Dilapan-S®

HYGROSCOPIC CERVICAL DILATOR

GENTLE. PREDICTABLE. MANAGEABLE.

MEDISAFE
DISTRIBUTION INC.

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What is Dilapan-S?

Dilapan-S is an osmotic hygroscopic cervical dilator from a patented Aquacryl hydrogel that guarantees consistency of action. It is a rigid gel rod that increases in volume by absorbing fluids, gradually dilating the cervix. Simultaneously, Dilapan-S initiates endogenous prostaglandin release, causing collagen degradation which softens the cervix.

Dilapan-S is sterilized by irradiation. It is manufactured in an ISO 9001 Certified facility and is fully CE certified under the Medical Device Directive (EN46002). Approved by the FDA for sales in the United States.

Indications for use:

Cervical ripening prior to the induction of labor

Cervical dilation prior to instrumentation of the uterine cavity, e.g., termination of pregnancy, ERPC, fetal demise, etc.

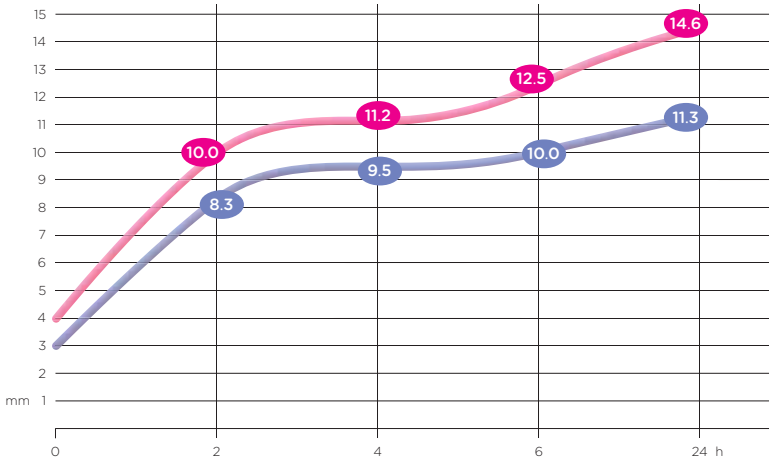
Contraindications:

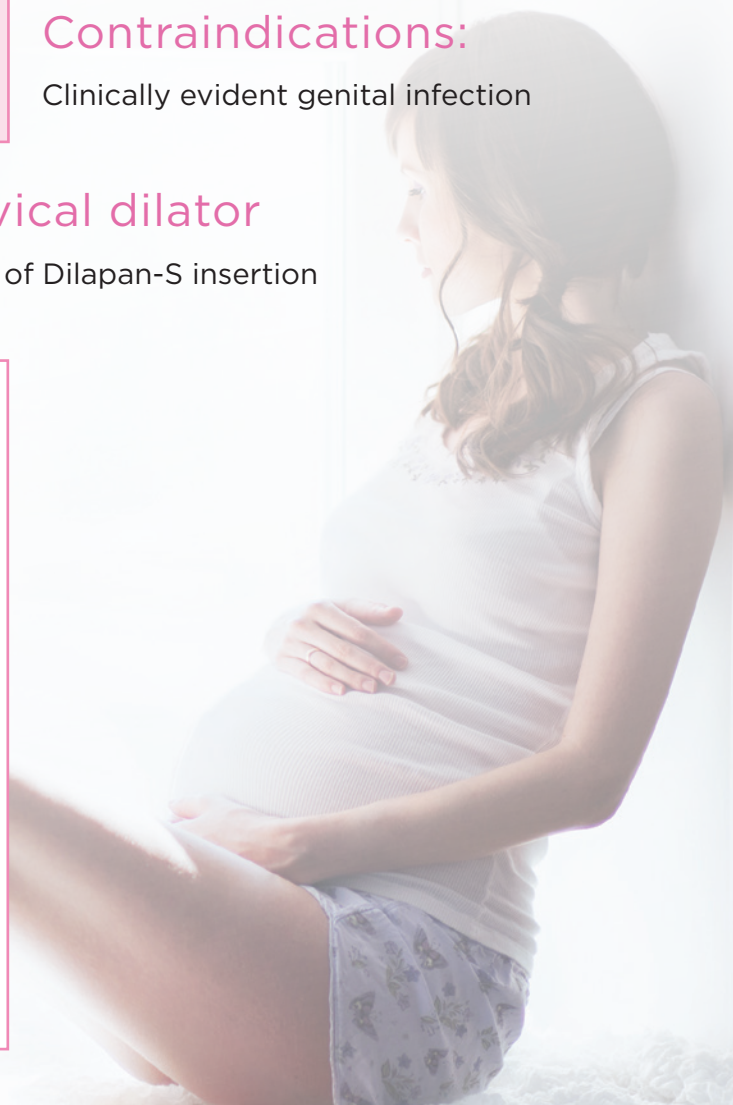
Clinically evident genital infection

Fast-acting synthetic osmotic cervical dilator

Magnitude of cervical dilation depends on the duration of Dilapan-S insertion

Achieved cervical dilation depending on length of Dilapan-S insertion



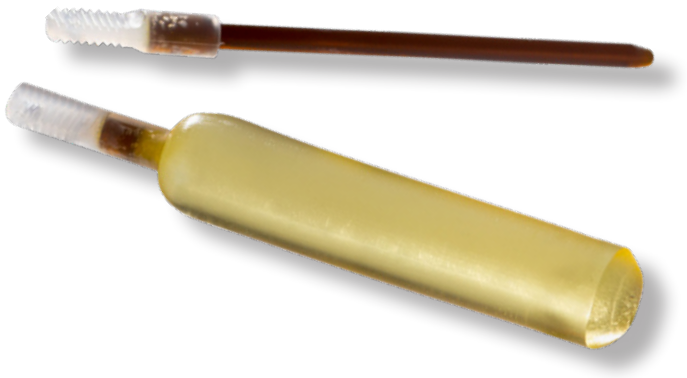


Recommendation for use:

Size:	Indication:
3x55mm	When Dilapan-S 4mm cannot be inserted in early pregnancy, or when removal is to be accomplished in less than 4 hours
4x55mm	Cervical ripening prior to induction of labor
4x65mm	Cervical preparation prior to the termination of pregnancy

Dilapan-S tips for insertion:

- Moisten Dilapan–S® with sterile water or saline to lubricate the surface prior to insertion.
- A sponge forceps may be used to stabilize the cervix and to straighten the cervical canal.
- Grasp Dilapan–S® at the handle. Gradually and without undue force, insert Dilapan–S® until it traverses the external and internal os.
- Do not insert Dilapan–S® past the handle. The border of the handle should rest at the external os.
- If inserting multiple Dilapan–S®, repeat the above steps for each one.
- Do not leave Dilapan–S® in place more than 24 hours.



- To remove Dilapan–S®, grasp the handle only with forceps and apply steady downward traction, in line with the long axis of the dilator. Do not twist excessively and do not use the marker string.
- For detailed instructions for use, please read the leaflet in each pack.

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Dilapan-S Comparison with Laminaria

Products' Characteristics

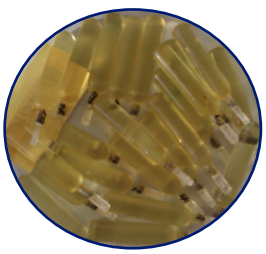
	Laminaria	Dilapan-S
Material	Natural Made of sea-grown plant	Synthetic Made of patented hydrogel Aquacryl
Diameter	2-10mm	3 and 4mm
Length	60-85mm	55 and 65mm
Time to minimal effect	6 hours	2 hours
Time to maximum effect	12-24 hours	4-6 hours*
Maximum dilation achieved	Approximately 3 times dehydrated diameter	Approximately 4 times dehydrated diameter
Sterilization	Ethylene Oxide	Irradiation
Predictability and consistency of action	Low. Its properties, shape, and dimensions are inconsistent since it's a natural product	High, thanks to pre-defined synthetic material
Risk of allergic reactions	Higher. Natural material. Residues of sterilizing agent can be present.	Lower / inert synthetic material
Risk of infection	Higher. More difficult to sterilize. Natural product can transfer spores.	Lower because of synthetic material

Summary/Clinical Impact

- Dilapan-S is evaluated as the best osmotic dilator (Society of Family Planning Guidelines 2014) [21]
- Dilapan-S is faster: higher dilation can be reached with 1 piece in shortened time frame, fewer pieces can be used to reach the same dilation
- Dilapan-S is suitable and recommended for 1-day D&E procedure, whereas laminaria is not
- In head-to-head clinical study, Dilapan-S reached significantly higher efficacy—98%, whereas laminaria efficacy was 40% and 56% respectively (two laminaria cohorts evaluated)
- Dilapan-S is superior over laminaria in predictability and consistency of action thanks to synthetic material—patented hydrogel AQUACRYL 90
- Dilapan-S sterilization by irradiation assures lower/ no risk of allergic reactions when compared to laminaria sterilized by ethylene oxide
- Dilapan-S offers higher safety profile. Synthetic material eliminates the risk of transmission of spores/infections from natural product

Significant difference in predictability and consistency of action

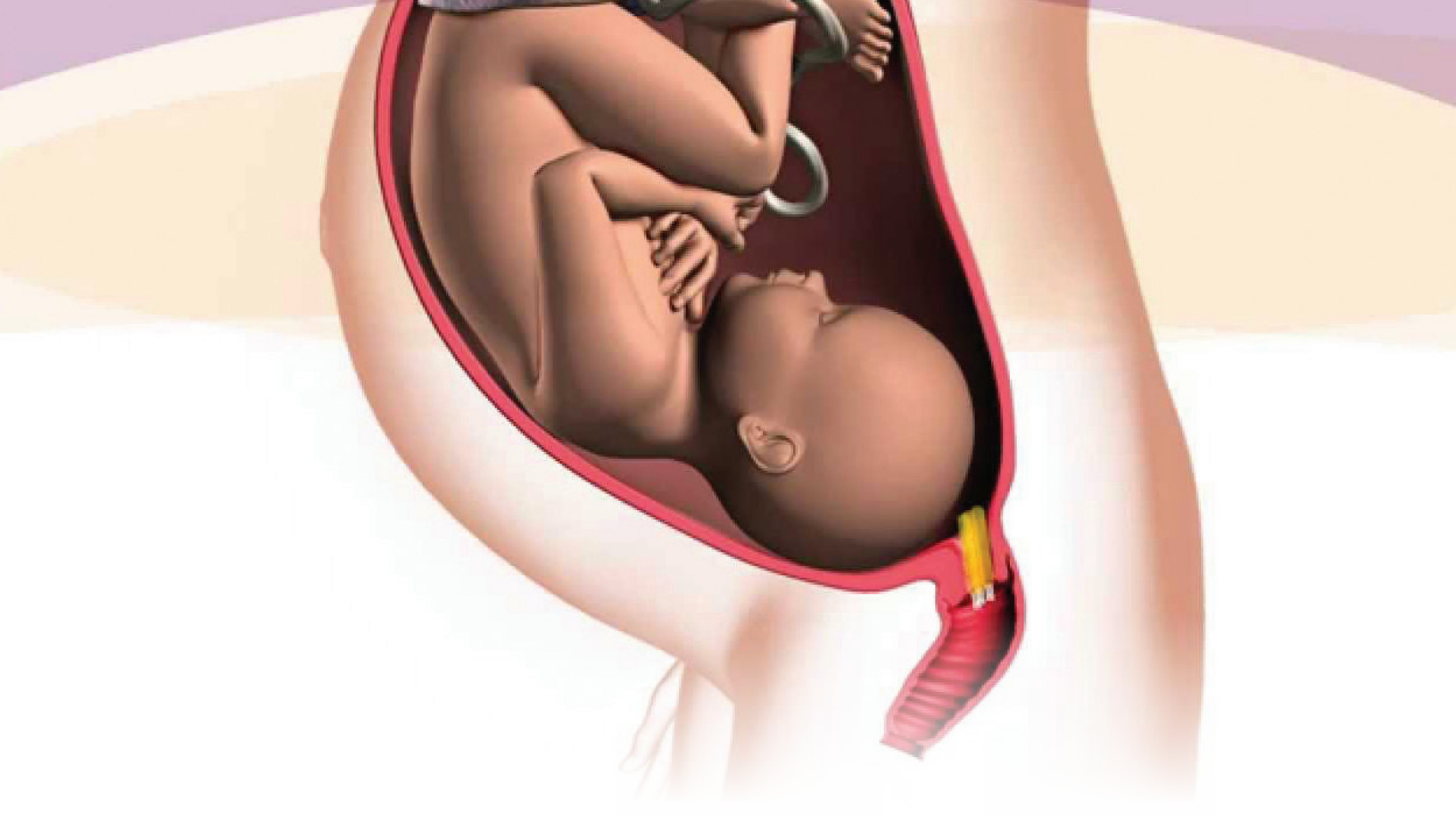
Laminaria



Dilapan-S

Swollen rods are illustrative of difference in predictability and consistency of action between synthetic hydrogel AQUACRYL (DILAPAN-S) and natural material (laminaria)

