A randomized trial of synthetic osmotic cervical dilator for induction of labor vs dinoprostone vaginal insert

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BACKGROUND: Induction of labor is a commonly performed obstetrical intervention. Vaginal prostaglandin E2 (dinoprostone) is a first-choice agent. Mechanical methods of induction are slower in achieving cervical ripening but have a lower risk of adverse effects.

OBJECTIVE: This study aimed to compare the efficacy, maternal and neonatal safety, and maternal satisfaction of a synthetic osmotic cervical dilator (Dilapan-S) with those of dinoprostone.

STUDY DESIGN: This was an open-label superiority randomized controlled trial in 4 English hospitals. Eligible participants were women ≥16 years of age undergoing induction of labor for a singleton pregnancy at ≥37 weeks' gestation with vertex presentation and intact membranes. The women were randomly assigned to receive either Dilapan-S or dinoprostone using a telephone randomization system minimized by hospital, parity, body mass index, and maternal age. The induction agent was replaced as required until the cervix was assessed as favorable for labor by the Bishop score. The primary outcome was failure to achieve vaginal delivery (ieor a cesarean delivery being performed). The secondary outcome measures included maternal and neonatal adverse events. Analysis was by intention-to-treat, adjusting for design variables where possible.

RESULTS: Between December 19, 2017 and January 26, 2021, 674 women were randomized (337 to Dilapan-S, and 337 to dinoprostone). The trial did not reach its planned sample size of 860 participants because of restrictions on research during the COVID-19 pandemic.

The primary outcome was missing for 2 women in the dinoprostone group. Failure to achieve vaginal delivery (or a cesarean delivery being performed) occurred in 126 women (37.4%) allocated to Dilapan-S and in 115 (34.3%) women allocated to dinoprostone (adjusted risk difference, 0.02; 95% confidence interval, −0.05 to 0.10). There were similar maternal and neonatal adverse events between the groups.

CONCLUSION: Women undergoing induction of labor with Dilapan-S have similar rates of cesarean delivery and maternal and neonatal adverse events compared with dinoprostone.

Key words: cervical ripening, cesarean delivery, dinoprostone, induced, labor, pregnancy, randomized controlled trial

Introduction

Over 30% of labors in England were induced during 2017 and− 2018, and the rate has risen annually since 2007 and 2008.[1] Various methods are available to achieve iatrogenic cervical ripening.[2] These include surgical (amniotomy), pharmacologic (prostaglandins as vaginal gels, tablets, or pessaries and oxytocin as a slow intravenous infusion), and mechanical methods (balloon catheters into or through the cervix and extra-amniotic space, synthetic osmotic cervical dilators, and natural seaweed laminaria tents). Continuous

EDITOR'S CHOICE

slow-release vaginal prostaglandin E2 pessaries promote cervical ripening and simultaneously induce uterine contractions, with dinoprostone recommended as the first choice medical induction agent in the United Kingdom. Synthetic osmotic dilators such as Dilapan-S soften the cervix by dehydrating it, applying radial pressure to the internal and external cervical os and indirectly increasing the local release of endogenous prostaglandin, or oxytocin, or both.

Reduction in the risk of perinatal death is the ultimate aim of induction. However, the mode of childbirth and the interval from induction to birth are important surrogates. Prostaglandins are associated with uterine tachysystole and hyperstimulation, with effects on the fetus that cause fetal heart rate changes. Cardiotocography is often used to monitor the fetus. Outpatient induction with dinoprostone is feasible for low-risk women provided that they are given clear verbal and written instructions.[3] Maternal satisfaction with the birth process will influence the acceptance of alternative induction methods.[3] Other considerations for the choice of induction intervention include previous cesarean childbirth or myomectomy, which precludes the use of prostaglandins according to some national guidelines, and requirement for fetal monitoring.[4,5]

One of the main advantages of mechanical methods is the absence of pharmacologic-related side-effects.[6−8] Randomized controlled trials have shown that Dilapan-S is noninferior to balloon catheters in achieving a vaginal birth and is associated with higher maternal satisfaction rates.[9] In another randomized trial, it was observed that Dilapan-S reduces the rates of hyperstimulation and has a better safety profile, maternal satisfaction, and pain scores than oral misoprostol.[10]

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AJOG MFM at a Glance

Why was this study conducted?

Prostaglandins are associated with uterine tachysystole and hyperstimulation, whereas mechanical methods provide better maternal satisfaction and lower pain scores.

We compared the efficacy, maternal and neonatal safety, and maternal satisfaction of a synthetic osmotic cervical dilator (Dilapan-S) with that of vaginal prostaglandin E2 (dinoprostone) in cervical ripening for induction of labor.

Key findings

Our study indicates that women undergoing cervical ripening with Dilapan-S have similar vaginal delivery rates compared with dinoprostone but with fewer instances of uterine tachysystole, hyperstimulation, and adverse effects on the fetus.

What does this add to what is known?

This trial provides the best-quality evidence to date in support of allowing Dilapan-S to be considered as another method for induction of labor.

induction of Labor in comparison to dinoprostone Vaginal insErt (SOLVE) investigated vaginal delivery rates in women with a term singleton pregnancy receiving either Dilapan-S or prostaglandin E2.

Materials and Methods

Trial design

We did an open-label, multicenter randomized controlled trial in 4 hospitals in England. The protocol was approved by the East Midlands Leicester Central Research Ethics Committee (17/EM/0011) and was prospectively registered with the International Standard Randomised Controlled Trial Number (ISRCTN) Registry (ISCRTN20131893). A Trial Steering Committee (TSC) provided independent oversight of the trial. Confidential interim analysis of all the available data alongside anonymized reports of adverse events experienced by the participants were reviewed by an independent Data Monitoring Committee on 3 occasions. The TSC approved a change of the primary outcome during recruitment to the trial in June 2019 without access to the accumulating data (detailed below).

Participants

Pregnant women scheduled for induction of labor who were ≥16 years of age, capable of providing informed consent, with a singleton pregnancy at ≥37+0 weeks' gestation (determined by ultrasound dating scan), and with the fetus in a vertex presentation with intact membranes were eligible for inclusion. Initially, ultrasound dating was required when the estimated gestational age was between 11 and 14 weeks. However, this requirement was removed in April 2018, as it was too restrictive in recruiting potential women who were just outside this gestational age range. The need to have a preintervention Bishop score of ≤6 was also removed in April 2018 to eliminate the need for a vaginal examination solely to assess eligibility. Women already receiving oxytocin, those who had a diagnosis of fulminant preeclampsia or eclampsia, and those who had a contraindication to Dilapan-S or dinoprostone were ineligible. The recruiting sites could choose whether to recruit women who had a previous cesarean delivery or myomectomy on the basis of their local policy. These women were at an increased risk of uterine rupture with dinoprostone use.

Randomization and masking

Participants were randomized into the trial at a time as close as possible to the commencement of induction of labor in a 1:1 ratio to either synthetic osmotic cervical dilator (Dilapan-S) or prostaglandin E2 as a 10-mg controlled-release vaginal pessary (dinoprostone). Randomization was provided by a 24-hour telephone system hosted by the University of Aberdeen using a minimization algorithm to ensure balance between the groups on the following variables: parity (nulliparous vs multiparous); maternal obesity (body mass index [BMI] ≥30 kg/m^2 vs BMI <30 kg/m^2 at the first antenatal consultation); maternal age (<20, 20 to <30, 30 to <40, and ≥40 years); and randomizing hospital. The random allocation sequence was concealed until eligibility was confirmed and minimization variables were provided. Given the nature of the interventions, the SOLVE trial was not blinded.

Interventions

In the Dilapan-S group, research midwives or doctors who had completed the training package for insertion of the Dilapan-S rods, inserted the rods. The women lay on a bed supine or with their legs supported on padded stirrups to allow the insertion of a sterile vaginal speculum into the vagina. Following visualization of the cervix, which was cleansed with an antiseptic, the anterior lip of the cervix was grasped with sponge forceps or a vulsellum and up to a maximum of 5 rods were inserted into the cervical canal, ensuring that the tip of each rod crossed through and past the internal os. The rods were left in place for a minimum of 12 hours and up to a maximum of 24 hours. If the cervix remained unfavorable after the first series (Bishop score < 6), a second (then third) series of dilators were placed for an additional 12 to 24 hours.

