*Article*

# A new approach in the induction of labor with misoprostol vaginal insert in high-risk pregnancy obese women

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**Abstract:** Background and objectives: Induction of labor (IOL) is an event that occurs in up to one-quarter of pregnancies; less is known about the outcomes and safety of IOL in obese pregnant woman; no data is available on misoprostol vaginal insert (MVI) IOL in high-risk pregnancy obese women. Objectives: (1) to evaluate the rate of successful IOL with 200 μg MVI in obese (Body Mass Index - BMI over 30 kg/m$^2$) high-risk pregnant women: late-term pregnancy, hypertension or diabetes, compared to obese non-high-risk ones; (2) to evaluate the safety profile of MVI in high-risk pregnancy obese patients. Study design: We conducted a cross-sectional study in "Filantropia" Clinical Hospital, Bucharest, Romania, from June 2017 to September 2019 (28 months). From a total of 11,096 registered live births, IOL was performed in 206 obese patients; 74 obese high-risk pregnant patients matched the inclusion criteria; of these, 33.8% pregnancies (n=25) were late-term (41 – 41+6 weeks), 43.2% (n=32) had associated pathologies (hypertension and diabetes); labor induction was guided using a standardized protocol. We evaluated the maternal and gestational age, parity, fetal tachysystole, hyper-stimulation, initial cervical status, time from induction to delivery, drug side effects, mode of delivery, and neonatal outcomes. Results: (a) The overall successful labor induction rate, evaluated by the vaginal delivery rate, was 71.6% (n=53), spontaneously or instrumentally assisted; 28.4% (n=21) births were unsuccessful MVI IOL, converted into caesareans. (b) No significant differences were found regarding the maternal outcomes; in terms of perinatal outcomes of safety, four cases of high-risk pregnancies vaginally delivered were associated with neonatal intensive care unit (NICU) admissions and a one-minute Apgar score under seven (5.4%). Most cases with adverse effects of misoprostol have been managed by vaginal delivery, except three cases of emergency *C-* section. Conclusions: Misoprostol vaginal insert is a safe choice in IOL in obese high-risk pregnancies with good maternal and perinatal outcomes.

**Keywords:** misoprostol; induction of labor; high-risk pregnancy; obesity; perinatal outcome.

## 1. Introduction

Induction of labor (IOL – artificially initiated labor) is an event that occurs in up to 25% of pregnancies [1]. Cervical status is a good predictor of vaginal delivery, evaluated using the Bishop's scoring system [2]. Any induction method is effective in a woman with a favorable cervix (Bishop's

score ≥ 6), but the likelihood of obtaining a vaginal delivery decreases in women with an unfavorable cervix (posterior, firm, and long) [2-4].

Cervical ripening is a physical process that increases the softening and distensibility of the cervix leading to cervical effacement and dilatation; this mechanism is governed by complex biochemical, hormonal, inflammatory, and vasodilatory changes [5]. The endogen prostaglandins, originating from the cervix, uterus, placenta, and fetal membranes, play a critical role in cervical ripening [5]. Whenever necessary, the iatrogenic cervical ripening is obtained using mechanical agents (insertion of catheters, cervical dilators, amniotomy) or pharmacological agents (application of prostaglandins, oxytocin, and smooth muscle stimulants, such as herbs or castor oil) [1-3,6-8]. The main problems experienced during the induction of labor are ineffective labor and excessive uterine activity, which may cause fetal distress and lead to an increased risk of C-section [8].

Prostaglandins (PGs) are eicosanoids derived from arachidonic acid, which is liberated from membrane phospholipids by phospholipase A2 or by the action of phospholipase C and diacylglycerol lipase, in response to a variety of physical, chemical, and neuro-hormonal factors [5, 9,10]. PG's modulating activity in multiple physiological systems all over the body or its implication in the complex inflammatory and immune responses are carried out through specific transmembrane receptors – G protein-coupled receptors (GPCR) [10]. The therapeutically use natural PGs are limited due to their rapid metabolism, the complex physiological activity that generates numerous (side) effects, and their chemical instability, leading to short shelf life [11].

Two different types of synthetic prostaglandins are therapeutically used for the induction of labor: prostaglandin E2 (PGE2) analog dinoprostone and (most commonly used) the synthetic analog of the natural prostaglandin E1 (PGE1), misoprostol [12].

The FDA initially approved misoprostol (Misodel®, Ferring Pharmaceuticals, Switzerland) to treat and prevent non-steroidal anti-inflammatory drugs (NSAIDs) - induced peptic ulcers [13]; it inhibits the gastric acid and pepsin secretion and enhances the resistance of the mucosa to injury [14]. Until 2002, misoprostol was off-label used for cervical ripening and induction of labor [15,16] in the uterotonics class G02AD [17]. In 2002, FDA removed from the label misoprostol's absolute contraindication in pregnancy [15]. Compared to other prostaglandin analogs, misoprostol is economical, widely available, stable at room temperature, and has few side effects [11,15]. Misoprostol chemical structures differ from PGE1 by a methyl ester group at C-1, a methyl group at C-16, and a hydroxyl group at C-16 rather than at C-15 (Figure 1). These minor differences increase the anti-secretory potency, improve oral activity, increase the duration of action, and improve the drug's safety profile [11].
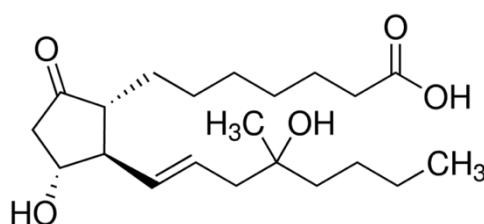
**Figure 1**. Misoprostol chemical structure. (±)-15-Deoxy-(16RS)-16-hydroxy-16-methyl prostaglandin E1 [14].

Tang *et al.* (2003) showed in a series of studies that misoprostol's pharmacokinetics is related to the administration route. Searches revealed that after sublingual use of a single dose of misoprostol, the time to peak misoprostol concentration was significantly shorter. The peak plasma concentration and bioavailability were significantly higher than those obtained after vaginal administration. The plasma levels of misoprostol were sustained for a long time after vaginal administration (six hours vaginal route vs. four hours via sublingual route) [11,18-20]. Adequate plasma levels enable vaginal misoprostol in specific applications such as second-trimester medical abortion [18, 21].

