Dilapan-S vs standard methods for cervical ripening in term pregnancies: an individual patient data meta-analysis

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OBJECTIVES: Dilapan-S is a cervical ripening agent approved by the FDA that has been found to be just as effective as other agents and can be utilized for outpatient ripening. No large-scale studies have been conducted to compare cesarean delivery rates between Dilapan-S and other ripening methods. Our objective was to combine these trials to compare cesarean delivery rates for Dilapan-S with other cervical ripening methods, overall and in sub-groups.

DATA SOURCES: The time period for this study was from January 1994 to April 2023. Ovid MEDLINE, Embase via Ovid, Ovid Emcare, CINAHL Plus, ClinicalTrials.gov, euclinicaltrialsregister.eu, and Scopus were searched. The study was conducted according to the Preferred Reporting Item for Systematic Reviews guidelines and was registered with PROSPERO (CRD42023423573).

STUDY ELIGIBILITY CRITERIA: This was a systematic review and meta-analysis of individual patient data from randomized controlled trials comparing Dilapan-S to other mechanical or pharmacologic cervical ripening methods for labor induction in singleton gestations. The main outcome measure assessed was the cesarean delivery (CD) rate in comparing Dilapan-S to alternative methods. Secondary maternal outcomes included changes in Bishop score postintervention, vaginal delivery without complications, postpartum hemorrhage, cervical ripening issues, uterine infection, and patient satisfaction. Secondary neonatal outcomes were Apgar score <7 at 5 minutes, arterial cord pH <7.1, meconium presence, NICU admission and length of stay, hypoxic-ischemic encephalopathy, intraventricular hemorrhage, infant infection, and infant death. This study exclusively included randomized controlled trials (RCTs) involving participants who underwent labor induction during the third trimester of a singleton pregnancy. At least one group within these trials received Dilapan-S for the purpose of cervical ripening. Trials were excluded if induction occurred prior to 37 weeks of gestation or if cervical ripening was deemed unnecessary.

STUDY APPRAISAL AND SYNTHESIS: Two reviewers independently selected studies, assessed the risk of bias using the Cochrane Risk of Bias Tool for RCTs, and extracted the data. Prespecified subgroup analysis was performed for parity, body mass index, Bishop score, and gestational age. Pooled odds ratios (ORs) adjusted for maternal age and parity with 95% confidence intervals (CI) were calculated using frequentist and Bayesian approaches.

RESULTS: Four RCTs were identified, with 1731 women included (1036 allocated to Dilapan-S; 695 to alternative cervical ripening methods). CD rates were 28% and 30% with Dilapan-S and other methods, respectively. There was no difference in maternal age and parity-adjusted CD rates between Dilapan-S and other methods (OR 1.03, 95% CI 0.8−1.3). Bayesian inference indicated a 95% probability of being noninferior (5% margin) and a 4.5% probability of being inferior to other methods. Subgroup analysis demonstrated significant interaction with parity with a 99% probability of lowering cesarean rates among multiparous women treated with Dilapan-S (RR 0.61, 95% CrI 0.4−0.9) compared to a 6% probability of benefit among nulliparous women (RR 1.13, 95% CrI 0.97−1.33). Pain levels ≥4 were significantly lower in the Dilapan-S group (46% vs 62%; OR 0.5, 95% CI 0.40−0.64). Complication rates during cervical ripening (uterine hypertonus, uterine tachysystole, nonreassuring fetal heart tracing, and others) were also lower in the Dilapan-S group (19% vs 47%; OR 0.28, 95% CI 0.28−0.37). Higher patient satisfaction was reported with Dilapan-S.

Introduction

In the United States, induction of labor is a common procedure, with a significant number of pregnant women requiring effective cervical ripening methods.[1−4] Synthetic osmotic dilators like Dilapan-S, approved by the FDA, have emerged as notable options among these methods. Recent studies[5−9] demonstrate that Dilapan-S is effective in cervical ripening and offers several advantages over traditional mechanical methods, such as the Foley balloon,

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Tweetable Statement: Dilapan-S is as effective as other ripening agents, lowering cesarean rates in multiparous women, with higher patient satisfaction and fewer complications.

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CONCLUSION: Dilapan-S was at least noninferior and marginally superior in lowering cesarean rates compared to other preinduction cervical ripening agents. Parity impacted efficacy, with multiparous women benefiting the most.

Key words: cervical ripening, cesarean delivery rates, Dilapan-S, labor induction, maternal complications, meta-analysis, patient satisfaction, randomized controlled trials, systematic review

AJOG MFM at a Glance

A. Why was this study conducted?

To compare the cesarean delivery (CD) rate of Dilapan-S to alternatives, evaluating its effectiveness, safety, and patient satisfaction against traditional cervical ripening methods for clinical decision-making in labor induction.

B. What are the key findings?

Dilapan-S is as effective as other methods, with reduced cesarean rates in multiparous women and higher patient satisfaction.

