Cervical priming made easy

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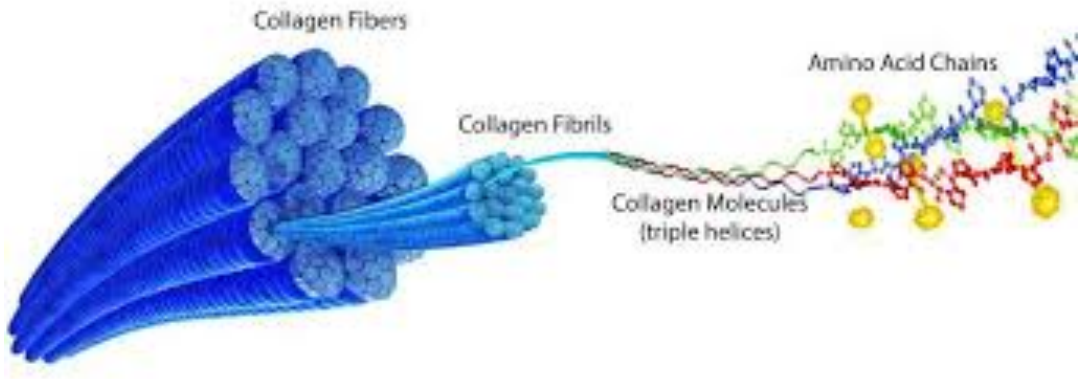
What, why, when and how

What is priming

Cervical tissue properties

Mechanical
Medical

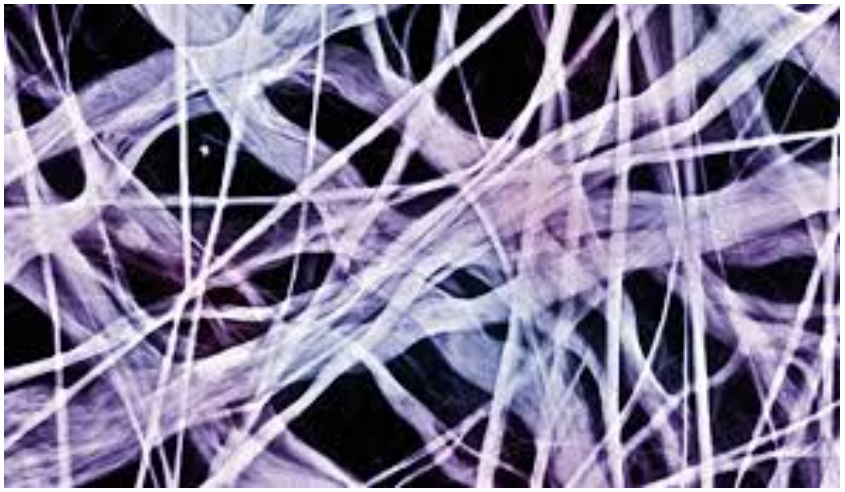


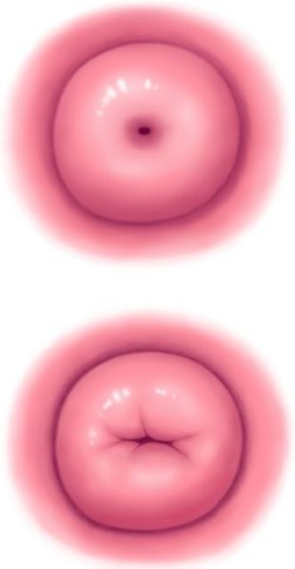
Cervical tissue properties

Collagen dominated matrix

Untreated cervical internal os 4.1 mm in nulliparous women

Medical priming causes infux of water, and disintegration of the collagen fibres

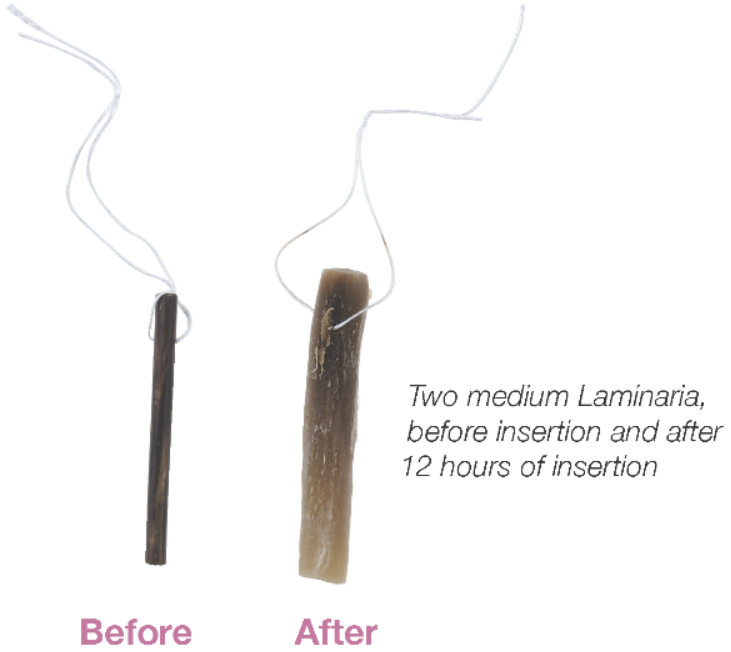




Mechanical dilatation

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

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

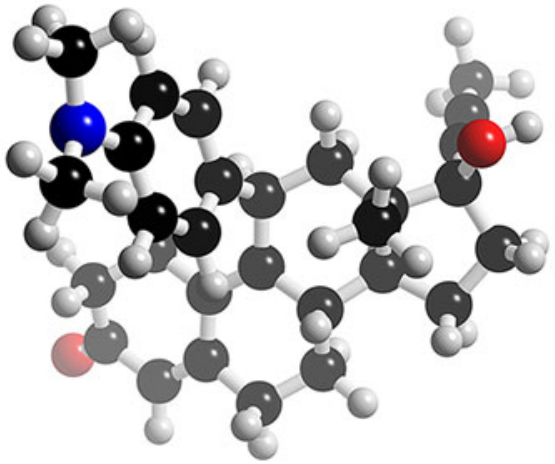


Two medium Laminaria, before insertion and after 12 hours of insertion

Medical priming

Prostaglandin analouges
(Gemeprost®, Cervagem®, misoprostol)

Anti-progesteron (mifepristone)



Why?

