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INCREASING ACCESS TO MEDICAL ABORTION

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To my family

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

Mahmood Fathalla, former FIGO president
ABSTRACT

Introduction: Unsafe abortion kills approximately 47000 women per year. However, women in high resource settings may also have difficulties in accessing safe abortion facilities due to high cost, a large number of visits required or difficulty in finding an abortion provider. The object of this thesis was to examine ways to increase access to medical abortion.

Materials, methods and results:
Study I: Home use of misoprostol may decrease cost, the number of required visits and by attracting women who dislike hospitals. A total of 395 women with gestational age up to and including 63 days were recruited to investigate efficacy and acceptability of home use of misoprostol. Women with gestational length lower than 50 days were compared to women with gestational length of 50 days or higher. Efficacy of the procedure was high (97.5%). Overall acceptability of the procedure did not differ between the groups (p=0.36) and was not related to gestational age (p=0.097).

Study II: In the second study the objective was to assess which factors had a significant influence on the acceptability of home use of misoprostol in the same group of patients. Potentially influential factors were recoded into categorical variables and evaluated using logistic regression. In the final models parity (p=0.003) and feeling calm after the administration of misoprostol (p<0.001) had a positive influence on the experience in relation to expectation whereas having a positive u-hcg test on follow up had a negative influence (p=0.003). Women who had a partner/friend present during the abortion were more likely (p=0.021) whereas women with a positive u-hcg on follow up were less likely to prefer home administration of misoprostol (p=0.002).

Study III: Letrozole is an aromatase inhibitor and has been shown to increase the number of complete abortions when used with misoprostol only. A total of 16 women scheduled for surgical abortion were randomized to either pretreatment with letrozole or no pretreatment. Uterine contractility was measured before and after the cervical priming dose of misoprostol was given. The results were analyzed using repeated measures ANOVA. No difference in time to tonus increase (p=0.243), maximum tonus (p=0.953) or contractility between the two groups was detected (p=0.423).

Study IV: Task shifting from physicians to midlevel providers may increase access to abortion services where physicians are scarce or unwilling to perform abortion provision. Before any examination had been made 1180 women were randomized to medical abortion provision by a physician or nurse midwife. Both provisions were equally effective with the risk difference of 1.6% within the set margin of equivalence of 5% (p=0.027). Women randomized to nurse midwife were significantly more likely to prefer seeing a midwife again were they to have another medical abortion (p<0.001).

Conclusions: This thesis shows that increased access to medical abortion can be achieved in several ways by either increasing use of home use of misoprostol, finding new drugs without previous abortion stigma to replace mifepristone or by task shifting provision of medical abortion from physicians to midlevel providers.
LIST OF PUBLICATIONS

I. **Kopp Kallner H.**, Fiala C., Stephansson O., Gemzell Danielsson K. “Home self-administration of vaginal misoprostol for medical abortion at 50-63 days compared with gestation of below 50 days.” Hum Reprod25(5): 1153-7


IV. **Kopp Kallner H.**, Gomperts R., Johanson M., Salomonsson. E, Marions L., Gemzell Danielsson K. “The efficacy, safety and acceptability of medical abortion provided by midlevel providers or physicians- a randomized controlled equivalence trial”. (submitted)
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**LIST OF ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>mg</td>
<td>Milligrams</td>
</tr>
<tr>
<td>mcg</td>
<td>Micrograms</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>GnRH</td>
<td>Gonadotropin releasing hormone</td>
</tr>
<tr>
<td>WHO-CCR</td>
<td>World Health Organization Collaborating Center for Research</td>
</tr>
<tr>
<td>u-hcg</td>
<td>Urinary human chorionic gonadotropin</td>
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1 INTRODUCTION

1.1 HISTORY OF ABORTION

1.1.1 Abortion in ancient times

The oldest existing description of abortion is in the Eber’s Papyrus from approximately 1550 B.C. which is the oldest known preserved medical document. The Eber’s Papyrus suggests that an abortion can be induced with the use of a plant-fiber tampon coated with a compound that included honey and crushed dates.

The Bible contains little references to abortion or contraception but in the Numbers (the fourth book of the Old Testament) there is reference to a woman accused of adultery who is forced to imbibe a drink, “the bitter water that causeth the curse...”¹, which, if she were an adulteress, would cause her to miscarry. If she had not committed the crime the pregnancy would live on.

Pennroyal, part of the mint family, was used in Greece and also in Europe for its contraceptive and abortifacient properties. References to it exist in the classic Greek play Lysistrata by Aristophanes (448 BC-380 BC) where a beautiful girl was “well cropped, and trimmed and spruced with pennroyal”. ² However, pennroyal had to be administered in the correct amount to induce abortion. If overdosed it was toxic to the liver. To this day pennroyal is used as an abortifacient in countries with restricted access to legal abortion and 2 cases of death have occurred in the USA in modern times.³

In his writing Politics VII Aristotle (384 BC- 322 BC) reflects on the perfect state. In order to achieve the perfect state children cannot be produced in excess. He states that “if children are then conceived in excess of the limit so fixed, to have miscarriage induced before sense and life have begun in the embryo”.⁴ Life and sense are hard to interpret. Aristotle makes the distinction between the nutritive soul, the perceptive soul, and the rational soul. He concludes that the embryo possesses only the nutritive soul, that is, a soul of minimum capacity and development that lacks the characteristics of a fuller existence. Aristotle could thereby allow abortion to take place before the fortieth day of gestation.

Soranos of Ephesus was a Greek obstetrician and gynecologist. He stated that women should take the juice from a chick-pea size of the Silphium plant and drink it with water once per month. This not only “prevented conception but destroyed anything already existing”. Thus,

Figure I. Coins from Cyrene showing the plant Silphium.
Silphium, which only grew on the shores of Cyrene was both a contraceptive and an abortifacient. It became extinct due to over harvesting. Silphium was so important to the Cyrene economy that it appeared on many coins.

Closely related to Silphium is the species Ferula (Fenel) which contains Ferujol. Ferujol has been tested and can prevent pregnancies in rats. Soranus also recommended jumping up and down with knees bent back so that the heels touched the buttocks. If done repeatedly this would induce abortion. He called this the Lacedaemonian leap.

Hippocrates is often interpreted as having had strong views against abortion and for including these views in the Hippocratic oath. There are, however, different translations of the oath. Some say that the oath only forbids the use of pessaries (vaginal suppositories) to induce abortion. Modern scholarship suggests that pessaries were banned because they were reported to cause vaginal ulcers. Others suggest that Hippocrates advised against all dangerous methods for abortion.5

In Asia massage abortion is depicted in Angkor Wat, Cambodia, 1150 AD. Massage abortion usually took place from gestational week 12 to 20. The legs of the supine woman were raised and the uterus compressed against the symphysis and the spine and pounded upon until miscarriage was induced. It is still practiced in Burma, Thailand, Malaysia, the Philippines, and Indonesia.6

1.1.2 Early Christianity

In early Christianity the views on abortion were not always clear. There are writings to support that all abortion was wrong and punishable such as the Didache in which it is stated “do not murder a child by abortion or kill a newborn infant”7. However, there are also writings to support that abortion was possible before the fetus had acquired human form or a soul. Abortion could also be performed to save a woman’s life. The clergy often wrote down local customs and beliefs and these frequently contained knowledge on abortifacient herbs and methods for termination of pregnancy.

