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TASK SHIFTING IN THE PROVISION OF MEDICAL ABORTION

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Task shifting in the provision of medical abortion

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Introduction: Unsafe abortion is one of the main causes of maternal mortality. Each year, approximately 21.6 million women worldwide still undergo an unsafe abortion resulting in an estimated 47000 deaths. Currently 39% of the population lives in countries with highly restrictive abortion laws. However also in countries where abortion is legal, obstructive administrative procedures and insufficient services or providers reduce access to safe abortion services. Medical abortion is one of the safest medical procedures, with minimal morbidity and a negligible risk of death. Task shifting may result in increased access to and availability of medical abortion services while maintaining the same quality of care. While task shifting can be done to other healthcare professionals, it can also be done to women themselves with the use of telemedicine.

Material, methods and results:
Study 1 describes the outcome of medical abortions provided via Women on Web, a telemedical abortion service for women with an unwanted pregnancy up to 9 weeks living in countries without safe abortion care. This retrospective study analyzed interactive web-based questionnaires, follow-up forms, emails, and telephone calls from 484 women who received a medical abortion at their home addresses. Sixteen of the 265 (6.0%) women who provided follow-up information reported that they did not use the medication. Of the remaining 249 women who did the medical abortion at home, 13.6% reported having a surgical intervention afterwards and 1.6% reported a continuing pregnancy. After the follow up rate increased from 54.8% to 77.6% of the cases, 12.6% of the women reported they did not take the medication and only 6.8% of the women having the medical abortion at home underwent a surgical intervention afterwards.

Study 2 explored the factors that influence the surgical intervention rate after home medical abortion provided through Women on Web to women with a pregnancy up to 9 weeks. Of the 2323 women who did the medical abortion, 289 (12.4%) received a surgical intervention. High rates were found in Eastern Europe (14.8%), Latin America (14.4%) and Asia/Oceania (11.0%) and low rates in Western Europe (5.8%), the Middle East (4.7%) and Africa (6.1%;

p=0.000). More interventions were carried out when women had a longer gestational age (p=0.000). Women without a surgical intervention reported satisfaction with the treatment more frequently (p=0.000).

Study 3 evaluated the need for and outcome of self-administered medical abortion in Brazil, provided through telemedicine. Of the 370 women used the medicines, 307 women provided follow-up information about the outcome of the medical abortion. Of this group, 207 (67.4%) of the women were up to 9 weeks pregnant, 71 (23.1%) were 10, 11 or 12 weeks pregnant, and 29 (9.5%) of the women were at least 13 weeks pregnant. There was a significant difference in surgical intervention rates after the medical abortion at the different gestations (19.3% at <9 weeks, 15.5% at 10-12 weeks and 44.8% at >13 weeks, p=0.06). However, 42.2% of the women who had received a surgical intervention afterwards did not have any symptoms of a complication.

Study 4 assessed the efficacy, safety and acceptability of midlevel provision of medical abortion in a clinical high resource setting. In total 1180 women eligible for inclusion were recruited and randomized to either a nurse midwife or a gynecologist for counseling, examination including ultrasound and treatment. The provision of medical abortion by midlevel providers proved to be as effective and safe as the medical abortion provided by physicians. The risk difference for efficacy was 1.6%, which falls within the 5% margin that was set for equivalence (p=0.027). Women were significantly more likely to prefer a midwife for the consultation (p<0,001).

Conclusion: The research shows that medical abortion can be safely and effectively provided by midlevel health care providers as well as women themselves through telemedicine. The acceptability and outcome of medical abortion up to 9 weeks of pregnancy is similar when provided by doctors, nurse midwives or administered by women themselves via telemedicine. Surgical intervention rates after the medical abortion provided via telemedicine reflect local medical practices. The risk of surgical intervention and ongoing pregnancy after home medical abortion only tends to increase after 12 weeks of pregnancy.

LIST OF SCIENTIFIC PAPERS

I. Gomperts RJ, Jelinska K, Davies S, Gemzell-Danielsson K, Kleiverda G. Using telemedicine for termination of pregnancy with mifepristone and misoprostol in settings where there is no access to safe services. BJOG 2008 Aug;115(9):1171-5.

II. Gomperts R, Petow SA, Jelinska K, Steen L, Gemzell-Danielsson K, Kleiverda G. Regional differences in surgical intervention following medical termination of pregnancy provided by telemedicine. Acta Obstet Gynecol Scand. 2012 Feb;91(2):226-31.

III. Gomperts R, van der Vleuten K, Jelinska K, da Costa CV, Gemzell-Danielsson K, Kleiverda G. Provision of medical abortion using telemedicine in Brazil. Contraception 2014 Feb;89(2):129-33.

IV. Kopp Kallner H, Gomperts R, Salomonsson E, Johansson M, Marions L, Gemzell Danielsson K. The efficacy, safety, and acceptability of medical abortion provided by midlevel providers or physicians in a high resource setting- a randomized controlled equivalence trial (submitted for publication).

CONTENTS

LIST OF ABBREVIATIONS

D&C	Dilatation and (sharp) Curretage
D&E	Dilatation and Evaculation
EC	Emergency Contraceptives
EUR	Euro
FIGO	The International Federation of Gynaecology and Obstetrics
HCG	Human Chorionic Gonadotropin
LMP	Last Mentrual Period
PPH	Post Partum Heamorrage
UK	United Kingdom
US	United States
USSR	Union of Soviet Socialist Republics
VA	Vacuum Aspiration
WHO	World Health Organisation
WoW	Women on Web

1 INTRODUCTION

1.1 ABORTION WORLDWIDE

Abortions have been available in all cultures since ancient times (1, 2).

Nowadays, an estimated 43.8 million abortions are carried out worldwide each year. About one in five pregnancies ends in an abortion (3).

Each year, approximately 21.6 million women worldwide still undergo an unsafe abortion, resulting in an estimated 47000 deaths, largely among the most vulnerable women, such as poor, unmarried and young women in particular. Apart from the deaths caused by unsafe abortions, another 5 million women per year have to deal with temporary or permanent disabilities and are accompanied by huge financial and social costs to themselves, their families and the health care systems (4, 5).

Goal 5 of the Millennium Development Goals is to reduce the maternal mortality ratio in 25 years by 75% and to achieve universal access to reproductive health care by 2015 (6). Unsafe abortion is one of the main causes of maternal mortality and could be prevented. Complications from unsafe abortion accounted for an estimated 13% of all maternal deaths worldwide (7).

The definition of unsafe abortion by the World Health Organization (WHO) is: 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 standards, or both. Recently, the WHO added the following: “The persons, skills, and medical standards considered safe in the provision of abortion are different for medical and surgical abortion, and also depend on the duration of pregnancy. What is considered “safe” should be interpreted in line with the current WHO technical and policy guidance” (8).

In countries where abortion is permitted on broad legal grounds, it is generally carried out safely. However, in countries where abortion is highly restricted, it is

carried out largely unsafely. Almost all unsafe procedures are carried out in developing countries. Women in the poorest countries are generally most at risk of suffering serious consequences from unsafe abortion (4,5,6,9,10).

1.1.1 Human right to safe Abortion care

As early as 1967 the World Health Assembly identified unsafe abortion as a serious public health problem threatening women in many countries (11).

The World Health Organization's definition of health is: "Health is a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity" (12).

The right to health has been recognized in numerous international human rights treaties, such as: the Universal Declaration of Human Rights: Article 25.1 in 1948; the International Convention on the Elimination of All Forms of Racial Discrimination: Article 5 (e) (iv) in 1965; the International Covenant on Economic, Social and Cultural Rights: Article 12.1 in 1966; the Convention on the Elimination of All Forms of Discrimination against Women: Articles 11 (1) (f), 12 and 14 (2) (b) in 1979; the 1989 Convention on the Rights of the Child: Article 24; the International Convention on the Protection of the Rights of All Migrant Workers and Members of Their Families: Articles 28, 43 (e) and 45 (c) in 1990, and the Convention on the Rights of Persons with Disabilities: Article 25 in 2006 (13).

In 1994, the Program of Action of the International Conference on Population and Development was the first major international agreement to make recommendations to reduce unsafe abortion, by stating the following:

"All governments and relevant intergovernmental and non-governmental organizations are urged to strengthen their commitment to women's health, to deal with the health impact of unsafe abortion as a major public health concern" and "In circumstances where abortion is not against the law, such abortion should be safe. In all cases, women should have access to quality services for the management of complications arising from abortion" (14). In 2009, the United

Nations Human Right Council (UN) accepted a resolution on the recognition of maternal mortality as a violation of human rights (15).

