



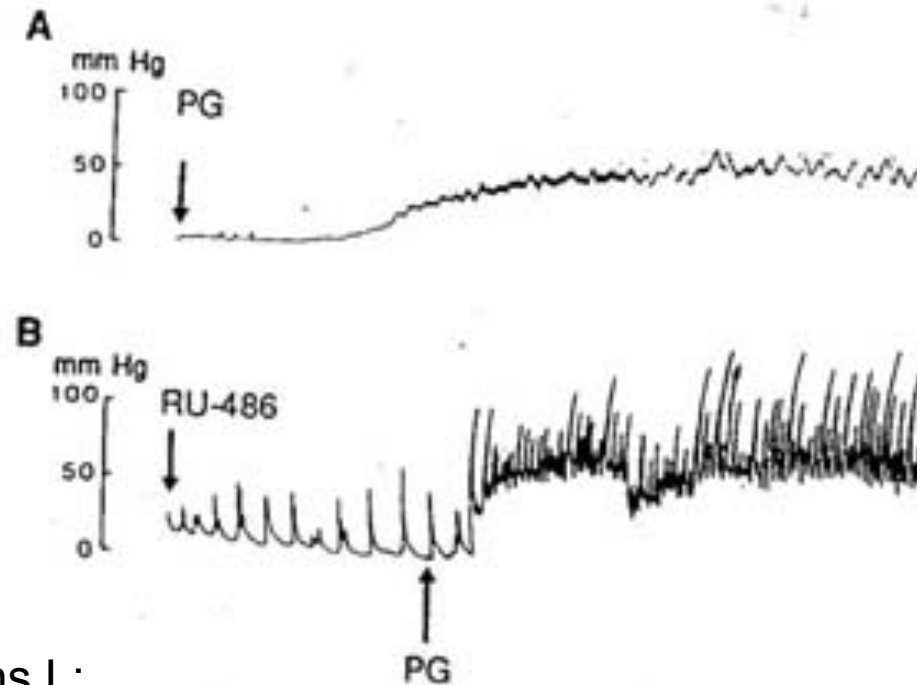
**Karolinska
Institutet**

Medicinsk abort

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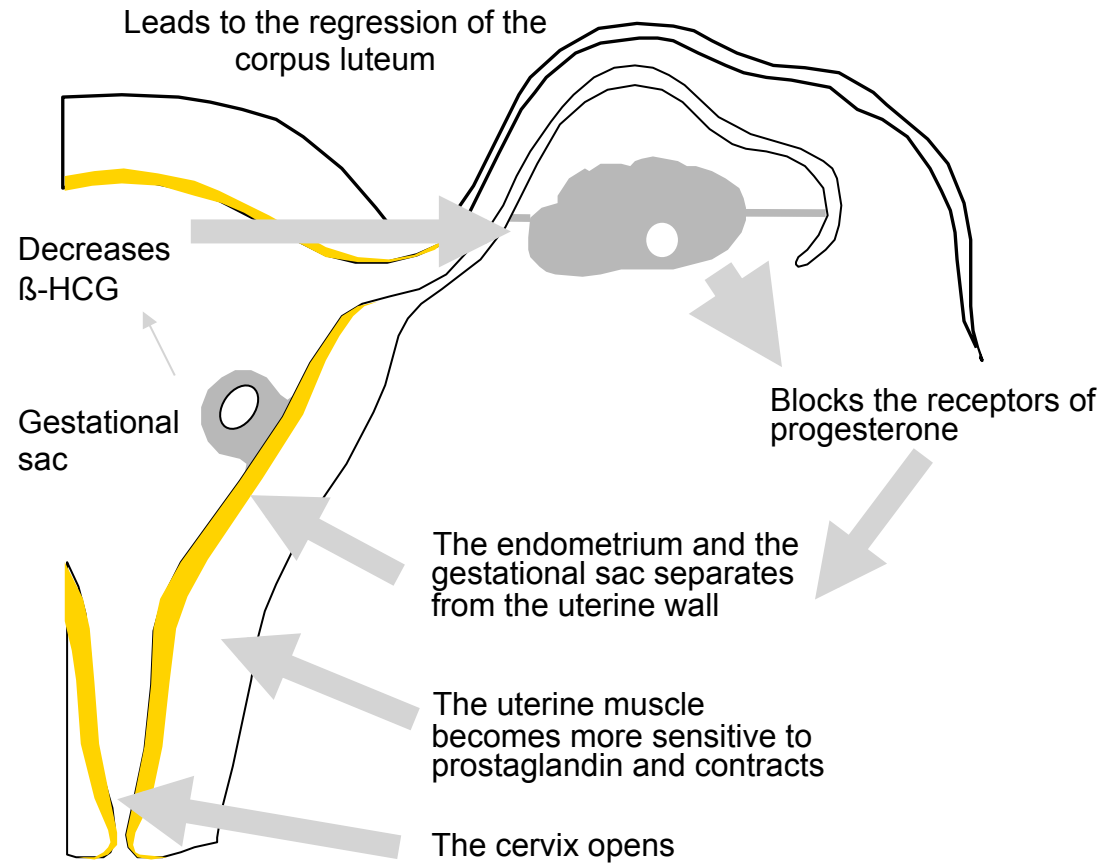
Development of safe and effective abortion care

- 70ies, Prostaglandin analogues discovered by Sune Bergström and his team at KI, Awarded the Nobel Price in 1982
- Induced uterine contractions and cervical ripening;
- Shown to act in synergy with progesterone receptor modulator
→ Developed to Medical abortion



Bygdeman M, Gemzell Danielsson K, Marions L:
JAMWA 55: 3: 195-6, 2000.

