

Induction of Labor at Term with Oral Misoprostol or as a Vaginal Insert and Dinoprostone Vaginal Insert – A Multicenter Prospective Cohort Study

Geburtseinleitung am Termin mit Misoprostol oral oder als Vaginalinsert und Dinoproston Vaginalinsert – eine multizentrische prospektive Kohortenstudie



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ABSTRACT

Introduction The efficacy, safety, and perinatal outcome of oral misoprostol (OM), a misoprostol vaginal insert (MVI), and a dinoprostone vaginal insert (DVI) for induction of labor at term was examined in a prospective multicenter cohort study (ethics committee vote 4154–07/14). The primary aims of the study were the induction-birth interval (IBI), the cumulative delivery rates after 12 h, 24 h, and 48 h as well as the mode of delivery.

Method 322 pregnant women were included in four German tertiary perinatal centers (MVI 110, DVI 64, OM 148). They did not vary in age or BMI. Statistical analysis was carried out using a multivariate linear regression analysis and binary logistic regression analysis.

Results With regards to the median IBI, MVI and OM were equally effective and superior to the DVI (MVI 823 min [202, 5587]; DVI 1226 min [209, 4909]; OM 847 min [105, 5201]; $p = 0.006$). Within 24 hours, 64% were able to deliver with DVI, 85.5% with MVI and 87.5% with OM ($p < 0.01$). The rates of secondary Caesarean sections (MVI 24.5%; DVI 26.6%; OM 18.9%) did not differ significantly. Uterine tachysystole was found in 20% with MVI, 4.7% with DVI and 1.4% with OM ($p < 0.001$). A uterine rupture did not occur in any of the cases. Perinatal acidosis occurred (umbilical cord arterial pH < 7.10) in 8.3% with MVI, 4.7 with DVI and 1% with OM ($p = 0.32$). Neonatal condition was only impaired in three cases (5-minute Apgar score < 5).

Summary Induction of labor at term using the prostaglandins misoprostol and dinoprostone is an effective intervention that is safe for the mother and child. Oral application of misoprostol demonstrated the highest efficacy while maintaining a favorable safety profile.

ZUSAMMENFASSUNG

Einleitung In einer prospektiven multizentrischen Kohortenstudie wurden die Effektivität, Sicherheit und das perinatale Outcome von oralem Misoprostol (MO), einem Misoprostol-Vaginalinsert (MVI) und einem Dinoproston-Vaginalinsert (DVI) zur Geburtseinleitung am Termin untersucht (Ethikvotum 4154–07/14). Primäre Studienziele waren das Induktions-Geburtsintervall (IGI), die kumulativen Entbindungsraten nach 12 h, 24 h und 48 h sowie der Entbindungsmodus.

Methode Es wurden 322 Schwangere in 4 deutschen Level-1-Perinatalzentren eingeschlossen (MVI 110, DVI 64, MO 148), die sich nicht in Alter und BMI unterschieden. Die statistische Auswertung erfolgte mittels multivariater linearer Regressionsanalyse und binärer logistischer Regressionsanalyse.

Ergebnisse Hinsichtlich der medianen IGI waren MVI und MO äquieffektiv und dem DVI überlegen (MVI 823 min [202,

5587]; DVI 1226 min [209, 4909]; MO 847 min [105, 5201]; $p = 0,006$). Innerhalb von 24 Stunden konnten 64% mit DVI, 85,5% mit MVI und 87,5% mit MO entbunden werden ($p < 0,01$). Die Raten an sekundären Sectiones (MVI 24,5%; DVI 26,6%; MO 18,9%) unterschieden sich nicht signifikant. Eine uterine Tachysystolie fand sich in 20% bei MVI, 4,7% bei DVI und 1,4% bei MO ($p < 0,001$). In keinem Fall ereignete sich eine Uterusruptur. Perinatale Azidosen (arterieller Nabelschnur-pH $< 7,10$) traten in 8,3% bei MVI, 4,7% bei DVI und 1% bei MO auf ($p = 0,32$). In nur 3 Fällen war der neonatale Zustand beeinträchtigt (5-Minuten-Apgar < 5).

