The influence of dinoprostone on uterine cervix ripening and the course of labor

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Abstract

OBJECTIVES: The aim of the study was to estimate the influence of dinoprostone in two different forms on the ripening of uterine cervix and the course of labor.
MATERIAL AND METHODS: 128 pregnant women with indications for labor induction and uterine cervix Bishop's scores <6, divided into 2 groups: I - 62 patients who had dinoprostone in the form of a gel applied for labor preinduction; II - 66 women who were administered dinoprostone in the form of vaginal inserts. The effectiveness of both forms of dinoprostone were estimated and compared.
RESULTS: No differences in Bishop's score changes were noticeable between the groups after 6–8 hours from application, however they were significant at the beginning of induction: I - 7.8±1.3 vs. II - 6.9±1.6 (p=0.0007). Almost half of the patients from group II had spontaneous contractions and required no labor induction at all. The average time from dinoprostone application till delivery was shorter in group II.
CONCLUSIONS: Dinoprostone vaginal inserts seem to influence both uterine cervix and muscle, while gel – prepare uterine cervix for delivery more effectively.

INTRODUCTION

There are some clinical situation, in which the continuation of pregnancy is of a higher risk for the mother-to-be and the fetus than terminating it. An obstetrician often faces the decision of having to end a pregnancy before spontaneous uterine contractions impose themselves upon an unprepared uterine cervix. Therefore, cervical ripeness could be considered the most important indicator of successful vaginal delivery. A special scale was prepared by Bishop in 1964 (Table 1). When Bishop's score is below 6 points and there are indications for labor induction, it is important to consider and choose a way to prepare the cervix for delivery by inducing its ripeness (so-called labor preinduction). Its condition is crucial for the success of induction [6]. The objective of labor preinduction, therefore, is to

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Table 1. Bishop's score for cervical ripeness assessment.

Score (points)	0	1	2	3
Cervical dilation (cm)	<1	1–2	3–4	>4
Cervical effacement (%)	0	<50	50–75	>75
Cervical consistency	firm	average	soft	–––
Cervical position	posterior	middle	anterior	
Presenting part level (cm from ischias spines)	–3	–2	–1	

decrease the rate of unsuccessful inductions ending in cesarean sections and to shorten hospitalization time. There are various known methods of stimulating cervical ripeness, however, prostaglandins (PG) preparations are commonly used for labor preinduction. The therapeutic effect of these substances is based on the stimulation of uterine muscle contractility and the loosening effect on connective tissue through increased collagenase activity and cervical proteoglicans metabolism. The only prostaglandin registered in obstetrics in Poland is PGE2 (dinoprostone). It is administered locally: into the posterior vaginal fornix or into the cervical canal.

The aim of the study was to estimate the influence of dinoprostone in two different pharmaceutical forms on the ripening of uterine cervix and the course of labor.

MATERIALS AND METHODS

The study material consisted of 128 pregnant women. They were hospitalized at the 1st Department of Obstetrics and Gynecology, Medical University of Warsaw, in the year 2004, and had both indications for labor induction and uterine cervix Bishop's scores below 6. Inclusion criteria for the study were as follows: singleton pregnancies, cephalic presentation, maternal and/or fetal indications for labor induction with no contraindications for prostaglandin administration. Among the indications for labor induction there were: post-term pregnancy (10 days or more), fetal heart rate abnormalities and pregnancy accompanying pathologies hazardous for fetal and/or mother well-being (gestational diabetes, pregnancy induced hypertension, cholestasis of pregnancy, feto-maternal immunization, oligohydramnion and intrauterine growth retardation). All the patients were haphazardly divided into 2 groups. Group I consisted of 62 patients who had a single dose of dinoprostone in the form of a gel applied for labor preinduction (Prepidil gel 0.5 mg/3 mg; Pharmacia Corporation). Group II consisted of 66 women who were administered dinoprostone in the form of vaginal inserts (Propess 0.01 g; Controlled Therapeutics; in each case removed no later than after 12 hours from application). Both forms of the drug were

inserted either into the cervical canal (if possible) or into the posterior vaginal fornix. The application was followed by a 2-hour intensive cardiotocographic monitoring. Intravenous oxytocin and/or artificial rupture of membranes (arom) were used for labor induction in both groups. However, intravenous oxytocin flow was not used earlier than 6 hours after PG application.

The effectiveness of dinoprostone in form of gel and vaginal insert was estimated by comparison of:
- uterine cervix ripeness in Bishop's score 6–8 hours after PG application
- percentage of patients who presented with spontaneous uterine contractions
- time from labor induction (intravenous oxytocin administration prior to contractions) to delivery
- percentage of cesarean sections in both groups.