* Dilation reached with laminaria in 24 hours can be reached with DILAPAN-S in 4-6 hours



Cervical Ripening Prior to the Induction of Labor

- Gentle and predictable cervical ripening
- No pharmacological side effects
- Easily managed on-site or at home
- High level of patient comfort
- Effective and safe for VBAC

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Dilapan-S® key benefits:

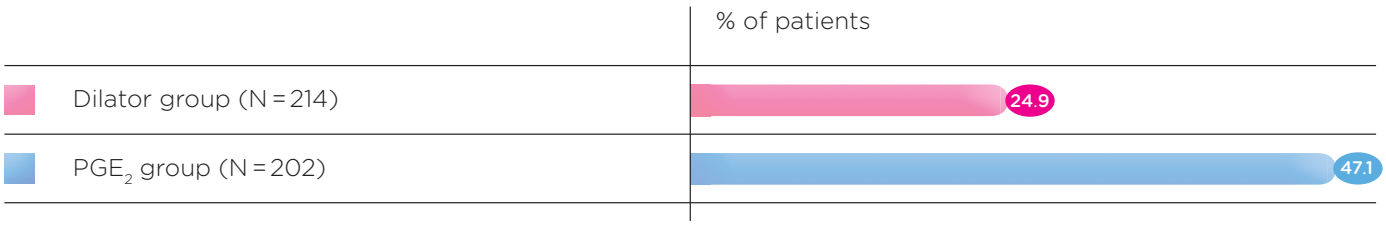
- significant increase in cervical ripening and Bishop score[17, 18]
- high predictability due to material and mode of action
- minimal risk of uterine hyperstimulation and impact on the fetal heart rate[18, 19]
- no pharmacological side effects
- effective and safe even in women with Caesarean section in medical history[11]
- accentuates the physiological processes of labor
- very high patient acceptability

Hygroscopic dilators produce minimal uterine activity during the ripening process[18, 20]

"Onset of regular uterine activity as a result of preinduction is a negative and unwanted side effect"[14]

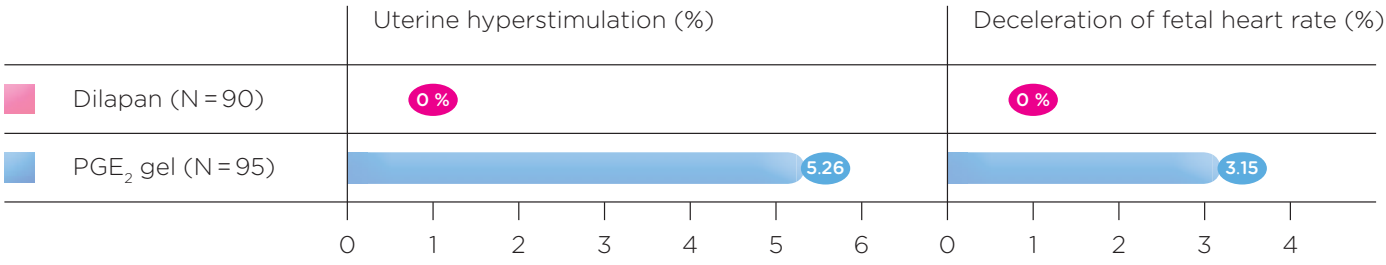
"The principal role of the agents used for cervical ripening is to soften an unripe cervix independent of uterine activity"[16]

Uterine contraction during ripening phase



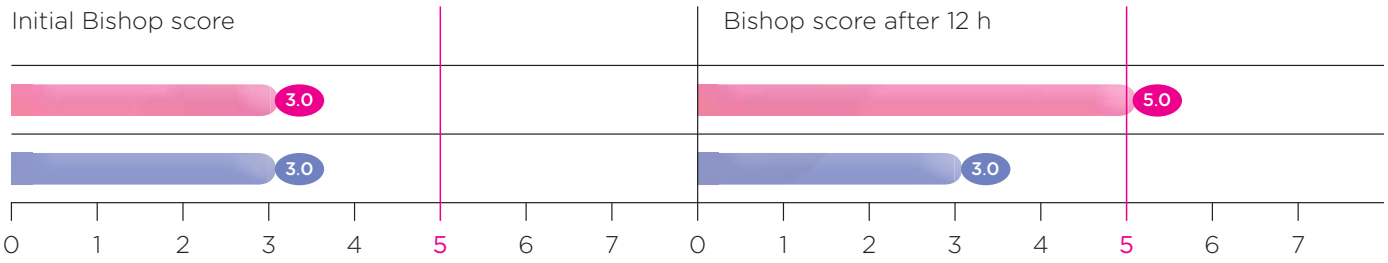
p = 0.001

Uterine hyperstimulation and abnormal fetal heart rate changes



Hygroscopic dilators (like Dilapan-S) significantly enhance cervical ripening and increase the Bishop score, enabling smoother labor induction [17, 18]

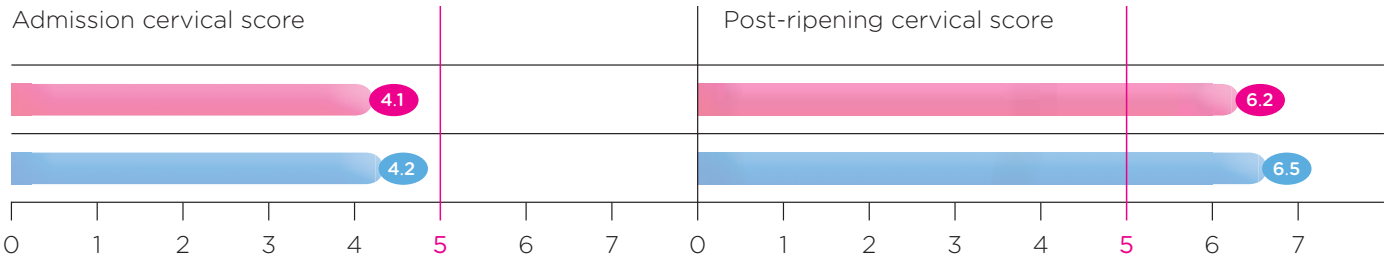
Comparison with control group



Dilator group (N = 112)
Control group (N = 128)

p = 0.001

Comparison with PGE_2



Dilator group (N = 214)
PGE_2 group (N = 202)

Non-significant difference

"Successful labor induction is clearly related to the state of the cervix. Women with an unfavorable cervix who have not experienced cervical ripening phase before labor present the greatest challenge with regard to labor induction" [16]

"Labor should only be induced if the Bishop Score is 5 or higher—this indicates sufficient cervical ripening" [15]

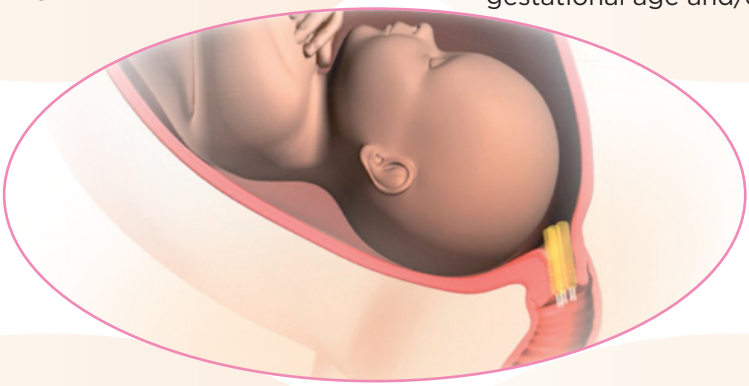
High Therapeutic Potential

Efficacy

- Significant Bishop score increase[2–11] and vaginal delivery rate up to 80%[2,3,4]
- Spontaneous vaginal delivery with no pharmacological intervention up to 20%[2,3,5–8,11]
- Suitable for VBAC[2,3,6,10]

Safety[2-11]

- No hyperstimulation or fetal pathology during cervical ripening
- No infectious complications related to the use of Dilapan-S®
- No limitation related to mother's gestational age and/or comorbidities



Patient satisfaction

- Low rate of uterine contractions during cervical ripening [2,3,5–8,10,11]
- Up to 90% of women can relax or sleep during cervical ripening [5–8]
- Minimizing of vaginal examination during cervical ripening

Cost-effectiveness

- Potential prevention of C. sections in high-risk groups of patients [2,3,5–8,10,11]
- Outpatient regimen (home cervical ripening) for low-risk groups of patients [2,3,4]
- Saving time of health care professionals thanks to one-time application and no need of continuous CTG monitoring[12]

Unique combination of efficacy, safety, and patient satisfaction

- For clinicians, helps to minimize safety risks while maintaining high efficiency [2–11]
- For mothers, ensures gentle and predictable cervical ripening and promotes natural vaginal delivery [2–11]
- For health care providers, offers reduction of overall healthcare cost [2,3,4]

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Multiple modes of action[1] mimic physiological processes of the labor

- Mechanical: Controlled pressure on the cervical wall dilates the cervix
- Biophysical: Partial reversible osmotic dehydration softens the tissue
- Physiological: Promotion of endogenous prostaglandin release, causing collagen degradation and tissue restructuring

Dilapan–S® doesn't contain any pharmacologically active substance that could be released during its use.

Efficacy and safety confirmed by

- **International observational e-registry on the use of Dilapan–S® osmotic dilator for cervical ripening prior to labor induction (ongoing)[2,3]**
  - 11 study sites from 7 countries participate in the project to collect induction of labor clinical data
  - 543 subjects enrolled/444 subjects eligible for analysis
- **Prospective clinical study comparing Dilapan–S® with PGE_2 gel and Estradiol gel[4]**
  - 247 patients randomized, 82 treated by Dilapan–S®
- **Prospective, observational, multicenter data collection on the use of osmotic dilator Dilapan–S® in labor preinduction in females with/without Caesarean section in medical history[5–8]**
  - 6 study sites collected data from 96 patients, including women with previous Caesarean section
- **Prospective observational study evaluating Dilapan–S® efficacy and safety[9]**
  - 92 patients
- **Retrospective study evaluating efficacy and safety of Dilapan–S® in labor preinduction[10,11]**
  - 68 patients, incl. women with previous Caesarean section

General recommendation for the treatment regimen:

Cervical ripening	Labor induction (promotion of uterine contraction)
3-5 pieces of Dilapan-S® 4x55 mm for 12-15 hours*	ARM** + uterotonic***

* Number of pieces can differ depending on initial Bishop score.

** Artificial rupture of membranes can be proceeded if beneficial and in line with local clinical protocol.

*** Dilapan–S® ripens the cervix independently on uterine contractions. After the cervical ripenening, a uterotonic such as oxytocin is recommended to promote adequate uterine contractions, if cervical ripening does not develop into spontaneous vaginal birth.