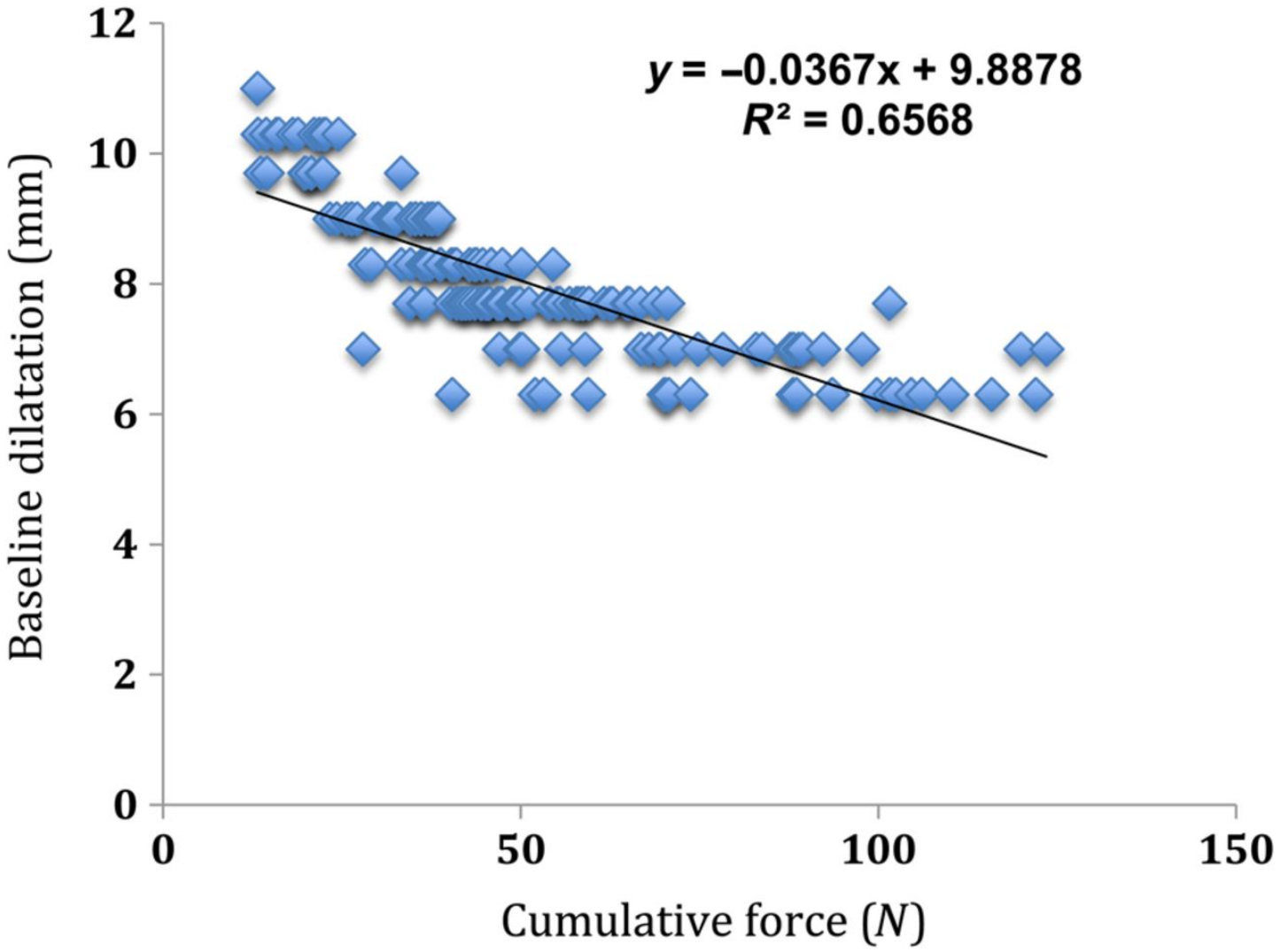
Mechanical damage directly related to the force used for dilating

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

Tietze et al, Stud Fam Plann 1974, Hulka et al Am J Obstet Gynecol1974, El-Refaey et al Lancet 1994, Krishna et al Contraception1986, Meirik et al Lancet 2012

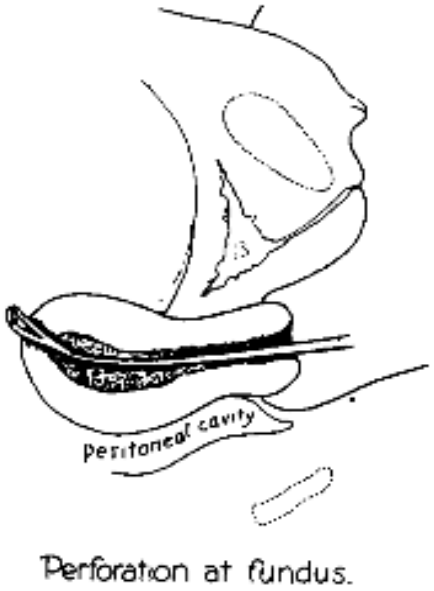
Mechanical dilatation after the medical priming

Correlation between baseline cervical dilatation and cumulative force needed for dilatation in women undergoing surgical abortion.

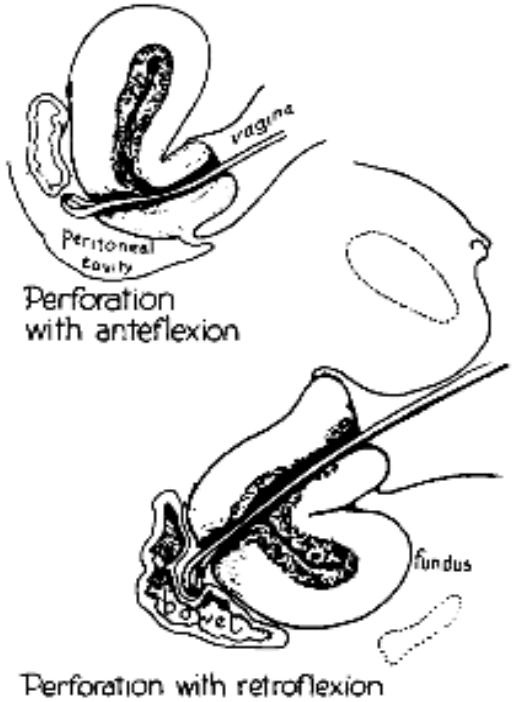


Ingrid Sääv et al. Hum. Reprod. 2015;30:1314-1322

human reproduction



Perforation at fundus.