Statistical analysis was performed afterwards with the use of Student T-test, where p-value <0.05 was considered significant.

RESULTS

The studied groups did not differ significantly in regard to age and parity. Mean duration of pregnancy was 39.4±1.8 (35–41) weeks in group I vs. 38.6±1.8 (36–41) in group II (p=ns). The percentage of primiparas vs multiparas within the groups was also similar: 77.5% vs. 22.5% in group I and 63.3% vs. 36.4% in group II (p=ns).

Patients from both groups had cervical ripeness preliminarily evaluated as less than 6 points in Bishop's score – it averaged 2.2±1.1 in group I and 2.3±0.9 in group II (p=ns). It was again evaluated in each patient 6 to 8 hours after the application of dinoprostone. No differences in efficiency were noticeable between the two forms of the drug – cervical ripeness averaged 6.7±3.2 in group I and 6.6±3.1 in group II; p=ns. Uterine cervix was reevaluated at the beginning of labor induction (only in patients who required intravenous oxytocin administration to induce uterine contractions), with significant differences between the gel (7.8±1.3 points) and vaginal insert (6.9±1.6 points) groups (p=0.0007). The ripeness of the cervix at assigned points is illustrated in Figure 1. However, a high percentage of patients from both groups presented with spontaneous uterine contractions and

Table 2. The rates of spontaneous uterine contractions after preinduction alone in both groups in regard to parity.

Parity	Group	Spontaneous contractions rate	p-value
Primiparas	Group I	33.3%	0.0258
	Group II	57.1%	
Multiparas	Group I	42.9%	ns
	Group II	41.7%	
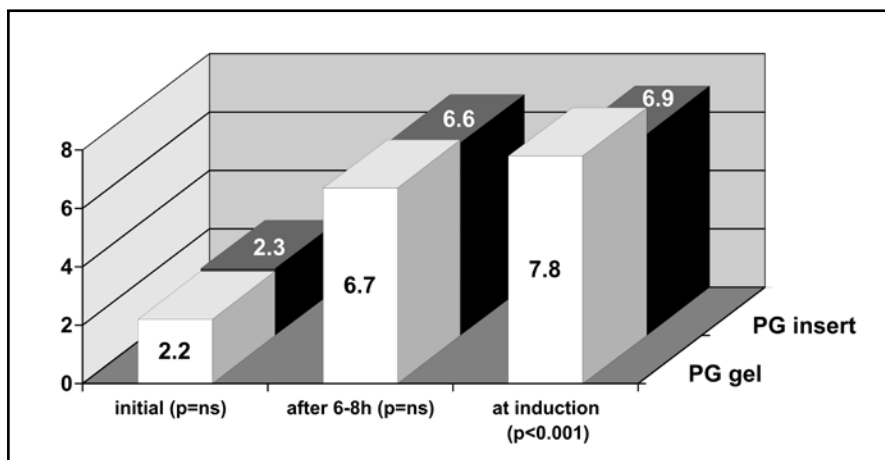
Figure 1. The assessment of cervical ripeness in Bishop's score (averaged) in the studied groups at assigned time points.

required no labor induction at all (48.5% in group II vs. 35.5% in group I; p=ns) – they therefore were not taken into account when Bishop's score at induction was assessed. We observed that labor more often started spontaneously in primiparas from group II (Table 2). There was no need of oxytocin use throughout the first stage of labor in 12.5% of all studied patients (group I: 12.9% vs group II: 12.1%; p=ns). Arom was performed in 54.8% of the patients from group I and in 57.6% from group II. Propess was inserted into the posterior vaginal fornix in 66.6% of cases and in 33.3% into the cervical canal, whereas Prepidil was administered mostly into the latter (95%). Therefore the changes in cervical ripening were calculated according to the site of administration only in group II – no significant differences were found both after 6–8 hours and before labor induction (6.0±0.9 vs. 6.7±3.3 and 7.3±2.1 vs. 6.6±1.1, respectively; p=ns). However, more patients presented with spontaneous uterine contractions and no need for additional induction when Propess was inserted into the posterior vaginal fornix (54.5% vs. 18.2%; p=0.0064).