C. What does this add to what is known?

This is the first comprehensive meta-analysis using Individual Participant Data (IPD) to compare Dilapan-S with other methods, highlighting its effectiveness, lower cesarean rates in certain populations, and enhanced patient satisfaction.

and pharmacological agents like misoprostol. For instance, the DILAFOL trial found that Dilapan-S resulted in a higher rate of vaginal delivery (81.3%) compared to the Foley balloon (76.1%), while also providing better patient satisfaction due to less discomfort and fewer side effects.[8]

Moreover, in a large multicenter international observational study, Dilapan-S was associated with a high overall vaginal delivery rate of 76.6% within 12 hours of insertion, with low rates of maternal and neonatal complications.[6] Another randomized controlled trial (RCT) comparing Dilapan-S to oral misoprostol highlighted that Dilapan-S was noninferior in achieving vaginal delivery within 36 hours, with fewer instances of tachysystole and higher patient satisfaction.[5] Despite these findings, more research still needs to directly compare Dilapan-S with other widely used cervical ripening methods regarding their impact on cesarean delivery (CD) rates. Given the rising rates of labor induction,[10] particularly in cases of unfavorable cervixes, we sought to guide healthcare providers in selecting the most effective method for cervical ripening that maximizes comfort, minimizes side effects, and offers convenience in both application and duration of use, with the ultimate goal of improving maternal and neonatal outcomes.

This systematic review and individual patient data meta-analysis (IPD-MA) aims to fill this gap by systematically reviewing all randomized trials comparing these synthetic osmotic dilators to other cervical ripening methods. We focus mainly on CD rates, both overall and in specific subgroups. This is particularly relevant as achieving a favorable Bishop score after successful cervical ripening is an independent determinant factor for a successful vaginal delivery.

Methods

Data sources and search strategy

The study protocol for this MA was registered in PROSPERO. The reporting adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analyses of Individual Participant Data statement.[11] All included studies were granted individual ethical approval. Written informed consent was obtained from all patients. No additional ethical approval was obtained for this study as all data used were anonymized.

We conducted a search on April 2023 in Ovid Medline, CINAHL Plus, Scopus, ClinicalTrials.gov, and the EU Clinical Trials Register to identify RCTs The time period was from January 1994 to April 2023. Search terms were strategically chosen to encompass "Dilapan" or "Dilapan-S" in conjunction with "randomized trials," and the selection was narrowed down to English language publications within the specified year range. Additionally, the literature was thoroughly scanned for any significant references. This approach ensured a comprehensive and inclusive dataset for the MA. Two independent reviewers (AS and RG) conducted this search, and disagreements were resolved via discussion.

Study selection

This study included RCTs of participants undergoing labor induction in the third trimester of a singleton pregnancy. At least 1 group received Dilapan-S for cervical ripening. Trials were excluded if the induction occurred before 37 weeks of gestation or if cervical ripening was not required.

Data extraction

IPDs were requested from the primary authors of each trial selected for inclusion. All principal investigators from the included trials provided the necessary data for the analysis. Each PI shared deidentified patient-level data, which allowed us to perform the IPD analysis. The data used in this study are comprehensive and were supplied by all major contributors, ensuring consistency and accuracy in our analysis. Data accuracy was assured by replicating all results reported in the RCT publication, including baseline characteristics and outcome data. Discrepancies were communicated to primary authors, who could then respond to resolve or update the data.

Variables collected were determined through extensive consultation, ensuring comprehensive data on participant-level characteristics, including maternal age, race/ethnicity, body mass index

(BMI), parity, gestational age at delivery, baseline Bishop score, mode of delivery, and relevant maternal and neonatal outcomes. Methods were also established to standardize and translate variables across different IPD datasets to maintain consistency in scales and measurements.

Assessment of risk of bias

Two reviewers (AS, RG) evaluated the study quality and bias using the second version of the Cochrane risk-of-bias tool for randomized trials (RoB2).[12] A third reviewer (GS) was consulted to reach a consensus on any disagreements. The RoB2 tool divides its assessment into five key areas, determining the bias risk as either high, low, or uncertain. These areas include the process of randomization, discrepancies from planned interventions, the absence of outcome data, the accuracy of outcome measurement, and the impartiality in reporting outcomes. An overarching bias risk evaluation was carried out for every study involved. The findings were visually represented through the robvis package in R software.[13] Publication bias analysis was performed using Egger's test.[14]

Outcomes

The primary outcome was CD. Secondary maternal outcomes were a change in Bishop score from randomization to post-intervention, vaginal delivery without maternal or neonatal complications (vaginal delivery without any of: maternal site wound or uterine infection; infant death; infant hypoxic-ischemic encephalopathy; infant infection; meconium; infant intraventricular hemorrhage; Apgar score at 5 minutes<7), postpartum hemorrhage, cervical ripening complications (uterine hypertonus, uterine tachysystole, nonreassuring fetal heart tracing, gastrointestinal symptoms (diarrhea, nausea, vomiting), fever, spontaneous device expulsion, device entrapment or fragmentation, retraction into the uterine cavity, vaginal bleeding, cervical lacerations/injury, rupture of membranes, patient pain, allergic reactions, vasovagal reactions, hypotension, maternal tachycardia, and suspected chorioamnionitis), uterine infection, and patient satisfaction. Secondary neonatal outcomes were Apgar score at 5 minutes<7, arterial cord pH<7.1, meconium, NICU admission, NICU length of stay, hypoxic-ischemic encephalopathy, intraventricular hemorrhage, infant infection, and infant death.

