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MISOPROSTOL AS A FAMILY PLANNING DRUG
Use in pregnant and non-pregnant women

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MISOPROSTOL AS A FAMILY PLANNING DRUG
Use in pregnant and non-pregnant women

Thesis for doctoral degree (PhD)

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“Women are not dying because of diseases we cannot treat. They are dying because societies have yet to make the decision that their lives are worth saving”

Professor M F Fathalla
Former President of the International Federation of Gynaecology and Obstetrics
Professor of Obstetrics and Gynaecology, Assiut University, Egypt

Till minnet av mormor

ABSTRACT

Background: Availability of comprehensive family planning services is fundamental in improving and ensuring women's right to life and health. An estimated 222 million women have an unmet need for contraception, and 43.8 million pregnancies are terminated each year, of which 21.6 million are considered to be unsafe and one of the main contributors to maternal mortality and morbidity. Medical abortion using misoprostol alone, or preferably the combined regimen of mifepristone and misoprostol, is the medical development that could turn out to be the most important in the goal of reducing maternal mortality worldwide. Modern equipment and training cannot be provided where abortion is illegal. Thus, a medical method, administered by women themselves is a promising way to modernise and make abortion safe and accessible. Medical priming prior to vacuum aspiration has been proven to reduce the rate of complications, and should be standard care. Information on dosage and priming interval is crucial for safety and effectiveness.

The effectiveness of long-acting reversible contraception (LARC) such as intrauterine contraception (IUC) is superior to short-acting contraception, the difference being most pronounced in young women. Furthermore, women, who have an IUC inserted post abortion, are less likely to have a repeat unwanted pregnancy and abortion. Therefore efforts are needed to facilitate IUC use in these groups.

Methods and Results:

Study I: Nulliparous women requesting a Cu-IUD were recruited (n=80), and randomised to priming with misoprostol and diclofenac, or to only diclofenac one hour prior to IUC insertion. Misoprostol was shown to facilitate insertion of IUC in nulliparous women, and to decrease the rate of difficult and failed insertions. Priming with misoprostol did not reduce pain associated with the IUC placement.

Study II: Lactating mothers undergoing medical abortion were recruited and samples of breast-milk collected during the first seven days after mifepristone treatment (n=12). Levels of mifepristone in breast-milk were low, with milk-plasma levels of 0.042:1 or less and calculated RID of 0.5 %.

Study III: Healthy women requesting medical first trimester abortion and IUC post abortion were recruited (n=129), and randomized to early insertion during the first week, or to routine, delayed insertion. There was no increased rate of expulsions, PID or bleeding complications after early IUC insertion.

Study IV: Healthy women undergoing vacuum aspiration were recruited (n=184), and randomised to priming with misoprostol sublingual (SL) or vaginal (PV), one or three hours before surgery. SL misoprostol was proven to be as effective after one hour as after three hours priming interval in regard to baseline cervical dilatation, peak force and cumulative force. SL misoprostol was more effective compared with PV misoprostol after one hour priming. Fewer women started bleeding prior to surgical intervention when priming interval was one hour.

Conclusion: SL misoprostol reduces the cervical resistance after one hour priming interval, and can be used to facilitate insertion of an IUC to reduce difficult or failed insertions. Priming with SL misoprostol prior to vacuum aspiration is as effective after one hour as after three hours, and fewer women start bleeding before surgery. If PV misoprostol is used, the priming interval should remain at three hours. Medical abortion can be the method of choice for nursing mothers, and breastfeeding can be safely continued in an uninterrupted manner. After first trimester medical abortion, early IUC insertion is safe with no increased risk of expulsion or complications, and should therefore be offered as a routine, to ensure rapid initiation of highly effective contraception.

LIST OF SCIENTIFIC PAPERS

I. Ingrid Sääv, Annette Aronsson, Lena Marions, Olof Stephansson and Kristina Gemzell-Danielsson

Cervical priming with sublingual misoprostol prior to insertion of an intrauterine device in nulliparous women:a randomized controlled trial

Human Reproduction 2007;22: 2647–2652

II. Ingrid Sääv, Christian Fiala, Jonna M Hämäläinen, Oskari Heikinheimo and Kristina Gemzell-Danielsson

Medical abortion in lactating women – low levels of mifepristone in breast milk

Acta Obstetricia et Gynecologica. 2010; 89: 618–622

III. Ingrid Sääv, Olof Stephansson, and Kristina Gemzell-Danielsson

Early versus Delayed Insertion of Intrauterine Contraception after Medical Abortion - A Randomized Controlled Trial

PLoS ONE 7(11): e48948. doi:10.1371/journal.pone.0048948

IV. Ingrid Sääv, Helena Kopp Kallner, Christian Fiala, Kristina Gemzell-Danielsson

Sublingual versus vaginal misoprostol for cervical dilatation 1 or 3 hours prior to surgical abortion. A randomised, controlled, double-blinded trial.

Manuscript

CONTENTS

LIST OF ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
Cu-IUD	Copper coated intrauterine device
D&E	Dilatation and evacuation
FIGO	International Federation of Gynecology and Obstetrics
IUB	Intrauterine ball
IUC	Intrauterine contraception
IUD	Intrauterine device
IUFD	Intrauterine foetal death
IUS	Intrauterine system
LARC	Long-acting reversible contraception
LNG-IUS	Levonorgestrel-releasing intrauterine system
MVA	Manual vacuum aspiration
NSAID	Non steroidal anti-inflammatory drugs
PID	Pelvic inflammatory disease
PO	Per oral
PV	Per vagina
RCT	Randimised controlled trialEnter the explanation
RU 486	Mifepristone
SL	Sub lingual
UK	United Kingdom
WHO	World Health Organisation

1 INTRODUCTION

1.1 WORLDWIDE PERSPECTIVE

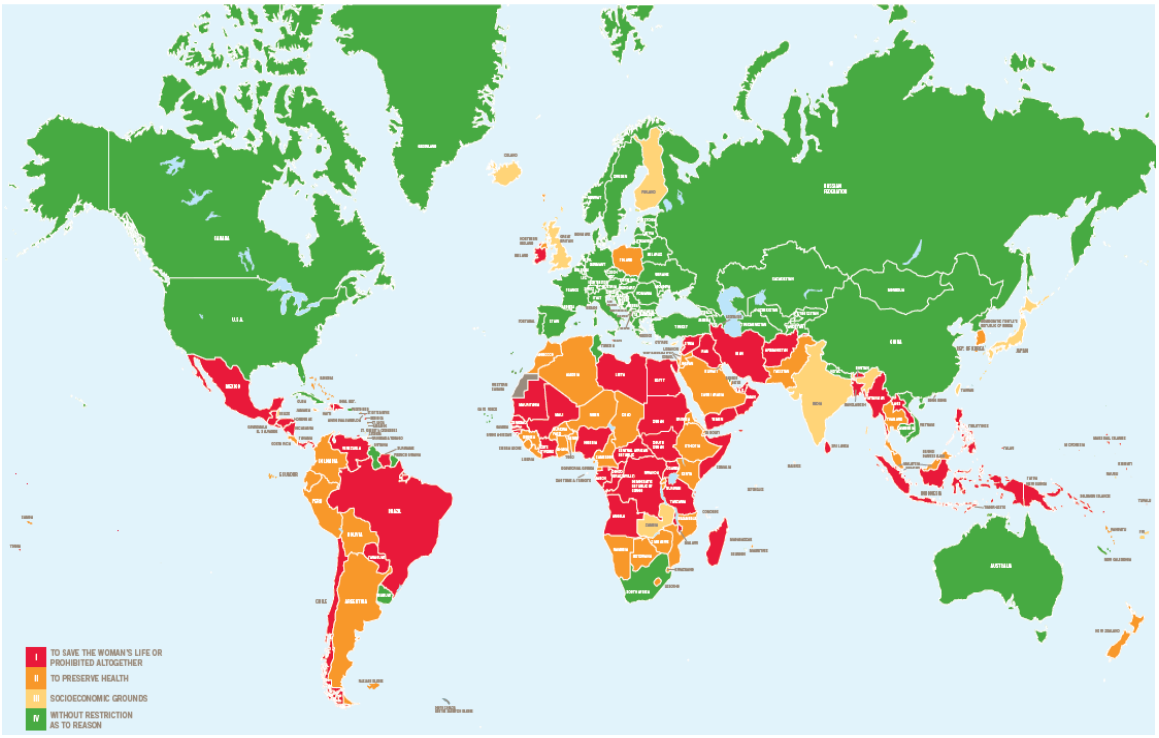
Availability of family planning services is a fundamental part in improving and ensuring women's right to life and health. When improving women's health and influence on fertility control, the general health in the society improves with a significant impact on health economics. This also includes the reduction of under-five child mortality (Cleland 2006). Increasingly, women's rights to contraception and abortion services are being recognized as human rights issues (Mbizvo et al 2013).

The availability of modern contraception reduces, but can never eliminate the need for abortion. When women have access to safe abortion services and safe contraceptive methods, the abortion rate declines (Bongaarts and Westhoff 2000). An estimated 40% of pregnancies are unplanned after non-use of contraception, ineffective contraception or method failure. If the need for contraception could be fully met, it is estimated that 75% of unsafe abortions could be prevented. Currently more than 222 million women have an unmet need for contraception (Mbizvo et al 2013). When abortion services are legal and performed by safe modern methods, morbidity and mortality is minimal (Ipas (2014) Clinical Updates in Reproductive health).

Increasing the knowledge of bodily functions and contraceptive methods as well as increasing access to modern contraception can reduce the number of unplanned pregnancies. Improving literacy and infrastructure will improve women's knowledge and access to modern contraceptive methods, but will also enable early diagnosis of pregnancy, reducing the time span from confirmation of unwanted pregnancy to abortion, reducing the proportion of abortion being done as late abortions, and increasing access to safe abortion methods. All this will in different ways improve women's health by reducing the total number of abortions and the mortality and morbidity per abortion.

Worldwide, it is estimated that 43.8 million pregnancies are terminated each year, of which 21.6 million are considered to be unsafe (Sedgh G et al 2012, Shah I and Åhman E 2010, WHO Safe abortion: technical and policy guidance for health systems 2012). WHO defines an unsafe abortion as a procedure for terminating a pregnancy that is performed by an individual lacking the necessary skills, or in an environment that does not conform to minimal medical standard, or both (Bull World Health Organ 2014). Unsafe abortions have been estimated to contribute to 13% of maternal mortality, but in some countries where abortion is illegal but where infrastructure and emergency obstetric care is of good standard, the proportion can be as high as 49% (WHO Unsafe abortion incidence and mortality 2012, Khan KS et al 2006). Women of all reproductive ages are at risk when abortion care is sub-standard, but the women who actually die, are more often younger, unmarried and have abortions later than 14 gestational weeks, illustrating the vulnerability of this group (Dragoman et al 2014). In some settings, contraceptives are also not available for single unmarried women. When abortion is restricted, more often abortion care uses old-fashioned methods, such as dilatation and sharp curettage, known to cause substantially more

complications than MVA (manual vacuum aspiration) or medical abortion (Dragoman et al 2014).



