

A critical appraisal of the misoprostol removable, controlled-release vaginal delivery system of labor induction

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Background: Induction of labor is a major issue in pregnancy management. Finding strategies to increase rate and decrease time to vaginal delivery is an important goal, but maternal or neonatal safety must remain the primary objective. Misoprostol is a synthetic analogue of prostaglandin used off label to ripen the cervix and induce labor. The misoprostol vaginal insert (MVI) was designed to allow a controlled-release delivery of misoprostol (from 50 to 200 µg) with a removal tape. The objective of this review was to make a critical appraisal of this device referring to the literature.

Methods: A literature search was performed in the PubMed and Cochrane databases using the keywords “vaginal misoprostol insert”.

Results: Several studies compared different doses of MVI (50, 100, 150, and 200 µg) with the 10 mg dinoprostone insert. The 100 µg MVI compared with the dinoprostone vaginal insert (DVI) showed similar efficacy and no significant differences in cesarean delivery rate. MVI 200 µg compared with DVI showed a reduced time to vaginal delivery and oxytocin need but had an increased risk of uterine hyperstimulation. The rate of hyperstimulation syndrome was two to three times more frequent with the 200 µg MVI than the 100 µg.

Conclusion: Current data suggest that the 100 µg MVI would provide the best balance between efficacy and safety. Further studies should be performed to evaluate this dose, especially in high-risk situations needing induction of labor.

Keywords: prostaglandins, efficacy, safety, pregnancy

Introduction

Induction of labor is a very common obstetrical intervention and has been the subject of international recommendation from the World Health Organization (WHO) in 2011.¹ The rate of induction of labor has doubled from the 1980s to the 1990s due to medical indication rise and achievement of cervical ripening techniques and stabilized, since then, approximately 20% of the patients in numerous developed countries (23.3% in the USA in 2012 and 22.7% in France in 2010).^{2,3} It rises with gestational age, especially after 41 weeks of gestation, and with estimated fetal weight.

Because it is a very common obstetrical situation, physicians have to evaluate the better balance between efficacy of induction (ie, a high rate of vaginal delivery) and maternal and fetal safety of this intervention. Induction is indicated when the continuation of pregnancy endangers the well-being of the mother or the fetus. Induction of labor is proposed postterm or for pathological obstetrical situations such as gestational diabetes, gestational hypertension, preeclampsia, or fetal pathologies like intrauterine growth retardation or laparoschisis.

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Induction of labor can be obtained by two actions: cervical ripening or induction of contractions, which can be more or less combined. Cervical status has long been recognized as the most important prediction success factor of induction of labor, especially when cervical ripening is needed.⁴ The Bishop scoring system published in 1964 became the most widely used score to predict success induction of labor.⁵ The highest the score is, the better the proportion of vaginal delivery will be. A Bishop score of more than six allows obstetrician to induce labor with oxytocin by inducing contraction. In this situation, cervical ripening is useless. When the Bishop score is below 6, cervical ripening is needed. To ripen the cervix, nonpharmacologic or pharmacologic methods can be used. The WHO and the US Food and Drug Administration (FDA) recommend the use of prostaglandins as they have been shown to increase vaginal delivery rates within 24 hours of labor induction and decrease the need for the administration of oxytocin, with no effect on the rate of Cesarean delivery in women with an unscarred uterus.⁶

Prostaglandins are used for both cervical ripening and labor induction. There are two different types of prostaglandins: prostaglandins E2 (PGE2) that are well studied and broadly used and analogues of prostaglandins E1 (PGE1) called misoprostol. Misoprostol has only been approved for the prevention of gastric ulcers induced by nonsteroidal anti-inflammatory drugs. However, it is widely used in obstetrics as an adjunct to mifepristone in medical abortion, for treatment of postpartum hemorrhage in the presence of uterine atony, and also, for preinduction cervical ripening and stimulation of uterine contractions.

A Cochrane review of literature by Hofmeyr et al in 2010 compelled 121 studies that compared the use of vaginal misoprostol with other vaginal devices for the induction of labor.⁶ They found that time to vaginal delivery was lower with a dose of 25 µg of misoprostol insert vaginally every 4 hours than conventional methods. The increased rate of uterine tachysystole with or without fetal heart rate (FHR) changes was not associated with an increased Cesarean rate. In contrast, there was no difference in serious neonatal or maternal mortality for women receiving misoprostol compared with women who received PGE2. The use of misoprostol have increased in many countries, especially in developing countries, as misoprostol can be stored at room temperature unlike other approved drugs that must be refrigerated.

