Synthetic Osmotic Dilators for Pre-Induction Cervical Ripening – an Evidence-Based Review

Synthetische osmotische Dilatatoren zur Zervixreifung vor Geburtseinleitung – eine evidenzbasierte Übersicht

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ABSTRACT

Mechanical methods have gained growing interest for pre-induction cervical ripening in women with an unripe cervix, since they have a better safety profile compared to prostaglandins. Balloon catheters have been the gold standard method for decades, while there was a lack of data on synthetic osmotic cervical dilators.

Not until 2015, when Dilapan-S was approved by the Food and Drug Administration (FDA) for induction of labor, numerous studies have been published on the use of Dilapan-S in this field. The rate of vaginal deliveries associated with the use of Dilapan-S ranges from 61.6 to 81.7%, and no serious complications needing further interventions have been reported to this date.

Dilapan-S was shown to be as effective as the Foley balloon catheter as well as the 10 mg PGE_2 vaginal insert and orally applied misoprostol (25 µg every 2 hours) in achieving vaginal delivery, but patient's satisfaction during the cervical ripening process was significantly higher compared to the other methods and the rate of uterine hyperstimulation was significantly lower compared to prostaglandins (PGs).

Minor complications (e.g. vaginal bleeding) associated with the use of Dilapan-S were < 2%, and maternal infectious morbidity was not higher compared to Foley balloon and vaginal PGE_2 or misoprostol.

Due to these beneficial properties Dilapan-S might be an ideal option for outpatient cervical ripening, as shown in a recent randomized clinical trial comparing inpatient to outpatient cervical ripening.

Furthermore, according to the manufacturers' product information, Dilapan-S is the only cervical ripening method that is not contraindicated for induction of labor in women with a previous cesarean section. Upcoming guidelines should consider synthetic osmotic cervical dilators as an effective and safe method for cervical ripening/induction of labor acknowledging that more evidence-based data are mandatory, particularly in patients with a previous cesarean section.

ZUSAMMENFASSUNG

Mechanische Methoden haben zur Zervixreifung/Geburtseinleitung bei Schwangeren mit unreifer Zervix zunehmendes Interesse erlangt, da diese ein höheres Sicherheitsprofil aufweisen als Prostaglandine. Ballonkatheter sind seit Jahrzehnten der Goldstandard, während es bisher nur wenige Daten zu synthetischen osmotischen Zervixdilatatoren gibt.

Erst als Dilapan-S 2015 von der Food and Drug Administration (FDA) zur Geburtseinleitung zugelassen wurde, wurden zahlreiche Studien zum Einsatz von Dilapan-S veröffentlicht. Die Rate vaginaler Entbindungen im Zusammenhang mit der Anwendung von Dilapan-S liegt zwischen 61,5 und 81,7 %, wobei bis heute über keine schwerwiegenden Komplikationen mit Notwendigkeit zu weiteren Interventionen berichtet wurde.

Dilapan-S erwies sich bezüglich der Rate vaginaler Geburten als vergleichbar effektiv wie der Foley-Ballonkatheter, das 10-mg-Prostaglandin-E_2-(PGE_2-)Vaginalinsert und Misoprostol oral (25 µg alle 2 Stunden). Allerdings zeigte sich eine wesentlich höhere Patientinnenzufriedenheit während des Zervixreifungsprozesses im Vergleich zu den anderen Methoden, und darüber hinaus war die Rate an uterinen Hyperstimulationen signifikant geringer im Vergleich zu Prostaglandinen.

Die Rate leichter Komplikationen (z. B. vaginale Blutung) im Zusammenhang mit der Anwendung von Dilapan-S liegt < 2 %, und die infektionsbedingte maternale Morbidität war im Vergleich zum Foley-Ballonkatheter, zu vaginalem PGE_2 und Misoprostol nicht höher.

Aufgrund dieser vorteilhaften Eigenschaften könnte Dilapan-S eine ideale Option für die ambulante Zervixreifung darstellen, wie erst kürzlich in einer randomisierten klinischen Studie gezeigt werden konnte, in welcher die stationäre mit der ambulanten Zervixreifung verglichen wurde.

Darüber hinaus ist Dilapan-S, laut Produktinformation des Herstellers, die einzige Methode zur Zervixreifung, die im Rahmen der Geburtseinleitung bei Schwangeren mit vorangegangenem Kaiserschnitt nicht kontraindiziert ist. Zukünftige Leitlinien sollten daher synthetische osmotische Zervixdilatatoren als eine wirksame und sichere Methode zur Zervixreifung/Geburtseinleitung berücksichtigen, allerdings sind mehr evidenzbasierte Daten zwingend erforderlich, insbesondere bei Patientinnen mit vorangegangenem Kaiserschnitt.