Cervical ripening was expressed as a difference between Bishop's scores at labor induction and at the primary examination – the result was in favor of group I (4.7±0.5 vs. 4.0±1.9; p=0.0057), but the patients who presented with spontaneous contractions were excluded from this analysis. Only in a small percentage of patients we observed to have insufficient reaction to dinopros-

tone: 6.4% from group I and 3% in group II (p=ns) did not reach 6 points in Bishop's score after preinduction (evaluated after 24 hours). The influence of prostaglandins was also assessed in regard to parity – the only differences were observed in multiparas (Table 3).

The rate of successful vaginal delivery in both analyzed groups was similar: 64.5% for gel and 63.6% for the insert (p=ns). The mean time from the onset of labor induction till delivery, excluding cesarean sections and patients with spontaneous contractions, did not differ significantly between group I and II: 326±190 min vs. 336±197 min, respectively (p=ns). However, the average time calculated from dinoprostone application till delivery, again excluding cesarean sections, was significantly shorter in group II (1 487±1 445 min vs. 2 084±1 567 min in group I; p=0.0267).

The percentage of cesarean sections was similar in both groups: 35.5% in I and 36.4% in II (p=ns), as well as the indications for it. Although we had no case of uterine hyperstimulation in our material (here defined as an excessive uterine stimulation requiring intravenous tocolysis or immediate cesarean section due to fetal distress), the most common indication was fetal distress (36.4% vs. 33.3%, respectively; p=ns). Additionally, in group II 6.1% of patients had instrumental delivery (vacuum extractor) due to the above condition. Dystocia was the second most frequent indication, comparable in two groups (27.3% vs. 25%, respectively; p=ns). Cesarean section

Table 3. The assessment of cervical ripeness in Bishop's score in regard to parity as time and medical preparation derivative.

Parity	Group	Initial score	p-value	After 6–8 hours	p-value	At labor induction	p-value
Primiparas	Group I	2.1±1.0	ns	6.3±2.7	ns	7.2±1.2	ns
	Group II	2.1±0.9		7.4±2.8		7.2±1.9	
Multiparas	Group I	2.6±1.5	ns	9.0±5.2	<0.001	9.0±1.0	<0.001
	Group II	2.7±1.7		3.0±1.4		6.3±0.8	

Table 4. Newborns' condition according to Apgar scale in the first minute of life.

Newbors' condition (Apgar score)	Group I	Group II	p-value
good (10–8 points)	80.7%	97%	0.0037
average (7–4 points)	16.1%	3%	0.0121
asphyxia (3–1 points)	3.2%	0%	ns

was performed in 45.6% of patients from group II who had Propess inserted into the posterior vaginal fornix, while only in 18.2% of those, who had it inserted into the cervical canal (p=0.0329). No case of ineffectiveness or dystocia was observed after dinoprostone application into the cervical canal. Postpartum uterine curettage due to incomplete afterbirth was performed in 16.1% of patients from group I and 15.1% from group II (p=ns). Two patients from group I had manual removal of the placenta.

The average newborns' birthweight was similar in both groups: 3 329±540 vs. 3 327±527, respectively (p=ns). However, general neonatal condition according to Apgar scale in the first minute of life was significantly worse in group I– it seems to be related to slightly higher percentage of fetal distress as an indication for operative delivery (Table 4). Apgar scores in 5th and 10th minute of life did not differ between the analyzed groups (all the newborns were in good general condition).

DISCUSSION

Labor induction is currently one of the most often performed procedures in obstetrics. In United States alone its frequency has risen from 10 to 20% over the last decade [18]. Today, prostaglandin (PG) preparations administered locally are thought to be the most effective in labor preinduction. Since 1960s different medical forms of PGs have appeared, such as tablets, gels, suppositories or vaginal inserts [6]. The only limitation for their common use is relatively high cost. Royal College of Obstetricians and Gynecologists (RCOG) recommends the usage of vaginal form of PGE2, regardless of parity or cervical condition [15].

Hofmeyr, basing on Cochrane database analysis, published a review of various labor preinduction methods and their effectiveness in comparison to vaginal dinoprostone, considered a golden standard [6]. The efficacy comparison of different medical forms and ways of PG administration has been discussed in various researches. In the above study we have shown high effectiveness of both vaginal gel and insert, which is also supported in literature worldwide. Veligati et al. [17] compared the efficacy and safety of PGE2 inserts (10 mg) and gel (2×4 mg) in 200 patients. They published similar results for both medical forms, obtaining a high rate (over 80%)