Data synthesis

The primary analysis was based on a one-step MA using a Bayesian logistic hierarchical model with intervention (Dilapan-S vs control) as a covariate adjusting for maternal age and parity and including trial as a random intercept. The Bayesian framework allowed us to calculate posterior probabilities of noninferiority and superiority, providing intuitive estimates of the effectiveness of Dilapan-S compared to other methods. This approach helps account for variability across studies and gives a probabilistic interpretation of the results. Prespecified subgroup analyses for the primary outcome were performed for parity, BMI (<35, 35−40, >40 kg/m^2), Bishop score at insertion (≤5, >5), and gestational age (<39, ≥39 weeks), including an interaction term between intervention and parity with all other model components, the same as for the primary analysis. Relative risk, risk difference (RD), 95% credible intervals (CrI), and probability of noninferiority (RD being within a ± 5% margin of noninferiority) were calculated from the posterior distribution of the fitted logistic model. We used a neutral prior distribution centered at an odds ratio (OR) of 1.0 with 95% CrI of 0.25 to 4 (a normal distribution with a mean of 0 and standard deviation of 0.70) for all covariates in the model and half-normal (mean=0, standard deviation=0.80) for the random intercept. We report probability of noninferiority [Pr (−0.05<RD<0.05)] for the primary analysis and probability of benefit (decreased CD rate, ie, RR<1.0) for subgroup analyses comparing Dilapan-S to other methods.

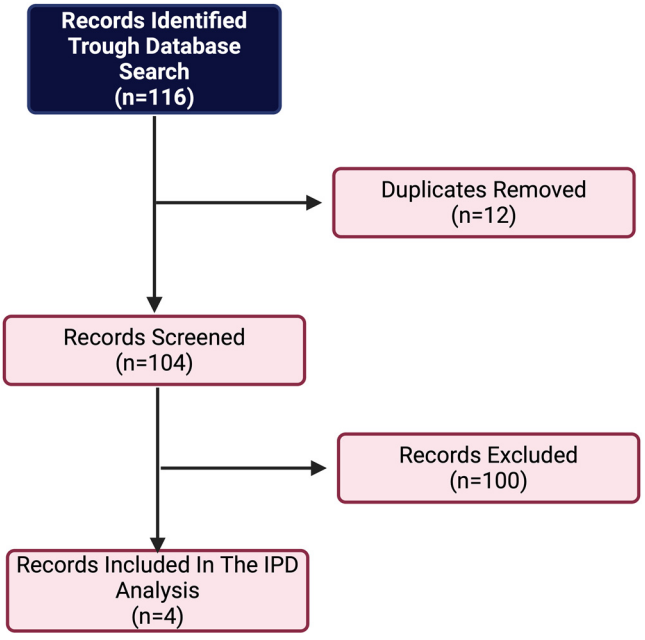
Secondary outcomes were analyzed using 1-stage frequentist hierarchical logistic or linear mixed models, including intervention, maternal age, and parity as fixed-effect covariates and trial as a random intercept. Pooled ORs (control as reference group) or Mean Difference (MD; Dilapan-S minus control) with 95% confidence intervals (CI) are reported. The degree of variability across the studies was examined using the I^2 statistic. All analyses were conducted in R software version 4.2.3 (R Foundation for Statistical Computing). We used the package "brms" to fit the Bayesian models using 3 Markov chain Monte Carlo chains of 10,000 iterations each. Convergence was checked via visual inspection of trace plots and Rhat metric for all parameters.

Results

Study selection and characteristics

Four RCTs were identified as eligible,[5,7–9] with 1731 women included (1036 allocated to Dilapan-S; 695 to alternative cervical ripening methods). All four randomized trials meeting the inclusion criteria were included and analyzed (Figure 1). The HOMECARE[7] trial fundamentally differed from the other included RCTs, in that both arms received Dilapan-S. The key difference in this trial was the setting for cervical ripening—inpatient vs outpatient—rather than a comparison with another cervical ripening method. In contrast, the other trials focused on comparing Dilapan-S with alternative methods: the Foley balloon catheter in the DILAFOL trial,[8] low-dose oral misoprostol in the COMRED trial,[5] and dinoprostone vaginal insert in the SOLVE trial.[9] In all these trials, cervical ripening was conducted in an inpatient setting, except for the outpatient arm in the HOMECARE trial. The primary authors provided us with deidentified databases, including all randomized patients. Table 1 describes the characteristics of the included trials, and supplemental Tables present descriptive data for each trial, including participant characteristics, cervical parameters, sample size, details of the intervention, and outcome definitions. The primary outcomes in each trial were vaginal delivery[5,8] (DILAFOL, COMRED), length of hospital stay[7] (HOMECARE), and CD [9]

FIGURE 1
Flow diagram of studies identified in the systematic review.



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(SOLVE). The latter was mainly performed in nulliparous women. The comparator or control alternative methods consisted of Foley balloon catheter[8] (DILAFOL), low-dose oral misoprostol[5] (COMRED), and dinoprostone vaginal insert[9] (SOLVE). Each of the four studies under consideration was reported to have conducted an intention-to-treat analysis. All authors have provided adequate descriptions of the randomization methods, and allocation concealment has been sufficiently addressed for each study. None of the studies could be conducted as double-blind trials due to the nature of the intervention. The selected outcomes for the total population and the prespecified subgroups are shown in Tables 2 to 5. All included studies had a low risk of bias (Figure 2). Egger's test did not indicate presence of publication bias.