Introduction

In the last 20 years, labor induction rates have almost doubled in high-income countries, with reported rates of 31.4 % in the USA in 2020 [1], 34% in the United Kingdom in 2021 [2] and 21.8% in Germany 2020 [3]. There is an increasing tendency to only induce contractions after sufficient cervical ripening [4].

Inducing labor when the cervix is still unripe does not accelerate the birth; instead, it places additional stress on the fetoplacental unit due to contraction-related uterine hypoperfusion, which may be harmful in pregnancies with reduced fetal reserve.

It is also associated with longer induction-to-delivery intervals compared to induction when the cervix is already ripe, with increasing costs and low patient's acceptance due to painful contractions [5].

In this context, mechanical methods (balloon catheters, synthetic osmotic cervical dilators) for pre-induction cervical ripening have gained growing interest [6].

While in a German-wide survey 2013 [7] only 1.8% of obstetric units used mechanical methods for cervical ripening/induction of labor, this rate was 38% for synthetic osmotic dilators and 53% for balloon catheters, respectively, in a recent German-wide survey from 2020 [8].

Compared to prostaglandin E_2 (PGE_2)/misoprostol the use of mechanical methods for pre-induction cervical ripening is associated with a significantly lower rate of uterine hyperstimulation, lower monitoring cost during the cervical ripening period, lower overall costs, the absence of serious maternal and fetal side effects and higher patient's satisfaction [5].

In the light of rising hospital costs and increasing burden on obstetric staff, particularly during the COVID-19 pandemic, mechanical methods have shown a promising approach for outpatient pre-induction in low-risk patients with an unripe cervix at term [5]. On the other hand, mechanical methods require the additional administration of oxytocin to induce/augment labor more often when compared to PGE_2/misoprostol [5] and they may be associated with an increased risk of infectious morbidity [9].

During the past several decades, the vast majority of studies on mechanical methods for cervical ripening/induction of labor investigated the use of balloon catheters [6], while data on the use of synthetic osmotic cervical dilators were somewhat limited.

Dilapan-S is a second generation synthetic osmotic dilator made from a patented anisotropic xerogel AQUAACRYL. It is a synthetic gel rod, which increases in volume by absorbing fluids from the surrounding tissues throughout the cervical canal and thus exerting steady radial pressure on the cervical wall, which dilates the cervix. This pressure also promotes the release of endogenous prostaglandins, which causes collagen degradation and therefore further softens the cervix [10].

Experimental and clinical studies have shown that Dilapan-S is superior to laminaria regarding the degree and speed of cervical dilatation associated with shorter induction-to-delivery intervals [11, 12, 13]. The thin rod (4 mm) can expand up to 12 mm over a

12 hours period and 92% dilatation was reached within 8 hours, as recently shown in vivo in the USE Dilapan Ultrasound study [14].

In the nineties of the last millennium, numerous randomized studies have compared Dilapan (the first generation) with intracervically applied PGE₂ gel for cervical ripening in patients with an un-ripe cervix [15, 16, 17, 18, 19]. It has been shown that the use of Dilapan was as effective as PGE_2 in pre-induction cervical ripening and associated with lower costs and better patient's convenience [15]. Outpatient cervical ripening with Dilapan seemed as effective and safe as in the inpatient setting [20]. Surprisingly, however, there is a gap in publications on Dilapan after 1999. One explanation may be that Dilapan-S (the second generation of the device) was awaiting approval from the Food and Drug Administration (FDA), which was acquired in 2015.

The goal of this review is to evaluate clinical studies on the use of Dilapan-S for cervical ripening/induction of labor published between 2015 and 2022 in order to develop evidence-based recommendations for clinical practice.

Cervical ripening/induction of labor with Dilapan-S

An observational, non-interventional study from Germany 2015 [21] evaluated 83 patients near term with a Bishop Score (BS) < 4, who underwent cervical ripening with Dilapan-S left in place for at least 12 hours ('overnight') in an outpatient setting followed by intravenous oxytocin or PGE_2 gel or misoprostol orally.

The primary outcome was the rate of vaginal delivery: 65% of all patients delivered vaginally (82.6% of multiparous women). The average time from cervical ripening to delivery was 36 hours. No adverse fetal or maternal outcomes were observed.

The main limitations of this study are its low level of evidence (LoE III), the lack of a comparison group and missing data on the improvement of BS (gain in BS) after the cervical ripening period, the mean number of rods used, and some perinatal outcome parameters as well as the inadequate statistical power with regard to method-related complications (e.g. rate of uterine hyperstimulation or infectious morbidity).