Mode of action of mifepristone



Medicinsk abort

- Optimal mifepristone dos
 - Optimal prostaglandin- typ, dos, administrationsväg
 - Graviditetslängd versus effektivitet
 - Acceptans
-

Medical abortion

Mifepristone

- Mifepristone - alone is not effective (60-80%)
 - Mifepristone primes the cervix, increases contractility and increases the sensitivity of the myometrium to PG
 - Non-linear pharmacokinetics. Low side effects
 - Provided the dose is enough for priming of the cervix and the myometrium –increasing the dose doesn't increase efficacy and cannot compensate for an insufficient prostaglandin analogue/ dose/ route
-

Medicinsk abort 600 mg mifepristone → 200 mg

1988 Frankrike	49d., 0.4 mg misoprostol
1991 UK	63d., 1mg gemeprost
(1992 Kina (25mg tabl)	49d., 0.6mg miso)
1992 Sverige	63d., 1mg gemeprost, 1994 II trimester
2000 USA	49d., 0.4 mg misoprostol
2009 EMA	63d. 200mg mifepristone, 1mg gemeprost
2012 EMA	63d. 200mg mifepristone, 0.8 mg misoprostol pv. (Medabon)
2016, USA	70d, 200mg mifepristone, 0.8 mg misoprostol bc

What is Misoprostol?

- An orally active prostaglandin analogue
- Several advantages over other prostaglandin analogues
(safe, less side effects, stable at room temperature, flexible administration, cheaper)
- Marketed in 1985
- Potential to reduce maternal mortality
- Correct dosage and administration is vital for success and to prevent complications.
- WHO essential medicine list; 5 indications



Medical abortion

Misoprostol

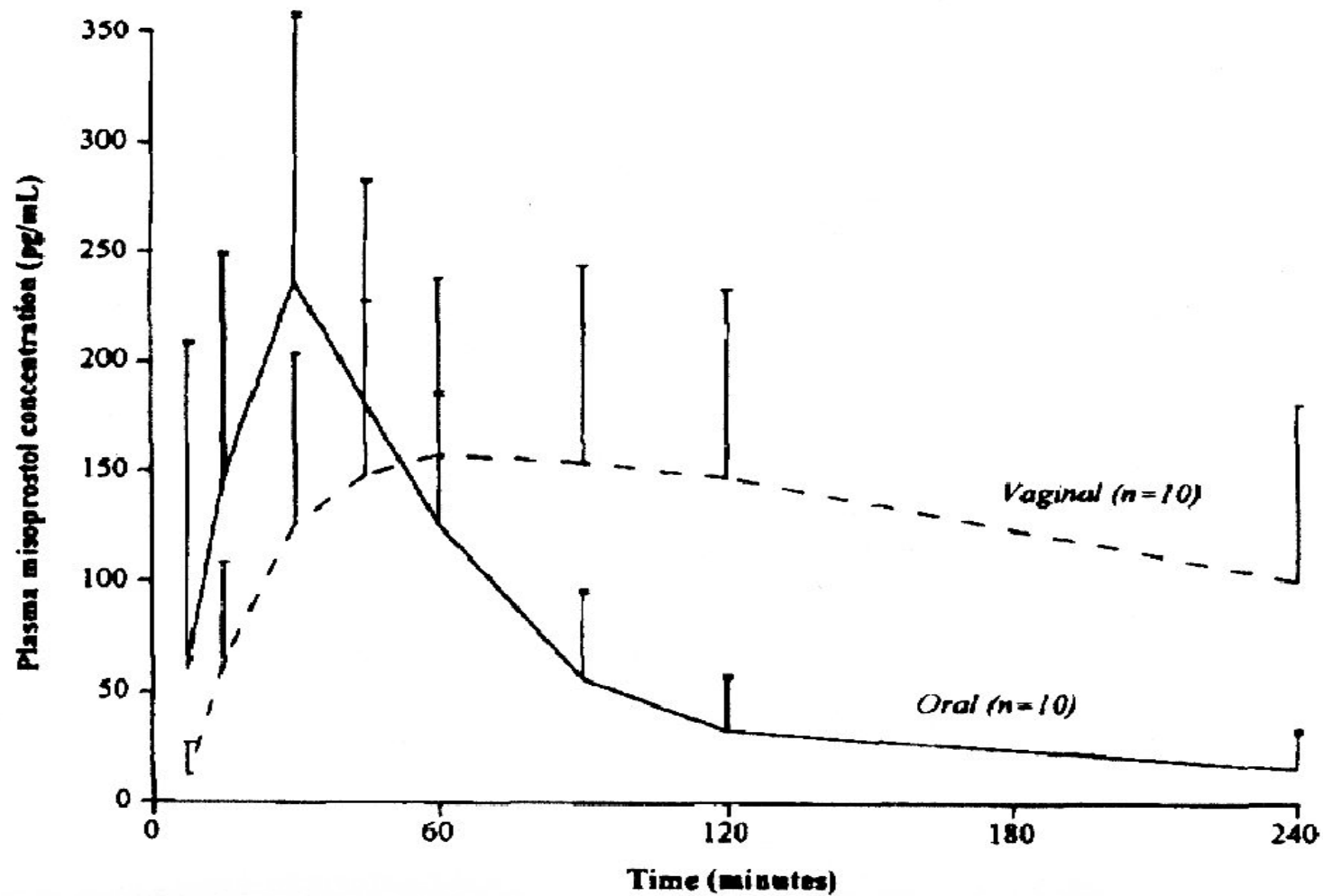
- Misoprostol– alone highly effective
- Side effects mild and dose dependent
- Priming with mifepristone increases efficacy, allows lower dose and less side effects
- Route of administration more important than the dose
- Oral misoprostol not effective beyond 49-56 days.