Zusammenfassung Geburtseinleitung am Termin mit den Prostaglandinen Misoprostol und Dinoproston ist eine effektive und für Mutter und Kind sichere Intervention. Die höchste Effektivität bei gleichzeitig günstigstem Sicherheitsprofil weist die orale Misoprostolanwendung auf.

Introduction

Since February 2020, media coverage on the use of the prostaglandin E1 analog misoprostol has led to considerable uncertainty among the public, but particularly pregnant women and their attending midwives and physicians [1, 2]. To bring some objectivity into the debate, the German professional associations made a joint statement in which they referred to the existing medical knowledge and broad scientific basis from more than 80 randomized controlled studies on the use of oral misoprostol for induction of labor, and dozens of randomized controlled studies on its vaginal application [3]. Misoprostol is classified by the WHO as an essential medication and is recommended for induction of labor [4]. The use of 50 to a maximum of 100 µg of misoprostol orally as a single dose is recommended in the German S2k guideline 015–088 from 2020 and in a current Cochrane review by Kerr et al. 2021 [5, 6].

In 2014, the misoprostol vaginal insert received European approval and was therefore also able to be used in routine clinical practice in Germany. However, after completion of the study that was submitted, the preparation was no longer sold on the German market by the manufacturer for commercial reasons.

Since summer 2021, an oral misoprostol preparation for induction of labor has once again been permitted in Germany as well [7].

There is no direct systematic comparison between the prostaglandin vaginal insert and oral application of misoprostol in the literature to date. The aim of this prospective multicenter cohort study is to compare the efficacy and safety as well as the side effect profile of oral misoprostol (OM) for induction of labor with the vaginal inserts that are approved for that purpose containing the prostaglandin E1 analog misoprostol (MVI), or the prostaglandin E2 analog dinoprostone (DVI).

Method and Patients

322 pregnant women with an indication of induction of labor from 40/0 weeks of pregnancy (wks) were included in an investigator-initiated, prospective multicenter cohort study at four German level 1 perinatal centers (173 women in Jena, 65 women in Neukölln, Berlin, 63 women in Halle (Saale), and 21 women in Tempelhof, Berlin) between July 2014 and October 2015. Only the two vaginal inserts were used in the Halle and Tempelhof, Berlin study centers. The inclusion and exclusion criteria are shown in

► Table 1.

Out of the 322 participants in the study, 110 patients received the misoprostol insert, 64 received the dinoprostone insert and 148 received oral misoprostol. The demographic data of the women in the study did not differ in terms of age, BMI and gravidity (► Table 2).

► Table 1 Inclusion and exclusion criteria.

Inclusion criteria

All induction indications from 40/0 wks

- Late term $> 41/0$ wks
- Oligohydramnion
- Pre-eclampsia/pregnancy-induced hypertension
- Insulin-dependent gestational diabetes
- At the request of the pregnant women

Exclusion criteria

- Previous Caesarean section or other uterine surgeries
- Premature rupture of membranes
- Duration of pregnancy $< 40/0$ wks
- Suspected placental insufficiency or fetal growth restriction
- Twins

wks = week of pregnancy

► **Table 2** Demographic characterization of the study population (mean values ± standard deviation), statistical analysis with Mann-Whitney U test and Fisher's exact test: * = MVI; ** = DVI, $p < 0.05$.

	MVI n = 110	DVI n = 64	OM n = 148	P value
Age	29.3 ± 6.0	29.5 ± 6.0	29.7 ± 5.0	0.265
BMI (kg/m ²)	28.7 ± 5.6	28.2 ± 6.4	28.3 ± 5.7	0.782
Pregnancy	1.6 ± 1.0	1.6 ± 1.1	1.9 ± 1.3	0.224
Parity	0.4 ± 0.7	0.4 ± 1.6	0.6 ± 0.8*, **	0.018
Primiparity	79 (72%)	45 (70%)	85 (57%)	0.034
Modified Bishop score	2.9 ± 1.5	3.3 ± 1.5*	2.7 ± 1.3**	0.016
Gestational age (days)	286.2 ± 3.6	287.2 ± 3.2	285.5 ± 3.6**	0.01

Study Protocol

The study was conducted exclusively with the institutional support of the participating hospitals, and without third-party sponsorship. The study protocol was registered with the local regulatory authorities and approved by a vote of the ethics committee of the Jena University Hospital (No. 4154–07/14). All participants were provided with extensive information, both written and oral, and gave their written consent to participate in the study.