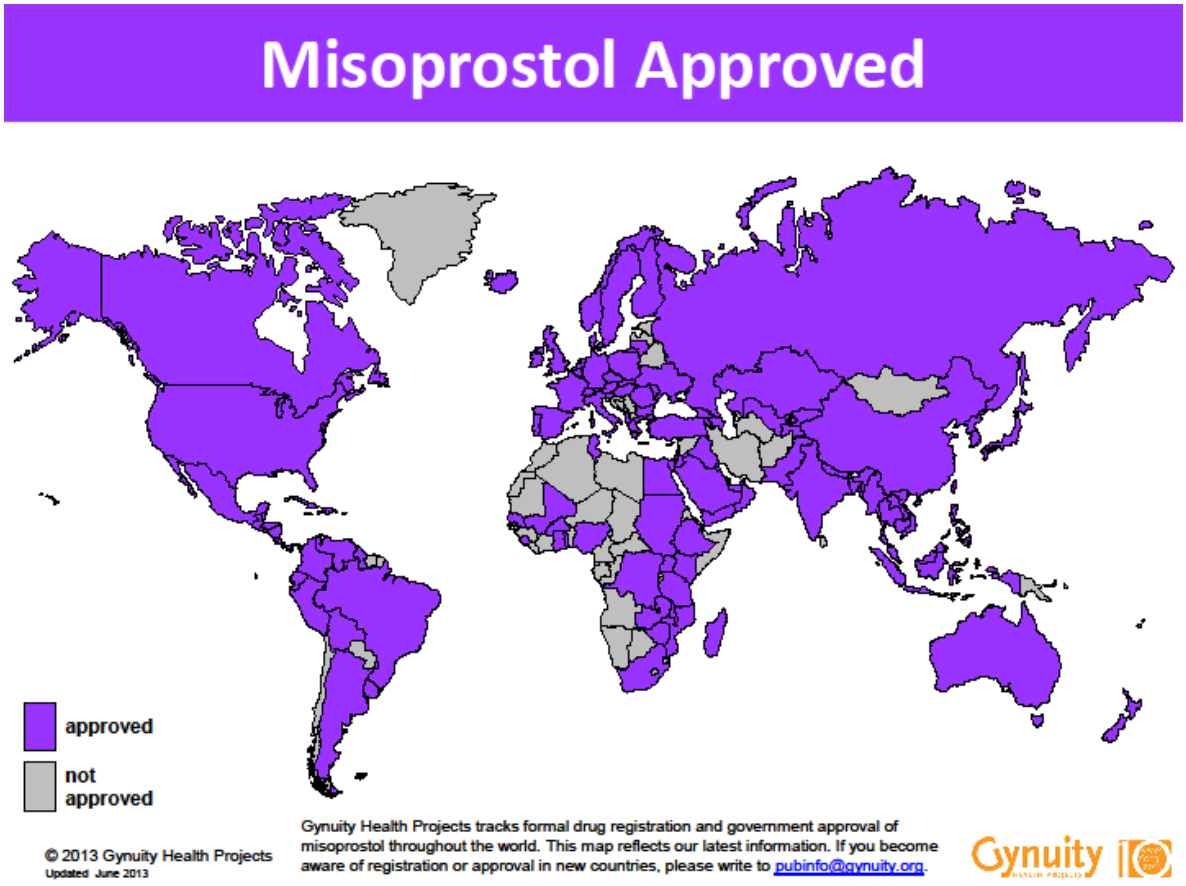
Worldwide, it is estimated that 43.8 million pregnancies are terminated each year, of which 21.6 million are considered to be unsafe (Sedgh G et al 2012, Shah I and Åhman E 2009, WHO Safe abortion: technical and policy guidance for health systems 2012). WHO defines an unsafe abortion as a procedure for terminating a pregnancy that is performed by an individual lacking the necessary skills, or in an environment that does not conform to minimal medical standard, or both (Bull World Health Organ 2014). Unsafe abortions have been estimated to contribute to 13% of maternal mortality, but in some countries where abortion is illegal but where infrastructure and emergency obstetric care is of good standard, the proportion can be as high as 49% (WHO Unsafe abortion incidence and mortality 2012, Khan KS et al 2006). Women of all reproductive ages are at risk when abortion care is sub-standard, but the women who actually die, are more often younger, unmarried and have abortions later than 14 gestational weeks, illustrating the vulnerability of this group (Dragoman et al 2014). In some settings, contraceptives are also not available for single unmarried women. When abortion is restricted, more often abortion care uses old-fashioned methods, such as dilatation and sharp curettage, known to cause substantially more complications than MVA (manual vacuum aspiration) or medical abortion (Dragoman et al 2014).

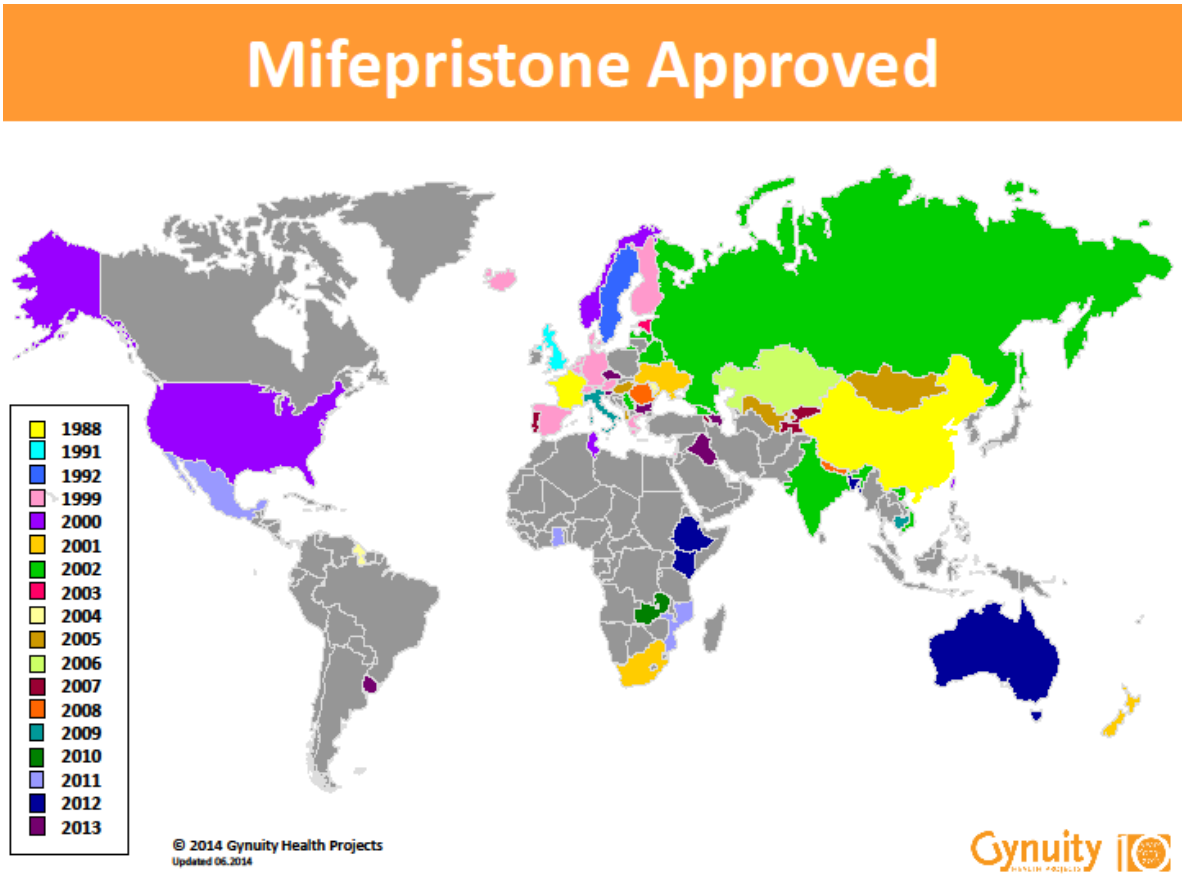
Several studies illustrate the connection between maternal mortality and liberal abortion laws. The most illustrative examples are the increased maternal mortality rates in Romania following the restrictive laws between 1966 and 1988, after which the rate of maternal mortality declined in complete harmony with the rate of illegal unsafe abortion (Stephenson P et al 1992). In South Africa maternal mortality from unsafe abortion declined by 91% after legalization of abortion in 1993 (Jewkes R et al 2005). More recent examples of decline in

maternal mortality after legalizing abortion can be found in Mexico City (van Dijk et al 2012) and Nepal (Henderson JT et al 2013).

Modern equipment and training cannot be provided where abortion is illegal. Thus, a medical method, administered by the women themselves is a promising way to modernise and make abortion safe outside the law. In spite of restrictive abortion laws, use of misoprostol has been shown to correlate with dramatic decreases in observed complications from unsafe abortion, with an estimated 45% reduction of maternal mortality if 60% of the abortions are misoprostol-induced (Miller et al 2005, Briozzo et al 2006, Harper et al 2007). In Brazil, despite restrictive abortion laws, self-use of misoprostol has been shown to be associated with significant reductions of abortion related complications such as infections and excessive bleeding post abortion (Costa and Vessay1993) Most of the decline occurred in the years 1992-1997, during which years misoprostol was approved and became available to women (Guedes et al 2000,Singh et al 2006). In 2005, WHO listed mifepristone and misoprostol as essential medicines.

Indeed, medical abortion using misoprostol alone, or preferably mifepristone and misoprostol, is the medical development that could turn out to be the most important one in the goal of reducing maternal mortality worldwide.

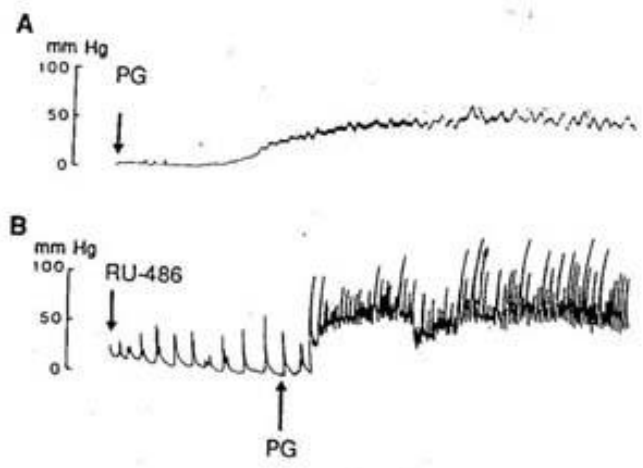




1.2 MEDICAL ABORTION

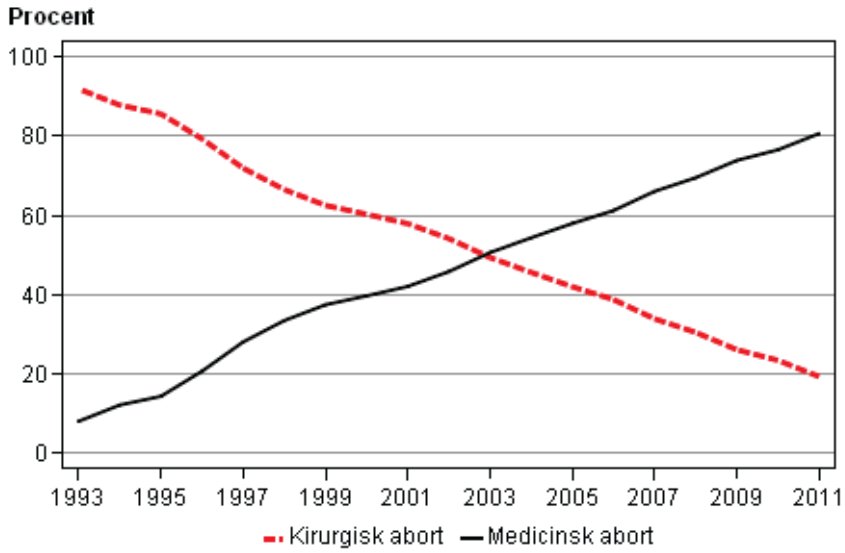
Primary prostaglandins have been used for termination of pregnancy since 1969 (Roth-Brandel U et al 1970).Various routes of administration were used; intravenously, intramuscular, vaginally, intraamniotically and extra-amniotically. Modern development of medical abortion started in the 1970s with prostaglandin injections intra-amniotically in second trimester abortion (Bygdeman and Wiqvist 1974). Also in the 1970s , a vaginal application of natural prostaglandin was developed, but this had a short duration with half-lives in the circulation of less than a minute and required high and repeated doses (Lundström et al 1977). These high doses also caused a high rate of side-effects and pain. After the development of the synthetic antiprogesterone mifepristone (RU 486) there was a breakthrough for non-surgical methods to terminate early pregnancy. Mifepristone was found to be insufficiently effective for causing complete abortion on its own with only a 60 % success rate (Herrman et al 1982, Kovacs et al 1984, Baulieu 1989). Of major importance was the discovery that mifepristone could sensitise the myometrium to endogenous and exogenous prostaglandins. By combining mifepristone and a prostaglandin analogue it was possible to increase the uterine response to prostaglandin and thus reduce the doses of prostaglandin needed to induce abortion. In this way the total dose of the prostaglandin analogue could be five times lower, thus reducing the side-effects, with an increased rate of complete abortions to 94% (Bygdeman and Swahn 1985, Swahn and Bygdeman 1988). In 1994 medical abortion was also approved for second trimester termination of pregnancy.

