Induction of Labor using Misoprostol in a Tertiary Hospital in the Southeast of Brazil

Indução de parto utilizando misoprostol em um hospital terciário no sudeste do Brasil

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Abstract

Purpose To assess cases of labor induction with vaginal 25-µg tablets of misoprostol and maternal outcomes in a tertiary hospital in southeastern Brazil.

Methods This was a retrospective cohort study of 412 pregnant women with indication for labor induction. Labor induction was performed with vaginal 25-µg tablets of misoprostol in pregnant women with Bishop scores < 6. Stepwise regression analysis was used to identify the factors present at the beginning of induction that could be used as predictors of successful labor induction.

Results A total of 69% of the pregnant women who underwent labor induction progressed to vaginal delivery, and 31% of the women progressed to cesarean section. One or two misoprostol tablets were used in 244 patients (59.2%). Of the 412 patients, 197 (47.8%) required oxytocin later on in the labor process, after induction with misoprostol. The stepwise regression analysis showed that only Bishop scores of 4 and 5 and previous vaginal delivery were independent factors with statistical significance in the prediction of successful vaginal labor induction ($\beta = 0.23$, $p < 0.001$, for a Bishop score of 4 and 5, and $\beta = 0.22$, $p < 0.001$, for previous vaginal delivery).

Conclusion Higher Bishop scores and previous vaginal delivery were the best predictors of successful labor induction with vaginal 25-µg tablets of misoprostol.

Keywords
- labor induction
- misoprostol
- oxytocin
- cesarean sections

Resumo

Objetivo Avaliar os casos de indução do trabalho de parto com misoprostol 25 mcg por via vaginal e seus desfechos maternos em um hospital terciário do Sudeste do Brasil.

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Métodos Realizou-se um estudo retrospectivo de coorte com 412 gestantes com indicações para indução de trabalho de parto. A indução do trabalho de parto foi realizada com misoprostol 25 mcg vaginal em gestantes com índice de Bishop < 6. Realizou-se análise de regressão *stepwise* para identificar os fatores presentes ao início da indução que poderiam ser usados como prognosticadores do sucesso da indução do trabalho de parto.

Resultados A indução de trabalho de parto determinou 69% de partos normais, sendo que 31% evoluíram para cesárea. Em relação ao número de comprimidos de misoprostol, 1 ou 2 comprimidos foram utilizados em 244 pacientes (59,2%). Das 412 pacientes, 197 (47,8%) necessitaram de ocitocina após a indução com misoprostol para dar continuidade ao trabalho de parto. Na análise de regressão *stepwise*, apenas a presença de índice de Bishop 4 e 5 e parto vaginal prévio foram fatores independentes com significância estatística na predição do sucesso da indução em obter parto vaginal ($\beta = 0{,}23$, $p < 0{,}001$, para índice de Bishop 4 e 5, e $\beta = 0{,}22$, $p < 0{,}001$, para parto vaginal prévio).

Conclusão Maiores índices de Bishop e parto vaginal prévio são os maiores prognosticadores do sucesso de indução de trabalho de parto com misoprostol 25 mcg vaginal.

Palavras-chave
- indução de parto
- misoprostol
- ocitocina
- parto cesárea

Introduction

Labor induction is any procedure that stimulates uterine contraction before labor begins naturally.[1,2] It is indicated when the maternal/fetal associated risks with the pregnancy are higher than the maternal/fetal associated risks of early delivery.[3] The most common causes of labor induction are prolonged gestation ($>$ 42 weeks), preeclampsia, and premature rupture of membranes.[3]

For the induction of labor, it is necessary to administer labor inducers. The main mechanical methods are the following: artificial rupture of membranes (amniotomy), breast stimulation, cervical dilators (Hegar dilators and laminaria tents), and digital sweeping in the lower segment.[4] Pharmacological methods include the use of oxytocin and synthetic prostaglandins.[1,2]

Misoprostol is a synthetic prostaglandin E1 (PGE1) analogue that acts as an inducer of the ripening process, thus favoring dilation and causing uterine contractions.[5] It is indicated for labor induction in cases of unfavorable uterine cervix (Bishop score < 6).[6] Misoprostol can be administered via the vaginal,[7] oral,[8] and sublingual[9] routes, with the vaginal route being the preferred one. However, misoprostol has contraindications, such as previous cesarean delivery, previous uterine surgery, placenta previa, asthma, coronary disease, and cephalopelvic disproportion.[10] The risks associated with labor induction using misoprostol are uterine hyperstimulation with hypertonia, tachysystole, and uterine rupture.[11]

The objective of this study was to evaluate pregnant women submitted to induction of labor through vaginal 25-µg tablets of misoprostol and the maternal outcomes in a tertiary hospital in the Southeast of Brazil.