However, the use of misoprostol is associated with some concerns, especially in countries where off-label use can lead to legal suits. The recommended dose of 25 µg is

not available widely. Thus, intravaginal administration of tablet fragments may not provide accurate dose strengths of misoprostol. Because of the uncertainty regarding the correct dose to use with tablets inserted vaginally and difficulty to remove those when adverse effects happen, a vaginal insert with removable tape and controlled-release reservoir of misoprostol has been developed. The misoprostol vaginal insert (MVI) is composed of misoprostol and nonbiodegradable hydrogel polymer that allows moisture absorption without dissolving. Misoprostol would be administered locally to the target tissues in a controlled-release manner. The vaginal application would provide a constant supply of misoprostol with low maximal systemic levels, thus expecting to reduce the incidence of adverse events. The vaginal insert's retrieval tape would allow easy, rapid removal of the product, immediately stopping delivery of additional drug if needed. The objective of this review was to make a critical appraisal of the misoprostol removable, controlled-release vaginal delivery system for labor induction referring to the literature.

Methods

We performed a literature search, limited to English language, in the PubMed® and Cochrane library databases using the keywords "misoprostol vaginal insert". We considered pharmacological studies, retrospective studies, randomized clinical trials, secondary analyses, and review of use of the MVI. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed.

We mainly focused on the bioavailability of misoprostol administered by MVI and also on efficacy and safety for maternal and fetal outcomes related to induction of labor. Even if randomized, clinical trials that compared misoprostol tablets introduced orally, sublingually, or vaginally with other cervical ripening methods were not included in our analysis but were used to discuss the current evidence available about the use of misoprostol as a labor induction drug. Indeed, because the aim of this review was to analyze the efficacy and safety of the MVI device, every other method using misoprostol for the induction of labor were excluded from the analysis of the results.

Results

Types of studies

Thirty-six articles were found. Over the 36 items, 16 were directly related to MVI. We excluded eight trials about induction of labor using misoprostol tablets introduced vaginally compared with dinoprostone vaginal insert (DVI) and two

using misoprostol tablets given orally compared with DVI. Five reviews or meta-analyses regarding DVI compared with misoprostol tablets or about DVI only for the induction of labor were also excluded. We also excluded one national survey on off-label use of misoprostol, one case report of complication after the use of oral misoprostol, and three papers about abortion using misoprostol.

Description of the studies

There were two pharmacological studies,^{7,8} one study about the maximum tolerable dose,⁹ four randomized double-blind multicenter studies,^{10–12} six secondary analyses, two reviews, and one commentary of the last performed trial. The characteristics of the major studies are summarized in Table 1.

Pharmacological studies

Two Phase I trials about pharmacological characteristics of MVI were performed in both nonpregnant and pregnant women. Powers et al reported the pharmacokinetic parameters of misoprostol acid after introduction of MVI 100, 200, and 400 µg compared with a 200 µg misoprostol oral dose.⁷ This study included 12 nonpregnant women. Plasma concentration was dose proportional and peaked slower and for a longer lasting time with MVI compared with oral form.⁷ Rayburn et al in 2006 studied this device in 31 pregnant nulliparous women. They recorded the pharmacokinetics parameters after MVI dosing with 25, 50, 100, 200, and 300 µg. The results were similar to the Power's study with a dose-dependent plasma concentration and a quick elimination of the free acid of misoprostol in the systemic circulation after removal, with a half-life of less than an hour.⁸

Comparison of different doses of misoprostol given by the MVI and comparisons of MVI vs DVI

Several studies tried to compare different doses of misoprostol provided by MVI, and MVI to DVI. Castañeda et al⁹ in 2005 tried to evaluate the maximum tolerable dose of misoprostol delivered vaginally with a controlled-release insert. This was a multicenter Phase II trial involving nulliparous pregnant women experiencing induction of labor. Six patients for each dose were included. Five doses of MVI were used (25, 50, 100, 200, and 300 µg). Median time to vaginal delivery was significantly shortened with doses from 100 µg and above compared with 25 µg reservoir. The 25 µg group had a median time to vaginal birth of 43.3 hours compared with 14.2 ($P<0.01$) for the 100 µg group. Doses >100 µg did not

reduce in a consistent manner the time to vaginal delivery, which suggests a threshold effect at this dose reservoir. Moreover, the proportion of vaginal birth within 24 hours in the 100 µg group was significantly higher than in the 25 µg group (83% vs 0%; $P<0.003$). Regarding the safety of the compound, uterine hyperstimulation syndrome was defined by a uterine tachysystole (more than five contractions within 10 minutes) or uterine hypertonus (contraction lasting more than 2 minutes) associated with abnormal FHR. This syndrome was associated with a Cesarean delivery for two women in the 300 µg group and none with the other groups. There were no low Apgar score and no adverse maternal event in this study.