Synthesis of results

CD rates were 28% vs 30% with Dilapan-S vs other methods, respectively. There was no difference in age and parity-adjusted analyses of CD rates between Dilapan-S and other methods (OR 1.04, 95% CrI 0.8−1.3). Bayesian analysis indicated a 95% probability of Dilapan-S being noninferior (5% margin) and a 4.5% probability of being inferior to other methods (Figure 3). Subgroup analysis (Figure 4) demonstrated significant interaction with parity with a 99% probability of lowering CD rates among multiparous women treated with Dilapan-S (RR 0.61, 95% CrI 0.42−0.88; Table 4) compared to a 6% probability of benefit among nulliparous women (RR 1.13, 95% CrI 0.97 −1.33). No other subgroups exhibited heterogeneity in the intervention effect (Figure 4).

Secondary maternal and neonatal outcomes (Tables 2 and 3) were similar between Dilapan-S and the control group (other methods), except for a longer time from insertion to delivery (adjusted mean difference 5.0, 95% CI, 2.5−7.6 hours; Figure 5) and a significantly lower rate of complications during ripening (19% vs 47%; OR 0.28, 95% CI, 0.28 −0.37) in Dilapan-S group compared to the control group (Table 2). Heterogeneity across studies ranged from low to high (I^2 of 0%−93%) in maternal outcomes and from low to moderate (I^2 of 0%−53%) in neonatal outcomes. Analysis for meconium and maternal hemorrhage requiring transfusion could not be performed because some studies contained zero counts.

Regarding patient satisfaction, while this outcome was assessed across multiple trials, the specific questions used to measure satisfaction, such as those detailed in Table 5, were universal across all studies. Dilapan-S group

TABLE 1
Characteristics of included studies

Study	Trial name	No. of participants	Intervention	Control	Recruitment period	Primary outcome
Saad et al[8]	DILAFOL	417	Dilapan-S	Foley balloon	2016−2018	Vaginal delivery
Gupta et al[9]	SOLVE	672	Dilapan-S	Dinoprostone vaginal insert	2017−2021	Cesarean delivery
Gavara et al[5]	COMRED	303	Dilapan-S	Oral misoprostol	2018−2021	Vaginal delivery within 36 h
Saad et al[7]	HOMECARE	339	Dilapan-S outpatient	Dilapan-S inpatient	2018−2021	Hospital stay longer than 48 h

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TABLE 2
Frequentist analysis of secondary maternal outcomes

Outcome	Dilapan-S, *N*=1036[a]	Control, *N*=695[a]	Effect estimate (95% CI)[b]	*P* value
Time from randomization to delivery, h	40.1 (29.9) [*N*=826.0]	46.8 (37.5) [*N*=486.0]	MD: 3.3 (−0.36, 6.9)	.08
Time from admission to delivery, h	24.4 (13.0) [*N*=699.0]	28.0 (11.8) [*N*=360.0]	MD: 1.2 (−0.44, 2.8)	.15
Time from randomization to discharge, d	3.3 (2.0) [*N*=826.0]	4.1 (2.7) [*N*=486.0]	MD: −0.05 (−0.30, 0.21)	.72
Time from admission to discharge, d	2.3 (0.9) [*N*=699.0]	2.5 (1.0) [*N*=359.0]	MD: 0.03 (−0.09, 0.15)	.58
Change in Bishop score	2.7 (2.2) [*N*=889.0]	3.1 (2.5) [*N*=541.0]	MD: −0.20 (−0.46, 0.06)	.13
Vaginal delivery without maternal or neonatal complications	673/1030 (65%)	433/685 (63%)	OR: 1.03 (0.82, 1.30)	.80
Vaginal delivery without maternal or neonatal complications (w/hemorrhage)	470/877 (54%)	236/544 (43%)	OR: 1.08 (0.82, 1.41)	.59
Complications[d] during ripening	198/1021 (19%)	299/633 (47%)	OR: 0.28 (0.21, 0.37)	<.001
Maternal hemorrhage[e]	153/827 (19%)	141/487 (29%)	OR: 0.97 (0.721, 1.31)	.84
Maternal hemorrhage requiring transfusion	5/827 (0.6%)	3/487 (0.6%)	[c]	
Uterine infection	86/1034 (8.3%)	43/693 (6.2%)	OR: 1.32 (0.85, 2.04)	.21

[a] Mean (SD) [*N*=*N*]; *n*/*N* (%).; [b] MD=mean difference (Dilapan-S minus control), OR=odds ratio (control is reference group), CI=confidence interval.; [c] Estimates could not be combined across studies because some studies had zero counts.; [d] Include: uterine hypertonus, uterine tachysystole, nonreassuring fetal heart tracing, gastrointestinal symptoms (diarrhea, nausea, vomiting), fever, spontaneous device expulsion, device entrapment or fragmentation, retraction into the uterine cavity, vaginal bleeding, cervical lacerations/injury, rupture of membranes, patient pain, allergic reactions, vasovagal reactions, hypotension, maternal tachycardia, and suspected chorioamnionitis.; [e] Defined: SOLVE: estimated blood loss (EBL) >500 mL; COMRED & HOMECARE: EBL>1000 mL; DILAFOL: not captured.