1.1.3 Islam and abortion

The holy Quran does not mention abortion. However, it mentions the development of the fetus and upholds the sanctity of human life. It also states “And do not kill your (born or unborn) children for fear of poverty: We give them sustenance and yourselves (too): surely to kill them is a great wrong”.8 According to the Quran the fetus is first “a drop” which develops into “a clot of blood” which assumes “the shape of a small tissue”. It then “develops into bones” which are in turn “covered with flesh”. At this point God makes it another creation, ie a human being with a soul (Ruh). A narrative of
the prophet Mohammed limits the lasting of the “drop”, “clot” and “tissue” stages to 40 days each. Thus abortion could be said to be allowed for the first 120 days of pregnancy. However, with access to ultrasound and modern embryology many Muslims interpret the Quran to allow abortion before the fetus has a heartbeat (often interpreted as 40 days gestation). The exact time at which “God makes it another creation” remains a topic for debate in Islam. However, if the life of the mother is at risk, Islam values the life of the mother and abortion is allowed.

1.1.4 Christianity after 1000 AD

In English literature the idea of “the quickening” was established by Henry de Bracton (1210-1268). Quickening means fetal movement and the idea that the fetus could be aborted before the quickening established a tolerant way of looking at abortion. It was firmly part of English common law at the end of the 13th century. Abortion before the quickening was legal, whereas after the quickening it was a misdemeanor. If the baby was born alive it was homicide.

1.1.5 Catholicism and abortion

In the catechism of the Catholic Church it is stated that “Human life must be respected and protected absolutely from the moment of conception”. From the first moment of its existence, a human being must be recognized as having the rights of a person—among which is the inviolable right of every innocent being to life”. Although the Bible does not explicitly mention abortion the catechism cites the Bible: “Before I formed you in the womb I knew you, and before you were born I consecrated you” (Jer 1:5; cf. Job10:8-12). The catechism states that “Since the first century the Church has affirmed the moral evil of every procured abortion”. This teaching has not changed and remains unchangeable. Direct abortion, that is to say, abortion willed either as an end or a means, is gravely contrary to the moral law: “You shall not kill the embryo by abortion and shall not cause the newborn to perish” (The Didache).

To this day the Catholic Church remains ardently opposed to abortion and contraception. Interestingly the major researcher behind the first clinical trials of the contraceptive pill was the Catholic gynecologist John Rock. As there were no effective contraceptive methods before the contraceptive pill the Catholic Church had no official view on contraception before this time.

However, there is evidence to show that the Catholic followers do not always agree with the position of the Catholic Church. In the USA 28% of women obtaining an abortion identify themselves as Catholic (Guttmacher institute official statistics). Thus catholic followers are overrepresented in abortion statistics as only 22% of the population of the USA is Catholic.

The catechism of the Catholic Church further states that: “Formal cooperation in an abortion constitutes a grave offense. The Church attaches the canonical penalty of excommunication to this crime against human life. The Church does not thereby intend to restrict the scope of mercy. Rather, she makes clear the gravity of the crime committed, the irreparable harm done to the innocent who is put to death, as well as to the parents and the whole of society.”

3
In practice, this resistance to contraception and abortion limits the freedom of charities affiliated with the Catholic Church in providing family planning services in countries where childbirth can be a life threatening endeavour.

1.1.6 Buddhism and abortion

There are no written references concerning abortion in Buddhism. The Dalai Lama has taken an active stand for birth control and has spoken that “abortion, from a Buddhist viewpoint, is an act of killing and is negative, generally speaking. But it depends on the circumstances. If the unborn child will be retarded or if the birth will create serious problems for the parents, these are cases where there can be an exception.”

1.1.7 18th and 19th century laws on abortion

1.1.7.1 Great Britain

During the 18th and 19th century the abortion laws became more restrictive and detailed as to what was to be punished and how. Edward Coke in his Institutes of the Laws of England (1803) stated that after the quickening the abortion was a great misprision (meaning something that was not supposed to be done). If the child was born alive it was murder. Abortion penalties varied greatly. Later during the 19th century the death penalty for abortions after the quickening was abolished and homicide was only used for children “born alive”. However, using drugs or instruments to procure abortion became illegal. In Ireland and Northern Ireland the Offenses against the Person Act of 1861 is still the basis for the ban on abortions.

1.1.7.2 United States of America

The English common law with the idea of pre (legal) and post quickening (illegal) abortion was adopted into the United States law. In the United States there was a rapid movement towards banning abortion in the early 19th century with Connecticut imposing sanctions on apothecaries who sold potions for inducing abortions. In 1829 New York passed a law making post quickening abortions illegal. By 1900 abortion was illegal in every state but provisions existed in some states for performing abortions under certain circumstances.

In the Roe vs. Wade case, which challenged the ban on abortions, the supreme court of the United States points out that historically under English common law the unborn have never been recognized as persons in the whole sense and abortion can therefore never be seen as murder. However, though there is access to legal abortion according to the law they can be hard to come by as neither public nor private health providers are forced to perform abortions.
1.1.8 Abortion in Sweden

The earliest law in Sweden mentioning abortion is from the 13th century (Västgötalagen). It contains the felony “bälgmord”, “murder in the belly”. It was not equaled to murder. The punishment consisted of paying a fine. In the law from 1734 abortion was punishable but considered a lesser offense if the child had not “come alive”. If accused, the woman had to produce several other women as witnesses to testify that she was innocent. If a woman was falsely accused, the accuser had to pay a fine. Killing of unwanted children after birth and hiding of pregnancies was common practice. However, murder of a child born alive was ranked into 5 different categories with different penalties depending on the circumstances. Most likely, this was an adjustment to reality.

In the law from 1864 the punishment for abortion was 2-6 years of hard labor. Later the law was changed so the punishment for the woman was milder than for the person providing the abortion. On average 21 women per year were punished due to having had an abortion. Before 1939 approximately 20 000 illegal abortions were performed in Sweden and approximately 75 women died every year as a result of clandestine abortions. The new law in 1939 allowed abortions under certain circumstances such as the health of the mother or for eugenic reasons. In 1946 the law was changed to allow abortion for psycho-social reasons (2 doctors had to sign for the abortion). During the 1960’s a lively debate on the abortion issue took place in Sweden when it also became known that Swedish women travelled to Poland for abortions. The new abortion law from 1974 is the current abortion law in Sweden.

1.1.9 Modern laws on abortion in Europe

As late as 1945 abortion was punishable by death in Austria. Before and during the second world war Hitler changed the German law from allowing abortion in the first trimester to forbidding abortion in Aryan women. After the fall of Hitler both the German countries went back to allowing abortion in the first trimester.