Methods

A retrospective cohort study was conducted between November 2014 and August 2016 in a maternity in the Southeast of Brazil. The sample comprised pregnant women with indication for labor induction with vaginal misoprostol. The inclusion criteria were singleton pregnancy with live fetus, gestational age $>$ 40 weeks, and premature rupture of membranes $>$ 34 weeks in the absence of signs of maternal infection. The exclusion criteria were previous uterine scar, cephalopelvic disproportion, and abnormal presentations. The study was approved by the Research Ethics Committee (CAAE: 62832016.7.0000.5145), and informed consent was obtained from the participants.

Labor induction was performed with 25-µg tablets of misoprostol in pregnant women with Bishop scores < 6. The drug was inserted in the posterior vaginal fornix at a dosage of 1 tablet every 6 hours for a maximum period of 48 hours (200 µg = 8 tablets). In the cases in which labor was initiated, oxytocin was administered by a continuous infusion pump at an initial rate of 12 mL/h and increasing to 196 mL/h. In cases of absence of labor, induction was deemed unsuccessful after eight tablets were inserted in the vagina of a pregnant woman with an intact amniotic sac and without changes in the uterine cervix. In cases of premature rupture of membranes, induction was deemed unsuccessful after four tablets were inserted and no changes occurred in the uterine cervix.

The dependent variables of this study were mode of delivery (vaginal or cesarean section), amniotic sac condition (intact or ruptured), number of tablets used (one to eight tablets), and duration of labor (time in hours between the beginning of induction and delivery). The control variables were maternal age and parity. The women selected for the study were

recruited through a search in the computerized medical record system (Soul MV, MV Informática Nordeste Ltda, Recipe, PE, Brazil) of one of our institutions using the term *misoprostol 25 μg* as the search filter. Subsequently, an active search on the medical records obtained from the previous search to collect the relevant data on the procedure was conducted.

The data were entered into an Excel 2010 spreadsheet (Microsoft Corp., Redmond, WA, USA), and the statistical analyses were performed using the IBM SPSS statistics software, version 23.0 (IBM Corp., Armonk, NY, USA). We considered vaginal deliveries as successful inductions of labor, and the absence of uterine contractions/uterine cervix modifications or any intercurrence during the labor culminating with cesarean section was considered as unsuccessful induction of labor.

Initially, we compared the maternal variables of the pregnant women with those of the women who progressed to cesarean delivery using the unpaired Student *t*-test and Fisher exact test. Then, we performed a stepwise regression analysis to identify the factors present at the beginning of induction that could be used as predictors of successful induction. Subsequently, we compared the women that exhibited these characteristics with those who did not. In all of the analyses, the level of significance (p) was set at 5%.

Results

The study included 412 pregnant women with indication for labor induction. The majority of patients (51%) were aged between 20 and 30 years. In 244 patients (59.2%), 1 or 2 tablets of misoprostol were sufficient to achieve the expected effect, and 117 patients (28.4%) required 3 or 4 tablets. Regarding the Bishop score before labor induction, 241 patients (58.5%) had a score between 2 and 3, and 171 patients (41.5%) had scores between 4 and 5.

In our sample, 197 (47.8%) patients required oxytocin after induction with misoprostol for labor progression, and 215 patients (52.2%) did not need it. The induction of labor led to 69% of normal deliveries, and 31% of women progressed to cesarean delivery. The indications for cesarean section were the following: unsuccessful induction (10.9%); fetal bradycardia (10.7%); placental abruption (0.7%); secondary arrest of dilation (7.8%); and secondary arrest of descent (1.7%). The distribution of women according to the time (in hours) elapsed between the beginning of induction and delivery was the following: 12% between 4 and 7 hours; 18% between 8 and 11 hours; 17% between 12 and 15 hours; 13% between 16 and 19 hours; 23% between 20 and 29 hours; and 16% > 30 hours of induction.