Dinoprostone was administered high up into the posterior vaginal fornix using only small amounts of water-soluble lubricants to aid insertion. Each series of dinoprostone remained in place for up to 24 hours or up to 32 hours according to the local hospital policy.

All the women were instructed to report any excessive bleeding, pain, or other concerns and were informed that they should not remove any of the interventions themselves.

If spontaneous labor had not started, amniotomy was conducted after the Bishop score was ≥6. Oxytocin infusion using a syringe pump was used as per hospital protocols, commencing no

sooner than 30 minutes after the removal of the last series of Dilapan-S or dinoprostone, and with continuous fetal monitoring.

Outcomes

The primary outcome was failure to achieve vaginal delivery following a protocol amendment described below. Failure to achieve a vaginal delivery within 24, 36, and 48 hours of randomization were included as secondary outcomes. Other maternal secondary outcomes were as follows: change of Bishop score; use of analgesia or anesthesia during cervical ripening and labor; maternal complications during cervical ripening, labor, the immediate postpartum period, or before discharge from hospital; use of amniotomy or oxytocin for induction or augmentation of labor; and the mode of childbirth, including reasons for instrumental or cesarean delivery. The intervals between each stage—from randomization through the insertion of the induction intervention and from labor to discharge from hospital—are presented. Maternal satisfaction during insertion of the intervention, during cervical ripening, and overall was assessed using a questionnaire consisting of 23 questions. The neonatal outcomes were as follows: birthweight; Apgar scores at 1, 5, and 10 minutes; meconium staining of amniotic fluid; metabolic acidosis; neonatal medical review; admission to neonatal unit and length of stay; antibiotic administration for confirmed or suspected infection and duration of administration; and perinatal mortality. Adherence to the randomized allocation was assessed by collecting information on the induction intervention used; the number of series of each intervention; the number of occurrences when the intervention could not be inserted, fell out, or was removed or replaced; the duration of each series; and the total duration of intervention. The number of Dilapan-S rods inserted into the cervix was also recorded. The safety of the interventions was assessed by the reasons for removal of the induction intervention and adverse events, specifically, diagnosis of vaginal or uterine infection and associated antibiotic use, secondary postpartum hemorrhage, neonatal sepsis, and meconium aspiration syndrome. Serious, life-threatening adverse events requiring prolongation of hospital stay occurring with the mother or baby were reported, and the causality with respect to the induction intervention was considered.

Statistical analysis

The initial sample size calculation was based on the original primary outcome of failure to deliver vaginally within 36 hours after randomization. Estimates from previous studies of vaginal birth rate within 36 hours following the use of dinoprostone varied between 30% and 40%.[11−13] We chose a plausible effect size of an absolute difference of 9% between the groups. Assuming a 35% primary outcome rate in the dinoprostone group, a total of 410 participants per group were needed to detect a 9% absolute reduction to 26% in the Dilapan-S group with 80% power and a type 1 error rate of 5%. We assumed that the time and mode of delivery would be available for all the participants but anticipated that approximately 5% of women would not receive either intervention and adjusted the total target to 860 participants.

After 290 women had been randomized by June 2019, not all of them were able to receive a timely amniotomy once a favorable cervix had been achieved because of demands on the clinical service, potentially pausing or reversing the physiological process of cervical ripening. Because a delayed amniotomy could increase the overall length of labor, a vaginal delivery within 36 hours was deemed less likely for reasons unrelated to the induction agent. The TSC—blind to any comparison between the trial groups—approved an amendment to the protocol to remove the 36-hour time limit for the primary outcome. The interim pooled estimate of the rate for the revised primary outcome was 36.6% (106/290) (95% confidence interval [CI], 31.1−42.4). Using this and a fixed sample size of 860, plausible absolute differences of 8%−9% could still be detected with 80% power.

Trial recruitment was interrupted in the first 6 months of the COVID-19 pandemic. Because of the unavailability of research midwives who were redeployed to clinical work, a decision was made by the investigators and the TSC to stop recruitment in January 2021 when 674 women had been recruited.

An a priori Statistical Analysis Plan was agreed to give point estimates, 95% CIs, and *P* values from two-sided tests for all the outcome measures. We considered *P* values of <.05 to indicate statistical significance. The primary analysis for all the outcomes was by intention-to-treat, with participants analyzed in the groups to which they were assigned regardless of protocol noncompliances. The complications are presented according to the treatment received. The outcomes were adjusted for the minimization variables where possible. Hospitals were treated as a random effect and all other minimization factors as fixed effects. For binomial outcomes, mixed effects binomial regression models were used with an identity link to calculate the risk differences, and a log link was used to calculate the risk ratios and the associated 95% CIs and *P* values. If normally distributed, the continuous outcomes were analyzed using mixed effects linear regression, with the adjusted mean differences, 95% CIs, and their associated *P* values presented. Otherwise, the median differences or geometric mean ratios were calculated. The appropriate summary statistics are presented for each outcome (eg, proportions [percentages], mean [standard deviation], or median [interquartile range]).

Sensitivity analyses consisted of the following: restricted analyses excluding women who were nonadherent to their allocated intervention according to strict criteria (women who received their allocated intervention for all series) and lenient criteria (women who received their allocated intervention for at least the first series); an analysis excluding women who did not receive either of the interventions because their Bishop score on initiation of cervical ripening was >6; and an analysis to assess the effect of missing responses for the primary outcome if the number of missing responses was >5% of all the women randomized.

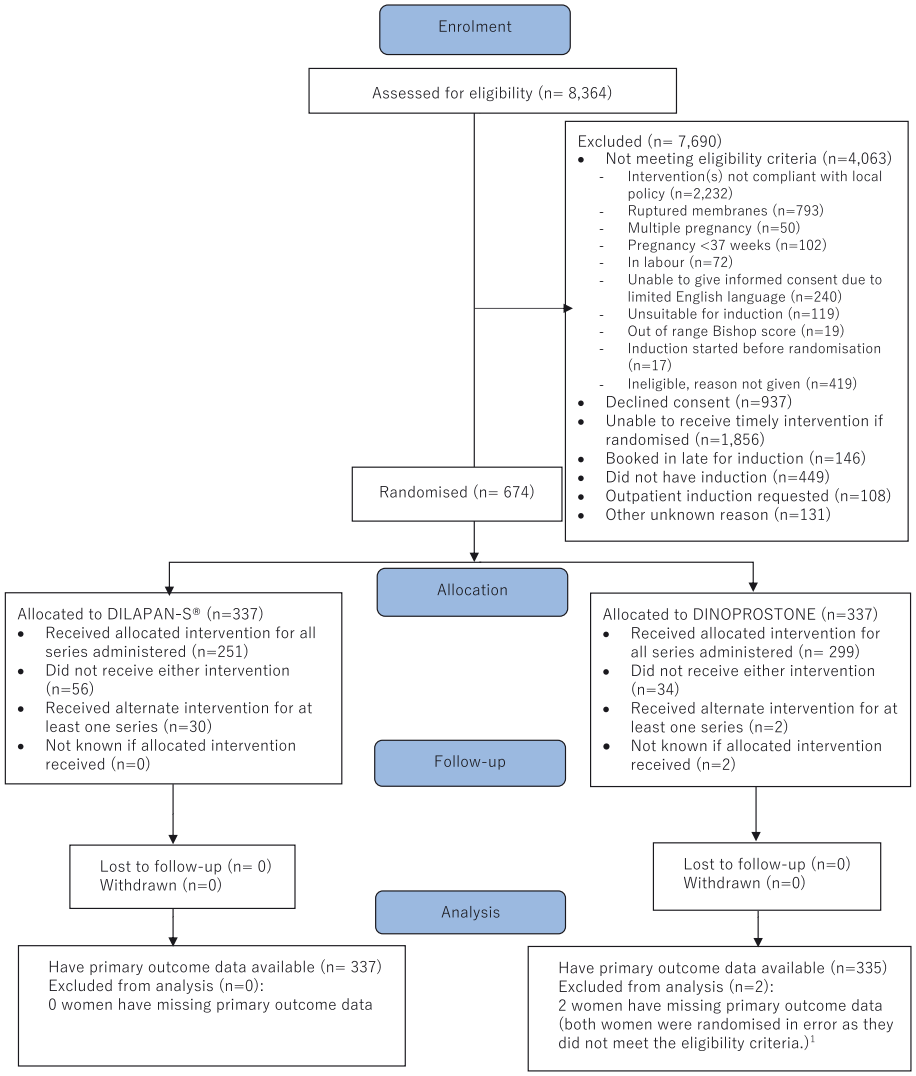
Subgroup analyses for the primary outcome were limited to the minimization variables. Tests for statistical heterogeneity were presented alongside effect estimates within subgroups. The results of subgroup analyses were treated with caution and used for the purpose of hypothesis generation only.