In modern Europe there are several different laws on abortion. They can be divided into abortion on demand, abortion after mandatory waiting period or abortion for physical or mental health reasons which have to be judged by a physician and/or social worker/psychologist. Often a country has a combination depending on the gestational length of the pregnancy. In Malta and Ireland abortions are not permitted under any circumstances. Traditionally northern and eastern Europe have had more liberal laws but laws in eastern Europe are now becoming more restrictive with several countries and most notably Poland imposing a complete ban. In most countries in Europe abortion is generally allowed before 12 weeks gestation with the exceptions being Ireland, Malta and Poland where abortion is illegal.
1.1.10 Current abortion law in Sweden

In Sweden abortion is legal on request by the woman up to 18 weeks gestational length (18 weeks + 0 days). Beyond 18 weeks gestation permission for abortion has to be granted by the National Board of Health and Welfare (Socialstyrelsen). It can only be granted in cases of malformation of the child or for social or health reasons. After 18 weeks gestation the patient has to see a counselor in addition to a gynecologist. There is no fixed upper limit in the abortion law but this is defined by viability of the fetus. Thus, in practice the upper limit today for socioeconomic indications is 22 weeks +0 days. After this “interruption of pregnancy” can be performed for which there is no upper limit. The indication can be fetal or maternal.

1.2 METHODS FOR ABORTION

There are surgical or medical methods for abortion. Surgical abortion involves using instruments to evacuate the uterus. In medical abortion a miscarriage is induced by administration of a drug which induces softening of the cervix, contractions of the uterus and detachment and subsequent expulsion of the pregnancy.

1.2.1 Surgical abortion

One of the first evidences of instruments being used to extract fetuses is from the Christian scholar Tertullian who worked and acted in Carthage. He writes “Accordingly, among surgeons’ tools there is a certain instrument, which is formed with a nicely-adjusted flexible frame for opening the uterus first of all, and keeping it open; it is further furnished with an annular blade. There is also another instrument in the shape of a copper needle or spike, by which the actual death is managed in this furtive robbery of life. Such apparatus was possessed both by Hippocrates, and Asclepiades, and Erasistratus, and Herophilus and Soranus himself, who all knew well enough that a living being had been conceived, and pitied this most luckless infant state, which had first to be put to death, to escape being tortured alive”.14 The instruments were also used to extract fetuses which were impacted and could not be born naturally.

The instruments described above seem much like the instruments used today; the curette and the forceps. The curette was developed in France in 1723 and the word is derived from “curer”, the French word for “to cleanse”. In 1842 it was developed for specific gynecological use. In 1870 the German gynecologist Alfred Hegar developed the Hegar dilator which is used to this day although conical dilators are now recommended. Dilation and curettage became widely practiced in Europe at the end of the 19th century15 and is still used in many countries. Often the procedure is performed using a sharp curette which causes unnecessary harm to the endometrium and carries an unnecessarily high risk of perforation of the uterus and other major complications such as hemorrhage.16
With the advent of caesarian section safety, hysterotomies or sectio parva came into use as an abortion method. It is associated with high mortality and morbidity and should not be used in modern times\textsuperscript{16}.

Vacuum aspiration was developed in the latter part of the 19\textsuperscript{th} century but it never gained popularity. In 1927 it was again described by a Russian physician Bykov. However, it was developed further in China and Japan and use of it increased after a conference in 1968 sponsored by the Association for the Study of abortion. Studies proved that there was lesser blood loss and fewer complications (infections, intrauterine adhesions and perforations) compared to dilation and curettage.\textsuperscript{15}

Today most gynecologist in Europe use vacuum aspiration which is also the recommended method for surgical abortion according to the WHO. Vacuum aspiration can be performed using either an electrical vacuum or manual vacuum. The methods are comparable in efficacy, safety and acceptability.

For second trimester abortion Dilation and Evacuation is used in many countries such as Great Britain, USA, the Netherlands and Spain whereas in the Nordic countries it is not used at all. In Dilation and Evacuation the cervix is heavily primed using prostaglandin analogues or osmotic dilators such as Laminaria or Dilapan\textsuperscript{®}. Thereafter, the cervix is dilated and the amniotic sac is opened. In some protocols the umbilical cord is tied off or fetal demise is otherwise induced. The head of the fetus is captured using a forceps and the fetus is extracted in its entirety. The placenta is removed using a curette. There are no comparative studies between Dilation and evacuation and modern methods for medical abortion in the second trimester (Pubmed search).\textsuperscript{17}

\subsection*{1.2.2 Medical abortion}

Hypertonic saline was becoming widely used during the 1960\textsuperscript{'s} and was the first truly effective method for medical termination of pregnancy. A needle punctured the abdomen of the pregnant woman, some amniotic fluid was aspirated and 150-250 ml of 20\% saline solution was injected into the amniotic sac. Due to need for intra amniotic injections this could usually not be done before gestational week 15. Most women aborted within 24-36 hours. Complication included hypernatremia, coagulation disorders, hemorrhage and infection.

In the 1970\textsuperscript{'s} studies on intra and extra amniotic injection of prostaglandins showed it to be effective and with lesser complications and shorter induction to abortion interval. Side effects were common and included diarrhea and vomiting. Serious complications did occur and included bronchospasm, hypotension and bradycardia in addition to hemorrhage and infection. Urea was also tried alone or in combination with the prostaglandins.
Rivanol® (Ethacridine lactate) came into use in the 1970’s. It was an oily irritant that was injected extra amniotically through a Foley catheter. 10ml per week of gestational length was used with a maximum of 150ml being injected. Often an addition of oxytocin was used. Temperature elevation was common but there were no deaths or septicemias. Rivanol® is still used in China, India and Eastern Europe to this day.

The prostaglandins soon came to overshadow the other treatments due to their efficacy. Many different prostaglandins have been examined in abortion. In addition, all possible routes of administration have since been tried in addition to the above mentioned routes. These include intramuscular, intravenous, vaginal, oral, buccal and sublingual administration.

1.2.3 Modern methods for medical abortion

The true breakthrough in medical abortion came after the discovery that a drug, RU 486 or mifepristone, could be combined with prostaglandins for increased efficacy. Mifepristone is a selective progesterone receptor antagonist. Progesterone is produced by the corpus luteum. The importance of the corpus luteum in maintenance of pregnancy was first shown by Csapo et al. Mifepristone blocked the effect of the progesterone produced by the corpus luteum medically by binding with high affinity to the progesterone receptor. Disappointingly, the dose finding studies showed that mifepristone was not an effective abortifacient in itself. It induced abortion in only 60-80% of women when used alone. However, Bygdeman and collaborators showed that when Mifepristone was taken before a prostaglandin the effect of the prostaglandin was potentiated and uterine contractions became more pronounced. This became the basis for future development of medical abortion. Research since then has focused on the dose of mifepristone, the interval between mifepristone and the prostaglandin, the type of prostaglandin, the dose of the prostaglandin and the administration route of the prostaglandin.

![Classic polygraph curve of Swahn and Bygdeman showing increased effect of prostaglandin (PG) on uterine contractions following administration of mifepristone (RU-486).](image-url)
Misoprostol is the currently most common prostaglandin analogue used in abortion. It was originally developed for protection of the gastric mucosa. The tablets are developed for oral use but they are now used for oral, sublingual, buccal and vaginal administration.

For early abortion before 9 weeks and 0 days the most effective regimen to this day is 200mg mifepristone followed 24-48 hours later by 0,8 mg of the prostaglandin analogue misoprostol taken vaginally. If no bleeding ensues, another 0,4 mg of misoprostol is taken orally 3 hours after the vaginal misoprostol. This regimen is 96-98% effective. In Sweden in 2010 87,3% of all abortions performed before 9 weeks and 0 gestation were medical abortions.

