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Comparison of Misoprostol for Labor Induction: Vaginal Insert *Versus* Oral Application Concerning Efficiency and Safety

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Abstract. *Background/Aim: The aim of the present retrospective study was to examine the efficiency and safety of the induction of labor with Misoprostol, administered either vaginally or orally. Patients and Methods: This retrospective cohort study included pregnant women with a gestational age of ≥36 +0 weeks and a singleton pregnancy who underwent induction of labor with Misoprostol as vaginal insert or as tablet (oral) between January 2014 and January 2019 at the Department of Obstetrics and Gynecology of the University Hospital of Cologne. The objective of this study was to analyze the time until delivery and the maternal and neonatal outcomes. Results: A total of 1,511 patients were included in this retrospective analysis, of whom 1,035 patients (68.5%) underwent induction of labor with a misoprostol vaginal insert (MVI) and 476 (31.5%) with tablets (oral misoprostol: OM). MVI significantly shortened the time from application to delivery (p<0.001) in comparison to OM, reduced the need for epidural anesthesia (EA) (p=0.018) without an increase in caesarean sections (CS) (p=1), ventouse deliveries (VD) (p=0.715), maternal birth injuries or a reduced neonatal outcome (APGAR-Score, umbilical cord pH). Conclusion: MVI is superior to OM in terms of efficiency (primary outcome: time from application to delivery) and is equally safe (primary outcome: CS rate). Our study, along with existing literature, highlights the need for further research, particularly regarding neonatal outcomes. Additionally, it underscores the importance of careful consideration when inducing labor and ensuring informed consent.*

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The induction of labor (IOL) is one of the most frequent procedures in obstetrics. Its use has increased worldwide during the last twenty years. Numbers vary in different countries among Europe. An induction rate above 20% (range=7-33%) was found in 15 of 25 European countries in 2005 (1). Induction rates also have risen in the USA [from 9.5% in 1990 to 22.3% in 2005 (2) and to 23.8% in 2015 (3)]. Efforts within the obstetrics community have focused on reducing nonmedically indicated IOL prior to a gestational age of 39 weeks (3). Numerous methods have been practiced over the decades. The five most commonly used methods for cervical ripening in women with intact membranes are Foley catheter, vaginal misoprostol, oral misoprostol, vaginal dinoprostone and intracervical dinoprostone (4). Chen *et al.* stated in 2017: "Research studies comparing the safety and effectiveness of different methods of cervical ripening are inconsistent, such that the optimal method of induction of labor remains unclear" (4). Prostaglandins have been used successfully in obstetrics since the 1970s (5). The advantages of the PGE_1 analogues (*e.g.*, misoprostol) over the PGE_2 analogues (*e.g.*, dinoprostone) are widely known: they are stable at room temperature, less expensive, and more safely applicable by mouth because of their chemical properties (6). Misoprostol, which received approval from the U.S. Food and Drug Administration in 1988 to prevent gastric ulcers associated with nonsteroidal anti-inflammatory drugs (7), has been increasingly used for a range of off-label maternal health indications, including: medical abortion, cervical ripening, induction of labor, and as a uterotonic agent in the management of third stage labor (7) since the 1990s and was put on the WHO Essential Medicines List (EML) (8). Misoprostol tablets (orally administered PGE_1-analogue) were withdrawn from the German market in 2006 by *Pfizer*,

therefore they may only be used "off-label" in gynecology and obstetrics and must be reimported. According to Pfizer, Misoprostol cannot be used in obstetrics in France since March 2018 due to serious unwanted side effects, although Pfizer has not provided details. Despite this, Misoprostol is still used in obstetrics in 79 other countries, including Austria and Switzerland. It is unknown if patients in those countries are affected by similar problems (9). With the approval of the Misoprostol vaginal insert (active agent also misoprostol, vaginal release system) in 2014, a misoprostol preparation, which is approved for IOL, has predictable drug release and estimable plasma levels (10), is available. The burden of "off-label use" [separate information to the patient; no detailed information on dosage/dosage effects/adverse events, risk of recourse claims by health insurances, heterogeneous schedules in obstetric departments (and therefore difficult comparability with regard to effectiveness and safety) (11, 12)] in everyday clinical practice could be high. We based this study on the initial assumption that the outcome of mother and child can be improved by the induction of labor if indicated (13-18). To "replace" a clinically proven drug (misoprostol tablets) with a potentially safer and more effective one (19), it must be adequately monitored and validated in clinical practice for safety and efficacy, even after approval. The Vaginal insert has been subject of interest to numerous different studies. It shows better efficiency in comparison to vaginally applied misoprostol tablets (20, 21) or other vaginally applied prostaglandins such as dinoprostone (22, 23). The present retrospective study examined the safety and efficiency of the induction of labor with Misoprostol, either as vaginal insert or as an oral tablet. The goal is to improve clinical standards and achieve an even higher level of safety for mother and child.

