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Labor induction at full-term and post-term pregnancies

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Abstract: **Introduction:** Induction of labor is an intervention in the obstetrics, which aim is to achieve cervical ripening and stimulate contractions of uterus before beginning of labor. The purpose of our study was to evaluate efficacy of combinations of vaginal misoprostol, intracervical dinoprostone and Foley catheter at term with regard to mode of delivery and rate of emergency C-sections due to birth asphyxia.

Material and Methods: 403 singleton pregnant women, who underwent pharmacological labor induction at term, were reviewed. Patients were divided into 2 main cohorts due to beginning of induction algorithm: vaginal misoprostol (66) or intracervical dinoprostone (337) consisting of 3 subgroups — PGE₂ alone (184), PGE₂+Foley catheter (125), PGE₂+Foley catheter+PGE₁ (28).

Results: Comparison of maternal age, presence of cervical dilation and parity revealed no major differences between cohorts. Effectiveness of labor induction with misoprostol, dinoprostone and dinoprostone followed by Foley catheter were respectively 90.9%, 51.3%, and 82.8%. Addition of PGE₁ was effective in 83% of patients with negative response to PGE₂ followed by Foley catheter. There was no statistically significant difference in rate of C-sections between dinoprostone and misoprostol cohorts, C-section due to birth asphyxia were insignificantly more frequent in PGE₁ than in PGE₂ cohort. Efficacy in the subgroup administered only dinoprostone was significantly higher in 40th than in 41th (p = 0.016). **Conclusion:** Intracervical dinoprostone seems to be safer, but less effective in labor induction than vaginal misoprostol. Following PGE₂ by other methods increased efficacy of induction in this cohort.

Key words: induction of labor, misoprostol, dinoprostone, Foley catheter, prostaglandins.

Introduction

Induction of labor is one of the most commonly performed interventions in the obstetrics. The aim of the procedure is to achieve cervical ripening and stimulate contractions of uterus before beginning of labor and it is performed due to fetal or obstetric indications (e.g. postterm pregnancy, prelabor rupture of membranes at term) [1, 2]. Labor induction rate has risen in the recent decades leading to 1 in 4 newborns in the UK in 2013–2014 being born with the help of this intervention [3]. Similar numbers and trends have been observed in other developed countries all over the world [4–6]. There are various methods of labor induction, which can be divided into non-pharmacological (i.e. amniotomy, mechanical methods including extra-amniotic Foley catheter or the Cook Cervical Ripening Balloon) and pharmacological (e.g. prostaglandins). Prostaglandins have been used for inducing labor since 1960s and are probably the most common methods of induction. They can be administered orally, intravenously, extra-amniotically, vaginally or intracervically [7]. Local routes of administration reduce a risk of side effects, nonetheless all the methods of induction entail an increased risk of labor complications such as non-reassuring fetal status, emergency caesarean section or hyperstimulation [8–10]. Although there are several papers analyzing different methods of labor induction, there is still no strong evidence as for which method is the most effective and, at the same time, safe for both a woman and a child. Furthermore, only few studies compare vaginally administered prostaglandin E₁ (misoprostol) and intracervically administered prostaglandin E₂ (dinoprostone) combined with mechanical methods of induction [11]. The aim of our study was to evaluate combinations of methods of inducing labour including vaginally administered misoprostol, intracervically administered dinoprostone in combination of Foley catheter and to determine, which of the methods has the highest effectiveness with regard to number of failures of induction, mode of delivery as well as rate of emergency caesarean sections due to birth asphyxia. Other investigated parameters were need of oxytocin. The analysis was performed for whole study population and for patients at full-term and post-term separately.

Material and Methods

180 women at full term pregnancy (gestational age between 40 and 41 weeks — stayed in the text 40/52) and 233 women at post term (gestational age of 41 weeks and over — stayed in the text 41/52), who underwent pharmacological labor induction with intact membranes, were reviewed. Informed consent was obtained from all individuals on admission included in these study. In our study population (403 patients) first step of induction was pharmacological induction. Patients were divided into 2 groups.

