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Obstetric outcomes of pre-induction of labor with a 200 µg misoprostol vaginal insert

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ABSTRACT

Objectives: Labor induction is indicated in 20% to 40% of pregnancies. Over half of pregnancies qualified for the induction of labor require stimulation of the cervix to ripen. The drug used increasingly more often in pre-induction is the PGE-1 prostaglandin analog — misoprostol 200 µg.

Material and methods: The study includes a total of 100 patients qualified for labor pre-induction with Misodel® (misoprostol 200 µg vaginal insert). The study group comprises two subgroups: primigravidas and multiparas. Assessments included: indications for labor pre-induction, time from Misodel application to delivery, caesarean section rate and indications, duration of first and second stage of labor, rate of vaginal deliveries, need for oxytocin or fenoterol administration side effects and newborn condition.

Results: The most common indication for labor induction was gestational diabetes and pregnancy past term. The average time to vaginal delivery was 14 h 45 min, time to the onset of active phase of labor — 11 h 45 min, time to membranes' rupture — 15 h, time to vaginal delivery — 14 h 18 min. The times of multiparas were significantly shorter. The rate of vaginal deliveries within 12 hours amounted to 42.42%, while within 24 hours it reached 83.33%. The overall caesarean section rate was 33%. The most common indication for caesarean section was the risk of intrauterine hypoxia. Tachysystole and hyperstimulation was observed in 4% of cases, while abnormalities in the cardiotocographic tracing in 43%.

Conclusions: Misodel is an effective method for labor pre-induction, without affecting the caesarean section rate and has no adverse effect on the newborn condition.

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

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INTRODUCTION

Induction of labor is an obstetric procedure that is used increasingly more often (20–40% of pregnancies) [1–7]. The reason for that may be the increased proportion of pregnant patients with a chronic condition (for instance obesity, hypertension, diabetes mellitus) and the advancements in diagnostic methods during prenatal care that allow early detection of threats to fetal well-being [1, 4]. This is relevant since labor induction is indicated when the risks for mother and/or fetus of continuing pregnancy outweigh the risks of resolving it. The aim of induction is to stimulate contractions, hence labor and vaginal delivery within 12 to 24 hours [8, 9]. Whether induction is successful depends on the cervix maturity, which is assessed usually with a modified Bishop score. When the cervix is not mature, pre-induction is required for the cervix to ripen [1, 5, 10]. Different methods can be used for pre-induction including mechanical (Foley catheter or Cook balloon) and pharmacological (prostaglandins) [1, 2, 5, 8, 10]. The WHO and FDA recommend the use of prostaglandins in labor induction and pre-induction for numerous reasons. Most studies confirm high efficacy of prostaglandins in inducing labor within 24 hours with no related increase in caesarean section rate and with lower oxytocin use. Factors to be taken into account are the risk of overstimulation and uterine tachysystole as well as the contraindications for prostaglandin use such as previous

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caesarean section or other surgical intervention on the uterus [1–3]. The misoprostol vaginal insert (MVI) containing 200 [µg] of misoprostol is a novel product that releases the PGE1 synthetic analog at the rate of 7 µg per hour for 24 hours [12]. Since misoprostol has a dual action, it is clinically both a pre-induction agent and a factitious induction agent at the same time, since it stimulates ripening of cervix through remodeling and it acts on uterine smooth muscle cells promoting their contraction [12].

The aim of this paper is to assess the effectiveness and safety of labor pre-induction with the use of 200 µg misoprostol vaginal insert.