Recently medical abortion has been developed for gestations between 9 and 13 weeks. The most effective regimen is 200mg mifepristone followed by 0,8 mg vaginal misoprostol 36-48 hours later. Misoprostol 0,4 mg is then taken orally or sublingually every 3 hours, up to 5 doses, until abortion is complete. The method is 96% effective. In Sweden this method is still being introduced as an alternative to vacuum aspiration. It is not available in all hospitals.

For second trimester abortions the same regimen is used. If not successful the procedure is repeated. If no abortion ensues the cervix can be mechanically dilated and the membranes broken. Oxytocin infusion may be used in addition to misoprostol. For abortion in the second trimester medical abortion is the standard method in Sweden.

1.2.4 Home use of misoprostol

When medical abortion was first introduced providers were anxious to monitor patients closely due to fear of excessive hemorrhage during the expulsion of the pregnancy. However, women expected a “natural” expulsion of the pregnancy much like a miscarriage. Providers quickly realized that these expected excessive hemorrhages did not occur and soon after the implementation of medical abortion two studies on home use of misoprostol up to 49 days gestational length were published. Since then studies have included women up to 63 days gestational length. Efficacy has been shown to be comparable to medical abortion in the clinic and acceptability has been shown to be high before and after 49 days gestation.

Home use of misoprostol became the standard treatment when medical abortion with mifepristone was introduced in the USA in 2000. There are no studies on home use of misoprostol after 63 days gestation (Pubmed search).
In Europe legal requirements are hampering the introduction of home use of misoprostol. In Great Britain, one study was performed on home use of misoprostol which was then deemed illegal. However, as the legal situation was not clear before the study no person involved in the study was prosecuted. Since then studies have been published on the possible acceptability of home administration of misoprostol. In these studies women undergoing conventional medical abortion answered questionnaires about acceptability of the procedure and if they would have welcomed the option of having the abortion at home. These studies showed that women in Great Britain would welcome this choice.

1.2.5 Unsafe abortion

Abortions are generally classified into legal or illegal but most importantly safe and unsafe. The latest statistics from the WHO give reason for concern. The worldwide abortion rate is now approximately 29/1000 women aged 15-44 years. Abortion rates are lower in regions with legal abortion but the most significant factor speaking for legalizing abortion is that maternal mortality from abortion is strictly related to legality which can be shown by an example from Romania. Ceausescu made abortion illegal to increase the birth rate in Romania. Abortion related mortality rose steadily until the legalization of abortion after which it dropped sharply.

Figure VIII: Abortion related mortality in Romania, WHO/European Regional Office: European Health for all Database 2009
For several years there has been a drop in abortion numbers and the number of unsafe abortions. However, the trend of increasing safe abortion numbers has now been broken. In 2008 49% of abortions were unsafe compared to 44% in 1995. Many of these unsafe abortions are surgical abortions performed under unhygienic conditions by untrained providers. This leads to a higher degree of complications such as perforation and septicemia. However, also medical abortion may be unsafe when less effective regimens are used. Often these regimens do not involve use of mifepristone, which is not available in all countries due to its association with abortion, and sometimes also inadequate doses of misoprostol. These regimens may lead to incomplete abortions with hemorrhage or prolonged bleeding and infections.\textsuperscript{36}

1.3 INCREASING ACCESS TO MEDICAL ABORTION

To have a safe surgical abortion you need to find a trained provider. In countries where abortion is illegal these services are difficult to access. Medical abortion has a lower need for trained providers and can therefore increase safety in countries where abortion is illegal.

Increased access to medical abortion can be achieved by lowering the need for resources surrounding the abortion by introducing home administration of misoprostol. However, it can also be achieved by finding new legal drugs for medical abortion, training of midlevel providers in abortion services and increasing the use of internet or telemedicine in abortion.

1.3.1 Finding new legal drugs for medical abortion

Mifepristone is only allowed in 53 countries in the world as shown by this map.

Figure IX: Map of Mifepristone approval. Published by permission of Gynuity.
Other regimens for medical abortion have therefore been developed. However, none of these regimens are as effective as the combined regimen of mifepristone and misoprostol. The search for new drugs to improve medical abortion is complicated. A new drug would surely be outlawed in countries where abortion is illegal. Therefore the search has been directed into investigating if drugs already present on the legal drug market can be used for medical abortion.

1.3.1.1 Misoprostol only

Without pre-treatment with mifepristone the recommended dose of misoprostol for termination of pregnancy before 9 weeks and 0 days gestation is 3 doses of 800 mcg misoprostol 12-hourly. This regimen is 90% effective. However 4-8% of pregnancies are ongoing.\textsuperscript{37} Thus, the efficacy of the treatment is far below the combined treatment with mifepristone and proves that an increased dose of misoprostol cannot compensate for the lack of mifepristone.

1.3.1.2 Tamoxifen

Tamoxifen is an anti-estrogenic drug used primarily in the adjuvant treatment for breast cancer in pre-menopausal women. Although tamoxifen acts as an anti-estrogenic drug in the breast, it may cause proliferation in the endometrium as is well known by clinicians. However, as tamoxifen is anti-estrogenic and estrogen levels are high in pregnancy it has been hypothesized that blocking the effect of estrogen can help induce abortions. Tamoxifen has been examined in medical abortion. A regimen with 40mg of tamoxifen followed by 800 mcg misoprostol vaginally 2-3 days later resulted in 85.7% complete abortions.\textsuperscript{38}

1.3.1.3 Methotrexate

Methotrexate is the primary drug used in the industrialized world when mifepristone is not available. It is currently used to induce abortion mainly in Canada. However, it was used extensively in the USA before mifepristone was allowed.

Methotrexate is an anti-metabolite and acts by blocking folate. It is currently used for treatment of malignancies and autoimmune disease. In gynecology it is used for treatment of ectopic pregnancies. In abortion the first study came in 1993.\textsuperscript{39} It has been shown that the most effective regimen is 50 mg/m2 intramuscularly or orally followed by 800 mcg vaginal misoprostol 5-7 days later. Efficacy using this regimen is approximately 90%.\textsuperscript{40} If the dose of misoprostol is increased the time to abortion is shorter but total efficacy is not increased.\textsuperscript{41} The major downside of using methotrexate is the long waiting period between methotrexate and the misoprostol treatment. Methotrexate use is not recommended by the WHO.
1.3.1.4 Letrozole

Letrozole is an aromatase inhibitor. It effectively lowers estrogen levels in all places where synthesis occurs. It inhibits the conversion of androstenedione into estrone and the conversion of testosterone into estradiol.\textsuperscript{42, 43} Letrozole acts differently from Tamoxifen in that it does not compete for the estrogen receptor but instead inhibits synthesis of estrogen (see below).

Letrozole is currently used as adjuvant treatment for breast cancer in post-menopausal women. In pre-menopausal women the reduction of estrogen causes superovulation as the lowered levels of estrogen cause a rise in FSH by a negative feedback loop. Letrozole is therefore used in ovulation induction. It has an advantage over clomifen citrate in that its half-life is short. It therefore does not affect endometrial thickness as negatively as clomifen citrate. Letrozole is also used as an adjuvant in in vitro fertilization treatment in combination with a GnRH-antagonist.

Letrozole has recently been investigated in medical abortion. The project has been part of the WHO-CCR in human reproduction’s special programme’s strategy aimed at finding improved regimens for medical termination of pregnancy. So far four studies aimed at investigating letrozole in medical abortion have been published and letrozole seems to be a promising alternative to mifepristone in countries where mifepristone is not available.

