Labor induction with misoprostol versus dinoprostone: A meta-analysis of seven randomized trials

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OBJECTIVE: To compare the efficacy and safety of two prostaglandin analogs, misoprostol and dinoprostone, for labor induction of third trimester pregnancies with fetus and cervices unfavorable to oxytocin, as reported by recently published studies.
METHODS: Seven randomized, controlled and prospective studies, comparing intravaginally applied misoprostol (n=500) with dinoprostone (n=498) were selected from Medline. *For each variable analyzed in each of the seven studies reviewed, we used SerSimonian and Laird's method to evaluate the homogeneity of treatment effects. To analyze the results of each clinical trial, the relative risk was calculated with a 95% Confidence Interval; a "common" RR for different outcomes was also calculated using the Mantel-Haens method, with the SAS statistical package. The following outcomes were evaluated in our study: need for oxytocin augmentation; need for cesarean section; meconium passage; 1- and 5-minute Apgar scores.*
RESULTS: When misoprostol was used instead of dinoprostone, there was a decrease of approximately 50% in the need to use oxytocin (RR = 0.55; 0.49-0.63). No difference was found regarding the need to perform cesarean sections in the misoprostol group when compared to the dinoprostone group (RR = 1.04; 0.81-1.34). There was a slightly higher incidence of meconium passage among the group that used misoprostol (RR = 1.39; 1.03-1.86). No significant difference in the incidence of Apgar score smaller than 7 was observed between the misoprostol or dinoprostone group, either at the 1st (RR = 1.36; 0.92-2.26) or at the 5th minute (RR = 1.39; 0.36-5.36).
CONCLUSIONS: For the labor induction in third trimester pregnacies, with live fetus and unfavorable cervices, misoprostol is as effective and as safe as dinoprostone. A 50 mg dose of misoprostol may cause a higher incidence of meconium passage, however, it doesn't compromise the perinatal performance of the newborn. The cost of misoprostol treatment was significantly lower than the cost of dinoprostone treatment according to the three studies that assessed this variable.

Key-words: Cervix uteri; dinoprostone; induced labor; misoprostol; oxytocin.

Indução do parto com misoprostol versus dinoprostone: uma meta-análise de sete ensaios clínicos randomizados
OBJETIVO: Comparar a eficácia e a segurança de dois análogos das prostaglandinas, misoprostol e dinoprostone, na indução do parto em gestações de terceiro trimestre com feto vivo e cérvice desfavorável ao uso de ocitocina, conforme relatos recentes

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na literatura.

MÉTODOS: Foram selecionados do sistema Medline *sete estudos randomizados, controlados e prospectivos, comparando misoprostol (n = 500) com dinoprostone (n = 498) utilizados por via vaginal. Utilizou-se o método de DerSimonian e Laird para avaliar a homogeneidade do efeito do tratamento para cada variável analisada pelos sete estudos. Optou-se pelo risco relativo com intervalo de confiança de 95% para avaliar o resultado de cada ensaio clínico, calculando-se também o RR "comum" para os diferentes desfechos pelo método de Mantel-Haenszel, utilizando-se o pacote estatístico SAS. Os seguintes desfechos foram analizados: uso de ocitocina; índice de cesariana; eliminação de mecônio; escore de Apgar no 1º e 5º minutos.*

RESULTADOS: Houve uma diminuição significativa – aproximadamente 50% – na necessidade de uso de ocitocina com a aplicação do misoprostol em relação ao dinoprostone (RR = 0,55; 0,49-0,63). Não foi encontrada nenhuma diferença na necessidade de cesariana entre o grupo que utilizou misoprostol (RR = 1,04; 0,81-1,34) e o que utilizou dinoprostone. Houve uma incidência ligeiramente aumentada de eliminação mecônio no grupo do misoprostol (RR = 1,39; 1,03-1,86) em relação ao dinoprostone. Não foi encontrada nenhuma diferença significativa entre o grupo que utilizou misoprostol e o grupo que utilizou dinoprostone em relação à incidência de escores de Apgar menor do que 7, tanto no 1º minuto (RR = 1,36; 0,92-2,26), como no 5º minuto (RR = 1,39; 0,36-5,36).