The obesity prevalence is increasing progressively during the last ten years in alarming figures [22]. A large meta-analysis on over one million pregnancies (Goldstein, 2017) showed that 47% of pregnant women have a higher gestational weight gain than the recommended figures [23], 17.3% of

pregnant women are obese, generating potential higher incidence of maternal and fetal complications [24,25].

Several studies focused on the post-birth outcomes of obesity on mother and child, but less is known about the clinical experience with MVI in obese patients. No data is available on the success rate of misoprostol vaginal insert induction of labor and the additional risks carried by the associated pathologies in high-risk obese pregnant women induced with misoprostol vaginal insert.

Therefore, the purpose of the present study is *primarily* to evaluate the rate of success in the induction of labor with MVI in obese (BMI>30 kg/m$^2$) pregnant women (i.e., late-term pregnancy, hypertension, or diabetes in pregnant women) compared to obese non-high-risk ones; *secondarily*, to evaluate the safety profile of MVI reported to the mother and newborn outcomes in high-risk pregnant obese women.

## 2. Materials and Methods

We developed a cross-sectional clinical study in order to evaluate: (1) the rate of successful induction of labor with 200 μg MVI in obese high-risk pregnant women compared to obese non-high-risk ones; (2) the safety profile of MVI reported to the mother and newborn outcomes in high-risk pregnancy obese patients on a period of 28 months.

We used the Quetelet's index (BMI) to classify obese pregnant women as Class I - between 30 – 34,9 kg/m$^2$ defined as moderately obese; Class II - between 35 – 39,9 kg/m$^2$ - severely obese, Class III over 40 kg/m$^2$ - very severely obese). Weight (kg) and height (m) were determined at admission to the hospital for induction of labor; the Quetelet index (BMI) was calculated as weight (kg)/height squared (m$^2$).
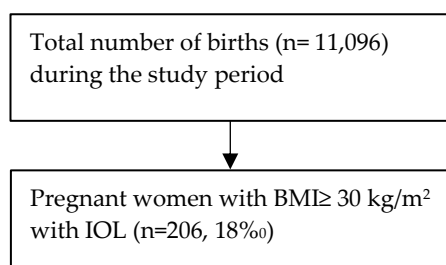
### 2.1 Study design

We conducted a cross-sectional study in "Filantropia" Clinical Hospital, University of Medicine and Pharmacy "Carol Davila", Bucharest - one of the most well-known OB-GYN clinics in Romania - from June 2017 to September 2019 (28 months). In the selected cases, IOL was indicated for various maternal and fetal conditions according to the clinic's standard practice protocols. We collected and analyzed data from 74 selected patients, obese and with high-risk comorbidities that performed MVI IOL according to the protocol.

Inclusion criteria

The inclusion criteria into the study were: alive singleton pregnancy, cephalic presentation, gestational age of 37 completed weeks and above (on-term pregnancies **or** late-term defined as delivery at 41 + 0 – 41 + 6 weeks of gestation), less than three parity, **and** obese – with BMI>30 kg/m$^2$, with **or** without associated high-risk factors: hypertensive disorders (preeclampsia, gestational hypertension, and chronic hypertension), diabetes [gestational diabetes mellitus (DM), pre-conceptional controlled insulin-dependent or noninsulin-dependent DM].

Exclusion criteria

The exclusion criteria were: more than three parity, women with previous cesarean section, signs of fetal distress, antepartum hemorrhage, pre-labor rupture of membrane (PROM), BMI <30 kg/m$^2$, severe preeclampsia or HELLP syndrome, significant cardiovascular renal or hepatic disease, complicated diabetes (nephropathy, retinopathy, neuropathy, arteriopathy). The sampling method was consecutive (Figure 2).
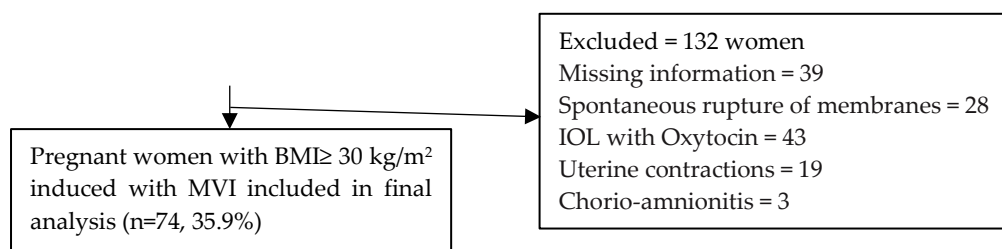
Total number of births (n= 11,096) during the study period

Pregnant women with BMI≥ 30 kg/m$^2$ with IOL (n=206, 18‰)

Excluded = 132 women
Missing information = 39
Spontaneous rupture of membranes = 28
IOL with Oxytocin = 43
Uterine contractions = 19
Chorio-amnionitis = 3

Pregnant women with BMI≥ 30 kg/m² induced with MVI included in final analysis (n=74, 35.9%)

**Figure 2**. Flow-diagram of patient selection and distribution.

Ethical Approval

The Research Medical Ethics Committee of the "Filantropia" University Hospital approved the survey protocol (No. 25/10.2020). The ethical standards of the declaration of Helsinki were followed. Before the labor induction procedure, all patients were apprised and signed the informed consent form regarding the intervention and enrollment agreement in the clinical study.

*2.2 Clinical evaluation and data collection*

(1) Before starting the procedure, the ultrasound evaluation of the amniotic fluid was performed, the assessment of the fetal presentation, fetal status, and weight. The gestational age was established by the correlation between the first-trimester ultrasound scan and the first day of the last menstrual period (LMP). Each patient underwent at least 20 minutes of cardiotocography assessment to ensure fetal status and evaluate the uterine contraction pattern for signs indicative of active labor. A clinical examination was performed to determine the baseline Bishop's score. The reason for labor induction was recorded in the medical file.

(2) Labor induction was guided using a standardized protocol for the procedure, using the vaginal insert system consisting of a controlled-release, retrievable polymer for gradual delivery of 200 micrograms of misoprostol over 24 hours, placed in the posterior vaginal fornix. Patients were monitored for uterine activity and fetal heart rate activity for at least 30 minutes after administering prostaglandins and throughout the entire labor, except for short periods (the need for toileting or ambulation).

