Cervical priming made easy

Ingrid Sääv, MD, PhD
Senior consultant Gynaecology dep Norrtälje hospital
What, why, when and how
What is priming

Cervical tissue properties

Mechanical
Medical
Cervical tissue properties

Collagen dominated matrix

Untreated cervical internal os 4.1 mm in nulliparous women

Medical priming causes influx of water, and disintegration of the collagen fibres
Mechanical dilatation

Root, screws and dilators inserted into the cervix (Braxton-Hicks)

Osmotic dilators that are inserted and allowed to slowly swell (Laminaria, Dilaphan, Lamical)

Two medium Laminaria, before insertion and after 12 hours of insertion
Medical priming

Prostaglandin analogues
(Gemeprost®, Cervagem®, misoprostol)

Anti-progesteron (mifepristone)
Why?

Mechanical damage directly related to the force used for dilating

Easier access – less risk of not succeeding with the procedure
Less risk of perforation

Mechanical dilatation after the medical priming
Correlation between baseline cervical dilatation and cumulative force needed for dilatation in women undergoing surgical abortion.

\[ y = -0.0367x + 9.8878 \]

\[ R^2 = 0.6568 \]


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The force needed for dilatations is directly associated with the risk of surgical damage.

After medical priming – less force is needed to dilate the cervix.
Why medical priming?

Reduces complication in surgical abortion procedures:

- Reduces bleeding,
- Reduces risk of incomplete abortion,
- Reduces risk of infection

Meirik et al. Lancet 2012
Misoprostol

- The drug of choice for practical reasons, for being cheap and for drug profile in terms of safety and side-effects.
Misoprostol

Prostaglandin E1 analogue

- Stable at room temperature
- Long shelf-life
- Few and self-limiting side-effects, and no cardio-vascular side-effects
Misoprostol, practical aspects

Must not be exposed to humidity

Is easy to administrate, and does not need skilled attendants or iv-access

Is widely available and is on the WHO list of essential drugs
Misoprostol, pharmacokinetics

Can be administered orally, vaginally, sub-lingually or buccal

Plasma half-life of 20-40 min after oral administration

Metabolised in the liver to active misoprostol acid

Does not induce the cytochrome p 450 system and has no known drug interaction

Safety margin of 500-1000-fold between therapeutic dose and estimated lethal dose
Safety

No cardiovascular, haematological, endocrine, biochemical, immunological, respiratory, or ophthalmo logic side-effects.

High doses could cause a decrease in blood pressure, why vaginal administration is recommended to patients with severe congenital heart malformations.

Reduced dose also to previously c-sectioned patients, but priming usually lower doses.

www.misoprostol.org
FIGO guidelines
Misoprostol, teratogenecity

Exposure of misoprostol in early pregnancy is related to a risk of birth defects

The risk increases after high repeated doses such as attempted abortion "misoprostol alone" regimen, and peaks during gestation week 5-8, no risk for malformation after gestational week 13

Incidence is less than 10 per 1000 exposures

The most common malformations are clubfoot, cranial nerves injury and absence of fingers

*da Silva Dal Pizzol et al Reprod Toxicol 2006,*
*Philip et al Population Council 2002, Gynuity 2002*
Misoprostol, side effects

Gastrointestinal; nausea, vomiting, diarrhea
Abdominal pain and cramping
Shivering, chills and fever
Vaginal bleeding or expulsion
Misoprostol, administration

Can be administered oral, sublingual, buccal or vaginal

Completely different plasma concentration, half-life, efficacy and side-effects depending on administration route!
Misoprostol, absorption

Zieman et al 1997
Mean plasma concentrations of misoprostol acid over time (arrowbars = 1 SD).

Mean Serum concentrations of MPA over time.

A, slow release; B, sublingual; C, vaginal
What efficacy do we expect?

0.4 mg misoprostol increased cervical diameter from 3.7 to 7.8 mm in nullaparous women and from 6.0 to 9.8 mm in parous women, when compared with placebo.