Patients and Methods

In this retrospective cohort study, patients who underwent induction of labor between January 2014 and January 2019 in the University Hospital Cologne at the Department of Obstetrics and Gynecology were included.

Inclusion criteria. Pregnant women with a gestational age of at least 36+0 weeks and a singleton pregnancy who underwent induction of labor with Misoprostol.

Exclusion criteria. Pregnant women with a gestational age of less than 36 +0 weeks, a multiple pregnancy or those, who did not undergo induction of labor with a vaginal insert or a tablet (Table I).

A retrospective analysis was performed for the following parameters: patient age, gestational age, parity, obtained medication for induction of labor, indication for induction of labor; birthweight, neonatal sex, APGAR-Score and umbilical cord-pH; mode of delivery, indication and type of caesarean section (secondary or emergency), type of vaginal delivery (assisted, spontaneous), type of applied anesthesia and maternal birth injury (by monitoring episiotomy rate or postpartum hemorrhage). The primary outcomes were time interval from induction to delivery (TID), rate of caesarean section (CS) and neonatal outcomes at birth (APGAR-Score, arterial cord pH). The secondary outcomes were delivery mode [assisted (ventouse, forceps), spontaneous], usage of epidural anesthesia (EA), maternal birth injury (perineal tears, postpartum hemorrhage) and episiotomy.

Statistical analysis. Statistical evaluation was conducted using Microsoft EXCEL (Microsoft Corporation, Redmond, WA, USA) and SPSS (IBM SPSS Statistics, V. 22, IBM, Armonk, NY, USA). The mean value, standard deviation, minimum and maximum values as well as frequency distributions of the different parameters were used for the descriptive analysis. Various tests were used for detection of potential significance between the two delivery groups or induction medications used.

Nominally scaled data were analyzed using contingency tables and chi-square tests. For interval and time-scaled data, the *t*-test was used. Independent sample variance homogeneity was confirmed using Levene's test. In case of comparing two groups of ordinal variables we resorted to the Mann–Whitney-*U* and Wilcoxon–*W* test, respectively. Also, if indicated, the rank correlation coefficient was used. Statistical significance was set at $p<0.05$. We assumed a trend when $p>0.05$ but $p<0.10$.

Results

In total, 1,511 patients were included in this retrospective analysis, of which 1,035 patients (68.5%) underwent IOL with the misoprostol vaginal insert and 476 (31.5%) with misoprostol tablets (Table II). The average age was 32 years in both groups. The average gestational age at the time of induction was 39 weeks in both groups. There was no significant difference in the age of patients and the gestational age at the time of induction or parity (percentage of Nullipara/Multipara, $p=0.267$) between the two groups. The occurring mean difference in gestational age [39.3 weeks in the misoprostol vaginal insert (MVI) group; 39.08 weeks in the OM group] is not clinically relevant.

The statistical analysis did not show a significant difference in terms of maternal outcome/complications as endpoints defined by CS rate (MVI: 6.1%, OM: 6.0%; $p=1$), postpartum hemorrhage [MVI: 6.7%, oral misoprostol (OM): 6.3%; $p=0.821$ ns (not significant)], and high grade perineal tears (grade 3 or 4 and/or labial and/or vaginal tear; $p=0.371$; no grade 4 in the OM group) but there was a trend in the number of emergency CSs (MVI>OM $p=0.078$) and the rate of episiotomies (MVI<OM $p=0.088$).