CONCLUSÕES: O misoprostol por via vaginal é tão efetivo e tão seguro quanto o dinoprostone para a indução do parto em gestações de terceiro trimestre com feto vivo e cérvice desfavorável ao uso de citocina. A dose de 50 mg de misoprostol pode provocar um aumento na eliminação de mecônio, sem contudo comprometer o desempenho perinatal dos recém nascidos. O custo do tratamento com misoprostol foi significativamente menor nos três estudos que avaliaram este item.

UNITERMOS: Cérvix: dinoprostone; parto induzido; misoprostol, ocitocina.

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Introduction

Cervical ripening is a vital phenomenon for the success of labor induction. It is characterized by the onset of uterine contractions that initiate labor. Induction methods have been studied since the 16th century, and, except for the introduction of oxytocin and prostaglandins, there has been very little change in these methods. Pregnant women with small uterine cervical dilation (Bishop score less than or equal to 5) rarely respond well to labor induction with oxytocin. At Hospital de Clínicas de Porto Alegre (HCPA), the two most frequent reasons for cesarean section indication (20.4% of all indications) are failure to induce labor using oxytocin and presence of cervices unfavorable to induction (1).

In recent years, many researchers have dedicated themselves to study the development of agents that can be used to promote cervical ripening (2-5). Dinoprostone, an estradiol prostaglandin analog (PgE_2), the only pharmaceutical agent for cervical ripening approved by the Food and Drug Administration in the United States, received this approval only after 5 years of research, and after publication of over 70 reports on clinical trials (6). Many researchers have shown the advantages of using another agent, misoprostol (PgE_1), an estrone prostaglandin analog (7-12). These studies suggest that misoprostol is safe, very effective, stable at room temperature, easy to store and that it costs less than dinoprostone. On the other hand, some authors have shown that the incidence of tachysystole, meconium passage and nonreactive cardiotocography is higher with

misoprostol (13, 14).

The objective of this study is to review published randomized clinical trials which compare dinoprostone and misoprostol in terms os their properties to promote cervical ripening and labor induction. The reported benefits and risks of using misoprostol will be evaluated through meta-analysis.

Materials and methods

After a bibliographic search in *Medline*, 31 articles about the use of misoprostol pregnant women were chosen. From these, seven were selected, since they fulfilled the criteria of being prospective, randomized, and controlled studies, and of comparing the effects of intracervical application of dinoprostone to the effects of intravaginal application of misoprostol in third trimester pregnancies with live fetus and unfavorable cervices to the use of oxytocin.

For each variable analyzed in each of the seven studies, DerSimonian and Laird's method (D&L method, modified Cochran method) was employed to assess the homogeneity of treatment effects (15, 16). Treatment effects were not considered heterogeneous in the various studies in terms of the variables analyzed for a significance level of 5% ($\alpha = 0.05$).

The results of each clinical trial were evaluated using the relative risk (RR) with a 95% confidence interval. Moreover, a "common" relative risk (typical RR) and its 95% confidence interval were calculated for specific outcomes reported by all the studies, through the MantelHaenszel method, using the SAS statistical package (17). We chose to determine the RR because it can estimate the magnitude of an association between exposure (PgE_1 or PgE_2) and outcome. From the variables analyzed in our study (since they were similarly analyzed in the seven clinical trials): need for oxytocin augmentation; need for cesarean sections; meconium passage; Apgar score smaller than 7 at the 1st and 5th minutes. When the relative risk could not be calculated due to the absence of magnitude, as in the variable Apgar score smaller than 7 at the 5th minute (8, 10, 13), a small constant (0.5) was added to make the calculation possible (18).