In a prospective multicenter international observational study including 444 pregnant women with ≥ 37 + 0 to 42 weeks of gestation Dilapan-S (n = 276) and Dilasoft (n = 168) were used for cervical ripening/induction of labor in patients with an unripe cervix (BS 2.9 ± 1.2) [10]. Up to 5 rods were placed and they were removed after 12 or 24 hours. After cervical ripening with Dilapan-S, labor induction was carried out mostly with PGE_1- and PGE_2- compounds (not specified) or oxytocin intravenously with or without artificial rupture of membranes.

The primary outcome criteria were the duration of Dilapan-S insertion (hours), total induction-delivery interval and the rate of vaginal delivery within 24 hours. The results are shown in ▶ **Table 1**.

The mean vaginal delivery rate was significantly higher (76.6 vs. 64.8%; p = 0.0077), when Dilapan-S was inserted for < 12 hours. Spontaneous labors (no induction agent needed) after cervical ripening with Dilapan-S occurred in 10.1% of women.

The mean number of dilators used was 3.8 (± 1.2) and the mean gain in BS was 3.6 being approximately 6.5 (± 2.8) after extraction of Dilapan. In total, 3.4% of women experienced non-

serious complications such as bleeding during device insertion/ removal (2.7%), cramping or pain (0.2%) and other not specified (0.4%); 2% had spontaneous dilator expulsions. The rate of uterine hyperstimulation was 0.2%.

Maternal infections were observed in 3.2% of patients, which to the authors' opinion were not attributed to the effects of Dilapan-S.

This is the largest cohort study evaluating the efficacy of Dilapan-S/Dilasoft as a ripening agent prior to induction of labor. The limitations of this study are the moderate level of evidence (LoE IIb), the lack of a comparison group, the great variability of labor induction methods following the use of Dilapan-S/Dilasoft possibly influencing outcomes.

It is to be regretted that the study includes no analysis on patient's satisfaction with the use of Dilapan.

A secondary analysis of this international multicenter study was conducted [29] evaluating the determinants of vaginal delivery and safety in women undergoing cervical ripening with Dilapan-S prior to induction of labor.

Most of the results presented in this paper have already been reported in the previous publication of the same group [10]. It has been shown that vaginal delivery rates were significantly correlated with Bishop Scores of pre Dilapan-S, post Dilapan-S and difference (Spearman's coefficient, 0.82, 0.86 and 0.7 respectively; p < 0.05). In the multivariate analysis prior vaginal delivery and post Dilapan-S Bishop Scores were identified as strong predictors of vaginal delivery.

Comparison of cervical ripening with Dilapan-S versus balloon catheters

A retrospective, observational study from Japan [22] including a total of 17363 nulliparous women compared the efficacy and safety of four mechanical methods (synthetic osmotic dilators n = 4350, balloon catheter with a filling volume < 40 ml n = 4103, balloon catheter with a filling volume ≥ 40 ml n = 6618, overlapping groups = combination of methods n = 1990) for cervical ripening/induction of labor near term. The primary outcome was the rate of vaginal delivery. The results of the study are shown in ▶ **Table 1**. The perinatal outcome (Apgar Score, umbilical artery pH) was significantly better in the dilator group.

The study has several limitations: the low level of evidence (LoE III) and the lack of data on the kind of devices used, their time left in place, the pre- and post-Bishop scores, induction-to-delivery-intervals, the mode of labor induction (oxytocin?, PGs?), the rates of uterine hyperstimulation or other complications associated with the use of the devices and on infectious morbidity.

The objective of a single-center, randomized, open-label trial was to test the hypothesis that Dilapan-S is not inferior to the Foley catheter for pre-induction cervical ripening at term [23]; 419 women with an unfavorable cervix (BS < 6) were randomized; 209 to Foley balloon (filling volume 60 ml, time left in place at least 12 hours), and 210 to Dilapan-S (time left in place 12 hours but no longer than 24 hours). As many rods as possible were inserted into the cervical canal.

In both groups, second round of dilators/balloon catheters were used, if the cervix remained still unfavorable (BS < 6).

▶ **Table 1** Dilapan-S for cervical ripening/induction of labor: studies 2015–2022.