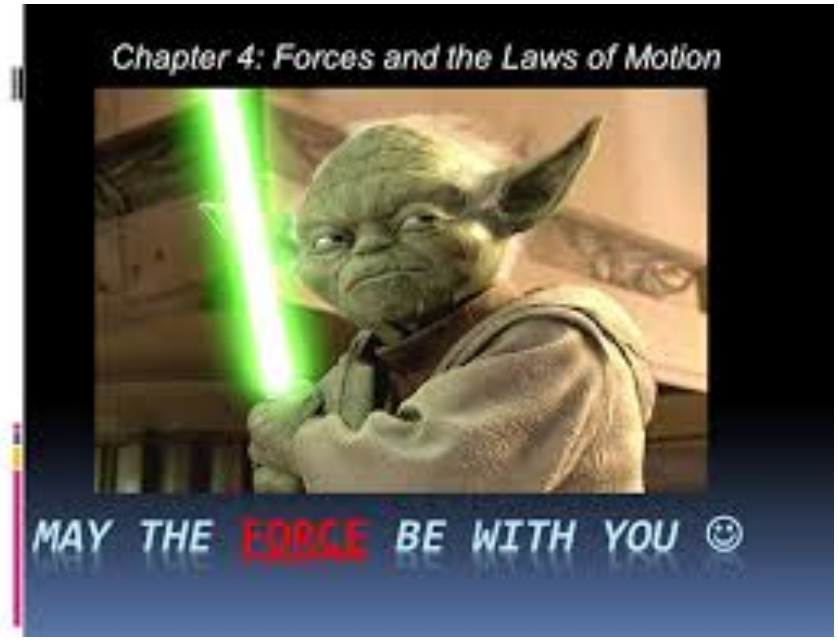


Perforation with anteflexion

Perforation with retroflexion

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

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



Why medical priming ?

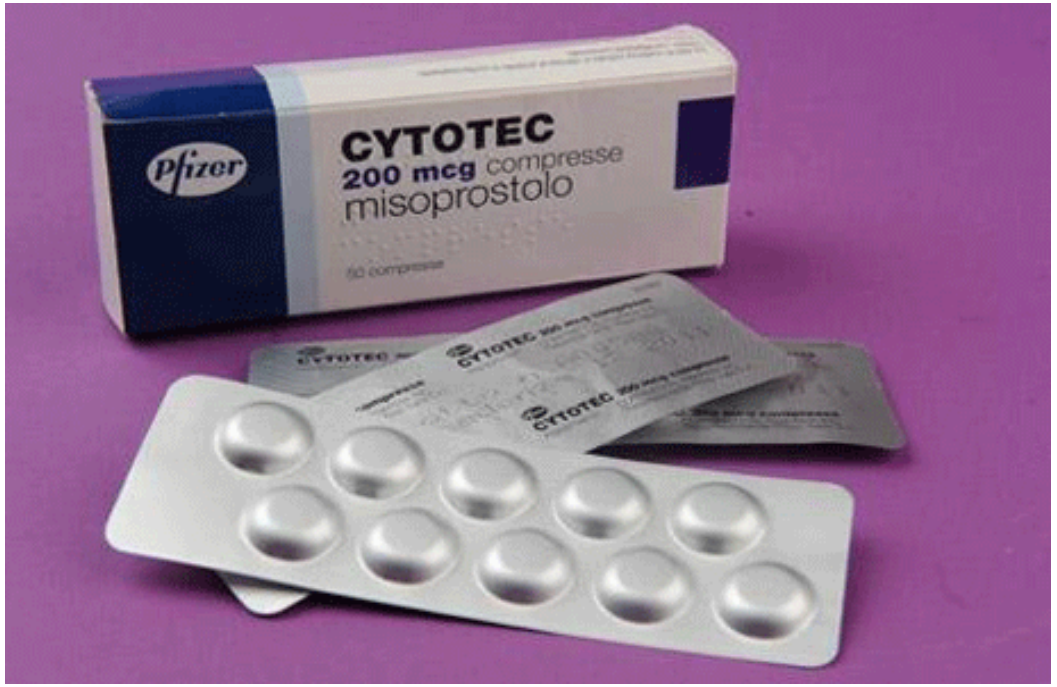
Reduces complication in surgical abortion procedures:

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

Meirik et al Lancet 2012

Misoprostol

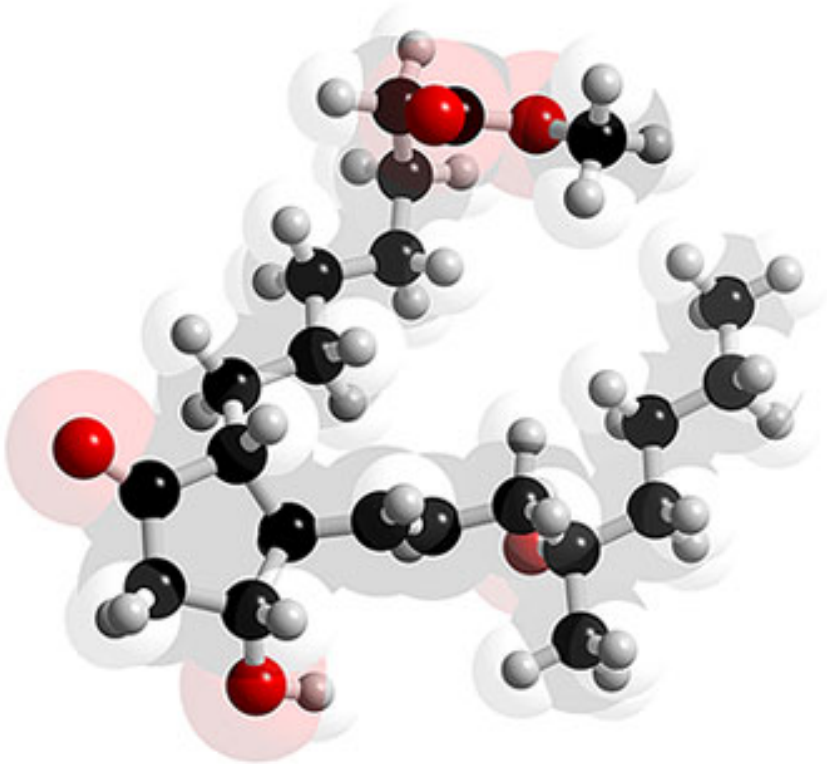
- The drug of choice for practical reasons, for being cheap and for drugprofile in terms om safety and side-effects.