Group I (66 women) was inducted with 200 mcg vaginally administered misoprostol. Group II (337 patients) received 0.5 mg intracervically administered dinoprostone (Step 1). The women in study group I and II were compared in terms of age, BMI, parity, previous cervical procedures and presence or absence of cervical dilation, drugs abuse and gestational age at the time of prostaglandin application. The choice of the method of induction used for each woman was based on individual practitioner preferences. The women from group II whose initial labor induction with PGE₂ was unsuccessful were consequently subjected to mechanical induction with the use of Foley catheter (FC) (Step 2). In case, when the induction with the catheter remained ineffective, the patients received PGE₁ (Step 3). Algorithm is presented in Figure 1. Criteria of effectiveness for the individual groups included progress of cervical dilation or onset of labor within time specified in the corresponding Summaries of Product Characteristics and are presented in Table 1.

Table 1. Criteria of effectiveness of particular steps.

Method of induction	Number of step	Definition of effectiveness	Definition of ineffectiveness	Groups of patients who received the step
PGE ₁ as beginning of induction	Step 1	Progress of cervical dilation <i>or</i> Beginning of labor up to 24 h	Lack of progress of cervical dilation <i>and</i> Beginning of labor after 24 h	I
PGE ₂ as beginning of induction	Step 1	Progress of cervical dilation <i>or</i> Beginning of labor up to 6 h	Lack of progress of cervical dilation <i>and</i> Beginning of labor after 6 h	Whole group II consisting of IIA IIB IIC
Foley catheter after PGE ₂	Step 2	Progress of cervical dilation <i>or</i> Beginning of labor up to 24 h	Lack of progress of cervical dilation <i>and</i> Beginning of labor after 24 h	IIB IIC
PGE ₁ after PGE ₂ and Foley catheter	Step 3	Progress of cervical dilation <i>or</i> Beginning of labor up to 24 h	Lack of progress of cervical dilation <i>and</i> Beginning of labor after 24 h	IIC