Author/year	n	study	comparing group	primary outcomes	results
Maier JT 2015 [21]	83	observational	–	rate of vaginal delivery	65% (parous: 82.6%)
Gupta JK 2018 [10]	444	multicenter observational	–	duration of Dilapan insertion total insertion–delivery rate of vaginal delivery/24 hours	25.4 ± 4.5 h 24.2 h < 12 h in place 39.1 h > 12 h in place 46% (total 69.8%)
Shindo R 2017 [22]	17363	retrospective observational	balloon < 40 ml balloon ≥ 40 ml	rate of vaginal delivery	cervical dilators: 74.6% balloon < 40 ml: 72.3% [NS] balloon ≥ 40 ml: 73.8%
Saad AF 2019 [23]	419	RCT	Foley balloon (60 ml, 12 h)	rate of vaginal delivery	Dilapan-S: 81.3% Foley balloon: 76.1% [NS] higher maternal satisfaction with Dilapan-S
Baev OR 2019 [24]	127	prospective	Dilapan + pretreatment of 200 µg oral mifepristone	rate of vaginal delivery (total/24 h)	Dilapan-S: 60.3% (43.1%/24 h) Mifepristone/Dilapan-S: 76.8% (73.9%/24 h) [p < 0.045]
Pekarev OG 2020 [25]	200	prospective	Dilapan + mifepristone Foley balloon (12 h) intracervical PGE$_2$ (0.5 mg)	improvement in BS (mean)	Dilapan-S + mifepristone: 11.4 [S] Dilapan-S: 10.2 Foley balloon: 9.4 PGE$_2$: 9.7
Crosby DA 2018 [26]	52	prospective observational	10 mg PGE$_2$ vaginal pessary	maternal neonatal infections uterine hyperstimulation perinatal outcomes	15.4 vs. 15.4% 0 vs. 0% no significant differences
Gupta JK 2022 [27]	674	RCT	10 mg PGE$_2$ vaginal pessary	failure to achieve vaginal delivery	Dilapan-S: 37.4% PGE$_2$ vaginal pessary: 34.3% ▪ complications (e.g. uterine hyperstimulation): Dilapan-S: 7.6% PGE$_2$ vaginal pessary: 22.6% ▪ better maternal satisfaction with Dilapan-S
Gavara R 2022 [28]	303	RCT	oral misoprostol (25 µg every 2 h)	Rate of vaginal delivery within 36 hours	Dilapan-S: 61.6% oral misoprostol: 59% ▪ uterine tachysystole: 23.3 vs. 46.4% p = 0.01 ▪ better sleep, lower pain score with Dilapan-S (p < 0.05)

h = hours; NS = nonsignificant; RCT = randomized controlled trial; S = significant

In cases of a favorable cervix, intravenous oxytocin was started up to a maximal dose of 30 mU/min.

The primary outcome of the study was the rate of vaginal delivery, which was 81.3% in the Dilapan- and 76.1% in the balloon catheter-group (p = 0.197) indicating noninferiority for the prespecified margin (10%).

Secondary outcomes (e.g. changes in BS, induction-to-delivery-interval, maternal and neonatal adverse events, hospital stay) were not significantly different between groups except for a longer time the device remained in place (Dilapan-S: 774 ± 295 min. vs. Foley balloon 666 ± 319 min, p = 0.005). The second round of application was needed in 13.1% with Dilapan-S and 9.8% in Foley balloon, respectively not statistically significant (NS). There were also no significant differences between Dilapan-S and Foley balloon in the frequency of vaginal bleeding (3.1 vs. 0.9%), cervical lacerations (1 vs. 0.5%), uterine hyperstimulation (0 vs. 0%) and maternal infectious morbidity (14.3 vs. 13.1%). Patients with Dilapan-S were significantly more satisfied than patients with Foley balloon as far as sleep (p = 0.01), relaxing time (p = 0.001) and performance of desired daily activities (p = 0.001).

This is still the largest RCT comparing the efficacy and safety of Dilapan-S versus Foley balloon catheter for pre-induction cervical ripening at term (LoE Ib).

A potential selection bias cannot be excluded, however, given the nature of intervention, randomization was not an option.

Minor limitations of this study are the lack of data on the number of patients requiring oxytocin for labor induction/augmentation, the rate of dilator/balloon catheter expulsions, the frequency of pain/discomfort at insertion/removal of the devices and costs associated with both methods.

A prospective open-label study included 200 pregnant women at term with a BS between 0–6 points (mean 3.5) eligible for labor pre-induction [25]. Cervical ripening was performed with four different methods:

1. Dilapan-S combined with two doses of oral mifepristone (200 mg each) 24 h apart (n = 50)
2. Dilapan-S (4 rods) only for 12 hours (n = 50)
3. Foley catheter for 12 hours (n = 50) and
4. two doses of intracervical PGE_2 gel (0.5 mg each) 6 h apart.

Cervical maturation was assessed using the BS and the ultrasound cervicometry with the color mapping and calculation of strain ratio (SR) before the start of pre-induction and 12 hours after.