Figure X: Steroid hormone synthesis pathways. Red markers indicate where letrozole acts.
The first study published on letrozole in medical abortion was a pilot study from our collaborators in Hong Kong. In Hong Kong, mifepristone may only be used in scientific studies and is not generally approved. In this study, it was shown that letrozole 7.5 mg given daily for 2 days and then followed by 800 mcg of vaginal misoprostol induced complete abortion in 80% of patients. In this study, no second dose of misoprostol was offered.

In the second study from the same group in Hong Kong, the dose of letrozole was increased to 10 mg daily for 3 days prior to misoprostol administration. Again, no second dose of misoprostol was offered. The trial included 168 women who were randomized to either treatment or controls receiving placebo for 3 days and then misoprostol. The complete abortion rate in the treatment group was 86.8% compared with 72.6% in the control group.

In the third clinical study from Hong Kong on letrozole in abortion, the pre-treatment with letrozole was extended to 7 days. The overall complete abortion rate increased to 95%. The abortion rate was higher for lower gestations. It has not yet been investigated if adding a second dose of 400 mcg oral misoprostol, as is now done in mifepristone protocols, will increase efficacy.

The fourth study on letrozole in abortion is included in this thesis.

1.3.2 Involvement of midlevel providers in medical abortion

In many countries, the access to physicians is limited. Specially trained midlevel providers can often perform services generally performed by physicians. This concept has been tried in many settings such as midlevel providers performing caesarean sections in countries where there is a lack of trained gynecologists.

Midlevel providers who supply post abortion care including manual vacuum aspiration for incomplete abortion have been shown to be safe and effective. In countries such as South Africa, India, Bangladesh, and Nepal, midlevel providers supply medication and information and thereby perform medical abortions. Medical abortion provided by midlevel providers in a low resource setting was recently evaluated in Nepal and it was found to be safe and effective. In some countries, midlevel providers also perform primary vacuum aspiration for surgical abortion and this has been shown to be equally effective as vacuum aspiration performed by physicians. The gestational length of the pregnancy in a low resource setting is determined by the date of the last menstrual period and pelvic exams. Ultrasound and pregnancy tests are rarely performed.

In high resource settings, abortion is usually provided after the patient has had an ultrasound determining the gestational length. This is provided by a trained physician. However, access to appointments for ultrasound may in fact increase the waiting time to have an abortion. There is therefore a current discussion on training midlevel providers to perform ultrasounds and thereby increase access to medical abortion also in developed countries.
1.3.3 Use of internet and telemedicine in medical abortion

There is currently one provider of medical abortion through tele- and internet medicine. The service is named Women on Web (www.womenonweb.com) and was founded by general practitioner Rebecca Gomperts. Rebecca Gomperts has now entered PhD-studies at Karolinska Institutet with a project designed to scientifically evaluate the services provided.

Women on web provides advice in several languages and offers on-line consultations with medical staff. Women are encouraged to have an ultrasound before the abortion but it is not required. A donation to the service is encouraged but not mandatory. A package containing 200mg Mifepristone and six tablets 200 mcg misoprostol is sent by mail to the woman who performs the abortion herself. According to the instructions provided women are informed to take the misoprostol sublingually for fear of remnants of vaginal tablets as proof of self-induced abortion if the woman seeks medical advice in her country. To be able to evaluate the services provided women are encouraged to fill in follow-up questionnaires. Based on these questionnaires the success rate is comparable to traditional medical abortion but if the woman seeks medical attention after the abortion the rate of surgical intervention varies depending on which country the woman lives in.\textsuperscript{50, 51}

Fig IX Part of Women on web start page

Fig XII Cytotec placed under tongue
2 AIMS OF THE STUDY

The overall aim of this thesis was to investigate methods to increase access to early medical abortion.

The specific objectives were to:

- assess efficacy, feasibility, and acceptability of home use of vaginal misoprostol for medical termination of pregnancy at 50 to 63 days compared with gestation of below 50 days among women who chose to administer misoprostol at home.

- assess significant factors which affect acceptability of medical abortion with home administration of misoprostol.

- to investigate if letrozole, a drug newly introduced in medical abortion research, potentiates the uterine contractility induced by misoprostol.

- assess efficacy, safety and acceptability of task shifting from gynecologists to nurse midwives in medical abortion in a high resource setting where vaginal ultrasound is part of the protocol.
3 MATERIAL AND METHODS

3.1 STUDY SUBJECTS

3.1.1 Study 1 and 2- Home use of misoprostol
For the first two studies we recruited healthy women requesting home administration of misoprostol for termination of early pregnancy. Gestational age was up to and including 63 days. Patients were included in the study if they had not contraindication for medical termination and if they were willing to participate. Additional inclusion criteria were being above 18 years of age, living within one hour of the hospital and being able to understand spoken and written Swedish or English. The exclusion criteria were abnormal pregnancy or a contraindication to mifepristone or misoprostol.

In addition all women were screened for Chlamydia trachomatis and bacterial vaginosis according to clinical routine. If patients were found to have an infection treatment was initiated with doxycycline and metronidazole respectively.

3.1.2 Study 3- letrozole and uterine contractility
Patients seeking surgical termination of pregnancy were recruited for this study. Due to the insertion of an intrauterine pressure catheter only parous women were considered for this study. The inclusion criteria were previous vaginal birth, general good health, no ongoing medication and a normal intrauterine pregnancy with gestational age ranging from 7 to 12 weeks.

Exclusion criteria were insufficient knowledge of the Swedish or English language or any contraindication to letrozole or misoprostol.

3.1.3 Study 4- midlevel provision of medical abortion
Patients over 18 years of age seeking medical termination of pregnancy were recruited. Women were eligible if they were in good general health with no on-going medication for chronic disease and had a pregnancy of no more than 63 days gestational length. Women were randomized prior to examination and thus women had to be excluded after examination and randomization.

Women were excluded if they had suspected ectopic pregnancy, chose surgical abortion after counseling, chose to postpone the abortion to the second trimester or had too advanced gestational age according to ultrasound. In addition patients with undiagnosed adnexal mass or any contraindication to medical abortion were excluded. All patients were screened for Chlamydia trachomatis and bacterial vaginosis according to clinical routine. If patients were found to have an infection treatment was initiated with doxycycline and metronidazole respectively.
3.2 SAMPLE SIZE CALCULATION

3.2.1 Study 1 and 2- home use of misoprostol

Sample size calculation for study 1 was based on women’s satisfaction with home administration of misoprostol below 50 days gestation. In a previous study from our group, 98% of women reported to be satisfied with their choice of home-use of misoprostol. If we assumed that 90% of women with a gestation between 50-63 days were to report that they were satisfied with the method, 200 women in each group (below 50 days and between 50-63 days of gestation) would give a power of 92.4% to detect a difference in satisfaction between the groups.

Study 2 used the same material as study 1. No new power calculation was done.

3.2.2 Study 3- letrozole and uterine contractility

Based on previous data, uterine contraction measured as Montevideo Units following 400 mcg misoprostol was 46.3± 9.6 mmHg (mean ± standard deviation). Assuming that the combination of letrozole and misoprostol would increase the uterine contractions by 25%, 8 subjects in each arm would be required to detect any difference at 5% significance level (α=0.05) with a power of 80%.