(3) The other parameters monitored to analyze drug's safety profile were: cervical status, time from induction to delivery, drug side effects, mode of delivery, and neonatal outcomes. Safety and efficacy analysis of the drug was done following maternal and neonatal outcomes. After drug insertion, vaginal examinations were performed every 4 hours until 24 hours if the delivery had not occurred, the Bishop score being recorded each time.

The time and mode of delivery of the neonate and instrumental vaginal delivery or C-section were recorded. The vaginal insert was removed (a) at the onset of active labor (defined as ≥ three contractions in 10 minutes, lasting 45 seconds, cervical change reaching 4 cm dilatation); (b) after the 24-hour dosing period or (c) at the occurrence of any intrapartum adverse event. If the membranes spontaneously rupture, the vaginal insert was removed, and antibiotic prophylaxis was started after 12 hours or immediately if a vaginal group B streptococcal smear test was positive.

Uterine tachysystole was defined as ≥ five contractions in 10 minutes over three consecutive 10 - minute periods, and in this situation, the tocolysis was initiated to control uterine activity. The initiation of the C-section protocol defined unsuccessful IOL.

*2.3 Statistics*

Data analysis was performed by using the SPSS® 27.0 software (IBM Corp., NY, USA). Kolmogorov–Smirnov test checked the normal data distribution for all variables. We described the continuous variables using the median (range), mean and standard deviation with a 95% CI or count (percent), when appropriate. To compare proportions and the interdependence of qualitative characteristics, we have used the Chi-square test ($\chi^2$), applied in frequency comparisons. For continuous data we performed the ANOVA test to establish the existence of the influence of high risk

subgroups on continuous data (Bishop score, fetal weight, gestational age). In these cases, a One Way ANOVA test was performed. Results with p<0.05 were considered statistically significant.

## 3. Results

During the study period of 28 months, out of the total 11,096 registered live births, 206 pregnant and obese patients were initially screened for our study eligibility. The period prevalence of obese pregnant-labor induced was 186/10,000 births. 132 cases were excepted due to exclusion criteria. Out of the total obese MVI induced births, 35.9% (n=74) of the patients fitted the inclusion criteria (Figure 2).

### 3.1. Description of the studied group

The cases' stratification was done according to parity (91.9% nulliparous, 8.1% multiparous), maternal age, gestational age (Table 1). The distribution of patients was following: 33.7%, late-term pregnancies (41 – 41+6 weeks of pregnancy) (n=25), 43.3%, pregnancies had associated pathology (20 cases of diabetes, 12 cases of hypertension) (n=32) (Table 1, Figure 3); 22.97% (n=17) obese on-term pregnancy patients with IOL had no associated pathologies.

**Table 1.** Description of study participant group structure and characteristics.

| Parameter | Study group | |
|---|---|---|
| | % | n |
| Sample size | 100% | 74 |
| **Parity** | | |
| no prior pregnancy *vs*\* | 91.9% | 68 |
| more than one and less than three prior pregnancies | 8.1% | 6 |
| **Maternal age** | | |
| under 35 years | 90.5% | 67 |
| 35 years and above | 9.4% | 7 |
| **Gestational age at delivery (weeks)** | | |
| < 41weeks (on-term pregnancy) | 66.3% | 49 |
| 41 – 41+6 weeks (late-term pregnancy) | 33.7% | 25 |
| **Associated pathology** | | |
| women *without* associated pathology | 56.7% | 42 |
| women *with* associated pathologies | 43.3% | 32 |
| **Bishop score** | | |
| 0 - 2 | 67.5% | 50 |
| 3 - 4 | 32.5% | 24 |
| **Supplementary pharmacotherapy** | | |
| Epidural anesthesia | 55.4% | 41 |
| Oxytocin | 75.6% | 56 |

\**vs.* – versus

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        │ Obese pregnant patients with MVI    │
        │ induction of labor - included into  │
        │ the study, n=74                     │
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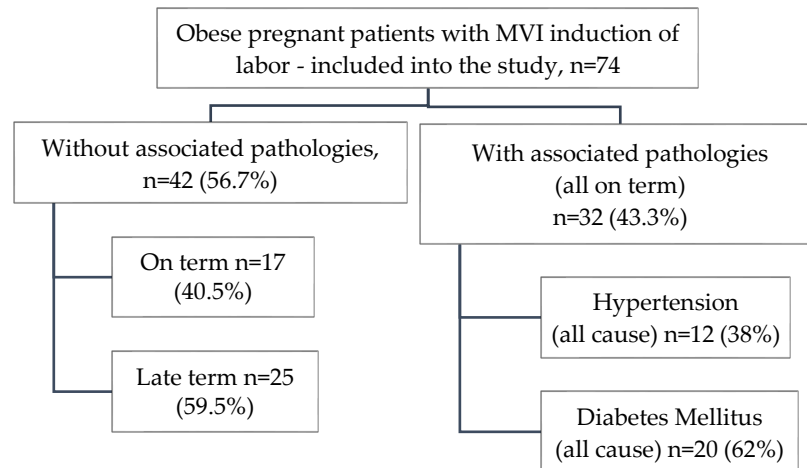
Figure 3. Distribution of the subjects in the study based on high-risk criteria in obese pregnant patients with MVI IOL.

The outcomes of the MVI IOL in the studied group by type of risk factor, and by type of birth were recorded (Table 2, 3).