The primary outcome of the study was the change in BS and sonoelastographic cervical maturation after the intervention. The results are shown in ▶ Table 1.

This corresponded to the sonoelastographic SR values, which were lowest among the patients receiving the combination of Dilapan-S and mifepristone and highest among the patients receiving intracervical gel.

Further details on cervical sonoelastographic findings are presented in the paper.

This is the first prospective study evaluating cervical ripening with different mechanical and pharmacological methods by using the BS and ultrasound cervicometry with the color mapping.

The authors concluded that cervical sonoelastography allows an objective assessment of cervical maturation, specifically the degree of softening after pre-induction which is a strong predictor of labor induction success. It should be noted that mifepristone is contraindicated for induction of labor in the third trimester in women with a viable fetus.

Comparison of cervical ripening with Dilapan-S and Prostaglandin E$_2$/misoprostol

In a single-center prospective observational pilot study 52 low-risk nulliparous women with an unfavorable cervix (BS ≤ 6) and post-date pregnancy (≥ 41 weeks gestation) received either Dilapan-S (n = 26, 1–5 rods, left in place for up to 24 hours) or the 10 mg PGE_2 vaginal pessary (n = 26, left in place for up to 24 hours) [26].

If the cervix was still unfavorable after intervention, up to two intracervical applications of PGE_2 gel were used in both groups for further induction.

The primary outcome measures were compliance with study protocol, maternal infection, rate of uterine hyperstimulation and perinatal/neonatal outcomes.

Compliance to study protocol was 25/26 (96%); it was possible to insert Dilapan-S in all but one woman.

There were no significant differences between the groups regarding primary outcomes (▶ Table 1). The mean change in BS was comparable (3.3 vs 3.7) as well as the rate of vaginal delivery/ 24 h (19.2 vs 15.4%, NS). Dilapan was left in place longer than the PGE_2 vaginal pessary (22.8 vs. 17.3 h, p = 0.005). The mean number of rods used was 2.6 (range 1–4), and the mean pain score out of ten at Dilapan-S insertion was 2.2 (range 0–7).

The limitations of this otherwise well-designed pilot study are the low level of evidence (LoE III), the lack of randomization and the insufficient number of pregnant women included in the study, which resulted in an inadequate statistical power for some primary outcome criteria (e.g. rate of uterine hyperstimulation, maternal and neonatal infection).

The aim of an open-label randomized trial including 674 women ≥ 37 + 0 weeks' gestation, was to compare the efficacy, maternal and neonatal safety, and maternal satisfaction of Dilapan-S (n = 337) to 10 mg PGE_2 vaginal insert (n = 337) for induction of labor [27]. The proportion of nulliparous women was rather high (79.7% in Dilapan-S group and 80.7% in PGE_2 group).

Up to five rods were inserted into the cervical canal and left in place for a minimum of 12 hours and up to a maximum of 24 hours. If the cervix remained unfavorable after first round (BS < 6), a second (then third) round of dilators were planned for an additional 12 to 24 hours. The PGE_2 vaginal insert remained in place for up to 24–32 hours.

If spontaneous labor had not started, amniotomy was conducted after the BS was > 6, followed by intravenous oxytocin according to the hospital protocols.

The most common indications for induction of labor were post-term pregnancy, fetal growth restriction (FGR) and reduced fetal movements.

The primary outcome was failure to achieve vaginal delivery within 36 hours after randomization (i.e. cesarean delivery being performed), which occurred in 37.4% of patients allocated to Dilapan-S and 34.3% of patients allocated to the PGE_2 vaginal pessary (adjusted risk difference: 0.02; 95% CI 0.05 to 0.10). Analgesia during cervical ripening was significantly more often required in women receiving PGE_2 compared to women with Dilapan-S (66.3 vs. 51.2%, p < 0.0001), and the rate of complications was higher with vaginal PGE_2 (22.6%) than with Dilapan-S (7.6%); e.g. uterine tachysystole: 5.0 vs. 0.4%, uterine hyperstimulation with non-reassuring/abnormal fetal heart rate (FHR): 4.3% vs. 0.

There was also a higher need for reinsertion of vaginal PGE_2 by approximately 10%.

Amniotomy undertaken for induction of labor was significantly more frequently needed in the Dilapan-S group (70.2 vs. 42.6%, p < 0.0001) as well as oxytocin required for induction of labor compared to the PGE_2 group (62.7 vs. 39.3%; p < 0.0001). There was no evidence of any difference in neonatal outcomes between the groups. Using a questionnaire consisting of 23 questions maternal satisfaction during the cervical ripening process was better with the use of Dilapan-S compared to the PGE_2 vaginal pessary.