Uterine contractility after prostaglandin without and with pretreatment of mifepristone (Bygdeman and Swahn 1985, Bygdeman personal communication 2014)

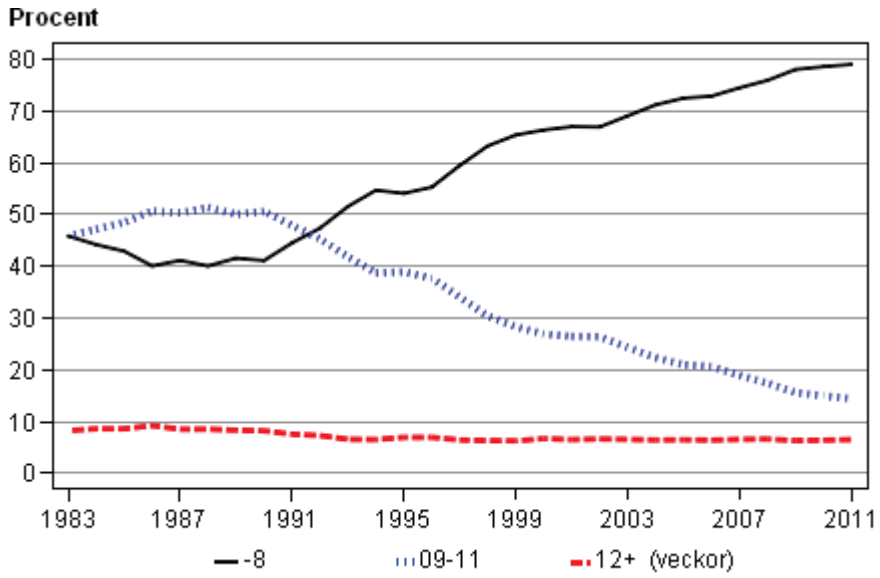


Medical abortion using mifepristone followed by a prostaglandin analogue was licensed by Exelgyn (Paris, France) and first approved for use up to 49 gestational days (7+0 weeks) in France in 1988. The initial approval included the use of sulprostone prostaglandin analogue, administered intramuscularly which was associated with severe cardiovascular side-effects. Later on the prostaglandin of choice for the French (European) approval became misoprostol. In collaboration with WHO, medical abortion with a vaginally administered prostaglandin analogue was developed for use up to 63 days of gestation (9+0 weeks), and approved in UK and Sweden in 1991-1992. The use of gemeprost has gradually been replaced by misoprostol.

Today, medical abortion is one of the safest procedures in medical practice, with minimal morbidity and mortality risks (ipas (2014) Clinical Updates in Reproductive health). The recommended most effective protocol today with a success rate of 95-98% up to 9 weeks gestation is 200 mg of mifepristone followed 24 to 48 hours later by 800µg misoprostol vaginally or sublingually (Ashok et al 1998, Schaff et al 2000, Bartley et al 2001, WHO Clinical practice handbook for Safe abortion 2014). The risk of ongoing pregnancy is 0.5%, and the risk of incomplete abortion with need of extra doses of misoprostol or surgical intervention is around 3% (Goldstone et al 2012, Cleland et al 2013). Risks of morbidity or death are minimal – with the rate of serious complications of 0.16% and death rate of 0.4 per 100.000 medical abortion procedures, and it is equally safe for young and nulliparous women (Cleland at al 2013, Goldstone et al 2012, Niinimäki et al 2011) Using this regimen, it is even more effective than surgical abortion in terms of inducing complete abortion during very early pregnancy (RCOG 2004). In most countries in Europe the rate of medical abortion compared with surgical interventions has increased, and in some countries now exceeds 90 % (www.socialstyrelsen.se, www.socialstyrelsen.se/statistik/statistikdatabas/abort, Heikinheimo, personal communication 2014, http://urn.fi/URN:NBN:fi-fe201303202579), and this coincides with a higher proportion of very early abortions.



Andel aborter före utgången av 9:e graviditetsveckan utförd med medicinsk eller kirurgisk metod, 1993–2011 (www.socialstyrelsen.se)



Andel aborter efter graviditetslängd 1983–2011 (www.socialstyrelsen.se)

hours (www.misoprostol.org, WHO clinical practice handbook for safe abortions 2014). This regimen is less effective with a success rate of 85-90 % up to 12 weeks gestation and carries a higher rate of side-effects due to the higher doses needed of prostaglandins (WHO Safe abortion: technical and policy guidance for health systems 2012, von Hertzen et al 2007, Kulier R Complication rate is substantially higher after second-trimester abortion compared with early first trimester abortion. Also, the proportion of serious complications and maternal death are higher after second trimester abortion. Among the severe complications, requiring advanced medical care, are haemorrhage, cervical tearing, uterine perforation, endometritis, septic abortion, bowel injury and abdominal abscesses, and those are comparably more often associated with surgical D&E compared with medical second trimester abortion. The rate of serious complications (requiring surgery or blood transfusion) after medical second trimester

abortion is less than 1 %, and the overall rate of uterine rupture 0.08%, with a rate of 0.28% in women with previous caesarean section (Goyal 2009).

In countries where access to abortion is limited and mifepristone is not available, there is a possibility to perform a safe self-administrated abortion using misoprostol alone. Recommended protocol is three doses of four tablets misoprostol sublingually every three 2011).

Recent development regarding medical abortion has focused on simplifying the treatment procedure to increase access and acceptability including safety of home-use and self-determination of complete abortion (Kopp-Kallner et al 2012, Oppegaard et al 2014). Although this has many advantages for simplifying the process and increasing access, it may also have an implication on the choice of contraception.

1.3 SURGICAL ABORTION

There are several surgical methods used in abortion care. In many countries where abortion is legal, vacuum aspiration is the most common method used for elective first trimester abortion (WHO Medical methods for termination of pregnancy 1997, WHO Safe abortion: technical and policy guidance for health systems 2012). However, in many countries where access is limited, surgical abortion is still performed using the method of dilatation and sharp curettage. This method is associated with substantially more serious complications such as surgical damage to the cervix and uterus, massive haemorrhage, incomplete abortion and infection compared with MVA, and the leading causes of death after abortion of infection and sepsis. (Shah and Åhman 2008). Using the gold standard technique of vacuum aspiration (manual or electric) for first trimester abortion, the success rate is 98% and equal to that of medical abortion, and the complication rate is only 1% (WHO safe abortion: technical and policy guidelines 2003, Bartlett LA et al 2004).

Complications such as cervical tearing and uterine perforation are directly related to the force required to mechanically dilate the cervical canal (Tietze et al 1974, Hulka et al 1974, Moberg et al 1976, Schultz et al 1983). Therefore, as little force as possible should be used when dilating the cervix in order to cause as little damage as possible. Dilatation is often performed using Hegar dilators, with a rounded tip, even though these dilators do not allow a gradual dilatation. In a comparison between instruments, the tapered Pratt dilator was shown to require less force to reach equal dilatation of the cervix (Hulka el at 1974). It was also shown that more experienced operators used less force to dilate, corresponding to facts well known; skills and experience in operative technique is an important factor in minimizing complications.

Before the development of medical priming agents, such as gemeprost, misoprostol and mifepristone, mechanical methods were used to dilate and soften the cervix before the surgical intervention, first described by Braxton-Hicks (Braxton-Hicks 1869). The agents included different roots, screws and dilators, and later intracervical tents such as the Laminaria, Dilaphan and Lamicel, which where osmotic dilators that were placed in the

cervical canal and allowed to swell and slowly dilate (Newton 1972, Lauersen et al 1982, Bokström and Wiqvist 1989).

Medical priming prior to dilatation has been proven to reduce the rate of complications after surgical abortion, and has been recommended for a long time prior to dilatation in women with an increased risk for complicated mechanical dilatation, such as young and nulliparous women, or women pregnant in the second trimester (Ngai et al., 1995, Fiala et al., 2007). Prostaglandins have also been proven to reduce the blood loss associated with vacuum aspiration, compared with placebo (El-Refaey H et al 1994) and Laminaria-tent (Krishna u et al 1986). Recently a large multi centre study proved misoprostol reduced the rate of complications to surgical abortion when administered as a medical priming agent prior to vacuum aspiration, both in nulliparous and parous women (Meirik et al 2012).

1.4 MISOPROSTOL PHARMACOKINETICS

Misoprostol is a prostaglandin E_1 analogue, initially developed to prevent gastric ulcer in 1973. After oral administration, it is rapidly and almost completely absorbed, and converted to its active metabolite misoprostol acid by the liver passage. Plasma half-life after oral administration is 20-40 minutes (Foote et al 1995, Zieman et al 1997, Product information of Cytotec®). It is metabolised by the liver, and less than 1% is excreted in the urine. It has no known drug interactions and does not induce the P-450 cytochrome system. Toxicology studies show a safety margin of 500-1000-fold between lethal doses in animals and therapeutic doses in humans (Kotsonis et al 1985).

Compared with most other prostaglandins, misoprostol carries fewer side-effects with no evidence of cardiovascular effects, and has logistical advantages, being stable at room temperature, widely available and cheap (Cytotec® product information). Misoprostol should however be manufactured and stored in a dry place, and analyses from different manufacturers detected samples with insufficient active ingredients (Hall 2011). Misoprostol can become inactive if exposed to heat or humidity for a prolonged time, and if the blister pack is cut and blisters inadvertently opened, the potency of misoprostol degrades within 48 hours and continues to degrade thereafter (Berard and Fiala 2012).

Side-effects of misoprostol are mainly gastrointestinal with diarrhoea, nausea and vomiting; all of which are dose-dependent, self-limiting and usually resolve 2-6 hours after intake of misoprostol. Fever and chills are reported after being exposed to high serum levels. There have been no findings of any haematological, endocrine, biochemical, immunological, respiratory ophthalmic or cardiovascular side-effects. Exposure to misoprostol in early pregnancy is associated with a variety of congenital defects. The risk of birth defects increases where abortion is performed with misoprostol-only regimen, as a combination of less efficient regimen, and exposure of higher prostaglandin doses. The teratogenicity of misoprostol is thought to be induced not by any toxicological effect but rather by the effect of uterine contractions leading to vascular disruption and the following reduction of blood supply to the developing embryo (Pastuszak et al 1998, Shepard 1995). The incidence of malformation peaks if misoprostol is used between five and eight weeks after a woman's last menstrual period, and there is no association regarding anomalies with misoprostol after 13

weeks. The most common anomalies are clubfoot, cranial nerve injuries (Möbius syndrome) and absence of fingers, although the absolute risk of teratogenicity appears to be low, with less than 10 defects per 1000 exposures (da Silva Dal Pizzol et al 2006, Philip et al 2002, Gynuity 2002).

When misoprostol is administered in low doses in term pregnancy to induce labour, there have been no reports of adverse effects on the foetus, apart from the speculation of a direct effect on the bowel and increased frequency of meconium stain in the amniotic fluid (Alfirevic Z and Weeks A 2014). Pharmacokinetic studies of misoprostol in breast milk show a peak concentration one hour after oral administration, with a milk:plasma ratio of 0.06. The level in breast milk then drops rapidly to become un-detectable after 4-5 hours (Vogel et al 2004, Abdel-Aleem et al 2003). Concentrations could be lower after vaginal administration, and last longer after vaginal or sublingual administration; however effects on the infant are thought to be negligible with gastrointestinal effects being the most common.

Due to the short half-life after oral administration, different routes of administration have been studied and give surprisingly different effects on plasma levels of the active substance, misoprostol free acid, cervical priming and uterine contractility. With vaginal misoprostol compared with oral, the plasma concentration does not reach the same high peak value; however, plasma concentrations remain elevated during a longer period of time (Aronsson et al 2007). The peak plasma concentration is highest after sublingual administration, whereas vaginal administration has a slower increase. Both sublingual and vaginal administration give a longer lasting elevation in plasma concentration compared with oral administration (Zieman et al 1997, Gemzell Danielsson et al 1999, Tang et al 2002). In correlation with lower plasma levels vaginal application of misoprostol results in fewer side-effects, particularly gastrointestinal (el-Refaey et al 1995). The effect of a single dose oral misoprostol is an increase in tonus, but with no development of regular contractions (Gemzell Danielsson et al 1999, Norman et al 1991). Due to the more prolonged plasma-concentrations, the vaginal and sublingual route of administration are more effective in terms of stimulating regular uterine contractions (Zieman et al 1997, Gemzell Danielsson et al 1999, Aronsson et al 2004), with vaginal administration producing the most long-lasting elevation of misoprostol acid levels and sublingual the most rapid uptake and highest plasma-concentration(Aronsson et al 2007). In all cases, in whatever doses or for which indications misoprostol is administered, NSAID can be used as pain relief without reducing the efficacy of the drug (Fiala et al 2005, Li et al 2003, Creinin and Schulman 1997).

1.5 INDICATIONS FOR MISOPROSTOL (OTHER THAN MEDICAL ABORTION)

Misoprostol has been studied for a variety of indications within the gynaecological and obstetrical field, and is a recommended drug for treatment of incomplete miscarriage or missed abortion, induced abortion, cervical priming prior to mechanical dilatation, as well as labour induction in term pregnancies and treatment of postpartum haemorrhage (Goldberg et al 2001, Blanchard et al 2002). In spite of this, the holder of the patent for Cytotec®, the first and most widely licensed misoprostol tablet, never applied for a licence in the gynaecology or obstetrical field, probably due to fear of being associated with induced abortion (Weeks et al

2005).Today there are several new brands and companies involved in production and marketing of misoprostol.