►**Table 1** shows the maternal outcomes of the pregnant women submitted to induction of labor with misoprostol that progressed to vaginal delivery (successful induction) or cesarean delivery (unsuccessful induction). The variables previous deliveries, parity, Bishop score, number of misoprostol tablets, time of induction, use of oxytocin, and previous vaginal delivery were associated with successful labor induction.

The stepwise regression analysis showed that only Bishop scores of 4 and 5 (►**Table 2**) and previous vaginal delivery (►**Table 3**) were independent factors with statistical significance in the prediction of successful vaginal labor induction with misoprostol ($\beta = 0.23$, $p < 0.001$, for Bishop scores of 4 and 5, and $\beta = 0.22$, $p < 0.001$, for previous vaginal delivery).

Discussion

Misoprostol is considered the standard method for obtaining cervical maturity and, currently, for inducing labor. It is believed that 25 μg of this drug administered vaginally is the ideal dosage for pregnant women with viable fetuses.[12,13]

Table 1 Comparison between the maternal variables according to successful (vaginal birth) and unsuccessful (cesarean section) labor inductions with misoprostol

	Successful vaginal birth ($n = 285$)		Cesarean section ($n = 127$)		
	Mean	SD	Mean	SD	*p*
Age (years)	24.7	6.2	24.2	6.0	0.45
Number of previous deliveries	2.0	1.4	1.6	0.9	0.001
Parity	0.9	1.2	0.3	0.8	< 0.001
Number of previous miscarriages	0.1	0.4	0.2	0.5	0.06
Bishop score	3.5	1.1	2.8	0.8	< 0.001
Number of misoprostol tablets	2.3	1.5	3.6	2.4	< 0.001
Time of induction (hours)	16.5	9.9	23.6	13.9	< 0.001
	N/n	%	N/n	%	*p*
Ruptured amniotic sac	103/285	36%	40/127	31%	0.37
Use of oxytocin	151/285	53%	46/127	36%	0.002
Previous vaginal birth	130/285	46%	23/127	18%	< 0.001
Successful vaginal birth	144/285	51%	27/127	21%	< 0.001

Abbreviation: SD, standard deviation.

Table 2 Stepwise regression analysis to predict the success of labor induction with misoprostol according to Bishop score

	Bishop score between 4 and 5 ($n = 171$)		Bishop score between 2 and 3 ($n = 241$)		
	Mean	SD	Mean	SD	p^*
Age (years)	25.0	6.1	24.3	6.1	0.23
Number of previous births	2.1	1.4	1.7	1.1	0.001
Parity	0.9	1.3	0.5	1.0	0.001
Number of previous miscarriages	0.2	0.4	0.2	0.5	0.96
Bishop score	4.4	0.5	2.5	0.5	< 0.001
Number of misoprostol tablets	1.8	1.2	3.3	2.1	< 0.001
Time of induction (hours)	13.2	8.1	22.6	12.3	< 0.001
	N/n	%	N/n	%	p^{**}
Ruptured amniotic sac	85/171	50%	58/241	24%	< 0.001
Use of oxytocin	75/171	44%	122/241	51%	0.19
Previous vaginal birth	82/171	48%	71/241	29%	< 0.001
Successful vaginal birth	144/171	84%	141/241	59%	< 0.001

Abbreviation: SD, standard deviation.
Notes: *p value obtained using the unpaired Student t-test; **p value obtained using the Fisher exact test.

We found a higher incidence of cases of induced labor with misoprostol among pregnant women between 20 and 30 years of age, which is similar to the data found in the literature.[14] Maternal age can influence the unsuccessful labor induction due to: the less robust vasculature and an insufficient hemodynamic demand during pregnancy;[15] the gradual decrease in myometrial contraction function;[16] and the higher incidence of medical comorbidities in advanced maternal age.[17] Regardless of parity, advanced maternal age ($\geq$ 35 years) is independently associated with an increased risk of cesarean section following labor induction (adjusted odds ratio [OR]: 2.29; 95% confidence interval [95%CI]: 1.64–3.20; $p < 0.001$).[18]

Table 3 Stepwise regression analysis to predict the success of labor induction with misoprostol according to previous vaginal delivery