**Table 2**. Outcomes of the MVI IOL in the studied group by type of risk factor.

| | No risk obese MVI IOL | | High risk obese MVI IOL | |
|---|---|---|---|---|
| **Parameter** | On-term pregnancies (n=17) X± SD* | Late-term pregnancies (n=25) X± SD | Preeclampsia (n=12) X± SD | Diabetes Mellitus (n=20) X± SD |
| Gestational age (weeks) | 39.9 ± 0.9 | 41.3 ± 0.2 | 38.9 ± 0.6 | 38.9 ± 0.6 |
| Misoprostol action (h) | 12.34 ± 5.7 | 11.0 ± 5.9 | 12.3 ± 6.6 | 10.8 ± 3.9 |
| Time from induction to delivery (h) | 18.75 ± 8.47 | 16.78 ± 5.57 | 17.37 ± 7.42 | 16.62 ± 4.69 |
| Initial Bishop score | 2.2 ± 0.8 | 1.28 ± 1.5 | 2.7 ±1.1 | 1.7 ± 1.2 |
| One-min* Apgar score | 8.5 ± 0.8 | 8.56 ± 0.7 | 8.41 ± 0.8 | 8.4 ± 1.2 |
| Five-min* Apgar score | 9.2 ± 0.7 | 9.08 ± 0.6 | 9 ± 0.6 | 9 ± 0.6 |
| Fetal weight (grams) | 3205.2 ± 434.4 | 3450 ± 301.4 | 3417.5 ± 478.8 | 3417.5 ± 478.8 |

**X± SD - Data are expressed as mean ± standard deviation or n (%) unless otherwise specified, * min –minute

**Table 3**. Outcomes of the MVI IOL in the studied group by type of birth.

| Parameter | Vaginal births (n=53) X± SD* | | Cesareans (n=21) X± SD |
|---|---|---|---|
| | Spontaneous (n=42) | Instrumental maneuvers (n=11) | |
| Gestational age (weeks) | 40.2 ± 1.2 | 39.4 ± 1.4 | 39.7 ± 1.3 |
| Misoprostol action (h) | 11.9 ± 6.1 | 11.1 ± 4.9 | 10.91 ± 4.4 |
| Time from induction to delivery (h) | 17.85 ± 7.14 | 16.2 ± 5.9 | 16.87 ± 4.7 |
| Bishop's score | 1.7 ± 1.3 | 1.7 ± 0.9 | 2.1 ± 1.4 |
| One-min Apgar score | 8.6 ± 0.7 | 8.7 ± 1.0 | 8.1 ± 1.1 |

| | | | |
|---|---|---|---|
| Five-min Apgar score | 9.1 ± 0.6 | 9.2 ± 0.7 | 8.9 ± 0.7 |
| Fetal weight (grams) | 3439.2 ± 399.6 | 3204.5 ± 507.2 | 3257.1 ± 99.3 |

*X± SD - Data are expressed as mean ± standard deviation or n (%) unless otherwise specified, * min –minute

*3.2 Evaluation of the success rate for IOL with MVI*

The overall rate of successful labor induction associated with a vaginal delivery was 71.6% (n=53). The initial Bishop score was 1.8 ± 1.3 (95% CI 1.54 to 2.13). The mean interval with MVI effective action was 11.5 ± 5.4 hours (95% CI 10.21 to 12.74), and the mean interval from induction to delivery was 17.3 ± 6.3 hours (95% CI 15.8 to 18.8).

From the total of 53 vaginal deliveries, 56.7% (n=42) were spontaneous vaginal deliveries and 14.9% (n=11) instrumental vaginal deliveries.

23.4%, respectively 21 patients of entire study group (n=74) were converted into cesareans. Out of the 21 cesareans, 52.4% (n=11) were carried out for the failure of induction (lack of uterine contraction or cervical ripening after 24 hours), 14.3% (n=3) for ineffective labor, 14.3% (n=3) were carried out for fetal distress, and 19% (n=4) for cephalo-pelvic disproportion (Figure 4).
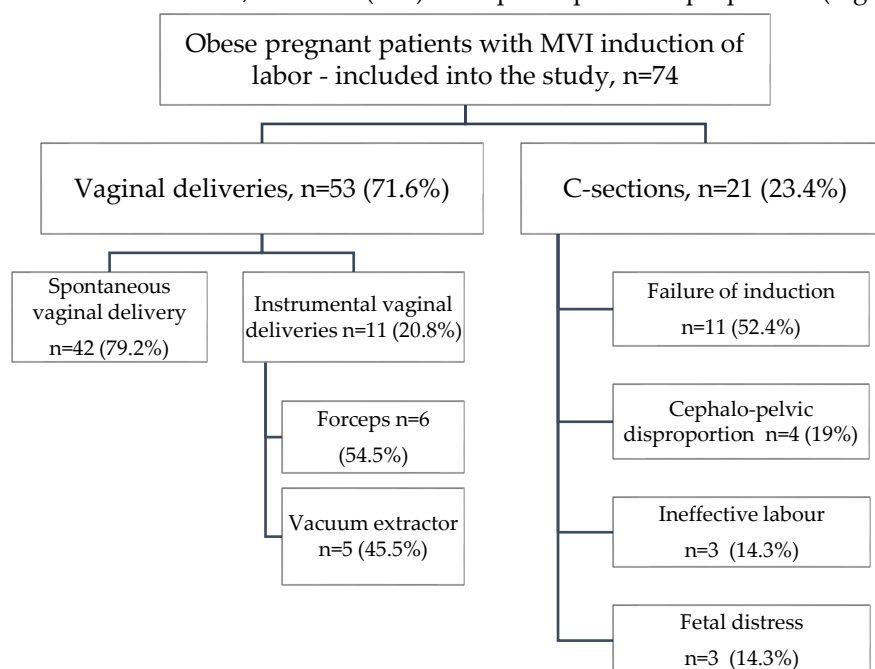


**Figure 4**. The distribution of delivery types in the study group.

*3.3 Outcomes for mother and neonate.*

According to parity or maternal age, there were no statistically significant differences in maternal and neonatal outcomes in the studied pool. The time from induction to delivery was shorter in multiparous women than in nulliparous women (16.34 ± 3.2 hours versus 17.1 ± 5.1 hours, p=0.04).

The unfavorable fetal outcome assessed by the neonatal intensive care unit admissions (NICU) and the initial one-minute Apgar score under seven - were associated with vaginal deliveries in the high-risk pregnancies group (n=4, representing 5.4% of the total deliveries, p - not significant).

We found a good correlation on vaginal delivery between Bishop Score and the duration of misoprostol action in late-term (r=0.51, p < 0.03) and hypertension (r = 0.97, p < 0.003) pregnancy subgroups. We found a satisfactorily correlation between Bishop score and the gestational age in diabetic pregnant women (r=0.55, p<0.07) subgroup.

Several studies have demonstrated that induction between 38 - 39 weeks (a) did not increase the cesarean delivery rate, (b) significantly decreased the incidence of large-for-gestational-age infants, macrosomia, and shoulder dystocia [2,3]. The fetal weight above 4,000 grams is an independent risk factor for the indication of a cesarean section.