Cannot be compensated for by:

- increased dose of mifepristone
 - increased dose of oral misoprostol
 - repeat doses of oral misoprostol
-

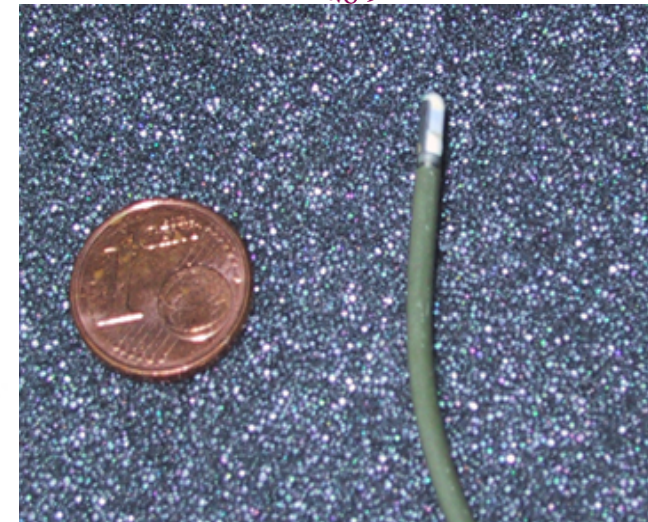
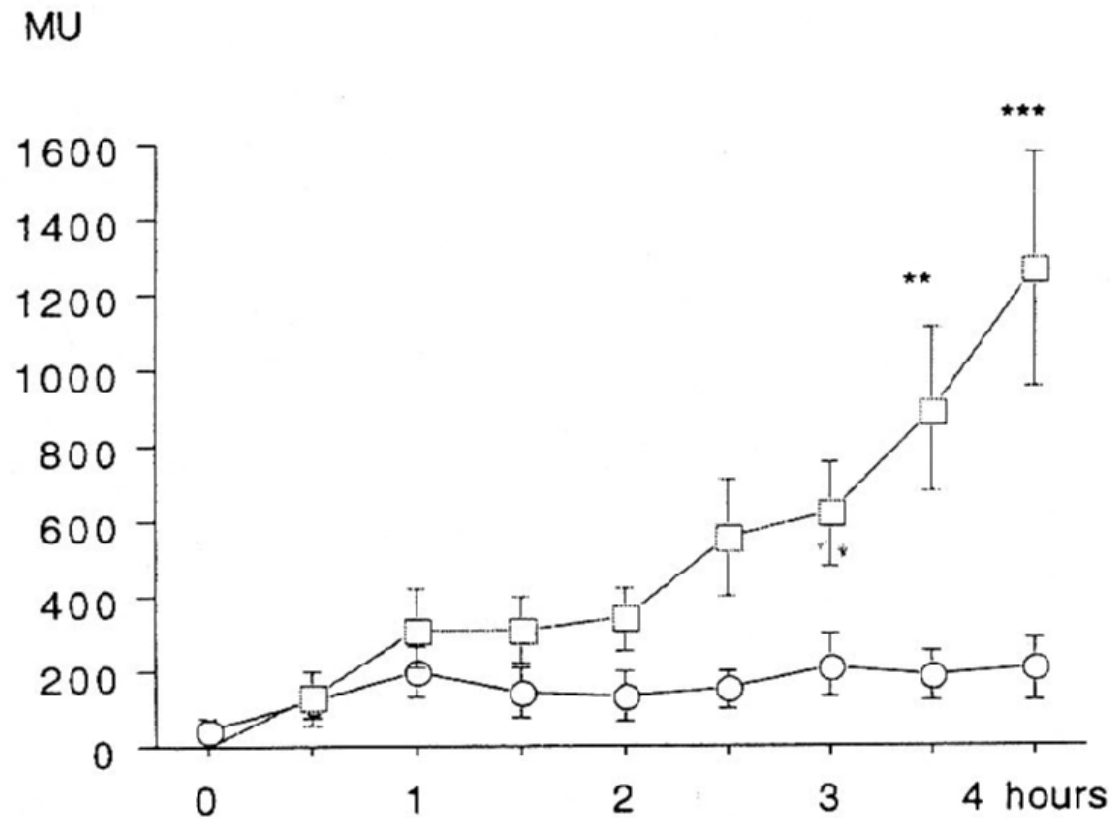
Why is the route of administration important?