	Previous vaginal birth ($n = 153$)		No previous vaginal birth ($n = 259$)		
	Mean	SD	Mean	SD	p^*
Age (years)	28.4	5.8	22.3	5.1	< 0.001
Number of previous births	3.1	1.3	1.1	0.4	< 0.001
Parity	1.9	1.2	0.0	0.0	< 0.001
Number of previous miscarriages	0.2	0.5	0.1	0.4	0.13
Bishop score	3.6	1.0	3.2	1.0	< 0.001
Number of misoprostol tablets	2.6	1.9	2.7	1.9	0.39
Time of induction (hours)	17.3	11.8	19.5	11.6	0.07
	N/n	%	N/n	%	p^{**}
Ruptured amniotic sac	42/153	27%	101/259	39%	0.02
Use of oxytocin	72/153	47%	125/259	48%	0.84
Bishop score > 6	82/153	54%	89/259	34%	< 0.001
Successful vaginal birth	130/153	85%	155/259	60%	< 0.001

Abbreviation: SD, standard deviation.
Notes: *p value obtained using the unpaired Student t-test; **p value obtained using the Fisher exact test.

Successful labor induction with misoprostol occurred in the majority of the pregnant women (59.2%) with a low dose of this drug (25 µg to 50 µg). This result is consistent with the findings reported by Tsikouras et al,[19] which confirmed the safety and efficacy of 50 µg of misoprostol in inducing labor in low-risk and postterm pregnant women ($>$ 40 weeks), as well as in women with an unfavorable cervix (Bishop score $\leq$ 6). A lower dose of misoprostol is also associated with a lower incidence of adverse effects on the mother and fetus, such as tachysystole, uterine hyperstimulation and fetal metabolic acidosis.[20]

According to some protocols, PGE1 is administered to promote cervical ripening as the first step in the labor induction of pregnant women with unfavorable uterine cervices. Prostaglandin E1 alone initiates labor, and oxytocin is obviously needed for the conduction of labor.[21] In our study, 197 pregnant women (47.8%) required oxytocin after induction with misoprostol to continue labor.

Brusati et al[22] evaluated the efficacy of 25 µg of sublingual misoprostol in inducing labor in single births. They found that vaginal birth occurred within 24 hours in 78% of multiparous women and in 65% of nulliparous women. In our study, not only parity, but also the Bishop score, the amount of misoprostol administered, the time of induction, the use of oxytocin, and prior vaginal births were all associated with the successful induction of labor.

Many studies have shown that, when compared with expectant management, induced labor in cases of full-term pregnancy is associated with a reduction in perinatal mortality.[23–25] The traditional method for predicting whether labor will be induced successfully in cases of vaginal birth is the presence of a favorable cervix, as determined by the Bishop score. In the past, some studies demonstrated that the Bishop score rarely predicted the success of induced labor.[26–28] Recently, a review of the Cochrane Library, which included 234 patients, compared the Bishop score to the assessment of cervix length by transvaginal ultrasound to determine the success of induced labor.[29] According to this review, there is no clear superiority of one method over another to assess the pre-induction of the cervix for the following post-natal outcomes: vaginal birth (OR: 1.07; 95% CI: 0.92–1.25); cesarean section (OR: 0.81; 95%CI: 0.49–1.34); and admission to a neonatal intensive care unit (OR: 1.67; 95%CI: 0.41–6.71). Our study used a stepwise regression analysis to identify the pre-induction factors that could be used as predictors of a successfully induced labor. We found that a Bishop score between 4 and 5 and previous vaginal birth were independent factors with statistical significance in the prediction of a successful vaginal birth.

The most common indication for cesarean section was unsuccessful induction (10.9%). According to a study by Pajak et al[30], 12% of post term pregnant women had unsuccessful labor induction with misoprostol 50 µg every 12 hours (maximum: 150 µg). A total of 18% of the pregnant women required 8 to 11 hours between the start of labor and delivery. Sharami et al[31] obtained an average of 13.2 hours in a group of 633 primigravidae who received a 50-µg vaginal dose of misoprostol. Santo et al[32] used 25 µg of misoprostol placed in the posterior vaginal fornix and found an average time between induction and the start of the active phase of labor of 10 hours and 20 minutes, while labor lasted for an average of 15 hours and 35 minutes.

One limitation of our study is the fact that it is a retrospective study. In addition, we did not evaluate the influence of body mass index on the success of induced labor. However, this study included 412 patients who were duly monitored until the end of labor, which enabled the proper assessment of the maternal outcomes.

Conclusion

The present study concluded that successful labor induction with misoprostol occurred in the majority of the pregnant women with a low dose of this drug. Higher Bishop scores and previous vaginal deliveries were the best predictors of vaginal delivery when 25 µg of misoprostol was administrated vaginally.

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