Results

Women were randomized between December 19, 2017 and January 26, 2021. Table S2 shows the numbers of women recruited by each hospital. Of the 8364 women assessed for eligibility, 674 women were randomized, with 337 women being allocated to Dilapan-S and 337 to dinoprostone (Figure 1). Two women from the dinoprostone group were excluded from the final analysis, as they had missing primary outcomes data (both women were randomized in error, as they did not meet the prevailing eligibility criteria) (Figure).

The groups were well-balanced for all characteristics at baseline (Table 1 and

FIGURE 1
CONSORT diagram



The *superscript letter a* denotes that 1 woman was found to have not had a dating scan until 15+1 weeks, making her ineligible (before removal of dating scan from the eligibility criteria). She was informed that her data would not be collected.

One woman was found to not be suitable for Dilapan-S or dinoprostone before randomization but proceeded to be randomized in error. No data were collected, and this is listed as a protocol deviation.

CONSORT, Consolidated Standards of Reporting Trials.

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TABLE 1
Baseline characteristics

Variable	Measure	Dilapan-S (n=337)	Dinoprostone (n=337)	Overall (N=674)
Minimization variables				
Maternal age (y)	<20	19 (5.6)	19 (5.6)	38 (5.6)
	20 to <30	148 (43.9)	150 (44.5)	298 (44.2)
	30 to <40	149 (44.2)	147 (43.6)	296 (43.9)
	>40	21 (6.2)	21 (6.2)	42 (6.2)
	Mean (SD)	30.0 (6.1)	29.9 (6.2)	30.0 (6.1)
	Min–max	17.8–46.0	16.2–48.7	16.2–48.7
Maternal obesity at first antenatal visit	BMI <30	221 (65.6)	219 (65.0)	440 (65.3)
	BMI ≥30	116 (34.4)	118 (35.0)	234 (34.7)
BMI (kg/m^2)	Mean (SD)	28.4 (6.6)	28.1 (6.6)	28.2 (6.6)
	Min–Max	16.4–53.2	16.5–51.8	16.4–53.2
	Missing[a]	0	2	2
Parity	Nulliparous	269 (79.8)	272 (80.7)	541 (80.3)
	Multiparous	68 (20.2)	65 (19.3)	133 (19.7)
Demographic and other baseline variables				
Weight at booking antenatal visit (kg)	Mean (SD)	76.4 (19.3)	75.2 (18.5)	75.8 (18.9)
	Min–max	40.0–152.0	44.0–155.0	40.0–155.0
	Missing	0	2	2
Height (cm)	Mean (SD)	164.0 (7.1)	163.6 (6.7)	163.8 (6.9)
	Min–max	148.0–189.0	144.0–183.0	144.0–189.0
	Missing	0	2	2
Ethnicity	White (British/Irish/other)	223 (66.2)	228 (68.3)	451 (67.2)
	Black/Black British (Caribbean/African/other)	33 (9.8)	19 (5.7)	52 (7.8)
	Asian/Asian British (Indian/Pakistani/ Bangladeshi/Chinese/other)	60 (17.8)	63 (18.9)	123 (18.3)
	Mixed (White/Black/Asian/other)	6 (1.8)	7 (2.1)	13 (1.9)
	Other	14 (4.2)	16 (4.8)	30 (4.5)
	Declined to give information	1 (0.3)	1 (0.3)	2 (0.3)
	Missing	0	3	3
Indications for induction				
Postterm pregnancy	Yes	120 (35.6)	133 (39.7)	253 (37.7)
	Missing	0	2	2
Intrauterine growth restriction and/or oligohydramnios	Yes	75 (22.3)	81 (24.2)	156 (23.2)
	Missing	0	2	2
Reduced fetal movement	Yes	73 (21.7)	57 (17.0)	130 (19.3)
	Missing	0	2	2
Diabetes mellitus and/or gestational diabetes	Yes	52 (15.4)	45 (13.4)	97 (14.4)
	Missing	0	2	2
Large for gestational age	Yes	42 (12.5)	44 (13.1)	86 (12.8)
	Missing	0	2	2

(continued)

TABLE 1
Baseline characteristics *(continued)*

Variable	Measure	Dilapan-S (n=337)	Dinoprostone (n=337)	Overall (N=674)
Preeclampsia	Yes	13 (3.9)	18 (5.4)	31 (4.6)
	Missing	0	2	2
Gestational hypertension	Yes	13 (3.9)	11 (3.3)	24 (3.6)
	Missing	0	2	2
Small for gestational age	Yes	16 (4.8)	8 (2.4)	24 (3.6)
	Missing	0	2	2
Maternal age	Yes	11 (3.3)	11 (3.3)	22 (3.3)
	Missing	0	2	2
Low PAPP-A	Yes	10 (3.0)	7 (2.1)	17 (2.5)
	Missing	0	2	2
Maternal hepatic disease	Yes	4 (1.2)	3 (0.9)	7 (1.0)
	Missing	0	2	2
Elected by mother	Yes	3 (0.9)	4 (1.2)	7 (1.0)
	Missing	0	2	2
Rhesus isoimmunization and/or increasing antibody titer	Yes	4 (1.2)	1 (0.3)	5 (0.7)
	Missing	0	2	2
Maternal renal disease	Yes	2 (0.6)	2 (0.6)	4 (0.6)
	Missing	0	2	2
Other maternal disease	Yes	33 (9.8)	32 (9.6)	65 (9.7)
	Missing	0	2	2
	If yes, what types?			
	Antepartum hemorrhage	0 (—)	3 (0.9)	3 (0.5)
	Epileptic	2 (0.6)	0 (—)	2 (0.3)
	Fetal anomaly	6 (1.8)	4 (1.2)	10 (1.5)
	Gestational hypertension	3 (0.9)	3 (0.9)	6 (0.9)
	Maternal arthritis	2 (0.6)	0 (—)	2 (0.3)
	Mental health	1 (0.3)	1 (0.3)	2 (0.3)
	Obstetrical cholestasis	6 (1.8)	3 (0.9)	9 (1.3)
	Raised BMI	0 (—)	3 (0.9)	3 (0.5)
	Raised pulsatility index	4 (1.2)	3 (0.9)	7 (1.0)
	Symphysis pubis dysfunction	2 (0.6)	2 (0.6)	4 (0.6)
	Other[b]	7 (2.1)	10 (3.0)	17 (2.5)
Previous pregnancies				
Previous miscarriages	0	248 (73.6)	254 (75.8)	502 (74.7)
	≥ 1	89 (26.4)	81 (24.2)	170 (25.3)
	Missing	0	2	2
Previous termination of pregnancies	0	292 (86.7)	300 (89.6)	592 (88.1)
	≥1	45 (13.3)	35 (10.4)	80 (11.9)
	Missing	0	2	2
Previous deliveries >24 wks	No	268 (79.5)	270 (80.6)	538 (80.1)
	Yes	69 (20.5)	65 (19.4)	134 (19.9)

(continued)

TABLE 1
Baseline characteristics *(continued)*

Variable	Measure	Dilapan-S (n=337)	Dinoprostone (n=337)	Overall (N=674)
Missing	0	2	2	
For previous deliveries >24 wks[c]				
Was the mode of delivery unassisted vaginal?	Yes	50 (72.5)	49 (75.4)	99 (73.9)
Was the mode of delivery instrumental vaginal?	Yes	14 (20.3)	7 (10.8)	21 (15.7)
Was the mode of delivery elective cesarean?	Yes	6 (8.7)	4 (6.2)	10 (7.5)
Was the mode of delivery emergency cesarean?	Yes	22 (31.9)	20 (30.8)	42 (31.3)
For previous deliveries >24 wks				
Type of previous birth(s)	Vaginal only	40 (58.8)	41 (63.1)	81 (60.9)
	Vaginal and cesarean delivery	16 (23.5)	12 (18.5)	28 (21.1)
	Cesarean delivery only	12 (17.7)	12 (18.5)	24 (18.1)
	Missing	1	0	1
Current pregnancy				
Presence of risk factor for GBS[d]	Yes	25 (7.4)	31 (9.3)	56 (8.3)
	Missing	0	2	2
Bishop score on initiation of cervical ripening				
Bishop score on initiation of cervical ripening ≥ 6	Yes	53 (15.7)	49 (14.6)	102 (15.2)
	Missing	0	1	1

Data are presented as number (percentage) unless stated otherwise.