Misoprostol

Prostaglandin E1 analouge

- Stable at room temterature
- Long shelf-life
- Few and self-limiting side-effects, and no cardio-vascular side-effects



Misoprostol, practical aspects

Must not be exposed fo 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 minafter 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 ophtalmologic 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 previasly c-sectioned patients, but priming usually lower doses

www.misoprostol.org
FIGO guidelines

Misoprostol, teratogenecity

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

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

Incidense is less then 10 per 1000 exposures

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

da Silva Dal Pizzol et al Reprod Toxicil 2006,
Philip et al Population Council 2002, Gynuity 2002

Misoprostol, sideeffects

Gastrointestinal; nausea, vomiting, diarrhea

Abdominal pain and cramping

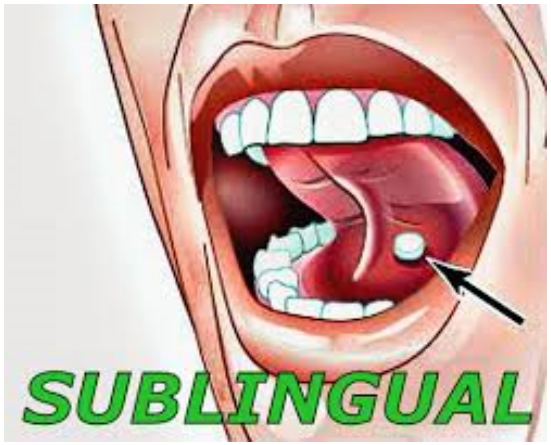
Shivering, chills and fever

Vaginal bleeding or expulsion

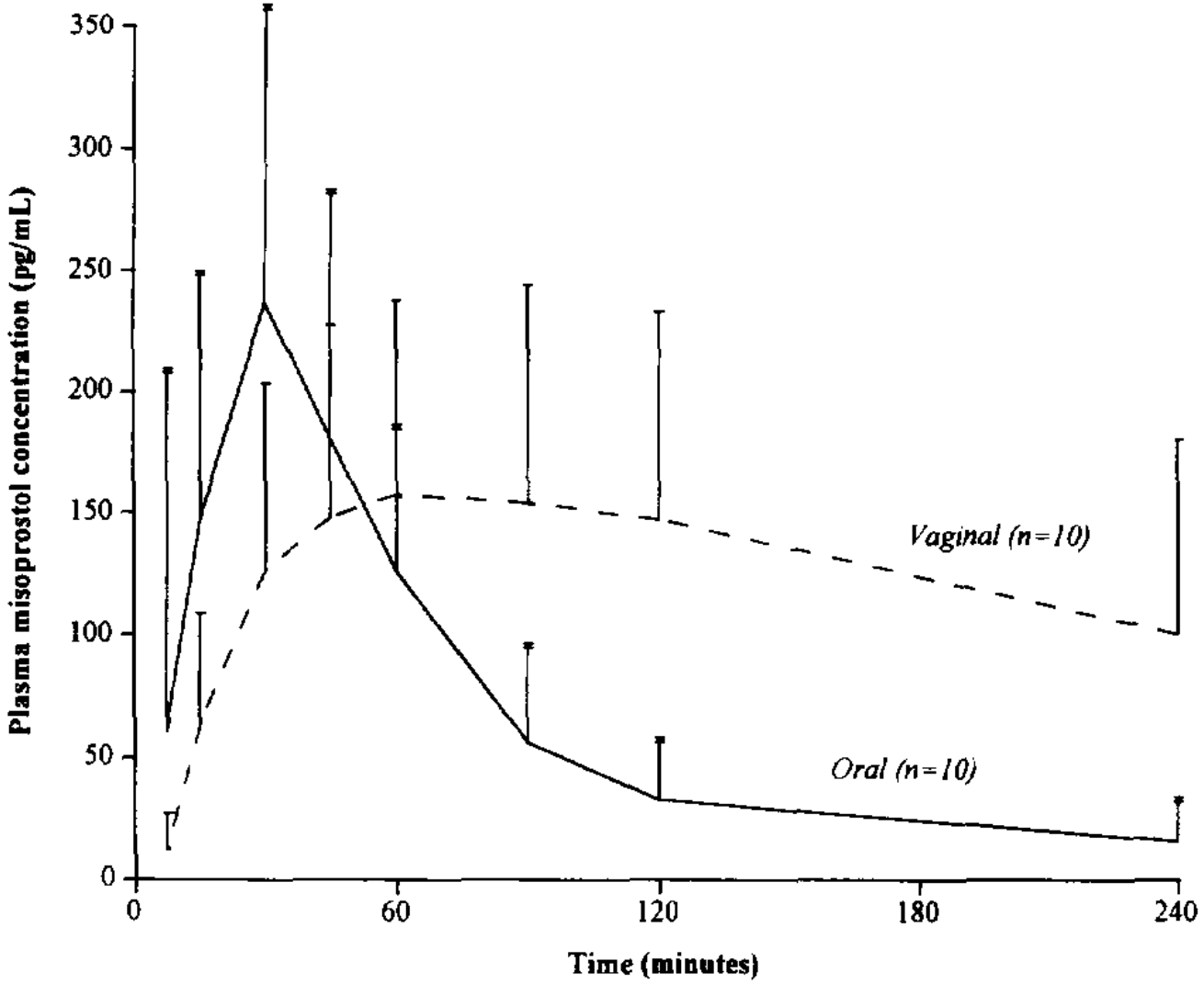
Misoprostol, administration

Can be administered oral, sublingual, buccal or vaginal

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

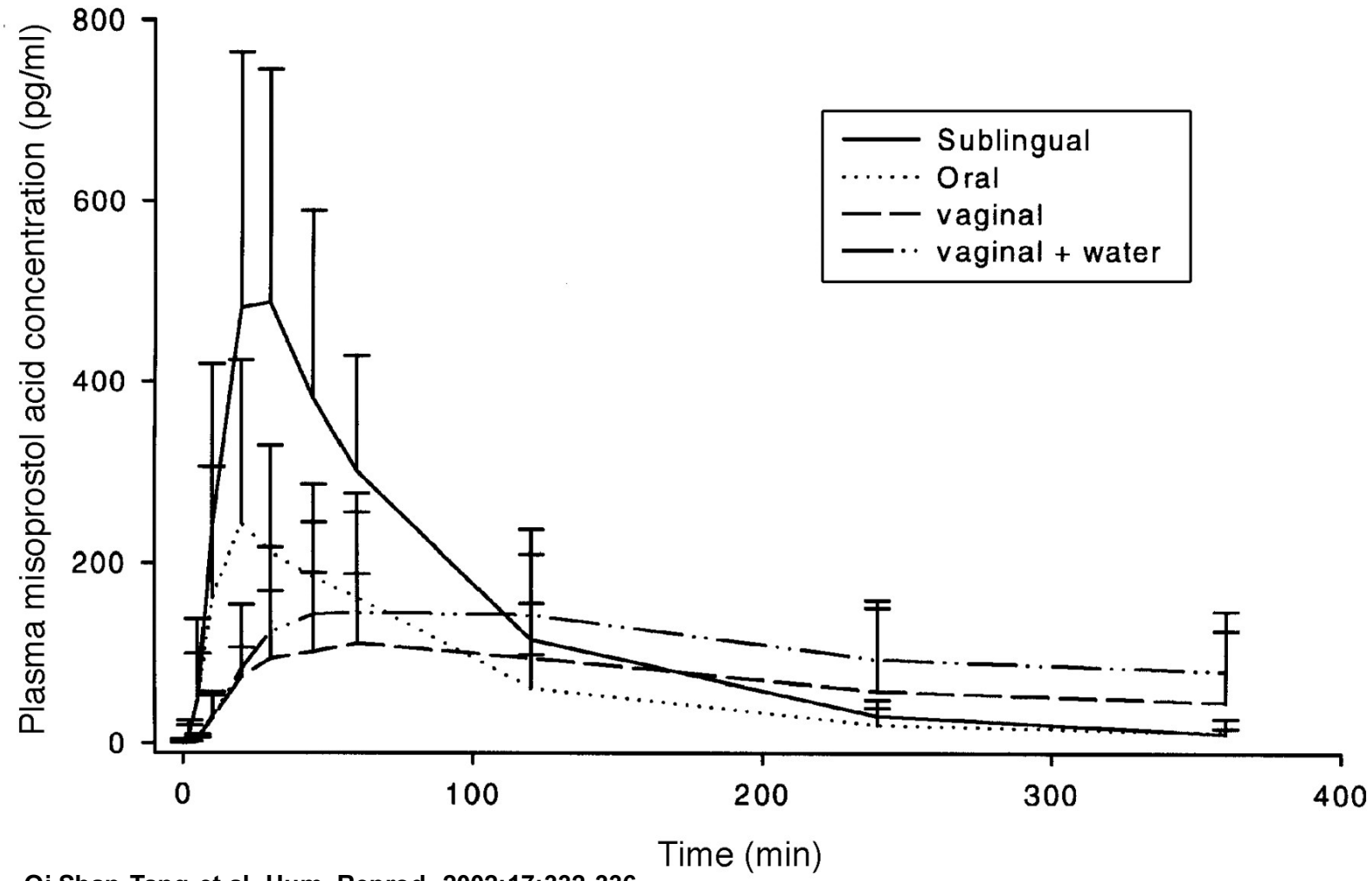


Misoprostol, absorption



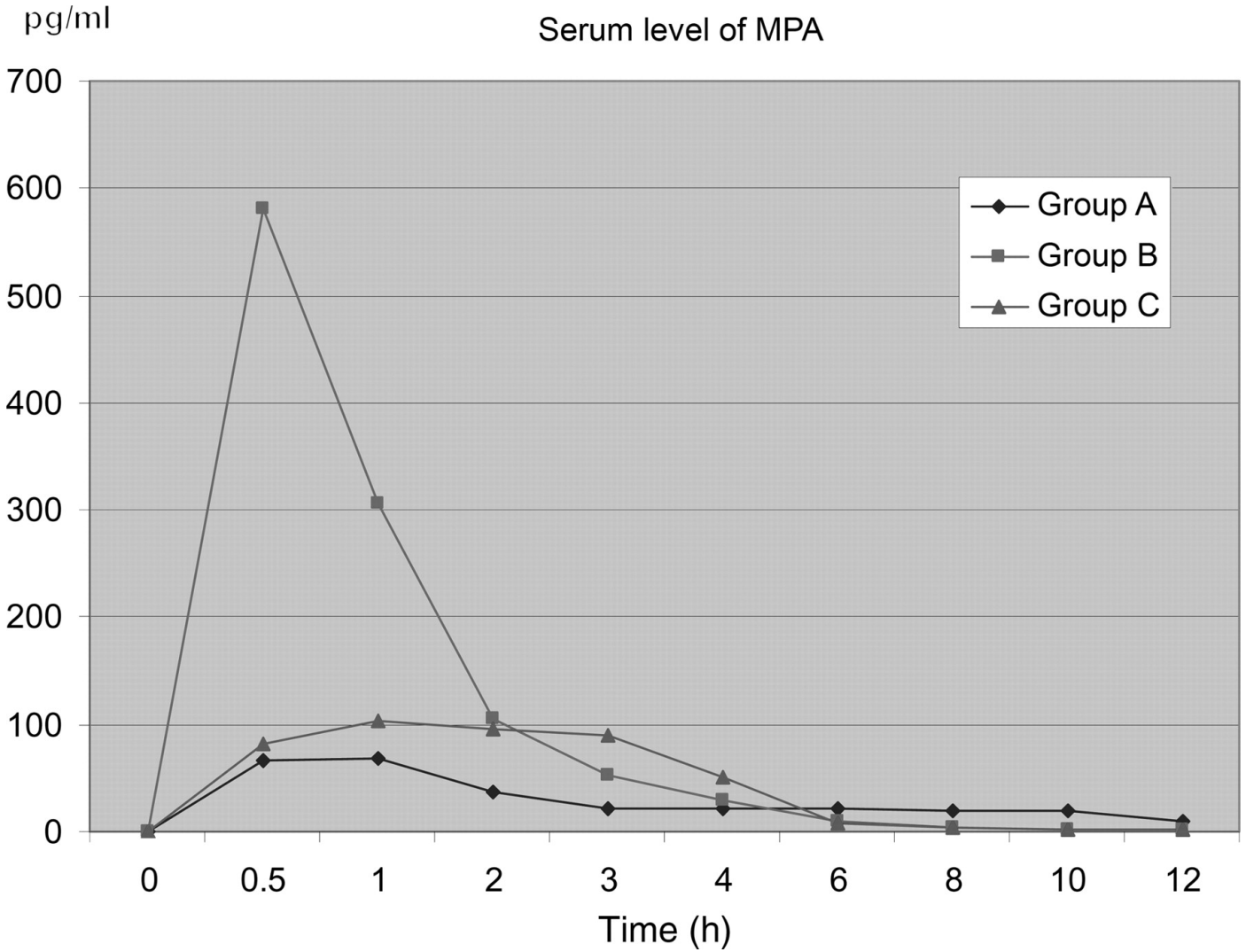
Zieman et al 1997

Mean plasma concentrations of misoprostol acid over time (arrowbars = 1 SD).