There was no statistically significant difference between (a) sub-groups in Bishop scores at the time of admission, (b) the number of subjects who required oxytocin therapy during labor, or (c) the mean amount of oxytocin administered.

The distribution by type of indications in the study group was recorded in Table 4.

**Table 4**. The distribution of C-sections in the study group by indications.

| Indications | On-term pregnancies (n=17) | | Late-term pregnancies (n=25) | | Preeclampsia (n=12) | | Diabetes (n=20) | |
|---|---|---|---|---|---|---|---|---|
| | *n* | *%* | *n* | *%* | *n* | *%* | *n* | *%* |
| Failed induction | 3 | (14.2%) | 3 | (14.2%) | 3 | (14.2%) | 2 | (9.5%) |
| Uncertain fetal status | 1 | (4.7%) | | - | 1 | (4.7%) | 1 | (4.7%) |
| Cephalopelvic disproportion | | - | 1 | (4.7%) | 1 | (4.7%) | 2 | (9.5%) |
| Abnormal uterine contractility | | - | 2 | (9.5%) | | - | 1 | (4.7%) |

Out of 21 C-sections recorded in the study group, 52.4% (n=11) were performed in the subgroup of the patients with associated pathology, 28.6% (n=6) were necessary for the subgroup with late-term pregnancy, and only 19.0% (n=4) for on term pregnancy without pathology subgroup (Figure 6).
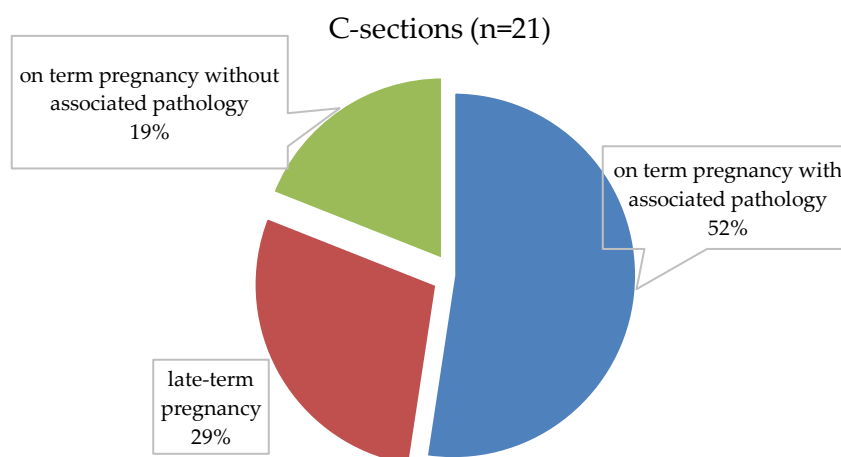


**Figure 5**. The distribution of C-sections in the study group. No late term pregnancy with associated pathology and C section was identified

Further prospective studies - capable of producing more robust evidence, such as randomized clinical trials - are necessary to confirm the present data's validity.

*3.4 Correlations between study subgroups and outcomes*

3.4.1 Correlations between the gestational age, misoprostol indication, and Bishop score

There is a significant statistical correlation between late-term pregnancy and misoprostol indication and ($p < 0.001$) (Figure 6).
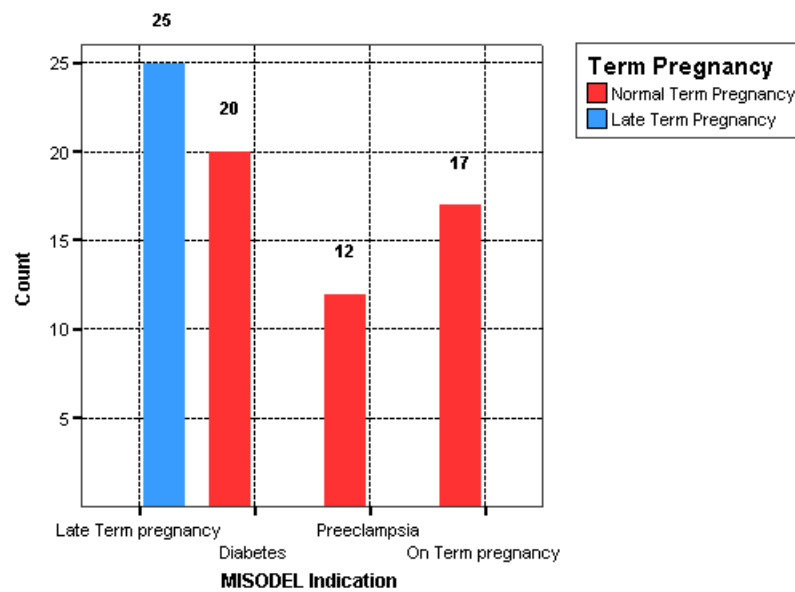
**Figure 6.** Significant statistical correlation between misoprostol indication and late-term pregnancy ($p < 0.001$).

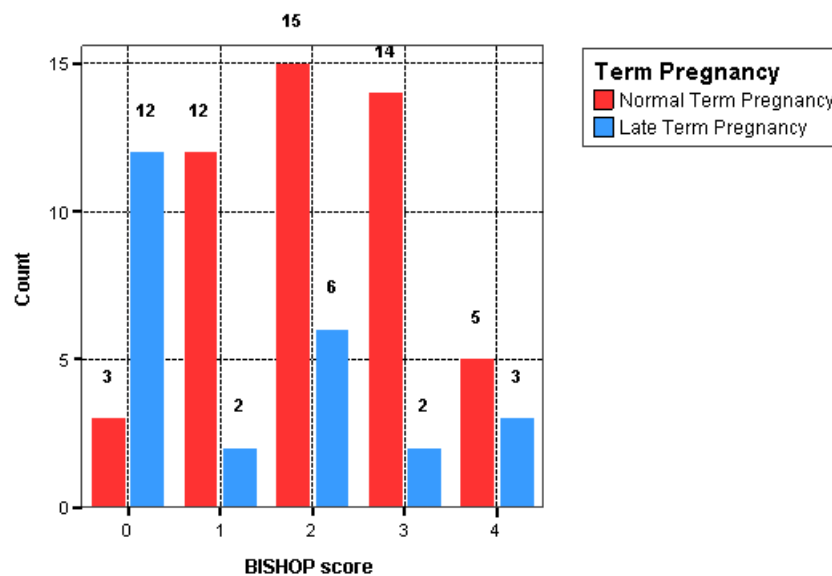There is a significant correlation between the pregnancy term and Bishop score ($p = 0.001$) (Figure 7).