BMI, body mass index; *GBS*, Group B *Streptococcus*; *PAPP-A*, pregnancy associated plasma protein A; *SD*, standard deviation.

[a] Missing data of height and weight for 2 women were collected postrandomization to calculate the BMI; [b] These are detailed in Appendix A; [c] Categories are not mutually exclusive so may total to >100%; [d] Group B *Streptococcus* infection.

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S1). The most common indications for induction of labor were postterm pregnancy, intrauterine growth restriction, and reduced fetal movements.

The total duration of cervical ripening was comparable (Table 2 and S3). Using the strict adherence criteria, 86 (25.5%) and 36 (11.0%) women did not receive Dilapan-S and dinoprostone, respectively (Table 2 and S6). The dinoprostone inserts fell out and had to be reinserted for more women compared with Dilapan-S (Tables S4 and S5). There were more occurrences when dinoprostone was removed because of complications; 63 compared with 19 women in the Dilapan-S group, principally owing to uterine tachysystole (11 vs 3 women), uterine hyperstimulation with a nonreassuring fetal heart rate (9 vs 3 women), and abnormal cardiotocograph changes (26 vs 13 fetuses).

The primary outcome of failure to achieve vaginal delivery (cesarean delivery) occurred in 126 (37.4%) of 337 women in the Dilapan-S group and in 115 (34.3%) of 335 women in the dinoprostone group (adjusted risk difference, 0.02; 95% CI, −0.05 to 0.10; adjusted risk ratio, 1.10; 95% CI, 0.90 −1.35; *P* value for risk ratio, 0.33) (Table 3). Sensitivity analyses showed results similar to the intention-to-treat analysis (Table S13 and Figure S2).

There is evidence to suggest that the change in the Bishop score from baseline was better in the dinoprostone group (Table 3). Initially, more women had inhalation analgesia with entonox during the placement of the Dilapan-S rods, but more women had opiate analgesia during the cervical ripening process in the dinoprostone group. More women in the Dilapan-S group underwent amniotomy and augmentation with oxytocin. More women failed to achieve vaginal delivery within 24 hours from randomization in the Dilapan-S group, but there was no evidence of any differences at 36 and 48 hours from randomization. There is no evidence of a difference in the instrumental delivery rates between the groups, but a higher cesarean delivery rate is seen in the Dilapan-S group because of maternal or fetal reasons (at least 1 of the following: delay in first or second stage of labor, fetal heart rate abnormalities, or abnormal fetal blood gases). There is no evidence of a difference between the groups in maternal complications, antibiotic use, or length of stay from delivery until discharge.

There were more complications in those receiving dinoprostone during the cervical ripening period (68/301 [22.6%] vs 19/249 [7.6%]), primarily relating to more cases of uterine

TABLE 2
Description of the interventions

Treatment description	Measure	Allocated intervention	
		Dilapan-S (n=337)	Dinoprostone (n=337)
Total duration of intervention received (h)[a]	Mean (SD)	24.9 (16.2)	28.6 (18.9)
	Median (IQR)	21.3 (16.1–24.8)	24.4 (13.9–34.1)
	Min–max	0.3–169.8[b]	1.1–94.9
	Missing	58	52
Received the randomly allocated intervention for all series (strictly adherent[c])	Number adherent	251 (74.5)	290 (89.0)
	Number nonadherent	86 (25.5)	36 (11.0)
	Missing	0	11
Received the randomly allocated intervention for at least series 1 (leniently adherent[d])	Number adherent	268 (79.5)	301 (89.9)
	Number nonadherent	69 (20.5)	34 (10.2)
	Missing	0	2

Data are presented as number (percentage) unless stated otherwise.

IQR, interquartile range; *SD*, standard deviation.

[a] Regardless of whether the intervention received was the same as that allocated and calculated as the duration between insertion of the first series and removal (or falling out) of the last series; [b] One woman had a 1-week interval between removal of series 1 and insertion of series 2; [c] Strict adherence threshold is defined as follows: if the intervention received matches the intervention allocated for all the treatment series, the woman is categorized as adherent; if this is not the case (ie, another intervention or no intervention is received for at least 1 of the series), the woman is categorized as nonadherent; [d] Lenient adherence threshold is defined as follows: if the intervention received matches the intervention allocated for at least the first series of treatment, the woman is categorized as adherent; if this is not the case (ie, no intervention is received or another intervention is received for the first series), the woman is categorized as nonadherent.

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tachysystole, hyperstimulation, and effects on the fetus identified by cardiotocograph monitoring. Complications during or after labor are similar in both the groups (Table 4).

There is no evidence of any differences in neonatal outcomes between the groups (Table 5).

More women in the Dilapan-S group reported better satisfaction in terms of ability to perform their desired daily activities such as walking, dressing, maintaining hygiene, showering, ability to sleep, and relax and reported less frequent and less intense uterine contractions (Table 6).

There were more protocol deviations in the Dilapan-S group, with 31 women having a delayed removal of Dilapan-S after the 24-hour window and 60 women who did not have the cervix cleaned before insertion of Dilapan (Table S8). Dilapan-S could not be inserted in 10 women, and attempts were abandoned in a further 10 participants (Table S4). The timings between randomization and birth were similar in both the groups (Table S9).

The number of adverse and serious adverse events reported were similar in both the groups (Tables S10 and S11). Most of the maternal and neonatal events were suspected sepsis and/or postpartum hemorrhage, which were judged to be unrelated to the intervention. There was 1 serious adverse reaction in the dinoprostone group because of placental abruption, which occurred 2 hours and 25 minutes after the intervention was removed. There was 1 suspected, unexpected serious adverse reaction reported in the dinoprostone group of a neonatal death with severe perinatal asphyxia, sepsis, and suspected hypoxic ischemic encephalopathy (Table S11).

There was no evidence of heterogeneity of the treatment effect for the primary outcome between nulliparous and multiparous women, for BMI of <30 vs ≥30, or between the age groups (Table S12 and Figure S1).

Comment

Principal findings

This is a large trial comparing Dilapan-S and dinoprostone in cervical ripening for induction of labor. In this randomized trial, we found that cervical ripening at term in primarily primigravid women using either Dilapan-S or dinoprostone results in no evidence of a difference in failure to achieve vaginal delivery (ie or cesarean delivery being performed). We had to curtail our recruitment to 674 women because of the impact of the COVID-19 pandemic and did not achieve the original target of 870 women.

Entonox inhalation was used more commonly in the Dilapan-S group, and more opiate analgesia was used in the dinoprostone group during the cervical ripening process. There were more women with uterine tachysystole, hyperstimulation, and cardiotocographic abnormalities in the dinoprostone group than the Dilapan-S group. There was also a higher need for reinsertion of dinoprostone by approximately 10% (intervention was not reinserted for 78.9% of women in the Dilapan-S group vs in 69.5% in the dinoprostone group).