After that trial, two Phase II studies were performed. Ewert et al in 2006, compared MVI 25, 50, 100, and 200 µg for induction of labor in 124 pregnant women.¹⁰ The second one was the Wing trial published in 2011 that compared different doses of MVI at 100, 150, and 200 µg.¹¹ The primary efficacy outcome of those studies was time to vaginal delivery for Ewert et al¹⁰ and proportion of vaginal birth within 24 hours for Wing.¹¹

Wing et al published two Phase III trials with co-primary outcomes: time to vaginal delivery and Cesarean rate.^{12,13} Secondary end points included time to any delivery mode, time to onset of active labor, and oxytocin use.

The results of these different clinical trials are summarized in Tables 2–4 and will be discussed thereafter.

Six secondary analyses were realized using the results of these studies (Table 1). Pevzner et al^{14,15} carried two secondary analysis of the Wing trial published in 2008 comparing MVI 50 µg and 100 µg to DVI.^{14,15} The first one, published in 2009, analyzed the maternal and pregnancy characteristics that independently predict successful induction of labor.¹⁴ The major statistically significant results are compiled in Table 5. An age of ≥ 35 and a BMI over 30 kg/m² at admission were independent factors of decrease in likelihood of vaginal birth (odds ratio [OR] =0.55, 95% confidence interval [CI] =0.35–0.87, and OR =0.63, 95% CI =0.43–0.91, respectively). The Bishop score was not a predictor of successful induction of labor in this secondary analysis. The second one, published in 2011, tried to characterize the incidence and timing of cardiotocographic abnormalities associated with misoprostol and DVIs during labor induction. A total of 6.8% of MVI 50 µg-treated group experienced uterine tachysystole or hyperstimulation, compared with 17.4% with dinoprostone insert ($P<0.001$) and 17.3% with MVI 100 µg ($P<0.001$).¹⁵ There was no significant difference in incidence of FHR abnormalities that occurred with the study drug: 11.2% with dinoprostone

Table 1 Main characteristics of the study on misoprostol vaginal insert

Type of study	Author (year)	Characteristics of the study	Patients	Inclusion criteria	Primary end point
Pharmacological trials					
	Rayburn et al ⁸ (2006)	Single center Ascending dose 25 µg, 50 µg, 100 µg, 200 µg, and 300 µg MVI	31	Nulliparous pregnant women	Pharmacokinetics properties of MVI at term
	Powers et al ⁷ (2008)	Single center Ascending dose 100 µg, 200 µg, and 400 µg MVI compared with 200 µg oral misoprostol	12	Nonpregnant 18–40 years Under contraception	Characteristics of MVI in vivo release
Clinical trials					
	Castañeda et al ⁹ (2005)	Multicenter Dose ranging 25 µg, 50 µg, 100 µg, 200 µg, and 300 µg MVI	31	Nulliparous singleton >37 WG Over 18 years Cephalic presentation Bishop score <6	Maximum tolerable dose (dose below occurrence of hyperstimulation syndrome in at least two of the cohorts)
Phase II trials	Ewert et al ¹⁰ (2006)	Multicenter Double-blinded Randomized Dose ranging 25 µg, 50 µg, 100 µg, and 200 µg MVI	124	Parous women singleton >37 WG Over 18 years Cephalic presentation Bishop score <6	Time to vaginal delivery
Clinical trials					
	Wing ¹¹ (2011)	Multicenter Double-blinded Randomized Dose ranging 100 µg, 150 µg, and 200 µg MVI	374	Parous women singleton >36 WG Over 18 years Cephalic presentation Bishop score <4	Proportion of vaginal birth within 24 hours
Phase III trials					
	Wing et al ¹² (2008)	Multicenter Double-blinded Randomized MVI 50 µg and 100 µg compared with DVI	1,308	Parous women singleton >36 WG Over 18 years Cephalic presentation Bishop score <4	Time to vaginal delivery and cesarean rate
Phase III trials					
	Wing et al ¹³ (2013)	Multicenter Double-blinded Randomized MVI 200 µg compared with DVI	1,358	Parous women singleton >36 WG Over 18 years Cephalic presentation Bishop score <4	Time to vaginal delivery and cesarean rate
Secondary analysis					
	Wing et al (2008) ⁴⁰	Combination of two Phase II studies	168	Pregnant women >37 WG Over 18 years Singleton	Induction to vaginal delivery interval Uterine hyperstimulation Cesarean rate