1.5.1 Cervical priming in pregnant and non-pregnant women.

Misoprostol induces a softening "priming" effect on the cervix, making mechanical dilation less difficult (El-Refaey et al 1994, Ngai et al 1995). The action seems mainly to affect the collagen tissue of the cervix, causing disintegration and dissolution (El-Refaey 1994). As a priming agent, misoprostol has several advantages over other priming agents. Compared with osmotic dilators, misoprostol gives equal cervical dilatation in a shorter time, is easier to administer and is more convenient to the patient. (Krishna et al 1986, MacIsaac L et al 1999, Darwish AM et al 2004). Compared with mifepristone, misoprostol is actually less effective for cervical priming, but by far quicker acting, with a proven effect already after three hours vaginally (Fiala et al 2007), while mifepristone requires an interval of 24-48 hours (Rådestad et al 1988, Ashok PW et al 2000). Sublingual administration of 400mcg misoprostol has been proven equally effective compared with vaginal administration after three hours interval to surgery (Hamoda 2004).

Misoprostol has also been proven effective in non-pregnant women prior to hysteroscopy (Ngai SW et al 1997), but the results concerning post-menopausal women have been conflicting. Not all studies have separated pre- and post- menopausal non-pregnant women, which could be a reason for conflicting results regarding the efficacy (Thomas JA et al 2002, Darwish et al 2004). Study comparing defined groups of postmenopausal women prior to hysteroscopy, showed no efficacy of misoprostol in the postmenopausal group (Ngai SW et al 2001, Oppegaard et at 2008), however it was shown that there is a possibility to reach priming effect with misoprostol after 14 days of estrogen supplement (Oppegaard et al 2010).

1.5.2 Medical treatment of incomplete abortion and missed abortion

Treating incomplete abortion and missed abortion with misoprostol is safe and cost-effective. It has been shown to shorten the time to complete expulsion compared with conservative expectant management, and reduces the proportion of women who need to undergo surgical evacuation (Blum et al 2007, Gemzell-Danielsson et al 2007). The recommended dose is 600 mcg orally or 400 mcg sublingually as a single dose when uterine size is up to 12 weeks. For missed abortion, the recommended dose is 800 mcg vaginally or 600 mcg sublingually every three hours for a maximum of three doses (FIGO 2012). Follow up is recommended in all cases after 7-14 days (WHO Clinical practice handbook for Safe abortion 2014). Neither expectant management nor misoprostol increases risk of infection when compared with surgical treatment (Trinder J et al 2006).

Complications such as infection and cervical trauma are less frequent after misoprostol compared with manual vacuum aspiration (Weeks et al 2005). When the miscarriage is diagnosed as a missed abortion, with no or little bleeding, empty gestational sac or embryo without cardiac activity, results of medical treatment with misoprostol have a slightly lower success rate of 77-89 % compared with incomplete abortion where efficacy is between 61-

100% depending on the interval to follow-up (Gemzell-Danielsson et al 2007, WHO Clinical practice handbook for Safe abortion 2014). Efficacy of misoprostol treatment has been shown to be 96% compared with MVA 92% (Weeks et al 2005), at follow-up 7-14 days after treatment.

1.5.3 Medical second trimester abortion and induction of labour after intrauterine foetal death during second and third trimester

For second trimester induced abortion, medically induced abortion is recommended as an alternative to dilatation and evacuation (D&E) (WHO safe abortion technical and policy guidelines 2014). Medical methods in the second trimester are considered equally safe and efficient as surgical D&E, when D&E is performed under perfect conditions. In areas with limited surgically trained staff and suboptimal equipment, medical methods are to be preferred. Medical methods are also "minimal invasive", whilst the surgical D&E should be regarded as second-line therapy. However, some abortion providers regard the medical methods as "traumatic", inducing more pain during a longer period of time, as well as risking the woman seeing the foetus after expulsion.

Present dose recommendations from WHO recommend dose reduction after 24 gestational weeks, to avoid hyperstimulation and uterine rupture, but there is limited evidence for recommendations beyond this week (WHO Clinical practice handbook for Safe abortion 2014). FIGO guidelines recommend a reduction to half the ordinary dose of misoprostol in all women with previous uterine scarring undergoing medical second trimester abortion, when using misoprostol alone-regimen (FIGO 2012). Other sources recommend dose reduction only after 22 weeks of gestation after previous uterine scarring, but individual dose reduction could be indicated in women with more than one previous caesarean section (Ipas 2014 Clinical Updates in reproductive health).

In case of foetal death, a lower dose of 200 mcg is recommended between gestational week 13-17, and 100 mcg between 18-26 weeks. After 26 gestational weeks, the same doses are recommended as for labour induction (FIGO 2012). Some recommendations state however that higher doses can be used after IUFD since there is a possible decrease in uterine sensitivity , and doses of 200 mcg (up to 34 gestational weeks) or 100 mcg vaginally (from 34 gestational weeks) have been used with good result. There is evidence of induction of labour after late IUFD using a combination of mifepristone and misoprostol, with good results and short time to delivery after start of misoprostol treatment (Wagaarachchi et al 2002).

1.5.4 Labour induction

Prostaglandins have been proven useful for induction of labour when the cervix is unfavourable, but the prostaglandins registered and labelled for this purpose have all been expensive and unstable at room temperature (Keirse 1993, MacKenzie 1997). In comparison, misoprostol has been proven to have higher efficacy compared with both oxytocin and other

prostaglandins for inductions of labour at term (Alfirevic Z and Weeks A 2014), when outcome has been vaginal birth within 24 hours. Misoprostol has also been shown to be associated with a lower risk of caesarean section compared with other prostaglandins. There is however a fear for increased risk of uterine rupture, and misoprostol has therefore not been recommended to women with previous caesarean section (Alfirevic Z and Weeks A 2014).

To avoid hyper stimulation, recent research has focused on very low vaginal doses of 25 mcg, and oral 25-50 mcg misoprostol. When comparing the different routes of administration, oral misoprostol had a lower risk of low apgar score <7 at five minutes. Solution of 200 mcg tablets of Cytotec® (Pfizer, NY, USA) has been shown to be suitable for oral administration of misoprostol, and gives a high accuracy of the doses (www.mpa.se, www.sfog.se). Due to the regimen with administration of misoprostol every second hour and recommendation of hospitalisation and foetal heart-monitoring, there might be a practical aspect when choosing misoprostol for induction of labour – particularly if induction cannot be initiated in the morning.

1.5.5 Prevention and treatment of postpartum haemorrhage

Having a similar effect on the myometrium and uterine contractility as oxytocin, misoprostol is an alternative for prevention and treatment of atonic uterus. Misoprostol has logistical advantages compared with oxytocin, as it is stable in room temperature, (at least if the product is not exposed to a humid environment), and can be administrated orally or sublingually, thus not requiring intravenous access or skilled personnel. Misoprostol has been proven efficient for prevention of postpartum haemorrhage, but is less effective than oxytocin (Gulmezoglu et al 2001, Alfirevic et al 2007, Tuncalp et al 2012). In treatment of postpartum haemorrhage, misoprostol does not have an advantage regarding efficacy over oxytocin (Widmer et al 2010, Blum et al 2010, Winikoff et al 2010). Misoprostol is a safer alternative compared with ergometrine and prostaglandin F2 alpha, due to the cardiovascular and pulmonary side-effects of these drugs (Goldberg et al 2001). In contrast to oxytocin, misoprostol does not have a decreasing effect on blood pressure. The common side effects of misoprostol; fever, chills, nausea and diarrhoea are uncomfortable but self-limiting and harmless in the longer perspective (Durocher et al 2010). Misoprostol has also been tried intraumbilically, for conservative treatment of retained placenta (Rogers et al 2007). Recently, misoprostol was approved by the EMA for treatment of post partum haemorrhage (Hemoprostol®, LinePharma, Paris, France).

MISOPROSTOL

Recommended Dosages 2012

	1st Trimester	2nd Trimester	3rd Trimester	Post-Partum
800µg	**Induced abortion**[1] 800µg pv or sl 3 hrly (max x3 within 12hrs)[a]			**PPH treatment** 800µg sl single dose[f]
	Missed abortion 800µg pv 3 hrly (max x2) or 600µg sl 3 hrly (max x2)[b]			
600µg				**PPH prophylaxis**[2] 600µg po single dose[e]
	Incomplete abortion[2,3] 600µg po single dose[a] or 400µg sl single dose[a]			
400µg				
	Cervical ripening pre-instrumentation 400µg pv 3 hrs or sl 2-3 hrs before procedure[a]	**Induced abortion**[1,4] **/ Interruption of pregnancy** 400µg pv or sl 3 hrly (max x5)[a]		
200µg		**Intrauterine foetal death**[4] **13-17 wks** 200µg pv 6 hrly (max x4)[c]		
100µg		**Intrauterine foetal death**[4] **18-26 wks** 100µg pv 6 hrly (max x4)[c]		
25µg			**Intrauterine foetal death**[5] 25µg pv 6 hrly or 25µg po 2 hrly[d]	
			Induction of labour[2,5] 25µg pv 6 hrly or 25µg po 2 hrly[d]	
		Care with previous uterine scar and caesarean section		

Check for updates at www.figo.org

Notes

1. Only use where legal and with mifepristone, where available
2. Included in the WHO Model List of Essential Medicines
3. Leave to work for 1-2 weeks unless excessive bleeding or infection
4. Halve dose if previous caesarean section or uterine scar
5. Make sure you use the correct dosage - overdose can lead to complications. Do not use if previous caesarean section

References

a WHO/RHR. Safe abortion: technical and policy guidance for health systems (2nd edition), 2012
b Gemzell-Danielsson et al. IJGO, 2007
c Gómez Ponce de León et al. IJGO, 2007
d WHO recommendations for induction of labour, 2011
e FIGO Guidelines: Prevention of PPH with misoprostol, 2012
f FIGO Guidelines: Treatment of PPH with misoprostol, 2012

Abbreviations pv - vaginal; sl - under the tongue; po - oral; PPH - post-partum haemorrhage; µg - microgramme

1.6 MIFEPRISTONE PHARMACOKINETICS

Mifepristone is a synthetic anti- progesteron which works as an antagonist to progesterone and glucocorticoid at receptor level (Baulieu and Ullman 1985). Following oral administration, absorption is rapid with peak concentration after one to three hours, and half-life of 20-40 hours (Lähteenmäki et al 1987, Heikinheimo et al 1990, van Look and Bygdeman 1989). Absorption after vaginal administration is insufficient for reaching clinical effect (Heikinheimo et al 1987). Mifepristone metabolites are excreted in the urine (10%) and in the faeces via the biliary system (90%). Its affinity to the progesterone receptor is five times that of natural progesterone, and to the glucocorticoid receptor with an affinity of three times that of dexamethasone. It also binds to a lesser extent to the androgen receptor (Moguilewsky and Philibert 1985, Lähteenmäki et al 1987). Mifepristone antagonizes the effect of progesteron and glucocorticoid by occupying the receptor, but without stimulating the gene transcripton (Spitz and Bardin 1993, Christin-Maitre et al 2000). Mifepristone behaves as a pure antagonist with minimal agonist activity (Moguilewsky and Philibert 1985).

Anti- glucocortiocid activity has been proven following a single dose of 400 mg of mifepristone, which lasts for at least 24 hours, affecting both the central actions of cortisol (inhibition of feedback control) and peripheral effects; however no effect is seen on the mineral-corticoid axis (Gaillard et al 1984, Raux-Demay et al 1990). The inhibitory effect on the negative feedback system counteracts the effects in healthy individuals, increasing ACTH (adrenocorticotropic hormone) secretion and re-establishing an equilibrium (Healy et al 1985). When treating patients with adrenal failure and long-time corticosteroid replacement therapy, this anti-glucocorticoid effect can be counteracted by administration of >1 mg dexamethasone (Raux-Demay 1990), or by increasing the dose of the steroid medication (Davey 2006). The only contraindication to treatment with mifepristone is severe, poorly controlled asthma; due to fear of exacerbation of the life-threatening condition (Christin-Maitre et al 2000, Sitruk-Ware 2006). Asthma treated with inhaled corticosteroid is not a contraindication (Creinin and Gemzell Danielsson 2009). There have been cautions when treating nursing mothers, due to the anti-glucocorticoid effect. Mifepristone crosses the placental barrier, resulting in maternal:fetal ratios in plasma of 9:1 to 17:1. Foetal aldosterone levels are elevated for 24 hours after single dose of 600 mg mifepristone, but no effects have been shown on foetal progesterone, estradiol or cortisone levels (Hill et al 1991). Mifepristone does not seem to have teratogenic effects, in case of exposure of an ongoing pregnancy (Bernard et al 2013).