3.2.3 Study 4- midlevel provision of medical abortion

This study was designed as a randomized two-sided equivalence trial with efficacy defined as successful completion of abortion without the need for vacuum aspiration as primary outcome. An overall efficacy rate in both groups was estimated at 95%. The clinically relevant margin of equivalence was set at 5%. A sample size of 400 women in each arm would be sufficient to demonstrate equivalence with 80% power with 95% confidence interval (α=0.05). To allow for women who for various reasons chose or could not have the medical abortion and to allow loss to follow up a total of 1180 women were recruited.

3.3 STUDY TREATMENT

3.3.1 Study 1 and 2- Home use of misoprostol

Following appropriate counseling by a gynecologist and midwife each patient received 200mg mifepristone (Mifegyne®, Exelgyn, Paris, France) to be swallowed in the presence of a midwife according to Swedish law. Patients received oral and written information and were instructed to insert 4 tablets of misoprostol (Cytotec®, Pfizer, New York, USA) vaginally 36-48 hours after initial intake of mifepristone.

Women were instructed to take prophylactic pain medication with oral diclofenac (100mg) and paracetamol (500mg) plus dihydrocodein (10mg). Women received additional pain medication to take as needed. This consisted of paracetamol 500mg plus dihydrocodein 10mg (Citodon®, Astra Zeneca, Stockholm, Sweden). They were instructed to take 1-2 tablets four to six hourly if required.
3.3.2 Study 3- letrozole and uterine contractility

Women were randomized to pretreatment with letrozole 7,5mg (Femar®, Novartis AB, Täby, Sweden) daily for 3 days or to no pretreatment. In total 16 women were randomized. All patients came to the clinic on the morning of the surgical abortion and had an ultrasound after which the intrauterine pressure catheter (Millar Microptips PC 771; Millar Instruments Inc., USA) was inserted so that the tip was placed 1-2 cm from the uterine fundus. After an initial 30 minutes baseline recording 400mcg misoprostol was inserted vaginally by the responsible investigator. Uterine pressure was measured for 3.5 hours (polygraph and software from Medtronics, Stockholm, Sweden). After the recording the pregnancy was terminated surgically through vacuum aspiration after dilatation with Hegar instruments.

3.3.3 Study 4- midlevel provision of medical abortion

Women were informed about the study at the first contact with the family planning unit. If they were eligible and willing to participate they were randomized to examination and counseling by a midwife or gynecologist respectively. Follow up was by midwife according to clinical routine.

Women swallowed 200mg Mifepristone (Mifegyne®, Nordic Drugs, Sweden) in the presence of a nurse according to Swedish law. Women had a free choice to take 800 mcg of vaginal misoprostol (Cytotec®, Pfizer, Sweden) at home or in the clinic. If no bleeding occurred within 3 hours women were instructed to take 400mcg misoprostol orally. Women were instructed to take prophylactic pain treatment at the time of vaginal misoprostol administration consisting of 1g paracetamol (Alvedon® 1g, Astra Zeneca, Sweden) and 100mg diclofenac (Voltaren®, Novartis, Sweden). Additional pain treatment was supplied for patients choosing home administration of misoprostol. Patients choosing clinic administration had access to pain medication supplied by a midwife as needed.

3.4 EVALUATED PARAMETERS AND STATISTICAL METHODS

3.4.1 Evaluated parameters Study 1 and 2- home use of misoprostol

Women filled in questionnaires and symptoms diaries which were previously used in research. Questionnaires were filled in prior to, during treatment and at follow up. The questionnaire prior to the termination included questions concerning health and outcome of previous pregnancies. During and after treatment women also filled in daily symptom diaries. In the diaries women recorded use of extra analgesia and intensity of pain at each intake. Intensity of bleeding was reported in relation to normal menstrual bleeding. After the treatment women were asked to fill in a questionnaire about acceptability of the procedure. They were asked to rank if they perceived that they had received enough information concerning the treatment (1=complete satisfaction) or not (5=complete dissatisfaction). They were asked to indicate on a scale from 1 to 5 if they felt calm during the treatment and at follow-up. Women were asked to state if the termination procedure overall was as expected, less dramatic or worse than expected. In
addition they were asked to state their preferred choice, home or hospital treatment, were they to have another medical termination.

One part of the questionnaire was directed to the partner/friend present during the abortion. The partner/friend was asked to evaluate on a scale from 1 to 5 if he/she was content with their partners/friends choice of termination method. The partner/friend was also asked to rate on a scale from 1 to 5 if they felt they could help or not during the termination process. In addition patients stated if they had visited the emergency room or had had any other complication which they believed related to the treatment.

3.4.2 Statistics study 1- comparison of home use of misoprostol before and after 50 days gestation

For Study 1 we evaluated if the acceptability of the procedure was correlated to being above 49 days gestation or below 50 days gestation.

Continuous variables with a normal distribution were presented as means with standard deviations and comparisons were made by using the independent t test. Non-parametric continuous variables were presented as medians and ranges, assessment for normality and comparisons were made using the Mann–Whitney U test. Comparisons between the two groups were made using the χ² test or Fisher’s exact test as appropriate for independent nominal data. Differences were regarded as statistically significant if P<0.05.

3.4.3 Statistics study 2- assessment of significant factors for acceptability of home use of misoprostol

For Study 2 a logistic regression analysis was performed in addition to the statistics above. This necessitated the recoding of several variables in order to fit the regression model. Acceptability of the procedure was correlated to all factors which were considered to possibly affect acceptability.

A logistic regression analysis was performed for overall acceptability of the procedure where women had to state their preferred choice were they ever to have a medical termination of pregnancy again. A second logistic regression analysis was performed for experience in relation to expectation.

Continuous variables such as age, were recoded into categorical variables. Ordinal variables such as “sense of calmness and safety” were recoded into dichotomous variables with values 1, 2 and 3 indicating “sense of calmness and safety” and values 4 and 5 indicating “no sense of calmness and safety”. Factors affecting acceptability were evaluated using the backward elimination method for logistic regression. Thus, a ratio of more than 10 to 1 to the least common outcome was maintained.
Dependent variables were acceptability with preference of home use of misoprostol or clinic use of misoprostol and the experience of the abortion in relation to expectation. Independent variables were age, gestational length, reproductive history, extra analgesia requirement; sense of calmness and safety, having a partner/friend present and the outcome of treatment (screened with low sensitivity urine-hCG). Missing values were not included in the analyses for neither dependent nor independent variables.

Results are presented as adjusted odds ratios (OR) with 95% confidence intervals. Results were considered significant if $p \leq 0.05$. Goodness of fit was determined using the Hosmer-Lemeshow test. No factors in the final regression analysis were judged to be closely related. No interaction was found between age and parity. Statistical analysis was carried out using PASW Statistics 18 (IBM SPSS Statistics, Chicago, Illinois, US).

3.4.4 Evaluated parameters Study 3- letrozole and uterine contractility

After the patient came to the clinic on the morning of her scheduled termination, an intrauterine pressure catheter was inserted extra-amniotically and intrauterine pressure was recorded. The baseline was measured in mmHg. Contractions were measured in Montevideo Units. Montevideo Units are defined as the increase in mmHg for all significant contractions during 10 minutes. Any contraction with an increase in pressure above 5 mmHg is considered significant.