Furthermore, both groups did not show a significant difference concerning children's birth weight ($p=0.085$) and neonatal outcome regarding APGAR-Score (one minute: $p=0.923$; five minutes: $p=0.419$; 10 min: $p=0.240$). The mean difference in umbilical pH (7.25±0.08 in the MVI group compared to 7.27±0.08 in the OM group) is not clinically relevant.

Table I. *Vaginal insert and tablet*.

Vaginal insert	Oral
- Drug release system to be placed vaginally in the posterior fornix, crosslinked hydrogel polymer - Active agent: Misoprostol - Dosage: 200 µg - Release ~7 µg/h in 24 h - Must be removed after 24 h, if there are more than three contractions in 10 min or strong contractions or by the hunch of fetal abnormal conditions	- Pill to be taken orally - Active agent: Misoprostol - Initial dosage: 25 µg - To be repeated every two hours - Dosage might be increased if cervical ripening does not progress
- Indications: placental insufficiency, gestational diabetes, fetal macrosomia, preeclampsia, HELLP-syndrome, intrauterine fetal demise, fetal malformations, late- and post-term pregnancy, maternal diseases, oligohydramnios, preterm premature rupture of the membranes, intrauterine growth restriction, *etc*. - Maternal and fetal well-being, contractions and progress of labor need to be monitored - Be prepared for tocolysis - PGE_1-analogues: are NOT to be used in women with previous CS - Not suitable for women with chronic inflammatory bowel disease, but for patients suffering from asthma - Oxytocin: earliest 30 min after MVI has been removed, 60 min after the last OM	

HELLP: Hemolysis, Elevated Liver enzymes and Low Platelets; CS: caesarian section; OM: oral misoprostol; PGE1: prostaglandin E.

Table II. *Baseline characteristics*.

Characteristics	MVI N (%) ± SD	OM N (%) ± SD	*p*-Value
Number of patients n=1,511 (%)	1,035 (68.5%)	476 (31.5%)	
Parity (multi)	491 (47.4%)	211 (44.3%)	0.267
Mothers age at delivery	32.1±5.6	32.0±5.4	0.971
Gestational age at delivery	39.3	39.08	<0.001
Children's birth weight (g)	3,444±516	3,394±523	0.085

n: Number; SD: standard deviation; MVI: Misoprostol vaginal-insert; OM: oral misoprostol.

Though there was no significant difference in the duration of the expulsive phase in both groups, a trend in the duration of the opening phase (MVI<OM, p=0.060) and a significant difference in the duration of the phase of pushing contractions (MVI<OM p=0.001), duration of labor (DOL) (MVI<OM p=0.001; Figure 1), and therefore a significant difference in the total time between administration of medication and delivery (MVI<OM p=0.001) was observed (Table III).

There was also a significant difference in the use of anesthesia. More women in the misoprostol tablets group (44.8%) needed epidural anesthesia than in the MVI group (38.3%; p=0.022). As we mentioned before, the average DOL was distinctly shorter when IOL was performed with MVI (MVI: 4.43 h±4.21; OM: 5.52 h±5.11; p<0.001). The difference remains, if DOL is linked with the drug administered and the use of epidural. DOL was 2.99 h±3.05 in the MVI group and 3.58 h±3.87 in the OM group with no epidural (p=0.020) and 6.73 h±4.745 (MVI) 7.87 h±5.438 (OM) with epidural (p=0.010).

Besides these findings the statistical analysis did not show a significant difference between the two groups regarding a higher number of ventouse (MVI: 19.1%, OM: 18.1%; p=0.715) (Table IV).

Discussion

Our retrospective cohort study is not the first to address this or any similar issue, but direct comparisons of misoprostol vaginal insert and misoprostol tablets are rare. So far, four recently published studies are available (10, 24-26).