Mifepristone was shown to effectively interfere with the viability of early pregnancy (Herrman 1982, Kovacs et al 1984). Treatment with mifepristone will serve as an antagonist to the progesterone produced by the corpus luteum in early pregnancy and in the placenta, by reversing the hyperpolarisation of the cell membranes in the myometrium and stimulating the gap junction formation (Garfield and Baulieu 1987, Garfield et al 1988, Norman et al 1991), thus increasing the sensitivity of the myometrium to prostaglandin (Bygdeman and Swhn 1985, Swahn and Bygdeman 1988). Mifepristooe also induces an endogenous production of prostaglandines in the deciduas (Norman et al 1991). In addition, mifepristone has a slow priming effect on the cervix (Bygdeman et al 1991). Studies have proven that a mifepristone 100 mg single dose as almost equally effective, or five doses of 25 mg administered with 12

hours intervals as equally effective as doses of 200 mg or higher for termination of pregnancy, although reducing the dose further resulted in decreased efficacy (WHO task force on post -ovulatory methods of Fertility Regulation 1993, WHO task force on post-ovulatory methods of Fertility Regulation1991, von Hertzen et al 2009).

1.7 INTRAUTERINE CONTRACEPTION

Intrauterine contraception is the most widely used reversible contraceptive method in the world (NICE clinical guidelines 2005). The effectiveness of long-acting reversible contraception (LARC) is superior to short-acting contraception and is not altered in young or nulliparous women (Winner et al 2012). IUC is also safe and highly acceptable in younger women, with rapid return of fertility when discontinuing, and no increased risk of tubal infertility (Rybo et al 1993, Mansour et al 2011, Secura et al 2014). A smaller uterus does not reduce the efficacy of an IUC, and both efficacy and continuation rates of IUC are similar for nulliparous and parous women (Duenas et al 1996, Meirik et al 2001). The only contraindication to intrauterine contraception, apart from established pregnancy is PID (pelvic inflammatory disease), septic abortion and puerperal sepsis until the infection is fully resolved (WHO technical and policy guidelines for health systems 2012). There is no increased risk of PID in IUC users, after the first 20 days following insertion (Farley et al 1992, Grimes et al 2000). The incidence of PID in LNG-IUS (Levonorgestrel releasing intrauterine system) users is significantly lower than in women using a Cu-IUD (copper-coated intrauterine device), possibly due to the cervical mucus, rendering it less permeable to sperms and pathogens (Andersson et al 1994)

The most common IUCs used today are the copper coated intrauterine devices (Cu-IUD) in different models (life-span 5-10 years), and the Levonorgestrel-releasing system (LNG-IUS), Mirena (lifespan 5 years). There are also frameless copper-devises, which are “anchored” in the fundal region. A copper-coated intrauterine ball (IUB), which has a small diameter when inserted and that curls to a spherical shape when released in the uterine cavity has recently been developed (Baram et al 2014). In some parts of the world, copper devises without treads are still common (Grafenberg ring) (Searle 2014). A new LNG-IUS has been developed in recent years, (Jaydess®), releasing a lower levonorgestrel dose, and with a life-span of three years. Among the IUCs it is only the Cu-IUDs which have been shown to be effective for emergency contraception. Cu-IUD should be remembered and offered, being the most efficient emergency contraception available (Raymond Li et al 2014).

The hormonal device was developed to reduce expulsion and reduce the side effects of ordinary copper-IUDs. The first hormonal IUS was Progestasert®, which had a lower pregnancy rate compared with inert IUC, as well as reduced menstrual bleeding, however, the life-span was only 12 months (Place et al 1974). Levonorgestrel has a more profound and uniform effect on the endometrium, and is not metabolized as rapidly as progesterone. An IUS, releasing levonorgestrel 20 mcg/24 hours was developed, with similar high contraceptive efficacy, positive effects on reducing menstrual bleeding and dysmenorrhoea but with a life span of 5 years (Nilsson CG 1975). The LNG-IUS has been shown to reduce heavy menstrual bleeding in women with and without uterine leiomyomas, to also reduce

menstrual pain in women with adenomyosis and endometriosis, and is superior to systemic progestins to treat endometrial hyperplasia, as well as to reduce the risk of endometrial cancer and cervical cancer (Hubacher and Grimes 2002, Heikinheimo et al 2012, Castellsague et al 2011). In a large American study including almost 10000 women, the 20mcg LNG-IUS proved to be the most effective and acceptable contraceptive choice with the highest continuation rate (Winner et al 2012). One of the areas for improvement in medical abortion is post abortion bleeding, which is unpredictable, and may be heavy and long-lasting. Therefore, the effect of post abortion contraception and in particular IUCs is important to study.

1.8 POSTABORTION CONTRACEPTION

Contraception use should be initiated immediately post-abortion to reduce the risk of repeat unwanted pregnancy and abortions. Ovulation can occur as early as 8 days after induced abortion, and 83 % ovulate during the first cycle (Schreiber et al 2011, Lähteenmäki et al 1978). A majority of women reinitiate sexual activity within two weeks after an abortion (Boesen et al 2004). The most effective contraception methods in terms of reducing the risk of repeat abortion are long-acting reversible contraception (LARC), i.e. copper intrauterine device (Cu-IUD), levonorgestrel-releasing intra-uterine system (LNG-IUS), implants and injectables (Langston et al 2014, Secura et al 2014).

Young and nulliparous women are less likely to use an IUC after abortion, although it has been proven as safe and effective for this group of women (Secura et al 2014). Those women who have had an IUC inserted post abortion, are much less likely to have a repeat abortion (Roberts et al 2010, Cameron et al 2012). Those methods also have a higher continuation rate compared with other short-acting methods such as contraceptive pills (Cameron et al 2012). Hormonal method can be started on the same day as the abortion with no risk of affecting the abortion treatment (Gaffield et al 2009, WHO Medical eligibility criteria for contraceptive use 2010, Tang et al 2002). Intra-uterine contraception (IUC) can be inserted immediately after an uncomplicated surgical abortion, although there is a slightly elevated risk of expulsion with increasing gestational duration (Bednarek et al 2011, Grimes et al 2010). After medical abortion, the standard clinical routine has been to insert IUC at the follow-up visit three to four weeks after the abortion. This is complicated by the increased number of women not returning for the follow-up and IUC insertion, and several studies indicate that the proportion using IUS is higher after immediate insertion (Stanek et al 2009, Bednarek et al 2011, Cameron 2012).Thus, the possibility of earlier insertion of IUC after medical abortion is crucial to help women avoid a repeat unwanted pregnancy.

2 AIMS OF THE STUDY

The overall aim of the thesis is to increase access to intrauterine contraception and safe abortion methods. Misoprostol has become the drug of choice for various indications in the gynecological and obstetrical field; however, the optimal dosages for several of the indications remain undefined. In the combined regimen of mifepristone and misoprostol for medical abortion misoprostol is also considered safe for nursing mothers and their infants, while knowledge on the transmission of mifepristone has been limited. For women undergoing medical abortion, one of the most important aspects is future contraception, of which IUC is one of the most efficient and acceptable options. Investigating the safety and limitations of immediate/early IUC insertion is crucial to ensure women the possibility of choosing a medical method for termination of pregnancy as well as IUC for post-abortion contraception.

The specific aims of this thesis were therefore

- To investigate the efficacy of priming with misoprostol in nulliparous, non-pregnant women prior to insertion of a Cu-IUD
- To investigate the transmission of mifepristone to human breast-milk in women undergoing medical abortion
- To study the timing of insertion of IUC after first trimester medical abortion, and
- To define the optimal interval and route of administration of misoprostol for cervical priming prior to mechanical dilatation and vacuum aspiration.

3 MATERIAL AND METHODS

The studies were conducted at the department of Obstetrics and Gynaecology, Sesam (outpatient unit for sexual and reproductive health) and C21 day care clinic, Karolinska University Hospital, the WHO collaboration centre, Department of Women's and Children's Health, Karolinska Institutet, and (study III) GynMed Ambulatorium Clinic in Vienna and Salzburg, Austria. Analyses of mifepristone in breast milk were performed at the Biomedicum Institute in Helsinki, Finland (Study III). The studies were approved by the regional ethics committee at Karolinska Institutet and by the Swedish Medical Product Agency (Läkemedelsverket). All women gave their written informed consent before being enrolled into the studies.

Study design

Study I, III and IV were randomized controlled trials. Study III was a phase II pharmacokinetic study.

Table I. Overview of the studies

Study and topic	Inclusion date	% Nulliparous	No of patients	Gestational length	Misoprostol dose	Mifepristone dose
I IUD insertion after misoprostol	Sept 2004 – July 2006	100%	80	Non-pregnant	400 µg sublingually	-
II Mifepristone in breast milk	June 2003 – August 2006	0%	12	47 – 123 days	400 µg orally or 800 µg vaginally	600 mg or 200 mg
III IUC after medical abortion	Feb 2007 – Oct 2010	34 %	129	27-63 days	800 µg vaginally	200 mg
IV Misoprostol prior to surgical abortion	June 2007 – mars 2014	100 %	184	42 – 85 days	400 µg sublingually or vaginally	-

3.1.1 Study I

This study was a randomised, controlled trial, comparing treatment with sublingual misoprostol and diclofenac to diclofenac-alone given one hour prior to insertion of a copper – intra-uterine device (Cu-IUD).

A total of 80 women were recruited between September 2004 and July 2006 among healthy nulliparous women over 18 years of age, requesting a cu-IUD (Nova-T, Schering AG,

Berlin). Exclusion criteria were any signs of genital infection, contraindication to misoprostol, or a positive pregnancy test. Patients were randomised to either treatment with 400 mcg sublingual misoprostol and 50 mg diclofenac (PO), or to 50 mg diclofenac (PO). The medication was administered by a study nurse one hour before the IUD insertion. The drug administered was unknown (blinded) to the investigators, but not to the women. The information was kept concealed from the investigating doctors until the study was completed.

The main outcome was measured as the cervical resistance and the ease or difficulty of IUD placement experienced by the investigator and was classified as "easy", "moderate" or "difficult".

Cervical dilatation was recorded prior to the insertion of the IUD. The degree of dilatation was determined by whether or not Hegar dilators with a diameter of 4 mm (corresponding to the diameter of the uterine sound) or smaller could pass through the internal cervical os without resistance. Any resistance or need for dilatation was recorded. Pain was indicated by the women on a visual analogue scale (VAS) graded from 0 to 10, 0 representing no pain at all and 10 worst possible pain imaginable. Side effects such as nausea, diarrhoea, skin rash, fever/shivering, bradycardia or syncope were recorded by the study nurse after questioning the patients.

Women were asked to keep daily records of pain, bleeding and any side effects experienced after the IUD insertion until the follow-up visit four weeks after the insertion. At the follow up visit a vaginal examination was performed to check that the IUD was in place, and the diary was collected.

The main outcome of the study was the cervical resistance during cu-IUD insertion as judged by the investigator, who was blinded to treatment allocation. Secondary outcomes included the effect of treatment on cervical dilatation, side effects, pain, bleeding and acceptability.

3.1.2 Study II

This study was a pharmacokinetic study aimed at investigating the levels of mifepristone in breast milk from women undergoing medical abortion. Between June 2003 and August 2006, 12 healthy lactating women over 18 years of age requesting medical termination of pregnancy were recruited (six in Stockholm and six in Vienna) The laboratory analysis of mifepristone levels in plasma and breast milk were performed during September 2008 at the Biomedicum institute, Helsinki, Finland.

Medical termination of pregnancy was performed according to clinical routine, however, during the recruitment period, the protocol concerning mifepristone dose changed in Stockholm from 600 mg to 200 mg. On day one of treatment the women received either 600 mg (n=10) or 200 mg (n=2) mifepristone orally, followed by 400 mcg misoprostol orally or 800 mcg misoprostol vaginally 36-48 hours later (treatment day 3) depending on the length of gestation. At this time, the clinical routine was to advise the women to discard breast milk for three days following mifepristone administration. The women in the study were asked to collect 10-20 ml of milk from each pumping session during the first three days following mifepristone treatment and if possible continue to sample breast milk for another four days up

to seven days following treatment. The samples were frozen and stored at -20^0 C until analysed. Serum samples were collected from four of the women on day three.

In the analysis, mifepristone was separated from its cross-reacting metabolites using Chromosorb® column chromatography, after which the levels of mifepristone in serum and breast milk were quantified by radioimmunoassay (RIA). The breast-milk samples were diluted with phosphate-buffered saline in the ratios 1:10, 1:20 and 1:50 to reduce the influence of fat. The detection limit of the mifepristone assay when using milk was 0.013 µmol/l. The intra- and inter-assay co-efficient of variation in these assays were 11.8 and 19.6%, respectively.

The main outcome was the levels of mifepristone in breast milk quantified in radioimmunoassay.