All women handed in daily symptom diaries. The diaries contained information on side effects. The patient chart was consulted for demographic characteristics.

3.4.5 Statistics study 3- letrozole and uterine contractility

For comparison of the groups with regard to demographic characteristics and side effects the Mann-Whitney U-test and the Fischer’s exact test were used as appropriate. Repeated measures analysis of variance (ANOVA) with comparison of the two groups was made for both tonus (mmHg) and contractions (Montevideo units). All statistical calculations were made using IBM SPSS Statistics version 18 (IBM Corporation, Somers, NY, USA).

3.4.6 Evaluated parameters study 4- midlevel provision of medical abortion

Women filled in questionnaires and symptoms diaries which were previously used in research. Questionnaires were filled in prior to, during treatment and at follow up. The questionnaire prior to the termination included questions concerning health and outcome of previous pregnancies.
After the treatment women were asked to fill in a questionnaire about the acceptability of the procedure. They were asked to rank if they perceived that they had received enough information concerning the treatment (1=complete satisfaction) or not (5=complete dissatisfaction). They were asked to indicate on a scale from 1 to 5 if they felt calm during the treatment and at follow-up and if they had had a partner/friend present during the abortion. In addition they were asked to state their preferred choice, midwife or gynecologist or indifference concerning who they wished to perform the examination and counseling, were they to have another medical termination. Data on contraceptive method before the abortion and after counseling was recorded. In addition patients stated if they had visited the emergency room or had had any other complication which they believed related to the treatment.

3.4.7 Statistics study 4- midlevel provision of medical abortion

Non-parametric continuous variables were presented as medians and ranges. Assessment for normality was performed and if the variable was skewed comparisons were made using the Mann–Whitney \( U \) test. Comparisons of normally distributed continuous variables were made using the Student’s t-test. Comparisons between the two groups regarding categorical data were made using the \( \chi^2 \) test for independent nominal data. Differences were regarded as statistically significant if \( P<0.05 \). These analyses were made using IBM SPSS version 20 (IBM Corporation, Somers, NY, USA). To assess equivalence between the groups a generalized estimating equation was used with method of physician or midlevel provision as a fixed factor and the individual provider as a random effect. This analysis was done in the PROC GENMOD procedure of SAS version 9.3 (SAS Institute, Gary, NC, USA). Analysis was per protocol according to recommendation and followed the Consort guidelines for equivalence trials.
4 RESULTS, SIGNIFICANCE AND DISCUSSION

4.1 STUDY 1

The results of Study 1 show that there were no significant demographic differences between women seeking termination above or below 50 days gestational length. The groups were equal in size (203 women below 50 days and 192 women above 49 days). Efficacy in both treatment groups was high (98% and 96.6% respectively). Overall acceptability was high with 72.4% of women stating they would prefer home administration of misoprostol were they to have another medical termination of pregnancy in the future.

Gestational length above 50 days was not associated with a worse experience of the abortion in relation to expectation (p=0.30). There was no significant difference between the two groups concerning preference for home or hospital administration of misoprostol in case of a future termination of pregnancy (p=0.097).

Study 1 warranted its own publication due to the significance of the results and the importance for countries where home administration above 49 days gestation is currently not allowed, home administration is currently not available or where it is currently being implemented. Study 1 is reassuring in that women with gestational length above 49 days find home administration of misoprostol highly acceptable.

Many countries have introduced limitations on the gestational length of pregnancies for home administration of misoprostol. Often home administration is not allowed after 49 or 56 days gestation. The limitation is often set because of fear of pain for the women which could lead to lower acceptability. This in turn is based on earlier studies on medical abortion with clinic administration of misoprostol in which it was found that women with a more progressed gestational length had more pain.54

There are no published data on home administration of misoprostol for termination of pregnancy beyond 63 days according to ultrasound or last menstrual period.

4.2 STUDY 2

In Study 1 we found that gestational length was not associated with the acceptability of the procedure. The next step was to proceed to find out which factors were in fact associated with the acceptability.

We found that factors in the multivariate logistic regression analysis for preferred choice of future abortion method with a significant influence on acceptability were having a positive u-hCG at follow-up (negative influence, OR 3.81, CI 1.618-9.068, p=0.002) and having a partner/friend present (positive influence, OR 0.221, CI 0.61-0.799, p=0.021).
The final model for experience in relation to expectation in which all factors were significant included parity (positive influence, OR 2.498, CI 1.54-4.608, p= 0.003), having a positive u-hCG at follow-up (negative influence, OR 10.381, CI 4.939-21.823, p<0.001) and having a sense of calmness and safety after administration of misoprostol (positive influence, OR 3.283, CI 1.519-7.095, p= 0.003).

Women with a positive u-hcg at follow-up had significantly lower acceptability ratings than those with a negative u-hcg at follow-up. In this study the follow-up was at 2 weeks post abortion. At 2 weeks after the abortion it is possible that the result of the u-hcg is positive although the abortion is complete. Most of the women with a positive u-hcg at follow-up in this study had a complete abortion when examined with ultrasound. Follow-up after medical termination of pregnancy is now usually at 3-4 weeks post abortion which leads to fewer “false positive” results. However, the risk with a later follow-up is always that continuing pregnancies are not found until late. The postponing of follow-up should always be accompanied with thorough information to seek advice if the woman suspects a continuing pregnancy due to symptoms.

Having a partner/friend present during the home administration of misoprostol was significantly associated with a higher acceptability of the procedure. A partner/friend may indicate a social support for the pregnancy. Women who are not able to have a partner/friend present during the abortion may benefit from clinic administration of misoprostol with present staff who can support her during the termination process. Women who have home administration of misoprostol should be advised to have a partner/friend present.

When we examined the experience of the procedure in relation to expectation we found that being parous affected the experience positively although it did not affect overall acceptability. These women have previously experienced child birth and may have a more realistic outlook on the possible pain and bleeding of the procedure. Producing realistic expectations in nulliparous women is therefore important.

Women who felt calm after the administration of misoprostol rated the experience of the procedure more positively in relation to experience than women who did not feel calm. Women should be encouraged to call the number provided if they feel worried after the administration of misoprostol. The staff of the clinic can then offer support via the telephone or advice the woman to come to the clinic for support.

The written and oral information we provide women with before the home administration of misoprostol is evidently very important but there is little evidence on what information should be given. The emphasis in the information is often on the pills and how they should be taken. This study shows that emphasis should also be on the experience of pain and the importance of support during the procedure. We should advice women to have a partner/friend present and be explicit on the details of the procedure. We should encourage women to use the telephone number provided and be wary of signs of distress.
4.3 STUDY 3

In study 3 we investigated if letrozole potentiates the uterine contractions caused by misoprostol.

There were no significant differences between the groups concerning demographic characteristics or gestational length. Side effects included nausea, vomiting, lower abdominal pain, headache and diarrhea but did not differ between the groups.

None of the women aborted prior to surgery. At baseline, prior to administration of misoprostol, the uterine tonus was low and contractions were absent in both groups. Pretreatment with letrozole did not result in increased baseline tonus nor did it induce uterine contractions. A significant effect was observed in both groups with regard to uterine tonus and contractility following administration of misoprostol which has been previously shown and is the basis for treatment with misoprostol for termination of pregnancy. However, when the effect of misoprostol was compared between the two groups no significant difference in uterine tonus was shown (F=0.56, p=0.818). Post hoc test confirmed this finding (Bonferroni 0.818). There was no significant difference between the two groups in time to tonus increase (p=0.243) or in time to maximum tonus (p=0.953). Likewise, the effect on uterine contractions showed no significant difference between the groups (F=0.697, p=0.423, Bonferroni 0.423).