This is the only randomized trial comparing Dilapan-S to vaginally applied PGE_2 [LoE 1b].

To achieve adequate statistical power regarding the primary outcome a total of 410 participants per group was needed; however, final recruitment had to be interrupted because of the impact of the COVID-19 pandemic (unavailability of research midwives).

Although from the investigator's point of view the original primary outcome of failure to deliver vaginally within 36 hours after randomization appears reasonable, it may be somewhat arbitrary, since Cochrane Collaboration Reviews and the National Institute for Health and Care Excellence (NICE) propose the vaginal birth rate within 24 hours of the start of induction of labor as the clinically most relevant measure. The abandonment of assessing a

pre-induction BS may be debatable since an unripe cervix (BS < 6) is a common inclusion criterion in most such comparative studies.

Induction of labor by using vaginal PGE$_2$ in women with FGR (below which centile not specified) or with reduced fetal movements (based on patient's information? or verified by CTG?) may raise concern, particularly, if there is no information on fetal Doppler sonographic findings presented.

It should be considered that a significant proportion of small fetuses close or at term is affected by placental insufficiency thus being at higher risk of decompensation during labor especially once exposed to uterine hyperstimulation [30].

A limitation of this study is that more women in the Dilapan-S groups did not receive the allocated intervention (25–50%) compared with the PGE$_2$ group (11%) because of the initial lack of available trained staff to fit in Dilapan-S rods.

The authors stated that despite of this difference in adherence levels between the groups, sensitivity analyses suggest that conclusions remain robust when excluding women not adherent to the intervention.

In an open-label, noninferiority randomized trial including 303 pregnant women ≥ 37 + 0 weeks of gestation with Bishop score < 6 mechanical cervical dilatation by using Dilapan-S was compared to 25 μg misoprostol orally every 2 hours (up to six doses) for induction of labor [28].

After 12 hours of cervical ripening, oxytocin was initiated with a maximum dose limited to 40 mU/min and amniotomy was performed as soon as clinically feasible.

The most common indication for induction of labor was post-term pregnancy, followed by elective induction.

The primary outcome was the rate of vaginal delivery within 36 hours of the study intervention: 61.6% of patients achieved vaginal delivery within 36 hours of initiation of study intervention in the Dilapan-S group versus 59.2% in the misoprostol group, with an absolute difference of 2.4% (95% CI; 9% to 13%), indicating noninferiority for the prespecified margin of 10%. There were no significant differences between groups in secondary outcomes such as median change in BS (2 vs. 3), vaginal delivery rate (72.8 vs. 72.3%), duration from initiation of cervical ripening to vaginal delivery (24.9 ± 8.98 vs. 25.8 ± 16.19 hours), intrapartum maternal fever (8.9 vs. 11.2%) and neonatal outcomes.

Uterine tachysystole during clinical ripening occurred in 53.6% of patients receiving oral misoprostol, which was significantly more frequent than the 25.7% in the Dilapan-S group (p < 0.01). Failure to place Dilapan-S was found in 2.6% of women. Patients who received Dilapan-S reported lower pain scores (p = 0.02), had less abdominal discomfort (p = 0.04) and were able to sleep more (p = 0.03) during cervical ripening compared to patients receiving misoprostol.

This is so far the only randomized trial comparing the use of Dilapan-S with orally applied misoprostol for induction of labor near term (LoE Ib).

One limitation of the study was the inability to blind the participants and investigators owing to the nature of the intervention, however, the likelihood of selection bias is low because the outcomes were prespecified and not affected by subjective interpretation. Another limitation is that the study had inadequate statistical power to detect the differences in secondary outcomes and rare events. The primary outcome criterion may be worthy of discussion similar to the primary outcome in the SOLVE trial [27], as discussed above.

In addition, there is a lack of data on the BS before the intervention, the number of cervical dilators required for cervical ripening, the rate of complications associated with the insertion/ removal of Dilapan-S (e.g. cervical injury, bleeding), and the number of patients requiring oxytocin in each group and on costs. The authors themselves acknowledged that unique differences in each intervention's labor-management protocols could have affected the outcomes.

Discussion

Mechanical methods have shown to be an attractive alternative to prostaglandins for cervical ripening/induction of labor at term.

According to a recent Cochrane Review mechanical induction using balloon catheters is as effective as induction of labor using vaginally applied PGE$_2$ but is associated with a more favorable safety profile [31], however, there was not enough research on other mechanical methods such as osmotic dilators to reach a robust conclusion [31, 32].