Misoprostol, farmakokinetik



Zieman et al. 1997

Effekt av misoprostol på uteruskontraktilitet

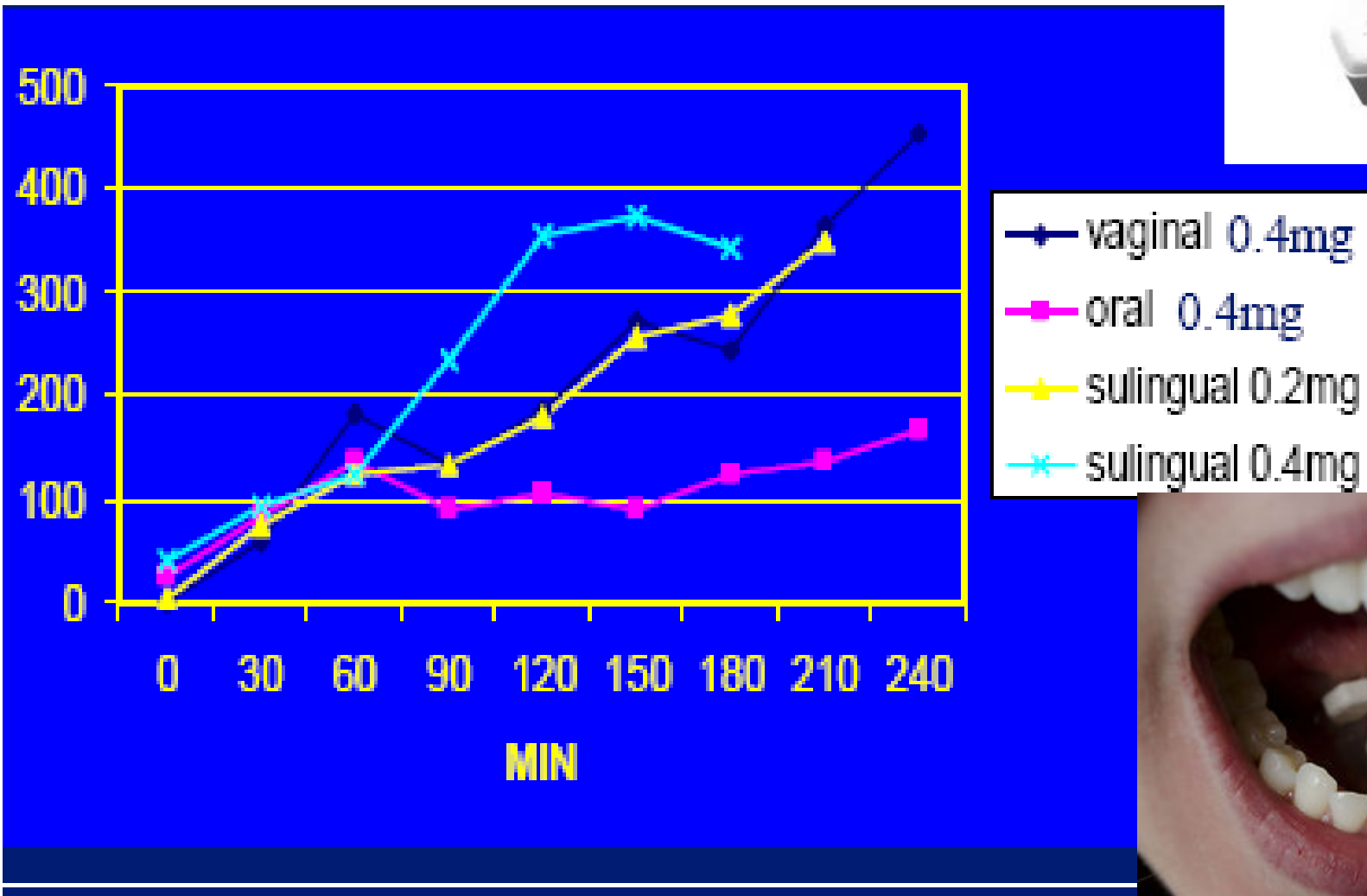


○ per oral
□ vaginal

Misoprostol for use in OB/Gyn

Uterine contractility - different routes of administration

Aronsson A et al., Hum Reprod. 2004 Jan;19(1):81-4.