MATERIAL AND METHODS

The study group comprises 100 pregnant women admitted to Obstetrics Clinic in Bydgoszcz, Poland, between the 15th of May 2015 and the 30th of January 2017 who underwent pre-induction with MVI. Information about the patients and the course of labor was obtained from the hospital's documentation. The inclusion criteria are as follows: single pregnancy; gestation of at least full 36 weeks; longitudinal lie with cephalic presentation; Bishop score < 4. The exclusion criteria are: placental pathology; unexplained vaginal bleeding; intrauterine infection; abnormal FHR tracing; previous caesarean section or other surgical intervention on the uterus; any other condition for which natural delivery is contraindicated. We obtained informed consent from all patients participating in the study. Before MVI application, the cervix maturity was estimated with modified Bishop score. Nonstress test was performed for at least 30 minutes both before and after the application of misoprostol. The MVI was removed at the start of: regular contractions, active phase of labor (dilation ≥ 4 cm), tachysystole occurrence, hyperstimulation or abnormal cardiotocography tracing. In concordance with the producer's indications, the MVI was removed after 24 hours the latest. If contractions were still absent after 30 minutes from the removal of MVI, the patient was administered oxytocin IV with constant infusion pump in the labor room, as recommended by Polish Society of Gynecologists and Obstetricians. The study group was subdivided into Primigravidas and Multiparas. When analyzing groups we assessed the following parameters: indications for labor induction; time from MVI to vaginal or other delivery; the rate of vaginal delivery after 12, 24, 36 and 48 hours; time to rupture of membranes; duration of first and second stage of labor; rate of caesarean sections including indications; the use of oxytocin and fenoterol; adverse events such as hyperstimulation, tachysystole, meconium stained amniotic fluid; reasons for MVI removal. Also, fetal parameters were assessed including birth weight, Apgar score and umbilical blood pH. The results were compared between the subgroups. The statistical analysis was performed with the use of Statistica 13.0 software from Dell Inc. The differences were tested with Student's t-test. Interdependence of categorical variables was measured with a non-parametric Chi^2 test. Statistical significance was set at $p < 0,05$ and marked with an asterisk.

The Bioethics Committee has approved the study and the authors report no conflict of interest.

RESULTS

MVI was used in a total of 100 patients, which constitute 3.5% of all delivering patients in the clinic during the study period. The primigravidas constitute 69% of the study group. The multiparas were older and had a better Bishop score ($p < 0.05$). The median duration of pregnancy was 40 weeks (range = 36–42) (Table 1). The most common indication for induction was term pregnancy complicated with gestational diabetes for both the study group and the multipara subgroup (35% and 41% respectively) and a continued pregnancy past 41 weeks for the primigravida subgroup (Table 2). The average time to any sort of delivery (irrespectively of mode of delivery) amounted to 14 hours and 20 minutes, while that to vaginal delivery was almost the same — 14 hours and 45 minutes. The labor of multiparas was shorter by about 2 hours than that of primigravidas ($p < 0.05$). The regular contractions and/or the active phase of labor for multiparas and primigravidas initiated after on average 11 [h] and 45 [min] and 12 [h] and 18 [min] respectively. Both labor stages (first and second) were shorter in the multipara subgroup. The removal of MVI usually took place after 12 [h] and 38 [min]. A premature rupture of membranes before second stage

Table 1. Demographic characteristics

	The study group (n = 100)	Primigravidas (n = 69)	Multiparas (n = 31)	p-value
Age (years)	28.91 ± 5.78	27.71 ± 5.45	31.58 ± 5.68	0.0016*
Gestational age (weeks)	40 ± 1	40 ± 1	40 ± 1	0.8944
BMI [kg/m^2]	30.37 ± 4.99	30.12 ± 5.03	30.92 ± 4.94	0.4637
Bishop score	1.47 ± 1.19	1.29 ± 1.21	1.87 ± 1.06	0.0235*

*Statistically significant

Table 2. Indications for labor induction

Indications	The study group (n = 100)	Primigravidas (n = 69)	Multiparas (n = 31)
GDM/PGDM Hbd 40 + 0	35 (35.00%)	22 (31.88%)	13 (41.94%)
Late term pregnancy Hbd 41 + 1	28 (28.00%)	20 (28.99%)	8 (25.81%)
Hypertension/preeclampsia	14 (14.00%)	10 (14.49%)	4 (12.90%)
IUGR	7 (7.00%)	5 (7.25%)	2 (6.45%)
Intrahepatic cholestasis of pregnancy	6 (6.00%)	4 (5.80%)	2 (6.45%)
Hemolytic disease of the fetus	3 (3.00%)	2 (2.90%)	1 (3.23%)
Other	7 (7.00%)	6 (8.70%)	1 (3.23%)