Truly, among mechanical methods for cervical ripening Foley balloon has been the gold standard method for decades. In recent years, a paradigm shift has become obvious from the perspective of labor induction. While so far most studies and Cochrane Reviews used the criterion of delivery within 24 hours to assess the effectiveness of labor induction, this view is being challenged as it has been increasingly recognized that achieving a safe vaginal birth is more important than timescale alone [10].

This point of view has led to a renaissance of mechanical methods including balloon catheters and synthetic osmotic cervical dilators for labor induction.

Efficacy and safety

In 2015 Dilapan-S was approved by the FDA for cervical ripening in the third trimester. Since then, numerous clinical trials and RCTs have confirmed that Dilapan-S is a safe, efficient and cost-effective method for cervical ripening/induction of labor associated with high maternal satisfaction [23, 27, 28]. Depending on the definition of outcome criteria the rate of vaginal delivery ranges from 61.6 to 81.3% [27, 28].

In the largest RCT there were no significant differences in the rate of vaginal delivery between Dilapan-S (81.3%) versus Foley catheter (76.1%), however, patients with Dilapan-S were more satisfied than patients with the Foley balloon [23].

The advantages of Dilapan-S over Foley balloon catheter are the approval by national authorities (e.g. FDA), no protrusion from the introitus, no need to keep under tension, higher patient's satisfaction and the less invasiveness of method, since Dilapan-S is strictly placed into the cervical canal, while the Foley balloon has to be applied extraamniotically.

A further advantage of Dilapan-S compared to Foley balloon is, that it is only contraindicated in patients with the presence of clinically apparent genital tract infection, while the commercially available and approved double-balloon catheter has several contraindications (e.g. patients receiving or planning to undergo exogenous

PG administration, prior hysterotomy, ruptured membranes, maternal heart disease). In contrast to the double-balloon catheter, Dilapan-S is not contraindicated in patients with a previous cesarean section when considering the manufacturer's product information.

The beneficial cervical softening effect with the use of Dilapan-S has also to be experimentally verified by cervical sono-elastographic findings [25].

Two open-label randomized trials compared the efficacy and safety of Dilapan-S with those of a 10 mg PGE$_2$ vaginal insert [27] and the oral administration of 25 μg misoprostol every 2 hours [28].

Both RCTs came to the conclusion that Dilapan-S is as effective as vaginal PGE$_2$ and oral misoprostol, respectively, in achieving vaginal delivery, however, the rate of complications, in particular, uterine hyperstimulations with and without non-reassuring FHR, was significantly higher using PGE$_2$ and misoprostol.

An increasingly important issue associated with labor induction is maternal satisfaction, which has shown to be significantly better when using Dilapan-S compared to PGE$_2$/misoprostol [27, 28].

Other studies have found that Dilapan-S was as effective as extraamniotic saline infusion and oral misoprostol in nulliparous women with an unripe cervix at term [33], and that the combination of Dilapan-S and mifepristone led to a significancy higher rate of vaginal deliveries compared to the use of Dilapan-S alone (76.8 vs. 60.3, p = 0.045) [24]. However, mifepristone is contraindicated in women with induction of labor in the third trimester and a viable fetus.

As highlighted by Gupta et al. [27] Dilapan-S would be a benefit in women with intrauterine growth restriction and reduced fetal reserve, as it is associated with a low risk of uterine hyperstimulation.

According to a recent meta-analysis there is limited evidence on the optimal type of labor induction in pregnancies with small fetuses, but it was pointed out that mechanical methods seem to be associated with a lower occurrence of adverse intrapartum outcomes [30].

In pregnancies complicated by a small fetus, the choice of the optimal method to induction labor should be guided by the need to reduce the risk of adverse events related to hypoxemia, rather than of achieving delivery in the shortest period of time [27]. Hence, Dilapan-S may be an appropriate option for labor induction in these patients.

The adequate use of Dilapan-S requires passing a 'learning curve' on how to insert the rods into the cervical canal the proper way. According to the IFU and published studies [10, 23, 27] as many rods as possible (usually 4–5) should be placed in the cervical canal and it should be ensured that the tip of the rod slightly passes the internal os.

Failed insertion might be a problem: only two studies reported on failed insertion in 2.6% and 3.8% of cases, respectively [26, 28].

Expulsion of rods might be another concern; in the multi-center study by Gupta et al. [10] spontaneous dilator expulsion occurred in 2% of cases, while others did not report on this problem. Retention of whole or fragmented products or fragmentation of rods

were complications with an earlier version of Dilapan [9], but not recorded with Dilapan-S when considering studies since 2015.

