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Analysis of intravaginal misoprostol 0.2 mg versus intracervical dinoprostone 0.5 mg doses for labor induction at term pregnancies

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ABSTRACT

Objectives: Labor-induction methods are used in about 23% of labors. Most commonly, pharmacological methods are used to pre-induct the labor with dinoprostone — a PGE2 analog, and misoprostol — a PGE1 analog. The aim of this study was to evaluate two pharmacological methods of labor induction with the use of prostaglandins applied via an intravaginal insert containing misoprostol at a dose of 0.2 mg and intracervical gel containing dinoprostone at a dose of 0.5 mg.

Material and methods: This retrospective study was conducted on a group of 50 adult patients qualified for the pre-induction of labor. Following data were recorded: the time from the drug administration to the beginning of regular contractile function, the time from administration to amniotic fluid rupture, the time from medicament administration to the vaginal labor or caesarean section, the duration of I, II and III stages of labor, the delivery method and in the event of caesarean section — the indications for surgery.

Results: In comparison to dinoprostone, the misoprostol application was found to shorten the time from drug administration to amniotic fluid rupture by 14.1 hours, the time to the beginning of the first stage of labor by 11.7 hours and from the drug administration to the delivery by 17.3 hours (p-value < 0.05). The duration of the first stage of labor in the misoprostol group was shorter by 1.2 hours than in dinoprostone group (p-value < 0.05).

Conclusions: Application of intravaginal insert with misoprostol at a dose of 0.2 mg appears to be a more effective method of labor induction in comparison to intracervical gel with dinoprostone at a dose of 0.5mg. Thorough analysis of these methods requires further studies.

Key words: labor, induction, pregnancy, prostaglandins, misoprostol, dinoprostone

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INTRODUCTION

Induction of labor is one of the most commonly performed procedures in obstetrics. This is a process for the commencement of delivery when the risk of pregnancy continuation exceeds the potential risk of its completion before the appearance of spontaneous contractile function. Based on the national registries in Great Britain and the United States, it is estimated that in developed countries the pregnancy rate, in which any method of induction is being used, is about 23% [1]. Moreover, in recently reported research on the American population the rate of induced births turns out to be even higher — 42.9% and 31.8% for the primigravidas and multigravidas, respectively. There is a correlation between the use of labor induction and perinatal results, in particular in reducing the perinatal maternal-fetal mortality, as well as in the percentage of surgical births [2, 3].

The use of pharmacological or mechanical methods for labor induction occurs when there is no spontaneous regular contractile function with preserved amniotic sac. The effectiveness of this depends on a proper preparation of the cervix. It turns out that the higher failure rate of la-

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bor induction is associated with a low grade on the Bishop scale [2]. Synthetic prostaglandins have a proven effect on the uterine cervix in labor induction as they increase smooth muscle fiber contractility and accelerate cervical ripening [4]. According to data, the use of prostaglandins increases the probability of spontaneous delivery and reduces the need for subsequent doses of oxytocin without increasing the proportion of caesarean sections [5]. Nevertheless, there is an increased risk of excessive contractile function (hyperstimulation) associated with this method. Currently, the most commonly used drug to pre-induct the labor is dinoprostone, which is a PGE2 analog and misoprostol, aPGE1 analog [6].

Misoprostol can be applied via an intravaginal insert, a rectal suppository or an oral tablet. Dinoprostone occurs in intravaginal systems and in a form of an intracervical gel. There are many publications available in literature on the effectiveness of different forms of prostaglandins administration [4]. It should be noted, however, that the vast majority of researches use misoprostol in the form of tablets given vaginally in the scheme, which in Poland is currently used only for the induction of abortion or stillbirth. Therefore, the only acceptable form of the labor induction is currently the use of intravaginal inserts containing misoprostol at a dose of 0.2 mg. Likewise, in Poland the only available form of administration of dinoprostone is via intracervical gel at a dose of 0.5mg. So far, there were only a few studies carried out to compare these two methods of labor induction.

OBJECTIVES

The aim of this study was to evaluate equally applied pharmacological methods of labor induction with the use of prostaglandins in the third degree reference center by using intravaginal insert containing misoprostol at a dose of 0.2 mg and intracervical gel containing dinoprostone at a dose of 0.5 mg.