Results

Use for oxytocin

There is a reduction of approximately 50% in the need for oxytocin augmentation when misoprostol is used, in comparison with dinoprostone (Figure 1). This reduction happened in all studies, independently of the dosage of misoprostol or dinoprostone (typical RR = 0.55; 0.49-0.63). This benefit was less evident in the study by Fletcher et al. (7), in which relatively higher doses of dinoprostone (3 mg) were used (RR = 0.65; 0.20-2.07), and in the study by Wing et al. (10), in which smaller doses of misoprostol (25 μg) were used (RR = 0.64; 0.52-0.79).

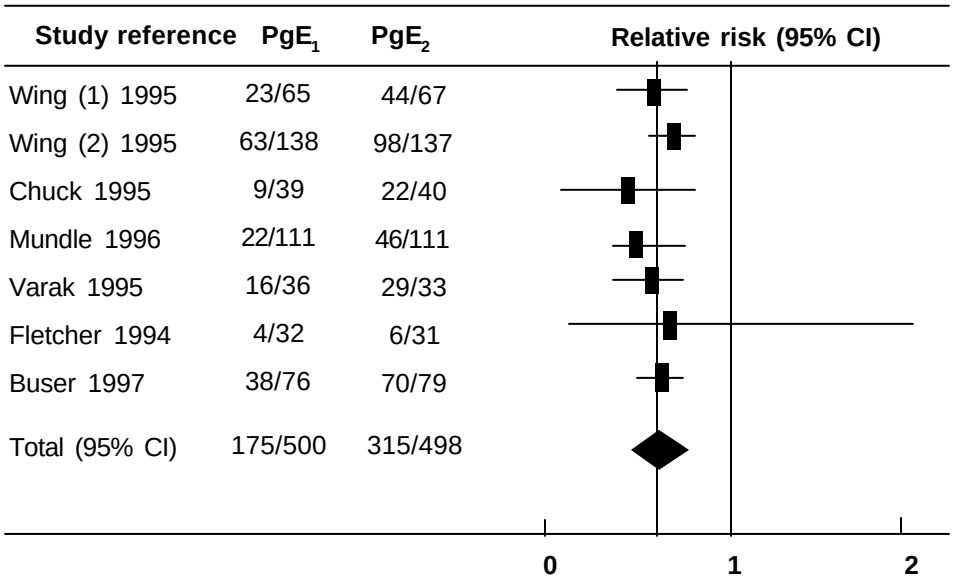

Figure 1. Need for oxytocin augmentation. Typical RR = 0.55; χ^2 for heterogeneity = 4.161.

Cesarean section

No difference was found regarding need for cesarean section deliveries between the misoprostol group and the dinoprostone group (RR = 1.04; 0.81-1.34) (Figure 2). The need for cesarean sections ranged, among the various studies, from 3.1 to 35.5% for the misoprostol group and from 9.6% to 21.5% for the dinoprostone group (7, 14). Such variations are related to a more or less tolerant conduct with respect to cesarean sections, and they do not reflect the type of prostaglandin used.