In October 2011, Anand Grover, the UN Special Rapporteur on the Right to Health, submitted a report to the UN General Assembly which stated: “Criminal laws penalizing and restricting induced abortion are the paradigmatic examples of impermissible barriers to the realization of women's right to health and must be eliminated. These laws infringe women's dignity and autonomy by severely restricting decision-making by women in respect of their sexual and reproductive health” (16).

1.2 BARRIERS TO ACCESS SAFE ABORTION SERVICES

1.2.1 Countries where abortion is legal

At the beginning of twentieth century, abortion was illegal almost everywhere. In November 1920, Soviet Russia was the first country to legalize abortion. Although the USSR banned abortions again in 1936, this ban was reversed in 1955. Hungary legalized abortion in 1953, Bulgaria in 1956, and the Czech Republic in 1957. Abortion is now legal in all former USSR countries (including Estonia, Latvia, Lithuania, Kazakhstan, Uzbekistan, Turkmenistan, Azerbaijan, Kyrgyzstan, Tajikistan, Kosovo, Uzbekistan) (17).

Next, several West European countries legalized abortion: namely the UK (1969), Austria (1974), Denmark (1973), Sweden (1974), France (1975), Greece (1978), Italy (1978), the Netherlands (1981), Belgium (1990), Germany (1992), Switzerland (2002), Portugal (2007) and Spain (2009) (18).

The US legalized abortion in 1973.

A number of countries in the South, like Cambodia, Vietnam (1989), Guyana (1995), South Africa (1996), Nepal (2009), Mexico City (2008), Uruguay (2012), and parts of Australia (Capital Territory, Victoria, Tasmania and Western Australia) liberalized their abortion laws (19, 20, 21).

Currently, approximately 40% of the world population is living in 60 countries where abortion is permitted regardless of reason, though there are often limits to the gestational age or other restrictions such as mandatory counseling or waiting periods. As a result, in these countries too, there are often social, economic and health care system-related barriers to the delivery of safe abortion services (22).

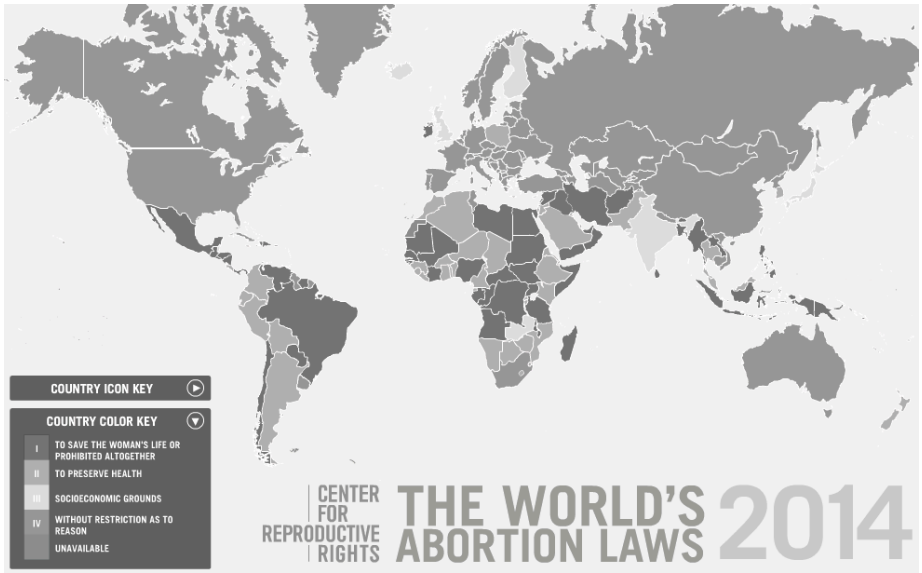

Figure 1: Map by the Center for Reproductive rights

1.2.2 Logistical, financial, administrative, procedural and geographical barriers to access abortion.

Logistical barriers that hinder access to abortion care can be a result of a lack of healthcare providers willing to offer abortion services and a lack of services in rural areas.

In Ghana, there are not sufficient health care professionals willing to provide legal abortion care. In addition, the majority of family planning nurses and obstetricians/gynecologists have a highly- judgmental attitude towards women seeking abortion care (23).

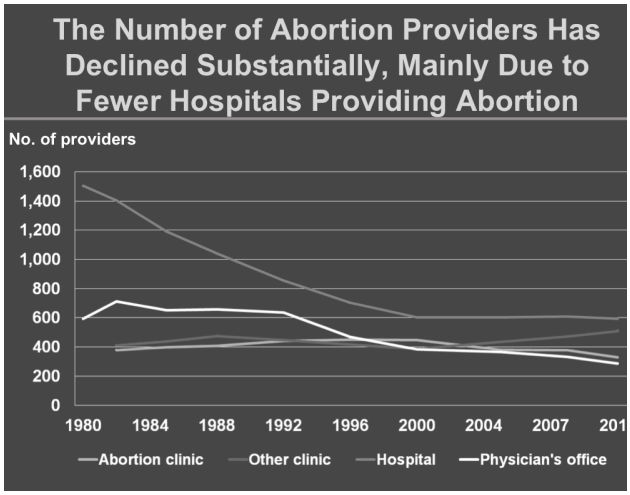

Figure 2. Slide from the presentation *"An overview of abortion in the United States",* by the Guttmacher Institute in February 2014.

In the US 11% of the women are forced to travel 50 to 100 miles in order to have access to abortion services, and another 6 % travel even more than 100 miles. About 7% of the women had to cross state borders to have access to abortion care. Among women living in rural areas, 31% travel more than 100 miles to have access to abortion services (24).

Financial barriers preventing women from accessing safe abortion care are a result of the high costs for service or medicines. In many countries, only private clinics or providers offer abortions. Usually they are only available to economically privileged women due to the high costs of these services, especially in countries where abortions are illegal.

In Poland where abortion is illegal, costs of a surgical abortion (D&C) varied from 380–500,- to 1000,- EUR in 2006, and the costs of a medical abortion varied from 100–250,- EUR. The costs of a surgical abortion exceeded the average monthly income of Polish citizens (25).

Abortions are not always covered by national health insurance schemes in countries where they are legal. In the US, for example, in 22% of women seeking second trimester abortion care, the delay was due to financial barriers (26).

In some countries where mifepristone is registered its costs are unreasonably high. In Australia, where mifepristone became a registered medicine in 2012, the costs of a single tablet amounts to 308 Australian dollars (27).

In countries where abortion is legal, administrative procedures such as requiring spousal or parental consent, signatures from multiple doctors, waiting periods, obligatory waiting periods, obligatory counseling and limiting the availability of services to specially-licensed facilities or providers (only doctors, for example) or restricting certain types of abortion services (medical abortion) also reduce the access to safe abortion services (22).

In the Netherlands, there is a mandatory waiting period of 5 days, in France of 7 days and in Hungary of 3 days. In the Netherlands, Hungary and Germany, women are required to undergo obligatory counseling before the abortion is carried out, and in the UK an abortion can only be provided after two doctor signatures have been obtained (28).

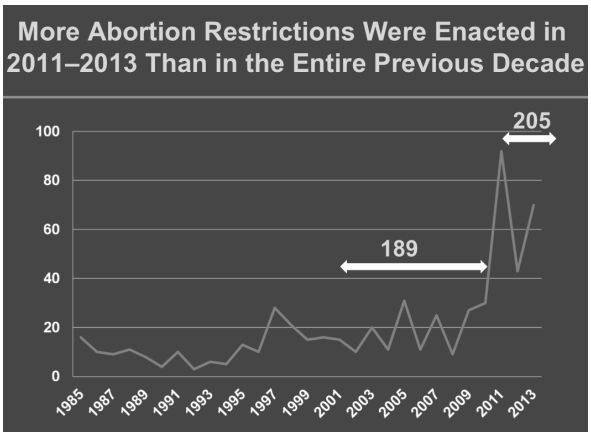

Figure 3. Slide from the presentation *An overview of abortion in the United states*, February 2014. Guttmacher Insitute

Similar procedural barriers have also been introduced in the United States. At present, 26 US states require have a 24-hour waiting period. Restrictions have also been imposed in Central and Eastern European countries. In 2011, Russia installed a mandatory waiting period for abortions, too. In 2009, the Slovak Republic introduced a 48-hour waiting period (20, 29 30).

In Hungary, the Food and Drug Administration refused to authorize the distribution of mifepristone in May 2012 (31).

1.2.3 Gestational limits

Thirty-two countries allow second trimester abortions to be carried out on broad social-economic grounds, including the US, the UK, Sweden, Norway, the Netherlands, Spain, Albania, Azerbaijan, Bahrain, Belarus, Belize, Canada, China, Cuba, Denmark, Georgia, Germany, Hong Kong, Japan, Kazakhstan, Norway, South Africa, and Iceland.