3.1.3 Study III

This was a randomised, controlled trial investigating the safety and efficacy of early IUC insertion on day 5-9, compared with routine delayed IUC insertion 4 weeks after medical abortion. A total of 129 healthy women over 18 years of age, requesting medical termination of pregnancy up to gestational length of 9 weeks (63 days) and an IUC as post-abortion contraception were recruited between February 2007 and October 2010. Women with a poor understanding of the Swedish language or abnormal pregnancies were excluded from participating, as well as women planning a pregnancy within the next year. Women were free to choose between the Cu-IUD (NovaT, Bayer, Berlin, Germany) or the LNG-IUS (Mirena®, Bayer AG, Berlin, Germany), and within each stratum randomised to either early insertion or delayed insertion in a ratio of 1:1. The randomisation list was kept concealed from the study investigators until the study was completed.

The medical termination of pregnancy was performed according to clinical routine. All women were screened for bacterial vaginosis and Chlamydia infection, and treated if positive but not excluded from participation. Gestational age was determined by transvaginal ultrasound. Women were administered 200 mg mifepristone orally at the clinic, and the day of mifepristone treatment was counted as day one. 36 to 48 hours later women self-administered 800 µg vaginally either at home or at the clinic. Before administration of misoprostol, analgesics according to clinical routine were also administered. All women were advised to abstain from intercourse until insertion of the IUC. An ultrasound examination was performed prior to insertion of the IUC, and the thickness of the endometrium and signs of remnants of gestational products were recorded. Women with continuing pregnancy or missed abortion with intact gestational sac on the day of planned insertion, with surgical intervention or genital infection after the abortion treatment were excluded from the trial. Intensity of pain was recorded as judged by the patient on the visual analogue scale (VAS) from zero to ten directly after the insertion. Serum haemoglobin (S-Hb) and human chorion gonadotropin (S-hcg) were determined on day one, on the day of IUC insertion and at the four week follow-up visit after insertion. Women were asked to keep a daily diary of the bleeding pattern as well as any other adverse event or concomitant medication.

The patients were scheduled for a follow-up visit four weeks after the IUC insertion. The diary was collected from the patients. Any complications such as expulsion, uterine perforation, and genital infection were recorded. The patients were contacted by telephone after six months, and answered a questionnaire about pregnancy, expulsion, bleeding patterns, pelvic pain, pelvic infections, continued use and overall satisfaction concerning the contraceptive method.

The main outcome in the study was the incidence of expulsion, and secondary outcomes were rates of insertion and complications after insertion, as well as differences in bleeding patterns and compliance during the first six months of use.

3.1.4 Study IV

This study was a randomised placebo-controlled trial aiming at investigating the optimal priming interval and administration route of misoprostol prior to surgical abortion. 184 patients were recruited between June 2007 and march 2014 among nulliparous women requesting surgical termination of first trimester pregnancy (gestational week 6 - 13). In those who had been pregnant preciously, all pregnancies had ended during the first trimester, either by termination of pregnancy or miscarriage. Women with general good health, over 18 years of age and with a normal first trimester pregnancy who opted for surgical termination of pregnancy were offered to participate in the study. Exclusion criteria were any contraindication for misoprostol, previous history of surgery to the cervix and uterus (other than vacuum aspiration), untreated genital infection or an abnormal pregnancy. Women participating in the study were randomised into four different treatment groups, receiving misoprostol either sublingually or vaginally, and priming time either one or three hours. The randomisation list was kept concealed from the investigating doctors until the study was completed.

The patients received 2 tablets of misoprostol, either vaginally or sublingually, and two identical placebo-tablets, thus the route of administration of active substance was concealed. The patients were allowed to administer the tablets themselves. According to clinical routine, the patients also received 100 mg of diclofenac orally for pain relief. Immediately before surgery, the women were asked if they had experienced any side effects, and which route of administration they would have preferred.

The exact priming time and signs of preoperative bleeding were recorded. Cervical dilatation and vacuum aspiration was performed by one of two investigating physicians. The vacuum aspiration was performed under general anaesthesia according to clinical routine. Dilatation was performed using Pratt-dilatators and the resistance of the cervix was objectively assessed using a force-sensing handle attached to the dilator (tonometer). The cervical canal was dilated with dilators from 6.3 mm (19 French) up to 9.7 mm (29 French), or in some cases with pregnancies over 11 weeks of gestation up to 11 mm (33 French). The peak force of each dilator was recorded. The cumulative force was calculated by adding the peak force for each dilator up to 9.7 mm. Baseline dilatation was considered to be the largest dilator that could enter the cervical os using a force less than 8N. If the smallest dilator could not enter

the cervical canal, the baseline was considered to be 4.1 mm, which is the mean baseline in untreated, nulliparous women.

The main outcome in the study was the baseline dilatation of the cervix after medical priming. Secondary outcomes were cumulative force and peak force needed for mechanical dilatation of the cervix, intraoperative blood loss, duration of surgery and dilatation, bleeding prior to surgery, side-effects from medication and preference concerning the route of administration.

3.2 STATISTICS

Study I: To evaluate the differences between the two groups with regard to cervical resistance indicated by difficulty or ease of insertion, judged by the investigators, the Fisher's Exact test was used (one-sided mid-P-value). The Fisher's Exact test (two-sided) or the Chi-squared test was used for independent nominal data such as side effects and overall experience from the insertion as judged by the patient. Continuous variables were compared using the unpaired t-test, and discrete numerical values were compared using the Mann-Whitney U-test.

Study III: To evaluate the differences between the early insertion group and the delayed insertion group, regarding independent nominal data such as expulsion, side-effects and compliance, the Chi squared test was used. Continuous variables with normal distribution such as age, and discrete numerical variables such as parity and bleeding patterns were compared using the Mann-Whitney U-test.

Study IV: To evaluate differences between the groups, all groups were compared to the others using the Student's t-test (two-sided). Continuous variables such as age and discrete variables such as bleeding before surgery were compared using the Mann-Whitney U test. For testing if the group of sublingual treatment 1 hour was non-inferior to 3 hours, a non-inferiority test was performed. The non-inferiority test was assessed through a two-sided 95% confidence interval. A difference of less than 0.5 mm in baseline dilatation was considered clinically irrelevant. The non-inferiority test was also performed for peak force, where a difference of less than 5N was considered clinically irrelevant, and a cumulative force of less than 10 N was considered clinically irrelevant.

Differences were considered statistically significant if p-value was <0.05.

4 RESULTS

4.1.1 Misoprostol for cervical priming (study I and IV)

Following priming with misoprostol administered sublingually one hour before the procedure to nulliparous women prior to insertion of an IUD, IUD insertion was significantly more often judged as easy by the physician (p=0.039). The insertion was judged to be easy in 29/40 women in the misoprostol group compared with 22/40 women in the control group, and intermediate or difficult in 10/40 women in the misoprostol group compared with 18/40 in the control group. The assumption of the blinded investigators was that 27 of the women in the misoprostol group and 20 of the women in the control group had received treatment, indicating that insertion of an IUD does not need to be difficult, even in nulliparous women. However, there were two failed insertions in the control group, and none in the misoprostol group (ns).

There was no difference in pain estimated by the patients; median VAS estimation was 7 in the misoprostol group and 6.5 in the control group (ns). Shivering and diarrhoea were more common in women treated with misoprostol (p= 0.0084, and p= 0.075, respectively). There was no difference in bleeding or pain during the first month after the insertion. There were no pelvic infections or expulsions in the trial.

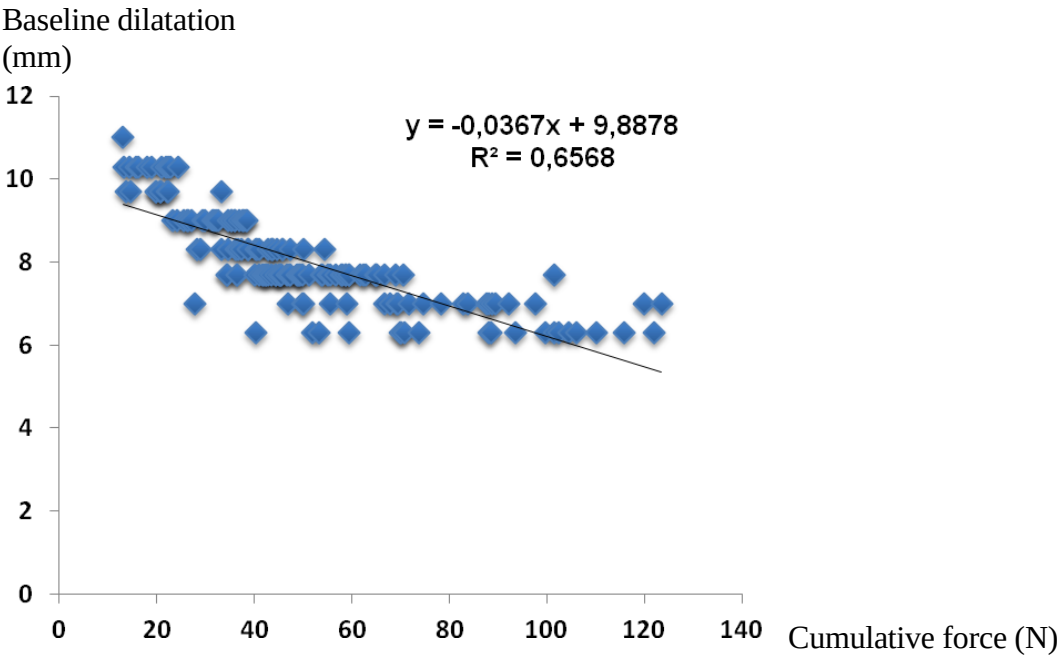
In study IV it was further evaluated if priming with sublingual misoprostol prior to surgical abortion could reach significant efficacy already after one hour. Sublingual priming with misoprostol was shown to be as effective after one hour as after three hours, with no difference in baseline dilatation (p=0.45), peak force (p=0.73), or cumulative force (p=0.68). Sublingual one hour priming was also proven to be non-inferior compared with sublingual three hours priming for baseline dilatation (CI -0.42 – 0.95), peak force (CI -4.1 – 2.9) and cumulative force (CI -14.4 – 9.5). Also, sublingual priming was more effective than vaginal when priming time was reduced to one hour with greater baseline dilatation (p=0.038) and less cumulative force was needed for dilatation p=0.048).

Table 4. Effect of misoprostol on cervical dilatation regarding route of administration and priming interval (Study IV).

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)

SL=sublingual, PV per vagina
Results are expressed as mean (SD). Figures indicate significant differences between groups

There was a clear correlation between the results of baseline cervical dilatation and cumulative force (Study IV).



The proportion of women who had started bleeding before surgery was significantly reduced when priming time was shortened to one hour when comparing the sublingual groups (p=0.0008). Significantly fewer women reported abdominal pain in the vaginal administration group after a priming time of 1 hour (p=0.0001). The groups did not differ concerning the duration of surgery, amount of bleeding and the rate of side-effects, such as nausea and shivering. Women in our study preferred vaginal treatment, as they disliked the taste of the misoprostol tablets. (p=0.0001).

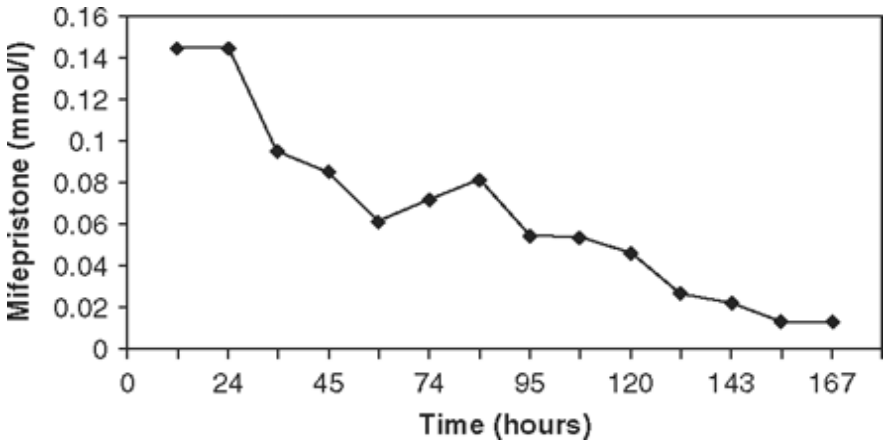
Table 3 side-effects (Study IV).