Oi Shan Tang et al. Hum. Reprod. 2002;17:332-336

Mean Serum concentrations of MPA over time.



A, slow release;
B, sublingual;
C, vaginal

A. Aronsson et al. Hum. Reprod. 2007;22:1912-1918

human reproduction

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 mmm in parous women, when compared with placebo

Ngai et al Hum Reprod 1995

Comparison efficacy medical priming sublingual with oral

	Sublingual	Vaginal
	(*n* = 40)	(*n* = 40)
Baseline cervical dilatation (mm)		
Mean (SD)	7.6 (1.3)	7.7 (0.73)
Median (range)	8.0 (4.5–10)	8.0 (6.0–9.5)
Cumulative force (N)		
Mean (SD)	9.0 (9.8)	6.6 (5.4)
Median (range)	5.5 (0–38)	5.0 (1–21)
Blood loss (ml)		
Mean (SD)	52.1 (20.2)	48.3 (12.3)
Median (range)	50 (10–100)	50 (10–80)

Tang OS et al Hum Reprod 2004

Table II. Operative findings by treatment groups	**Placebo (*n* = 44)**	**Oral misoprostol**		**Vaginal misoprostol**	
		200 µg	**400 µg**	**200 µg**	**400 µg**
		(*n* = 43)	**(*n* = 40)**	**(*n* = 40)**	**(*n* = 37)**
Baseline cervical dilatation (mm)					
Mean (SD)	5.5 (1.4)[a]	6.6 (0.9)[b,c]	7.2 (1.0)[b,d]	6.8 (1.2)[b,d]	6.8 (1.3)[b,d]
Median (range)	5.5 (2–8)	6.0 (5–8)	7.5 (5–8)	7.0 (3–8)	7.0 (3–8)
Cumulative force (N)					
Mean (SD)	47.6 (27.6)[c]	27.5 (15.8)[d]	21.7 (18.9)[d]	25.9 (22.3)[d]	24.2 (16.4)[d]
Median (range)	48 (3–248)	26 (1–77)	19 (1–101)	17 (1–102)	22 (5–71)
Duration of operation (min)					
Mean (SD)	4.9 (2.1)	5.4 (2.6)	5.8 (2.3)	5.2 (2.7)	4.9 (1.9)
Median (range)	5.0 (2.0–12.0)	5.0 (2.0–10.0)	5.0 (2.0–10.0)	5.0 (2.0–15.0)	5.0 (2.0–15.0)
Blood loss (ml)					
Mean (SD)	128.3 (123.1)[c]	90 (68.4)[d]	88 (71.4)[d]	59.5 (52.6)[d]	57.0 (40.4)[d]
Median (range)	100.0	50.0	50.0	50.0	50.0

Ngai SW et at Hum Reprod 1999

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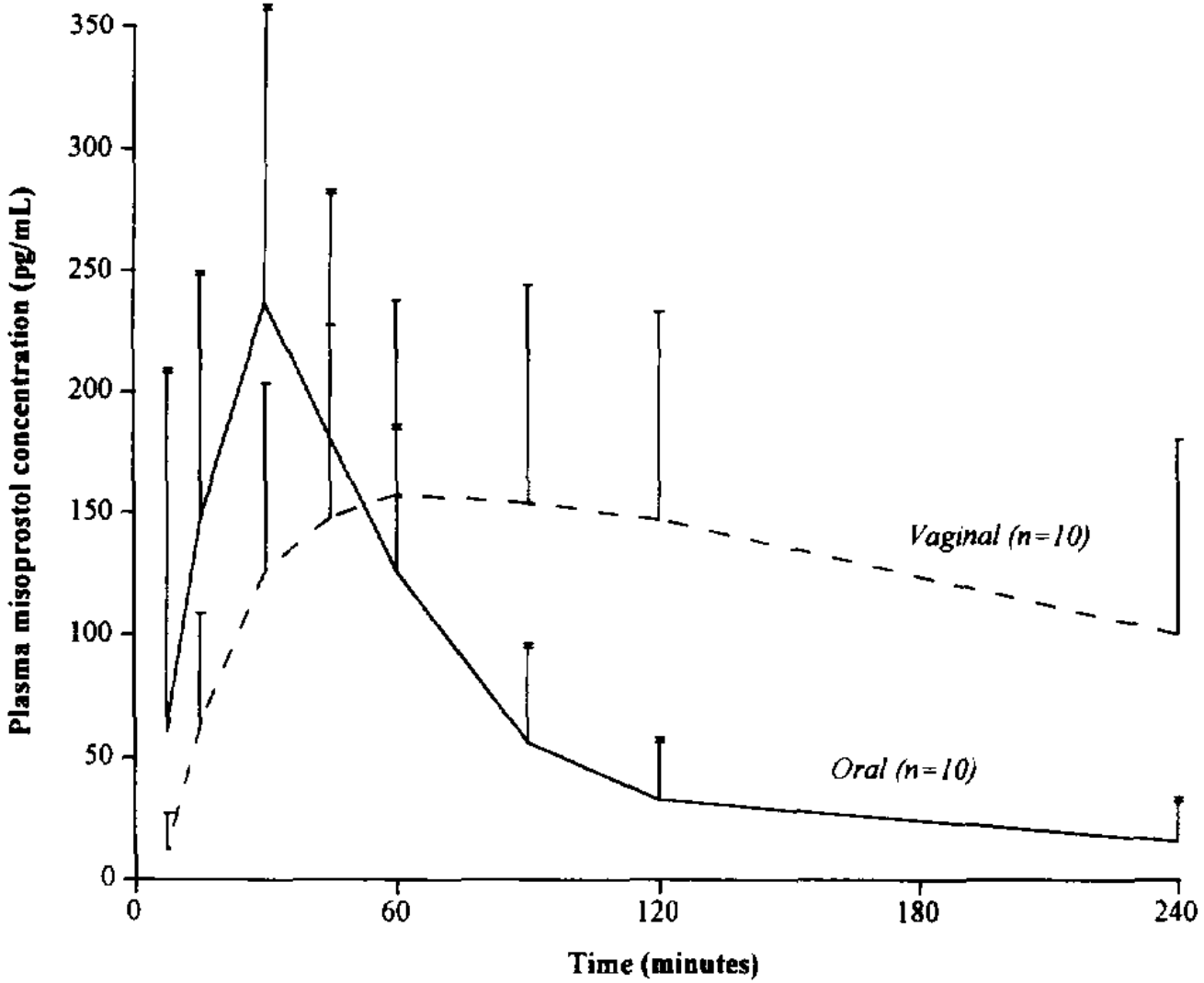
Plasma misoprostol concentration (pg/mL)
350
300
250
200
150
100
50
0
0
60
120
180
240
Time (minutes)
Vaginal (n=10)
Oral (n=10)