Only ten countries permit second trimester abortion on request. The majority of countries have set a time limit to second trimester abortions, ranging from 16 weeks (2 countries) to 22 weeks (10 countries) of pregnancy. Another legal limit is set at the viability of the fetus (2 countries)(32).

Recently more and more states in the US states imposed restrictions on the availability of second trimester abortions (33, 34).

In Russia, the access to second trimester is restricted as well as the list of social indications allowing for abortion to be carried out in the second trimester only consists of one item (rape) as from 2012. (17, 30)

1.2.4 Conscientious objection

Health service providers sometimes invoke conscientious objection or the right to act according to their own moral believes, when refusing to provide for example abortion care or contraceptives. In these cases a conflict of human rights arises because women also have the right to access healthcare. Although the right to freedom of thought, conscience and religion is protected by international human rights laws, these laws also state that the freedom to manifest one's religion or beliefs may be subject to limitations in order to protect other people’s the fundamental human rights. The WHO safe abortion guideline states that healthcare professionals who claim conscientious objection are obliged to refer women to a willing and trained service provider in the same or another easily-accessible healthcare facility (35).

The use of conscious objection by healthcare providers often leads to denying women access to legal reproductive healthcare services and violating of fundamental human rights.

Within Europe, the practice of conscientious objection is not allowed in Sweden, Finland, Iceland, Bulgaria and the Czech Republic. In the other European countries where abortion is legal as well as Norway and Switzerland, conscientious objections are allowed (36).

FIGO is of the opinion that the primary conscientious duty of obstetrician-gynecologists is at all times to treat, or provide benefit and prevent harm to, the patients for whose care they are responsible. Any conscientious objection to treating a patient is secondary to this primary duty (37).

Furthermore states are actually obliged to act pursuant to international human rights law (38).

Unfortunately the practice of conscientious objection in reproductive healthcare settings is becoming more and more common because of religious or moral values as well as beliefs as to when life actually begins (38).

Still even some non-religious doctors refer to the text in the Hippocratic oath regarding abortion, which has been broadly translated as followed: “Similarly I will not give a woman an abortive remedy” hence providing an argument to make conscious objections to providing abortion services. However the literal translation of the oath text in question is: “similarly (will I not give) to a woman an improper pessary”. This text has a very different meaning and is more in line with some other texts from Hippocrates in which he even describes herbs that have abortive properties (39).

1.2.5 Restrictive abortion laws

Currently, 39% of the world population lives in countries with highly restrictive laws governing abortion. In 68 countries, abortions are prohibited entirely or only allowed in order to save a woman’s life. In another 57 countries abortions are only allowed in order to protect a woman’s life and health (19).

The majority of countries where abortion is illegal are low-resource countries in the South. All countries in South America except Cuba, some Caribbean Islands, Uruguay as well as French and English Guyana have highly restrictive laws. Almost all Sub-Saharan countries except South Africa and Zambia outlaw abortion. In the Middle East and North Africa only Tunisia and Bahrain have legal abortion services. In South and South East Asia only Cambodia, Vietnam, Nepal, India have legalized abortion.

El Salvador and Nicaragua are among the countries that changed their already restrictive laws and now outlaw abortion entirely (19, 20, 21, 29). Within the European Union (EU) too, several countries have restrictive abortion legislation such as Ireland, Malta and Poland (18).

In Poland, abortion was legal until 1993. After the collapse of the Soviet Union, access to abortion was highly restricted (18). In 2011, the Polish parliament narrowly rejected a bill to introduce an absolute ban on abortion (25). Unfortunately anti-abortion rights groups in favor of a complete ban on abortion continue their efforts.

In Ireland the 1992 Supreme Court X verdict permitted abortion in case a mother's life is in danger. Despite this ruling, Savita Halappanavar a 31-year-old dentist died at the University Hospital Galway in October 2012 after being denied proper medical treatment for a miscarriage. In response to the public outrage and call for legalization in Ireland, the government adapted the Protection Of Life During Pregnancy Bill, which still only allows an abortion to be carried out when there is the risk of loss of life of pregnant woman (40).

The new law also imposes more severe penalties for illegal abortions (which applies to them women involved as well). Thos found guilty of the offence to "intentionally destroy unborn human life," can now be imprisoned for up to 14 years. This is 11 years more than the 3 years imprisonment under the old Section 59 of the Offences against the Person Act from1861 (41)!

In December 2013 a proposal to impose legal restrictions on abortion was approved by the Spanish centre-right government, after abortion had been legalized in 2010 (42, 43).

1.2.6 Religious views on abortion.

The majority of restrictive laws are justified by referring to religious doctrines. Before 1869, abortion was considered a forgivable sin under Pope Gregory XIV's doctrine of the not-yet-animated fetus.

In 1869 Pope Pius IX published Apostolicae Sedis moderationi, declaring that those who procured an effective abortion incurred excommunication (44). This implied that the legal, canonical penalty (excommunication) was no longer only applicable to the abortion of the animated fetus (or late abortion), but also to the abortion of the unanimated fetus (or early abortion). From that moment on, this penalty was imposed automatically for abortion at any stage of pregnancy. This legislation was incorporated into the Code of 1917 and is maintained in Canon 1398 of the present Code. (45). Canon 1398 states the following: a person who procures a completed abortion incurs a latae sententiae excommunication (46). As a result abortion is illegal in all countries with a predominant catholic population, except for France, Italy, Portugal and Austria.

Unlike Catholicism, Islam does not have a central hierarchical structure. Islamic thought is influenced by multiple schools and theological theories.

For Muslims, the Quran and Sunnah, the guiding texts of Islamic religious authority, form the main sources of Sharia law, the legal system prevalent in many Muslim countries.

Although, the Qur'an condemns the killing of human beings it does not mention abortion (Al-Ijhadh) explicitly. Neither the Quran nor the Sunnah directly addresses intentional abortion. A fatwa is a legal interpretation of Islamic law as determined by scholars (or ‘muftis’). Though not legally binding or enforced, fatwas are an important influence on Sharia law. The majority of early Islamic theologians permitted abortion up to the fortieth day of pregnancy and

sometimes even up to hundred-and-twenty days, more recent fatwas issued by conservative muftis prohibit abortion entirely or only find it acceptable if the pregnant women's life or health is threatened or if the fetus is expected to be deformed.

Although there is no consensus within Islam on abortion and in most Islamic countries abortion is illegal, Tunisia was the first Muslim, African, and Arab country to liberalize its abortion law in 1973.

However the majority of with a predominant Muslim population only legally permit abortions in case a pregnant woman's life is in danger. Those countries include Indonesia, Egypt, Saudi Arabia, Afghanistan, Libya, Iraq, Syria, Lebanon, Somalia and Mauretania.

In total ten countries with a predominantly Muslim population allow abortion 'on request' but most of them are former the former Soviet Republics where abortion was legalized in 1955 (Kazakhstan, Uzbekistan, Turkmenistan, Azerbaijan, Kyrgyzstan, Tajikistan, Kosovo, Uzbekistan) (47).

1.2.7 Health effects of restricted abortion access

There are many case studies that illustrate the importance of liberalizing abortion laws to protect women's life and health. The main example is Romania. After restrictive abortion laws were passed in that country in 1966, there was a dramatic increase in maternal mortality ratios up to 180 per 100,000 live births in 1988. After the legalization of abortion in 1989, maternal mortality decreased dramatically to 40 deaths per 100,000 live births in 1992 (48).

In South Africa the legalization of abortion in 1993 led to a 91% decrease of abortion related maternal deaths (49).

Before abortion was legalized in Mexico City in 2007, 7.2% of all maternal deaths were abortion-related. Since the legalization of abortion, only few abortion-related deaths occurred (50, 51). In Nepal too, evidence shows that the legalization of abortion in 2001 has contributed to the decrease of mortality and morbidity from unsafe abortion. The steepest decline occurred after the

implementation of a safe abortion program that included the training midlevel providers and the increase of access to medical abortion (52).