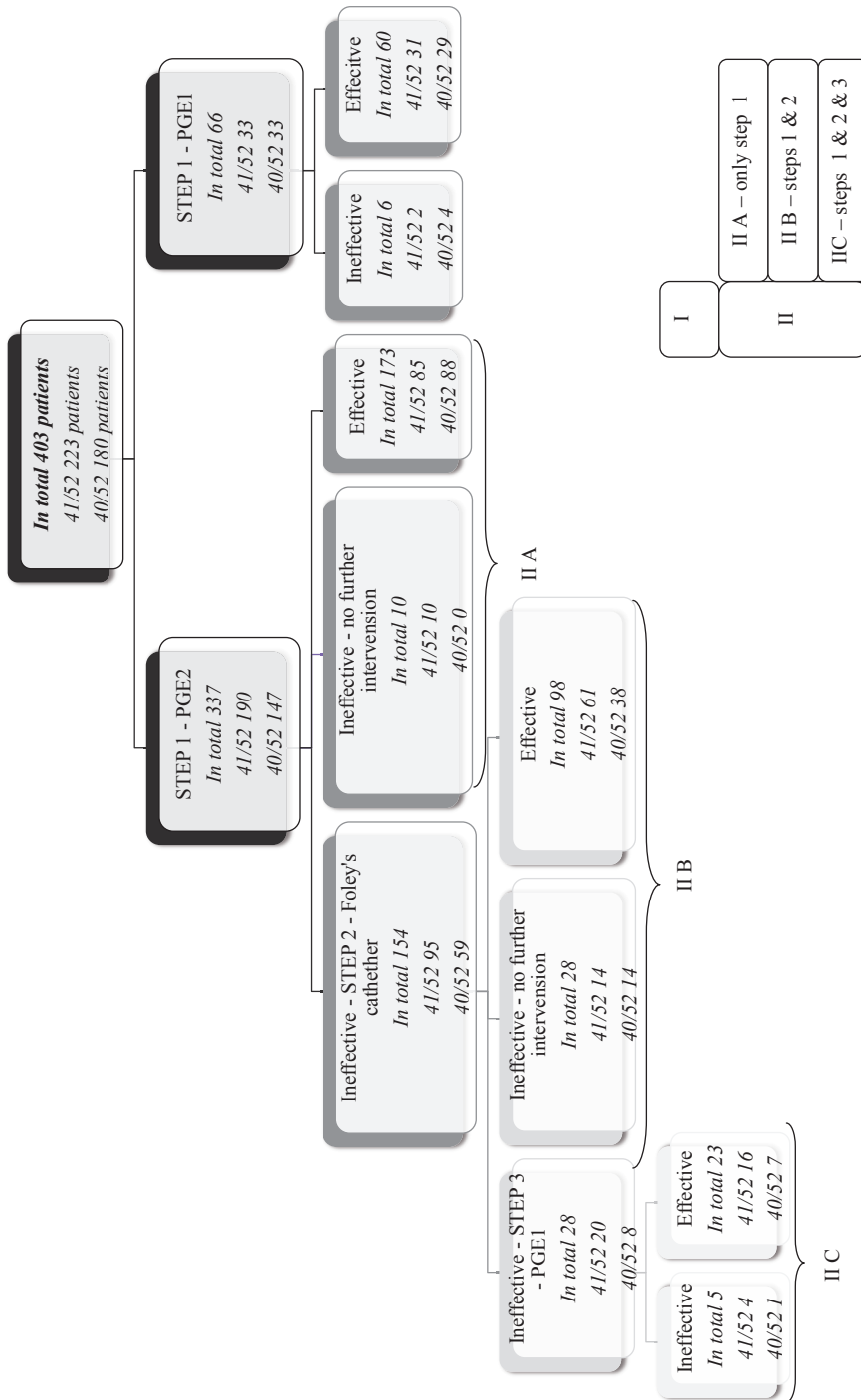


Fig. 1. Induction algorithm.

The effectiveness of combinations of methods inside group II were also analyzed:

- Combination of Step 1 and 1&2 (as achievement of expected effect after administration of PGE₂ alone or PGE₂ followed by Foley catheter — according to Table 1). Patients, who didn't receive Foley catheter as Step 2 in spite of lack of effect after PGE₂ administration (part of group IIA — see Fig. 1) were excluded from this part of analysis (as the patients who did not complete the study).
- Combination of Step 1 and 1&2 and 1&2&3 (as achievement of expected effect after administration of PGE₂ alone or PGE₂ followed by Foley catheter or PGE₂ followed by Foley catheter and PGE₁ — according to Table 1). Patients, who didn't receive Foley catheter as Step 2 in spite of lack of effect after PGE₂ administration (part of group IIA — see Fig. 1) and patients, who didn't receive PGE₁ as Step 3 in spite of lack of effect after PGE₂ and Foley catheter administration (part of group IIB — see Fig. 1) were excluded from this part of analysis (as the patients who did not complete the study).

Statistical analysis

Data were analyzed using *STATISTICA 13.1* statistical analysis software. A value of $p < 0.05$ was considered statistically significant. The normality was tested via Shapiro–Wilk test. Due to not fulfilled parametric test prerequisites, relationships between qualitative and quantitative variables were assessed with the Chi-squared test and Mann–Whitney U test, respectively.

Results

Group I vs group II

General characteristics of the patients are presented in Table 2. Comparison of all the women who received initial labor induction with misoprostol (group I) to those administered dinoprostone (group II) revealed difference in median age of the patients ($p = 0.04$; PGE₁ cohort was younger than PGE₂ cohort, the median difference was 1 year). The groups did not differ with regards to parity, BMI, gestational age, previous cervical procedures, presence of cervical dilation, birth weight and drug abuse. In the whole study, there were significant differences in effectiveness; 90.9% vs 51.3% $p = 0.0000$ for misoprostol and dinoprostone respectively. 70% of patients who responded to misoprostol delivered vaginally and 30% had a caesarean section. Birth asphyxia was indication in 21.7% patients, who underwent cesarean section; it constituted 72.2% as an indication of CS. In the group of the patients, who received dinoprostone, in case of effective induction — 72.8% women delivered vaginally and 27.2% had a caesarean section. In this group, birth asphyxia was indication for