Table 3. Pre-induction with MVI — time to end-points

Parameter	The study group (hours and minutes)	Primigravidas (hours and minutes)	Multiparas (hours and minutes)	p-value
Time from vaginal insert to regular uterine contractions or active phase of the labor	11 h 45 min ± 6 h 52 min	12 h 18 min ± 7 h 13 min	10 h 38 min ± 6 h 4 min	0.2808
Time from vaginal insert to amniotic fluid rupture	15 h 0 min ± 16 h 28 min	16 h 27 min ±19 h 40 min	12 h 4 min ± 5 h 5 min	0.1275
Time from vaginal insert to removal of MVI	12 h 38 min ± 6 h 23 min	12 h 50 min ± 6 h 2 min	12 h 2 min ± 6 h 24 min	0.6596
Duration of the first stage of labor	3 h 45 min ± 2 h 3 min	4 h 17 min ± 132.17	2 h 50 min ± 1 h 24 min	0.0041*
Duration of the second stage of labor	31 min ± 31 min	42 min ± 33 min	11 min ± 13 min	0.0001*
Time to vaginal delivery	14 h 45 min ± 7 h 28 min	13 h 36 min ± 7 h 55 min	11 h 43 min ± 5 h 36 min	0.0089*
Time to any delivery	14 h 20 min ± 7 h 2 min	18 h 34 min ± 19 h 56 min	13 h 3 min ± 7 h 47 min	0.1292

*Statistically significant; MVI — misoprostol vaginal insert

Table 4. Mode of delivery after MVI

Parameter	The study group (100%)	Primigravidas (100%)	Multiparas (100%)	p-value chi^2
Unassisted vaginal birth	65.00%	56.52%	83.87%	0.0269*
Forceps-assisted vaginal birth	2.00%	2.90%	0.00%	
Cesarean delivery	33.00%	40.58%	16.13%	

*Statistically significant; MVI — misoprostol vaginal insert

of labor was observed in 51% after on average 15 [h] and 16 [min] (Table 3).

The most common mode of delivery in the study group was vaginal (67%) (Table 4). Only 2 cases required forceps. When the subgroups are analyzed, the vaginal delivery constituted respectively 84% and 59% for multiparas and primigravidas respectively. The latter had a higher caesarean rate compared to multiparas (40.58% vs. 16.13%). Almost all caesarean sections were performed at first stage of labor (nearly 88%) while the most common indication was risk of intrauterine hypoxia and stagnant first stage of labor (66.66% and 12.12% respectively) (Table 5). The proportion of pre-inductions that led to delivery within 48 hours irrespectively of mode of delivery reached 97%. In turn, within only 12 hours from MVI application such proportion was 57% and 31% for multiparas and primigravidas respectively ($p < 0.05$). For the remaining time spans (24 and 36 [h] after pre-induction) the differences were not statistically significant (Table 6). Table 7 also presents proportions of deliveries within 12, 24, 36 and 48 [h] after MVI application, but they concern only vaginal mode of delivery. In this case 100% of deliveries took place within 48 hours from pre-induction. Nearly 90% of multiparas and nearly 80% of primigravidas delivered within 24 hours from pre-induction. In turn, within only 12 hours many more multiparas delivered (64%) compared to primiparas (29.27%). The most common adverse event observed was the abnormal cardiotocograph (43%), which was an indi-

Table 5. Indications for caesarean section

Indications	The study group (n = 33)	Primigravidas (n = 28)	Multiparas (n = 5)
Cardiotocography abnormalities	22 (66.66%)	19 (67.86%)	3 (60.00%)
Failure to progress during the first stage of labor	4 (12.12%)	2 (7.14%)	2 (40.00%)
Failure to progress during the second stage of labor	1 (3.03%)	1 (3.57%)	0 (0.00%)
Uterine hyperstimulation	2 (6.06%)	2 (7.14%)	0 (0.00%)
Failed induction	3 (9.09%)	3 (10.71%)	0 (0.00%)
Threatened intrauterine infection	1 (3.03%)	1 (3.57%)	0 (0.00%)