Clinical Evidence 1

International observational e-registry on the use of Dilapan-S osmotic dilator for cervical ripening prior to labor induction

Material and methods:

- Prospective observational international multicentric e-registry performed between May 2015 and April 2017.
- The main objective is to monitor clinical outcomes of the use of Dilapan-S®
  1) for cervical ripening and following procedures of induction of labor with the main focus on the duration of cervical ripening, overall duration of induced labor procedure and the rate of vaginal deliveries within 24 hours; estimated total sample size 600 women (IOL)

Project overview:

- 11 study sites / 7 countries (UK, Germany, USA, Czech Republic, Slovakia, India, Russia)
- Chief investigator: Prof. Janesh Gupta, MSc, MD, FRCOG, Birmingham Women's Hospital, Birmingham, UK
- Electronic data collection, continuous remote data monitoring
- 543 subjects enrolled/ 444 subjects eligible for analysis

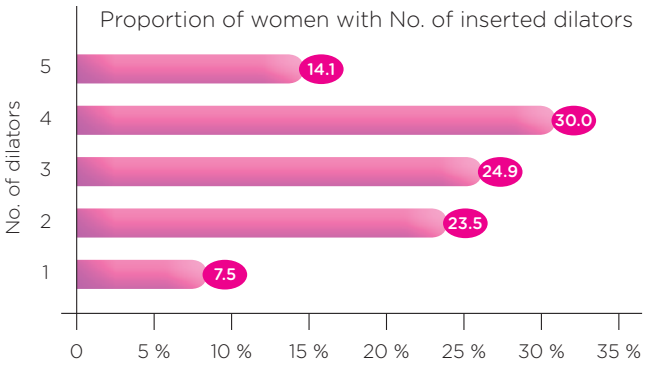
2015
14 sites currently recruiting
2 sites are ready to start
5 expecting EC approval

2016
Initiation of 100% of study sites
Interim data reports
Presentation of interim results

2017+
Closing of data records
Final study reports
Publication and presentations of complete clinical results

Country	Study Center	No. of subjects enrolled	No. of subjects analyzed
UK	Birmingham Women's Hospital, Birmingham	53	45
Germany	Klinikum im Friedrichshain Vivantes, Berlin	106	28
Germany	Buerger Hospital, Frankfurt am Main	51	42
Czech Republic	Masaryk University Hospital Brno	89	88
Slovakia	University Hospital Trnava	40	40
India	UCMS Guru Teg Bahadur Hospital, New Delhi	40	40
India	Sri Ramachandra Medical College, Chennai	41	40
India	Fernandez Hospital, Hyderabad	40	39
Russia	Research Center Obstet & Gynecol & Perinatol, Moscow	34	34
USA	Bellevue Hospital of New York University, NY	9	9
USA	University of Texas Medical Branch Galveston, TX	40	39
Total	11	543	444

- Number of inserted dilators varied from one to five pieces



Gain in Bishop Score	Mean	SD	Mean Gain
All women (N=444)			
Bishop score prior to insertion	2.9	(±1.2)	3.6
Bishop score after extraction	6.5	(±2.3)	
Nulliparas (N=289)			
Bishop score prior to insertion	2.9	(±1.3)	3.7
Bishop score after extraction	6.6	(±2.3)	
Women with previous C. section (N=41)			
Bishop score prior to insertion	2.6	(±1.1)	3.8
Bishop score after extraction	6.4	(±1.7)	
Multiparas (N=114)			
Bishop score prior to insertion	2.9	(±1.1)	3.5
Bishop score after extraction	6.3	(±2.3)	

- The average increase of Bishop score was +3.60 (measured on the 13-point scale).
- Average rate of vaginal delivery was 69.8% and varied from 51% to 83% in relation of each study site.

Summary of Primary and Secondary Outcomes (N=444)	Dilators insertion<12 hrs (N=188)	Dilators insertion>12 hrs (N=256)	P-Value
Mean gain in Bishop S.	3.6 (± 2.3)	3.7 (± 2.2)	0.8330
Mean overall vaginal deliveries (VD)	**76.6%**	**64.8%**	**0.0077**
Mean VD rate within 24 hrs	45.7%	16%	<.0001
Mean VD rate within 36 hrs	66%	48.4%	0.0002
Mean VD rate within 48 hrs	75.5%	54.7%	<.0001
Mean insertion-delivery interval (hours)	**24.3(±10.4)**	**39.1(±29.2)**	**<.0001**

- Uterine contractions during cervical ripening reported in 25% of subjects (low frequency, mild intensity)
- Only 3.4% of women reported not-serious complications or discomfort
- Only 1 uterine hyperstimulation reported during cervical ripening based on CTG
- Maternal infectious complications were observed in 14 cases (3.2%). No association of infection with the use of osmotic dilator.
- 1 suspected fetal pathology reported during cervical ripening based on CTG

Conclusion:

- **Application of Dilapan-S is a safe and efficient technique of cervical ripening.**
- **Dilapan-S can contribute to the achievement of high vaginal delivery rate.**
- **No serious adverse outcome for mother and newborn reported.**
- **Low occurrence of uterine contractions during cervical ripening.**
- **Potential to prevent unnecessary Caesarean sections in high-risk patients.**
- **This application of Dilapan-S can be an outpatient procedure in low-risk patients and therefore cost-effective.**

References: 1. Gupta JK et al. Mechanical methods of cervical ripening. Oral presentation at All India Congress of Obstetrics and Gynaecology 2016. Agra, India 13-17 January 2016. 2. Data on file

Clinical Evidence 2

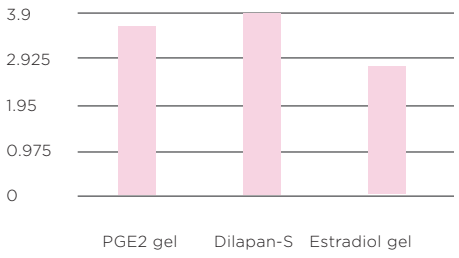
Prospective clinical study comparing Dilapan-S with PGE2 gel and Estradiol gel

Material and methods:

- 247 patients were randomized to one of the following preinduction protocols.
  - four hygroscopic dilators (Dilapan-S) applied intracervically (n=82) for 14 hours
  - 0.5mg of Prostaglandin E2 gel (Prepidil gel) administered intracervically (n=83)
  - 150mg of Estradiol gel administered intravaginally (n=82)
- Including criteria: patient informed consent, singleton pregnancy of more than 36 weeks, cephalic presentation, Bishop score < 5 points, reactive non-stress test.
- Cervical ripening was evaluated as successful if Bishop Score increased to ≥ 5 (measured on the 10-point scale) and/or by at least 2 points in a time period of 14 hours.

Results:

- Average Bishop score increase (measured on the 10-point scale).
  - Dilapan-S: 3.9
  - PGE2 gel: 3.7
  - Estradiol gel: 2.8
- Vaginal delivery rate in Dilapan-S group: 80.5%



	Successful preinduction rate	Labor induced by preinduction alone	Induction to delivery interval	Caesarean section rate
Dilapan-S	89%	20.7%	7hrs 49m	19.5%
PGE2 gel	85%	31.3%	7hrs 27m	24.4%
Estradiol gel	76.8%	17.1%	9hrs 15m	24.4%

- Neither serious side effects nor negative neonatal outcome were noted in either group, incl. infectious complications.

Conclusion:

- **Dilapan-S rods and PGE2 gel proved as similarly efficient to cervical ripening and with higher efficacy in comparison with Estradiol gel.**
- **Induction to delivery interval was shorter in the PGE2 gel and the Dilapan-S groups.**
- **The Dilapan-S group had the lowest Caesarean section rate.**
- **All cervical ripening methods were evaluated as safe.**
- **The labor and delivery should preferably take place during the daytime for high-risk patients. From this point of view, Dilapan-S seems more appropriate for preinduction of high-risk pregnancies.**
- **Safety profile of Dilapan-S suggests the product might be appropriate for outpatient cervical ripening for low-risk patients.**

Reference: Roztocil A et al. A comparison of three preinduction cervical priming methods: Prostaglandines E2 gel, Dilapan-S rods, and Estradiol gel. CZ Gynecol. 63, 1988. c.1, str. 3-9

Clinical Evidence 3

Prospective, observational, multicenter data collection on the use of the osmotic dilator Dilapan-S in labor preinduction in women with or without Caesarean section in medical history

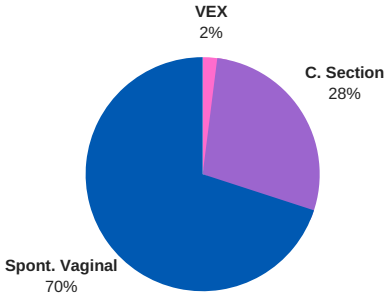
Material and methods:

- The study was performed between May 2013 and October 2013 at 6 clinical centers.
- 96 women with singleton pregnancy after 36 weeks of gestation with head longitudinal position of the baby and Bishop score <4 were included in the data analysis.
- 35 patients (36.5%) had Caesarean section reported in their medical history.
- Assessment of the primary objective and success of cervical ripening procedure was based on the Bishop score. Safety data collection was focused on fetal hypoxia, uterine hypertonus, clinical signs of infection and other potential adverse effects related to the use of Dilapan-S. In addition, patients' satisfaction was evaluated by personal patient questionnaire.

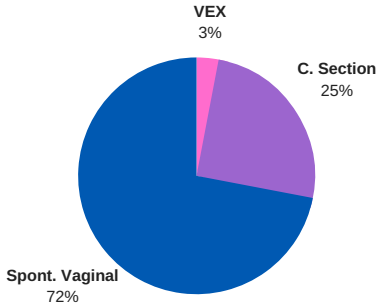
Results:

- Average number of inserted dilators was 2 (range from 2 to 5).
- Bishop score increase (measured on the 10-point scale) was +3.23 points (from 2.81 to 6.13). By 3.7 in group of women without previous C. section and by 2.7 in group of women with previous C. section, resp. (p-value) ≤ 0.003.
- Successful preinduction rate (Bishop score >5): 86.5%

	All women		Women with previous C. section		Women without previous C. section	
	n	%	n	%	n	%
Bishop score ≥ 5	83	86.5 %	29	82.7 %	54	88.5 %



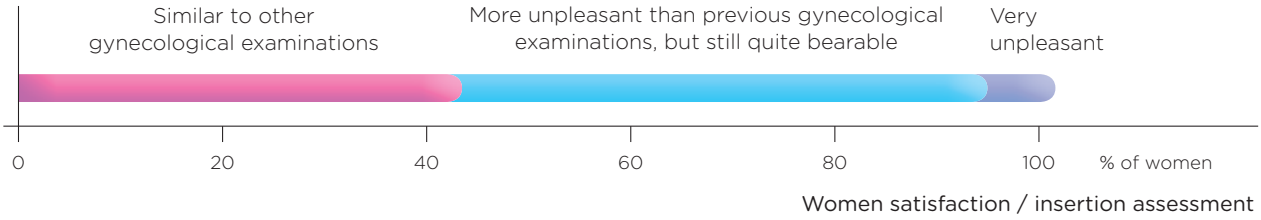
Mode of delivery in all women (n=95)



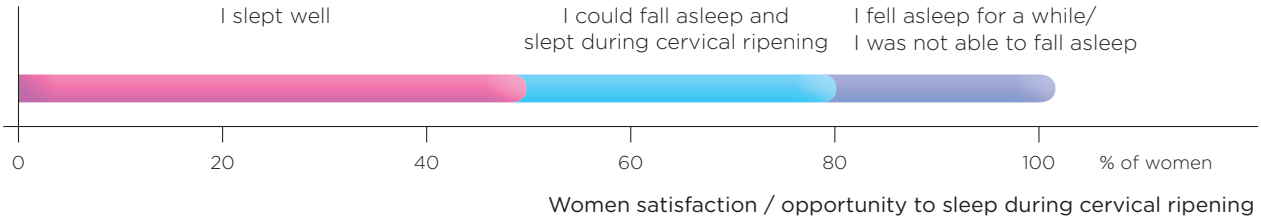
Mode of delivery in women without C. section in previous history (n=61)

- Vaginal delivery rate: 71.6% (75.4% in women without previous C. section and 64.7% in women with previous C. section, respectively).
- The mean time of Dilapan-S insertion was 16.99 hours (mainly overnight).
- Dilapan-S extraction was assessed by physicians as in 100%.
- No fetal hypoxia at CTG trace during preinduction.
- Uterine contractions measured by CTG occurred in 30 females (31.3%).
- No uterine hyperactivity (>5 contractions/10 minutes).
- Rupture of membranes associated with insertion of Dilapan-S was not reported.
- No infectious complications related to Dilapan-S use in mothers and newborns were reported.