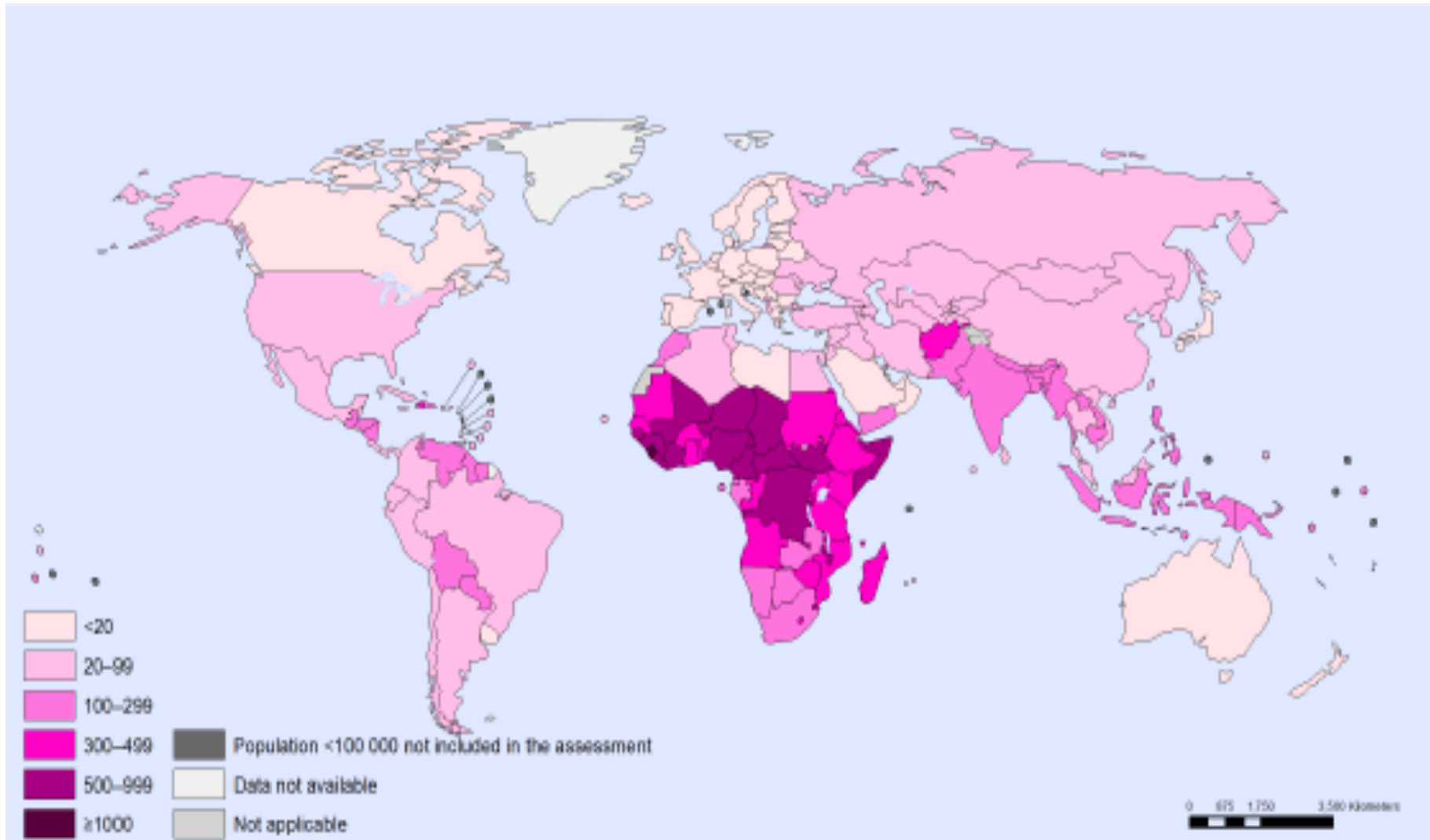


Sublingual vs. vaginal and oral misoprostol

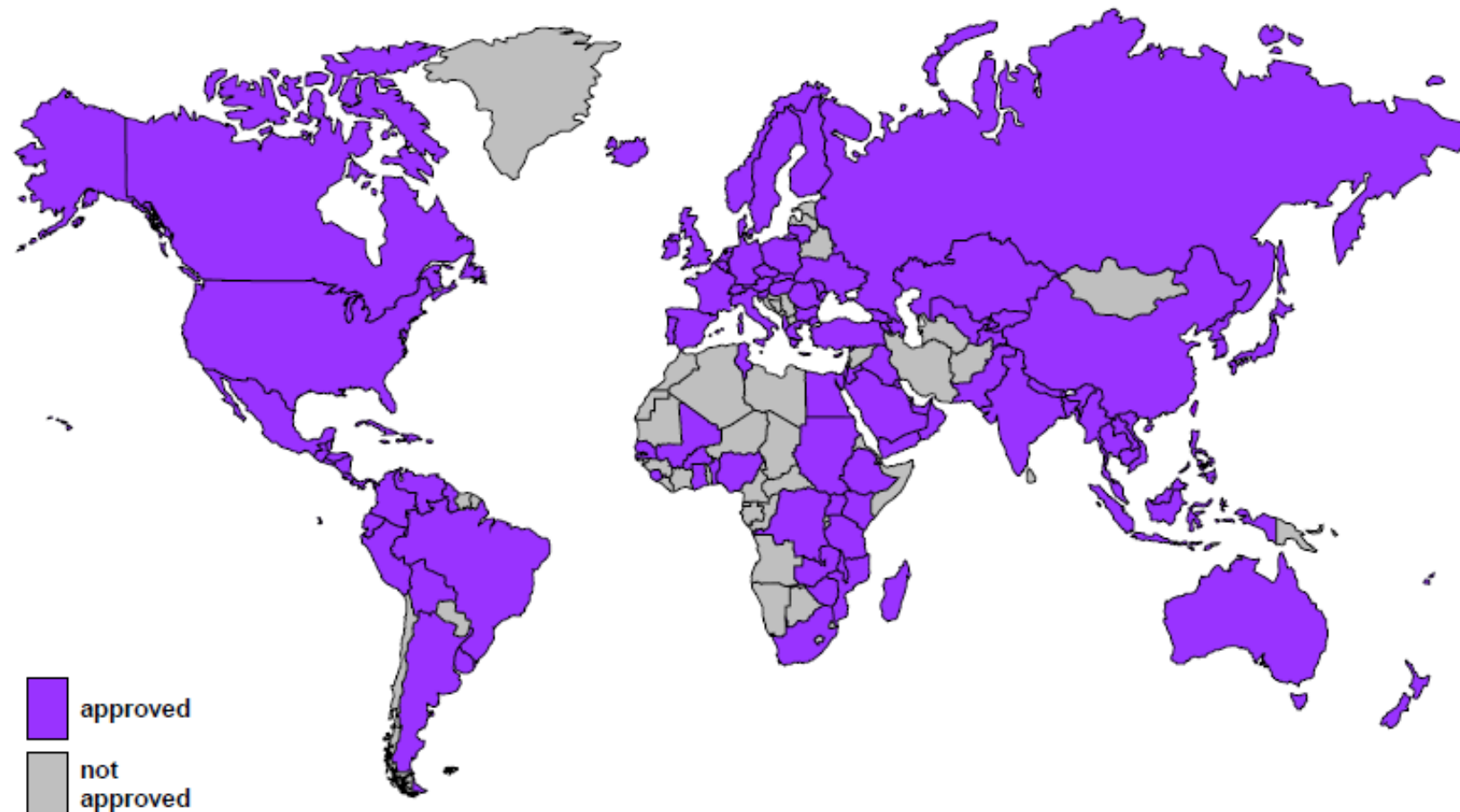
Sublingual administration- Pharmacokinetics:

- Tablets solved after 10-20 minutes
 - T_{max} similar to oral administration
 - C_{max} higher than oral
 - Bioavailability (AUC) highest serum levels higher than for vaginal misoprostol at 6h
-

Maternal mortality gap



Misoprostol Approved



 approved
 not approved

Misoprostol use in OB/Gyn

Guidelines developed in collaboration with FIGO and WHO

- Medical uterine evacuation after miscarriage or intrauterine fetal death
- Labour induction
- Postpartum haemorrhage,
 - Prevention,
 - Treatment
- Induced abortion
- Cervical ripening for gynaecological procedures (non-essential)



Medical abortion

Recommended regimen up to 63 days

Recommended by WHO, RCOG, FARG:

mifepristone 200 mg +

misoprostol 800 mcg vaginally or sublingually

(+ 400 mcg p.o/ sl vb.)

Repeat doses of misoprostol

- 200 mg mifepristone + 800 mcg misoprostol vaginally
- Up to 63 days of gestation
- 2.000 consecutive abortions
- 98% efficacy

Ashok et al., Hum Reprod 1998

- Following 2.000 cases treated with an additional dose of 400 mcg misoprostol if no bleeding in 4h
- Increased efficacy, influence of pregnancy length disappeared

Ashok et al., 2002

Interval mifepristone-misoprostol

200mg mifepristone + 800 mcg misoprostol vaginally:

24h as effective as a 48h interval up to 63 days of gestation

WHO 2007

→ Ökad flexibilitet; 24 to 72 timmars intervall möjligt till vecka 9

→ Därefter 36-48 timmar mellan mifepriston och misoprostol

Acceptans

Medicinsk vs. kirurgisk abort, **eget val:**

- Medicinsk abort, 95 %
 - Ej anestesi/ kirurgi
 - Mer "naturlig" metod
 - Kan göras tidigt
- Kirurgisk abort, 90 %
 - "Unconconscious"
 - Snabbt

UK Multicentre Study 1997

- 60-80% väljer medicinsk abort

FPP 1995, review 12 studies

Safety

Kontraindikationer

- Överkänslighet mot misoprostol/ mifepriston
- Porfyri
- Ektopisk graviditet

Försiktighet;

- Koagulationsrubbning
 - Kronisk binjurebarkssvikt eller långtidsbehandling med kortikosteroider
-

Jämförelse medicinsk och kirurgisk abort (63d)

Behandlingsresultat	Medicinsk abort (%)	Kirurgisk abort (%)
Komplett abort	96-99	98
Riklig blödning	0.1-0.3	1.1
Infektion	0.03	0.9
Mekanisk skada	-	0.2

Ulmann et al., acta obstet Scand 71:278, 1992, Friedman et al., Am J Pub Health 76:550, 1980
RCOG 2004

Medicinsk abort

- Ca. 49% aborterar inom 4h efter misoprostol
 - 75% inom 24h
 - 3-5 % aborterar efter mifepriston
 - Ca. 0.5% fortsatt graviditet
 - Blödningsmängd median 75.5 ml
 - Blödning duration medel 14d vs. 9d VA Davis 2000
 - < 0.1 % blodtransfusion
 - <1/500 - 1000 akut åtgärd inom 4h efter Cytotec
 - Akut stor blödning kan inträffa senare
-

Symptoms indicating possible complication (incomplete abortion) that might need a surgical intervention:

- Fever
- Heavy bleeding (soaking more than 2 max pads per hour during more than 2 hours)
- Severe lasting pain
- No bleeding at all (ongoing pregnancy in <0.5% of cases)

Surgical intervention is not needed if:

- sonogram shows there are no ongoing pregnancy
 - there are no complaints as indicated above
-

Safety

- 1987-1998 ca. 405 000 medicinska aborter
- cont. pregnancy: 71
- 8 malformations

- Mifepristone anses ej teratogent
- Misoprostol-oklart, Möbios syndrom

Lancet 1998

Medical abortion is one of the safest
medical procedures, with minimal
morbidity and a negligible risk of death.

Increased access to medical
abortion can lead to a decline in maternal morbidity
and mortality

Medical abortion

- Highly effective, safe and acceptable method
- Can be used for all gestational lengths
- Can replace surgical abortion
- Mifepristone –

Limited approval

Approved in about 60 countries

Expensive

Misoprostol– alone highly effective

But priming with mifepristone increases efficacy, allows lower dose
and less side effects

2012 Update of Updated WHO guidance on safe abortion

- Emphasizes the simplifying or streamlining of abortion care,
- Notes a high value on research to demedicalize abortion care
- Affirms that home use of misoprostol is a safe option for women
- The Guidance suggests the evaluation of internet provision and telemedicine, as further alternative service delivery channels of safe abortion, as a subject for future research

Simplifying medical abortion→

Increasing Access to Safe Abortion Services

How can we increase access to medical abortion with the most effective regimen?