Study group	SL 1 hour (n=45)	SL 3 hours (n=46)	PV 1 hour (n=43)	PV 3 hours (n=44)	Significance
Bleeding/expulsion before surgery	2 (4.4%)[1]	15 (33%)[1]	3 (7.0%)	8 (18%)	[1] P=0.0008
Abdominal pain	30 (67%)[1]	31 (67%)[2]	6 (14%)[1,2,3]	24 (57%)[3]	[1] P<0.0001 [2] P<0.0001 [3] P<0.0001
Freezing/shivering	6 (13%)	2 (4%)	2 (5%)	3 (7%)	ns
Nausea/vomiting	11 (24%)	9 (20%)	8 (19%)	4 (9%)	ns

SL= sublingual, PV= per vagina

4.1.2 Levels of mifepristone in human breast milk from women undergoing medical abortion (study II)

Declining concentrations were detected for up to 7 days following the higher (600 mg) dose of mifepristone. Six of the 12 women managed to collect the first samples during the first 6 hours after intake, and these samples were found to have the highest concentrations of mifepristone, ranging from 0.063 to 0.913 µmol/l.



Levels of mifepristone in samples of breast milk collected from a lactating woman undergoing medical abortion on days 1–7 following intake of 600 mg of mifepristone (StudyII)

Two women receiving the lower dose (200 mg) of mifepristone had mifepristone concentrations in breast milk under the detection limit, already during the first day following intake. Only very low levels were also detected following intake of the higher dose after day 3. The milk:serum ratio of mifepristone ranged from <0.013:1 to 0.042:1 on day three. Calculating with the highest detected concentration, in a whole day's milk-consumption for a baby of 6-12 months, the RID (relative infant dose) would only be 0.5-1.5%.

4.1.3 IUD and post-abortion contraception (study I and III)

There was a high acceptability among the young nulliparous women undergoing insertion of a cu- IUD in study I. No severe complications such as pelvic infections, perforation or expulsion were diagnosed among the study patients, and of the 77 successful insertions, only one patient was lost to follow up. A large majority, 82 % answered that they would go through an insertion of an IUD again, whereas 6.5% stated they would not.

For women undergoing medical abortion up to 9 weeks gestation, it was proven to be equally safe to have the IUD inserted during the first week after the abortion (study III). There was no difference in expulsion rate between early insertion on day 5-9 (9.7%) compared with routine, delayed insertion after 3-4 weeks (7.4%). These figures include both complete and incomplete expulsions.

Table 2. Outcomes of Early versus Delayed IUC insertion after medical abortion (Study III).

	Early insertion n = 62	Delayed insertion n = 54	Difference in observed Percentage	95% Confidence interval	p-value
Outcome	**n (%)**	**n (%)**	**(%)**	**(95% CI)**	
Expulsion all	6/62 (9.7)	4/54 (7.4)	2.3	−9.2–13.4	0.54
Copper IUD	2/30 (6.7)	0/25 (0.0)	6.7	−7.3–21.5	0.25
LNG-IUS	4/32 (12.5)	4/29 (13.8)	1.3	−20.3–16.9	0.99
Use at 6 months all	42/62 (67.7)	39/54 (72.2)	4.5	−20.9–12.5	0.55
Copper IUD	24/30 (80.0)	18/25 (72.0)	8.0	−14.7–31.2	0.38
LNG-IUS	18/32 (56.2)	21/29 (72.4)	16.2	−38.6–8.2	0.20

IUC denotes intrauterine contraception, IUD intrauterine device and LNG-IUS levonorgestrel intrauterine system.
doi:10.1371/journal.pone.0048948.t002

Early insertion was also proven safe, with no increased risks of pelvic infections, perforations or heavy and prolonged bleeding after the medical abortion. No risk association could be identified among the women with expulsion, with regard to parity or ultrasound findings such as endometrial thickness. When comparing the copper-IUD with LNG-IUS, there were fewer days with heavy bleeding post abortion in the LNG-IUS group ($p<0.01$) already during the first 4 weeks after the abortion compared with the copper-IUD group.

More women did not show up for IUC insertion in the delayed group (n=7, 11%) than in the early group (n= 1, 1.5%) (p=0.03) (Proportion difference 10%, 95% CI: 1.8-20.6%, p=0.015). Also, the women in the delayed insertion group were more likely to have had an unprotected intercourse prior to the IUC insertion (p=0.015). Of the women in the delayed group, 41% had unprotected intercourse after the abortion and prior to the IUC insertion, compared with 16% in the early group.

5 DISCUSSION

5.1 GENERAL ASPECTS

Improving women's knowledge and access regarding LARC is crucial to improving women's health and to avoiding unnecessary unplanned pregnancies. After abortion fast initiation of LARC will prevent repeat abortion. IUC is underused, and particularly among younger women – a group that generally has more failures of other contraceptive methods, and who are overrepresented in the group of women suffering from serious adverse maternal outcomes after abortion, including maternal deaths. After medical abortion, there has been little evidence on the best timing for IUC insertion and proof of safety if initiated shortly after the abortion. This is again of particular interest, where surgical procedures should be avoided due to sub-standard care and where women may have difficulties in travelling long distances for abortion.

Misoprostol has been proven to be a useful prostaglandin analogue in many areas of the gynaecological and obstetrical field. Compared with the initial prostaglandins, the modern substances have a longer duration of action and do not have the same side-effects regarding the cardiovascular system. When the primary substances need to be administered intravenously or intraamniotically, the modern prostaglandin E_1 analogue (misoprostol) can be administered orally, sublingually and vaginally. In comparison with other modern prostaglandin analogues, misoprostol has logistical advantages of being available in tablets, possible to use orally, stable at room temperature, widely available around the globe and cheap. Studies in regard to efficacy, plasma concentrations and half –life in pregnancy have been performed previously in recent years; however there has been a lack of studies on clinical efficacy after certain routes of administration, as well as of a defined optimal dose and priming interval for surgical abortion as well as use in non-pregnant women.

Understanding of the pharmacokinetics of misoprostol, as well as defining the optimal doses and routes of administration, is crucial to define efficacy and for acceptance of its use, and to ensure safety of the drug. Spreading the information of proper use of misoprostol, and to some extent mifepristone in combined regimens, will provide women with safe and effective, minimal invasive treatment in a variety of gynaecological and obstetrical indications, and very importantly – give women with no access to safe, legal family planning services a safe option for self-administration in case of need for an abortion. There is a need for simplified regimens and guidelines that can be made available to the population, including self-diagnosis of pregnancy, home-use of correct doses of misoprostol (and mifepristone where available), self-assessment of complete abortion and prompt access to post abortion contraception.

5.2 MISOPROSTOL FOR CERVICAL PRIMING

Priming of the cervix prior to surgical procedures may be indicated depending on the intended procedure or on the history of the woman. It was recently shown that priming with

misoprostol reduces the complications rate for all women, nulliparous and multiparous, when undergoing first trimester surgical abortion (Meirik et al 2012). Prior to hysteroscopy, priming is usually desired, and misoprostol has also been proven effective in non-pregnant women (Ngai et al 1997, Fiala et al 2007). Prior to insertion of IUC, priming is not always necessary, but can be desired in a subgroup of nulliparous women, i.e. women with cervical stenosis, amenorrhea or after a failed attempt.

In study I, we concluded that the insertion of IUC is usually also uncomplicated in nulliparous women; however, there was a priming effect on the cervix, measurable as technically easier insertion already after one hour priming with sublingual misoprostol. There was no effect on the patient's estimation of pain during the insertion, but if insertion is facilitated, a technically more complicated insertion that often takes longer time can be avoided. Short duration of pain was an important factor for the 79% of patients that stated that they would go through the procedure again if necessary. Since misoprostol has known side-effects (particularly after rapid increase in plasma levels, such as after sublingual administration) such as nausea, diarrhoea, abdominal pain and chills, it can be argued that routine administration is not indicated before IUC insertion. When insertion fails, however, this rapid efficacy can be used for treatment and a new attempt of insertion can already be made during the visit. If a difficult insertion is anticipated, and medical priming with misoprostol is planned, misoprostol can be administered vaginally, but the priming interval should then be increased to three hours based on data from pregnant women (study IV). In our study we used only the smaller copper-IUD Nova-T, to ensure comparability. When inserting the larger LNG-IUS (Mirena), the risk of failed insertion and the need for medical priming could increase. The importance of facilitating IUC insertion is demonstrated by the huge interest in our study (study I, Sääv et al 2007) which has been followed by several RCTs and observational studies (Scavuzzi et al 2013, Heikinheimo et al 2010, Edelman et al 2011, Espey et al 2014, Ibrahim et al 2013). Importantly, this option could also be used for difficult IUC extractions.

When priming with misoprostol prior to surgical abortion, the most up-to-date gold standard has been 400 mcg misoprostol vaginally or sublingually three hours prior to surgery (Hamoda 2004). Since most surgical abortions are performed as day-care surgery, many women (in Sweden) take the misoprostol tablets at home to reach this priming interval. Some women will start bleeding and risk expulsion before reaching the clinic. In study IV we compared sublingual to vaginal misoprostol, with priming interval of one or three hours. In accordance with study I, we could show efficacy of sublingual priming already after one hour, while vaginal priming needs a longer interval to reach the same efficacy. Importantly, we had as good a priming effect after one hour sublingual priming as after three hours vaginal or sublingual priming, both when comparing cervical baseline dilatation, peak force and cumulative force needed to enter the cervical os (study IV). A clear correlation between baseline dilatation and cumulative force was also found. Both parameters are interesting, since the force needed to dilate the cervix has been proven to correlate to surgical complications and damage to the cervix and uterus (Hulka et al 1974), and the degree of cervical dilatation and cervical trauma has been associated with cervical insufficiency in future pregnancies (Berkowitz et al 1981, Martius et al 1998). Although it is known that all women benefit from misoprostol priming prior to vacuum aspiration (Meirik et al 2012), and

that it is our clinical routine to treat all, we chose to enrol only nulliparous women in the study to ensure comparability concerning cervical baseline dilatation. Ideally only primigravida women would have been recruited to reduce variation even more.

Significantly fewer women started bleeding prior to vacuum aspiration when sublingual priming time was reduced to one hour. Women treated with sublingual misoprostol had significantly more shivering and diarrhoea compared with the untreated group in study I. As expected, there was also a slightly lower rate of side-effects in the vaginal treatment groups compared with the sublingual groups in study IV. However, in our study, only abdominal pain reached significance, and was lower in the vaginal one hour priming group, corresponding to the lower priming efficacy in this group. In patients where nausea and vomiting makes sublingual treatment difficult, this knowledge could be used for choosing the vaginal route of administration instead. If the vaginal route is chosen the priming interval should be increased to three hours to reach equal efficacy. Priming intervals beyond three hours or using higher doses than 400 mcg of misoprostol results in more side effects but does not increase efficacy (Fiala et al 2007).

It has often been concluded that women prefer the oral or sublingual route of administration to the vaginal (Ho et al 1997, Ngai et al 2000, Tang et al 2002, Arvidsson et al 2005). Studies have also found that members of staff prefer oral administration, to "avoid vaginal examination" (Hamoda et al 2004). In study IV, there was an overwhelming majority preferring the vaginal route. Most women stated the long time for the tablets to dissolve and taste of the tablets as reasons (study IV). The women were also allowed to administer the tablets themselves, which is an important factor for the acceptability of the vaginal route. There might be an advantage of offering different administration routes, particularly if there is a problem with nausea, or if there is a shortage of time. Some of the disadvantages with sublingual administration could also be addressed, in developing a designed misoprostol product for this use.

5.3 MIFEPRISTONE AND MISOPROSTOL IN BREAST MILK

5.3.1 Misoprostol

Nursing mothers may need misoprostol for several reasons. When there is an unmet need for contraception, under-use of LARC and when contraception is too late after childbirth, women may resort to abortion to space childbirths. Generally, long-acting reversible contraception (LARC) is under-used, and women may be advised to delay initiation of LARC, or are prescribed less effective methods such as progesterone-only pills after delivery. In Finland up to 10 % of induced abortion patients are nursing mothers (Heikinheimo, personal communications 2010, www.stakes.fi/FI/). There are also cases where misoprostol could be administered in case of postpartum haemorrhage, endometritis, or suspected placental remainants after delivery. There are theoretical advantages of using misoprostol for these indications as well instead of the old-fashioned drugs such as ergometrine and prostaglandin F2 alpha. IUC insertion can be more difficult during the breastfeeding period, and the risk of perforation is higher for this group (Kaislasuo et al 2012). Misoprostol could be used to facilitate the insertion through a narrow cervix, instead of forceful dilatation.

There have been reports about periostal changes in infants treated with high doses of intravenous prostaglandin for cardiovascular indications (Ringel et al 1983), however, no such case is reported after misoprostol use during labour, in the post-partum period or during breast-feeding. The transfer of a drug into breast-milk depends on molecular size, hydrophilic/lipofilic nature and the degree of protein binding (Berlin and Briggs 2005, Anderson 2006).Since the active substance is misoprostol acid, and acidic drugs favour ionization in the slightly more alkaline plasma (pH7.4), compared with the slightly more acidic breast milk (pH7.1), there will be less transport into breast-milk, and also a reverse transportation back to maternal plasma. In general, milk:plasma ratios of acidic drugs will therefore be <1.0 (Berlin and Briggs 2005). Also, misoprostol acid is 80-90% bound to serum protein. Plasma-concentration of misoprostol acid in breast-milk reaches only 0.04 (0.001-0.198) after 30 minutes and 0.06 (0.02-0.16) after one hour after oral misoprostol (Vogel et al 2004). It has been concluded, that the effects of misoprostol in breast-milk on the term infant or the under one year-infant, should be negligible and self-limiting, consisting mainly of gastrointestinal side-effects.