The following dosages of the prostaglandin preparations were used over a maximum of 48 h:

- Orally administered misoprostol (Cytotec, Pfizer Inc., New York, USA), initially 50 µg and subsequently 100 µg every four hours by means of 50 µg capsules produced in the hospital pharmacy (max. 500 µg/d)
- Misoprostol as a vaginal insert (MVI, Misodel, Ferring Inc., Saint-Prex, Switzerland), 200 µg/24 h with 7 µg/h release (maximum 2 × 24 h)
- Dinoprostone as a vaginal insert (DVI, Propess, Ferring Inc., Saint-Prex, Switzerland), 10 mg/24 h with 0.3 µg/h release (maximum 2 × 24 h)

The prostaglandin was administered until regular contractions of three contractions/10 min and/or a cervical dilation of approx. 3 cm, and was terminated immediately (vaginal insert removed) if there were any side effects (pathological CTG changes, uterine hyperstimulation). Prostaglandin was not administered over more than 48 hours; augmentation of labor using oxytocin was possible. Induction was considered unsuccessful when the woman was exhausted or requested the termination of the induction efforts, and if onset of labor could not be achieved after 48 hours.

Maternal and fetal monitoring was in line with the clinical standards for induction of labor of the respective centers. To record the condition of the fetus, a 30-minute recording of the fetal heart rate pattern (CTG) and measurement of the maternal vital signs was performed before and after administration of prostaglandin and then every two hours.

Aims of the Study

The primary aim of the study was to compare the efficacy of the induction of labor by recording the induction-birth interval (IBI), the cumulative delivery rates after 12 h, 24 h and 48 h as well as the respective mode of delivery.

The secondary aim of the study was to determine the safety of inducing labor by recording the perinatal complications (pathological fetal heart rate patterns and uterine tachysystole with consequent interventions) and the postnatal outcomes (Apgar after 1/5/10 minutes, arterial and venous umbilical pH, base excess).

Statistics

The statistical analysis was performed using a multivariate linear regression analysis, binary logistic regression analysis, chi-squared test, Kruskal-Wallis test for independent samples, Mann-Whitney U test for independent samples and Fisher's exact test, and using SPSS where advisable in each case. Significant differences were assumed at $p < 0.05$.

Results

Differences were found between the treatment groups in the parameters that were recorded as influencing factors on the efficacy of induction—parity and cervical maturation measured by a semi-quantitative Bishop score; therefore, an adjustment was made for these parameters in the multivariate analysis.

Efficacy

With regards to the median induction-birth interval, MVI and OM were equally effective and superior to the DVI (MVI 823 min [202, 5587]; DVI 1226 min [209, 4909]; OM 847 min [105, 5201]; $p = 0.006$) (► **Table 3**). Additional oxytocin augmentation was required during the course of labor in 8.2% after MVI, however, in 24.3% after OM and 36% after DVI ($p < 0.001$). Within 24 hours, only 64% of all women were able to give birth with DVI, however, for MVI it was 85.5%, and 87.5% for OM ($p < 0.01$). However, within 48 hours of the start of induction, almost all women had given birth (MVI 97.5%; OM 98.3%; DVI 93.6%). In total, 11 women delivered by secondary Caesarean section due to unsuccessful induc-

tion (OM 4%; MVI 2%; DVI 8%, ns). No differences in the rate of secondary Caesarean sections and frequency of vaginal births were observed. (► **Table 3**).