TABLE 3
Maternal outcomes

Outcome	Measure	Dilapan-S (n=337)	Dinoprostone (n=337)	Adjusted RD (95% CI)[a]	Adjusted RR/MD/GMR (95% CI)[b]	*P* value for RR, MD, or GMR
Failure to achieve vaginal delivery (cesarean delivery)	Yes	126 (37.4)	115 (34.3)	RD[c] 0.02 (–0.05 to 0.10)	RR[d] 1.10 (0.90–1.35)	.33
	No	211 (62.6)	220 (65.7)			
	Missing	0	2			
Maternal outcomes during cervical ripening						
Change in Bishop score from baseline to completion of cervical ripening	Mean (SD)	3.2 (2.3)	3.6 (2.7)	—	MD[e] –0.54 (–0.90 to –0.18)	.0031
	Min–max	–2.0 to 11.0	–3.0 to 13.0			
	Missing	61	55			
Time between Bishop scores measured at baseline and completion of cervical ripening (h)	Geometric mean	22.5	22.5	—	GMR[f] 0.99 (0.87–1.15)	.99
	Median (IQR)	22.3 (16.3–36.5)	24.7 (12.9–41.2)			
	Min–max	0.0–243.0	0.0–227.5			
	Missing	50	45			
Use of analgesia during cervical ripening	Yes	170 (51.2)	220 (66.3)	RD[c] –0.14 (–0.26 to –0.02)	RR[d] 0.77 (0.67–0.87)	<.0001
	Missing	5	5			
	What types of analgesia?[g]			—	—	—
	Oral nonsteroidal anti-inflammatory drugs	8 (2.4)	17 (5.0)			
	Paracetamol	114 (33.8)	182 (54.0)			
	Oral opioid	72 (21.4)	148 (43.9)			
	Pethidine	21 (6.2)	59 (17.5)			
	Entonox	64 (19.0)	29 (8.6)			
	Epidural	1 (0.3)	3 (0.9)			
	TENS machine	0 (—)	1 (0.3)			
	Missing	0	1			
Time between randomization and start of analgesia use for cervical ripening (h)	Geometric mean	5.3	10.8	—	GMR[f] 0.49 (0.38–0.62)	<.0001
	Median (IQR)	6.2 (1.3–17.7)	10.2 (5.8–18.7)			

(continued)

TABLE 3
Maternal outcomes *(continued)*

Outcome	Measure	Dilapan-S (n=337)	Dinoprostone (n=337)	Adjusted RD (95% CI)[a]	Adjusted RR/MD/GMR (95% CI)[b]	*P* value for RR, MD, or GMR
	Min–max	0.11–209.0[h]	1.2–74.6			
	Analgesia not used	162 (48.8)	112 (33.7)			
	Missing	8	6			
Any complications during cervical ripening (details are provided in table 4)	Yes	35 (10.5)	66 (20.2)	RD[c] −0.10 (−0.15 to −0.04)	RR[i] 0.52 (0.35–0.79)	.0021
	Missing	4	10			
Maternal outcomes during labor and immediately after delivery						
Time between removal of last series of intervention to amniotomy (h)[j]	Geometric mean	12.7	14.5	—	GMR[f] 1.08 (0.78–1.49)	.63
	Median (IQR)	25.8 (5.9–45.3)	19.0 (5.4–44.5)			
	Min–max	0.0–121.3	0.0–229.1			
	Amniotomy for induction not performed	100 (29.9)	190 (57.4)			
	Missing	34	29			
Time between first insertion of intervention to when labor started (h)	Geometric mean	45.9	35.0	—	GMR[f] 1.34 (1.19–1.52)	<.0001
	Median (IQR)	47.4 (31.4–68.5)	38.3 (18.3–68.3)			
	Min–max	1.9–245.6	3.4–255.7			
	Missing	80	79			
Amniotomy undertaken for induction of labor	Yes	235 (70.2)	141 (42.6)	RD[c] 0.28 (0.20–0.35)	RR[d] 1.64 (1.43–1.89)	<.0001
	Missing	2	6			
Amniotomy undertaken for augmentation of labor	Yes	15 (4.5)	25 (7.6)	RD[c] −0.03 (−0.07 to 0.005)	RR[k] 0.58 (0.31–1.08)	.088
	Missing	1	6			
Required oxytocin for induction of labor	Yes	210 (62.7)	130 (39.3)	RD[l] 0.24 (0.16–0.31)	RR[k] 1.60 (1.28–1.99)	<.0001
	Missing	2	6			
Required oxytocin for augmentation of labor	Yes	25 (7.4)	43 (13.0)	RD[c] −0.06 (−0.10 to −0.01)	RR[d] 0.57 (0.36–0.91)	.019
	Missing	1	6			

(continued)

TABLE 3
Maternal outcomes *(continued)*

Outcome	Measure	Dilapan-S (n=337)	Dinoprostone (n=337)	Adjusted RD (95% CI)[a]	Adjusted RR/MD/GMR (95% CI)[b]	*P* value for RR, MD, or GMR
Use of analgesia or anesthesia (eg, epidural) during labor	Yes	299 (89.5)	278 (83.5)	RD[c] 0.06 (0.01–0.11)	RR[d] 1.07 (1.01–1.13)	.021
	Missing	3	4			
	Types of analgesia used[g]			—	—	—
	Oral nonsteroidal anti-inflammatory drugs	3 (0.9)	2 (0.6)			
	Paracetamol	31 (9.2)	34 (10.1)			
	Oral opioid	18 (5.3)	23 (6.8)			
	Systemic opioid	63 (18.7)	53 (15.7)			
	Remifentanil PCA	12 (3.6)	3 (0.9)			
	Entonox	198 (58.8)	185 (54.9)			
	Epidural/ spinal analgesia	187 (55.5)	174 (51.6)			
	General anesthesia	16 (4.8)	8 (2.4)			
	TENS machine	5 (1.5)	6 (1.8)			
	Aromatherapy	1 (0.3)	4 (1.2)			
	Pudendal block	4 (1.2)	3 (0.9)			
Any complications during or after labor (details are provided in table 4)	Yes	249 (73.9)	244 (72.8)	RD[c] 0.01 (–0.06 to 0.07)	RR[d] 1.00 (0.92–1.10)	.93
	Missing	0	2			
Failure to achieve vaginal delivery within 24 h from randomization	Yes[m]	306 (90.8)	272 (81.2)	RD[c] 0.10 (–0.04 to 0.24)	RR[d] 1.11 (1.05–1.18)	.0002
	Missing	0	2			
Failure to achieve vaginal delivery within 36 h from randomization	Yes[m]	273 (81.0)	232 (69.3)	RD[c] 0.11 (–0.02 to 0.24)	RR[i] 1.17 (0.98–1.39)	.082
	Missing	0	2			
Failure to achieve vaginal delivery within 48 h from randomization	Yes[m]	232 (68.8)	200 (59.7)	RD[c] 0.09 (–0.03 to 0.21)	RR[i] 1.15 (0.95–1.39)	.14
	Missing	0	2			
Spontaneous vaginal delivery	Yes	129 (38.3)	133 (39.7)	RD[c] –0.02 (–0.09 to 0.05)	RR[d] 0.94 (0.79–1.12)	.51
	Missing	0	2			

(continued)

TABLE 3
Maternal outcomes *(continued)*

Outcome	Measure	Dilapan-S (n=337)	Dinoprostone (n=337)	Adjusted RD (95% CI)[a]	Adjusted RR/MD/GMR (95% CI)[b]	*P* value for RR, MD, or GMR
Instrumental delivery because of delay in second stage of labor and/or fetal heart rate abnormalities and/or abnormal FBS	Yes	71 (21.1)	74 (22.2)	RD[c] 0.02 (–0.05 to 0.09)	RR[k] 0.97 (0.74–1.29)	.86
	Missing	0	3			
Cesarean delivery because of delay in first and/or second stage of labor, and/or fetal heart rate abnormalities and/or abnormal fetal blood sample (gases)	Yes	96 (28.5)	74 (22.1)	RD[c] 0.05 (–0.02 to 0.12)	RR[k] 1.31 (1.01–1.70)	.039
	Missing	0	2			
Maternal outcomes after delivery until discharge						
Complications from delivery until discharge	Yes	74 (22.0)	69 (20.6)	RD[c] 0.01 (–0.05 to 0.07)	RR[d] 1.07 (0.80–1.43)	.65
	Missing	0	2			
Antibiotic use for pelvic infection	Yes	3 (0.9)	2 (0.6)	RD[n] –0.003 (–0.010 to 0.016)	RR[d] 1.57 (0.26–9.37)	.62
	Missing	0	2			
Duration of antibiotic use for pelvic infection (d)	Mean (SD)	6.3 (4.6)	4.0 (2.8)	—	Not calculated	Not calculated
	Min–max	1.0–9.0	2.0–6.0			
	Missing[o]	334	335			
Length of stay from randomization (d)	Geometric mean	4.1	3.9	—	GMR[f] 1.06 (0.97–1.15)	.18
	Median (IQR)	4.0 (3.0–6.0)	4.0 (3.0–6.0)			
	Min–max	1.0–15.0	1.0–32.0			
	Missing	0	2			