Pevzner et al ¹⁴ (2009)	Multicenter Double-blinded Randomized Secondary analysis	1,274	Cephalic presentation Bishop score <6 Parous women singleton >36 WG Over 18 years Cephalic presentation Bishop score <4 Parous women singleton >36 WG Over 18 years	Maternal and pregnancy characteristics associated with successful labor induction
Pevzner et al ¹⁴ (2009)	Multicenter Double-blinded Randomized Secondary analysis	1,273	Cephalic presentation Bishop score <4 Parous women singleton >36 WG Over 18 years	Effects of maternal obesity on outcome and duration of MVI induction
Pevzner et al ¹⁵ (2011)	Multicenter Double-blinded Randomized Secondary analysis	1,308	Cephalic presentation Bishop score <4 Parous women singleton >36 WG Over 18 years	Incidence and timing of cardiotocographic abnormalities
Stephenson et al ¹⁶ (2013)	Multicenter Double-blinded Randomized Dose ranging 100 µg, 150 µg, and 200 µg MVI	374	Cephalic presentation Bishop score <4 Parous women singleton >36 WG Over 18 years	Incidence and timing of cardiotocographic abnormalities
Miller et al ¹² (2015)	Multicenter Double-blinded Randomized MVI 200 µg compared with DVI	1,358	Cephalic presentation Bishop score <4 Parous women singleton >36 WG Over 18 years	Optimal start time for achieving daytime deliveries

Abbreviations: MVI, misoprostol vaginal insert; DVI, dinoprostone vaginal insert; WG, weeks of gestation.

Table 2 Efficacy of misoprostol vaginal insert compared with dinoprostone vaginal insert and with different doses of misoprostol

	Comparison	Number of patients	Proportion of vaginal birth (%) within 24 hours	Time to vaginal birth (hour)
Ewert et al ¹⁰	Total	124	–	–
	25 µg	33	42	–
	50 µg	29	$\begin{bmatrix} 79 \\ 81 \\ 70 \end{bmatrix}$ $P=0.003^a$	19.1, $P=0.76^b$
	100 µg	32		13.1, $P=0.003^b$
	200 µg	30		10.6, $P<0.001^b$
Wing et al ¹²	Total	1,297	–	–
	50 µg	426		35.4, $P=0.01^c$
	100 µg	440		26.6, $P=0.97^c$
	DVI	431		27.5
Wing ¹¹	Total	373	–	–
	100 µg	117	63.8	23.3
	150 µg	125	66.7	22.2, $P=0.13^d$
	200 µg	131	76, $P=0.057^d$	17.4, $P<0.001^d$

Notes: ^aComparison for P calculation is not specified; ^bcomparison between 25 µg vs 50 µg, 100 µg and 200 µg; ^cvs DVI; ^dvs 100 µg. – Not calculated.

Abbreviation: DVI, dinoprostone vaginal insert.

compared with 9.9% with MVI 50 µg and 10.7% with MVI 100 µg. Cardiotocographic abnormalities were less frequent with MVI 50 µg than MVI 100 µg or dinoprostone but clinical outcomes were the same among the groups.

Similarly, Stephenson et al tried to characterize the incidence and timing of FHR and cardiotocographic abnormalities associated with different doses of MVI.¹⁶ It was a secondary analysis of the Wing et al 2011 trial that studied MVI 100 µg, 150 µg, and 200 µg. Although the rate of uterine tachysystole was significantly higher with 200 µg dose compared with 100 µg ($P<0.001$, relative risk [RR] = 2.11, 95% CI = 1.39–3.22), uterine hyperstimulation syndrome was not significantly different between the two groups. Neonatal outcome were similar between the groups.