Priming interval and efficacy

Effect of misoprostol on cervical dilatation regarding route of administration and priming interval

Study group	SL 1 hour (n=45)	SL 3 hours (n=46)	PV 1 hour (n=43)	PV 3 hours (n=44)	Significance
Baseline dilatation (mm)	7.9 (1.4) [1]	7.6 (1.8)	7.2 (1.5) [1]	7.9 (1.5)	[1]p=0.038 (CI 0.037-1.25)
Peak force (N)	16.5 (8.0)	17.1 (8.4)	20.3 (10.6) [1]	15.5 (8.2) [1]	[1]p= 0.021 (CI 0.73-8.94)
Cumulative force (N)	51.9 (27.0) [1]	54.4 (29.2)	64.6 (31.3) [1,2]	47.1 (23.3) [2]	[1]p=0.048 (CI 0.13 - 25.3) [2]p=0.005 (CI 5.45-29.6)

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 coninues 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

Study group	SL 1 hour n=45	SL 3 hours n=46	PV 1 hour n=43	PV 3 hours n=44	
Bleeding before surgery	2 (4.4%)	15 (33%)	3 (7.0%)	8 (18%)	
Abdominal pain	30 (67%)	31 (67%)	6 (14%)	24 (57%)	
Freezing/shivering	6 (13%)	2 (4%)	2 (5%)	3 (7%)	
Nausea/vomiting	(24%)	9 (20%)	8 (19%)	4 (9%)	

Sääv et al Hum Reprod 2015

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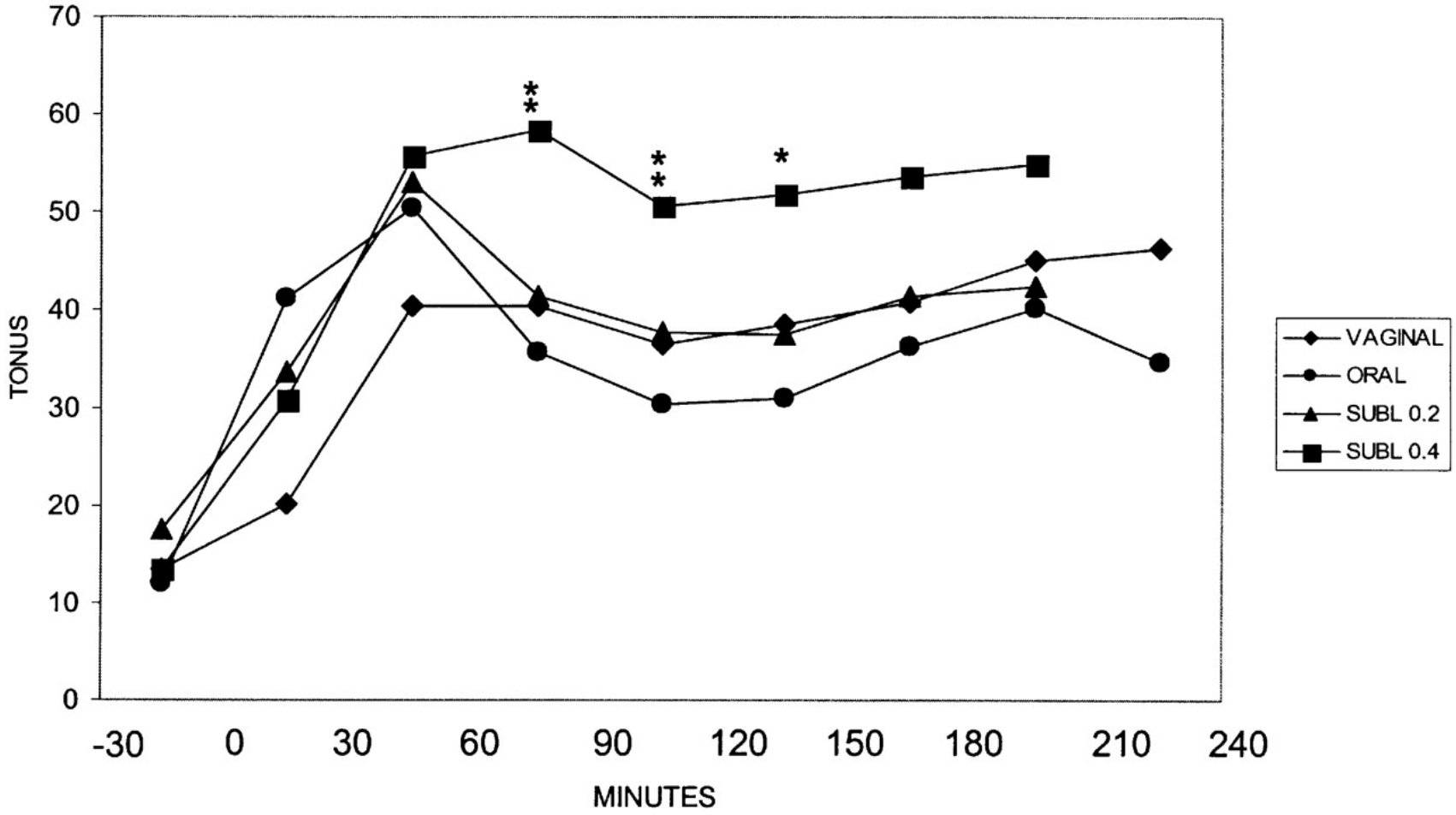
Sääv et al Hum Reprod 2015

Figure 1. Uterine tonus was measured in mmHg.



A. Aronsson et al. Hum. Reprod. 2004;19:81-84

Risk of expulsion of pregnancy before surgery;

Increases with *dose* and *time*, and differs between routes of administrion!