Table 6. Successful induction with MVI — any delivery

	The study group (100%)	Primigravidas (100%)	Multiparas (100%)	p-value
Delivery within 12 h of induction	38.14%	30.84%	56.67%	0.0269*
Delivery within 24 h of induction	83.50%	80.09%	90.00%	0.4889
Delivery within 36 h of induction	96.91%	95.52%	100%	0.5872
Delivery within 48 h of induction	97.94%	97.01%	100%	0.8546

*Statistically significant; MVI — misoprostol vaginal insert

Table 7. Successful induction with MVI — vaginal deliveries

	The study group (100%)	Primigravidas (100%)	Multiparas (100%)	p-value
Delivery within 12 h of induction	43.28%	29.27%	65.38%	0.0056*
Delivery within 24 h of induction	83.58%	78.05%	92.31%	0.2565
Delivery within 36 h of induction	98.51%	97.56%	100%	0.8012
Delivery within 48 h of induction	100%	100%	100%	1.0000

*Statistically significant; MVI — misoprostol vaginal insert

Table 8. Adverse events after MVI

Outcome	The study group (100%)	Primigravidas (100%)	Multiparas (100%)
Cardiotocography abnormalities	43.00%	47.83%	32.26%
Gastrointestinal disorder	1.00%	1.45%	0.00%
Postpartum hemorrhage	1.00%	1.45%	0.00%
Uterine tachysystole	2.00%	1.45%	3.23%
Uterine hyperstimulation	2.00%	2.90%	0.00%
Meconium in amniotic fluid	5.05%	7.35%	0.00%

MVI — misoprostol vaginal insert

cation for caesarean section in half of the cases. Complications that are potentially dangerous to mother and fetus (tachysystole and hyperstimulation) were observed in 4% of patients only (Table 8). Oxytocin was used in 56% of patients while fenoterol in 19%. Remifentanil and oxytocin was used significantly more often in primigravidas compared to multiparas (Table 9). Figure 1 shows a percentage breakdown of the reasons for MVI removal. The most common indication for removal was the initiation of active phase of labor or the start of regular contractions (72%). Only 9% of patients required the MVI to be removed after 24 hours. Table 10 presents fetal outcomes. 85% of newborns had Apgar score > 8. The overall average was 9 while the overall pH was 7.29. Only 2 newborns were in a severe condition.

Table 9. Pharmacotherapy during labor pre-induced with MVI

	The study group (n = 100)	Primagravidas (n = 69)	Multiparas (n = 31)	p-value
Oxytocin	50 (50.00%)	39 (56.52%)	11 (35.48%)	0.0517
Fenoterol	19 (19.00%)	18 (26.09%)	1 (3.23%)	0.0070*
Remifentanil	18 (18.00%)	16 (23.19%)	2 (6.45%)	0.0439*

*Statistically significant; MVI — misoprostol vaginal insert

Table 10. Newborn outcomes after MVI

	The study group (n = 100)	Primigravidas (n = 69)	Multiparas (n = 31)	p-value
Newborn weight [g]	3338 ± 487	3348 ± 466	3318 ± 536	0.7784
Apgar score [points]	9.00 ± 1.88	8.88 ± 2.07	9.26 ± 1.37	0.2877
pH	7.29 ± 0.09	7.29 ± 0.09	7.30 ± 0.09	0.4367