BMI, body mass index; *CI*, confidence interval; *FBS*, fasting blood sugar; *GMR*, geometric mean ratio; *IQR*, interquartile range; *MD*, mean difference; *PCA*, patient-controlled analgesia; *RD*, risk difference, *RR*, risk ratio; *SD*, standard deviation; *TENS*, transcutaneous electrical nerve stimulation.

[a] Dinoprostone is the reference category, and RDs <0 favor Dilapan-S, with the exception of spontaneous vaginal delivery where a RD <0 favors dinoprostone.; RD is not applicable for boxes shaded; [b] Dinoprostone is the reference category, and risk ratio values <1 favor Dilapan-S, with the exception of spontaneous vaginal delivery where a risk ratio value <1 favors dinoprostone. Mean differences <0 favor Dilapan-S. Geometric mean ratios <1 favor Dilapan-S. The geometric mean indicates the central tendency or typical value of a set of numbers by using the product of their values (as opposed to the arithmetic mean, which uses their sum) and is used for summarizing skewed data. Comparative analysis uses a ratio of the geometric means instead of the mean difference, and therefore, a ratio of 1 indicates no difference between the groups; [c] RD is estimated using a binomial model with an identity link adjusting for age, BMI, and parity; [d] Risk ratio is estimated using a binomial model with a log link adjusting for age, BMI, and parity as fixed effects; [e] Mean difference is estimated using a mixed effects linear regression adjusted for Bishop score in addition to minimization variables and randomizing center as a random effect; [f] The geometric mean ratio is estimated using a mixed effect linear regression adjusted for minimization variables and randomizing center as a random effect; [g] Categories are not mutually exclusive, so percentages may total to greater than expected; [h] One woman had a 6-day interval between removal of the last series and completion of the cervical ripening process; [i] Risk ratio is estimated using a mixed Poisson model, with a log link adjusting for age, BMI, and parity as fixed effects and randomizing center as a random effect; [j] Includes amniotomy undertaken for induction of labor only; [k] The risk ratio is estimated using a mixed binomial model with a log link adjusting for age, BMI, and parity and randomizing center as a random effect; [l] Risk difference is estimated using a mixed binomial model with an identity link adjusting for age, BMI, and parity as fixed effects and the randomizing center as a random effect; [m] 'Yes' indicates a cesarean delivery or vaginal delivery after the time frame specified; [n] Risk difference is estimated using an unadjusted binomial model with an identity link; [o] Missing category includes those who did not require antibiotic use for pelvic infection.

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TABLE 4
Complications in the as treated population

Timing of complication	Complication	Dilapan-S (n=251)	Dinoprostone (n=302)
Complications during cervical ripening	Yes	19 (7.6)	68 (22.6)
	Missing	2	1
	What was the complication?[a]		
	Cervical injury	2 (0.8)	0 (—)
	Uterine tachysystole	1 (0.4)	11 (5.0)
	Uterine hyperstimulation with nonreassuring or abnormal FHR	0 (—)	13 (4.3)
	Effect on fetus (CTG)	6 (2.4)	34 (11.3)
	Vomiting	0 (—)	7 (2.3)
	Diarrhea	1 (0.4)	2 (0.7)
	Fever	2 (0.8)	1 (0.3)
	Hypotension	1 (0.4)	4 (1.3)
	Maternal tachycardia	3 (1.2)	5 (1.7)
	Suspected chorioamnionitis	3 (1.2)	0 (—)
	Per vaginal bleed	5 (2.0)	5 (1.7)
	Other[b]	4 (1.6)	8 (2.7)
Complications during or after labor	Yes	184 (73.3)	223 (73.8)
	What was the complication?[a]:		
	Uterine hyperstimulation	4 (1.6)	6 (2.0)
	Perineal injury	127 (50.6)	156 (51.7)
	Manual removal of placenta	11 (4.4)	10 (3.3)
	Primary postpartum hemorrhage	85 (33.9)	118 (39.1)
	Cervical injury	2 (0.8)	2 (0.7)
	Other[c]	5 (2.0)	15 (5.0)

Data are presented as number (percentage).

CTG, cardiotocograph; *FHR*, fetal heart rate.

[a] Categories are not mutually exclusive, so percentages may total to greater than expected; [b] Dilapan-S other complications are as follows: 1 hypertension, 1 influenza, and 2 antepartum hemorrhage. Dinoprostone other complications are as follows: 1 cervix 4 cm dilated, 1 hypertension, 1 bradycardia, 1 prolonged contractions, 1 epileptic fit, 1 second dinoprostone not inserted correctly and 2 vaginal soreness; [c] Dilapan-S other complications are as follows: 1 maternal tachycardia, 1 shoulder dystocia, 1 uterine inversion, 1 raised temperature, and 1 large hematoma on vaginal lateral wall. Dinoprostone other complications are as follows: 1 maternal tachycardia, 1 labial tear, 1 uterine inversion, 1 sepsis, 1 placental abruption, 1 raised temperature, 1 worsening preeclampsia, 1 secondary postpartum hemorrhage, 2 chorioamnionitis, 2 antepartum hemorrhage, and 3 shoulder dystocia.

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Results in the context of what is known

Our results indicate higher maternal satisfaction rates in the Dilapan-S group throughout the duration of the cervical ripening process. This is in keeping with previous evidence from mechanical methods for cervical ripening with balloon catheters, which are associated with a lower risk of hyperstimulation and pain during the cervical ripening process and is safer than pharmacologic methods.[14] de Vaan et al[14] have shown that mechanical induction with a balloon catheter is probably as effective as induction of labor with vaginal dinoprostone but is associated with a more favorable safety profile. Their conclusion was that more research on this comparison does not seem warranted. When comparing balloon catheters with misoprostol, the former were less effective but were probably associated with a better safety profile; more research with regard to neonatal safety and maternal satisfaction is suggested. With the addition of direct comparisons with Dilapan-S and balloon catheters showing better maternal satisfaction rates with Dilapan-S, as there was no protrusion from the vagina and better maternal satisfaction and safety associated with Dilapan-S than with misoprostol, our trial reaffirms the better maternal satisfaction and safety profile with Dilapan-S compared with dinoprostone, with similar overall vaginal delivery rates.