MATERIAL AND METHODS

This was a retrospective study conducted on a group of 50 adult patients admitted to the Department of Obstetrics and Perinatology in their third trimester of pregnancy in the perinatal period. The inclusion criteria was the age of pregnancy between 37–41 weeks and that the patients qualified for pre-induction due to the duration and the biological maturity of pregnancy in the absence of spontaneous contractile function. In all the patients, the cervix maturity was found to be less than 4 points in the Bishop's scale at the time of medication administration. The exclusion criteria were: premature rupture of membranes or any known contraindication to vaginal birth [7].

Patients were divided in two groups to undergo labor pre-induction by intracervical administration dinoprostone gel at a dose of 0.5 mg or intravaginal insert of misoprostol at a dose of 0.2 mg. In the absence of contractile function the intracervical Foley catheter was administered. The time interval between the two methods was approximately 24 hours. Following medicament administration each patient had 2 hours bed regime and cardiotocography (CTG) was performed. In case of contractile function development the patient was examined every two hours or more frequently if any indications emerged. The following data were recorded: the time from the drug administration to the beginning of regular contractile function, the time from administration to amniotic fluid rupture, the time from medicament administration to the vaginal labor or caesarean section, the duration of I, II and III stages of labor, the delivery method and in the event of caesarean section — the indications for surgery.

The statistical analysis was conducted using Statistica v. 10.0. The results were analyzed in order to determine the statistically significant differences between the two groups. The differences were considered statistically significant at the confidence p-value below 0.05.

RESULTS

The study groups involved 50 patients. The median age of patients included in this study was 31 years (min. 19, max. 41). The characteristics of the group are shown in Table 1.

The U Mann-Whitney test was used to estimate the significant differences between the groups for the following data: the time from the drug administration to amniotic fluid rupture, the time from drug administration to the beginning of the first stage of labor and the time from drug administration to vaginal labor or caesarean section, as shown in Table 2.

Table 1. The characteristics of studied groups

Parameter	Dinoprostone group n (%)	Misoprostol group n (%)
Sample size	24	26
Parity: • Primigravidas • Multigravidas	 17 (70%) 7 (30%)	 15 (58%) 11 (42%)
History of miscarriage (at least one)	2 (8%)	6 (25%)
Indications for labor induction: • The duration of pregnancy > 41 weeks pregnancy • Oligohydramnios • No gain of the fetal weight • Abnormal CTG record • Others (cholestasis, preeclampsia)	 19 (80%) 1 (4%) 2 (8%) 1 (4%) 1 (4%)	 19 (73%) 3 (11%) 1 (4%) 1 (4%) 2 (8%)
Scheme of the administration: • Only prostaglandins • Prostaglandins with Foley catheter	 13 (54%) 11 (46%)	 24 (92%) 2 (8%)

Table 2. The results of comparison between the groups — time to endpoint

Parameter	Dinoprostone group (hours)	Misoprostol group (hours)	Mean difference	P value (U-Mann-Whitney)	Statistical power
The time from drug administration to amniotic fluid rupture	23.4	9.3	14.1 (6.0–22.2)	0.0019	75
The time from drug administration to the beginning of the first stage of labor	18.5	6.8	11.7 (4.6–18.7)	0.0025	72
The time from drug administration to labor	28.0	10.7	17.3 (9.5–25.1)	0.0000	89
The time from drug administration to vaginal delivery	24.4	10.9	13.4 (5.1–21.8)	0.0041	71
The time from drug administration to caesarean section	41.6	10.3	31.3 (13.3–49.3)	0.0027	51

In comparison to dinoprostone, the misoprostol application was found to shorten the time from drug administration to amniotic fluid rupture by 14.1 hours (Figure 1), the time to the beginning of the first stage of labor by 11.7 hours and from the drug administration to the delivery by 17.3 hours (Figure 2) with 13.4 hours for vaginal delivery and 31.3 hours for cesarean section, respectively. The result for dinoprostone should be interpreted with caution, as it was calculated from four records: 24, 26, 79, 19 hours — and there were only four patients to whom cesarean section was performed. The power of the tests was above 70%, except for the time after drug administration to caesarean section — the small power is due to a small number of trials performed, resulting in unreliable data, despite the statistical significance.