MVI — misoprostol vaginal insert

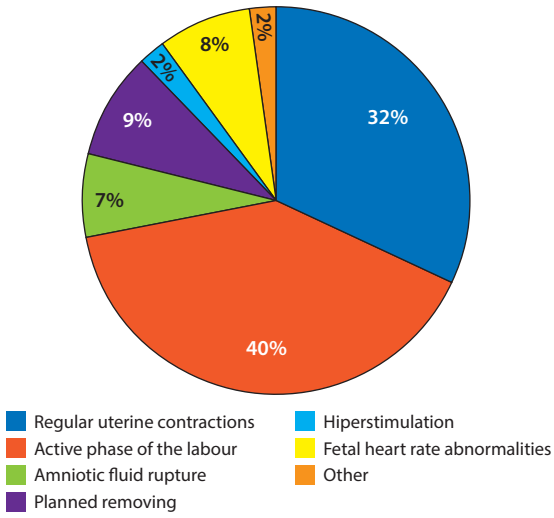

Figure 1. The reason for removing misoprostol vaginal insert

DISCUSSION

Out of pregnancies that have indications for labor induction over 50% require pre-induction for the cervix to ripen [13, 14]. The literature is rich is articles that compare and assess the effectiveness and safety of pre-induction methods involving prostaglandins such as dinoprostone gel and vaginal insert or misoprostol in form of tablets or inserts [7, 15–19]. Misoprostol tablets are registered in Europe for the prevention and treatment of gastric ulcers only. However, Polish Society of Gynecologists and Obstetricians has approved its use in labor induction in case of fetal demise [5, 9]. This shows that the registration of misoprostol vaginal insert for pre-induction had increased the optimal choice options. This paper presents obstetric outcomes of 100 pregnancies where MVI was used. Similarly to other studies, the assessment of drug effectiveness was estimated in light of time to vaginal delivery and the vaginal delivery rate within 12, 24, 36, 48 hours. Safety assessment in turn was based on caesarean section rate and newborn's condition [2–4, 15, 17, 20]. The results of this study concerning average age, parity and duration of pregnancy are comparable to the results reported in literature [4, 6, 21, 22]. Yet, similarly to studies of Wing et al., Tsicouras et al. or that of Kosińska-Kaczyńska et al., in our study the primigravidas prevail (65–82%), which is associated with the cervix being more immature in that subgroup, hence more often selected for pre-induction [2, 3, 7, 23]. To support this, we show that the Bishop score in our study was significantly higher compared to the multiparas subgroup.

Usually, the most common indications for labor induction are pregnancies beyond term, diabetes and preeclampsia [1, 2, 22, 24]. Similarly, the most common indications during this study were term pregnancies complicated with gestational diabetes and continuous pregnancies past 41 weeks. Many authors regard the pre-induction with misoprostol as a very effective method in case of premature rupture of membranes (PROM) [25]. In the study of Mayer et al. PROM was the second most common indication for the pre-induction with misoprostol [16]. In contrast, in our clinic such indication was made in 2% of cases only. This difference was most probably caused by insufficient experience of our doctors in pre-induction with MVI.

Most studies confirm that prostaglandins are superior to mechanical methods in pre-induction and induction of labor, while misoprostol is superior to dinoprostone [2, 3, 14, 17, 20, 22, 26]. Vaginal delivery in shortest time possible is the aim of every induction. In this study the average time to vaginal delivery amounted to 14 [h] and 45 [min] and was significantly longer than that of multiparas (11 [h] 43 [min]).

Other authors report comparable results [7, 16, 18, 21]. In our clinic the study yields a vaginal delivery rate within 12 hours equal to 43.28% and within 24 hours equal to 83.58%. However, in the study of Wing et al. and that of Draycott et al. the rate of vaginal deliveries within 24 hours was lower and amounted to 54.6% and 56%, respectively to the study [3, 18]. Moreover, our vaginal delivery rate within 12 hours was higher in multiparas ($p < 0.05$), while the rate within 24 hours converged between the groups. Also, in our study group over half of patients were observed to have PROM before the onset of second stage of labor, usually after 15 [h] 16 [min]. Górnisiewicz et al. compared the effectiveness of misoprostol with dinoprostone and found the time to PROM in MVI pre-induced group in to be shorter (9 [h] 18 [min]) [7].