Discussion

Pharmacology of misoprostol and focus on the MVI

Misoprostol is a synthetic analogue of prostaglandin E1. It binds to prostaglandin receptors to induce biological effects in different tissues. Prostaglandins are secreted by the fetus and the placenta to sensitize the myometrium to oxytocin. The major effects of Prostaglandins analogues are effacement, softening, and dilatation of the cervix. They also increase myometrial contractility. Misoprostol is in vivo rapidly de-esterified to its free acid, which is an active metabolite. Plasma concentration of misoprostol is thus not possible to detect in the systemic circulation. It is the misoprostol acid metabolite that is instead measured.

Table 3 Safety of misoprostol vaginal insert compared with dinoprostone vaginal insert and different doses of misoprostol

	Comparison	Number of patients	Cesarean rate (%)	UHS with abnormal FHR (%)	Apgar score <7 at 5 minutes
Ewert et al ¹⁰	Total	124			
	25 µg	33	6	3	3
	50 µg	29	3	0	0
	100 µg	32	0	6	0
	200 µg	30	10	10	0
Wing et al ¹²	Total	1,297			
	50 µg	426	28, $P=0.59^a$	2.9, $P=0.03^a$	1.6, $P=0.55^a$
	100 µg	440	27.8, $P=0.64^a$	6.1, $P=0.89^a$	0.9, $P=1^a$
	DVI	431	26.4	6.4	0.9
Wing ¹¹	Total	373			
	100 µg	117	31.4	6.8	0
	150 µg	125	30.4, $P=0.89^b$	9.6, $P=0.49^b$	0.8
	200 µg	131	22.9, $P=0.15^b$	12.2, $P=0.2^b$	0.8

Notes: ^avs DVI; ^bvs 100 µg.

Abbreviations: DVI, dinoprostone vaginal insert; UHS, uterine hyperstimulation syndrome; FHR, fetal heart rate.

Table 4 Focus on the results of the study comparing misoprostol vaginal insert 200 µg and dinoprostone vaginal insert

n=1,358 patients	MVI 200 µg	DVI	
Number of patients	678	680	
Proportion of vaginal birth within 24 hours (%)	54.6	34.0	P<0.001
Time to vaginal birth (hour)	21.5	32.8	P<0.001
Cesarean rate (%)	26	27.1	NS
UHS with abnormal FHR (%)	10.3	2.6	P<0.05
			RR =3.9
			95% CI =2.35–6.48
Apgar score <7 at 5 minutes	2.1	1.0	NS
			RR =2
			95% CI =0.81–4.94
Neonatal encephalopathy	0.6	0.1	NS
			RR =4
			95% CI =0.45–35.80

Note: Data from Wing et al.¹²

Abbreviations: MVI, misoprostol vaginal insert; DVI, dinoprostone vaginal insert; NS, not statistically different; UHS, uterine hyperstimulation syndrome; FHR, fetal heart rate; RR, relative risk; CI, confidence interval.

Misoprostol administration can be oral, sublingual, or vaginal. The oral administration provides a slow plasmatic concentration and a low bioavailability. The sublingual administration provides a high plasmatic concentration and bioavailability. The vaginal administration allows a good bioavailability and a low plasmatic level, but detectable plasma concentration last longer after vaginal administration. Tang et al have compared pharmacokinetic parameters of four different routes of administration of a single dose of 400 µg of misoprostol.¹⁷ They found that sublingual and oral administrations have the quickest onset of action when compared with vaginal administration with or without water. Sublingual administration can achieve the highest plasma concentration when compared with all other routes of administration. The systemic bioavailability was also highest after sublingual administration of misoprostol. Oral administration had only half of the bioavailability of sublingual administration. Different studies comparing the pharmacokinetics profiles of vaginal and oral administration of misoprostol found similar results.^{17–19} The peak plasma concentration of misoprostol free acid was higher and achieved earlier after oral administration, but the detectable plasma concentration lasted longer after vaginal administration. In contrast, the systemic bioavailability of vaginally administered misoprostol was not

consistent between the studies. Zieman et al found that the bioavailability of vaginally administered misoprostol was three times higher than the oral form, whereas Tang et al had similar results between the two regimens. Those differences may be explained by a wide variation in absorption of vaginal misoprostol. Moreover, despite similar bioavailability, use of misoprostol was first studied for the induction of abortion or second-trimester ending of pregnancies. Regarding those studies, more favorable clinical effects have been demonstrated with vaginal administration when compared with oral administration.^{20,21} Thus, taken together, those data suggest that misoprostol introduced vaginally seems to be the most appropriate way to induce contractions. One can then extrapolate that vaginal route for induction of labor with misoprostol could be the best option for high rate of vaginal deliveries. As induction of labor can occur in situations where the vaginal environment can be modified, Castañeda et al tested the MVI device in different pathological conditions.⁹ They showed that a vaginal pH change due to vaginal secretions, ruptured membranes, or blood does not affect the release of misoprostol in vivo or in vitro.