Fiala et al Int J Gyn & Obstet 2007

For which proceedures 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 vaccum 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,
***Oliver-Williams** C, Fleming M, Monteath K, Wood AM, Smith GC.*
*PLoS Med. **2013**;10(7):e1001481. doi: 10.1371/journal.pmed.1001481.*

IUS insertion and priming

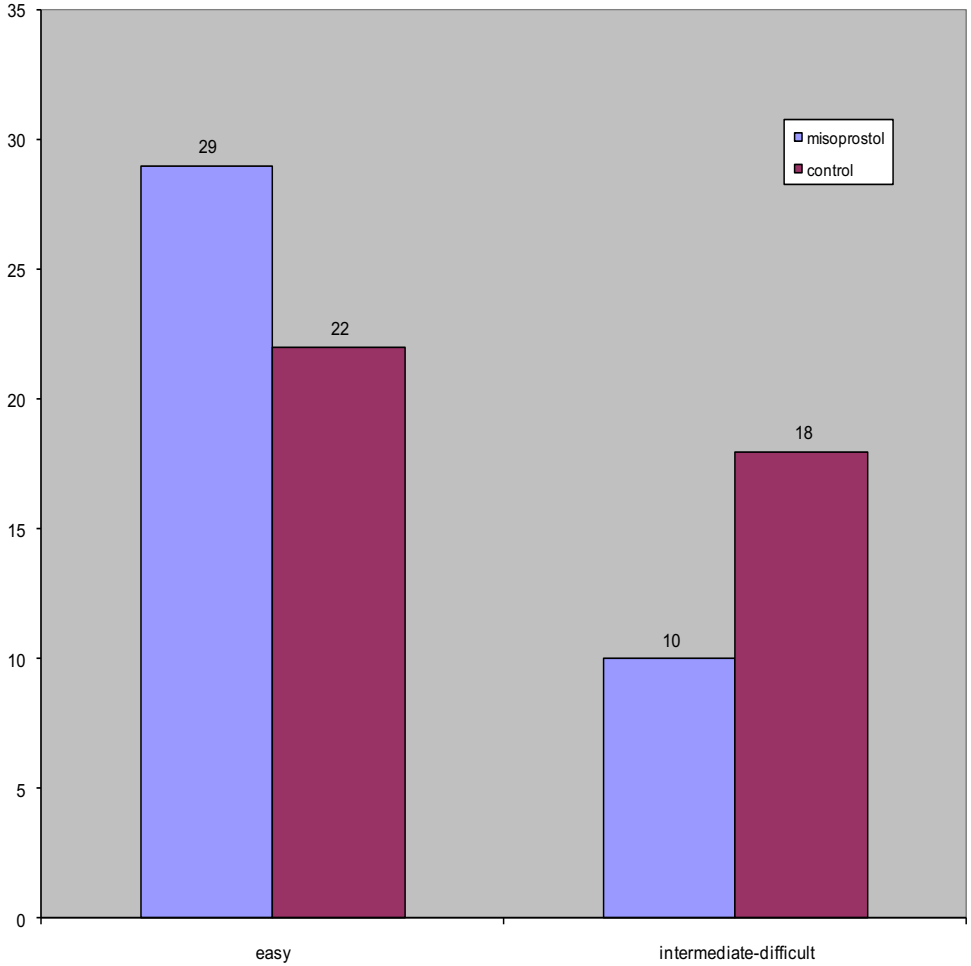
May be considered to nulliparous women

After failed attemp 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 requires 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 proceedures should we consider medical priming?

Surgical abortion

Always and for all!

IUC insertion

Nulliparous? Other factors predicting difficulties?

Hysteroscopy

Fertile women and therapeutic hysteroscopy

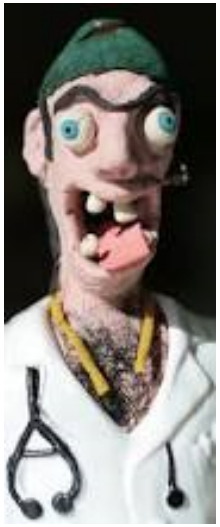
Diagnostic hysteroscopy?

Sääv et al, Hum Reprod, 2015, Ashok et al Am J Obstet Gynecol 2000,183; 998-1002, Meririk et al Lancet 2012;379:1817-1824.

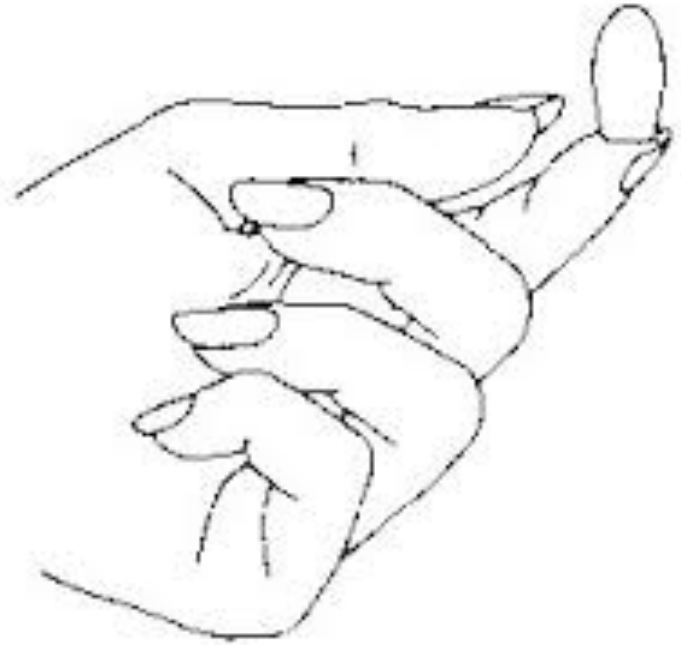
Womens preference?

Many articles state women do NOT prefer vaginal administration!

Ngai et al 2000, Ho et al 1997

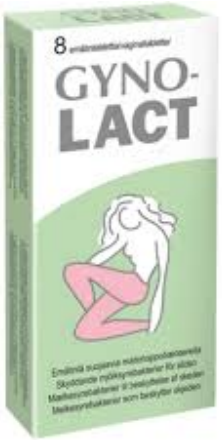


Who administrates?



Could women be trusted to find their own vagina?

Positive examples




Trust Women


We Can Do It!

75% preferred vaginal administration

16% preferred sublingual administration

Same argument dominated in both groups; Easy!

Sääv et al PLOS One 2015

How? Recommentations

Karolinska Institutet

Dose recommendation suggest 0.4 mg

Always pain relief at the same time – preferably NSAID

Karolinska Institutet

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 ang cramping
- Self-administered

Disagvantages

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

Longer priming interval than 1 hours do not result in greater effect, but increase side-effects

Sääv et al PLOS One 2015

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!

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