**Figure 7.** Significant correlation between the pregnancy term and Bishop score ($p = 0.001$).

There is a significant correlation between the Bishop score and misoprostol indication for induction of labor ($p = 0.003$) (Figure 8).
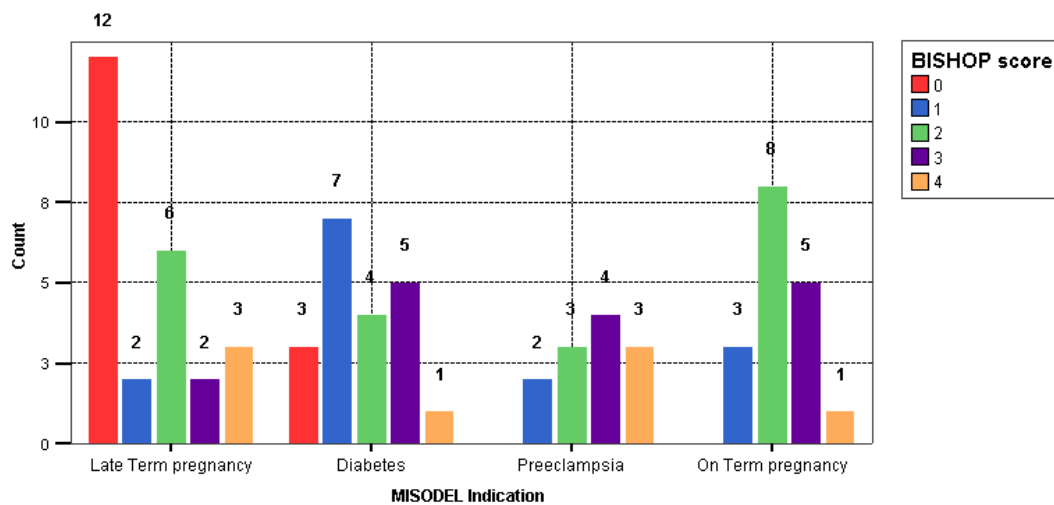
**Figure 8.** Significant correlation between the subgroups with misoprostol indication for induction of labor and the Bishop score (p = 0.003).

No correlation between birth type (spontaneous births, instrumental maneuvers, cesareans) and Bishop score (p = 0.286). No correlation was found between pregnancy term and birth type (spontaneous births, instrumental maneuvers, cesareans) (p = 0.318).

3.4.2 Correlations between obese patient age and pregnancy term

Mother age under 35 years were significantly linked to prolonged pregnancy (p = 0.047) (Figure 9). No statistical significance was found between age and misoprostol indication (p = 0.197) and birth type (spontaneous births, instrumental maneuvers, cesareans) (p = 0.468) or Bishop score (p = 0.062).



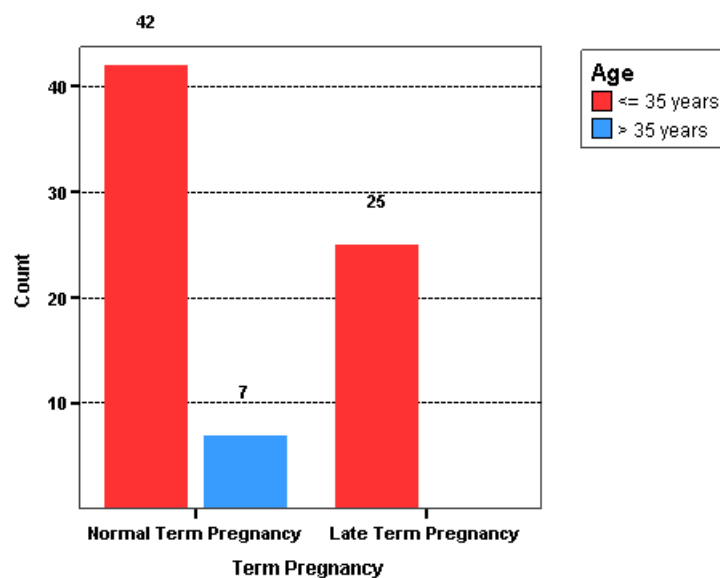**Figure 9.** Mother's age under 35 years significantly linked to prolonged pregnancy (p = 0.047).

*3.5 Side effects of misoprostol*

Side effects of misoprostol were registered in 17.6% cases (n = 13); two cases of tachysystole, one case of uterine hyper-stimulation, four cases of abnormal fetal heart rate (FHR) pattern, and six cases

of meconium passage, leading to three cases (4.1%) of emergency *C-* section to deliver the infant (Figure 10). We found a low rate of uterine hyper-stimulation, and there was no difference in neonatal morbidity between groups.
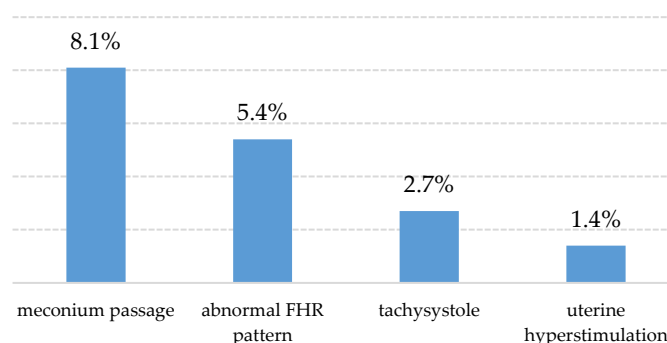


**Figure 10.** Side effects registered in the study group (n=13, 17.6 %)

The average one-minute Apgar score (at delivery) in the side effects sub-group was 8.5 ± 0.9 (95% CI 8.3 to 8.7), the five-minute Apgar score was 9.2 ± 0.6 (95% CI 8.9 to 9.2).

However, most cases with adverse effects of misoprostol have been managed conservatively with the extraction of the vaginal insert and i.v. tocolysis. The women were finally delivered vaginally without any significant impact on the Apgar score, except for three emergency C-section cases.