Powers et al studied the pharmacokinetic profile of the MVI with different doses on nonpregnant women and showed in their study that after oral administration of 200 µg of misoprostol, plasma concentration of misoprostol acid peaked quickly in approximately 20 minutes.⁷ With the MVI, misoprostol acid concentration in plasma was constant and durable during the first 12 hours of introduction and then decreased gradually. The maximum plasma concentration was less important and occurred a lot later for the MVI than the oral form. However, systemic exposure to misoprostol was three times greater with the 200 µg MVI than

Table 5 Major results of the study of Pevzner et al

Characteristics	Vaginal delivery (%)	Adjusted OR (95% CI)
Multiparous women	88.25	5.2 (3.7–7.41)
Elective induction of labor (16.5%)	86.7	2.1 (1.13–3.8)
Height 165 cm or more	76	2.0 (1.47–2.72)

Note: Data from Pevzner et al.¹⁴

Abbreviations: OR, odds ratio; CI, confidence interval.

the 200 µg oral tablet. Moreover, plasma concentration was dose proportional. Rayburn et al⁸ had the same conclusions using this device on pregnant women. Misoprostol was mainly excreted renally with a half-life less than an hour after removal of the vaginal insert. Those two Phase I trials allow to think that misoprostol introduced vaginally and with a controlled-release insert has a greater bioavailability with a lower plasma concentration than oral tablets. Thus, as adverse events due to misoprostol, such as hyperstimulation syndrome, are related to high plasma concentration, MVI could minimize those adverse events because of its pharmacokinetics parameters.

What are the current evidences of the use of misoprostol for induction of labor?

Misoprostol as an induction agent has been extensively studied. Hofmyer et al⁶ have compiled results of those studies in a large meta-analysis. They showed that misoprostol is an effective induction agent. Indeed, compared with placebo, misoprostol was associated with reduced failure to achieve vaginal delivery within 24 hours (RR = 0.51, 95% CI = 0.37–0.71). The need for oxytocin was reduced with misoprostol in comparisons with other conventional methods of induction of labor such as prostaglandins.

Regarding the safety of this molecule, several studies have shown an increased rate of side effects such as uterine tachysystole. Uterine tachysystole due to misoprostol was first reported by Mariani Neto et al in 1987 unrelated to dosage.²² Sanchez-Ramos et al in 1995 published data that confirmed an increased incidence of uterine tachysystole that was not associated with a statistically significant increase in adverse fetal outcome.²³ Hofmyer confirmed these data as they found that uterine hyperstimulation without FHR changes was increased with misoprostol compared with prostaglandins but lower doses of misoprostol compared with higher doses were associated with less uterine hyperstimulation, with and without FHR changes. Thus, the current dose of misoprostol recommended by WHO for induction of labor is 25 µg every 3–6 hours.

Uterine rupture following the use of misoprostol in patients with a history of Cesarean section is probably the most important issue of using this drug. Uterine rupture following the use of misoprostol for the induction of labor in patients with previous cesarean section has been reported by several studies.^{24–28} However, these studies were of low quality. Some randomized studies (three over 35) that compared misoprostol to other induction of labor methods included some patients with scarred uterus, but it was not

sufficient to assess this criterion.^{26,29–32} In a study comparing PGE2 and PGE1, Blanchette et al reported a uterine rupture rate of 18.8% (three cases) in the subgroup of 16 patients with a previous cesarean section.²⁶ A trial was interrupted early because of the rate of uterine rupture in the misoprostol group (2/17) after introduction of two and three doses of 25 µg misoprostol every 6 hours.³³ Aslan et al reported a rupture rate of 9.7% with misoprostol in 41 patients induced with a history of a previous Cesarean section. The protocol required a dose of 50 µg introduced vaginally followed by a second dose 4 hours later, and then 100 µg every 4 hours with a maximum of six doses.³⁴ With lower doses (25 µg introduced vaginally repeated 3 hours later), in a retrospective analysis of 89 patients by Plaut et al a rupture rate of 5.6% was observed.³⁵

Efficacy of MVI

Several studies aimed to compare different doses of MVI and MVI with DVI. Those studies were well designed and mainly conceived to answer to the question of efficacy. All inclusion criteria were similar between the studies. Patients with previous Cesarean or more than four vaginal births were excluded.