Safety

Pathological CTG changes tended to be more commonly an indication for operative deliveries after administrations of misoprostol (MVI 87% and OM 73%) than after dinoprostone (52%), while stalled labor after DVI led to a Caesarean section in 40% of women (MVI in 11%, OM in 23%). With MVI, uterine tachysystole was found as an expression of uterine hyperstimulation significantly more frequently than with DVI (20% vs. 4.7%) or oral misoprostol

(1.4%) ($p < 0.01$). Uterine rupture did not occur in any of the cases.

Neonatal Outcome

All the three induction options that were compared demonstrated high therapeutic safety for the neonate (► **Table 4**). Significant differences were found in the normal physiological range of the average arterial and venous umbilical blood pH without clinical relevance. The perinatal acidosis rates with arterial pH < 7.10 were 8.3% for the MVI, 4.7% for the DVI and only 1% for OM. However, due to the low frequency, the difference was not significant. Neonatal outcome was only impaired in three cases (0.9%) in total (5 min Apgar < 5).

► **Table 3** Efficacy of induction with misoprostol vaginal insert (MVI), dinoprostone vaginal insert (DVI) and oral misoprostol (OM), multivariate regression analysis, adjusted for parity, Bishop score and gestational age. * = MVI and OM.

	MVI n = 110	DVI n = 64	OM n = 148	P value
Induction-birth interval				
Median [min, max] (min)	823 [202, 5587]	1226 [209, 4909]*	847 [105, 5201]	< 0.01
within 24 h, n (%)	71 (85.5)	30 (64)*	104 (87.5)	< 0.01
within 48 h, n (%)	81 (97.5%)	44 (93.6%)	102 (98.3%)	ns
more than 48 h, n (%)	2 (2.5%)	3 (6.4%)	2 (1.7%)	ns
Augmentation with oxytocin n (%)	9 (8.2)	23 (36.0)	26 (24.3)	< 0.001
Type of delivery				
Spontaneous vaginal %	68.2	64.1	70.9	0.61
Vaginal operative %	7.3	9.4	10.1	0.81
Caesarean section %	24.5	26.6	18.9	0.375
of which due to CTG pathology	87%	52%	73%	
Due to birth arrest	11%	40%	23%	

► **Table 4** Safety of induction of labor using misoprostol vaginal insert (MVI), dinoprostone vaginal insert (DVI) and oral misoprostol and perinatal outcome (mean values \pm standard deviation), statistical analysis with Mann-Whitney U test and Fisher's exact test; * = MVI and OM, $p < 0.01$, in [] number of affected neonates.

	MVI n = 110	DVI n = 64	OM n = 148	P value
Birth weight (g)	3568 \pm 378	3666 \pm 431	3620 \pm 405	0.41
Uterine tachysystole n (%)	22 (20.0)	3 (4.7)	2 (1.4)	< 0.001
CTG pathology n (%)	57 (51.8)	18 (28.1)	40 (27.0)	< 0.001
arterial pH	7.21 \pm 0.07	7.25 \pm 0.08*	7.21 \pm 0.09	< 0.01
pH NA < 7.10	8.3% [9]	4.7 [3]	1% [16]	0.32
venous pH	7.30 \pm 0.07	7.34 \pm 0.07 *	7.32 \pm 0.09	< 0.01
Base excess (mmol/L)	- 5.7 \pm 3.15	- 4.67 \pm 3.49	- 5.24 \pm 3.23	0.14
Apgar 1 min	8.3 \pm 1.4	8.6 \pm 1.1	8.4 \pm 1.4	0.55
Apgar 5 min	9.3 \pm 1.0	9.4 \pm 0.7	9.2 \pm 1.1	0.71
Apgar 10 min	9.7 \pm 0.6	9.8 \pm 0.4	9.7 \pm 0.7	0.25
Apgar 5 min < 5	0.9% [1]	0	1.4% [2]	0.64

Discussion

Induction of labor is one of the most common interventions in obstetrics, and it has steadily increased in recent years. In Germany, labor was induced in 21.9% of all births and 33% of all late-term pregnancies in 2019 [8]. It has been proven that induction of labor has the benefit of reducing maternal and child morbidity, and also reducing the rate of operative deliveries [5, 9, 10, 11]. Prostaglandin analogs are considered the method of choice for induction of labor at term, subject to pre-existing cervical maturation [12, 13].