Efficiency. If we use "time from administration to delivery" as the primary efficiency endpoint, the results of our study show the superiority of MVI compared to OM (MVI group: M=18.17 h, SD=17.97 h; OM group: M=26.39 h, SD=22.26 h;

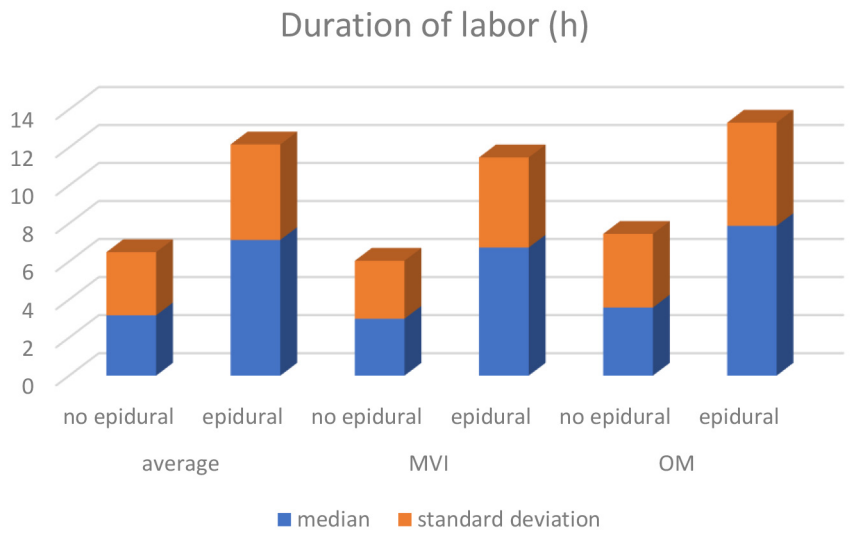

Figure 1. *Duration of labor.*

Table III. *Durations*.

Characteristics	MVI N (%) ± SD	OM N (%) ± SD	*p*-Value
Duration opening phase (h)	4.18±5.32	4.78±4.88	0.060
Duration expulsive phase (min)	51.90±61.46	55.31±60.72	0.906
Phase of pushing contractions (min)	15.23±11.47	18.18±14.54	<0.001
duration of labor (DOL)	4.43±4.21	5.52±5.11	<0.001
Administration of drug until delivery	18.17±17.97	26.39±22.26	<0.001
DOL with epidural	n=366 6.73±4.745	n=201 7.87±5.438	0.010
DOL without epidural	n=583 2.99±3.047	n=243 3.58±3.87	0.020
DOL (regardless the obtained medication)			
With epidural	n=567, 7.13±5.027		*p*<0.001
Without epidural	n=826, 3.17±3.320		*p*<0.001

n: Number; SD: standard deviation; DOL: duration of labor; MVI: Misoprostol vaginal-insert; OM: oral misoprostol.

p<0.001). Döbert *et al*.'s study in 2017 reports a difference in median time of approximately 10.48 h [mean time interval from application of drug to any mode of delivery: MDMVI=16.08 h; MDOM=26.57 h; *p*<0.001 (24)]. Similarly, our results regarding efficiency are in agreement with those of Redling *et al*.'s [MVI 15.91 h; MO 37.68 h; *p*<0.001 (25)] and Hokkila *et al*.'s studies in 2019 (MDMVI=24.5 h; MDOM=44.2 h; *p*<0.001 (26).

Safety – caesarean section. The CS rate in our study was lowest compared to the other three available direct comparisons of misoprostol vaginal insert and misoprostol tablets [MVI 6%; OM 6.1%; *p*=1; Redling *et al*. MVI 29.7%; OM 37.6%; *p*=0.297) (25); Hokkila *et al*.: MVI 33.8%, OM 29.6%; *p*=0.67 (26); Döbert *et al*.: MVI 39.1%, OM 21.7%, *p*=0.041 (24)]. Out of these four trials, Döbert *et al*. were the only ones to show a significant difference between the two groups, with a disadvantage for MVI. CS rates after induction with MVI (200 μg) vary in the different studies. In the MVI group of women enrolled into the Phase III trial "EXPEDITE" [MVI 200 μg *vs*. DVI (10 mg dinoprostone)], the CS rate was 26% (23). In a study comparing different dosages, the CS rate for the MVI 200 μg was 22.9% (27). The prospective clinical observational