93.7% of women evaluated Dilapan-S insertion as fully acceptable



Dilapan-S allows 4 from 5 women to sleep during the cervical ripening process



Conclusion:

- **High efficacy and safety, even in women with previous C. section, were confirmed.**
- **Low incidence of uterine activity promotes excellent patient satisfaction.**
- **The use of higher number of dilators improved clinical outcomes in terms of gain in Bishop score as well as in terms of achieving of vaginal births. Higher number of inserted dilators was not accompanied by more pain during insertion and did not affect ability to rest or sleep during preinduction.**
- **Achieving shorter preinduction time was not among the objectives of this study, but from the presented impact of the number of dilators on Bishop score can be assumed that higher number of dilators could potentially lead to shortening of the preinduction time.**

References: 1. Hruban L et al: Eff ectiveness and safety of the osmotic dilator Dilapan-S® for cervical ripening in females with/without C. section in medical history. Poster presentation. XXIV. European Congress of Perinatal Medicine, June 104, Florence, Italy 2. Zahumensky J et al: The impact of the number of pieces of osmotic dilator Dilapan-S® used for cervical ripening on the course and outcome of labor. Poster presentation, 13th World Congress in Fetal Medicine, June-July 2014, Nice, France 3. Vlk R et al: Efficacy and safety of the osmotic dilator Dilapan-S® for cervical ripening in women with/without C. section. Poster presentation. 13th World Congress in Fetal Medicine, June-July 2014, Nice, France

Clinical Evidence 4

Efficacy and Safety of the Synthetic Osmotic Dilator Prior to Induction of Labor: International Observational E-Registry

Objective:

The aim of this data collection is to monitor post-market clinical practice of the application of synthetic osmotic dilator for cervical ripening prior to induction of labor. The main focus was the rate of Caesarean sections. Additionally, we were aiming to confirm safety and tolerability of synthetic osmotic dilators in routine clinical practice as well as to provide clinical recommendations concerning number of dilators and duration of insertion.

Materials and method:

This is an interim analysis of a 2-year prospective observational international multicenter data collection involving 9 study sites in 7 countries. Demographic and procedural details and post-delivery complications for women undergoing induction of labor when synthetic osmotic dilators were used were recorded on a standardized form and entered into an electronic data capture system for analysis.

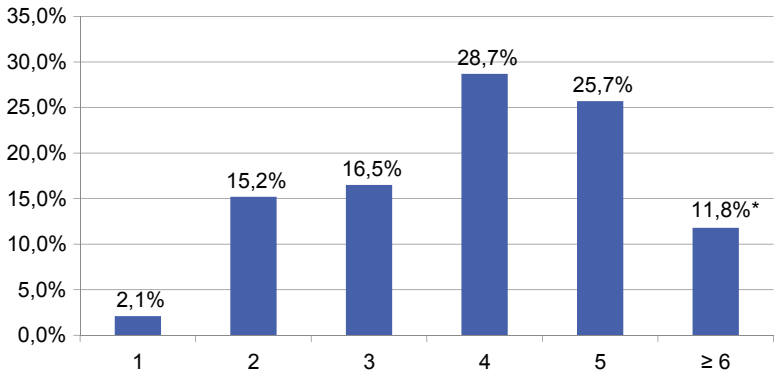
Tab. 1: Study sites overview

Country	Total No of study sites	Already initiated	No of sites involved into the analysis	No of Pts enrolled
UK	1	1	1	36
Germany	2	2	2	76
Czech Republic	1	1	1	43
Slovakia	1	1	1	40
India	3	3	3	102
USA	2	2	0	0
Russia	1	1	1	1
TOTAL	**11**	**11**	**9**	**298**

Results 1:

Between May 1, 2015 and March 21, 2016 298 women were enrolled. The mean age of subjects was 29 (18–45); the mean gestational age was 39.5 (33.1– 42.7) weeks. 67.1% of women were nulliparous, 23.2% had a previous vaginal delivery and 9.7% had previous Caesarean section. One to five synthetic osmotic dilators were used for cervical ripening per one round of dilators' insertion. In majority of women four (28.7%) or five (25.7%) osmotic dilators were used. In 41 women (13.8%) the sequential technique of insertion (2nd round of dilators after initial ripening) was provided.

Graph 1: Proportion of women with No. of inserted dilators

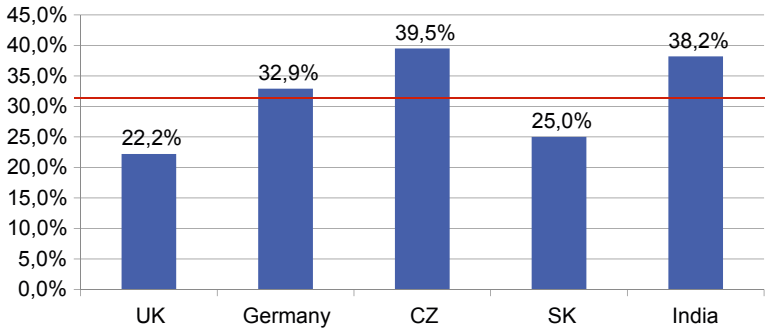


* In all cases, where ≥ 6 dilators were used, the sequential technique of insertion (2nd round of dilators after initial ripening) was provided.

Results 2:

The mean Caesarean section rate was 33.5% and varied from 22% to 39.5% in relation to each study site. 9.7% of women delivered spontaneously without any further induction method after dilators' extraction. The mean gain in Bishop score was +3.5 (3.2-3.7). Caesarean section rate in subgroup of women with previous C. section (N=29) was 48.3%.

Graph 2: Cesarean section rates reached within countries



Results 3:

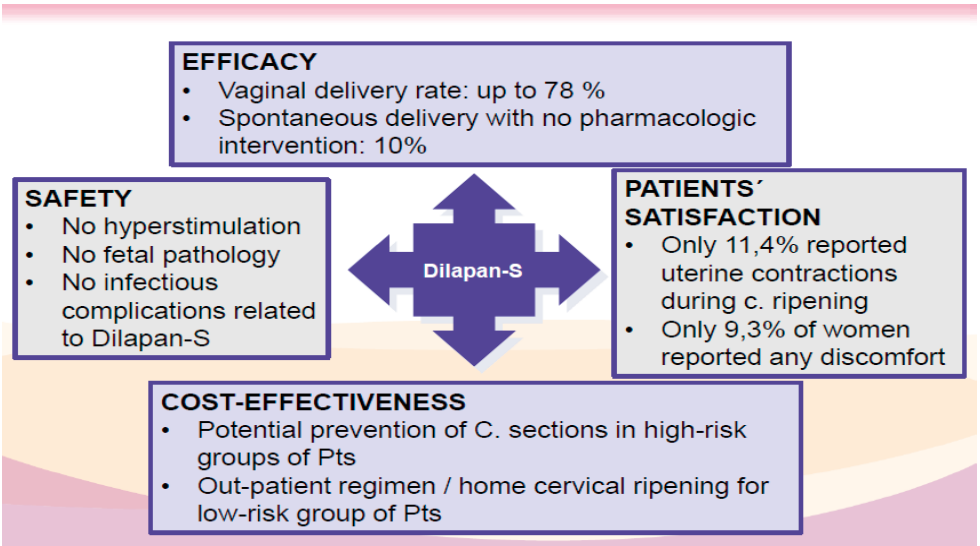
No uterine hyperstimulation and no fetal pathology were reported based on CTG during cervical ripening with osmotic cervical dilators. Only 11.4% of women experienced uterine contractions while the dilators were inserted. Complication or discomfort during cervical ripening occurred in 9.3% of women, while premature rupture of membranes as the sign of started labor, bleeding during insertion or extraction of dilators, or their spontaneous expulsion were reported. Maternal infectious complication was observed in 5 cases (1.7%).

No association of maternal infection and the use of osmotic dilator reported in these cases. One neonatal infectious complication was reported, while relation to the use of osmotic cervical dilator was not possible to evaluate as maternal Streptococcal B colonization was not investigated before labor:

Conclusion:

- The synthetic osmotic dilator has a capability to reach high vaginal delivery rate in observational design without any selection of patient population (additionally, 67% of enrolled women were nulliparas and 10% had previous C. section).
- If we left out time consideration, sequential technique offers successful treatment of highly unripe cervixes.
- No safety issues confirm the method is safe for mothers and newborns.
- Potential prevention of C. section in high-risk groups of women and the use in outpatient regimen (home cervical ripening) represent significant cost-effectiveness benefits.

Fig. 2: Conclusion scheme



Frequently asked questions about preinduction of labor

1. **Will the Dilapan-S rods break the waters during insertion?**

   Clinical evidence has not reported the issue would be connected with Dilapan-S use. Several studies have found no incidence of this at all. On the other hand, membrane rupture can occur spontaneously during the cervical ripening process as a part of onset of active labor. In these cases, it is recommended to remove the device to facilitate active labor management.

2. **Will the Dilapan-S rods fall out? How long will the patient have to stay in bed?**

   The issue is reported very rarely and usually is connected with spontaneous onset of labor or with incorrect insertion of the device, when the end of the active part of the rod didn't pass the internal os. Then the rod ripens the external part of the cervix, but the internal os remains closed, which can result in expulsion of the rod. Some doctors use vaginal tamponade to ensure correct dilator position, but it is not mandatory.

   Generally, patients can walk, go to the toilet, take a shower; on the other hand, they should be instructed to avoid bathing, douching and refrain from intercourse while Dilapan-S is in place.

3. **Do you still have to do cardiotocography (CTG) monitoring after insertion?**

   CTG monitoring is not mandatory during the use of Dilapan-S. Clinical evidence has confirmed that the use of the product is not connected with excessive uterine contractions or with uterine hyperactivity resulting in fetal distress, so the product offers significant safety benefit.

4. **Can Dilapan-S be used in women with a history of Caesarean section?**

   Dilapan-S can be used in this indication. Because it has no pharmacological content, cervical ripening is gentle and gradual, and it does not cause uterine hyperactivity nor fetal distress. Therefore Dilapan-S represents an optimal candidate for induction in women with previous CS history. In one study of 96 women, the cervical ripening success rate (defined as increase of Bishop score enabling induction of labor) in a subgroup of patients with previous Caesarean section was 83% and vaginal delivery rate 65%, respectively. Dilapan-S was evaluated as effective and safe in this subgroup of patients.

5. **How many Dilapan-S rods are used for preinduction of labor?**

   Instruction for use recommends using as many pieces as can be inserted without strong resistance. From clinical practice, we know that 2 pieces have the power to increase Bishop score at the level enabling labor induction, but generally 4-5 pieces are recommended.

Cervical Dilation Prior to Instrumentation of the Uterine Cavity

Uses:

- Termination of pregnancy/ERPC
- Fetal demise/Miscarriage Management
- In Vitro Fertilization, Embryo Transfer, Hysteroscopy, Endometrial Biopsy, etc.

Key Benefits:

- Significant increase in cervical ripening
- Gentle; high predictability of dilation
- No pharmacological side effects
- Very high patient acceptability

Gentle and Predictable Cervical Dilation Prior to Termination of Pregnancy

Dilapan-S represents one of the most preferred methods for cervical preparation prior to D&E procedure in second trimester thanks to its predictability, efficacy, and safety [19]

Society for Family Planning Clinical Guidelines, 2013 [21]

Conclusions and Recommendations:

Level A:

- When osmotic dilator placement and D&E are to be performed on the same day, Dilapan–S® is preferred over laminaria tents to achieve adequate priming more quickly.
- Osmotic dilators achieve more preoperative dilation than mifepristone or misoprostol.
- Dilapan–S® is safe and effective for cervical preparation prior to D&E.
- Use of osmotic dilators does not increase infectious morbidity.

Level B:

- Prior to 20 weeks' gestation, adequate cervical preparation may be achieved with a single set of osmotic dilators.
- Dilapan–S® placed 3–4 h prior to D&E is a safe alternative to overnight dilator placement up to 18 weeks' gestation.
- Use of misoprostol or mifepristone as an alternative to osmotic tents increases risk of inadequate cervical dilation.
- Routine use of adjunctive buccal misoprostol in addition to osmotic dilators is not recommended before 16 weeks' gestation but may be considered when difficult cervical dilation is anticipated or at later gestational ages.

Level C:

Only experienced providers capable of managing difficult cervical dilation should use protocols omitting osmotic tent placement prior to D&E.

- Overnight placement of osmotic dilators is recommended after 18 weeks' gestation. Highly experienced D&E providers may consider same-day procedures at later gestations utilizing a combination of osmotic and pharmacologic agents or serial doses of misoprostol.