Obviously, misoprostol has a dose-dependent effect (Table 2). The efficacy, evaluated by the time to vaginal delivery and the rate of vaginal delivery, increased with the doses from 25 to 100 µg but was almost similar with doses above 100 µg, that is, between 100 and 200 µg.⁹ In 2005, Castañeda et al studied the maximum tolerable dose of MVI on pregnant women and efficacy of different MVI doses. They showed that when >100 µg of misoprostol was administered, the median time to vaginal delivery was not shortened. These results were confirmed by Ewert et al in 2006 who compared different doses of MVI with an efficacy end point of reduced time to vaginal delivery.¹⁰ Time was significantly reduced with 100 and 200 µg MVI compared with lower doses. A few years later, Wing found that the time to vaginal delivery was significantly reduced with the administration of MVI 200 µg, but the proportion of women who delivered vaginally by 24 hours was not statistically different (NS) for 200 µg compared with 100 µg.¹¹

When compared with DVI, the 100 µg MVI had a similar efficacy for time to vaginal delivery (1,596 with MVI 100 µg vs 1,650 with DVI, NS) and for Cesarean deliveries (28.3% with MVI 100 µg vs 27.1% with DVI, NS).¹² When MVI 200 µg was compared with DVI, time to vaginal delivery in MVI group was reduced (Table 4, 21.5 hours in the MVI

group vs 32.8 hours in the DVI group, $P < 0.001$). The proportion of vaginal birth was NS between 200 µg MVI and DVI (73.3% vs 71.6%, $P = 0.50$).¹³

If we consider the patients' point of view, time to delivery is an important judgment criterion. When we ask the patients regarding the best care they would prefer, they claim for a quick and efficient labor without pain.³⁶ Shetty et al interviewed patients about their experience of induced labor. Postinduction, 40% of the women indicated that the speed of the induction was the most important aspect they would like to change about their induction if they were to have another one.³⁷

Thus, regarding efficacy and patients' expectations, 200 µg would be the right dose for MVI as the time to delivery is reduced with similar rate of vaginal delivery compared with the 100 µg MVI or the current available DVI. However, a work that studies this specific question should be carried out to answer this hypothesis.

Safety of MVI

Maternal and neonatal safety is critical when we consider the outcome of labor induction. Adverse events related to safety of MVI include emergency C-section, postpartum hemorrhage, uterine tachysystole with and without FHR abnormalities, meconium-stained amniotic fluid, Apgar score below 7, fetal acidosis, or neonatal complications. In all the studies but one,¹⁶ these outcomes were considered as secondary judgment criteria, which means that the number of patients was not calculated based on them. Then, we can assume that the number of patients in the different publications might be too small to show a difference as some adverse events related to labor induction, especially severe events such as fetal acidosis, are infrequent.

The most problematic issue concerns the occurrence of uterine tachysystole associated with FHR pattern or hyperstimulation syndrome (Table 3). The rate of uterine hyperstimulation syndrome was found to be 10% in the study by Ewert et al¹⁰ 10.3% by Wing et al¹³ and 12.2% by Wing¹¹ with 200 µg MVI. This rate was two to three times higher than the rate observed with the 100 µg MVI (3% in the study by Ewert et al¹⁰ 6.1% by Wing et al¹² and 6.8% by Wing¹¹) or with DVI (6.4% by Wing et al¹² and 2.6% by Wing et al¹³). It is well known that the reduced time to vaginal delivery with vaginal misoprostol is counterbalanced by an increase in uterine hyperstimulation with or without FHR abnormalities. All the trials using the MVI demonstrated a dose-dependent increase in uterine hyperstimulation syndrome. The highest rates were found with the 200 µg dose.

Nonreassuring FHR was not systematically associated with uterine hyperstimulation.