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showed significantly higher patient satisfaction during cervical ripening (Table 5). These standardized questionnaires generally assessed patient experiences during cervical ripening, with questions addressing the ability to walk, eat, shower, sleep, rest, and relax. Each question was scored on a 5-point Likert scale, ranging from "very dissatisfied" to "very satisfied," allowing for a consistent evaluation of satisfaction across different trials. In addition to the Likert scale, pain during cervical ripening was quantified using a visual analog scale, which captured patients' pain levels from "no pain" to "worst pain imaginable." These tools were administered both immediately after device placement and again after device extraction but before hospital discharge. 82% were able to walk, eat, and shower, compared to 63% in the control group (OR 1.96, 95% CI, 1.50−2.58). Additionally, 75% could sleep and rest (Dilapan-S), vs 51% in control (OR 2.19, 95% CI, 1.70−2.81). For relaxation, 72% in Dilapan-S vs 54% in control reported positive experiences (OR 2.22, 95% CI, 1.72−2.87). Compared to Dilapan-S, the control group experienced pain level ≥4, significantly higher while the drug/device was in place, 62% vs 46% (OR 0.5, 95% CI, 0.40−0.64), indicating a more comfortable and less painful patient experience using Dilapan-S (Table 5).

TABLE 3
Frequentist analysis of secondary neonatal outcomes

Outcome	Dilapan-S, *N*=1036[a]	Control, *N*=695[a]	Effect estimate (95% CI)[b]	*P* value
Admitted to NICU	84/1036 (8.1%)	66/695 (9.5%)	OR: 0.95 (0.66, 1.36)	.77
Infant death	0/1036 (0%)	1/694 (0.1%)		
Infant infection	35/1031 (3.4%)	45/690 (6.5%)	OR: 0.74 (0.46, 1.18)	.20
HIE	0/1036 (0%)	3/695 (0.4%)	[c]	
IVH	0/1036 (0%)	0/695 (0%)	[c]	
Meconium	31/1036 (3.0%)	4/694 (0.6%)	[c]	
Arterial pH<7.1	35/685 (5.1%)	40/461 (8.7%)	OR: 0.87 (0.53, 1.44)	.59
Apgar at 5 min<7	10/1032 (1.0%)	10/691 (1.4%)	OR: 0.76 (0.30, 1.91)	.56
NICU stay >48 h	51/1036 (4.9%)	39/694 (5.6%)	OR: 0.99 (0.63, 1.56)	.96
NICU length of stay, d	4.3 (7.2) [*N*=75.0]	3.7 (3.6) [*N*=57.0]	MD: −0.03 (−2.3, 2.2)	.98

[a] *n*/*N* (%); mean (SD) [*N*=*N*].; [b] OR=odds ratio (control is reference group), MD=mean difference (Dilapan-S minus control), CI=confidence interval.; [c] Estimates could not be combined across studies because some studies had zero counts.

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Comment

Principal findings

In our comprehensive MA, we identified several key findings regarding the use of Dilapan-S for cervical ripening. The data shows no significant difference in CD rates between Dilapan-S and other methods in the analysis. However, there is a 99% probability of reducing

TABLE 4
Bayesian subgroup analysis of cesarean delivery by parity comparing Dilapan-S to other methods

Outcome	Dilapan-S (*N*=1030) *n*/*N* (%)	Other methods (*N*=692) *n*/*N* (%)	Bayesian adjusted RR (95% CrI)	Bayesian posterior probability (%) of RR <1 with Dilapan-S
Cesarean delivery				
Multiparous	43/435 (9.9)	41/246 (17)	0.63 (0.43, 0.91)	99
Nulliparous	248/595 (42)	166/446 (37)	1.15 (0.99, 1.35)	4

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TABLE 5
Frequentist analysis of maternal satisfaction outcomes

Outcome	Dilapan-S, *N*=1036[a]	Control, *N*=695[a]	OR (95% CI)[b]	*P* value
During the cervical ripening process, I was able to walk, eat, and shower	711/872 (82%)	357/563 (63%)	1.96 (1.50, 2.58)	<.001
During the cervical ripening process, I was able to sleep and rest	655/872 (75%)	290/565 (51%)	2.19 (1.70, 2.81)	<.001
During the cervical ripening process, I was able to relax	387/537 (72%)	306/564 (54%)	2.22 (1.72, 2.87)	<.001
Pain level ≥4 while the drug/device was in place	397/870 (46%)	349/563 (62%)	0.50 (0.40, 0.64)	<.001

[a] *n*/*N* (%).; [b] OR=odds ratio (control is reference group).