RCOG Evidence-based Clinical Guidelines, No. 7, Nov 2011: [20]

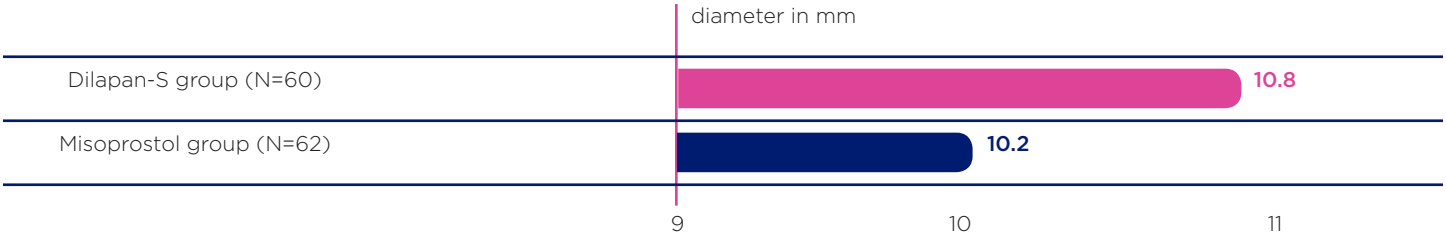
- After 14 weeks of gestation, osmotic dilators provide superior dilation to medical methods (grade B)

RCOG- Royal College of Obstetricians and Gynaecologists *D&E- dilation and evacuation*

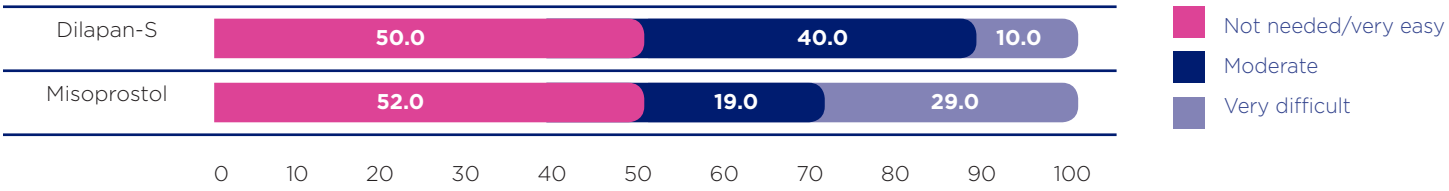
Fast-acting synthetic osmotic cervical dilator

Developed to enable same-day D&E procedure in late first and second trimester [19, 24]

Cervical dilation over the course of the 3-4 hour period [24]



Treatment with Dilapan-S demonstrated statistically improved dilation over misoprostol, when analysis was controlled for the inequity of Caesarean deliveries between the two arms (P= 0.049), and when the five participants misclassified according to the strata were removed in a per-protocol analysis (P= 0.047), respectively. [24]



Dilapan-S key benefits:

- in comparison with misoprostol, Dilapan-S offers higher efficacy and better predictability, helping to avoid challenging situations [19, 24]
- efficacy enables same-day D&E procedure in late 1st and 2nd trimester [18, 24]
- gradual atraumatic dilation
  - significantly reduces the risk of cervical injury and suture repair [19]
  - preserves full functionality of the cervix for future pregnancy
- no pharmacological side effects
- minimizing risk of uncontrolled abortions, e.g., during the night
- evaluated by SFP Guidelines as the best product in its class of osmotic cervical dilators [19]

Original Research

Same-Day Synthetic Osmotic Dilators Compared With Overnight *Laminaria* Before Abortion at 14–18 Weeks of Gestation

A Randomized Controlled Trial

Sara J. Newmann, MD, MPH, Abby Sokoloff, MPH, Mithu Tharyil, MD, Tushani Illangasekare, MD, Jody E. Steinauer, MD, MSc, and Eleanor A. Drey, MD, EdM

OBJECTIVE: To increase access to early second-trimester surgical abortion by determining noninferiority of same-day synthetic osmotic dilators compared with overnight *Laminaria* for cervical preparation before early second-trimester dilation and evacuation.

METHODS: We enrolled women between 14 and 18 weeks of gestation and randomized them to same-day synthetic osmotic dilators or overnight *Laminaria*. Study participants and clinicians were blinded to group assignment. The primary outcome was procedure duration. The trial was powered to assess noninferiority of synthetic osmotic dilators to exclude a mean difference of 5 minutes or longer.

RESULTS: We enrolled 72 patients: 36 were randomized to same-day synthetic osmotic dilators and 36 to overnight *Laminaria*. Mean procedure duration was 8.1 and 5.9 minutes, respectively, with a mean difference of 2.1 minutes (97.5% confidence interval −0.3 to 4.5). Same-day synthetic osmotic dilators resulted in less initial cervical dilation than overnight *Laminaria* (mean circumference 48 compared with 60 mm Pratt, $P<.001$) and required more mechanical dilation (69% compared with 27%, $P=.001$). There was no difference in complications, all of which were minor, or in the median procedural difficulty score rated by physicians. Most patients in both groups would choose a same-day procedure if necessary in the future.

CONCLUSION: Despite less initial cervical dilation and a greater need for mechanical dilation, same-day synthetic osmotic dilators are not inferior to overnight *Laminaria* with respect to procedure duration. Same-day osmotic dilation is preferred by patients and may be a reasonable alternative to overnight *Laminaria* for cervical preparation before early second-trimester dilation and evacuation.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, www.clinicaltrials.gov, NCT00775983.

(Obstet Gynecol 2014;123:271–8)

DOI: 10.1097/AOG.0000000000000080

LEVEL OF EVIDENCE: I

Many women in the United States have limited access to second-trimester surgical abortions. A small percentage of abortion providers offers second-trimester services, and women often have to travel long distances for care.[1] Surgical abortion between 14 and 18 weeks of gestation generally is offered as a 2-day procedure in which patients undergo cervical preparation with *Laminaria* for 24 hours before the abortion.[2] This multiday procedure creates further barriers to abortion access because women often have to travel, take several days off work, arrange for child care, or a combination of these to have the abortion completed.

Another option for dilation is same-day use of Dilapan-S, a synthetic osmotic cervical dilator that dilates

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the cervix more rapidly than *Laminaria*. It reaches its maximum diameter in 4–6 hours, whereas *Laminaria* reach their maximum diameter in 18–24 hours.[3,4] Multiple studies have been conducted investigating same-day methods for cervical preparation for second-trimester abortion, especially in the first half of the second trimester.[5–11] However, no randomized or prospective studies have been performed comparing same-day synthetic osmotic dilators with overnight *Laminaria* before early second-trimester surgical abortion.

We conducted a double-blind, randomized trial comparing same-day synthetic osmotic dilators with overnight *Laminaria* before early second-trimester surgical abortion between 14 and 18 weeks of gestation. We used a noninferiority design to determine whether same-day dilation with synthetic osmotic dilators is inferior to the widely used cervical preparation method of overnight *Laminaria* with respect to procedure duration.

MATERIALS AND METHODS

Women were recruited at the Women's Options Center at San Francisco General Hospital between October 2008 and February 2010. Two research assistants recruited and enrolled English- and Spanish-speaking women who were at least 18 years old and between 13 6/7 and 17 6/7 weeks of gestation by ultrasound dating the day before their abortions. We excluded women if they were incarcerated, did not understand Spanish or English, or had a known allergy to synthetic osmotic dilators or *Laminaria*. Our study was approved by the Committee on Human Research, the institutional review board of the University of California, San Francisco, and registered with ClinicalTrials.gov (NCT00775983). An Investigational Device Exemption was obtained from the U.S. Food and Drug Administration to study off-label use of the synthetic osmotic cervical dilator for research.

Women who consented to participate were randomized to receive either synthetic osmotic dilators on the day of the abortion or overnight *Laminaria*. Randomization was completed using a computer-generated, random number-producing algorithm with permuted block randomization in blocks of four and six. Study allocation was concealed in sequentially numbered, opaque, sealed envelopes prepared by a research assistant not involved in the study.

To maintain subject blinding, all study participants underwent a speculum examination on the day before the abortion. Women randomized to same-day dilators underwent a sham examination, including placement of a sterile gauze, and women randomized to overnight *Laminaria* received a paracervical block and insertion of medium *Laminaria* (mean diameter 4 mm) followed by placement of a sterile gauze. Medium-sized *Laminaria* were placed using the following guideline: number of weeks of gestation minus 10. The health care provider performing the examination was a resident physician, attending physician, or certified nurse midwife, all of whom had experience with dilator insertion and were not going to do the dilation and evacuation.

All women heard the same script from health care providers performing the "sham" or actual dilator placement. Health care providers were instructed to say sentences such as "This may be a little uncomfortable," "You're going to feel some pressure," or both while performing the speculum examination and "sham" or actual dilator placement. After the examination, patients were discharged from the clinic.

On day 2 of the study, all participants returned to the clinic in the morning and completed a questionnaire about their symptoms overnight. Participants then underwent a second speculum examination. Patients randomized to synthetic osmotic dilators had the gauze removed, a paracervical block placed, synthetic osmotic dilators inserted, and a sterile gauze placed. For patients between 14 0/7 and 15 6/7 weeks of gestation on the day of the abortion, two to three synthetic osmotic dilators were inserted. For patients between 16 0/7 and 18 0/7 weeks of gestation, two to five synthetic osmotic dilators were inserted. One medium *Laminaria* also was placed to facilitate the removal of the synthetic osmotic dilators before the abortion.[12] Patients randomized to *Laminaria* had a sham examination: the gauze was removed and replaced. Patients then waited 4–6 hours for their abortions.

Immediately before the abortion, patients completed a second questionnaire and reported any symptoms experienced during that day's waiting period. In the procedure room, a study staff member who was unblinded to group allocation removed the dilators and disposed of them out of sight of the dilation and evacuation provider–either an attending physician or family planning fellow who was blinded to the study arm. The health care provider then entered the procedure room, inserted a speculum, cleansed the cervix with povidone–iodine, and placed a paracervical block that included 5 units of vasopressin. We measured cervical dilation by using sequentially smaller dilators with initial dilation being that of the first dilator that passed without resistance.

A research assistant, blinded to group assignment, used a stopwatch to time the abortion, which either began with mechanical dilation of the cervix using

Pratt dilators if needed or insertion of a cannula to begin suction. Using ultrasonographic guidance, surgeons emptied the uterus by a combination of forceps and suction curettage with a 14-mm cannula. Procedure duration ended when the last instrument was removed from the uterus. The abortion provider completed a questionnaire after the abortion to assess difficulty of the procedure. Before discharge, patients filled out a final study questionnaire, which asked questions about symptoms and satisfaction with their clinic experience.

Our primary outcome was procedure duration with secondary outcomes including cervical dilation, difficulty of additional dilation, blood loss, major complications, and patient satisfaction. Procedure duration was chosen as the primary outcome because it is a marker for procedural difficulty and thus a proxy for potential procedural difficulty and complications. Additionally, we thought clinicians would be interested in the effect on procedure duration when considering protocol changes related to same-day cervical preparation. We chose a noninferiority margin of 5 minutes; thus, if the mean difference in procedure duration between the two study arms was within 5 minutes, synthetic osmotic dilators would be determined as being noninferior to overnight *Laminaria*. We felt that up to a 5-minute difference in procedure duration would be acceptable in terms of adopting a same-day dilation protocol for early second-trimester surgical abortion. However, we thought that more than a 5-minute difference could potentially disrupt clinic flow in a way that would not be acceptable for most busy abortion clinics.

Mean difference in procedure duration between the two groups and the 97.5% confidence interval (CI) were calculated to compare procedure durations between the two groups. Linear regression was completed to adjust for baseline covariates that were different between the two arms at a P level of $\leq .05$. Interaction terms were created, and assessed using linear regression, among patient age, parity, gestational duration, health care provider type, and anesthesia received during the dilation and evacuation because these covariates could plausibly interact with the relationship between study arm and procedure duration. Additional continuous outcomes were compared using the Student's t test or the Wilcoxon rank-sum test. We compared dichotomous outcomes using the Pearson χ^2 test or Fisher's exact test when any cell size included data from fewer than five study participants.