Table IV. *Mode of delivery and neonatal outcome.*

Characteristics	MVI N (%) ± SD	OM N (%) ± SD	*p*-Value
Caesarean section (secondary)	62 (6%)	29 (6.1%)	0.999
Caesarean section (emergency)	13 (1.3%)	1 (0.2%)	0.078
CTG (pathologic) which led to CS	25 (2.4%)	9 (1.9%)	0.581
Operative delivery	248 (24.0%)	110 (23.1%)	0.745
Ventouse delivery (VD)	186 (19.1%)	81 (18.1%)	0.715
Umbilical cord pH (median)	7.25±0.08	7.27±0.08	<0.001
APGAR-Score		1-/5/10-min: p=0.923/0.419/0.240	

n: Number; SD: standard deviation; CS: caesarian section; CTG: cardiotocography; MVI: misoprostol vaginal-insert; OM: oral misoprostol.

study of Schmidt *et al*. compared MVI in nulliparous and parous women and reported a CS rate of 31.1% (28), while Mayer *et al*. (MVI *vs*. DVI) presented a rate of 10.1% (29). Even though the overall percentage of CS after induction of labor was the lowest throughout the observed period of time (January 2014 until January 2019) in the University Hospital Cologne at the Department of Obstetrics and Gynecology and though there was no significant difference between the two groups, we have to mark a tendency regarding emergency CS (MVI: 1.3%, OM: 0.2%; p=0.078), which was shown neither by Döbert *et al*. nor by Hokkila *et al*. nor by Redling *et al*. The differing numbers concerning CS rates seem not surprising given the different study designs and differences in patient populations (numbers, inclusion criteria, exclusion criteria, number of nulliparous and parous women, percentage of high-risk pregnancies, percentage of elective inductions), thus comparisons should be made with caution. The CS rate in the Hokkila *et al*. study is of special interest, because they focused on nulliparous women. MVI was not shown to increase the CS rate in comparison to OM in nulliparous women (28). This is important, because "the most common reason for CS is repeat CS following previous CS (30). The rates of vaginal birth after CS (VBAC) differ due to different healthcare settings and countries (30). Repeat CS needs to be avoided because of "growing evidence regarding associated complications, including infection, bleeding, thromboembolic events, placenta accreta and neonatal respiratory morbidity" (31).

Safety – neonatal outcome. Using the APGAR-Score and the arterial cord pH as parameters for neonatal outcome, we could not reveal a difference between the two groups. This corresponds with the results of Hokilla *et al*. (26) and Redling *et al*. (25). In contrast to the present and the cited studies, Döbert *et al*. did show negative effects on neonatal outcomes. The mean APGAR-Score of 5 min after birth was significantly lower for any mode of delivery (MVI 9.64±0.7 *vs*. OM 9.87±0.4). These results have led to the authors hypothesis, "that the recovery period for newborns is shorter after OM" (24). There was also a lower arterial cord pH in the MVI group if there was an abnormal fetal scalp pH or abnormal fetal heart rate during birth; if none of these circumstances occurred during birth, after induction with the MVI, the APGAR-Scores after 1 and 10 min as well as the arterial cord pH showed a tendency towards lower values, but without significant difference (24). The results of our study cannot affirm this notion. The mean difference in umbilical pH (7.25±0.08 in the MVI group, 7.27±0.08 in the OM group; p<0.001) is statistically significant due to the sample size, yet this difference is not clinically relevant. Furthermore, both groups did not show a significant difference with regard to APGAR-Score (1 min: p=0.923; 5 min: p=0.419; 10 min: p=0.240). It is important to cite Beyer *et al*., Wing *et al*., Redling *et al*., Hokkila *et al*. and many more and to determine by consensus, that there is no difference in neonatal outcomes when comparing MVI to OM and/or other prostaglandins or misoprostol as vaginal tablet (VT) (20-23, 25, 26, 29). However, during further literature research, it was difficult to align the different results of the various studies and designs, patient populations and confounders with regard to the safety profile of the MVI.

Adverse events – Uterine tachysystole and uterine hyperstimulation. Uterine tachysystole is an adverse event (AE), which has to be expected when inducing labor with prostaglandins, especially with Misoprostol, irrespective of the form of application (4, 13, 32, 33). We did not include uterine tachysystole or uterine hyperstimulation as primary or secondary outcome in our work, which is partly caused by lack of data for intrapartal tocolysis. In summary, the numbers of cardiotocography (CTG) abnormalities, fetal acidosis or meconium-stained amniotic fluid that led to operative delivery (CS, ventouse or forceps delivery) were moderate. Uterine tachysystole and uterine hyperstimulation syndrome have been reported in different studies but inconsistently and in varying numbers. Comparisons should

Table V. *Secondary outcomes*.