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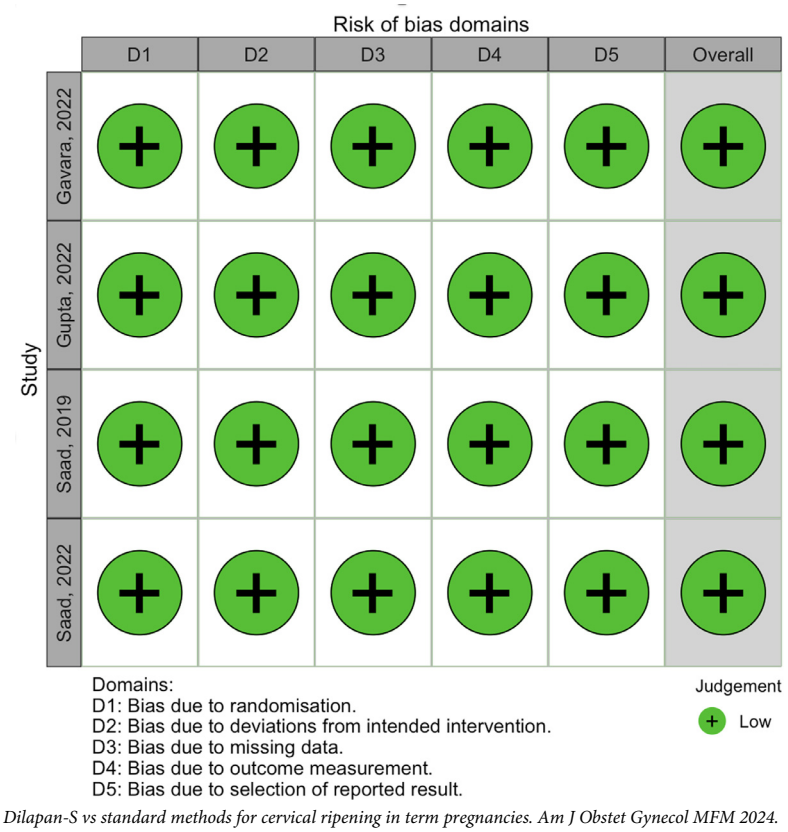
FIGURE 2
Study quality and bias using the Cochrane Risk-of-Bias tool for randomized trials (RoB2).



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CD rates among multiparous patients, thereby highlighting the potential benefits of Dilapan-S in such cases. Furthermore, Dilapan-S has an advantage in terms of lower complication rates during the ripening phase and higher patient satisfaction and comfort during the cervical ripening process. The data indicates that patients in the Dilapan-S group could engage in daily activities such as walking, eating, showering, sleeping, resting, and relaxing more comfortably and with lower pain levels than the control group.

Besides parity, none of the other subgroups demonstrated a notable heterogeneity in the intervention effect for CD. These findings reinforce the idea that Dilapan-S can be effectively used across a broad range of patient profiles, aside from the specific benefits seen in multiparous women.

Our findings suggest that Dilapan-S is at least as effective as other methods when considering all patients, but it also has a significant benefit in reducing CD rates in multiparous patients. While the exact mechanism behind this difference is not fully understood, several biological and clinical factors may explain it. Multiparous women generally have a more

FIGURE 3
Bayesian analysis of cesarean delivery.

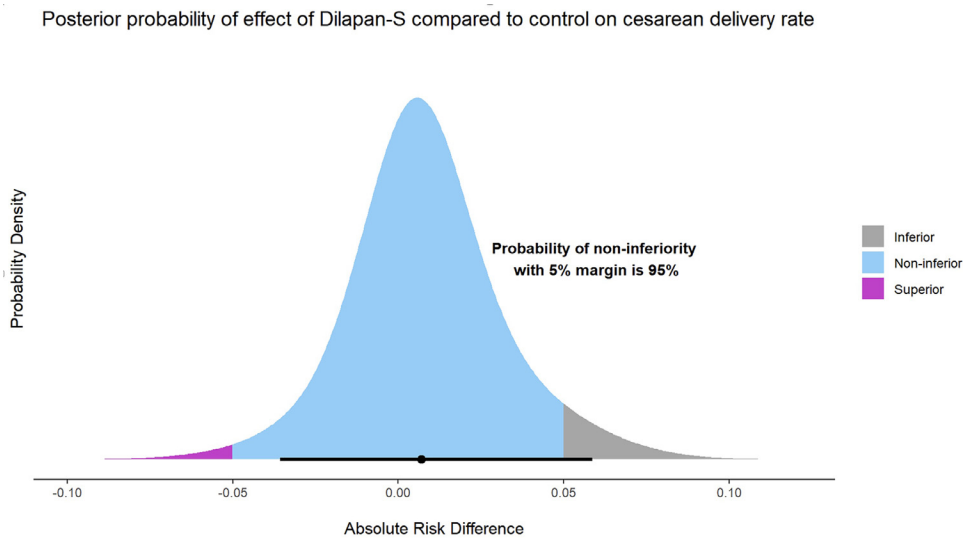

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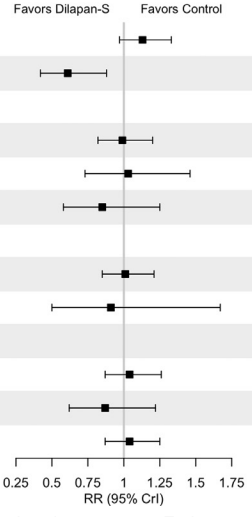
FIGURE 4
Bayesian subgroup analyses of cesarean delivery.