Clinical implications

In this trial, a significant number of women were being induced because of

TABLE 5
Neonatal secondary outcomes

Outcome	Measure	Dilapan-S (n=337)	Dinoprostone (n=337)	RD[a]	Adjusted RR/MD / MeD/GMR (95% CI)[b]	*P* value for MD, MeD, RR, or GMR
Baby born alive	Yes	337 (100)	335 (100)	Not estimable	Not estimable	—
	Missing	0	2			
Birthweight (g)	Mean (SD)	3362.6 (561.8)	3351.2 (557.9)		MD 6.3 (–77.2 to 89.8)	.88
	Min–max	1760.0–4880.0	1790.0–5500.0	—		
	Missing	0	2			
Apgar score at 1 min	Median (IQR)	9.0 (9.0–9.0)	9.0 (8.0–9.0)	—	MeD 0[c]	—[d]
	Min–max	2.0–10.0	0.0–10.0			
	Apgar score not recorded	1	1			
	Missing	0	2			
Apgar score at 5 min	Median (IQR)	9.0 (9.0–10.0)	9.0 (9.0–10.0)	—	MeD 0[c]	—[d]
	Min–max	3.0–10.0	0.0–10.0			
	Apgar score not recorded	3	2			
	Missing	0	2			
Apgar score at 10 min	Median (IQR)	10.0 (10.0–10.0)	10.0 (9.0–1.0)	—	MeD 0 (–0.17 to 0.17)	1.00
	Min–max	7.0–10.0	1.0–10.0			
	Apgar score not recorded	288	278			
	Missing	0	2			
Meconium staining noted	Yes	46 (13.7)	44 (13.1)	RD 0.02 (–0.03 to 0.07)	RR 1.03 (0.70–1.50)	.90
	Missing	1	2			
Metabolic acidosis	Yes	14 (9.5)	10 (6.4)	RD 0.03 (–0.03 to 0.10)	RR 1.20 (0.60–2.39)	.61
	Missing	190	181			
Requirement of review by doctor from neonatal team	Yes	123 (36.5)	124 (37.0)	RD 0.001 (–0.07 to 0.07)	RR 0.97 (0.80–1.18)	.77
	Missing	0	2			

(continued)

TABLE 5
Neonatal secondary outcomes *(continued)*

Outcome	Measure	Dilapan-S (n=337)	Dinoprostone (n=337)	RD[a]	Adjusted RR/MD / MeD/GMR (95% CI)[b]	*P* value for MD, MeD, RR, or GMR
Antibiotic use for neonatal infection[e]	Yes	60 (17.8)	60 (17.9)	RD 0.01 (–0.05 to 0.07)	RR 0.98 (0.71–1.35)	.90
	Missing	0	2			
Duration of antibiotic use for neonatal infection (d)	Geometric mean	3.1	4.0	—	GMR 0.79 (0.66–0.95)	.013
	Median (IQR)	3.0 (2.0–5.0)	5.0 (2.5–5.0)			
	Min–max	1.0–14.0	2.0–7.0			
	No antibiotic use for neonatal infection	276	275			
	Missing	1	2			
Admitted to neonatal unit	Yes	45 (13.3)	45 (13.4)	RD 0.01 (–0.05 to 0.06)	RR 0.99 (0.67–1.44)	.94
	Missing	0	2			
Length of stay in neonatal unit (d)	Geometric mean	2.9	2.4	—	GMR 1.36 (0.90–2.05)	.15
	Median (IQR)	3.0 (2.0–5.0)	3.0 (1.0–5.0)			
	Min–max	0.0–48.0	0.0–20.0			
	Not admitted to neonatal unit	292	290			
	Missing	0	3			

BMI, body mass index; *CI*, confidence interval; *GMR*, geometric mean ratio; *IQR*, interquartile range; *MeD*, median difference; *MD*, mean difference; *RD*, risk difference, *RR*, risk ratio; *SD*, standard deviation.

[a] The risk difference is used as an estimator of treatment effect for binary variables, where dinoprostone is the reference category, and risk differences< 0 favor Dilapan-S.; The risk differences are estimated using a fixed binomial model with an identity link adjusting for age, BMI, and parity. Risk difference is not applicable for the boxes shaded; [b] The risk ratio is used as an estimator of the treatment effect for binary variables, and the mean differences, median differences, and geometric mean ratios are used as an estimator of treatment effect for continuous variables; dinoprostone is the reference category and risk ratio values <1 favor Dilapan-S; mean differences and median differences < 0 favor dinoprostone; geometric mean ratios <1 favor Dilapan-S. The risk ratios are estimated using a mixed binomial model with a log link adjusting for age, BMI, and parity and the randomizing center as a random effect, with the exception of requirement of review by a neonatal doctor, which is estimated using a fixed binomial model with a log link adjusting for age, BMI, and parity.; The geometric mean ratios are estimated using a mixed effect linear regression adjusted for minimization variables and the randomizing center as a random effect; [c] Confidence interval not computed, as the estimated bootstrap variance is 0; [d] *P* value is not computed, as the estimated variance is 0; [e] Those who had no neonatal infection are included in the unpresented 'No' category.

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TABLE 6
Maternal satisfaction

Question	Response	Dilapan-S (n=337) Number of questionnaires received (n=260)	Dinoprostone (n=337) Number of questionnaires received (n=231)
Insertion of device or drug			
Before placement of the induction drug or device, were you worried about the insertion procedure itself?	Not at all	51 (24.6)	48 (21.6)
	Slightly	76 (36.7)	82 (36.9)
	Moderately	45 (21.7)	51 (23.0)
	Very	20 (9.7)	29 (13.1)
	Extremely	15 (7.3)	12 (5.4)
	Missing	24	38
Did insertion of the drug or device cause you to become anxious?	Not at all	84 (41.2)	75 (33.6)
	Slightly	62 (30.4)	62 (27.8)
	Moderately	27 (13.2)	51 (22.9)
	Very	19 (9.3)	26 (11.7)
	Extremely	12 (5.9)	9 (4.0)
	Missing	27	37
Did insertion of the drug or device cause you any discomfort?	Not at all	32 (15.8)	33 (14.8)
	Slightly	69 (34.2)	78 (35.0)
	Moderately	42 (20.8)	53 (23.8)
	Very	39 (19.3)	33 (14.8)
	Extremely	20 (9.9)	26 (11.7)
	Missing	29	37
How much pain did you have while the drug or device was being put in place?[a]	Mean (SD)	4.3 (2.8)	4.7 (2.7)
	Median (IQR)	4.0 (2.0–7.0)	4.0 (3.0–7.0)
	Min–max	0.0–10.0	0.0–10.0
	Missing	25	42
When device or drug was in place			
Were you able to perform your desired daily activities such as walking, dressing, maintaining hygiene, and showering?	Always	155 (76.0)	104 (46.9)
	Often	31 (15.2)	61 (27.5)
	Sometimes	13 (6.4)	35 (15.8)
	Seldom	4 (2.0)	20 (9.0)
	Never	1 (0.5)	2 (0.9)
	Missing	27	38
Were you able to get some time to relax?	Always	108 (52.9)	62 (27.9)
	Often	51 (25.0)	56 (25.2)
	Sometimes	32 (15.7)	61 (27.5)
	Seldom	8 (3.9)	24 (10.8)
	Never	5 (2.5)	19 (8.6)
	Missing	27	38
Were you able to get some sleeping time?	Always	97 (48.0)	49 (22.1)
	Often	49 (24.3)	47 (21.2)
	Sometimes	37 (18.3)	53 (23.9)
	Seldom	12 (5.9)	35 (15.8)
	Never	7 (3.5)	38 (17.1)
	Missing	29	38

(continued)

TABLE 6
Maternal satisfaction *(continued)*

Question	Response	Dilapan-S (n=337) Number of questionnaires received (n=260)	Dinoprostone (n=337) Number of questionnaires received (n=231)
Were you able to feel contractions?	Always	52 (26.3)	84 (37.8)
	Often	35 (17.7)	70 (31.5)
	Sometimes	38 (19.2)	33 (14.9)
	Seldom	25 (12.6)	17 (7.7)
	Never	48 (24.2)	18 (8.1)
	Missing	33	38
Were contractions frequent?	Not at all	73 (37.1)	28 (12.7)
	Slightly	44 (22.3)	40 (18.2)
	Moderately	40 (20.3)	55 (25.0)
	Very	29 (14.7)	57 (25.9)
	Extremely	11 (5.6)	40 (18.2)
	Missing	34	40
Were contractions intense?	Not at all	87 (44.2)	34 (15.5)
	Slightly	38 (19.3)	30 (13.7)
	Moderately	32 (16.2)	47 (21.5)
	Very	26 (13.2)	47 (21.5)
	Extremely	14 (7.1)	61 (27.9)
	Missing	34	41
Did you feel any discomfort with the drug or device in place?	Not at all	92 (46.2)	59 (22.7)
	Slightly	40 (20.1)	56 (25.3)
	Moderately	36 (18.1)	53 (24.0)
	Very	12 (6.0)	26 (11.8)
	Extremely	19 (9.6)	27 (12.2)
	Missing	32	39
Please rate the overall pain that you had while the drug or device was in place.[a]	Mean (SD)	3.1 (2.8)	5.6 (3.0)
	Median (IQR)	3.0 (0.0–5.0)	6.0 (3.0–8.0)
	Min–Max	0.0–10.0	0.0–10.0
	Missing	31	39
How likely is it that you would have the same drug or device in your next pregnancy if you needed an induction?[b]	Mean (SD)	6.6 (3.5)	4.5 (3.4)
	Median (IQR)	8.0 (5.0–10.0)	5.0 (1.0–7.0)
	Min–max	0.0–10.0	0.0–10.0
	Missing	26	39
How likely is it that you would recommend the same drug or device to a friend if they needed an induction?[b]	Mean (SD)	6.8 (3.4)	4.6 (3.4)
	Median (IQR)	8.0 (5.0–10.0)	5.0 (1.0–7.0)
	Min–max	0.0–10.0	0.0–10.0
	Missing	27	38
Overall experience			
I was satisfied with my overall childbirth experience	Strongly disagree	25 (12.1)	20 (8.9)
	Disagree	22 (10.6)	22 (9.8)
	Neutral	41 (19.8)	44 (19.6)
	Agree	71 (34.3)	86 (38.4)
	Strongly agree	48 (23.2)	52 (23.2)
	Missing	24	36