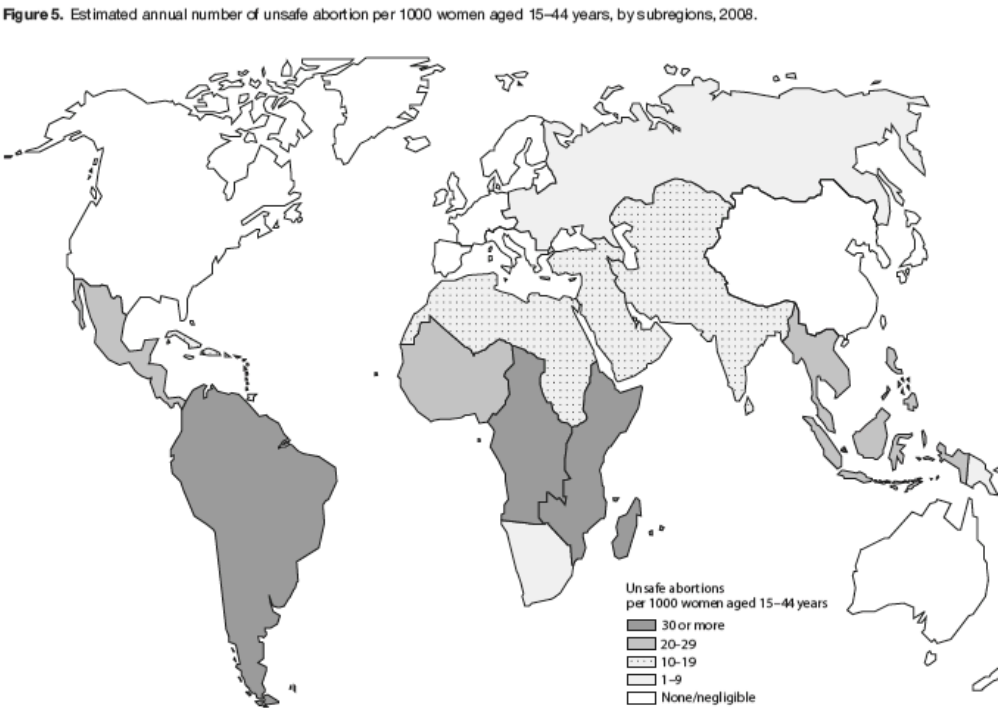

Figure 4. Map showing unsafe abortion rates, published by the WHO in *Unsafe abortion: global and regional estimates of the incidence of unsafe abortion and associated mortality in 2008.*

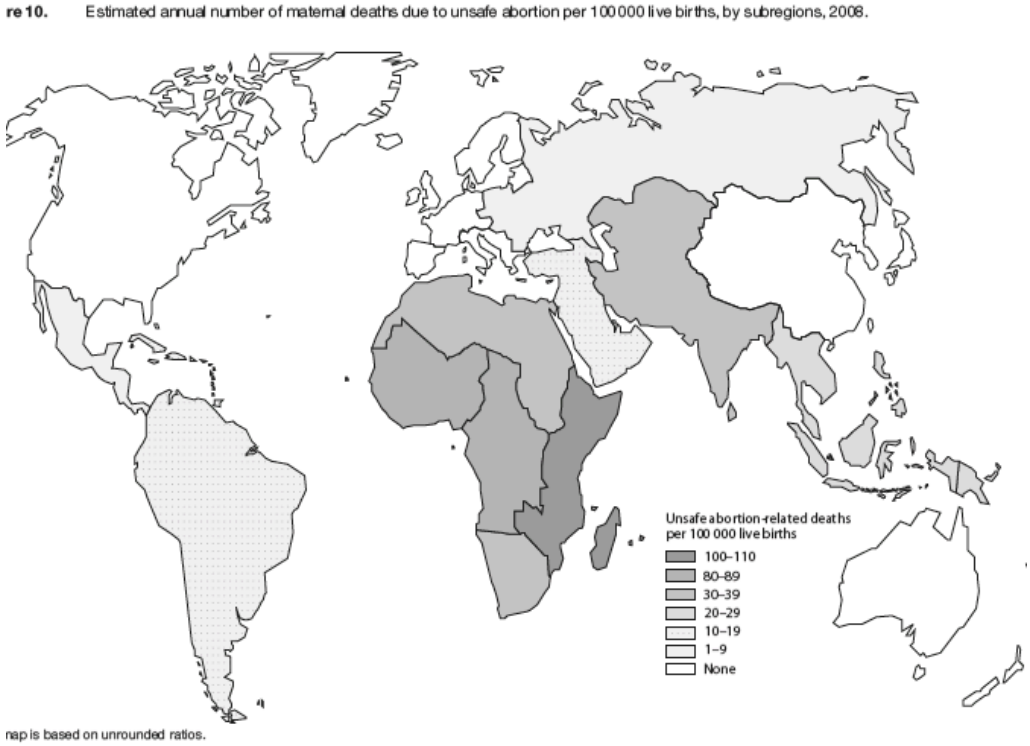

Figure 5. Map showing mortality rates caused by unsafe abortions, published by the WHO in *Unsafe abortion: global and regional estimates of the incidence of unsafe abortion and associated mortality in 2008*

1.3 MEDICAL ABORTION: A REVOLUTION

1.3.1 Background

Plato already mentioned the possibility of inducing abortions by administering medicines in his manuscript *Theaetus*: "SOCRATES: moreover, with the drugs and incantations they administer, midwifes can either bring on the pains of travail or allay them at their will, make a difficult labor easy and at an early stage cause miscarriage if they so decide"(53).

In 1970, Bygdeman reported the strong abortive effect of prostaglandin, with success rates of up to 94 % (54, 55, 56).

After the development of mifepristone in 1985, Bygdeman and his colleagues showed that when taking mifepristone before a prostaglandin potentiated the effect of the latter and uterine contractions became more pronounced and caused complete abortion in 94% of the cases. Gastrointestinal side effects were rare and uterine pain was significantly less frequent than if prostaglandin was used alone (57, 58, 59).

Medical abortion is one of the safest procedures in contemporary medical practice, with minimal morbidity and a negligible risk of death. Medical abortion can be induced with several medicines and protocols but the administration of 200 mg mifepristone followed 24 to 36 hours later by 800 mcg misoprostol sublingual, vaginal or buccal has proven to be the most effective method, with few serious complications and success rates of 95–98% when used in the first 9 weeks of pregnancy (60).

Mifepristone has very few adverse effects. Misoprostol induces uterine contractions and bleeding. Studies in countries where medical abortion services are available have shown that the majority of women prefer to use these medicines at home. Currently it is the standard method applied in the US and several European countries such as Sweden, Austria, France and the Netherlands. Research has shown that women also prefer using mifepristone at home and this is highly acceptable for both women and providers (61, 62, 63).

Evidence shows that performing a medical abortion at home is safe up to nine weeks of gestation. The risk of serious complication is exceptionally low compared to other medical interventions, and only few patients require emergency referral. Today, in many countries, it is common clinical practice that women administer misoprostol themselves at home. Women can carry out the treatment safely and deal with all stages of the abortion process themselves (63, 64).

Although the WHO listed mifepristone and misoprostol as essential medicines since 2005, in some countries the medicines are still not made available (65, 66, 67).

Barriers to full implementation of medical abortion include limited availability. Mifepristone is registered in only 59 countries worldwide (65). Even in countries where mifepristone is registered, access is highly controlled and generally it can only be provided under strict medical supervision due to the local abortion legislations. While misoprostol is registered in countries around the world more broadly access to this medicines is often similarly limited (66).

1.3.2 Mifepristone

Mifepristone was developed in France, where it was granted approval for being used to carry out medical abortions in 1989 (68).

Mifepristone is a synthetic C19 steroid, which is a potent progesterone receptor antagonist. It binds to both the progesterone receptor (PR) and the glucocorticosteroid receptor (69).

The main source of progesterone in humans is the corpus luteum in the ovary. In pregnancy, the corpus luteum produces progesterone until approximately the 10th week of gestation. After a transition period, the placenta becomes the main progesterone source by 7-10 weeks of gestation. Serum levels of progesterone increase progressively during human pregnancy and remain high until the placenta has been delivered at birth.

Progesterone is of major importance in the regulation of uterine contractility and the inactivity of the early pregnant uterus is progesterone dependent. Treatment with the antiprogestin mifepristone will convert the inactive early pregnant uterus to an active organ and will increase the sensitivity of the myometrium to prostaglandin. Progesterone also has a strong immunomodulatory effect that is important for the physiological immunotolerance during implantation (70). Mifepristone also has a softening effect on the cervix. The combined effects are responsible for the abortive properties of mifepristone (71).

1.3.3 Misoprostol

In contrast to previously available prostaglandin analogues, misoprostol is an orally active synthetic prostaglandin E1 analogue. Initially misoprostol was granted approval for the treatment and prevention of peptic ulcer disease in June 1984 (72). However misoprostol is can also be used to induce abortions, to treat incomplete miscarriages and to prevent and treat PPH.

Women themselves can administer misoprostol safely and effectively at home to induce an abortion (by using 3 doses of 4 X 200 mg tablets sublingually every 3 hours). Misoprostol-induced abortion has been shown to be safe and to have an 85-90% effectivity if administered 12 weeks of pregnancy (5, 73, 74).