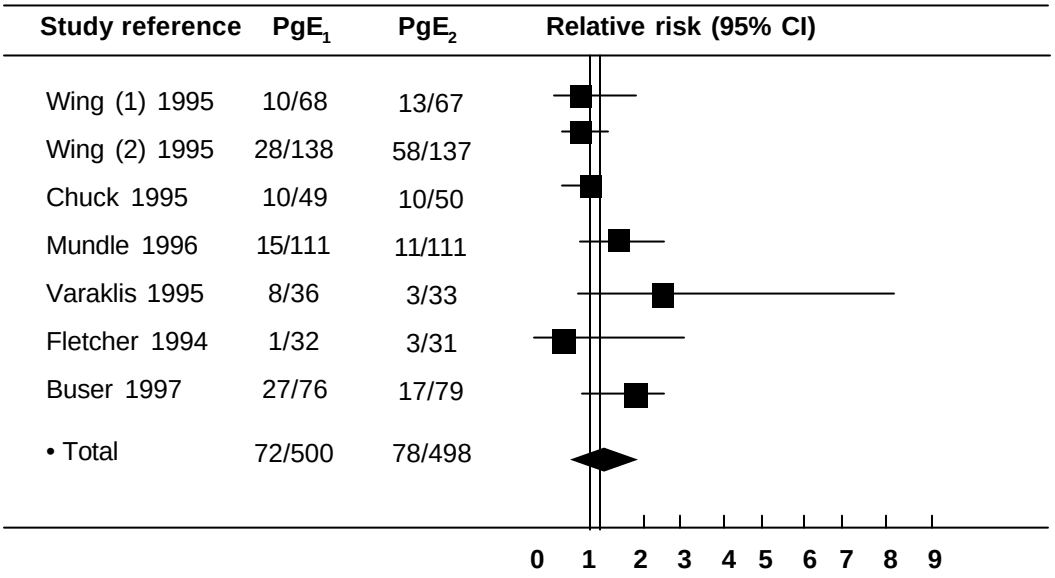

Figure 2. Need for cesarean section delivery. Typical RR = 1.04; χ^2 for heterogeneity = 10.00.

Meconium passage

Evaluation of this outcome was possible with only four of the seven studies analyzed (Figure 3). There was a slightly higher prevalence of meconium passage in the misoprostol group than in the dinoprostone group (typical RR = 1.39; 1.03-1.86). This was partly due to the study by Wing et al. (13), in which 50 μg doses of misoprostol were administrated every 3 hours, to a maximum of six doses (RR = 2.67; 1.20-5.95). This negative outcome was not observed when the same authors (10) used a 25 μg dose of misoprostol every 3 hours (RR = 1,25; 0.72-2.18). Likewise, this negative outcome was not observed in the studies of Chuck & Huffaker (8) (RR = 0.82; 0.23-2.86) and Mundle et al. (11) (RR = 1.25; 0.82-1.91), which used 50 μg doses of misoprostol, but at 4 hour intervals.

Apgar score smaller than 7

Comparing the misoprostol group to the dinoprostone group, there was no significant

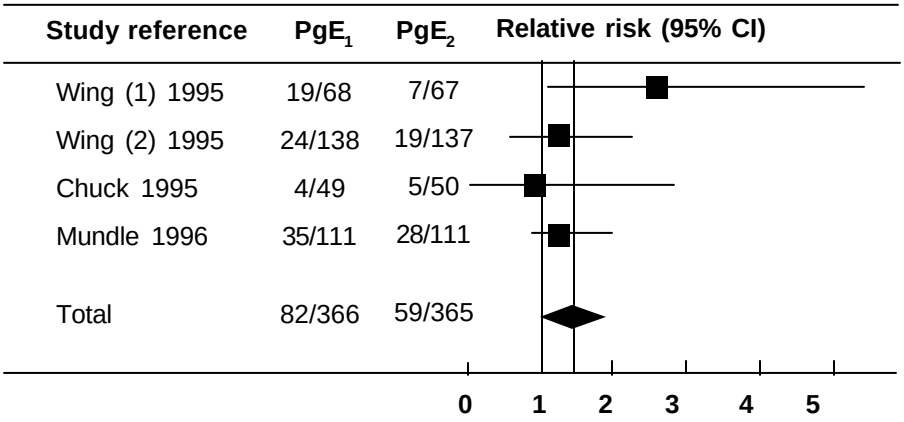

Figure 3. Meconium passage. Typical RR = 1.38; χ^2 for heterogeneity: 3.789.