Ngai et al Hum Reprod 1995
Comparison efficacy medical priming sublingual with oral

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<th></th>
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<th>Vaginal</th>
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<td></td>
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<td></td>
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</tr>
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<td>Mean (SD)</td>
<td>7.6 (1.3)</td>
<td>7.7 (0.73)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>8.0 (4.5–10)</td>
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</tr>
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<td>Cumulative force (N)</td>
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<td></td>
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<td>Mean (SD)</td>
<td>9.0 (9.8)</td>
<td>6.6 (5.4)</td>
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<tr>
<td>Median (range)</td>
<td>5.5 (0–38)</td>
<td>5.0 (1–21)</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
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<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>52.1 (20.2)</td>
<td>48.3 (12.3)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>50 (10–100)</td>
<td>50 (10–80)</td>
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*Tang OS et al Hum Reprod 2004*
### Table II.
Operative findings by treatment groups

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<tr>
<th></th>
<th>Placebo (n = 44)</th>
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<td>Duration of operation (min)</td>
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Ngai SW et al. Hum Reprod 1999
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Cervical priming made easy. Ingrid Sääv
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Sääv et al Hum Reprod 2015
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Sääv et al Hum Reprod 2015
Side-effects

Gastrointestinal; nausea, vomiting, diarrhea
More GI side-effects after oral administration, resolves after 2-6 hours

Shivering, chills and fever
Associated with high serum level as after sublingual intake

Abdominal pain
Related to the plasma level and plasma half-life – with sublingual and oral causing a continues increase in tonus, and vaginal and slowrealese regular contractions

Bleeding before surgery
Risk increases with effectiveness of treatment, and with time – higher risk after sublingual treatment unless the priming interval is shortened
# Priming interval and side-effects

## Side effects after misoprostol priming

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*Sääv et al Hum Reprod 2015*
Figure 1. Uterine tonus was measured in mmHg.

Risk of expulsion of pregnancy before surgery;

Increases with *dose* and *time*, and differs between routes of administration!
For which procedures should we consider medical priming?
Surgical abortion

Better effect of priming the more advanced the pregnancy

Mean dilatation of 7.8 mm (from baseline 4.1 mm) in first trimester pregnancies

Usually little need for mechanical dilatation after priming – easy access

Reduced risk of perforating when entering the cervical internal os
Surgical abortions (ie vacuum aspiration)

Always!

Reduces the risk of mechanical injury

Reduces risk of heavy bleeding, incomplete abortion and postabortion infection!

The association between previous abortion and subsequent preterm labour has dissapeared after introducing medical priming

Meirik et al Lancet 2012,
IUS insertion and priming

May be considered to nulliparous women

After failed attempt or history of previous difficult insertion

To women with amenorrhea – after use of nexplanon or depo-provera

Sääv et al Hum Reprod 2007,
Scavuzzi et al Hum Reprod 2013
IUC insertion after medical priming

- Significantly more easy insertions and fewer difficult insertions in the misoprostol group (p=0.039)
- No difference in pain estimation or bleeding days after insertion

Sääv et al. Hum Reprod 2007
Hysteroscopy

Many therapeutic procedures require dilatation up to 10-11mm.

No effect on postmenopausal women, unless pretreatment with estrogen is given for 2 weeks.

Ngai et al. Hum Reprod 2001,
Oppegard et al. Lancet 2010
For which procedures should we consider medical priming?

Surgical abortion
*Always and for all!*

IUC insertion
*Nulliparous? Other factors predicting difficulties?*

Hysteroscopy
*Fertile women and therapeutic hysteroscopy*  
*Diagnostic hysteroscopy?*

Womens preference?

Many articles state women do NOT prefer vaginal administration!

Ngai et al 2000, Ho et al 1997
Who administrates?
Could women be trusted to find their own vagina?
Positive examples
Cervical priming made easy. Ingrid Sääv
75% preferred vaginal administration

16% preferred sublingual administration

Same argument dominated in both groups; Easy!
How? Recommendations
Dose recommendation suggest 0.4 mg

Always pain relief at the same time – preferably NSAID
Sublingual, vaginal, oral or buccal – but not rectal!
Sublingual 0.4 mg misoprostol
Priming time 1 hour

- Advantages
  - Quickest effect
  - Can be administrated at the clinic
  - Less risk of bleeding prior to surgery
  - Less abdominal pain and cramping
  - Self-administered

- Disadvantages
  - More shivering and fever
  - More abdominal pain and risk of bleeding if priming-time is accidentally prolonged

*Longer priming interval than 1 hours do not result in greater effect, but increase side-effects*
Vaginal 0.4 mg misoprostol
Priming time 2-3 hours

Advantages
- No bad taste
- Less shivering
- Self-administered
- Less risk of bleeding and abdominal pain compared to sublingual after 3 hours

Disadvantages
- Longer priming interval necessary
- Needs to be taken before at home – risk of bleeding outside the clinic
- Not nice if not self-administered

*Longer priming interval than 3 hours do not result in greater effect, but increase side-effects*

_Fiala et al Int J Gyn % Obstet 2007_
For special cases remember alternative:

Mifepristone 200 mg (oral)

Priming time 24-48 hours
Thank you!

Ingrid Sääv, MD, PhD
Senior consultant Gynaecology dep Norrtälje hospital