This finding shows that letrozole differs in effect from mifepristone. Mifepristone acts by potentiating the effect of misoprostol on uterine contractility. It has been shown that letrozole increases the number of complete abortion when compared to a misoprostol only regimen. Mifepristone and misoprostol in combination is a highly effective regimen with a need for surgical intervention in 2-5% of patients. However, a number of patients experience prolonged bleeding due to incomplete abortions and a few still need surgical intervention. If letrozole acts as an abortifacient differently from mifepristone it might have an added effect to the present regimen with mifepristone and misoprostol and could potentially increase the number of complete abortions and shorten post abortion bleeding.

In countries where mifepristone is currently not available, medical abortion is less effective which leads to more surgical interventions. It would be beneficial if a drug that is already on the market could be used in combination with misoprostol for termination of pregnancy and thereby give access to a more effective regimen in these countries. Letrozole has the potential of becoming such a drug.
4.4 STUDY 4

In Study 4 we could show that midwives do not have higher rates of complications compared to physicians when they manage the complete medical abortion process.

A total of 1180 women were randomized whereof 597 to counseling by a midwife and 587 to counseling by a physician. Due to reasons listed above 105 women did not complete the treatment. A total of 7 women in the physician group did not receive the allocated treatment. Thus, 1067 women completed treatment whereof 534 in the midwife group and 533 in the physician group. In the midwife group 54 women were lost to follow up compared to 76 women in the physician group (total=130 woman, p=0.038). Analysis was per protocol.

There were no significant demographical differences between the groups.
No significant differences were seen between the groups in the satisfaction with information about the abortion, contraceptive counseling, feeling of calm and safety before, during or after the abortion. Satisfaction rates were high with rates above 92% for all variables in both groups. Furthermore, there were no significant differences in perceived bleeding or pain between the two groups, nor in the experience of the procedure as compared to expectation.

The risk difference for efficacy with provision method as a fixed factor and provider as a random effect was 1.6% with a confidence interval of 0.2-3.0% (p=0.027) which was within the -5% to 5% set margin of equivalence. Therefore, equivalence for the groups for the primary endpoint is established.

Women randomized to physicians were significantly more likely to choose home administration of misoprostol (310/533) compared to women randomized to midwives (266/534, p=0.006). It may be that women felt confidence in the midwife during the consultation and therefore decided to have the abortion in the clinic in the presence of a midwife. This has an economic impact on the clinic as there has to be room to accommodate the patients and staff to oversee the abortion.

Physicians asked for a second opinion in 4% of cases (21/533) whereas midwives consulted physicians in 26% of cases (139/534). The difference is significant (p<0.001). Midwives had certain conditions in which they had to consult a physician, such as twin pregnancies, empty uterus or vaginal bleeding. However, the frequency of consultations for midwives for ultrasound queries due to difficulties in interpretation went down as the study progressed indicating a learning curve.
Midwives spent significantly shorter time (average 42 minutes) on the examination and counseling of the patient compared to physicians (average 60 minutes, p<0.001). In the physician group patients still had to see a midwife to receive medication and practical information. Therefore, a lot of the information is likely to have been duplicated. This has practical and economic implications for the healthcare system. Although midwives spent shorter time on the consultation, patients randomized to midwives were significantly more likely to prefer seeing a midwife again were they to have another abortion. A majority of patients in both groups indicated indifference as to who examined and counseled them.

Among the women available for final analysis a total of 17 (17/962, 2%) patients had to have a vacuum aspiration whereof 5 (5/489, 1%) were in the midwife group and 12 (12/473, 2.5%) in the physician group. The difference did not reach significance (p=0.07). This confirms the high efficacy of medical abortion and is in line with previous studies from Sweden. The most common reason for vacuum aspiration was incomplete abortion with heavy or prolonged bleeding. The overall complication rate was 4.2% for women randomized to midwife (20/473, 41 missing) and 6.5% for women randomized to physician (29/443, 61 missing, p=0.38). There were no serious complications.

Nurse midwives prescribed long acting reversible contraceptives (290/532, 1 missing) to women significantly more often than physicians (241/528, 6 missing, p=0.004). This has implications for the rate of repeat abortion.
5 CONCLUSIONS

Medical abortion with home administration of misoprostol is highly acceptable. There is no significant difference in acceptability dependent on gestational length. Women should be well informed on what to expect during the abortion process and be prepared for the pain and bleeding. A present partner/friend may increase the acceptability of the abortion. Women who cannot have a partner/friend present should be offered clinic administration of misoprostol. If a woman shows distress after the administration of misoprostol she should be offered support via the telephone and offered to come to the clinic for support. Women who have a positive u-hcg after the abortion consider the procedure less acceptable. This may be due to a feeling that the abortion has failed. It is important that the follow up after medical abortion is adequate. The optimal follow up after medical abortion discovers continuing pregnancies but does not lead to unnecessary interventions. The optimal method for follow is a continuous topic for debate and remains to be investigated further.

New methods for medical abortion may increase the access to safer and more effective regimens than the current misoprostol only regimen in countries where mifepristone is not available. Letrozole has been shown to increase the efficacy of misoprostol when used in medical abortion. It may therefore be used as an alternative to mifepristone in countries where mifepristone is not available. Letrozole does not potentiate the effect of misoprostol by increasing uterine contractility or tonus. It thereby acts differently from mifepristone and may potentially increase the efficacy of medical abortion when used in addition to mifepristone and misoprostol. Increasing the efficacy of medical abortion may in turn shorten post-abortion bleeding and increase acceptability. This remains to be investigated.

Task shifting/sharing has been shown to be highly acceptable and safe in caesarian section provision and in provision of surgical abortion and medical abortion in low resource settings. However, task shifting/sharing may also be used in countries where physicians are unwilling to perform abortion provision. Task shifting/sharing of medical abortion provision in a high resource setting where vaginal ultrasound is part of the protocol is equally effective to that provided by physicians. In addition it is safe and highly acceptable to women. Increasing access to medical abortion in high resource setting may be achieved by task shifting/sharing of medical abortion provision from physicians to midlevel providers.

Increased access to medical abortion may be achieved by home use of misoprostol, adding new drugs without previous abortion stigma to misoprostol only regimens and by task shifting medical abortion provision from physicians to midlevel providers in high resource setting.
6 POPULÄRVETENSKAPLIG SAMMANFATTNING

Lagar som reglerar abort har funnits sedan urminnes tider. Lagar har mindre effekt på antalet aborter än på hur och var aborterna utförs. Länder med restriktiva lagar har ofta höga aborttal och hög abortrelaterad sjuklighet och dödlighet. I världen dör 47000 kvinnor varje år på abortrelaterade komplikationer.


letrozol till mifepriston och få ännu bättre utfall på medicinska aborter och även kortare blödningstid. Det behövs mera forskning på detta område.


Denna avhandling visar att det finns utrymme för att på flera sätt öka tillgången till medicinsk abort i världen och därmed ge fler kvinnor tillgång till säkrare och billigare abortvård.
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