Subgroup	No. of events/total patients (%) Dilapan-S	Control	RR (95% CrI)	Probability of benefit*, %
Parity				
Nulliparous	43/435 (9.9)	41/246 (17)	1.13 (0.97,1.33)	6
Multiparous	248/595 (42)	166/446 (37)	0.61 (0.42,0.88)	99
BMI				
<35	202/752 (27)	151/535 (28)	0.99 (0.82,1.2)	53
35-40	51/168 (30)	35/113 (31)	1.03 (0.73,1.46)	44
>40	38/114 (33)	21/47 (45)	0.85 (0.58,1.25)	81
Bishop score at insertion				
<=5	274/946 (29)	188/616 (31)	1.01 (0.85,1.21)	43
>5	13/65 (20)	12/60 (20)	0.91 (0.5,1.67)	62
Gestational age				
>=39	241/836 (29)	157/528 (30)	1.04 (0.87,1.26)	34
<39	51/200 (26)	49/166 (30)	0.87 (0.62,1.22)	79
Overall	292/1036 (28)	207/695 (30)	1.04 (0.87,1.25)	34

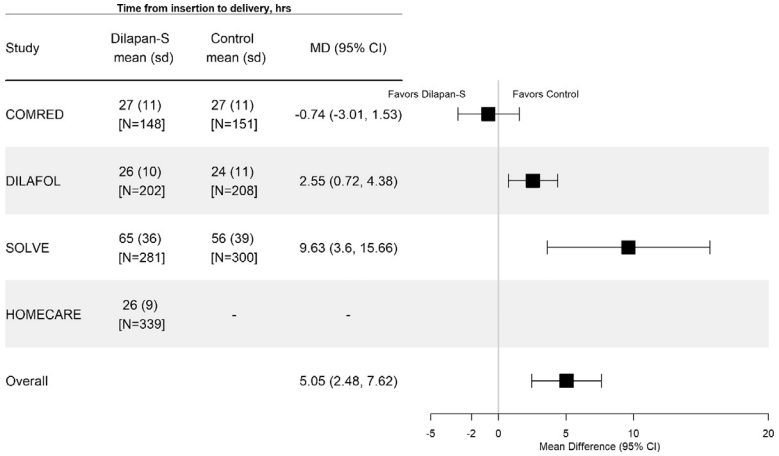


Relative risks for subgroups are defined by parity, BMI, Bishop score at insertion, and gestational age group. Estimates were derived from Bayesian logistic models, including intervention (Dilapan-S vs control), subgroup variable (one at a time), and their interaction as covariates adjusting for maternal age and study. *Probability of decreased cesarean delivery rate with Dilapan-S relative to control (relative risk <1).

Saad. Dilapan-S vs standard methods for cervical ripening in term pregnancies. Am J Obstet Gynecol MFM 2024.

favorable cervical environment for ripening, as prior deliveries may lead to increased cervical compliance and easier dilation. The presence of previous cervical stretching from prior pregnancies might make mechanical dilation with Dilapan-S more effective compared to nulliparous women, whose cervices are often less compliant. Dilapan-S also significantly improves the patient experience during labor induction. This is especially relevant in the current healthcare landscape, where patient comfort and satisfaction are increasingly recognized as crucial aspects of care quality.

FIGURE 5
Time from insertion to delivery in hours.



Saad. Dilapan-S vs standard methods for cervical ripening in term pregnancies. Am J Obstet Gynecol MFM 2024.

Comparison with existing literature

In the current literature, no other meta-analyses specifically compare the osmotic cervical dilator Dilapan-S to other cervical ripening methods. However, individual studies have shown that Dilapan-S is effective in cervical ripening and presents certain advantages over traditional mechanical methods, like the Foley balloon, and pharmacological agents such as misoprostol. For example, the DILAFOL[8] trial reported a higher rate of vaginal delivery with Dilapan-S (81.3%) compared to the Foley balloon (76.1%), alongside improved patient satisfaction due to reduced discomfort and fewer side effects. Additionally, a large multicenter international observational study found that Dilapan-S had a high overall vaginal delivery rate of 76.6% within 12 hours of insertion, with low maternal and neonatal complication rates.[6] Another RCT demonstrated that Dilapan-S was noninferior to oral misoprostol in achieving vaginal delivery within 36 hours, with fewer occurrences of tachysystole and greater patient satisfaction.[5]

A notable finding in our analysis is the longer time from insertion to delivery associated with Dilapan-S, particularly as highlighted by the SOLVE trial.[9] This extended time frame is driven largely by the data from SOLVE, where the total insertion-to-delivery time was more than that reported in other RCTs, both in the Dilapan-S and control arms. This discrepancy likely reflects fundamental differences in labor induction protocols between the UK, where the SOLVE trial was conducted, and the U.S. For instance, the SOLVE trial involved approximately 80% nulliparous women, and differences in patient management, labor augmentation practices, and patient populations could contribute to the longer times observed. In the U.K., practices such as the timing of artificial rupture of membranes (AROM), more conservative oxytocin usage, and different criteria for progressing to active labor may have extended the time from device insertion to delivery. In contrast, U.S. protocols typically involve more proactive use of oxytocin and earlier AROM to expedite labor progression. These variations in clinical practice likely contributed to the differences in time to delivery between the two regions, despite both arms receiving Dilapan-S.