1. Home use of (mifepristone) + misoprostol
 2. Telemedicine
 3. Task - shift / - sharing
 4. Simplified procedures for FU
-

1. Home use of misoprostol up to 63 days

Safety and acceptability established in a number of studies

- Reasons to choose home-use of misoprostol
 - Easier, More private, Feels more comfortable at home
- Home use an option in Sweden since 2004
(approved by the Board of Health and Welfare)
- 99 % would have preferred to take mifepristone at home

Fiala et al., 2004, Kopp-Kallner et al., 2010

- Extending outpatient medical abortion services through 70 days of gestational age.
-

2. Medical abortion at home using telemedicine

- www.womenonweb.org
 - Telemedicine service (English, Spanish, Portuguese, French, Polish, mfl)
 - Online consultation with a medical doctor
 - Medical abortion conducted by internet/ email
-

www.womenonweb.org

I need an abortion



Do you have an unwanted pregnancy? Click here. This online medical abortion service helps women gain access to a safe abortion with pills in order to reduce the number of deaths due

I had an abortion



Every year 42 million women have an abortion. Every 7 minutes a woman dies unnecessarily from an illegal abortion. Show your face, share your story, donate your money and help women around the world get access to safe abortions. Discuss and share information with others. Look for support if you are considering an abortion. Participate to support abortion rights, also if you did not have an abortion. Click on one of the portraits to find our more....

3. Task sharing - Medical abortion provided by physician or midwife

Equally safe and effective. Well accepted.

- Midlevel provision of medical abortion in Nepal – no difference in efficacy compared with physician

Warriner I et al., Lancet 2010

Main differences:

- No pre-selection of patients, Randomised at booking
- Examination incl. gynecological ultrasound
- Home use of misoprostol allowed

Kopp Kallner H, et al., BJOG 2014

Efterkontroll

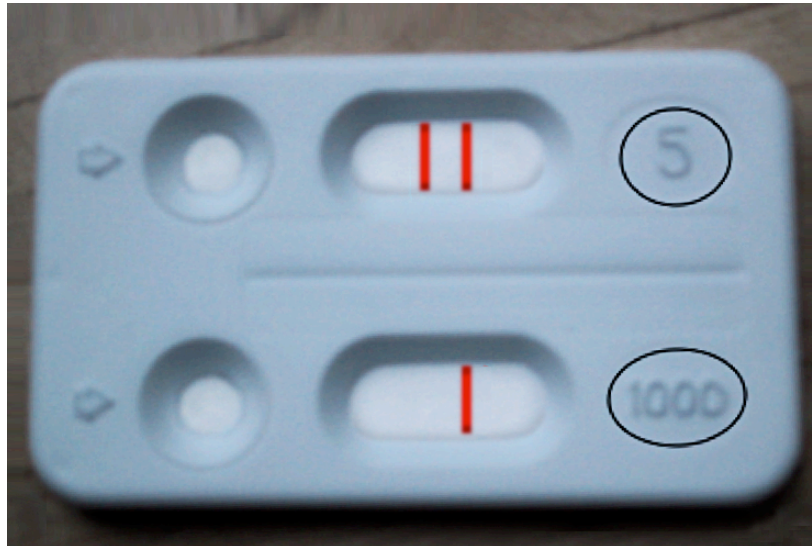
- Low rate of follow up (FU) after medical abortion
- Only reason for FU to detect an ongoing viable pregnancy
- s-hCG most effective but limitations, good correlation with u-hCG
- Ultrasound, reliable in most cases when the yolk sac or CRL can be visualised before treatment.

Not reliable in very early pregnancy,

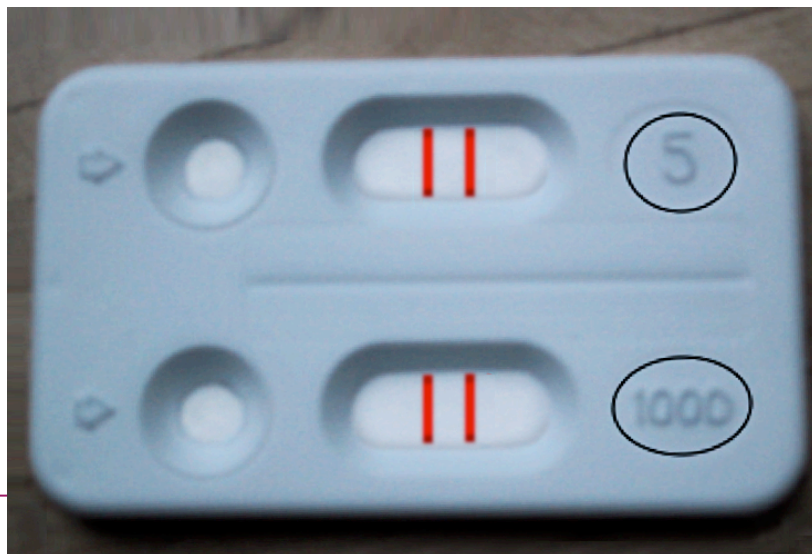
Endometrium is thick in many patients at FU

- Verify expelled material
 - Women's perception-low sensitivity
-

4. Home self test



Complete abortion



**Incomplete abortion
or failed test → 'Call the Clinic**

Hemtest

Simplifying medical abortion can help to increase access to safe abortion services through:

- Even women with low literacy can feasibly assess the outcome of an early medical abortion using the DuoTest (VedaLab, Paris France)
- New LSUP available in Europe (checkToP, Exelgyn, Paris, France)
- used in clinical routine in Sweden
- Cost:
 - DuoTest 1.05 Euro/test
 - checkToP approx 5 Euro/test



Checklist MA Home Assessment

Check the box when the answer is YES]

Complete abortion (when 2 or more):

- Did you see expulsion of products?
- If you had any pregnancy symptoms before, are they gone?
- Did the pregnancy test (1000) show negative?