Misoprostol is available in multiple brands. Globally the most widely available brand is Cytotec, which is produced by Pfizer though not registered for obstetric gynecological indications. Other brands available in various countries are: Cyprostol and Misotrol in Chile, Prostokos (25µg Misoprostol) and Vagiprost (25µg Misoprostol) in Brazil, Misotac in Egypt, Ghana, Sudan, Tanzania, Uganda and Zambia, Misofar in Spain, Cytopan in Pakistan, Noprostol, Gastrul and Chromalux in Indonesia. Further locally available brands in various countries are Cytel, Misoprolen, Mibetec, Cytomis, Miclofenac, Misoclo, Misofen, Misogon, Alsoben, Misel, Sintec, Gastrotec, Cystol, Gastec, Cirotec, Gistol, Misoplus, Zitotec, Prestakind, Misoprost, Cytolog, GMisoprostol, Mirolut and Gymiso (75).

Another widely available brand is Arthrotec, which is also produced by Pfizer. Besides misoprostol it also contains diclofenac and it is prescribed for rheumatoid arthritis. In Argentina it is available as Oxaprost. If administered to induce an abortion, a woman should put 4 tablets under her tongue for half an hour until the outer mantle, the misoprostol, is dissolved. Next, she should spit out the inner hard tablet, which contains diclofenac. This process should be repeated after 3 hours and again 3 hours later. By spitting out the remaining tablets after half an hour, she can prevent an overdose of diclofenac.

1.3.4 Different protocols for different gestational periods.

The WHO recommends the following protocols (76):

1.3.4.1 Mifepristone and misoprostol until 9 weeks of gestation.

For a medical abortion till 9 weeks of pregnancy, a woman should swallow 1 tablet mifepristone 200 mg, 24 to 48 hours later followed by 400 mcg misoprostol bucally or sublingually.

1.3.4.2 Mifepristone and misoprostol from 9 until 12 weeks of gestation.

The WHO recommends that medial abortions after 9 weeks of gestation should take place in a healthcare facility. A woman should swallow 200 mg of mifepriston, 36 to 48 hours later followed by 800 mcg misoprostol vaginally and 3 hours later by 400 mcg misoprostol vaginally or sublingually, which is repeated every 3 hours up to 5 doses.

1.3.4.3 Mifepristone and misoprostol after 12 weeks of gestation.

A woman should swallow mifepristone 200 mg, 36-48 hours later followed by 800 mcg vaginally or 400 mcg misoprostol orally, and then every 3 hours later by 400 mcg misoprostol vaginally or sublingually which can be repeated up to 5 doses.

1.3.4.4 The sole use of misoprostol until 12 weeks of gestation.

A woman should use 800 mcg misoprostol vaginally or sublingually, repeated every 3 to 12 hours, up to 3 doses.

1.3.4.5 The sole use of misoprostol after 12 weeks of gestation.

A woman should use 400 mcg misoprostol vaginally or sublingually, which is repeated every 3 hours up to 5 doses.

1.3.5 The comparison of medical abortion to surgical abortion.

Vacuum aspiration (VA) is the recommended technique used in surgical abortion for pregnancies of up to 12 to 14 weeks of gestation. After 12 weeks it should be carried out by specially trained health care professionals. After 14 weeks D&E (dilatation and evacuation) should be used. Dilatation and sharp curettage (D&C) should not be used.

Currently, there are no data available on the combined use of mifepristone/misoprostol in comparison with surgical abortion beyond the first trimester. In addition there are only few studies comparing other methods of medical abortion to surgical abortion. However VA carried out at 9 to 14 weeks of gestation is more effective and associated with fewer side effects though the rate of complications does not differ from VA. The duration of bleeding was longer in the medical abortion groups compared to vacuum aspiration group. The groups did not differ in ongoing pregnancies or infections (77, 78, 79, 80).

Patient preference and acceptability are similar for VA and medical abortion in the first trimester. A Chinese meta-analyses comparing acceptability of medical abortion to surgical abortion found that the satisfaction of both methods seemed similar (81, 82, 83). There are no data available for comparison of acceptability, side effects or women's satisfaction with the procedure in the second trimester.

1.3.6 Follow up

According to the WHO guidelines here is no need from a medical point of view for a routine follow-up visit following uncomplicated medical abortion (76).

Women in both developing and more developed countries can manage the effects of an abortion themselves, provided that they have information and access to medical care in case of an emergency (84, 85).

A medical abortion is accompanied by the same symptoms and has the same health impact as a spontaneous miscarriage. Usually women handle a miscarriage by themselves without additional medical supervision. Research has shown that expectant management of clinically stable women who have no signs

of a complication (excessive bleeding or fever) after a first-trimester miscarriage is safe and effective and avoids the need for surgery and the subsequent risk of anesthetics (86, 87).

Women who do need further medical attention because of a complication can easily be treated by any doctor. Post abortion case, which means the follow up treatment for incomplete miscarriage and induced abortion should be available and is legal everywhere. After an induced abortion a woman can report to a doctor that she has had a miscarriage. In case of an ongoing pregnancy, women can repeat the treatment.

1.3.7 Possible complications and treatment

Although life-threatening complications following safe abortion are rare, women should be informed of additional services available to them if needed. Possible complications following a medical abortion are described below.

1.3.7.1 Incomplete abortion

Symptoms indicating an incomplete abortion are continuing or heavy pain and/or bleeding after the medical abortion. Depending on the clinical condition of the woman in question and whether or not the size of the uterus at the time of treatment is equivalent to a pregnancy of gestational age of 13 weeks or less, either expectant management or vacuum aspiration or a single dose of oral misoprostol 600 mcg or sublingual misoprostol 400 mcg is recommended (76).

1.3.7.2 Infection

Symptoms indicating a possible infection are: fever for more than 24 hours after using misoprostol, foul-smelling vaginal discharge and abdominal pain. An infection should be treated with antibiotics. If the infection is caused by an incomplete abortion, a vacuum aspiration should be carried out as well. Women with severe infections should be referred to a hospital.

1.3.7.3 Hemorrhage

Hemorrhage after medical abortion can result from an incomplete abortion or coagulopathy. Women should be referred to a healthcare facility which has the means to provide the appropriate treatment. Although treatment for hemorrhage depends on the cause and severity, it may include vacuum aspiration, administration of uterotonic drugs and a blood transfusion (76).

1.3.8 The role of Midlevel Healthcare providers

Midlevel health care providers often work in rural or remote areas without doctors and only few surgical facilities available. Therefore, allowing them to provide medical abortions could improve access to safe abortion services (88).

Multiple studies have proven that manual vacuum aspiration carried out by midlevel care providers are as safe and effective as those carried out by doctors.

When we started our study there were no studies about the safety and effectivity of medical abortion by midlevel providers, though. While carrying out our research activities, a study in Nepal was published that showed that medical abortions provided by doctors had the same outcome as the ones provided by nurses (89).

In high resource setting in which ultrasound is part of the protocol, the provision of medical abortions by midlevel healthcare providers offers a lot of advantages. Access to abortion care may be limited by the reluctance of physicians to be involved in abortion care or by a shortage of physicians.

The WHO considers the provision of medical abortion at primary care level safe and advices to make abortion services available by setting up outpatient services. To improve access to safe abortion, abortion care can be provided by a properly trained healthcare provider (5, 7).

Unfortunately there are some legal obstacles to implement task shifting of medical abortion provision towards midlevel providers. Most countries abortion only allow for abortions to be performed only by a medical doctor. South Africa

was the he first country to make the provision of medical abortions by midlevel healthcare providers legal. English Guyana too permits midlevel healthcare providers to perform non-surgical abortion until 8 weeks of pregnancy (90). In Sweden, the board of health and welfare has stressed that midwives should be more involved in the provision of medical abortion.

1.3.9 The role of women themselves

In countries without any access to safe abortion, women can use misoprostol safely and effectively at home by themselves to induce an abortion (5, 73, 74).

Research has shown that the administration of misoprostol by women themselves in settings with restrictive abortion laws or significant access barriers has lead to decreased morbidity and mortality in countries where abortion is illegal (91, 92, 93, 94, 95).

Figure 6: Launching of safe abortion hotline in Ecuador 2008.

In areas with high mortality rates, a 15% reduction in mortality is predicted if only 20% of the procedures are misoprostol-induced; a 30% reduction in mortality is predicted if 40% of the abortions would be induced with misoprostol; and a 45% reduction in mortality is predicted if 60% of the abortions is misoprostol-induced. These figures correlate with 30500 lives saved annually (93).

