Current status & expected evidence in termination of pregnancy (TOP)

Jan Waclav; 31-05-2018
in

2nd TRIMESTER MEDICAL ABORTIONS
Induced Abortion Guidelines

These guidelines were reviewed by the Clinical Practice–Gynaecology Committee and the Social and Sexual Issues Committee and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

PRINCIPAL AUTHOR
Victoria Jane Davis, MD
• Mechanical dilatation of the cervix prior to medical termination in the second trimester reduces the risk of cervical laceration and uterine rupture.

• Pre-procedural dilatation of the cervix may be considered.

• Synthetic or osmotic dilators ... may be used.
Clinical Guidelines

Labor induction abortion in the second trimester

Release date February 2011
SFP Guideline 20111
Guidelines - USA (2011)

• Retrospective data doesn’t confirm the benefit of combination, but prospective trial(s) are needed

• Mifepristone followed 36–48 h later by misoprostol and Dilapan osmotic dilators did not result in outcomes different than that reported with the use of misoprostol alone

• Dilapan has also proven to be of no benefit in regimens with gemeprost
PRACTICE BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN—GYNECOLOGISTS

NUMBER 135, JUNE 2013

Second-Trimester Abortion
• Modern medical abortion methods include the use of one or more of the following: prostaglandin analogues, mifepristone, osmotic cervical dilators, Foley catheters, and oxytocin...

• Cervical softening and dilation can be achieved by placement of osmotic dilators before the procedure...

• *Osmotic cervical dilators are sometimes used in conjunction with pharmacologic uterotonic agents; however, osmotic dilators (=LAM) do not provide added benefit to induction with prostaglandin analogues*
Second trimester medical abortion

- Osmotic dilators should not be used as they do not shorten the induction time but increase pain. (=LAM)
Best practice in comprehensive abortion care

Best Practice Paper No. 2
June 2015
• No recommendation concerning dedicated cervical preparation (by eg. osmotic dilators) prior / during medical abortion procedure
## Guidelines summary

Dilapan-S in Medical abortions guidelines recommendation summary

<table>
<thead>
<tr>
<th>Support for Dilapan-S use</th>
<th>SOCG Canada</th>
<th>SFP US</th>
<th>ACOG US</th>
<th>NAF US</th>
<th>RCOG UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>? / NO</td>
<td>Possible, but no benefit</td>
<td>NO</td>
<td>NO</td>
<td></td>
</tr>
</tbody>
</table>
Medical abortions algorithm:

1. Mifepristone: 200mg after 12 hours
2. Dilapan-S: insertion of 2-4 rods after 6 hours
3. Misoprostol: first dose 400μg
Clinical evidence

- Retrospective trial
- Late 2TM (25 weeks)
- 2 centers
  - One with Dilapan-S on protocol, second without
- Primary outcome: IDI (induction to delivery interval)
  - IDI 1: first dose of miso in both centers
  - IDI 2: dilators placement in DS center / first dose of miso in second center
- 270 women included into analysis
### Clinical evidence

**Treatment protocols:**

<table>
<thead>
<tr>
<th>Test</th>
<th>Center with DS</th>
<th>Center without DS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mifepristone 600 mg</td>
<td>36-48 hrs before</td>
<td>-</td>
</tr>
<tr>
<td>Dilapan-S</td>
<td>3 pcs (in average) for 12 hrs</td>
<td>-</td>
</tr>
</tbody>
</table>
| Misoprostol | < 32 weeks: 400 ug/3 hrs  
> 32 weeks: 25 ug/3 hrs | 200 ug /3 hrs |
| Oxytocin | As Bishop score favourable | - |

**Clinical Evidence Diagram:**

- **DS**
  - Mifepristone 600 mg
  - Dilapan-S
  - 12 hrs
  - Admission to delivery room miso + OXY

- **no DS**
  - Mifepristone 600 mg
  - Dilapan-S
  - 36-48 hrs
  - Admission to delivery room miso + OXY

*Vincienne 2017*
Results:

- Misoprostol to amniotomy interval shorter in DS (0:47 vs 4:30hrs)
- Possibility of immediate amniotomy higher in DS (61.1 vs 19.8%)
- IDI 1 was significantly shorter in DS group (5:48 vs 10:18hrs)
- IDI 2 was significantly shorter in „no DS“ group (10:18 vs 18:24hrs)
- Delivery rate within 24hrs based on IDI 2 was similar (90 vs 91.5%)
- Total dose od miso tablets was lower in DS group (2.9 vs 3.4 tbl)
- There was no significant difference in complication rate (but in DS group was lower rate of PPH: 4.9 vs 10.4%)
- Total length of hospitalization was similar (2.4 vs 2.6 days)
Clinical evidence

Take home messages:

• Dilapan-S can significantly shorten stay at delivery room and save hospital budget.
• The use of Dilapan-S doesn´t extend total lenght of hospitalisation.
• Dilapan-S use can decrease total dose of used misoprostol.
• Complication rate was similar.
• Concerns of Dilapan-S side effects are unnecessary.
  • Ocurrence of pain or troubles during its insertion was insignificant.
• There could be an opportunity to shorten Dilapan-S insertion time and by that to shorten whole procedure and to improve IDI 2.
Clinical evidence

- Outcomes:
  - Induction to abortion interval
  - Blood loss after abortion
  - Complication rate
  - 70 women included into analysis

Wang 2017
Clinical evidence

• Treatment protocol:

<table>
<thead>
<tr>
<th></th>
<th>Dilapan-S group</th>
<th>Group without Dilapan-S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mifepristone 200 mg</td>
<td>24 hrs before</td>
<td></td>
</tr>
<tr>
<td>Dilapan-S simultaneously</td>
<td>1 rod for 12-18 hrs</td>
<td>-</td>
</tr>
<tr>
<td>Misoprostol</td>
<td>600 ug vaginally, followed by 400 ug orally every 3 hours. max 5 doses /24hrs</td>
<td></td>
</tr>
</tbody>
</table>

Wang 2017
Clinical evidence

• **Results:**
  - Higher rate of complete abortions within 48 hrs (*n.s.*)
  - Shorter induction to delivery interval
  - Shorter hospitalization
  - No difference in blood loss
  - No difference in rate of complications

<table>
<thead>
<tr>
<th>Group</th>
<th>DMM (n=35)</th>
<th>MM (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful abortion within 48 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate of complete abortion (%)</td>
<td>57.1 (20/35)</td>
<td>42.9 (15/35)</td>
</tr>
<tr>
<td>Rate of incomplete abortion (%)</td>
<td>40.0 (14/35)</td>
<td>51.4 (18/35)</td>
</tr>
<tr>
<td>Failure (%)</td>
<td>2.9 (1/35)</td>
<td>5.7 (2/35)</td>
</tr>
<tr>
<td>Induction-to-abortion interval in hours (h)</td>
<td>32.3 ± 10.3**</td>
<td>57.3 ± 18.1</td>
</tr>
<tr>
<td>Hospital stay (d)</td>
<td>2.3 ± 0.4**</td>
<td>3.9 ± 0.8</td>
</tr>
<tr>
<td>Blood loss after abortion at 2 h (ml)</td>
<td>95.43 ± 60.67</td>
<td>100.91 ± 64.15</td>
</tr>
</tbody>
</table>

****: *P*<0.01, compared with group MM

Wang 2017
e-Registry (2017)

• Prospective, international, observational trial
• 7 study sites / 4 countries
• 6-24 weeks of gestation
• 439 subjects eligible for analysis
  • 274 surgical abortion
  • 165 Medical abortion
    • 1st trimester - 32 subjects
    • 2nd trimester - 133 subjects
Medical abortion

Basic results:

<table>
<thead>
<tr>
<th></th>
<th>6-12 weeks</th>
<th>12-24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean # of dilators</td>
<td>2.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Mean insertion time</td>
<td>5.4 hrs</td>
<td>6.11 hrs</td>
</tr>
<tr>
<td>Simultaneous misoprostol</td>
<td>78%</td>
<td>75%</td>
</tr>
<tr>
<td>Mean insertion-delivery interval</td>
<td></td>
<td>10.7 hrs</td>
</tr>
<tr>
<td>Rate of one-day procedure completion (by 12 hrs)</td>
<td></td>
<td>81%</td>
</tr>
</tbody>
</table>
Results: Impact of adjunctive misoprostol used:

- Adjunctive = misoprostol at the same time as D-S inserted
- No adjunctive = miso administered after Dilapan-S removal

<table>
<thead>
<tr>
<th></th>
<th>Adjunctive misoprostol (N=77)</th>
<th>No adjunctive misoprostol (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean gestational age</td>
<td>15.2 weeks</td>
<td>16.6 weeks</td>
</tr>
<tr>
<td>Mean No of dilators</td>
<td>2.6</td>
<td>2.9</td>
</tr>
<tr>
<td>Duration of insertion</td>
<td>6.7 hours</td>
<td>7.1 hours</td>
</tr>
<tr>
<td>Total dose of misoprostol</td>
<td>1426 ug</td>
<td>1250 ug</td>
</tr>
<tr>
<td>Mean insertion - delivery interval</td>
<td>10.2 hours</td>
<td>16.9 hours</td>
</tr>
<tr>
<td>Complications of cervical preparation</td>
<td>5.2%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Complication of procedure</td>
<td>15.6%</td>
<td>11.1%</td>
</tr>
</tbody>
</table>
Article evaluating results in both arms, Surgical and Medical, was submitted for publication

*Acta Obstetricia et Gynecologica Scandinavica – IF=2.5*

**Synthetic Osmotic Dilators (Dilapan-S) For Cervical Preparation Prior To Abortion – An International Multicentre Observational Study**

Authors: Rohan Chodankar, Janesh Gupta et al.
Take home messages

» Combination of Dilapan-S and misoprostol for Medical abortion offers effective and safe procedure
» Insertion of 2-3 osmotic dilators for time interval of 4-7 hours provided effective cervical priming in majority of women.
» Fast mode of action enables one-day procedures in majority of medical abortions – 81%
» No serious adverse outcomes, including infectious complications associated with the use of synthetic osmotic cervical dilators were reported.
» Easy to insert & remove (>90%).

» Procedure, when misoprostol administration is initiated after Dilapan-S removal (no adjunctive misoprostol)
  » Prolongs insertion-delivery interval BUT
  » Decrease total dose of misoprostol
  » Has lower rate of complications
Aim: to investigate mifepristone as potential adjunct to Dilapan-S or alone as method of cervical preparation

Assumed result:
- Adjunct mifepristone doesn’t bring significant benefit
- Dilapan-S seems to be superior to mife alone
Interest of Cervical Dilators in Second Trimester Termination of Pregnancy (DILATOP)


» Aim: to evaluate whether Dilapan-S use for cervical ripening in second trimester medical TOP is effective to reduce duration of labor.

» Protocol:
  » Misoprostol alone
  » Misoprostol + Dilapan-S

» 280 participants assumed

» Initiated: June 2017

» Estimated study completion date: Q1/2021
No support in guidelines to use Dilapan-S for cervical preparation in 2TM medical abortions (except Canada)
  but the GLs have not been updated for many years

On the other hand there are clinical trials evaluating use of Dilapan-S in this indication (e-Registry, France, Russia, China)

Based on these it seems that Dilapan-S has capability to:
  shorten induction to delivery interval
  shorten stay at delivery room
  shorten hospitalisation time
  decrease total dose of misoprostol
  save hospital budget

Further clinical data needed to confirm
in

2nd TRIMESTER SURGICAL ABORTIONS
Mifepristone Versus Osmotic Dilator Insertion for Cervical Preparation Prior to Surgical Abortion at 15-18 weeks

- Boston University, 50 subjects enrolled, 2011 – 2017
- Trial completed, has results, no article
- Aim: mife + miso vs Dilapan-S alone for cervical preparation