## 4. Discussion

Misoprostol is a prostaglandin E1 analog initially approved by the FDA to prevent and treat gastric ulcers associated with NAISD's drug intake [13]. Misoprostol acts during pregnancy on both the uterus and the cervix. The biochemical effects of misoprostol include decreased total collagen content, increased collagen solubility, and an increase in collagen-lytic activity in the cervical stroma. In contrast, the effect of misoprostol on uterine contractility consists is an increase of uterine tonus. The studies on uterine contractility have shown that a sustained level, rather than a high serum level, is required to develop regular uterine contractions [11]. Its uterotonic and cervical-ripening actions are widely used in obstetrics and gynecology; more than 30 dosage regimens are described regarding this matter [21,26] with side effects dose-related, usually transitory, and well-tolerated [27]. Manifestations of toxicity include hypertonic uterine contractions, fetal distress and death, hyperthermia, rhabdomyolysis, hypoxemia, respiratory alkalosis, and metabolic acidosis. The toxic dosage in humans is unknown, and there is no specific antidot [27].

After oral administration, misoprostol is rapid and almost completely absorbed, reaching plasma level peaks at 15-30 minutes ($T_{max}$) with a decline of up to 120 minutes, while the vaginal absorption is inconsistent [11]. Food reduces the absorption rate of oral administrated misoprostol, but not the absorption extent, while the concomitant antacid use reduces the total bioavailability [28]. Alongside vaginal and oral route, sublingual, rectal, or buccal route have tested with success the efficacy of misoprostol for cervical ripening in cases of induction of abortion, induction of labor, or postpartum hemorrhage.

Although the use of oral or vaginal misoprostol for IOL is common practice, there is one major limitation of these methods: the failure to predict the effects of misoprostol, as well as the onset of the side-effects (diarrhea, nausea, excessive uterine activity, changes in fetal heart rate - FHR patterns), alongside the difficulties to manage them [16, 24]. The side effects are dose-dependent and more familiar with oral misoprostol than intravaginal preparations [16]. In order to overcome this limitation, a misoprostol vaginal insert (MVI) system was developed, comprising of a non-biodegradable hydrogel polymer loaded with 200μg of $PGE_1$ analog. MVI allows the release of misoprostol continuously for 24 hours (approximately 7μg/hour) while the insert remains in place, thus providing the correct dosing and reducing the incidence of adverse events, the reservoir being rapidly and easily removed if needed [16, 29].

Misoprostol is extensively absorbed and rapidly metabolized to misoprostolic acid – the active metabolite, with approximately 80% excreted by the kidney with a terminal half-life of less than 1 hour when dosed vaginally, and peak plasma levels noted at around 5-9 hours. After removing dose-ranging, median plasma misoprostol acid concentrations delivered from controlled-release MVI decreased logarithmically and became very low (5 pg/ml) at 2 hours post-removal the reservoir [30].

Induction of labor (IOL – artificially initiated labor) is an event that occurs in up to one-quarter of pregnancies; less is known about the outcomes and safety of IOL in obese pregnant woman [31]; no data is available on misoprostol vaginal insert (MVI) induction of labor (IOL) in obese high-risk pregnancy patients. In Europe, the overall rates of IOL are between 7% to 33.0% [32].

The current investigation aimed to determine for the first time the rate of success or failure of the MVI system in IOL in obese high-risk pregnancies and the drug's safety profile related to the mother and to the newborn outcomes.

In our study, the vaginal delivery rate was over 71.6%, while the median one-min Apgar score of 8.6 ± 0.9, regardless of the delivery route.

The mean interval from induction to delivery was 17.3 ± 6.3 (95% CI 15.8 to 18.8), recording shorter periods in women with IOL for high-risk pregnancy than women without risk (16.8 ± 5.6 versus 18.6 ± 8.5, p = 0.03, with an average initial Bishop score of 1.8 (1.5-2.1); in contrast to other study (Lassiter & *al.*) that affirmed a longer duration of induction of delivery and more misoprostol vaginal doses, mostly due to the median cervical ripening stage of patients included in the study (Bishop score median – one). Supporting our study is the study of Garabedian *et al.* that affirmes an augumentation of the expression of the oxytocin receptors directly related to the pregnant's woman BMI value [42]; furthermore, decreasing the time to delivery has several advantages: reduced infection rates, reduced use of antibiotics and oxytocin, lower maternal distress [13].

Lassiter *et al.* showed that obese women undergoing induction of labor with misoprostol have a longer duration of induction to delivery, require more oxytocin to augment labor, more misoprostol doses, and have a higher rate of cesarean delivery, probably due to an impaired uterine activity [34]. In obese post-date pregnant women, Zhang *et al.* identified impaired uterine contractility, which may be related to prolonged labor and higher caesareans rates [35].

We found shorter periods in women with IOL for high-risk pregnancy in multiparous than in nulliparous women (16.34 ± 3.2 hours versus 17.1 ± 5.1 hours, p = 0.04).

The single-dose misoprostol appears to be an acceptable alternative to a multiple-dose regimen for cervical ripening before the induction of labor in multiparous women with an unripe cervix [4]. In our study, a single-dose misoprostol regimen was enough to induce labor in obese high-risk pregnancies.

In a comparative study, Bolla *et al.* showed that labor induction with MVI has a significantly higher rate of vaginal delivery within 24 hours, a shorter hospital stay, a higher rate of tachysystole with no differences in maternal and neonatal outcomes as well as in operative deliveries and C-section when compared to the labor induction with misoprostol vaginal conventional tablets [33].

Golstein *et al.* and Lauth *et al.* reported that gestational weight gain is a significant predictor of maternal and fetal outcomes [23,31]. In our opinion, two factors are essential: the pre-conceptual BMI and gestational weight gain, because at the first visit, the obstetrician recommends the amount of weight gain during pregnancy in accordance with pre-pregnancy BMI.

There is a significant risk of hypertensive disease in (class II) obese women with prolonged pregnancy (Lauth, 2020) [31]. However, in hypertensive pregnant women is essential to know the severity and course of the disease. According to clinical practice, induction of labor in on-term pregnant diabetic women is associated with decreased perinatal mortality.

In our study, the MVI induction of labor in high-risk pregnancy does not increase the risk of cesarean section compared with an expectant attitude; moreover, it reduces the rate of cesarean section, in accordance with other studies [36,37]. In support of these statements, we found a significant positive correlation between the misoprostol indication for labor induction and the Bishop score (p = 0.003).

