated every 2–6 hours; maximum total dose 50–300  $\mu\text{g}$ ), misoprostol appeared to be more efficient than dinoprostone in terms of vaginal delivery within 24 hours (65.1% vs. 50.9%, respectively) but with

an increased incidence of uterine tachysystole and FHR involvement (7.7% vs. 2.3%, respectively).<sup>81</sup>

In a phase III, double-blind, multicenter study conducted in the United States, 1,358 women eligible for labor induction received a single-dose retrievable misoprostol 200- $\mu$ g vaginal insert (approved outside the United States) or a 10-mg dinoprostone vaginal insert.<sup>82</sup> The researchers reported that the misoprostol vaginal insert was associated with a significantly reduced median time to vaginal delivery as compared with the dinoprostone vaginal insert (21.5 vs. 32.8 hours, respectively). While the cesarean delivery rates were similar, uterine tachysystole occurred more often with misoprostol than with dinoprostone (13.3% vs. 4.0%, respectively).<sup>82</sup>

In a *post hoc* analysis, it was demonstrated that the misoprostol vaginal insert resulted in more insert retrievals due to adverse events as compared with the dinoprostone vaginal insert (11.4% vs. 4.0%, respectively).<sup>55</sup> The most common adverse events prompting retrieval were uterine tachysystole with category II and III FHR patterns. Median resolution times for uterine tachysystole with abnormal FHR patterns were also considerably longer with misoprostol than with dinoprostone (94.5 vs. 8.5 minutes, respectively).<sup>55</sup>

Similarly, in a recent meta-analysis of 96 randomized controlled trials (N=17,387 women) it was reported that although the misoprostol 200- $\mu$ g vaginal insert was more efficient in terms of cervical ripening and vaginal delivery within 24 hours as compared with dinoprostone, it was associated with a higher incidence of uterine tachysystole with FHR changes.<sup>83</sup> In comparison, the lowest rate of uterine hyperstimulation with FHR changes was associated with the use of a Foley catheter followed by dinoprostone, whereas oral misoprostol was associated with the lowest rate of cesarean sections.<sup>83</sup> In conclusion, no method could be considered overall superior when considering all clinical outcomes.

### Conclusions

In the clinical studies performed to date, the most frequently discussed primary objective of cervical ripening and induction of labor is efficacy, commonly assessed by the median time from induction to delivery within 24 hours. While the available data support the use of either dinoprostone or misoprostol when no contraindications are present, it is our opinion that a majority of the clinical

studies on prostaglandins for cervical ripening are underpowered, particularly when considering the relative infrequency of TEAEs. Furthermore, the ability to predict which patients will succeed in achieving vaginal delivery is limited, and there are conflicting opinions concerning the use of the various prostaglandin formulations. In view of this, it is difficult to draw definitive conclusions about safety and efficacy associated with the use of prostaglandins for cervical ripening and labor induction.

Therefore, we conclude that a thorough reexamination of the clinical evidence is warranted to establish more reliable prognostic indicators and to improve the safety of current cervical ripening protocols,<sup>32,33,84,85</sup> with the aim of reducing the risks of TEAEs while increasing efficacy and accounting for individual variations in patients.

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