<table>
<thead>
<tr>
<th></th>
<th>Mifepristone + Misoprostol</th>
<th>Osmotic Dilators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants Analyzed</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Length of Procedure</td>
<td>14 (12 to 17)</td>
<td>13.5 (11 to 16)</td>
</tr>
<tr>
<td>[Units: Minutes]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (95% Confidence Interval)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Ongoing RCT - future evidence

Laminaria Compared to Dilapan-S for Cervical Preparation Before Dilation and Evacuation at 18-24 weeks

- Planned Parenthood of New York City, Inc.
- 180 subjects randomized
- Recruitment completed in 2016, no results available

- Primary outcome: difference in procedure time, when Lams or Dilapan-S are used overnight for cervical preparation
Ongoing RCT - future evidence

Mifepristone Versus Osmotic Dilators in Conjunction With Misoprostol for Cervical Preparation prior to D&E at 14-19 weeks


» Stanford University; 100 subjects, 2016 – 2020

» Recruitment ongoing

» Primary outcome: procedure time (+ objective + subjective measures)

» Protocol:

<table>
<thead>
<tr>
<th></th>
<th>14– 16 weeks</th>
<th>17 – 19 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilapan-S</td>
<td>1-2 rods 24 hrs before</td>
<td>3-5 rods 24 hrs before + 200ug miso 30-90´before procedure</td>
</tr>
<tr>
<td>Mifepristone</td>
<td>200 mg mifepristone 24 hrs before + 400 ug miso 30-90´before the procedure</td>
<td></td>
</tr>
</tbody>
</table>
Ongoing RCT - future evidence

Same-day Cervical Preparation With Dilapan-S Plus Buccal Misoprostol Compared to Overnight Dilapan-S before D&E at 16 to 20 weeks


» Planned Parenthood of New York City, Inc.

» 92 subjects, 2016-2018

» Recruitment ongoing

» Primary outcome: procedure time

» Hypothesis: [same-day D-S + miso] non-inferior to [overnight D-S]
SUMMARY
Dilapan-S in 2TM surgical abortions

» No new clinical evidence

» Two RCTs completed
  » mife vs osmotic dilators (Lams & D-S) – unuseable?
  » Dilapan-S with Lams
  » publication unavailable

» Two RTCs ongoing
  » mife vs Dilapan-S
  » [same-day D-S + miso] vs. [overnight D-S alone]
Long term perspective

» R. LYUS (London, 2016)

» 2TM-D&E abortions → risk of damage to the cervix → reduced cervical integrity → risk for subsequent pregnancy

» Major risk = pre-term birth (PTB)

» Confirmed by meta-analysis by Saccone (2016)

» Retrospective analysis – 1500 mothers (4 trials)

» All involved osmotic dilation overnight (or 2 nights)

» No or little *clinically significant* impact on next pregnancy morbidity

» Such regimen substantially mitigates or eliminates the increased risk of PTB after D&E in 2TM

» ...is it wise to perform one-day-surgery...?
Case study – JAPAN

» When dumbelling occurred, Dilapan-S fragmented into two parts and broken fragment fell down into the uterine cavity...

» should the doctor administer antibiotics until he removes?

» patient was busy, so doctor expected to remove after a week!

» The patient realized bleeding at the second day after the procedure, so the fragment was removed at that time.

» As a result, no big problem happened.

» The picture below was taken by the doctor.
...feedback provided on entrapped fragment of dilator (retention) in uterine cavity, the **company's statement and general recommendation** is as follows:

» Every intervention must lead to the **removal of all fragments** of the dilator from the uterus. For example, a 14 or 16 mm suction curette can be used to remove dilator or its fragments.

» After the removal, the fragments of the dilator should be checked to verify that all fragments have been removed. In the event of any doubts, a **hysteroscopy or ultrasound** should be performed.

» The **effect of fragments** of the dilator left in the body on women’s health is not known.

» Indication of administration of **antibiotics** can only be assessed by the healthcare provider with knowledge of patients’ health status and other conditions and circumstances, while complying with the national or institutional standard of care.