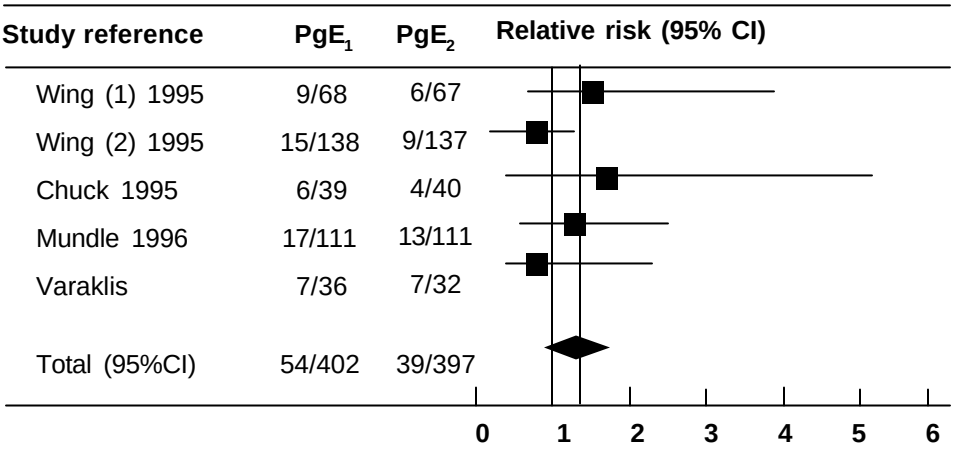

Figura 4. Apgar score < 7 at the 1st minute. Typical RR = 1.36; χ^2 for heterogeneity = 0.800.

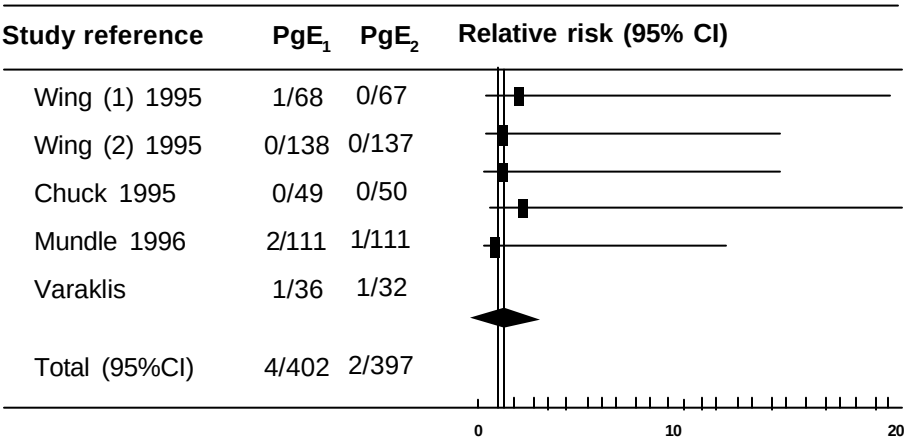

Figure 5. Apgar score < 7 at the 5th minute. Typical RR = 1.39; χ^2 for heterogeneity: 0.379.

difference for newborns regarding Apgar score smaller than 7, either at the 1st (typical RR = 1.36; 0.92-2.26) or at the 5th minute (typical RR = 1.39; 0.36-5.36) (Figures 4 and 5). As with the meconium passage variable, the study by Wing et al. (13), which employed a 50 μg dose of misoprostol at 3 hour intervals, had the highest RR for Apgar score smaller than 7 (RR = 1.94 at the 5th minute).

Discussion

The studies reviewed here selected to enable a comparison between two types of prostaglandins (misoprostol and dinoprostone), and not to compare prostaglandins with oxytocin. Clinical trials comparing prostaglandins with oxytocin are usually inconsistent, due to randomizing and control difficulties. Besides having excluded patients presenting contraindications to vaginal delivery and to prostaglandin use, all the authors reviewed have excluded from their studies patients with previous uterine scarring.