Afterwards, the duration times of labor stages I, II and III were compared between the dinoprostone and misoprostol groups. After removal of three outliers (defined by the Grubbs test) and confirming the homogeneity of variance, the Student t-test was performed to find the significant differences between the study groups — as shown in Table 3.

The duration of the first stage of labor in the misoprostol group was shorter by 1.2 hours than in the dinoprostone group. However, the duration of the second stage of labor was 11 minutes longer in patients undergoing misoprostol pre-induction in comparison to dinoprostone pre-induction. No differences were observed in the third stage of labor.

The number of deliveries completed within 24 hours from the beginning of drug administration was counted. The patients who gave birth within 24 hours accounted for 76% of the presented population. In dinoprostone group

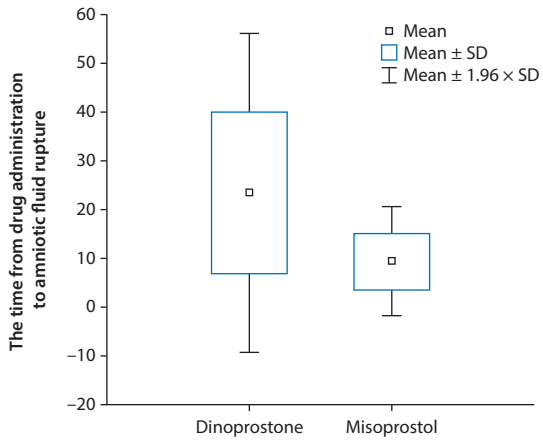

Figure 1. The time from drug administration to amniotic fluid rupture

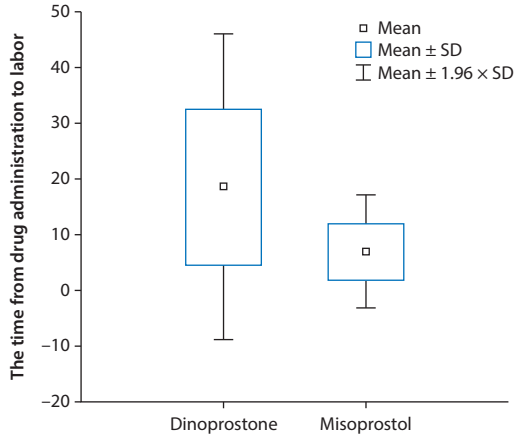

Figure 2. The time from drug administration to labor

Table 3. The duration time of labor stages

Parameter	Dinoprostone group (time)	Misoprostol group (time)	Mean difference	P value (U-Mann-Whitney)	Statistical power
Duration time of I stage of labor (hours)	5.4	4.2	1.2 (0.3–2.2)	0.0126	61
Duration time of II stage of labor (minutes)	12.8	23.9	11.1 (0.3–21.9)	0.0440	32
Duration time of III stage of labor (minutes)	7.5	8.3	0.8 (–0.9–2.7)	0.3503	14

it was represented by 54% patients, compared to 100% of deliveries in misoprostol group.

The mode of delivery between two study groups was compared. Indication for a caesarean section was most often the threatening fetal asphyxia (60% in the group with dinoprostone, 63% in the group with misoprostol) and lack of the labor progress (40% in the group with dinoprostone, 27% in the group with misoprostol). There were 4 caesarean sections performed in the group of patients undergoing pre-induction with dinoprostone which accounted for 17% of deliveries and compared to the group of misodel group wherein 10 caesarean sections were performed accounting for 38% of deliveries in this group. This result is not statistically significant (Chi2 test $p = 0.1255$) and the trial power at 34% level.

The need for the Oxytocin appeared in 52% of cases of labor pre-induction scheme using dinoprostone and 16% of cases in the scheme based on the misoprostol application.

Epidural during labor was performed in 50% of cases of labor pre-induction in the scheme of dinoprostone and 20% of cases in the scheme based on the misoprostol application.

There was one case in misoprostol group in which newborn scored 7 in Apgar scale. In other cases newborns scored 8 or more points.

DISCUSSION

In the presented material the vast majority of the patients were eligible for labor induction mainly due to the duration of pregnancy more than 41 weeks pregnancy (80% and 73% for dinoprostone and misoprostol respectively). Before the procedure in each of the patient's cervix was assessed of less than 4 in the Bishop scale. This is consistent with the current guidelines relating to the indications for the labor induction [7].