cesarean section in 12.7% of patients, it was an indication for 46.8% of CS (group IIA). Out of the patients who did not respond to dinoprostone (Step 1), 153 women were subjected to mechanical induction with the use of Foley catheter (Step 2). 10 women from group IIA for whom induction was ineffective did not obtain any additional labor induction (5 started to deliver after more than 6h and 5 underwent caesarean section because of another contradictions, not connected with previously induction). They were excluded in further analysis (see Fig. 1). The induction with Foley catheter (Step 2) was successful in 63.4% of patients: 64.9% delivered vaginally and 35.1% had caesarean section — 20.6% due to birth asphyxia, which determined an indication for 58.8% of CS (group IIB). Out of the patients who did not meet the efficiency criteria for induction with Foley catheter, 9 women started to deliver after more than 24 hours after procedure and 19 underwent C-section because of other contradictions (not related to induction). These women weren't included in further analysis (see Fig. 1). Out of the patients who did not respond to dinoprostone and mechanical induction (Step 2), 28 women were subjected to induction with the use of misoprostol (group IIC) (Step 3). This way of induction was successful in 82.2% of patients: 65.2% delivered vaginally and 34.8% had caesarean section (17.4% because of birth asphyxia — 50% of CS). Effectiveness of the induction in dinoprostone group is strongly related to gestational age at delivery — PGE₂ is statistically more efficient when used for induction in 40/52 than in 41/52 ($p = 0.016$). Regarding PGE₁, no correlation between efficacy of this prostaglandin and gestational age at delivery has been observed. No statistically significant differences in amount of caesarian sections, birth asphyxia frequency and proportion of birth asphyxia as indication for CS due to gestational age were observed in any group (Tables 3 and 4).

Group I vs group IIA

Differences in obstetric outcomes after administration only PGE₁ and only PGE₂ are expressed by comparison of group I (administered only PGE₁) and group IIA (administered only PGE₂). There were not revealed any statistical differences in general characteristics. In the group I percentage of caesarian sections after effective induction reached 30% whereas in group IIA it was 27.2%. There was no statistically significant difference observed in delivery mode. Statistical analysis revealed no significant differences on need for oxytocin in groups I and IIA. Considering frequency of birth asphyxia, statistically significant difference was observed only in 40/52 cohort ($p = 0.049$) and was absent in cohort 41/52 as in the whole study. 72% of CS in group I were performed because of birth asphyxia (and in cohort 40/52 it was indication for 87.5% of CS). However, comparison of indications for CS did not meet statistical criteria irrespective of gestational age.

Table 3. Effectiveness of particular steps — in total and in subgroups by gestational age.

	I		II				Effectiveness of Step 1	p-value
	Step 1 (PGE ₁)		Step 2 (Foley catheter after PGE ₂)				I vs II — in total	0.000
	Step 1 (PGE ₂)		Step 3 (PGE ₂ after PGE ₂ and Foley catheter)				I vs II — 41/52	0.000
	I		II = IIA+IIB+IIC				I vs II — 40/52	0.000
	40/52	41/52	IIB+IIC		IIC		41/52 vs 40/52 group I(PGE ₁)	>0.05
	Total	41/52	Total	40/52	41/52	Total	41/52 vs 40/52 group II(PGE ₂)	0.016
Effectiveness of the Step [%]	90.9	87.8	51.3	62.1	64.2	82.2		
						80		

Table 4. Results in individual groups — in total and in subgroups by gestational age.

	I (received Step 1 — PGE ₁)		IIA (received only Step 1 — PGE ₂ didn't received Step 2 or Step 3)		p-value I vs IIA		IIB (received Step 1 — PGE ₂ and Step 2 — Foley catheter, didn't received Step 3)		IIC (received Step 1 — PGE ₂ and Step 2 — Foley catheter and Step 3 — PGE ₁)		p-value I vs IIC					
	Total	40/52	41/52	Total	40/52	41/52	Total	40/52	41/52	Total	40/52	41/52				
Vaginal delivery if effective [%]	70	74.2	65.5	72.8	71.6	74.1	>0.05	64.9	61.1	67.2	65.2	42.8	75	>0.05	>0.05	>0.05
CS if effective [%]	30	25.8	34.5	27.2	28.4	25.9	>0.05	35.1	38.9	32.8	34.8	57.2	25	>0.05	>0.05	>0.05
Birth asphyxia if effective [%]	21.7	22.6	13.8	12.7	14.8	10.6	>0.05	20.6	25	18	17.4	28.6	12.5	>0.05	>0.05	—
Lack of progress of labor if effective [%]	8.3	3.2	20.7	14.5	13.6	15.3	>0.05	14.5	13.9	14.8	17.4	28.6	12.5	>0.05	>0.05	—
Oxytocin administration if effective [%]	22.2	29.6	14.8	28.8	29.9	27.7	>0.05	75.8	68.6	80	45	42.9	46.2	0.01	>0.05	0.01
Birth asphyxia as CS indication if effective [%]	72.2	87.5	40	46.8	52	40.9	>0.05	58.8	64.3	55	50	50	50	>0.05	>0.05	—
Lack of progress of labor as CS indication if effective [%]	27.8	12.5	60	53.2	48	59.1	>0.05	41.2	35.7	45	50	50	50	>0.05	>0.05	—