The differences in induction protocols may lead some to question the relevance of SOLVE findings to U.S. practices. However, the longer delivery time observed in SOLVE may not significantly affect overall outcomes, suggesting that the safety and effectiveness of Dilapan-S remain intact despite timing differences.

Clinicians should consider these differences when interpreting the results, especially if applying the findings to their practice settings. Further research may be needed to evaluate similar timeframes in U.S.-based protocols and understand the implications for clinical practice in different regions.

Strengths and limitations

Our evidence strength primarily comes from IPD provided by the primary study authors. The IPD approach allows for more detailed and robust analyses, enhancing accuracy and reliability by assessing outcome variability and consistency across different studies and patient populations.

This MA represents the first comprehensive comparison of Dilapan-S with other cervical ripening methods. Previous studies on cervical ripening have often been limited by aggregate data, which can obscure important nuances such as patient characteristics and specific clinical contexts that influence outcomes. Additionally, earlier research has typically focused on single-center studies or smaller sample sizes, limiting the generalizability of their findings. By leveraging IPD, our analysis overcomes these limitations, providing a more detailed and accurate comparison across a broader spectrum of clinical scenarios.

The analysis will inform clinical practices and decision-making, providing a new perspective on labor induction strategies. It reinforces evidence for Dilapan-S and highlights the importance of comprehensive data in shaping clinical guidelines and improving patient outcomes.

It is important to acknowledge that, like any MA, this study has inherent limitations that must be considered. These include the constraints of the individual trials, potential publication bias, and heterogeneity among the studies analyzed. To mitigate the risk of publication bias, we considered the possibility of incorporating unpublished data. While including unpublished data could strengthen the analysis by providing a more comprehensive view of the available evidence, we chose not to pursue this approach due to its challenges. These challenges include difficulties verifying unpublished studies' quality and rigor, the potential for introducing bias

if unpublished data differ significantly from published findings, and the logistical challenges of obtaining and standardizing such data. Consequently, the decision not to include unpublished data may be seen as a limitation. Still, it also maintains the integrity and reliability of our MA by focusing on peer-reviewed, published studies.

Additionally, while Bayesian analysis offers a flexible and probabilistic framework for estimating the effectiveness of interventions, it comes with certain limitations. Specifically, the conclusions drawn from Bayesian models are dependent on the priors selected, and alternative priors could potentially influence the results. Here we used a neutral prior centered at an OR of 1.0 (95% CrI: 0.25 −4.0). This prior assumes a 50 to 50 a priori likelihood of Dilapan-S decreasing CD rates compared to other methods indicating equipoise. Bayesian analyses provide probabilities of an outcome (such as the likelihood of noninferiority) rather than definitive answers. Therefore, the results should be interpreted as conditional probabilities, rather than absolute truths. This probabilistic interpretation is a strength in terms of clinical decision-making but introduces a degree of uncertainty that must be acknowledged.

Another significant limitation of this study is that only one of the included trials compared Dilapan-S to another mechanical ripening method. This restricts the breadth of our comparisons and underscores the need for further research in this area. The decision to utilize CD rates as an outcome measure is based on the robust correlation between successful cervical ripening and the likelihood of achieving a vaginal delivery. A favorable Bishop score following ripening is a well-established prognosticator of successful vaginal delivery. By minimizing the need for cesarean sections, we can enhance maternal outcomes, reduce recovery times, and mitigate the risk of surgical complications.

Conclusion

To gain a better understanding of Dilapan-S, future research should prioritize studying multiparous patients to determine why it appears to provide greater benefits to this group compared to nulliparous women. Research could explore whether anatomical or physiological differences in multiparous patients contribute to the effectiveness of Dilapan-S, and investigate the long-term maternal and neonatal outcomes associated with Dilapan-S, especially in the outpatient setting. Future studies could use longitudinal cohort designs or RCTs to assess the effectiveness and safety of Dilapan-S in outpatient labor induction protocols.

The potential benefits of improving patient comfort during labor induction should be studied further. This could involve combining quantitative measures of patient outcomes with qualitative assessments of patient experiences to develop more comprehensive clinical guidelines that consider physical, psychological, and emotional aspects. This would be beneficial for both healthcare providers and patients in obstetrics.

Further studies should explore potential biological or mechanical factors to understand Dilapan-S's superiority in multiparous patients. This could include cervical tissue elasticity responses and the effects of previous vaginal deliveries on cervical readiness for induction, informing the development of more effective cervical ripening protocols. ■

CRediT authorship contribution statement

Antonio F. Saad: Writing − review & editing, Writing − original draft, Resources, Methodology, Data curation, Conceptualization. **Claudia Pedroza:** Visualization, Validation, Software, Project administration, Methodology, Formal analysis, Data curation. **Rachana Gavara:** Writing − review & editing, Project administration, Methodology, Conceptualization. **Janesh Gupta:** Writing − review & editing. **Ronald J. Wapner:** Writing − review & editing, Writing − original draft, Conceptualization. **George R. Saade:** Writing − review & editing, Writing − original draft, Project administration, Methodology, Conceptualization.

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