All the authors reviewed assessed induction time using various parameters, such as: duration in relation to changes in Bishop score; time span from the beginning of labor induction until the actual delivery; duration of the 1st and 2nd labor stages; length of time until the onset of uterine contractions. This diversity of parameters got in the way of a more precise assessment of labor induction time, although all studies did show that misoprostol decreases the time interval between the start of treatment and the start of the active stage of labor or birth. This suggests that this misoprostol, administrated in 25 to 100 μg doses, is more powerful than dinoprostone in 0.5 or 3.0 mg doses, at least in relation to cervical effacement and onset of

uterine contractions. Wing et al. (10, 13) observed a higher incidence of tachysystole with 50 μg doses of misoprostol in comparison to 0.5 mg doses of dinoprostone; this was not observed with 25 μg doses of misoprostol. Buser et al. (14) did not observe a higher incidence of tachysystole in a group of 76 patients who received 50 μg of dinoprostone. The difficulty to find an effective and safe dosage also occurred in the first PgE_2 studies, when the vaginal gel was made from Prostin suppositories.

The presence or not of fetal distress is always taken into consideration when prescribing drugs for labor induction. In a study by Fletcher et al. (7), 63 patients received a single 100 mg dose of misoprostol or 3 mg of dinoprostone and were evaluated. There were no cases of perinatal death in either group. In the same study, no significant difference (9.4% for misoprostol and 13% for dinoprostone) was found in terms of hyperstimulation, that is, association of tachysystole and fetal bradycardia.

In a study in which Wing et al. (13) observed a higher frequency of meconium passage with 50 μg doses of misoprostol every 3 hours, no significant differences were registered in terms of more accurate indicators of fetal distress, such as Apgar score, need for resuscitation or admission to the neonatal intensive care unit. In another study using 25 μg doses of misoprostol, the same authors again found no significant difference between misoprostol or dinoprostone in terms of fetal distress (10). Varaklis et al. (9) registered similar pH values for the newborns' umbical cord venous and arterial blood for patients both in the misoprostol group and in the dinoprostone group, even when using 25 μg of misoprostol (every 2 hours) in comparison with 0.5 mg of dinoprostone (every 6 hours).

Among pregnant women who received either 50 μg of misoprostol or 0.5 mg of dinoprostone, Mundle and Young (11) did not observe any significant difference in terms of nonreactive cardiotocography, umbilical cord blood pH smaller than 7; meconium passage; or Apgar scores (1^{st} and 5^{th} minute) smaller than 7. On the other hand, Buser et al. (14) did observe a higher incidence of hyperstimulation in the misoprostol group (50 μg every 3 hours), compared to the dinoprostone group (0.5 mg every 6 hours). In the same study, no significant difference was found in association with incidence of 5-minute Apgar score smaller than 6, or to neonatal intensive care unit admission and days spent in the intensive care unit.

The treatment cost was also assessed in some studies. Wing et al. (13) reported a cost of 0.36 dollars for every 100 μg of misoprostol and 75 dollars for every 0.5 mg of dinoprostone; 100 μg of misoprostol yields four of the indicated 25 μg doses. Chuck and Huffaker (8) reported a cost of 0.20 dollars for each dose of misoprostol, compared to 65 dollars per dose of dinoprostone. Mundle and Young (11) mentioned an average cost of 0.22 Canadian dollars for PgE_1 treatment compared to 70 Canadian dollars for PgE_2 treatment. Such estimates suggest that a 50 μg dose of misoprostol has a cash value that is 318 to 416 times lower that of a 0.5 mg dose of dinoprostone.

Therefore, the present analysis, which reviewed seven randomized and controlled studies that included 998 patients (misoprostol n = 500; dinoprostone n = 498), leads to the conclusion that intravaginal misoprostol is as effective and as safe as dinoprostone for labor induction in third trimester pregnancies with live fetus and cervices unfavorable to oxytocin. A 50 μg dose of PgE_1 administered at 3 hour intervals is associated with a higher frequency of meconium passage, but without compromising the perinatal performance of the newborn. The cost of misoprostol treatment was significantly lower in the three studies that assessed this item.

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