Incomplete abortion/complications (when 1 or more):

- Are you still bleeding?
 - If **yes**, more than a normal period?
- Do you have severe abdominal cramps?
- Did the pregnancy test (1000) show positive?
- Do you feel sick?
 - Have you had a fever?
 - Have you had prolonged abdominal pain?
- Do you have excessive blood loss?
- Do you feel weak/ the whole body is aching?



**Contact
the clinic**

Home self-assessment

Women are able to safely have a medical abortion with home use of misoprostol 63 days of gestation and self assessment of the outcome of the treatment using a low sensitivity urine hCG-test.

Self assessment is resource-saving. A step in demedicalising abortion and women prefer it

Self assessment safe and effective also among rural and illiterate women

No negative impact on contraceptive uptake

Sunde Oppegaard K, Qvigstad, E, Fiala, C, Heikinheimo, O, Benson, L, Gemzell-Danielsson K. THE LANCET 2015; 385: 698–704.

Iyengar K, Paul M, Iyengar S, Klingberg Allvin M, Essén B, Bring J, Soni S, Gemzell- Danielsson K, Lancet Glob Health. 2015 Sep

Vad gäller vid Medicinsk abort

Läkare medicinsk ansvarig;

(ordination av läkemedel, efterkontroll)

Delegation till barnmorska

Vch ansvarar för att fastställa rutiner för efterkontroll

”Aborten ska ske på sjukhus” – juridisk definition (ej =
medicinsk) aborten = mifepriston intag

Mifepristone abortion in Sweden

- 1992: up to 63 days
 - 1994: II-trimester abortion
 - 600 mg mifepristone followed by gemeprost 1mg/ 3h
 - 2003: 600 mg mifepristone followed by “a suitable prostaglandin analogue” (misoprostol)
-

Medical abortion 9 -13 weeks

- 200 mg Mifepristone
- Vaginal misoprostol 800 mcg after 36-48 h (sublingual)
- Misoprostol repeated if required
- Results:
 - 95.8% complete abortions
 - 70% analgesia
 - Induction-to-abortion interval 4.4 h
- Partial randomised study vs. Surgical abortion;
 - Side effects more common with medical abortion but
 - no difference in major complications

Complications following induced abortion

Second trimester abortion constitute
10-15% of all induced abortions but are responsible for
two thirds of all major complications.

WHO 1997

Standard method of II-trimester induced abortion

- D&E standard method of II-trimester surgical abortion in many parts of the world.
 - In the US, 2000, D&E was used for 99% of abortions 13-15 weeks, 94.6%; 16-20 weeks, and 85% at 21 weeks or later (Elam-Evans et al., 2003).
 - Medical abortion standard method in Scandinavia and increasingly common in Europe
-

Induced second trimester abortion surgical vs medical abortion

- Cervical injury is more frequent with D&E in the second trimester, preoperative cervical priming reduces the complications
- Specialized training and the maintenance of an adequate caseload are required to perform D&E safely.
- “The appropriateness of D&E as a method of terminating second-trimester pregnancy is questionable when safe and effective medical alternatives exist”**

Report of Confidential Enquires into Maternal Deaths (UK 1994–1996);

Schulz *et al.*, 1983; Grimes *et al.*, 1984

Late Medical abortion

Recommended regimen, RCOG, FARG

Mifepristone 200 mg followed after 36 to 48h by

Misoprostol 800 mcg vaginally* + 400 mcg po/3h to max 4 doses

- 97% efficacy
- median dose of misoprostol: 1200 µg
- median induction-to-abortion interval: 5.2 - 6.5 h.
- <10% curettage
- > 75 % day cases

Ashok & Templeton 1999, 2004, Hamoda et al., 2005

* Alt sublingual

II to III-trimester abortion >24 weeks

Mifepristone 200 mg after 36-48 h followed by misoprostol

- > 24 weeks: 200 mcg p.v. followed by 200 mcg p.o/ 3h up to x 4
- > 34 weeks: 100 mcg p.v. followed by 100 mcg p.o/ 3h up to x 4
- N= 96, 1993-1999, IUFD 24-41.3 weeks
- mean induction-to-delivery interval 8.5 h, shorter with increasing gestation,
- 7.2% manual removal of placenta

Hamoda et al, 2002

II- and III- trimester abortion

- Caution should be shown in case of previous c-section. Few available studies
- Women with a prior delivery have a shorter and less painful abortion while
- younger age, more advanced pregnancy and repeated misoprostol is correlated to increased need for analgesics

Gemzell & Östlund 2002, Ashok & Templeton 1999, 2004

Hamoda et al., 2005

Pain prophylaxis

- Premedicinering med NSAID (T Ibuprofen 600mg) i samband med att misoprostol ges
- Vid meab/ II-trim ges NSAID (T Ibuprofen 600 mg) + tablett /supp paracetamol i samband med att misoprostol ges
- Vid behov av tilläggsmedicinering ges +(kodein eller annan) opeoid (t.ex. t Oxycontin, morfin)
- NSAID does not affect uterine contractility, cervical ripening or the induction-to-abortion interval

Mifepristone approved indications in Europe

1. medical termination of developing intra-uterine pregnancy
 2. softening and dilatation of the cervix uteri
 3. preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons
 4. labour induction in fetal death in utero
-

Guidelines developed by the WHO

- WHO Guidance on safe abortion care 2012,
- WHO Guidance on "task shifting" 2015
- WHO MEC 2015

Misoprostol in Obstetrics&Gynaecology;

- www.misoprostol.org
- www.figo.org



**Task shifting increases productivity and
increases access to health care**