Telephone hotlines can enhance access

to safer abortion care and help reduce complication rates by providing information on performing medical abortions with the proper use of misoprostol (96).

Unfortunately access to misoprostol is increasingly limited by restricted regulations and cost. In Brazil, for example, misoprostol was granted approval for use in 1986. Since 1987, it was available over the counter for women who started using it to induce abortions. The analysis of Cytotec's sales volumes showed a quick growth as from the moment it was introduced until the first 6 months of 1991, when the Ministry of Health restricted its use (97, 98).

Turkey was the last country to ban the sale of misoprostol in 2012.

In pharmacies in many countries, misoprostol is not easily available anymore (99). Therefore women try to find other ways of accessing medical abortion care, often with by using of the internet.

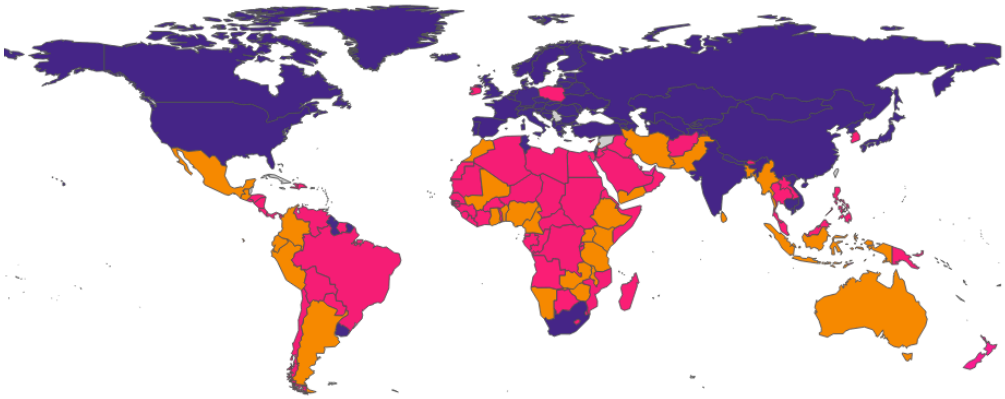

Figure 6: Orange: countries where abortion is illegal and misoprostol is easy available. Pink: countries where abortion is illegal and obtaining misoprostol very difficult. Purple: abortion legal.

1.3.10 The promise of telemedicine

In 1989, the World Wide Web was invented by Tim Berners-Lee and in April 1993, the World Wide Web technology was available to everyone (100).

On May 2005, the 58th World Health Assembly stated: "Noting the potential impact that advances in information and communication technologies could have on healthcare delivery, public health, research and health-related activities for the benefit of both low- and high-income countries" and "Stressing that eHealth is the cost-effective and secure use of information and communications technologies in support of health and health-related fields, including health-care services, health surveillance, health literature, and health education, knowledge and research" . It also stated: " Urges Member States: to endeavor to reach communities, including vulnerable groups, with eHealth services appropriate to their needs" (101).

Telemedical or eHealth interventions found to be therapeutically effective so far include online psychological interventions, chronic heart failure programs that include remote monitoring, home telemonitoring of respiratory conditions, telepsychiatry, internet and computer-based therapy for the treatment of anxiety and home telehealth programs for diabetes, heart disease and chronic obstructive pulmonary disease (102). Telemental health in particular has proven to be effective and to increase access to mental care (103).

Teleradiological services are available at a large percentage of all US hospitals and are regarded by many as mainstream medical services (104).

A 2011 literature review in the Journal of the American Academy of Dermatology showed that teledermatology consistently shortened service delivery times when compared to in-person dermatology consultations (105).

1.3.10.1 Telemedical abortion services

Women on Web (www.womenonweb.org) is a telemedicine abortion service supporting women in countries without any safe abortion services, allowing them to get access to safe medical abortion by using mifepristone and

misoprostol. Its aim is to reduce maternal mortality and improve reproductive health.

The website is owned by Women on Web International Foundation, a non-profit foundation, the goal of which is to support the access by women to safe medical abortion, especially by those in need, and to provide related educational information, thus benefiting women's reproductive health.

The Women on Web website went online in April 2006 and is now available in 11 languages (Arabic, English, Spanish, Portuguese, French, Polish, Bahasa Indonesia, Japanese, Thai, Tagalog and Turkish). Via the website women can fill out an interactive web-based questionnaire. The information provided by women during this online consultation are forwarded to a doctor. If there are no medical contraindications, a medical abortion kit with mifepristone and misoprostol is send by courier or another mail service to the woman's home address.

The users of the website are requested to make a donation of 90 euro. However if a woman does not have the financial means to do so, she will be helped for free. Approximately 10–15% of the women who are not able to make the 90 euro donation will receive sponsoring.

Similar to other safe abortion services, Women on Web provides information and support to the women who decide to undergo this procedure. Screening for contraindications via the internet is very similar to the screening process carried out during a face-to-face consultation. The doctor assesses the woman's circumstances by asking questions and relies on women to answer truthfully. Women are well aware of the specific medical conditions listed as contraindications for performing a home-based medical abortion.

The following conditions are considered a contraindication for the service. If a woman is being forced to end her pregnancy, is allergic to mifepristone, misoprostol or prostaglandins, has chronic adrenal failure, hemorrhagic disorder, inherited porphyrias, severe anemia or severe untreatable asthma, has a proven

ectopic pregnancy, cannot get to a hospital or first aid centre within an hour or has nobody to help her during the abortion process.

The determination of blood group and rhesus status are not considered prerequisites for early medical abortion. There is no need for a routine follow-up visit following uncomplicated medical abortion using mifepristone followed by misoprostol (84). However, women are advised to stay in the vicinity of a health facility. In case symptoms of an incomplete abortion or signs of another complication occur, women are always referred to local healthcare provider.

Women on Web mostly uses store-and-forward telemedicine. Store-and-forward telemedicine refers to the use of asynchronous (not real-time) computer-based

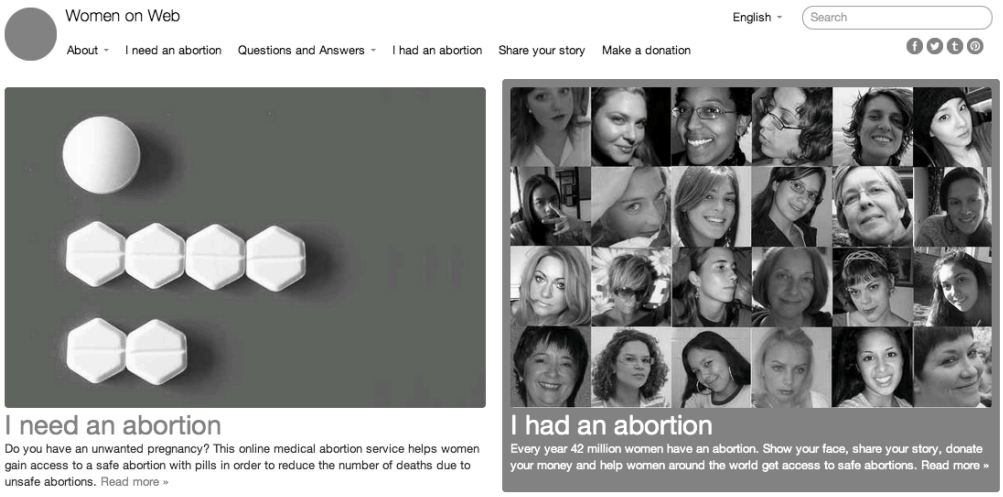

Figure 7: Screenshot homepage www.womenonweb.org website

communication between a patient, a consulting provider or a referring healthcare provider and a medical specialist at a distant site for the purpose of diagnostic and therapeutic assistance in the care of patients who otherwise cannot access to specialist care in time (105).

2 AIMS OF THE STUDY

A shortage of healthcare workers (for legal or geographic reasons) has hindered efforts to reduce maternal mortality and the provision of universal access to reproductive health. Task shifting and sharing may increase access to and availability of abortion services with the same quality of care (106).

The overall aim of this thesis was to investigate efficacy, safety, acceptability and factors influencing the outcome of medical abortion after task shifting the provision to midlevel providers and to women themselves through telemedicine to increase access to medical abortion.

The specific objectives were:

I. To evaluate the outcome and acceptability of home medical abortion provided via telemedicine.

II. To analyze which factors influence the surgical intervention rate following a medical abortion at home provided via telemedicine.

III. To analyze the duration of the pregnancy and the outcome of self-induced medical abortion provided to women living in Brazil via telemedicine.

IV. To assess the efficacy, safety and acceptability of medical abortion provided by trained mid-level healthcare professionals compared to physicians in a clinical high-resource setting in Sweden.