In the present three-armed prospective multicenter study, the high efficacy and safety for patients was able to be demonstrated for the first time in a direct comparison between the use of prostaglandin vaginal inserts as indicated, and off-label administration of misoprostol for induction of labor at term.

Efficacy

The efficacy of both misoprostol applications was significantly superior to the dinoprostone vaginal insert. The median induction time was shorter by more than six hours and the delivery rate within 24 hours was significantly higher.

A current Cochrane review of 61 studies reports that low-dose administration of misoprostol has many advantages over other methods of induction of labor [6].

Numerous comparative studies of DVI and MVI in recent years provide evidence for the higher efficacy of MVI and report significantly shorter induction times [14, 15, 16]. However, this was related to higher rates of uterine hyperstimulation, which also occurred in our study five times more frequently [14, 17].

More recent studies have compared the misoprostol vaginal insert with oral misoprostol [18, 19, 20, 21, 22]. In line with our results, Wallström et al. report a comparable IBI and delivery rate within 24 hours, however, at 50.5% and 55.7% respectively, these were quite lower than in our study population [18]. By contrast, in a Swiss cohort study, the rate of vaginal deliveries within 24 hours of MVI was higher and the IBI was significantly shorter [19]. Döbert et al. report comparable results, however, the risk of a Caesarean section was more than 2.5 times higher than after oral administration of misoprostol [20]. A randomized multicenter Finnish study found that MVI was significantly more effective than oral administration of misoprostol (IGI 24.5 h vs. 44.2 h), however, without increasing the rate of operative deliveries (34% vs. 30%) [21]. In contrast to our study design, this study used only three administrations of misoprostol per day (day one $3 \times 50 \mu\text{g}$; day two $3 \times 100 \mu\text{g}$).

Safety

Compared to oral administration of misoprostol and the dinoprostone vaginal insert, the misoprostol vaginal insert had a rather unfavorable safety profile with significantly higher rates of uterine hyperstimulation and CTG pathologies, however these did not result in a worse perinatal outcome in our study. In most compara-

tive studies, more frequent uterine tachysystole has been reported for MVI [14, 15, 16, 17, 18, 20, 21, 22]. This ultimately led to the preparation being withdrawn from the market.

However, as in our study, this has not resulted in a more unfavorable perinatal outcome compared to the dinoprostone insert [15, 16, 17] or oral misoprostol [18, 19, 21, 22]. Conversely, Döbert et al. report not only significantly higher rates of Caesarean sections, but also more than 4% perinatal acidosis <7.00 [20]. After the MVI insertion duration was reduced in this hospital from 24 to 10 hours, the incidence of uterine tachysystole was able to be reduced while maintaining similar efficacy, and the perinatal outcome was able to be significantly improved [23].

No valid conclusions could be drawn in a Cochrane meta-analysis with 14 000 study participants in relation to the serious side effects of oral misoprostol that have been highlighted in the media, as these side effects occur so infrequently that a study population twice to ten times as large would have been required in order to draw valid conclusions [24].

Strengths and Weaknesses

The strength of the study is the large number of cases and its multicentricity, which reflects the actual care profile of pregnant women at term in Germany. The significant limitation of the present multicenter prospective study is that the compared cohorts and the induction modalities were not randomized. This means that a selection bias within and between the study centers cannot be ruled out. Furthermore, questions were not asked about the subjective wellbeing and pain perception of the participants during induction of labor, therefore, no statements can be made about the individual experiences of the women in labor.