5.3.2 Mifepristone

Data have been lacking concerning the transfer of mifepristone into human breast milk. The transfer of mifepristone may be proportionally higher with a higher dose, since mifepristone strongly binds to human α1-acid glycoprotein in plasma (Sitruk-Ware and Spitz 2003), and the transfer occurs mainly of the free circulating mifepristone and metabolites, which increases after the protein-binding capacity is saturated. From this point of view, lowering the dose of mifepristone to 200 mg, thus reducing the proportion of free circulating mifepristone in plasma, increases safety margins during lactation. Given the long half-life of mifepristone of 20-40 hours, there is a potential effect on the foetus due to the antagonstic effect on the glucocortiocoid receptor. From studies on foetuses from second-trimester abortion, it has been shown that mifepristone can alter the steroid concentrations and elevate the aldosterone levels in the foetus, but there is no evidence of teratogenic effect in on-going pregnancies after exposure during the first trimester (Hill et al 1990, Bernard et al 2013). The low transfer of mifepristone into human breast milk was proven in our study (study II), with milk:serum ratios ranging from <0.013(detection limit):1 to 0.042:1.The relative infant dose (RID) will be 0.5% when calculated from the highest detected concentration, multiplied with the highest daily milk intake in a fully breast-fed infant (Wallgren 1945). As values of around 1% are generally considered safe (Berlin and Briggs 2005, Andersson 2006), all restrictions of medical abortion and continuing breastfeeding should be abolished.

5.4 IUC AND POST ABORTION CONTRACEPTION (STUDY I AND III).

Studies have shown that many women, including those who are young and nulliparous, choose a long-acting contraceptive method when they are able to choose freely (Secura et al 2014), and the LNG-IUS has been shown to have a higher continuation rate than oral contraceptives in nulliparous women (Suhonen et al 2004). There is no difference in efficacy between women of different ages and parity concerning IUC. In contrast to IUC oral contraceptive pills, the patch and the contraceptive vaginal ring have significantly higher

failure rates, which are also magnified in young women (Mc Nicholas and Peipert 2012). It is therefore important to improve information about the high efficacy and safety, and to improve contraceptive counselling concerning IUC. Apart from the highly effective contraceptive function of the LNG-IUS, and the various positive effects on limiting menstrual blood loss and dysmenorrhoea, there are also environmental benefits, both in regard of less hormonal waste compared with oral contraceptives, as well as decreased need for sanitary products due to the profound decrease in bleeding among users. In areas where there is a high burden of diseases such as malaria, sickle cell anaemia and high prevalence of uterine leiomyoma among the female population, the beneficial impact of Mirena® is difficult to overestimate.

In study I and III, we found a high acceptability for the IUC method among the nulliparous women in accordance with previous studies. In study I, only one woman out of 80 nulliparous women interrupted the insertion procedure, and 79% said they were willing to go though the procedure again. Since menorrhagia is less common in young women – there could be a higher acceptance for the Cu-IUD in this group. IUC and particularly LNG-IUS is currently underused in the young nulliparous group of women, and facilitating access and insertion has a potential in regard to reducing the number of unplanned pregnancies as well as repeat abortion (Gemzell Danielsson et al 2013, Cameron 2012).

Long-acting reversible contraception (LARC) is shown to reduce the risk of repeat abortions as well as unplanned pregnancies in comparison with other contraceptive methods (Cameron 2012). Following an induced abortion, many women feel motivated to try a contraceptive method. There are however great differences between the modern contraceptives in efficacy to reduce the risk of a repeat abortion. Intrauterine contraception has been proven to be highly effective to prevent a repeat abortion, with higher efficacy than oral contraceptives or any other non-IUC (Cameron 2012, Mc Nicholas and Peipert 2012, Heikinheimo et al 2008).

In comparison with surgical abortion, it has been a disadvantage of the medical method, that the IUC cannot be inserted immediately. This is also a disadvantage regarding home-abortion. However, as shown in study III (Sääv et al 2012) early IUC insertion after first trimester medical abortion was not associated with any increased risk of expulsion, infection, bleeding or pain when compared with routine inserting. Importantly, the delayed, routine insertion will in 83% of women occur after the first ovulation (Lähteenmäki and Luukkainen 1978). One reason for the low expulsion rate in the study could be that all IUC were confirmed to be in situ by ultrasound post insertion, thus no insertions should have been sub-optimal with the IUC in the cervix. Expulsion has been proven to be slightly higher when insertion takes place immediately after a surgical abortion, however when looking at IUC use 6 months post abortion, it is significantly higher in the group that receives the IUC immediately post abortion (Gillett et al 1980, Grimes et al 2010). It is now recommended, that IUC can be inserted as soon as the possibility of ongoing pregnancy or missed abortion has been ruled out, and does not carry a higher risk of PID than delayed insertion, and with low rates of expulsion (WHO Clinical practice handbook for Safe abortion 2014, Betstadt et al 2011, Shimoni et al 2011, Sääv et al 2012). Expulsion rate and safety also needs to be further investigated to define the best care after second trimester abortion, as it is of particular interest to avoid (sub-standard) surgical second trimester abortions.

In study III it was shown that women were significantly more likely to show up for insertion of an IUC, when scheduled early. Also, a substantial number of women had resumed intercourse before the IUC insertion both when scheduled early (16%) and according to routine (41%), with the important difference that the women undergoing early insertion had the IUC inserted before return of ovulation. Improving access and fast implementation of LARC is important after medical abortion to reduce the number of repeat abortions, but also to help women avoid a surgical abortion which they may not otherwise choose. It is an important advantage to offer IUC insertion early after first trimester medical abortion, which is the abortion method of choice for the majority of women (Winikoff 1995, Fiala and Gemzell Danielsson 2006). This is particularly important in settings where surgical care might not be performed with safe, modern methods. Also, WHO states, that second trimester abortion should be performed medically, where there is substandard care for surgical abortion and where trained operators are lacking (WHO Clinical practice handbook for Safe abortion 2014). It is also likely that an increasing number of women will choose home-abortion and the possibility of self-diagnosing complete abortion, and those women must be given the opportunity to initiate LARC promptly after the abortion.

6 CONCLUSIONS

6.1.1 Misoprostol for cervical priming in (Study I and IV)

Misoprostol reduces the cervical resistance, and can be used to facilitate insertion of an IUC and decrease the risk of difficult or failed insertions. Sublingual administration of misoprostol with a priming interval of one hour was proven effective, both for cervical priming prior to insertion of an IUC, and for cervical dilatation prior to surgical abortion. Sublingual priming with misoprostol was proven to be as effective after one hour as after three hours priming interval in regard to baseline cervical dilatation, peak force and cumulative force, and was more effective compared with vaginal administration when priming interval was reduced to one hour.

Reducing the priming interval to one hour when misoprostol is administered sublingually reduces the number of women who start bleeding prior to surgical abortion. Also, patients can be treated at admittance to the clinic and avoid bleeding and expulsion before reaching the clinic. More patients reported chills and shivering after sublingual misoprostol priming compared with controls. Fewer women reported abdominal pain one hour after vaginal misoprostol priming, corresponding to the difference in priming efficacy. There was no difference in duration of surgery or amount of bleeding between vaginal and sublingual groups regardless of priming interval. The majority of women preferred vaginal treatment to sublingual, most frequently due to the taste of the misoprostol tablets.

6.1.2 Levels of mifepristone in human breast milk in women undergoing medical abortion (study II)

Levels of mifepristone in breast milk after medical abortion were low, and in some cases even un-detectable after a single dose of 200 mg mifepristone. Milk:serum ratio ranged from <0.013:1 to 0.042:1 on day three. The relative infant dose was calculated to 0.5%. Medical abortion can be the method of choice also for nursing mothers, and breastfeeding can be safely continued in an uninterrupted manner.

6.1.3 IUC and post abortion contraception (Study I and III)

The incidence of expulsion after IUC insertion during the first week after medical abortion up to 9 weeks (9+0) was not increased compared with delayed insertion, and could not be predicted by the ultrasound examination. There was no increased risk of pelvic infections, perforations or heavy bleeding after early insertion after medical abortion. The LNG-IUS reduced the number of days with heavy bleeding after medical abortion compared with Cu-IUD. More women were motivated to return for IUC insertion when scheduled early. IUC use after 6 months was similar after early and delayed insertion. Early insertion should therefore be offered as a routine after medical abortion, to ensure fast initiation of contraception (LARC). There is a high acceptability of IUC also among nulliparous women.

Misoprostol improved the ease of insertion and did not increase the pain associated with the placement, however it did not reduce pain during IUC insertion, and carries side-effects such as shivering and diarrhoea. Therefore the use should be restricted to a subset of women with expected difficult insertion or after a failed attempt.

6.2 CLINICAL RECOMMENDATIONS

Misoprostol prior to IUC insertion

- Priming with misoprostol is usually not necessary, even in nulliparous women. It can be recommended if difficult insertion can be anticipated, i.e. after long use of depo-provera or implants, after previous difficult insertions or failed attempts.
- A single dose of 400 mcg misoprostol can be given either sublingually one hour prior to insertion. For this indication other routes of administration or intervals remain to be studied.

Medical abortion in lactating women

- Medical abortion can be the method of choice also for nursing mothers.
- Lactation should continue in an uninterrupted manner during medical abortion.

IUC after medical abortion

- IUC can be safely inserted as soon as an ongoing pregnancy has been ruled out, either by performing an ultrasound examination or by a semi-quantified s-hcg test
- Endometrial diameter does not correlate to the risk of IUC expulsion
- Women should be scheduled early for IUC insertion, immediately after expulsion of the gestational sac, or during the first week, to ensure fast initiation of IUC as
- women will be more likely to return for IUC insertion if scheduled shortly after the abortion

Priming with misoprostol prior to surgical abortion

- All women undergoing mechanical dilatation prior to vacuum aspiration should receive medical priming with 400 mcg misoprostol
- Misoprostol can be administered sublingually one hour prior to surgery (for example at admittance to the clinic)
- The priming interval should be reduced to one hour when misoprostol is administered sublingually to reduce side effects
- If vaginal administration of misoprostol is preferred, priming interval should be three hours.

6.3 POSSIBLE AREAS FOR FUTURE RESEARCH

- Development of designated misoprostol product for sublingual and vaginal administration
- Further studies on post abortion contraception (PAC), especially in low-income settings
- Second trimester abortion – safety, acceptability and ways of implementation compared with D&E
- IUC insertion early after 2nd trimester abortion; timing and evaluation of safety.
- IUC insertion after childbirth: Why should it not be feasible to insert an IUC between 48 hours and 4 weeks postpartum?
- Evaluate misoprostol for indications where patients today are treated with old-fashioned drugs, such as ergometrine and prostaglandin F2 Alpha; medical treatment of retained placenta, late postpartum bleeding and endometritis.

7 FILM RECOMMENDATIONS

For further inspiration, I wish to include a list of films that in different ways bring up abortion related issues. (With kind support from Rebecca Gomperts, Women on Web)

Drama:

Kreuzzug des weibes (1926)
Valborgsmässoafton(Walpurgis night)
Malice (Bill Pullman)
If these walls could talk
4 Months, 3 Weeks and 2 Days
Amok (1934 film)
Apio Verde
The Banishment
The Cider House Rules (film)
Citizen Ruth
The Crime of Father Amaro
Decalogue II
Devil Returns
Dirty Dancing
The Group (film)
Hinugot sa Langit
If These Walls Could Talk
The Marriage of Maria Braun
My Body, My Child
Obvious Child
October Baby
Ordet
País do Desejo
Palindromes
Polyester
A Private Matter
Rain Without Thunder
Sarah's Choice
The Scarlet Worm
A Simple Story (1978 film)
Stato interessante
Story of Women
Street Corner (1948 film)
Sulang Kirilli
Swing Vote (1999 film)
Under the Pavement Lies the Strand
Vera Drake

Documentaries:

The Abortion Pill
After Tiller
Eclipse of Reason
The Fragile Promise of Choice: Abortion in the United States Today
From Danger to Dignity: The Fight for Safe Abortion
Lake of Fire (film)
Live Free or Die (2000 film)
Maafa 21
Motherhood by Choice, Not Chance
Vessel (film)
What's the Matter with Kansas?
When Abortion Was Illegal: Untold Stories

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