V. To evaluate and compare the outcome of self-induced medical abortion with mifepristone followed by 1200 mcg, 1600 mcg or 2400 mcg misoprostol for second trimester abortions in Brazil provided via telemedicine.

3 MATERIAL AND METHODS

3.1 STUDY SUBJECTS

3.1.1 Study 1: Outcome and acceptability of medical abortion at home provided via telemedicine

Women living in countries without any access to safe abortion and who were able to use the telemedical abortion service of Women on Web from April to December 2006 and in January 2007 (107).

3.1.2 Study 2: Factors influencing the outcome of medical abortion at home provided via telemedicine

Women living in countries with restricted access to safe abortion and who completed the online consultation from February 2007 to September 2008, obtained the medical abortion and provided follow-up information, were included. Women who decided not to take the medication for various reasons, such as having a spontaneous miscarriage in the meantime or a wish to continue the pregnancy, were excluded from the data analyses (108).

3.1.3 Study 3: Medical abortion provided to women living in Brazil via telemedicine.

Women living in Brazil who completed the online consultation on the Women on Web website from 1 January through 31 December, 2011 and performed a medical abortion provided via Women on Web's telemedicine service (109).

3.1.4 Study 4: Midlevel provision of medical abortion.

Women older than 18 seeking medical abortion at the Karolinska University Hospital Solna were recruited and randomized for treatment by a midwife or routine provision by a physician. After undergoing an examination women were excluded if they had a suspected ectopic pregnancy, opted for a surgical abortion after counseling, opted for postponing the abortion, were not in good general health with on-going medication for chronic disease, had a pregnancy with a gestational age of more than 63 days, had an undiagnosed adnexal mass or any

other contraindication to medical abortion. All patients were screened for Chlamydia trachomatis and bacterial vaginosis in accordance with clinical routine procedures. In case test results were positive, they were treated with doxycycline and metronidazole respectively (110).

3.1.5 Study 5: Outcome of home medical abortions after 12 weeks of gestation with different misoprostol regiments.

Women from Brazil with a pregnancy of more than 12 weeks who completed the online consultation on the Women on Web website in 2011 and 2012 and performed a medical abortion provided via Women on Web's telemedicine service were included in the study.

3.2 EVALUATED PARAMETERS.

3.2.1 Study 1, 2, 3 and 5.

Data were obtained from the interactive web based questionnaire, follow-up forms, emails and telephone calls. Women fill out an online consultation form containing 25 – 30 questions to determine the woman's situation and to provide information about the medical abortion and possible alternatives. Through the web-based questionnaire women provided information about their pregnancy duration based on LMP or as confirmed with ultrasound. They also provided information about their age, parity, contraceptive use, any diseases or allergies, and the current use of medication. Contraindications and risk factors for potential complications were also identified. Contraindication for the service are the following: if a woman is being forced to end her pregnancy; has an allergy to mifepristone, misoprostol, or prostaglandins, has chronic adrenal failure, hemorrhagic disorder, inherited porphyrias, severe anaemia, or severe untreatable asthma, has a proven ectopic pregnancy, cannot get to a hospital or first aid centre within an hour or has nobody to help her during the abortion process. If necessary, additional questions are asked or advice is offered by email or telephone. Specially trained helpdesk members answered emails 7 days a week.

During the online consultation and in subsequent emails, the women were informed about complications, circumstances when they should seek additional medical assistance, what to do in case of a continuing pregnancy, and future contraceptive options.

Five weeks after delivery of the package, an email was sent containing a follow-up form enquiring about the outcome of the procedure, any complications, method acceptability (how the woman felt about undergoing an abortion obtained via internet service and doing it at home), and contraceptive use.

3.2.2 Study 1: Outcome and acceptability of home medical abortion provided via telemedicine.

Demographic data (age, parity, contraceptive use) duration of pregnancy at the time of the consultation and the outcome and acceptability of the abortion were analyzed in the online consultation and follow up form obtained from the women who used the service in 2006. An additional survey was performed in all the women who received a medical abortion in the month of January 2007 only. During this month, women who had not returned the follow-up form were actively contacted by telephone. In the follow-up questionnaire women were asked about their experiences of the abortion. They could choose between five answers: "grateful to be able to have the medical abortion"; "stressful but acceptable"; "no specific feeling"; "if I had known before how stressful it would be, I would never have done it myself" and "do not want to share". This questionnaire was designed in this way in which the women's right to keep their feelings for themselves was respected and women were also allowed to choose the option that they had experienced the abortion as a neutral event which did not evoke specific feelings.

3.2.3 Study 2: Factors influencing the outcome of home medical abortion provided via telemedicine.

Demographic data (age, parity, contraceptive use, geographic location) duration of pregnancy at the time of the consultation, doctor or hospital visit after the medical abortion and outcome of the abortion measured in ongoing pregnancy,

surgical intervention and acceptability of the abortion were analyzed by using data obtained from the online consultation and the follow up form provided by the women who used the service.

In order to analyze the outcome of the abortion in women from many countries (n=88), only the regions were reported instead of individual countries. Geographic location was divided into six regions: Western Europe, Eastern Europe, Middle East, Africa, Asia and Oceania and Latin America and the Caribbean

In order to measure the level of acceptability, women could choose between five options: “grateful to be able to do the medical abortion”, “stressed, but acceptable in order to do the medical abortion”, “if I had known before how stressful it would be, I would never have done it myself”, “no specific feeling”, and “do not want to share”.

3.2.4 Study 3: Medical abortion provided to women living in Brazil via telemedicine.

Demographic data (age, parity, contraceptive use) duration of pregnancy at the time of the medical abortion, signs of a complications, outcome of the abortion measured in ongoing pregnancy, surgical intervention, reason for surgical intervention and acceptability of the abortion were analyzed by using the online consultation data and data from the follow up forms filled out by the women who used the service.

The duration of pregnancy at the time of the medical abortion was calculated by adding the duration of pregnancy at the time of consultation (based on reported LMP or ultrasound), the shipment time of the package and the time the woman waited before using the medicines after having received the package. When a woman reported a gestational age in the email correspondence that differed from the one mentioned during the online consultation, the gestation of the email correspondence was used. All cases were divided into three categories: “9 weeks or less”, “10, 11 or 12 weeks”, or “13 weeks or more”.

In order to measure acceptability women could choose between the following option: “I felt grateful”, “I thought it was acceptable”, “it was not acceptable for me”.

Demographic data (age, parity, contraceptive use), complaints or signs of complications and the outcome of the abortion measured as ongoing pregnancy and surgical intervention after the medical abortion were compared among these 3 groups of women.

3.2.5 Study 4: Midlevel provision of medical abortion.

A web-based database was created for the study. Data from the case record forms on demographics and outcomes for each patient were entered continuously by a research midwife.

Questionnaires administered to the women were filled out prior to, during the abortion process as well as during follow up. The questionnaire prior to the abortion included questions concerning health and outcome of previous pregnancies. The form after the abortion included questions about the acceptability of the procedure and whether or not women had received enough information about the treatment (1=complete satisfaction) or not (5=complete dissatisfaction. On a scale from 1 to 5 a woman could indicate if she felt calm during the treatment and during follow-up. They were also asked if there had been a partner/friend present during the abortion. In addition they were asked if they would prefer a midwife or gynecologist to perform the examination and counseling might they need another abortion in the future or if they were indifferent. Furthermore patients stated if they had visited the emergency room or had had a treatment related complication.

3.2.6 Study 5: Outcome of home medical abortions after 12 weeks gestation with different misoprostol regiments.

Demographic data (age, parity, contraceptive use) duration of pregnancy at the time of the medical abortion, signs of a complications, outcome of the abortion measured in terms of ongoing pregnancy, surgical intervention, reason for a

surgical intervention and acceptability of the abortion were analyzed by using the online consultation data and data obtained from the follow up form filled out by the women who used the service.

The duration of pregnancy at the time of the medical abortion was calculated by adding the duration of pregnancy at the time of consultation (based on reported LMP or ultrasound), the shipment time of the package and the time the woman waited before using the medicines after having received the package. When a woman reported a gestational age in the email correspondence that differed from the one mentioned during the online consultation, the gestation of the email correspondence was used.

Only the data from women living in Brazil with a pregnancy of more than 12 weeks who used the service in 2011 and 2012 were included in the analyses.

In July 2012 the contend of the packages changed from 1 tablet 200 mg mifepristone and 6 tablets 200 mcg misoprostol (a total of 1200 mcg) into 1 tablet 200 mg mifepristone and 8 tablets 200 mcg misoprostol (a total of 1800 mcg). Furthermore women who indicated they were approaching 12 weeks during the consultation received 1 mifepristone and 12 misoprostol tablets (a total of 2800 mcg).