No general maternal side effects were recorded during IOL in our study. Though we experienced a total of 13 cases of fetal adverse side effects, only in three cases (4.0%), an emergency

C-section was necessary to deliver the infant. In the remaining ten cases (13.5%), the extraction of the vaginal insert and i.v. tocolysis was effective in controlling the uterine activity and normalized the fetal heart rate; Bolla *et al.* study support our data. The authors found that the use of MVI increases the incidence of uterine tachysystole without the possibility of the event prediction by demographic or clinical factors, without an increased rate of C-section [31].

Our study focused on obese patients with prolonged pregnancy sub-group (late-term: 41 – 41+6 weeks) and with associated pathology such as diabetes or hypertension. We found a good correlation on vaginal delivery between Bishop score and the duration of misoprostol action in late-term (r = 0.51, p<0.03) and hypertension (r = 0.97, p<0.003) pregnancy subgroups and a satisfactory correlation between Bishop score and the gestational age in diabetes pregnant women (r = 0.55, p<0.07) subgroup. Thus, late-term (41w – 41w + 6d) or post-term (>42w) pregnancies are, therefore, the most common complications in obese patients without comorbidities. In accordance, we identified a significant positive statistical correlation between misoprostol indication and late-term pregnancy (p < 0.001).

The use of the routine or elective induction of labor in obese patients in high-risk pregnancy does not increase maternal and neonatal morbidity (respiratory distress, admission in NICU and neonatal mortality), with a lower risk than allowing the pregnancy to progress after 41 weeks in case of prolonged pregnancy, or in case of complicated diabetes or hypertension.

We found significant differences in induction success rate and the number of cesarean sections – 11 from 32 (34.37%) cases in the subgroup of women with associated pathologies compared with six from 25 (24%) cases in the subgroup of women late-term pregnancies and four from 17 cases (23.5%) on term without associated pathologies. Although we had only 21 cesarean deliveries, 18 were carried out for the failure of induction, abnormal uterine contractility or cephalopelvic disproportion and 3 for fetal distress. However, the main indication for the C-section was complex because there was not always easy to incriminate one single responsibile factor.

In high-risk pregnancies, the moment of labor induction or the cesarean section's time is not established, especially when the obesity factor occurs. Thus, MVI for IOL was indicated or scheduled at >41weeks in prolonged pregnancy, or 38 weeks in case of diabetes, or anytime in hypertension - if maternal or fetal complication occurred.

In our study, we found a significant link between obese women maternal age under 35 years and prolonged pregnancy (p = 0.047), because in many cases, patients above 35 years are worried about the prolonged course of pregnancy and become very anxious.

At the first visit, the obstetrician should advise obese pregnant women about optimal weight gain, optimal blood pressure and optimal blood glucose level during pregnancy. It is mandatory to counsel about the chances of vaginal delivery in cases of MVI for induction of labor.

**Limitations**

Our study's main limitation is the small number of patients included; prospective future studies are needed to identify which predictive factors can be used to select the labor induction of the obese patients with increased obstetrical risk. Furthermore, we do not have direct information about the BMI at the first visit, nor preconceptual BMI in data collection from patients' records, because some of the patients started after the first trimester their antenatal care. It's crucial to analyze the correlation between gestational weight gain and our study outcomes in further studies.

**Strengths**

Our study is the first cross-sectional study investigating high-risk pregnancy - induction of labor outcomes with misoprostol vaginal insert in obese on-term or late-term patients. Previous studies on the effect of maternal obesity on labor induction evaluated only the late-term pregnancies, induced by multiple therapy protocols with misoprostol, by amniotomy and oxytocin infusion (Maged *et al.*, 2018) [3 – 7, 31, 38-40]. Viteri *et al.* (2020) [41] reported this year on nulliparous obese women with IOL, using combined Foley balloon and misoprostol, resulted in similar C-section rates compared to ripening with vaginal misoprostol alone.

### 5. Conclusions

Misoprostol vaginal insert system is an efficient and safe drug system for labor induction with no statistically negative impact on the maternal or fetal outcome when used in obese pregnant women late-term or with associated hypertensive and diabetes pathology, with good perinatal outcomes. Close monitoring of both mother and fetus represents the critical priority within the protocol for a favorable obstetrical outcome under this drug administration's safety profile. There are no significant differences between maternal and perinatal outcomes among high-risk pregnancies of obese patients submitted to labor induction with misoprostol in our study. Induction of labor in high-risk pregnancies is a reasonable and safe management option for obese women.

**Supplementary Materials:** The following are available online at www.mdpi.com/xxx/s1, Figure S1: Figure 2. Flow-diagram of patient distribution. Figure S2: Figure 3. Distribution of the subjects in the study based on high-risk criteria in obese pregnant patients with MVI IOL. Figure S3: Figure 4. The distribution of delivery types in the study group. Figure S4: Figure 5. The distribution of C-sections in the study group. No late term pregnancy with associated pathology and C section was identified; Figure S5: Figure 8. Significant correlation between the subgroups with misoprostol indication for induction of labor and the Bishop score (p = 0.003). Table S1: Table 1. – Study participant structure and characteristics, Table S2: Table 2. Outcomes of the MVI IOL in the studied group by type of risk factor, Table S3: Table 3. Outcomes of the MVI IOL in the studied group by type of birth., Table S4: Table 4. The distribution of C-sections in the study group by indications.

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**List of abbreviations:**

| | |
|---|---|
| BMI | Body Mass Index |
| *C*- section | Cesarean section |
| EU | European Union |
| FDA | Food Drug Administration |
| GPCR | G protein-coupled receptors |
| HELLP | Hemolysis, elevated liver enzymes, low platelet count. |
| IOL | Induction of labor - artificially initiated labor |
| MVI | Misoprostol Vaginal Insert |
| NICU | Neonatal intensive care unit |
| NSAIDs | Non-steroidal anti-inflammatory drugs |
| PROM | Prelabour rupture of membrane |
| P.G.s | Prostaglandins |
| PGE2 | Prostaglandin E2 |
| WHO | World Health Organization |
| SPSS® | Statistical Package for the Social Sciences, IBM® |
| $T_{max}$ | Time to peak plasma levels |

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