The first studies (Ewert et al,¹⁰ Wing et al,¹² and Wing¹¹) described a dose-dependent effect for uterine hyperstimulation syndrome but did not find an impact on the rates of C-section or Apgar score below 7 and fetal acidosis. Similar results between DVI and MVI 100 µg for hyperstimulation syndrome and low Apgar scores were obtained in the 2008 Wing's trial. The most recent study in 2013 highlighted a significant difference between DVI and MVI 200 µg for hyperstimulation syndrome with a RR of 3.9 (95% CI = 2.35–6.48, $P < 0.05$). The risk of low Apgar score was doubled and the risk of neonatal encephalopathy multiplied by 4 with MVI compared with DVI but the difference was not significant. Those results have to be taken cautiously because those trials were not powered to demonstrate a difference for these criteria. Using a two-sided χ^2 test with an alpha risk of 5% and a power of 80%, the necessary number of patients to detect a difference would have been 6,206 patients for Apgar score < 7 at 5 minutes, 5,860 patients for encephalopathy, or 10,410 patients for fetal acidosis.

The Cesarean rate was not increased in any studies using MVI.^{9–13} Cesarean attributable to nonreassuring FHR occurred more often with MVI 200 µg compared with MVI 100 µg, but the difference was not statistically significant.¹² For Wing in 2013, not only was this rate not significantly different, but it did not show noninferiority of MVI compared with DVI. The most common reason for Cesarean delivery was adverse event in both groups. It concerns hyperstimulation syndrome for MVI 200 µg group and arrest of cervical dilatation for DVI group.¹³ This study included only a low-risk population at/or near term. Many situations that require labor induction include high-risk fetuses such as intrauterine growth retardation, placental insufficiency (gestational hypertension and preeclampsia), and gestational diabetes. In these cases, we cannot rule out that the increased rate of tachysystole may not lead to more frequent Cesarean section or neonatal acidosis.

For maternal and neonatal safety, evidence suggests that the MVI 100 µg is better than the 200 µg. The rate of per partum and neonatal complications are significantly lower with the 100 µg MVI and similar to DVI.

Past studies about the use of misoprostol introduced vaginally lead to recommend low-dose misoprostol, 25 µg given every 6 hours. For a period of 24 hours, this represents a total dose of 100 µg. This is very similar to the total dose of 100 µg released by MVI. It is important to consider this

extrapolation with caution, as the tablets have not been designed for the vaginal route. Comparative research is needed to conclude that the total given doses is identical for tablets and MVI.

In conclusion, the 200 µg MVI allows a faster delivery but increases the risk of hyperstimulation syndrome, whereas the 100 µg MVI has the same rate of vaginal delivery with a mean time from induction to delivery prolonged by 3 hours. With 100 µg, there is far less uterine tachysystole associated with FHR patterns compared with the 200 µg MVI. It is true that many patients complain about the duration of induction. In a study about women's perceptions, expectations, and satisfaction with induced labor, all patients were induced with vaginal prostaglandins. Even if 40% of the patients felt their induction took longer than expected, 73.5% were generally satisfied with the induction process. When we consider their expectations before induction, they hope for a fast but safe induction. A total of 44.6% of women fear more chance of babies to be distressed and 70.7% want the induction method to be safe for the baby and them even if it takes longer.³⁷ After induction of labor, some patients blame the medical team for a stressful birth experience, especially when they had an emergency C-section due to FHR patterns. These emergency Cesarean sections are most of the time experienced as a mental trauma and lead to posttraumatic stress disorders during the postpartum period.³⁸ It is thereby necessary to find the best balance between efficacy and safety to answer both doctors' and patients' expectations. The current data suggest that the 100 µg MVI provides the best compromise for these outcomes. Regarding those considerations, it is therefore surprising that the choice of the pharmacological industry was to introduce the 200 µg dosage to the market.

It is clear that introducing on the market a labeled product will address a number of legal problems. However, as suggested by Rouse in an editorial, despite the methodological rigor of Wing trial,¹³ the use of 200 µg is not justified because even if it shortened the time to vaginal delivery, it increases uterine tachysystole, fetal distress, and use of tocolysis. He then thinks that one would replace an inexpensive and effective generic alternative with a much more expensive proprietary product that is probably not any better.³⁹ Further studies should be performed to compare the 100 µg MVI and low misoprostol dose (25 µg every 6 hours) using tablets given orally or vaginally.

Disclosure

The authors report no conflicts of interest in this work.

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