To power the study for our noninferiority hypothesis, we assumed a standard deviation of 5 minutes

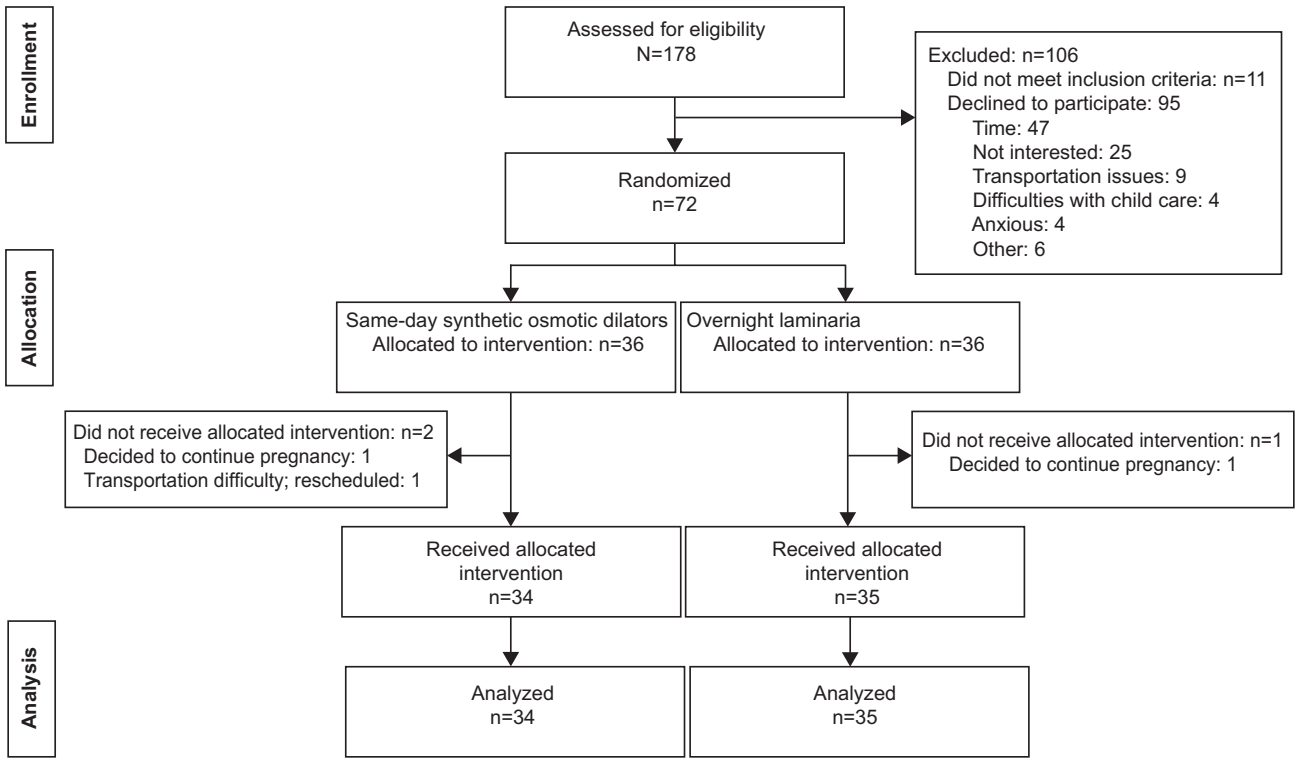

Fig. 1. Randomization table.

Newmann. Same-Day Synthetic Osmotic Dilators vs. Overnight Laminaria. Obstet Gynecol 2014.

based on historical data at The Women's Options Center for mean surgical abortion procedure duration performed between 14 and 18 weeks of gestation, an α of 0.025, and a noninferiority margin of 5 minutes as discussed previously. We calculated we would need 30 participants in each study arm to give 95% power assuming a 10% attrition rate to conclude noninferiority of same-day synthetic osmotic dilators compared with overnight *Laminaria*. Thus, if we found that same-day synthetic osmotic dilators are not inferior to overnight *Laminaria* with respect to dilation and evacuation duration, the upper bound of the 97.5% CI around the point estimate for mean difference in overall procedure duration would be 5 minutes or longer.

RESULTS

We enrolled 78 women into the study. Thirty-six participants were randomized to each study arm and three dropped out of the study: two from the same-day osmotic dilator arm and one from the overnight *Laminaria* arm (Fig. 1). Two women who had received the allocated overnight *Laminaria* decided on the morning of the abortion that they did not want to wait 4 hours to have the procedure. Their abortions were completed that morning and their clinical data were included in the intent-to-treat analysis; however, their corresponding subjective data were not available for analysis.

Baseline characteristics of the randomized groups differed in terms of insurance status, age, and gestational duration (Table 1). There was no difference between the two groups in the number of women who had multiple gestations or fetal anomalies.

The mean difference in overall procedure duration between the two groups was 2.1 minutes (97.5% CI −0.3 to 4.5; Table 2). Noninferiority was determined because the upper bound of the 97.5% CI around the mean difference in procedure duration was less than 5 minutes. The median procedure durations and interquartile duration ranges for the same-day synthetic osmotic dilators and overnight *Laminaria* groups were 6.4 (3.9–11.7) and 5.5 (3.5–9.8) minutes, respectively (P=.08). We also completed a sensitivity analysis excluding one procedure that took 32 minutes (same-day dilator arm). One nulliparous patient in

Table 1. Demographic and Clinical Characteristics of Women Randomized to Same-Day Synthetic Osmotic Dilators or Overnight *Laminaria* Before Early Second-Trimester Abortion

Characteristic	Same-Day Dilators (n=34)	Overnight *Laminaria* (n=35)	*P**
Demographic characteristics			
Age (y)	26.5 (22.0–32.0)	21.0 (19.0–26.0)	.03
Race			.55
White	8 (24.2)	4 (11.8)	
Black	15 (45.5)	16 (47.1)	
Latina	8 (24.2)	10 (29.4)	
Asian or Pacific Islander	2 (6.1)	4 (11.8)	
Public insurance	26 (76.5)	34 (97.1)	.01
Clinical characteristics			
Gestational duration (wk)	16.6±1.1	16.2±1.1	.03†
14–15 6/7	7 (20.6)	16 (45.7)	
16–18	27 (79.4)	19 (54.3)	
Body mass index (kg/m^2)	27.1 (23.4–31.4)	27.5 (23.6–32.6)	.81
Nulliparous	9 (26.5)	12 (34.3)	.48
Prior vaginal delivery	14 (41.2)	15 (42.9)	1.00
Prior cesarean delivery	11 (32.4)	9 (25.7)	.60
Prior induced abortion	22 (64.7)	22 (62.9)	.87
Prior pregnancies	4.0 (2.0–6.0)	3.0 (2.0–5.0)	.30
Sedation provider‡			.96
Nurse	29 (85.3)	30 (85.7)	
Anesthesiologist	5 (14.7)	5 (14.3)	
Clinician type			.48
Attending	25 (73.5)	23 (65.7)	
Fellow	9 (26.5)	12 (34.3)	

Data are median (interquartile range), n (%), or mean±standard deviation unless otherwise specified.
* Wilcoxon rank-sum, Pearson χ^2, or Fisher's exact test (if cell size is less than five).
† P=.12 for comparison of gestational duration as continuous variable with t test.
‡ Anesthesia administered by nurses included fentanyl and midazolam. Anesthesia administered by anesthesiologists included propofol, fentanyl, and midazolam.

Table 2. Differences in Procedure Duration and Interactions Between Clinically Significant Covariates Among Women Randomized to Same-Day Synthetic Osmotic Dilators or Overnight *Laminaria* Before Early Second-Trimester Abortion

Clinical Characteristics	Same-Day Dilators (n=34)	Overnight *Laminaria* (n=35)	Mean Difference (97.5% CI)	*P* for Interaction
Overall	8.1±5.5	5.9±2.9	2.1 (−0.3 to 4.5)	
Patient age (y)				.60
24 or younger (13, 22)*	9.8±7.3	6.5±3.2	3.23 (−0.9 to 7.4)	
Older than 24 (21, 13)	7.0±3.8	4.8±1.8	2.13 (−0.4 to 4.8)	
Parity				
Nulliparous (9, 12)	11.4±8.2	6.4±2.4	5.0 (−0.2 to 10.2)	.09
Prior vaginal delivery (14, 15)	7.3±4.5	5.7±2.7	1.7 (−1.1 to 4.5)	.72
Gestational duration on day of abortion (wk)				.17
14–15 6/7 (7, 16)	4.1±1.1	4.9±2.5	0.8 (−1.3 to 2.9)	
16–18 (27, 19)	9.1±5.7	6.8±2.9	2.3 (−0.99 to 5.6)	
Provider type				.95
Attending (25, 23)	7.9±5.9	5.8±2.7	2.1 (−0.6 to 4.8)	
Fellow (9, 12)	8.5±4.3	6.2±3.3	2.3 (−1.2 to 5.7)	
Sedation provider†				.38
Nurse (29, 30)	8.4±5.8	5.9±2.9	2.5 (0.1–4.9)	
Anesthesiologist (5, 5)	6.2±1.4	6.3±3.0	0.1 (−3.3 to 3.5)	

CI, confidence interval.
Data are mean procedure duration±standard deviation (minutes) unless otherwise specified.
* Parentheses next to variable strata include the number of patients in that stratum per treatment arm (n same-day dilators, n overnight *Laminaria*).
† Anesthesia administered by nurses included fentanyl and midazolam. Anesthesia administered by anesthesiologists included propofol, fentanyl, and midazolam.

the same-day synthetic osmotic dilator group whose abortion took 32 minutes was given 400 micrograms buccal misoprostol for 2 hours after several health care providers were unable to remove the dilators despite multiple attempts. After the misoprostol, the dilators were removed without difficulty. The mean time difference between the two groups when excluding this outlier was 1.2 minutes (97.5% CI −0.6 to 3.0). We applied the resampling method of bootstrapping to account for distortions within our study sample and

Table 3. Additional Clinical Outcomes Among Women Randomized to Same-Day Synthetic Osmotic Dilators or Overnight *Laminaria* Before Early Second-Trimester Abortion

Clinical Outcome	Same-Day Dilators (n=34)	Overnight *Laminaria* (n=35)	*P**
Dilation			
Initial dilation (circumference, mm)	48.0±11.3	59.7±10.0	<.001
Mechanical dilation required	22 (68.8)	8 (26.7)	.001
Complications			
Bleeding requiring uterotonics	7 (20.6)	10 (28.6)	.58
Respiration	3 (8.8)	2 (5.7)	.67
Cervical laceration	0	1 (2.9)	1.00
Blood loss			
Estimated blood loss (mL)	61.0±27.1	64.9±46.6	.68
Difference in preprocedure and postprocedure hemoglobin	−0.3±1.0	−0.6±1.6	.28
Analgesic use			
Preprocedure opiate use†	27 (79.4)	7 (20.0)	<.001
Intraoperative analgesia, standardized dose‡	17.2±5.8	18.7±7.0	.33
Postprocedure opiate use†	4 (11.6)	17 (48.6)	.001

Data are mean±standard deviation or n (%) unless otherwise specified.
* *t* test, Pearson χ^2, or Fisher's exact test (if cell size less than five).
† Opiate use included hydrocodone or acetaminophen, morphine, or hydromorphone hydrochloride.
‡ Intraoperative analgesics included propofol, midazolam, fentanyl, or all. Quantities of each were standardized to a mean of 10, standard deviation of 2. Standardized doses for each were then added to obtain the total.

to increase the accuracy of our estimate of the 97.5% CIs around the overall mean procedure duration. The result was a procedure time difference of 2.1 minutes (97.5% CI 0.3–4.6) with the upper bound 97.5% CI value less than 5. When adjusting for patient age, gestational duration, and insurance type–the three covariates found to be significantly different between the two study arms (Table 1)–the mean procedure time was 1.5 minutes (97.5% CI 1.0–4.0). Additionally, neither patient age, parity, gestational duration, provider type, or anesthesia received interacted significantly with the relationship between study arm and procedure time (Table 2).

Preoperative dilation was less with same-day synthetic osmotic dilators compared with overnight *Laminaria* (mean initial dilation circumference 48 mm compared with 60 mm, $P<.001$; Table 3). Fewer dilators were placed in the women in the same-day synthetic osmotic dilator arm compared with the women in the overnight *Laminaria* arm (mean number of dilators 4.5 compared with 5.4, $P<.01$, respectively). Fifteen patients in the *Laminaria* arm had one fewer *Laminaria* placed than recommended by study guidelines. One patient in the synthetic osmotic dilators arm at 17 6/7 weeks of gestation had only one synthetic osmotic dilator placed instead of two to five as recommended in the study protocol. More women in the same-day synthetic osmotic dilators group needed additional mechanical dilation compared with the overnight *Laminaria* group (68.8% compared with 26.7%, $P=.001$).