The basic element for evaluating the success of labor induction is time to reach the endpoints, in particular the contractile function appearance and consequently the delivery. Based on the collected material the time from drug administration to the contractile function appearance and the length of the various stages of labor were calculated. In the misoprostol group the effect was achieved significantly statistically faster — the time to the contractile function appearance was shortened by 11 hours, while to the delivery by 17 hours in comparison to dinoprostone group. The period from the beginning of labor induction to amniotic fluid rupture was shorter in misoprostol group. In previous studies, including large meta-analysis, the results were similar to those shown below [8]. Nevertheless, it should be noted that in the literature comparisons of exact these two types of prostaglandin administration are not available.

To objectively compare the results the number of deliveries completed within 24 hours from the beginning of drug administration is taken into consideration. In our material all patients in the group of misoprostol delivered within 24 hours in contrast to dinoprostone group in which approximately half of patients delivered in this period. Because of the small sample size we were not able to show the statistical difference, but this trend is consistent with previous reports. One study, where dinoprostone gel and misoprostol administered in form of vaginal tablets were compared, showed similar effects [9]. However, another study with misoprostol in the form of 0.2 mg intravaginal insert in numerous population of patients the percentage of giving birth within 24 hours was 54.6% [10].

The length of the respective labor stages differed. Interestingly, after the application of misoprostol, the first stage was shorter than for dinoprostone by about 1.2 hours, but the second stage lasted longer by about 11 minutes. Alas due to the small number of patients, the power of the test was limited and the improvement of the reliability may be increased by enlargement of the population included in the study. Given the lack of data on the labor stages in previous reports, it is difficult to confront our results. Certainly this observation requires further trials.

An important factor in determining not only the effectiveness, but also the safety of labor induction is the percentage of caesarean sections. In the collected material, the increased amount of surgical birth was observed in misoprostol group (42%) relatively to dinoprostone (21%), but the relationship was statistically insignificant. However, in both groups indications for cesarean section were similarly distributed, including threatening fetal asphyxia and the lack of the labor progress. In large meta-analysis, which took into account the various methods of labor induction, the percentage of caesarean sections was lower in misoprostol group 18.2% versus 29.7% for misoprostol and dinoprostone respectively and the trend could also be seen in other reports [5, 11, 12].

Interestingly, in this study the necessity of giving Oxytocin occurred in nearly half of patients in group induced with dinoprostone, meanwhile it concerned only 20% of deliveries in misoprostol group and a similar trend was visible in most reports on the subject [13, 14].

The study also assessed the condition of newborns as the sum of Apgar points in 1, 3 and 5 minutes of life. Both in misoprostol and dinoprostone group, the condition of newborns was satisfactory — the score within the normal range.

The data presented in this study is consistent with previous reports, as it was shown above. However, most studies show analysis of different modes of induction including prostaglandins, none of them compares two methods available currently in Poland — intracervical administration dinoprostone gel at a dose of 0.5 mg and intravaginal insert of misoprostol at a dose of 0.2 mg. Certainly both methods

deserve further observation. This analysis is a pilot study to further prospective study which goal is to collect a larger population of patients and assess the effectiveness of both methods. What is more, the analysis of cardiotocography should be included in the study — both on the fetal heart rate and pathological uterine contractions, as there were reports of increased risk of hypertonia, hyperstimulation and tachysystole when administering misoprostol [15].

CONCLUSIONS

The studies on the use of prostaglandin in the labor induction have been carried out for over several decades. Their use is particularly valuable in the groups of patients with an unprepared cervix. Following proper proceedings they are safe for both the mother and the fetus. Yet, there is no consensus on the appropriate dosage or timing as the optimal form of therapy is still being sought out.

The following factors are mentioned among the predictive factors of successful labor induction: the score in Bishop's scale, parity, body mass index, age, comorbidity, gestational age, estimated fetal weight and the experience of staff. Further research is therefore reasonable when including such factors [16]. The study shown is retrospective and applies to a relatively small group, hence comparing these two methods on a larger population in a randomized trial is crucial.

Deciding on the appropriate method of labor induction is a challenge. Like any medical intervention, labor induction should be preceded by a discussion of potential risks and benefits of various methods individually.

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