Characteristics	MVI N (%) ± SD	OM N (%) ± SD	*p*-Value
Epidural (EA)	383 (38.3%)	206 (44.8%)	0.022
Episiotomy	162 (15.7%)	92 (19.3%)	0.088
Postpartum hemorrhage (total)	68 (6.7%)	29 (6.3%)	0.821
Postpartum hemorrhage (vaginal)	62 (6.5%)	27 (6.3%)	
Maternal birth injury (grade 3 or 4 and/or labial and/or vaginal tear; no grade 4 in the OM group)			0.371

n: Number; SD: standard deviation; EA: epidural anesthesia; MVI: misoprostol vaginal-insert; OM: oral misoprostol.

be carried out cautiously and with special attention on different study designs and patient populations. Hokkila *et al*. found that tocolysis had to be employed significantly more often in the MVI group for tachysystole. However, this condition did not lead to an increase of CS or a decrease in neonatal outcomes in any study arms (26). Tachysystole occurred more often in the MVI study arm in the study of Redling *et al*.'s trial (MVI: 22.8%; OM: 5.0%; $p<0.001$). Even though they did not show a significant difference in overall CS, "women with tachysystole in the MVI group trended to need CS more often for non-reassuring fetal heart rates (17.4%) compared to women without tachysystole (7.7%) in the MVI group ($p=0.229$)" (25). Döbert *et al*. showed an increased number of uterine tachysystole and CS, and decreased neonatal outcomes (24). It remains unclear, whether tachysystole itself/alone led to lower APGAR-Scores and cord pHs, or if other circumstances contributed to those results [Döbert *et al*. did included an very high number of risk pregnancies (53.4%) in their study population (24)]. Wing *et al*. declared that there is no correlation between uterine tachysystole, CS rate and neonatal outcome (34). Twice as many cases of uterine tachysystole (not statistically significant compared to MVI 100 μg), uterine hyperstimulation syndrome and high numbers of non-reassuring fetal heart rate patterns in the 200 μg arm did somehow not lead to lower APGAR-Scores and were allegedly not responsible for any of the performed CS. We would carefully like to question the statistical evaluation as one did before (33). Further studies are needed to prove whether tachysystole itself, triggered through MVI, or other peripartum circumstances (maternal conditions such as preeclampsia as a time-relevant indication for IOL with MVI) could be responsible for any possible decrease in neonatal outcome. Furthermore, APGAR-Score and umbilical pH (35) might not be the optimal parameters to measure neonatal outcome despite their comparability. Even though a wide pH range of 7.00-7.16 is quoted in the literature for acidemia, there is a general consensus that a cord artery pH <7.00 is more significantly correlated with adverse neonatal outcome (26, 34). Babies with pH <7.00 are more likely to suffer complications in the short term, while long term outcome is correlated with neonatal encephalopathy rather than pH.

Safety – maternal outcome. The use of analgesia and/or anesthesia has been of irregular interest in the studies we referred to so far. While Döbert *et al*. did not mention any kind of analgesia or anesthesia (24), Hokkila *et al*. and Redling *et al*. focused on epidural anesthesia without finding a difference in their study arms (25, 26) and Redling *et al*. revealed a higher use of opioid analgesia during induction and before the onset of active labor in the MVI group (MVI: 31.7%; OM: 2.0%; $p<0.001$) (25). We detected a significantly higher rate of epidural anesthesia (EA) in the OM group (MVI: 36.3%; OM: 42.9%; $p=0.018$). The need of analgesia is of concern regarding the comfort and safety of the mother to be. On one hand, EA itself entails risks and requires human and material resources. On the other hand, DOL increases with EA, which leads to a longer stay in the delivery room ["increasing the burden on resources" (36)], a higher potential for traumatic birth experience (20, 25), an increased risk for infections [especially if premature rupture of membranes (PROM) was the indication for IOL (23, 25)] and use of antibiotics (25). The significantly longer time until delivery and/or DOL might be the reason for the higher demand for EA. In Döbert *et al*.'s study, data regarding maternal birth injuries were narrowed down to episiotomies (MVI: 12.2%; OM: 5.9%; *p*=not available) and difference of maternal hemoglobin levels before and after birth. No significance could be shown for either "all deliveries" or "vaginal deliveries" (24). Rates of episiotomies, postpartum hemorrhage and higher-grade perineal tears did not differ between the two groups in our study. When Redling et al. compared MVI to OM, they found higher-grade perineal tears (grade 3 and 4) in the MVI group (5.9%) compared to the OM group (1.0%); though the difference was not significant (p=0.118). Additionally, the MVI group had a significantly higher estimated blood loss compared to the OM group (613 ml±490 ml in the MVI group, 475 ml±214 ml in the OM group; p=0.037) (Table V). Given that