A greater proportion of women in the synthetic osmotic dilator group required opiates for pain before the abortion (79.4% compared with 20.0%, $P<.001$), whereas a greater proportion of women in the *Laminaria* group required opiates for pain postoperatively (48.6% compared with 11.6%, $P=.001$). There was no difference between study arms in the amount of pain medication administered during the dilation and evacuation and no difference in complications.

A greater proportion of physicians in the same-day synthetic osmotic dilators group reported the initial cervical dilation to be inadequate (59.4% compared with 23.3%, $P<.01$; Table 4). Surgeons reported no difference between the two groups regarding level of difficulty of mechanical dilation when needed or the difficulty of the abortion itself. A greater proportion of the physicians in the same-day synthetic osmotic dilators group was able to correctly identify to which study arm their patient had been randomized (56.3% compared with 40.0%, $P<.01$).

The majority of women in both groups reported being satisfied with their abortions and overall clinic experience (Table 5). One woman in the *Laminaria* group reported preferring overnight cervical preparation. In the same-day synthetic osmotic dilator group, 87.5% said they preferred same-day cervical preparation compared with 69.0% in the *Laminaria* group ($P=.15$).

Overnight, significantly more women in the *Laminaria* group reported being "a great deal" or "a very great deal" bothered by a variety of symptoms (Table 5). Immediately before the abortion, significantly more women in the same-day synthetic osmotic dilator group reported being bothered by a variety of symptoms. In the recovery room, women in the same-day dilator group reported having significantly less pain and required less pain medication than women in the *Laminaria* group with the majority already having received opiate analgesics while waiting for the dilation and evacuation. A greater proportion of women in the same-day dilator group accurately guessed what kind of dilators they had (75.8% compared with 55.2%, $P<.001$; Table 5). More women in the *Laminaria* group were unsure as to what kind of dilators had been placed.

Table 4. Physician Assessments of Procedural Difficulty and Dilator Type by Study Arm

Assessment	Same-Day Dilators (n=32)	Overnight *Laminaria* (n=30)	P*
Procedural difficulty			
Inadequate dilation	19 (59.4)	7 (23.3)	<.01
Difficulty of additional dilation†	0 (0–1)	0 (0–1)	.57
Difficulty of procedure†	0 (0–1)	0 (0–1)	.17
Ascertainment of dilator type			<.01
Correct	18 (56.3)	12 (40.0)	
Incorrect	3 (9.4)	6 (20.0)	
Do not know	11 (34.4)	12 (40.0)	

Data are n (%) or median (interquartile range) unless otherwise specified. Proportion percentages may vary slightly by variable as a result of occasional missing data.

* *t* test, Pearson χ^2, Fisher's exact test (if cell size less than five), or Wilcoxon rank-sum test.

† Difficulty scale: not difficult (0), mildly difficult (1), moderately difficult (2), very difficult (3), extremely difficult (4).

Table 5. Patients' Satisfaction, Side Effects, and Ascertainment of Dilator Type

Outcome	Same-Day Dilators (n=34)	Overnight *Laminaria* (n=33)	*P**
Satisfaction and patient preference†			
Satisfaction with abortion	26 (81.3)	24 (80.0)	1.0
Satisfaction with overall clinic experience	25 (89.3)	22 (84.6)	.70
Patient preference			.15
1-d procedure	28 (87.5)	20 (69.0)	
2-d procedure	0	1 (3.5)	
Do not know	4 (12.5)	8 (27.6)	
Side effects‡			
Overnight			
Abdominal pain or cramping	2 (6.1)	23 (71.9)	<.001
Vaginal bleeding	0	4 (12.5)	.05
Nausea	2 (5.8)	12 (37.5)	<.01
Vomiting	3 (8.8)	13 (41.99)	<.01
Diarrhea	1 (2.9)	1 (3.1)	1.00
Bothered by any symptoms	2 (5.9)	12 (34.3)	<.01
Immediately before abortion			
Abdominal pain or cramping	25 (73.5)	7 (23.3)	<.001
Vaginal bleeding	2 (6.1)	2 (6.9)	1.00
Nausea	6 (18.2)	6 (20.0)	1.00
Vomiting	5 (15.6)	5 (16.6)	1.00
Bothered by any symptoms	17 (50.0)	2 (5.7)	<.001
In recovery room			
Abdominal pain or cramping	8 (24.2)	16 (53.3)	.02
Vaginal bleeding	22 (66.7)	22 (73.3)	.60
Nausea	2 (6.1)	3 (10.0)	.66
Vomiting	3 (9.1)	3 (10.3)	1.00
Ascertainment of dilator type			<.001
Correct	25 (75.8)	16 (55.2)	
Incorrect	1 (3.0)	2 (6.9)	
Do not know	7 (21.2)	11 (37.9)	

Data are n (%) unless otherwise specified. Proportion percentages may vary slightly by variable as a result of occasional missing data.
* Pearson χ^2 or Fisher's exact test (if cell size less than five).
† Women who answered 4 or 5 (somewhat or very satisfied) on the satisfaction scale were considered satisfied with their abortions or overall clinic experience.
‡ Data are shown for patients who reported: moderate, severe or unbearable abdominal pain or cramping, nausea, or diarrhea; light, moderate, or heavy bleeding; one or more episodes of emesis during the time interval; or feeling bothered a great deal or a very great deal by their symptoms during the specific time interval shown.

DISCUSSION

Our findings show that same-day dilation with synthetic osmotic dilators is a reasonable alternative to overnight *Laminaria* when used before dilation and evacuations between 14 and 18 weeks of gestation. Same-day abortions could increase access for women in need of early second-trimester abortions and decrease the myriad logistical barriers frequently faced by women presenting for abortion later in pregnancy.[13]

Mean gestational duration was slightly higher in the synthetic dilator group, which likely increased the mean procedure duration in that study arm. Had randomization of women between 16 and 18 weeks of gestation been equal, we likely would have found a smaller difference in procedure durations and shown noninferiority of same-day synthetic osmotic dilators with greater precision.

Mechanical dilation was required in two-thirds of the patients who received same-day synthetic osmotic dilators and in only one-fourth of those with overnight *Laminaria*. Although we do not know the long-term consequences of mechanical dilation in the context of an osmotically prepared cervix, the theoretical concern remains that mechanical dilation could decrease cervical integrity and increase future risk of miscarriage or preterm births. However, this has not been documented in the literature.[14–16] Our results suggest the need for caution when using same-day synthetic osmotic dilators among nulliparous women in the early second trimester because their procedures took longer, although all abortions among nulliparous patients were completed without any significant difference in complications. It is also notable that one procedure in the synthetic osmotic dilator arm was significantly longer than the others as

a result of extreme difficulty removing the dilators. Health care providers who adopt a same-day protocol using synthetic osmotic dilators sometimes may experience difficult dilator removal as a result of their being wedged within a potentially noncompliant cervix.

Although our study was completed as a randomized trial, it has several limitations. Our study had inadequate power to compare complications directly between groups; thus, procedure duration was chosen as a proxy for procedural difficulty and potential complications. A much larger study is needed to assess whether immediate or long-term complications differ as a result of increased mechanical dilation, which was necessary with same-day osmotic dilators. None of the patients in our study actually had a 1-day experience; thus, our data regarding patient preference of a same-day procedure are based on patient supposition. It is always possible that blinding was not uniformly successful; however, given that a substantial proportion of health care providers and patients were unsure of dilator type or guessed incorrectly, blinding appeared somewhat effective.

Additionally, the trial was conducted as a noninferiority study with the primary outcome of procedure duration; some might prefer a superiority design or other outcomes to be considered primary. Finally, we conducted our study at a busy, urban, hospital-based clinic with high second-trimester abortion volume and multiple health care providers who are skilled in second-trimester abortion. Our study findings may not be generalizable to smaller clinics with fewer staff, different patient demographics, and less second-trimester abortion volume.

Same-day cervical preparation with synthetic osmotic dilators before early second-trimester abortion may be beneficial not only to increase women's access to abortion during this gestational duration, but also may benefit clinics by increasing the number of early second-trimester patients they can serve and by decreasing expenses associated with multiple clinic visits. The barriers to same-day protocols lie mainly with clinic flow. Health care practitioners and clinics who are considering instituting a same-day cervical preparation method for women who present for abortion within the early second trimester will need to consider the ways in which such a protocol would influence patient flow within the clinic with respect to ultrasound dating, dilator placement, waiting space and time, and medication and pain management. Medicine is transitioning to more patient-centered models,[17] and the majority of patients in this and previous studies[5,11] preferred a shorter procedure. Despite a greater need for mechanical dilation, same-day dilation with synthetic osmotic dilators is a reasonable alternative to overnight *Laminaria* for a cervical preparation before early second-trimester abortion among clinics that are able to accommodate the required changes in patient flow.

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Frequently asked questions about termination of pregnancy

1. How many Dilapan-S rods do you use in termination? How long do you leave the rods in for termination?

Preparation of the cervix prior to hysteroscopy or termination of pregnancy / missed abortion under 12 weeks of gestation: Usually 1 piece of DILAPAN- S® 3x55mm or 4x55mm.

Preparation of the cervix prior to the termination of pregnancy in later stage (2nd trimester): Usually, 2-3 pieces are used; however, it is possible to use more dilators if they can be inserted without major resistance (3-5) and leave DILAPAN-S® 4x65mm.

2. What gestation age is Dilapan-S typically used?

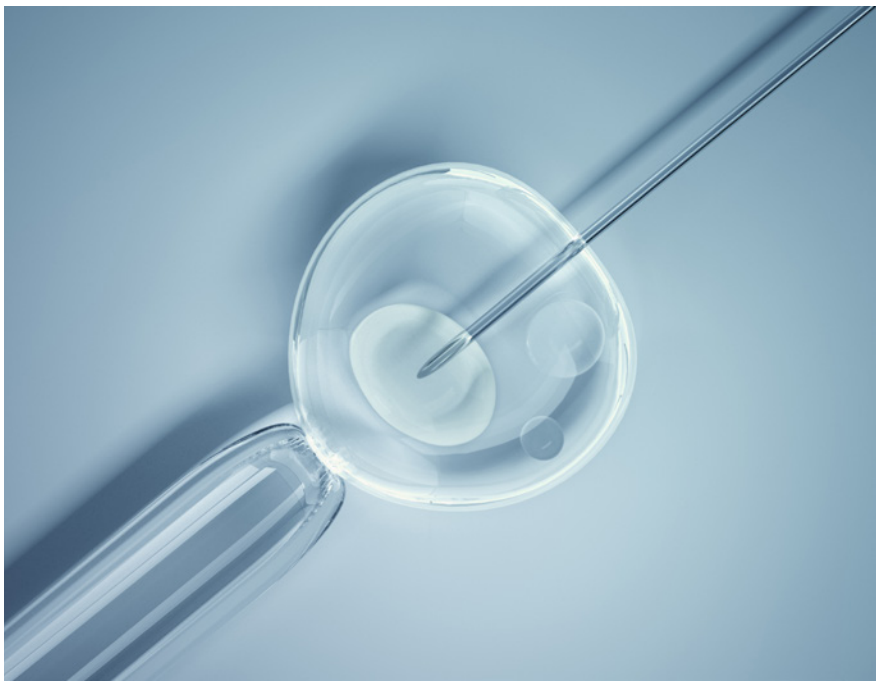
For missed abortion under 12 weeks of gestation, as well as in a later stage of pregnancy, such as the 2nd trimester.

3. What are the side effects of Dilapan-S?

There are no pharmacological side effects with Dilapan-S.