In choosing the optimal method for pre-induction, apart from effectiveness, also safety for the mother and the fetus plays a role. Most of researchers believe that labor induction is associated with higher operative rates and induction failure [5, 9]. Many authors focus on the increased caesarean section rate in the setting of labor induction [23, 27, 28]. The Genesis study involving 2336 patients confirms a higher caesarean section rate in the primigravidas with induced labor compared to spontaneous labor (31% vs. 36%) [27]. It seems however that the caesarean section rate can be minimized when patient is qualified properly, especially in case of pregnancies past the estimated delivery date [6, 10, 28]. Pregnancies that require labor induction are often complicated with concomitant conditions like preeclampsia, hypertension or gestational diabetes, which as such increase the risk of caesarean section rate. In our clinic, from among all deliveries since 2016, the rate of caesarean section has been at the level of 42%. Meanwhile, patients with MVI in our study had a lower caesarean section rate that equaled 33%. Yet, we observed this rate to be relatively higher in the primigravida group (40.58% vs. 16.13%) and in the group with concomitant preeclampsia or diabetes. However, other authors report the caesarean section rate after pre-induction with MVI to be even lower — from 22.9% to 27.1% [19, 24]. Similarly to other studies, we report the risk of intrauterine fetal hypoxia to be the most common indication for a caesarean section [3, 15, 24].

Despite the confirmed effectiveness of misoprostol in labor pre-induction, there considerations regarding risk of causing tachysystole, hyperstimulation, meconium-stained fluids or cardiotocographic abnormalities [8, 17, 18, 22–24, 29]. In our study we recorded only 2% of cases with tachysystoly, same for hyperstimulation. This is a very low proportion compared to literature, where such rate was reported to reach 13% to 53% of pregnancies [3, 15, 16, 19]. Abnormalities of cardiotocographic tracing were recorded in 43% of cases but less than half of them required caesarean section. The interpretation of the MVI effect in the tracing and eventual need for caesarean section should be cautious then. The half-life of misoprostol administered vaginally is below an hour and drops to a clinically irrelevant level within 2 hours [12]. Stephenson and Wing [14] report that caesarean sections were performed even 16 hours after tachysystole onset, which excludes the possibility of misoprostol to directly influence the caesarean section rate. When we analyzed retrospectively the documentation after deliveries, we found an umbilical cord factor (short cord, knot or nuchal cord) in all the cases with CTG abnormality. When it comes to newborns, similarly to other studies on misoprostol, their condition based on Apgar score and umbilical cord blood pH was assessed as good [3, 7, 15, 18].

Economic factors play a separate role in choosing the optimal treatment method. The costs are defined conditions such as necessity of extra drugs' use, duration of hospitalization, mode of delivery or eventual intensive therapy care. The most common extra drugs used in our study were oxytocin (56% of cases) and Fenoterol (19% of cases), both used more commonly in primigravidas. There are many studies confirming a less frequent use of drugs in the setting of MVI [3, 10, 14, 17, 20, 23]. Since the rate of deliveries in our clinic was high, duration of hospitalization was short and all our patients were discharged within 2–4 days. None of the mothers or newborns required staying at the intensive therapy unit. The acceptance of the method for induction from the patient standpoint is dependent on the time to delivery and the sense of safety related to the possibility of fast and easy removal of the medication. The studies analyzing patient satisfaction show that time to delivery is the most important decision factor in the choice of induction method [30].

Our studies confirm high effectiveness, safety and patient satisfaction with MVI as a pre-induction method. It shall be noted that the literature is scant in clinical studies focusing on MVI, not to mention their inferior sample size. With this study we hope to help the obstetricians in their choice of a clinically optimal pre-induction method for each of their patients.

CONCLUSIONS

1. Misoprostol vaginal insert Misodel® 200 µg is an effective pre-induction method, especially in case of immature cervix (Bishop score < 4).
2. The most common indications for pre-induction with MVI are: pregnancy past term and diabetes. Further studies are needed for the use of MVI in patients with PROM.
3. Misodel® does not increase the caesarean section rate.
4. According to our observations, tachysystole/hyperstimulation are very rare complications in pre-induction with MVI.
5. MVI has no adverse effect on the condition of the newborn.
6. The perinatal use of MVI may be regarded as economically justified. Yet, in needs more focused studies.

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