peripartum blood loss is difficult to objectify, we would like to exclude this parameter when creating the MVI safety-profile. Regarding ventouse delivery, Redling *et al*. (MVI: 17.8%; OM: 24.8%; p=0.302) and Hokkila *et al*. (MVI: 20.3%; OM: 13.3%; p=0.12; Döbert *et al*. not available) did not find differences between the two groups. This corresponds with our results: the statistical analysis did not show a significant difference between the two groups regarding a higher number of ventouse delivery (MVI: 19.1%, OM: 18.1%; p=0.715).

Strengths and limitations. The retrospective nature is a limitation of the study as well as the non-randomized analysis of the data from a single center. OM is still used off-label in obstetrics in Germany and therefore it seems challenging to compare it to a drug which is officially approved for IOL. Strengths of our study are the high number of patients with various indications for IOL and maternal and fetal conditions.

Conclusion

MVI is superior to OM regarding efficiency. It significantly shortens the time to delivery. This was proven by the present study and three others (24-26). The biggest pharmacological and pharmacokinetic advantages over OM are calculable plasma levels, continuous release of the active ingredient, the option to retrieve it if labor starts or AE occur, and its license for IOL.

MVI seems to be safe. Our study did not detect alarming results that might be of concern for the safety of mother or child. But still, high numbers of uterine tachysystole and/or uterine tachysystole syndrome (which may not respond to tocolysis) have been reported. We need further randomized studies to elucidate whether maternal or fetal conditions (such as preeclampsia) prior to IOL might contribute to the occurrence of AE and their direct impact on maternal and neonatal outcome. Ongoing clinical use and experience will contribute to the optimization in the use of the misoprostol vaginal insert. The reduced demand for EA when labor is induced with MVI is important for the safety and comfort of the women as well as from an economic point of view. According to the current state of relevant studies, labor should be induced after thorough control of indication with the right medication after considering potential risks and benefits for the mother and child. If possible, both application-types of misoprostol should be offered (also considering that a patient may feel more comfortable with the oral administration). The potentially higher rate of AE must be mentioned just as well as the shorter time to delivery in order to conform with "informed consent and shared decision-making". When inducing labor with a vaginal insert, the clinical staff needs to stick to recommendations of WHO and *Ferring Arzneimittel GmbH* in coordination with the Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices, BfArM) regarding indication and monitoring of mother and child and must be prepared for tocolysis.

We would like to conclude with two hypotheses, which desirably should be confirmed or disproved by us (or other medicals) in future studies:
- Hypothesis one: The induction of labor when using MVI is more urgent (state of mother and child worse compared to elective), which could lead to more AEs irrespective of the drug used. This has been deliberated before: "One clear limitation of the observational literature is that induction is often indicated by complications of pregnancy, which may independently increase the risk of caesarean section" (37),
- Hypothesis two: The period of time when MVI is to be removed might still be too vague - should we think about removing MVI even earlier to significantly reduce the risk for AEs and complications for mother and child (38)?

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Katherina Hide-Moser performed the data collection and contributed to the draft of the manuscript. Sunhwa Baek and Mirka Hunke performed the statistical analysis. Berthold Grüttner and Nina Mallmann-Gottschalk were involved in conceptualizing the study. Jessika Ratiu contributed to the collection and analysis of data. Peter Mallmann approved the final version. Dominik Ratiu conceptualized the study and contributed to the final version of the manuscript.

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