Other Uses of Dilapan-S For Cervical Dilation of the Uterine Cavity

- in Vitro Fertilization
- Embryo Transfer
- Hysteroscopy
- Endometrial Biopsy



"The use of Dilapan-S rods for cervical dilation in an outpatient setting prior to starting ovarian stimulation in patients who have previously had a difficult embryo transfer or mock embryo transfer is simple, cost-effective and allows a technically easier embryo transfer, and thus helps to achieve a higher pregnancy rate." [30]

Cervical dilatation with hygroscopic rods prior to ovarian stimulation facilitates embryo transfer

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BACKGROUND: Embryo transfer is a critical factor affecting the success of IVF—the ease of embryo transfer has a direct impact on the success rate. The aim of this study was to assess the value of cervical dilatation with hygroscopic cervical rods (Dilapan-S) in patients with difficult embryo transfer. METHODS: Fifty-four patients undergoing IVF treatment, who either failed to conceive after previous difficult embryo transfer or were noted to have difficult mock embryo transfer were retrospectively included in the study. In this way the patients acted as control for themselves. The Dilapan-S rods were placed intracervically and left for 4 h prior to starting gonadotrophin stimulation as an outpatient procedure. RESULTS: Of the 54 patients who originally had difficult embryo transfer, 43 patients (79.5%) had subsequent easy embryo transfer. Thirty patients managed to conceive, giving a clinical pregnancy rate of 55%. CONCLUSIONS: Cervical dilatation using hygroscopic dilators facilitates difficult embryo transfer and helps to improve the pregnancy rate.

Key words: difficult embryo transfer/Dilapan-S/IVF

Introduction

It is well established that embryo transfer is a critical factor affecting the outcome of IVF (Lass *et al*., 1999; Schoolcraft *et al*., 2001). The technique and ease of embryo transfer have a direct impact on the pregnancy rate, irrespective of quality of embryos available for transfer (Karande *et al*., 1999). Many factors have been shown to affect the embryo transfer technique and its outcome. These include the experience and dexterity of the clinician (Karande *et al*., 1999; Hearns-Stokes *et al*., 2000), the catheter type (Schoolcraft *et al*., 2001), the placement of the catheter tip in the mid-fundal area (Rosenlund *et al*., 1996) and the presence of cervical stenosis (Mansour and Aboulghar, 2002).

A mock embryo transfer has been shown to reduce the problems encountered during the actual embryo transfer (Mansour *et al*., 1990; Knutzen *et al*., 1992). It enables clinicians to exclude the presence of cervical stenosis or acute angulation, as well as allowing the assessment of the direction of the uterus and the length of the uterine cavity (Egbase *et al*., 2000).

Several studies have reported significant reduction in pregnancy rates as a result of technically difficult embryo transfer (Leeton *et al*., 1982; Englert *et al*., 1986; Diedrich *et al*., 1989; Visser *et al*., 1993; Goudas *et al*., 1998; Wood *et al*., 2000).

We report the first series of 54 patients with a history of previous difficult embryo transfer or difficult mock embryo transfer who underwent cervical dilatation using hygroscopic cervical rods (Dilapan-S) as an outpatient procedure prior to starting gonadotrophin stimulation. The aim of this study was to assess the value of cervical dilatation with hygroscopic cervical rods (Dilapan-S) in patients with difficult embryo transfer.

Materials and methods

From June 2000 to May 2002, 54 IVF patients aged 36.8 ± 5.6 years who either failed to conceive after previous difficult embryo transfer or were noted to have a difficult mock embryo transfer were included in the study.

This study could not have been carried out in a randomized case–control manner, as it would have been unethical to ignore our prior experience with difficult embryo transfer. On the other hand, this group of patients acted as self-controls. The mock embryo transfer was undertaken using the Edwards–Wallace catheter (Wallace, Colchester, UK) under ultrasound control in the month prior to starting stimulation with gonadotrophins. When difficulty was encountered, a tenaculum was used to straighten the cervical canal and the Wallace malleable stylet was used in order to negotiate the internal os. If difficulty was encountered while introducing the hard Wallace catheter, the patient was counselled about the possibility of having a difficult embryo transfer, and was offered the option of having a Dilapan-S (FEMA International, BV, Winssen, The Netherlands) insertion on day 4–5 of her next period.

The embryo transfer was performed on day 3 after vaginal egg collection. All our embryo transfers are carried out under ultrasound control with full bladder. The Wallace catheter was used in all cases and embryos were deposited in the middle of the uterine cavity.

Our embryo transfer grading is as follows: grade 1, easy; grade 2a, difficulty in negotiating the cervical canal with or without blood on the catheter, and the necessity to use a malleable stylet; grade 2b, as 2a plus necessity to use a tenaculum; grade 3, inability to negotiate the internal os.

The causes of infertility were as follows: tubal, nine (16.5%); unexplained, 13 (24%); male factor, 16 (29.6%); endometriosis, two (3.7%); ovulatory dysfunction, one (1.8%); and multifactorial, one (24%). Of the 54 patients, 39 underwent IVF/ICSI (72.2%), four underwent frozen–thawed embryo transfer (7.4%) and 11 were ovum recipients (20.3%).

The long GnRH agonist down-regulation regime was used for ovarian stimulation. Buserelin acetate nasal spray (Hoechst Marion Roussel, Uxbridge, UK) was started in the mid-luteal phase of the preceding menstrual cycle. Cervical dilatation with Dilapan-S was undertaken on day 4 or 5 of the period immediately before starting the gonadotrophin stimulation.

The technique of Dilapan-S insertion was as follows: patients were asked to have a full bladder and were given a 100 mg Diclofenac sodium suppository (Geigy, Surrey, UK) rectally 1 h before the procedure. The vagina was cleansed with an antiseptic solution. The cervix was identified and the upper lip was held with a tenaculum for stabilization of the cervix and straightening of the cervical canal. The hygroscopic rod was moistened with sterile water or saline to lubricate the surface prior to insertion. A 3 × 55 mm diameter Dilapan-S rod was then grasped at the handle and gradually inserted into the cervical canal under ultrasound control until it traversed the external and internal os. It was then left *in situ* for 4 h. To remove the Dilapan-S rod, the handle was grasped with forceps and a steady downward traction was applied in line with the long axis of the device. Extra care was taken during the removal as pulling on the marker string or twisting the device during removal may cause the device to break. An antibiotic was given to cover the procedure.

Ovarian stimulation was started on the same day using HMG (Menogon, Ferring, UK). Ovarian response was monitored using serial vaginal ultrasound scanning and serum estradiol assessment. HCG (Choragon, Ferring, UK) was administered 36 h prior to egg collection. The luteal phase was supported with progesterone vaginal pessaries 400 mg twice a day for 16 days (Cyclogest, Shire, UK). Clinical pregnancies were defined by ultrasound confirmation of an intrauterine gestational sac and fetal heart activity.

Results

Dilapan-S insertion was considered easy in 42 patients, difficult in 11 and not possible in one patient. The procedure was well tolerated. Eight patients complained of cramping lower abdominal pain while the Dilapan-S rod was *in situ*. A total of 43 out of 54 patients (79.6%) who originally had grade 2a, 2b or grade 3 transfers had subsequent easy (grade 1) embryo transfer after the use of Dilapan-S. Of the 37 patients who originally had a grade 2a transfer, Dilapan-S insertion did not improve the subsequent embryo transfer grading in nine (16.5%). Embryo transfer grading did not improve in one patient out of 10 (10%) who originally had a grade 2b embryo transfer. Of the seven patients who originally had a grade 3 transfer, only one patient (1.8%) showed no improvement in the subsequent embryo transfer grading despite using the Dilapan-S rod (Table I).

Table I. Embryo transfer grading before and after Dilapan-S insertion

Before Dilapan-S		After Dilapan-S	
Grade	Number	Grade	Number (%)
2a	37	1	28 (75.6)
2b	10	1	9 (90)
3	7	1	6 (85.7)
Total	54	1	43 (79.6)

This study included 54 patients. Two patients had oocytes that failed to fertilize. Thirty patients had a positive pregnancy test. The clinical pregnancy rate was 57.7%, the implantation rate was 24.4% and the miscarriage rate was 8.5%.

Discussion

Meticulous embryo transfer technique is essential to IVF success (Meldrum *et al*., 1987). Difficult embryo transfer, blood and mucus on the catheter, uterine contractions, expulsion and retained embryos have all been associated with problematic and unsuccessful embryo transfers. Mansour *et al*. (1990) showed that difficult embryo transfers had a significantly lower pregnancy rate and implantation rate (4% and 1%, respectively) compared with easy transfers (20.4% and 6.7%, respectively).

A variety of techniques has been proposed to overcome difficult embryo transfer. These include the use of full bladder to straighten out the uterine cavity (Sundstrom *et al*., 1984; Sharif *et al*., 1995), together with the use of ultrasound-guided transfer technique to visualize the position of the catheter (Coroleu *et al*., 2000). Ultrasonographic guidance has many potential advantages: it facilitates the placement of catheters; avoids touching the fundus; confirms that the catheter is beyond the internal os in cases of elongated cervical canal; and helps in avoiding disruption and trauma of the endometrium. Other techniques include the use of volsellum to straighten the utero-cervical angle (Lesny *et al*., 1999) and choosing an appropriate transfer catheter (Al-Shawaf *et al*., 1993). Despite of these measures, there exists a small but significant group of patients in whom embryo transfer remains extremely difficult. Under these circumstances, a laparoscopic tubal embryo transfer can be undertaken in patients with patent tubes. However, this method is invasive in nature, necessitates the use of general anaethesia and adds to the cost of an IVF cycle. For patients with history of tubal disease or pelvic adhesions, the transmyometrial-route 'Towako method' has been suggested (Kato *et al*., 1993). Whilst some authors have reported a very good outcome with this technique (Kato *et al*., 1993; Sharif *et al*., 1996), others have not (Groutz *et al*., 1997).

Cervical dilatation has been suggested as a mean to overcome difficult embryo transfer (Glatstein *et al*., 1997; Groutz *et al*., 1997; Abusheikha *et al*., 1999). Groutz *et al*. (1997) showed that whilst cervical dilatation on the day of the egg collection leads to an easier embryo transfer, the pregnancy rate after this procedure was very low (2.5%). They suggested that the 48-h interval between egg collection and embryo transfer was too short for a complete recovery of the cervix and the endometrium from the trauma inflicted by the dilatation.

Abusheikha *et al*. (1999) performed cervical dilatation prior to starting gonadotrophin stimulation. This led to an easier embryo transfer and improved the pregnancy rate. However, this approach necessitates general anaesthetic and added cost. The use of osmotic cervical dilators (laminaria tents) has been reported in two patients with cervical stenosis (Glatstein *et al*., 1997). In the first patient, a laminaria tent was inserted after cervical dilatation on the day of the egg collecion and was removed after 24 h. In the second patient the laminaria tent was inserted and kept *in situ* for 24 h before a frozen–thawed embryo transfer. Both patients conceived.

In our study, we used Dilapan-S hygroscopic rods for cervical dilatation. Dilapan-S is a hygroscopic cervical dilator that is manufactured from AQUACRYL, a proprietary hydrogel. The dilators are firm hygroscopic rods, similar in shape to natural laminaria tents. They absorb moisture through hygroscopic action and gradually swells in diameter with sufficient radial force to gently dilate the cervical canal. The dilators are capable of increasing in diameter on average from 3–4 to 8–12.5 mm within 4–6 h. They have been used for cervical ripening prior to induction of labour and for cervical preparation prior to suction termination of pregnancy.

In contrast to the two cases reported by Glatstein *et al*. (1997), in our study the Dilapan-S was inserted, and left for 4 h, prior to starting the gonadotrophin stimulation. Using conventional cervical dilatation under general anaethethesia, Abusheikha *et al*. (1999) showed that in 29.8% (17/57) of patients with cervical stenosis, embryo transfer remained difficult. In our study, embryo transfer remained difficult after the use of Dilapan-S in 20.4% (11/54) of patients. This suggests that conventional cervical dilatation under a general anaethetic does not seem to be more effective than the use of Dilapan-S.

We conclude that the use of Dilapan-S rods for cervical dilation in an outpatient setting prior to starting ovarian stimulation in patients who have previously had a difficult embryo transfer or mock embryo transfer is simple, cost effective and allows a technically easier embryo transfer, and thus helps to achieve a higher pregnancy rate.

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INDICATIONS:

Cervical Ripening Prior to the Induction of Labor

Cervical Dilation Prior to Instrumentation of the Uterine Cavity

- Termination of Pregnancy
- in Vitro Fertilization, Embryo Transfer, Endometrial Biopsy, Hysteroscopy, IUD Insertion

AVAILABLE SIZES:

3x55, 4x55, 4x65 mm

KEY BENEFITS:

- Significant increase in cervical ripening
- Very high patient acceptability
- No pharmacological side effects
- High predictability due to material and mode of action

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