Induction and birth weight

As for a birth weight, it is significantly correlated with a delivery mode. Among the women who were administered only dinoprostone (group IIA) differences in median body weight at birth met statistical significance criteria in the whole group of the patients (3700 g for CS versus 3470 g for a vaginal birth, $p = 0.004536$) as well as in the women in 41/52 (3720 g for CS versus 3500 g for a vaginal delivery, $p = 0.019$). No such association was found in the patients in 40/52 or in group I (the patients who initially received PGE₁). In the group II (all the patients who initially received PGE₂), the difference in median birth weights was 3635 g for caesarean section versus 3505 g for vaginal delivery ($p = 0.034$).

Combination of Steps

Combination of Steps 1 and 1&2 (after excluding patients, who did not complete the study — see Methods) was successful in 82.8% of patients: 70% delivered vaginally and 30% had caesarean section (15,6% due to birth asphyxia — indication for 51.8% of CS). Combination of Steps 1 and 1&2 and 1&2&3 (after excluding patients, who did not complete the study — see Methods): was successful in 98.3% of patients: 69.6% delivered vaginally and 30.4% had caesarean section (15.7% because of birth asphyxia — indication for 51.7% of CS). Results of particular steps and steps combinations are summarized in Table 5. Compared to PGE₂ administration as the only one intervention, the combinations of steps were significantly more effective — both in the assessment of the whole population and for subgroups by gestational age ($p \sim 0.00$). There was no statistically significant difference in amount of caesarian sections, birth asphyxia frequency and proportion of birth asphyxia as indication for CS, but values of these parameters were higher in the group of patients who received combined intervention than in the group in which only PGE₂ was used. Oxytocin was significantly more often administered in group with combined induction when assessing the whole population ($p = 0.0016$) as well as group 41/52 ($p = 0.0017$), but not 40/52.

The combination of Step 1 and 1&2 and 1&2&3 was significantly more effective than the combination of Steps 1 and 2 — regardless of gestational age (in total $p = 0.0000$, 41/52 $p = 0.0021$, 40/52 $p = 0.0000$). No significant difference was found in amount of caesarian sections, birth asphyxia frequency and proportion of birth asphyxia as indication for CS between those groups. The effectiveness of combination of Steps 1 and 1&2 was significantly higher in gestational age of 40 weeks than 41 weeks ($p = 0.012$), similar to the effectiveness of PGE₂ alone, while for combination of Steps 1 and 2 and 3 there were no significant differences in effectiveness depending on the gestational age. There was no difference in amount of caesarian sections, birth

asphyxia frequency and proportion of birth asphyxia as indication for CS depending on gestational age observed in any combination. Obstetric outcomes of combinations of steps in group II were compared to outcomes obtained after administration of PGE₁ in group I. The comparison of general characteristics of group in which patients received combination of 1 and 1&2 and group I revealed the statistically significant difference between mothers' age for the whole study population ($p = 0.0037$; but the median difference was <1 year) and in the frequency of cervix intervention in the past ($p = 0.0041$) for the gestational age of 41 weeks. A similar difference in the history of cervix interventions in group of gestational age of 41 weeks was found in comparison of PGE₁ group and group of patients who received combination of Steps 1 and 1&2 and 1&2&3 ($p = 0.0045$). The interventions were more frequent in PGE₁ group.

Comparing the results, oxytocin was significantly more often used in each combination than in PGE₁ group for the whole study population and for gestational age of 41 weeks. No differences were found in amount of caesarian sections, birth asphyxia frequency and proportion of birth asphyxia as indication for CS.