Summary

Induction of labor at term using the prostaglandins misoprostol and dinoprostone is an effective intervention that is safe for the mother and child. Oral application of misoprostol demonstrated the highest efficacy while maintaining a favorable safety profile. The misoprostol vaginal insert is associated with higher rates of uterine hyperstimulation and CTG abnormalities, although it did not lead to a higher rate of Caesarean sections, or risk to the newborn. Induction of labor using dinoprostone was associated with a considerable extension of the duration of birth, and therefore, physical and mental stress for the women in labor. Medicolegal issues are increasingly playing a role in the selection of effective treatment strategies, and causing pregnant women receiving care to feel uncertain.

Conflict of Interest

The authors declare that they have no conflict of interest.

References/Literatur

- [1] Langhans K. Wehensturm. . Accessed July 16, 2022 at: <https://projekte.sueddeutsche.de/artikel/gesundheit/im-wehensturm-e688113/?reduced=true>
- [2] Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e.V. (DGGG). Misoprostol in der Frauenheilkunde und Geburtshilfe – Brief an Spahn: große Sorge wegen erschwerten Zugangs zu Cytotec. *Geburtshilfe Frauenheilkd* 2021; 81: 603. doi:10.1055/a-1495-8331
- [3] Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e.V. (DGGG), Arbeitsgemeinschaft für Geburtshilfe und Pränatalmedizin e.V. (AGG) in der DGGG, Deutsche Gesellschaft für Perinatale Medizin e.V. (DGPM), Deutsche Gesellschaft für Pränatal- und Geburtsmedizin e.V. (DGPGM), Bundesarbeitsgemeinschaft Leitender Ärztinnen und Ärzte in der Frauenheilkunde und Geburtshilfe e.V. (BLFG). Stellungnahme der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe e.V. (DGGG) und der Arbeitsgemeinschaft für Geburtshilfe und Pränatalmedizin e.V. (AGG) in der DGGG, der Deutschen Gesellschaft für Perinatale Medizin e.V. (DGPM), der Deutschen Gesellschaft für Pränatal- und Geburtsmedizin e.V. (DGPGM) sowie der Bundesarbeitsgemeinschaft Leitender Ärztinnen und Ärzte in der Frauenheilkunde und Geburtshilfe e.V. (BLFG) zur Berichterstattung über „Cytotec zur Geburtseinleitung“. *Geburtshilfe Frauenheilkd* 2020; 80: 369–370. doi:10.1055/a-1109-0170
- [4] Tang J, Kapp N, Dragoman M et al. WHO recommendations for misoprostol use for obstetric and gynecologic indications. *Int J Gynaecol Obstet* 2013; 121: 186–189. doi:10.1016/j.ijgo.2012.12.009
- [5] Kehl S, Hösl I, Pecks U et al. Induction of Labour. Guideline of the DGGG, OEGGG and SGGG (S2 k, AWMF Registry No. 015–088, December 2020). *Geburtshilfe Frauenheilkd* 2021; 81: 870–895. doi:10.1055/a-1519-7713
- [6] Kerr RS, Kumar N, Williams MJ et al. Low-dose oral misoprostol for induction of labour. *Cochrane Database Syst Rev* 2021(6): CD014484. doi:10.1002/14651858.CD014484
- [7] Bagory H, De Broucker C, Tourneux P et al. Efficacy and safety of oral misoprostol 25 µg vs. vaginal dinoprostone in induction of labor at term. *Gynecol Obstet Fertil Senol* 2022; 50: 229–235. doi:10.1016/j.gofs.2021.11.011
- [8] IQTiC. Bundesauswertung zum Erfassungsjahr 2019. Geburtshilfe. Qualitätsindikatoren und Kennzahlen. . Accessed July 16, 2022 at: https://iqtig.org/downloads/auswertung/2019/16n1gebh/QSKH_16n1-GEBH_2019_BUAW_V02_2020-07-14.pdf
- [9] Kehl S, Weiss C, Dammer U et al. Induction of Labour in Growth Restricted and Small for Gestational Age Foetuses – A Historical Cohort Study. *Geburtshilfe Frauenheilkd* 2019; 79: 402–408. doi:10.1055/a-0834-8199