of spontaneous vaginal deliveries (in our material 64.1%). The rate of uterine hyperstimulation was only 5% (in our material – none). However, in the above presented study the superiority of vaginal gel in cervical ripening is deceptive. Lower Bishop's scores prior to labor induction in the vaginal insert group result from the fact that almost half of the patients (57.1% primiparas among them) presented with uterine contractions and spontaneous delivery took place with no need for additional induction. Therefore, only the rest of the group underwent cervical ripening assessments prior to induction. The advantage of vaginal inserts over gel is also visible in the higher rate of spontaneous deliveries, shorter time from PG application to delivery and comparable labor stages times despite lower Bishop's score at the beginning of induction. Kemp et al. [8] published the results of multicenter prospective study on 470 patients, in which vaginal gel application (2 mg PGE2) was compared with intracervical administration (0,5mg PGE2) in women with Bishop's score less than 5 points. The outcomes – cervical ripening after the first dose, rate of spontaneous deliveries in 24 hours and average time from induction to delivery – were in favor of the vaginal gel. The need of oxytocin administration, cesarean section and uterine hyperstimulation rates, as well as newborns' condition, were comparable in both groups. Similar results were also presented by Seeras [16] and Hales [5]. However, Dyson et al. [1] showed no significant differences in effectiveness between 3mg PGE2 administered vaginally and 0.5mg gel applied intracervically. Keirse et al. [7] in another multicenter randomized trial on 285 patients did not reveal any differences in efficacy and safety of PGE2 gel in regard to the way of administration, obtaining a high rate of spontaneous deliveries (77.7%).

In contrary to the above, a randomized study by Ekman et al. [2] proved better cervical ripening after intracervical gel application in women with very low Bishop's score (<3 points). Moreover, Facchinetti et al. [3] studied 112 patients after intracervical PGE2 gel administration – 60% of them presented with spontaneous uterine contractions with no further need for induction. Polish researchers also confirm high effectiveness of intracervical medical PG forms [10,14]. It seems that the presence of uterine muscle contractility during the first hour after dinoprostone application can be a good prognostic factor for spontaneous delivery [2].

As to vaginal inserts, their efficacy was studied by Goharkhay et al. [4] on 24 women with initially unripe uterine cervix: 75% of them delivered spontaneously, while fetal distress was the most frequent (20.9% of cases) indication for cesarean section. It was the most frequent indication in our material as well, with the overall rate of 34.8%. Goharkhay et al. also studied PGE2 serum levels after insert application and showed that they reach much higher concentrations in women presenting PG adverse effects, especially uterine hyperstimulation. After the inserts were removed, PGE2 serum levels dropped rapidly in all the cases. Thus, it can be indirectly concluded

that removable inserts are safer, therefore better, than gel forms if we consider prevention and reduction of PG side effects.

There have also been many studies comparing misoprostole (PGE1) with dinoprostone effectiveness in labor preinduction. In Poland such a study would be difficult to conduct, as PGE1 preparations are not registered for use in obstetrics. However, its efficacy and safety were studied by Leszczynska-Gorzelak *et al.*, after the approval of the Polish Bioethical Committee [9]. Ramsey *et al.* [12] compared the effectiveness of misoprostole and dinoprostone in the forms of both intracervically applied gel and vaginal inserts. They proved the superiority of PGE1 over both preparations of PGE2, and additionally a higher efficacy of vaginal inserts over gel (similar result to ours if two forms of PGE2 are considered). The average time from misoprostole administration to delivery in Ramsey's study was 24±10.8 hours (in our material time comparable with calculated for Propess), whereas for the dinoprostone insert and gel it was 32.2±14.7 and 33.9±16.2 hours, respectively (in our material time comparable with calculated for Prepidil gel). Ramsey *et al.* confirmed their observations in the following study 5 years later [13]. Liu *et al.* [11] presented their results of labor preinduction / induction with the use of misoprostole in a dose of 50 µg/4 h, obtaining a very high rate (81%) of spontaneous vaginal deliveries in 24 hours. However, in as many as 17.2% of patients with Bishop's score ≤4 it resulted with uterine hyperstimulation. Their results only confirm the necessity of being extremely cautious in using misoprostole preparations for labor preinduction.

Therefore, adverse effects of PGs always have to be considered when choosing their preparations for labor preinduction. To make the method effective, the proper dose and time interval before its following administration are crucial. It aims at prevention of, above all, uterine hyperstimulation, fetal heart abnormalities and cesarean section rate due to fetal distress.

CONCLUSIONS

PGE$_2$ in the form of vaginal inserts seems to influence both uterine cervix and uterine muscle, inducing spontaneous contractions and decreasing the rate of planned labor inductions especially in primiparas, while in the form of gel – prepare uterine cervix for delivery induction more effectively.

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