(continued)

TABLE 6
Maternal satisfaction *(continued)*

Question	Response	Dilapan-S (n=337) Number of questionnaires received (n=260)	Dinoprostone (n=337) Number of questionnaires received (n=231)
I was treated with respect by all the staff	Strongly disagree	6 (2.9)	5 (2.2)
	Disagree	11 (5.3)	1 (0.4)
	Neutral	6 (2.9)	14 (6.2)
	Agree	49 (23.8)	48 (21.3)
	Strongly agree	134 (65.1)	157 (69.8)
	Missing	25	35
I was involved in making decisions as much as I wanted	Strongly disagree	8 (3.9)	7 (3.1)
	Disagree	9 (4.4)	11 (4.9)
	Neutral	16 (7.8)	22 (9.8)
	Agree	58 (28.2)	78 (34.7)
	Strongly agree	115 (55.8)	107 (47.6)
	Missing	25	35
My expectations for labor and birth were met	Strongly disagree	26 (12.6)	16 (7.2)
	Disagree	32 (15.5)	41 (18.5)
	Neutral	46 (22.3)	49 (22.1)
	Agree	60 (29.1)	58 (26.1)
	Strongly agree	42 (20.4)	58 (26.1)
	Missing	25	35
I felt safe at all times	Strongly disagree	11 (5.3)	9 (4.0)
	Disagree	19 (9.1)	11 (4.9)
	Neutral	17 (8.2)	27 (12.0)
	Agree	60 (28.9)	67 (29.8)
	Strongly agree	101 (48.6)	111 (49.3)
	Missing	23	35
Good communication from the staff kept me well-informed	Strongly disagree	12 (5.8)	8 (3.6)
	Disagree	13 (6.3)	9 (4.0)
	Neutral	14 (6.7)	23 (10.3)
	Agree	67 (32.2)	74 (33.0)
	Strongly agree	102 (49.0)	110 (49.1)
	Missing	23	36
I felt in control	Strongly disagree	19 (9.2)	17 (7.6)
	Disagree	30 (14.5)	30 (1.43)
	Neutral	39 (18.8)	50 (22.3)
	Agree	70 (33.8)	73 (32.6)
	Strongly agree	49 (23.7)	54 (24.1)
	Missing	24	36
My induction drug or device was effective	Strongly disagree	30 (14.6)	25 (11.2)
	Disagree	25 (12.1)	29 (13.0)
	Neutral	20 (9.7)	22 (9.9)
	Agree	56 (27.2)	69 (30.9)
	Strongly agree	75 (36.4)	78 (35.0)
	Missing	25	37

(continued)

TABLE 6
Maternal satisfaction *(continued)*

Question	Response	Dilapan-S (n=337) Number of questionnaires received (n=260)	Dinoprostone (n=337) Number of questionnaires received (n=231)
I was satisfied with the overall induction of labor procedure	Strongly disagree	25 (12.1)	17 (7.6)
	Disagree	27 (13.1)	26 (11.6)
	Neutral	31 (15.1)	50 (22.3)
	Agree	59 (28.6)	76 (33.9)
	Strongly agree	64 (31.1)	55 (24.6)
	Missing	25	36

[a] Scale of response ranges from 0–10; higher scores indicate a more negative response; [b] Scale of response ranges from 0–10; higher scores indicate a more positive response.
Gupta. Randomized trial of Dilapan-S vs dinoprostone. Am J Obstet Gynecol MFM 2022.

intrauterine growth restriction or reduced fetal movements of their baby. These represent a group of women with reduced fetal reserve where Dilapan-S would be a benefit, as it is associated with a lower risk of uterine hyperstimulation.[15] This would suggest that Dilapan-S could also be used for cervical ripening in an outpatient procedure. The UK induction of labor guidelines were updated in 2021 and now suggest that mechanical methods of induction can be considered where pharmacologic methods are not suitable.[16] This includes women with previous uterine incisions for whom prostaglandins are contraindicated in some countries' guidelines. Dilapan-S has advantages over balloon catheters[9] and misoprostol[10], and our trial results are consistent with these findings.

Research implications

Current evidence suggests that balloon catheters can be used for a cervical ripening process in the outpatient setting[17,18] and for women who have had a previous cesarean delivery.[19] Previous research suggests that women are likely to prefer outpatient induction of labor, which is also associated with reduced hospital costs.[20–22] However, further research into the safety, acceptability, and cost-effectiveness of Dilapan-S in this setting is needed.

Strengths and limitations

More women in the Dilapan-S group did not receive the allocated intervention (86 [25.5%]) compared with the dinoprostone group (36 [11.0%]) because of the initial lack of available trained staff to fit Dilapan rods. Dilapan has to be correctly fitted, ensuring that the tip of the rod crosses the internal os, which requires specific training. As the trial progressed, additional training was provided at regular intervals at all recruitment sites, improving the availability of trained staff. Despite the difference in adherence levels between the groups, sensitivity analyses suggest that conclusions remain robust when excluding women not adherent to the intervention.

Cochrane Collaboration Reviews and National Institute for Health and Care Excellence (NICE) guidance identify birth within 24 hours of the start of induction of labor, cesarean delivery, and uterine hyperstimulation as the most clinically relevant measures. However, this conclusion is contested.[23] We removed the time interval for our primary outcome, which was initially failure to achieve a vaginal delivery within 36 hours. Our decision was driven by an interim observation that intervals from randomization to amniotomy and delivery were longer than anticipated, particularly because of the delays between women being ready for amniotomy and having the procedure. There was also a concern that the delays would reverse the cervical ripening effect achieved by either intervention; this was particularly for the Dilapan-S group, as the cervix rehydrated.

Conclusion

Evidence from this study has shown that women undergoing induction of labor with Dilapan-S have similar rates of cesarean delivery and maternal and neonatal adverse events compared with dinoprostone. This suggests that a slower approach to cervical ripening with Dilapan-S as opposed to the more rapid onset of ripening achieved by prostaglandins can be offered to women, following a discussion of the relative benefits of each approach.

SOLVE Collaborators Group

Janesh Gupta, Jane Daniels, and Lee Middleton contributed to the design of the trial. Janesh Gupta, Peter Brocklehurst, Jane Daniels, Pollyanna Hardy, and Clive Stubbs contributed to the delivery and interpretation of the trial; Elizabeth Adey and Kelly Hard contributed with delivery of the trial. Hannah Bensoussane, Alisha Maher, and Yongzhong Sun undertook the statistical analysis with oversight from Pollyanna Hardy. Amanda Cotterill, Chloe O'Hara, and Diane Whitehouse were responsible for the day-to-day management of the trial. Janesh Gupta, Alisha Maher, Peter Brocklehurst, Jane Daniels, Pollyanna Hardy, and Amanda Cotterill drafted the report, and all authors provided input into the editing for publication.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajogmf.2022.100628.

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