- [10] Schlembach D. Fetal Growth Restriction – Diagnostic Work-up, Management and Delivery. *Geburtshilfe Frauenheilkd* 2020; 80: 1016–1025. doi:10.1055/a-1232-1418
- [11] Middleton P, Shepherd E, Crowther CA. Induction of labour for improving birth outcomes for women at or beyond term. *Cochrane Database Syst Rev* 2018(5): CD004945. doi:10.1002/14651858.CD004945.pub4
- [12] Kehl S, Weiss C, Rath W et al. Labour Induction with Misoprostol in German Obstetric Clinics: What Are the Facts on Such Use? *Geburtshilfe Frauenheilkd* 2021; 81: 955–965. doi:10.1055/a-1538-2200
- [13] Voigt F, Goecke TW, Najjari L et al. Off-label use of misoprostol for labor induction in Germany: a national survey. *Eur J Obstet Gynecol Reprod Biol* 2015; 187: 85–89. doi:10.1016/j.ejogrb.2014.11.026
- [14] Wing DA, Brown R, Plante LA et al. Misoprostol vaginal insert and time to vaginal delivery: a randomized controlled trial. *Obstet Gynecol* 2013; 122: 201–209. doi:10.1097/AOG.0b013e31829a2dd6
- [15] Schmidt M, Neophytou M, Hars O et al. Clinical experience with misoprostol vaginal insert for induction of labor: a prospective clinical observational study. *Arch Gynecol Obstet* 2019; 299: 105–112. doi:10.1007/s00404-018-4942-y
- [16] Rankin K, Chodankar R, Raymond K et al. Misoprostol vaginal insert versus dinoprostone vaginal insert: A comparison of labour and delivery outcomes. *Eur J Obstet Gynecol Reprod Biol* 2019; 235: 93–96. doi:10.1016/j.ejogrb.2018.07.025
- [17] Maggi C, Mazzoni G, Gerosa V et al. Labor induction with misoprostol vaginal insert compared with dinoprostone vaginal insert. *Acta Obstet Gynecol Scand* 2019; 98: 1268–1273. doi:10.1111/aogs.13667
- [18] Wallström T, Strandberg M, Gemzell-Danielsson K et al. Slow-release vaginal insert of misoprostol versus orally administrated solution of misoprostol for the induction of labour in primiparous term pregnant women: a randomised controlled trial. *BJOG* 2019; 126: 1148–1155. doi:10.1111/1471-0528.15796
- [19] Redling K, Schaedelin S, Huhn EA et al. Efficacy and safety of misoprostol vaginal insert vs. oral misoprostol for induction of labor. *J Perinat Med* 2019; 47: 176–182. doi:10.1515/jpm-2018-0128
- [20] Döbert M, Brandstetter A, Henrich W et al. The misoprostol vaginal insert compared with oral misoprostol for labor induction in term pregnancies: a pair-matched case-control study. *J Perinat Med* 2018; 46: 309–316. doi:10.1515/jpm-2017-0049
- [21] Hökkila E, Krui H, Rahkonen L et al. The efficacy of misoprostol vaginal insert compared with oral Misoprostol in the induction of labor of nulliparous women: A randomized national multicenter trial. *Acta Obstet Gynecol Scand* 2019; 98: 1032–1039. doi:10.1111/aogs.13580
- [22] Wegener S, Koenigbauer JT, Laesser C et al. Do we need a 200 µg misoprostol vaginal insert? A retrospective cohort study comparing the misoprostol vaginal insert to oral misoprostol. *J Obstet Gynaecol Res* 2020; 46: 851–857. doi:10.1111/jog.14230
- [23] Brandstetter A, Döbert M, Schwaerzler P et al. Safety of misoprostol vaginal insert for labor induction using standard vs. adjusted retrieval criteria: a comparative cohort study. *J Perinat Med* 2020; 48: 488–494. doi:10.1515/jpm-2020-0071
- [24] Alfirevic Z, Keeney E, Dowswell T et al. Labour induction with prostaglandins: a systematic review and network meta-analysis. *BMJ* 2015; 350: h217. doi:10.1136/bmj.h217