The effectiveness of the combination of Steps 1 and 1&2 did not differ significantly from the effectiveness of PGE₁, while the effectiveness of combination of Steps 1 and 1&2 and 1&2&3 significantly exceeded the effectiveness of the PGE₁ — in the whole study population as well as in the subgroups by gestational age. Thus, the following relationship was observed: the effectiveness of PGE₂ as an only intervention was significantly lower than the effectiveness of PGE₁, the combination of 1 and 1&2 was similarly effective as PGE₁ and the combination of 1 and 1&2 and 1&2&3 was associated with higher efficiency than PGE₁.

Group I vs IIC

Using PGE₁ as Step 3 (group IIC) resulted in similar obstetric outcomes to those obtained by using this prostaglandin as Step 1 (group I). General characteristics of these two groups revealed significant difference in gestational age ($p = 0.04$). Obstetric outcomes — effectiveness, mode of delivery and CS indications did not vary significantly. Oxytocin was needed in group IIC more often. Group was not analyzed in subgroups due to poor plurality.

The whole population was analyzed with regards to factors reported to have strong effect on obstetric outcomes, such as initial cervical dilation, previous cervical procedures and parity. Neither an initial cervical dilation nor previous procedures on cervix had impact on efficacy of induction or mode of delivery, while primiparity was more often associated with caesarean section in the whole study population as well as in the group of women in 41/52. Nonetheless, no association between parity and effectiveness of induction was observed.

Table 5. Results of the patients who received particular steps and steps combinations of steps in group II — in total and divided by gestational age.

	Step 1 (group II) (PGE ₂)			Step 1 & 1+2 (PGE ₂ or PGE ₂ with Foley catheter)			Group I (PGE ₁) — (detailed results in Table 4) vs Step 1 and 1&2			Step 1 & 1+2 & 1+2+3 (PGE ₂ or PGE ₂ with Foley catheter or PGE ₂ with Foley catheter with PGE ₁)			Group I (PGE ₁) — (detailed results in Table 4) vs Step 1 and 1&2 & 1&2&3			
	Total	40/52	41/52	Total	40/52	41/52	Total	40/52	41/52	Total	40/52	41/52	Total	40/52	41/52	p-value
Effectiveness of Step (according to Table 1) [%]	51.3	59.9	44.7	82.8	84.9	81.1	>0.05	>0.05	>0.05	98.3	99.2	97.6	0.0014	0.0041	0.0094	
Vaginal delivery if effective [%]	72.8	71.6	74.1	70	68.6	71.2	>0.05	>0.05	>0.05	69.6	67.2	71.6	>0.05	>0.05	>0.05	>0.05
CS if effective [%]	27.2	28.4	25.9	30	31.4	28.8	>0.05	>0.05	>0.05	30.4	32.8	28.4	>0.05	>0.05	>0.05	>0.05
Birth asphyxia if effective [%]	12.7	14.8	10.6	15.6	17.7	13.7	>0.05	>0.05	>0.05	15.7	18.3	13.6	>0.05	>0.05	>0.05	>0.05
Lack of progress of labor if effective [%]	14.5	13.6	15.3	14.4	13.7	15.1	>0.05	>0.05	>0.05	14.7	14.5	14.8	>0.05	>0.05	>0.05	>0.05
Oxytocin administration if effective [%]	28.8	29.9	27.7	45.6	41.0	49.7	0.0014	>0.05	0.0008	45.6	41.1	49.4	0.0014	>0.05	0.0008	
Birth asphyxia as CS indication if effective [%]	46.8	52	40.9	51.8	56.4	47.6	>0.05	>0.05	>0.05	51.7	55.8	47.8	>0.05	>0.05	>0.05	>0.05
Lack of progress of labor as CS indication if effective [%]	53.2	48	59.1	48.2	43.6	52.4	>0.05	>0.05	>0.05	48.3	44.2	52.2	>0.05	>0.05	>0.05	>0.05

Table 5. Cont.