There are no reliable data on maternal infectious mortality associated with the use of Dilapan-S, however, recent studies have shown that maternal infection rates are not higher when compared to the use of Foley catheter [23], the PGE$_2$ vaginal insert [27] or oral misoprostol [28].

Cost-effectiveness

Outpatient cervical ripening with a balloon catheter or synthetic osmotic cervical dilators has become increasingly important, particularly in the context of COVID-19 pandemic.

A recent randomized clinical trial comparing outpatient with inpatient pre-induction cervical ripening using a synthetic osmotic dilator has shown that outpatient cervical ripening decreased hospital stay and time from administration to active labor without significant adverse outcomes [34].

According to a US cost consequence analysis outpatient cervical ripening with a synthetic osmotic cervical dilator has the potential to reduce hospital costs, hospital stay, and the cesarean section rate when compared to inpatients using the vaginal PGE$_2$ insert or the single balloon catheter [35]. A further UK cost-consequence model by the same group [36] comparing Dilapan-S with vaginal PGE$_2$ inserts (Propess) for inpatient induction of labor indicated that adoption of Dilapan-S is likely to be cost-neutral and reduces staff workload in comparison to Propess.

A retrospective analysis comparing cervical ripening with Dilapan-S in an outpatient procedure with the use of oral misoprostol or vaginal PGE$_2$ gel in an inpatient setting has shown that cervical ripening with Dilapan-S resulted in a significant reduction of time period from patient admission to the onset of labor, shorter inpatient stay from admission to delivery and fewer hospital days in the outpatient group thus decreasing socioeconomic costs [37].

Guidelines

The use of synthetic osmotic cervical dilators is inadequately represented in current guideline recommendations, which is probably due to the amount of available evidence-based data.

Only the most recent NICE guideline 2021 [38] states that for women with a BS of 6 or less mechanical methods to induce labor (balloon catheter or osmotic cervical dilators) should be considered if pharmacological methods are not suitable (e.g. in women with a higher risk of, or from hyperstimulation or those who have had a previous cesarean section) acknowledging that mechanical methods are less likely to cause hyperstimulation than pharmacological methods.

The German AWMF Guideline 015/088 [39] states that synthetic osmotic cervical dilators are a safe method for induction of labor in patients with an unripe cervix and are also safe in patients with a previous cesarean section.

The recent ACOG Practice Bulletin No. 205 'Vaginal Birth after Cesarean Delivery' 2019 [40] mentioned only the Foley catheter as an option for labor induction after a previous cesarean section, but did not report on synthetic osmotic cervical dilators.

This may be due to the fact that there exist only two prospective observational studies comparing Dilapan-S with vaginal PGE$_2$

for cervical ripening/induction of labor in women with a previous cesarean section [41, 42].

Both studies are from the same working group and it is not yet possible to make evidence-based recommendations based solely on these studies.

Overall, available evidence seems promising, but more well-designed, prospective, and preferably randomized studies are needed such as comparing the use of balloon catheters vs. synthetic osmotic cervical dilators for pre-induction cervical ripening in outpatient settings and in women with previous cesarean section, as well as investigating the efficacy and safety of Dilapan-S in patients with late fetal growth restriction affected by placental insufficiency.

Conclusion

The use of synthetic osmotic dilators (Dilapan-S) is an effective and safe method for pre-induction cervical ripening and not contraindicated for induction of labor in women with a previous cearean section. Dilapan-S is equally effective as Foley balloon catheter, the 10 mg PGE_2 vaginal insert and orally applied misoprostol in achieving vaginal delivery and has shown a better safety profile and higher patient's satisfaction. Hence, synthetic osmotic dilators are a suitable method for outpatient cervical ripening reducing hospital costs, hospital stay and staff-workload when compared to the use of vaginal PGE_2 in an inpatient setting. Potential problems associated with its use may be failed insertion and expulsion of the rods. The adequate use of Dilapan-S needs passing a 'learning curve' on how to insert the rods into the cervical canal the proper way. Compared to PGE_2/misoprostol additional administration of intravenous oxytocin is required more often to induce/augment labor. The use of synthetic osmotic dilators is inadequately represented in current guideline recommendations, which is probably due to the lack of available evidence-based data. The goal of future randomized controlled studies should be to compare Dilapan-S with balloon catheters for pre-induction cervical ripening in an outpatient setting and to evaluate its efficacy and safety for induction of labor after previous cesarean section in adequate statistically powered studies.

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Conflict of Interest

Patrick Stelzl has a part-time job agreement as consultant and speaker and is member of the Steering Committee in concerns of the LION ("Labour Induction Outcomes Network") project for Angusta 25 µg tablets from Norgine Pharma GmbH. The other authors declare that they have no conflict of interest.

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