	p-value	p-value	p-value
Effectiveness of combination	Total	40/52	41/52
Step 1 vs any combination — irrespective of gestational age	0.000	—	—
1 and 1&2 vs 1 and 1&2 and 1&2&3	0.000	0.000	0.0021
	p-value		
41/52 vs 40/52 — 1 and 1&2	0.012	—	—
41/52 vs 40/52 — 1 and 1&2 and 1&2&3	>0.05	—	—

Discussion

The main objective of the study was to compare effectiveness of two pharmacological methods of labor induction (misoprostol and dinoprostone). The measurement can be obtained by comparing induction effectiveness between PGE₁ and PGE₂ group. PGE₁ cohort, when compared to the patients who were given only PGE₂ (with no further pharmacological or mechanical induction), had a significantly higher effectiveness of labor inductions, which remains consistent with other studies [12]. Comparison of labor inductions between the patients who were initially administered misoprostol and the patients who received dinoprostone followed by Foley catheter revealed no differences. Adding PGE₁ as 3rd step of dinoprostone algorithm resulted in significantly higher effectiveness than the one achieved by application of misoprostol as first and only one intervention. In case of labor induction with only PGE₂, the effectiveness of induction is significantly correlated with gestational age at delivery — dinoprostone seems to be more efficient in 40/52 than in 41/52. Whereas no difference in effectiveness of PGE₁ depending on gestational age was revealed, we believe that in case of induction of labor in women in 41st gestational week obstetrician should rather consider the usage of PGE₁ than PGE₂ alone. Another important measure of labor induction effectiveness is oxytocin administration. In our study oxytocin augmentation was needed more frequently in the whole PGE₂ cohort than in the patients, who received PGE₁. Similar results can be found in other studies comparing vaginal dinoprostone with vaginally administered misoprostol [13–15]. Furthermore, Cochrane review from 2017 [16] states that the use of vaginally administered misoprostol is associated with a reduced need for oxytocin compared with the dinoprostone intracervical insert. The results may indicate greater potency of PGE₁ in labor induction. In our study population there was no statistically significant difference in caesarean section rate between misoprostol and dinoprostone cohort, which remains in consonance with the review by Cochrane [16]. At the same time

it appears that labor induction with PGE₁ was slightly more often associated with delivery via caesarean section. In their trial Farnaz K. Aghideh *et al.* observed that the use of vaginal misoprostol significantly increased caesarean section rate among multiparous women, when compared to vaginally administered dinoprostone. Still, other studies have not made such an observation and remain consistent that caesarean section frequency does not depend on the drug used for pharmacological induction of labor. Analysis of indications for caesarean delivery in both groups revealed that birth asphyxia was more frequently listed among the patients induced with PGE₁ than those induced with PGE₂ — especially in gestational age of 40/52. The result remains consistent with other studies [12]. In addition, in our research this indication was responsible for nearly 73% of all caesarean sections in misoprostol cohort. Therefore, we strongly believe that maternal and fetal well-being in course of labor induction with misoprostol should be closely monitored with cardiotocography. To weakness of these study belongs retrospective character and lack of randomization. Patients were qualified to an induction by specialists in gynecology and obstetrics; clinical experience and management style can affect choice of induction agent and decision of cesarean section. A strength of the study is analyzing compound algorithm and effectiveness of each step, which can lead to valuable conclusions.

Conclusions

Intracervical dinoprostone is less effective in labor induction than vaginally administered misoprostol. However, when intracervical application of PGE₂ is followed by other mechanical (Foley catheter) and pharmacological (PGE₁ vaginal insert) methods, the efficacy of such combinations is higher than the effectiveness of misoprostol alone. High efficiency of a three-component labor induction demonstrates a strong effect of PGE₁ on the cervix resistant to previously used PGE₂ followed by Foley catheter. Noteworthy is the fact that among the patients who initially received PGE₂, caesarean section rate and the risk of birth asphyxia is reported to slightly increase when combining dinoprostone with other methods of induction, but does not meet statistic criteria. Nevertheless, the use of dinoprostone in combination with other methods of induction seems to be associated with a similar rate of caesarean sections and insensibly decreased rate of birth asphyxia when compared to misoprostol administration.

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B. Adrianowicz — manuscript writing, M. Nowak — data collection, G. Wilczyńska — manuscript writing, H. Huras — project development.

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Conflict of interest

None declared.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

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