3.3 STUDY TREATMENT

3.3.1 Study 1, 2.

A package containing 1 tablet of 200 mg mifepristone and 6 tablets of 200 mcg misoprostol was send to the home address of the women.

Women with a gestational age up to 9 weeks were advised to take 200 mg mifepristone, followed 24 hours later by 800 mcg misoprostol sublingually and a repeat dose of 400 mcg misoprostol sublingually four hours later.

Although misoprostol can be used sublingually, bucally and vaginally, Women on Web always advises women sublingual usage. When used vaginally, misoprostol can take up to 4 days to dissolve. If remains of the tablets are found,

this can be used to prove that the abortion was intentionally induced, enabling the prosecution of women living in (some) countries where abortion is illegal.

All women received an email with information about the use of the medicines, including a description of signs and symptoms that might indicate a complication for which they need to seek medical care and to take pain medication as needed.

3.3.2 Study 3.

A package containing 1 tablet of 200 mg mifepristone and 6 tablets of 200 mcg misoprostol was send to the home address of the women.

Although Women on Web only intends to provide the medical abortions up to 9 weeks of pregnancy, a woman may acknowledge she is pregnant for more than 12 weeks after she has already obtained the package of medicines. In that case she will receive an additional email informing her that a medical abortion in a later gestational age can cause more pain and more blood loss, as well as a higher risk of undergoing a surgical intervention and ongoing pregnancy. She is also warned that she might recognize a fetus after expulsion of the pregnancy, which can be very distressing. The woman is strongly advised not to be alone during the procedure and to take the medication inside or close to a medical facility. In this email the woman is also informed about the protocol as recommended by the WHO to swallow 200 mg mifepristone, followed by vaginal application of 800 mcg misoprostol 36 hours later, followed by sublingual use of 400 mcg misoprostol 3 hours later repeated up to 5 times until abortion is effectuated. As the package only contains 6 tablets of misoprostol, women would not have enough misoprostol to complete the maximum 4 additional doses of misoprostol advised by the WHO if the abortion did not place after the second dose (5, 76).

3.3.3 Study 4.

Women were informed about the study during the first contact with the family planning unit. If they were eligible and willing to participate they were randomly

allocated to a midwife or gynecologist for examination and counseling. Follow up was conducted by midwife according to routine clinical procedure.

Women swallowed 200 mg mifepristone in the presence of a nurse according to Swedish law. Women were allowed to take 800 mcg vaginal misoprostol at home or at the clinic. If bleeding did not occur within 3 hours after taking this doses women were instructed to take 400 mcg misoprostol orally. Women were instructed to take prophylactic pain treatment at the time of vaginal misoprostol administration consisting of 1g paracetamol and 100mg diclofenac. Additional pain treatment was supplied to patients choosing home administration of misoprostol.

Patients opting for administration of misoprostol at the clinic had access to pain medication supplied by a midwife as needed.

3.3.4 Study 5.

If a woman informed WoW that she was more than 9 weeks pregnant at the time of the consultation she was sent 1 tablet of mifepristone and 12 tablets of misoprostol (a total of 2800 mcg). Furthermore, in July 2012 the content of the packages changed from 1 tablet 200 mg mifepristone and 6 tablets 200 mcg misoprostol (a total of 1200 mcg) into 1 tablet 200 mg mifepristone and 8 tablets 200 mcg misoprostol (a total of 1800 mcg). Women who inform the service that they are more than 12 weeks pregnant received an email that informed them that a medical abortion in a later gestational age can cause more pain and more blood loss, as well as a higher risk of undergoing a surgical intervention and ongoing pregnancy. She was also warned that she might recognize a fetus after expulsion of the pregnancy, which can be very distressing. The woman was strongly advised not to be alone during the procedure and to take the medication inside or close to a medical facility. In this email the woman was also informed about the protocol as recommended by the WHO. Depending on whether the package she received contained 6 or 8 or 12 tablets of misoprostol, women would be able to complete the maximum 4 additional doses of misoprostol advised by the WHO if the abortion did not take place after the second dose intake (5, 76).

3.4 DATA ANALYSES AND STATISTICS

3.4.1 Study 1: Outcome and acceptability of home medical abortion provided via telemedicine.

Statistical evaluation of the difference between groups was performed using the chi-square test.

3.4.2 Study 2: Factors influencing the outcome of home medical abortion provided via telemedicine

The statistical difference of the follow up between the regions was calculated with the Kruskal Wallis test. Data analysis was performed using the statistical program SPSS 16.0. Chi-squared tests were used for comparing groups. Nonparametric continuous variables are presented as medians and ranges. A p-value of <0.05 was considered significant. Factors affecting surgical intervention rates were evaluated using logistic regression.

3.4.3 Study 3: Medical abortion provided to women living in Brazil via telemedicine.

The dataset was entered into SPSS 20.0 for Windows. The data from the different gestational age groups were compared to each other by performing Chi-Square tests. P-values < 0.05 were considered statistically significant.

3.4.4 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. The overall efficacy rate in both groups was estimated at 95%. The clinically relevant margin of equivalence was set at 5%. A sample group size of 400 women in each group could demonstrate equivalence with 80% power with a 95% confidence interval (α=0,05). To allow for loss to follow up and a woman's choice for a surgical abortion, a total of 1180 women were recruited.

Non-parametric continuous variables were presented as medians and ranges. 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 SPSS version 20. In order 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 in accordance with the recommendation and followed the Consort guidelines for equivalence trials.

3.4.5 Study 5: Outcome of home medical abortions after 12 weeks gestation with different misoprostol regiments.

The data set was entered in SPSS 19.0. The outcomes of the abortions with the use of different doses of misoprostol were compared to each other by performing Chi-Square tests. A p-value of <0.05 was considered significant.

3.5 ETHICAL CONSIDERATION

Women using the Women on Web website consented to the use of de-identified data for research by clicking a box during the online consultation. Ethics permissions were obtained for all studies.

4 RESULTS

4.1 RESULTS STUDY 1, 2, 3 AND 5: PROVISION OF MEDICAL ABORTION THROUGH TELEMEDICE.

The results of these 4 studies can be categorized into: “demographic characteristics of the women using the service”, “complaints and symptoms”, “surgical intervention rate”, “ongoing pregnancy rate”, “gestational age” and “acceptability”.

4.1.1 Demographic characteristics of the women using the telemedical service.

The studies included in this thesis only report on the demographic statistics of the women who actually had the medical abortion instead of data from all women who complete the online consultation.

4.1.1.1 Study 1.

The mean age of the women who used the service was 27 years (range 15–46 years). Two hundred and twenty-seven (46.9%) women were nulliparous and 6 (1.2%) women reported an unwanted pregnancy as a result of rape (107).

4.1.1.2 Study 2.

The mean age of the women was also 27 years, with a range of 16–49 years. A slight majority (53.7%) of the women were nulliparous (108).

4.1.1.3 Study 3.

The mean age of the Brazilian women was slightly lower than that of the women participating in the other 2 studies, namely 26.5 years (range 16 to 49 years). Also a slightly higher percentage (67.1%) of the women was nulliparous compared to the other 2 studies and 66.1% of the women reported that the cause of the pregnancy was contraceptive failure (109).

4.1.1.4 Demographic characteristics of 400 women from Ireland and the Philippines who completed the online consultation form.

An additional analyses of the data of 200 women from the Philippines and 200 from Ireland who completed the online consultation form in 2012, found that women from the Philippines were younger and less likely to use contraceptive than women in Ireland. Women in Ireland often already had children and reported failed contraception as a reason for their pregnancy (Table 1).

	Ireland	Philippines	p-value
total	200	200	
mean age	28	26	
reason for abortion: i am too young	20 (10%)	50(25%)	0.0008
reason for abortion: i am too old	10 (5%)	2(1%)	0.012
reason for abortion: family is complete	51 (25.5%)	14(7%)	0
nulliparous	88 (44%)	106 (53%)	0.07
no contraceptive use	83 (41.5)	141(70.5%)	0

Table 1: Demographic information of women from Ireland and Philippines who completed the online consultation

4.1.2 Gestational age up to 9 weeks.

4.1.2.1 Study 1.

When WoW was initiated in 2006, mifepristone was only officially registered for use only up to 7 weeks of pregnancy although research had already shown that it could also be safely used up to 9 weeks of pregnancy. Therefore, the first study analysed the outcome for a duration of pregnancy up to 7 weeks and between 7 to 9 weeks pregnancy at the time of the online consultation. It was found that 80.0% of the women were less than 7 weeks pregnant and 20.0% were between

7 to 9 weeks pregnant at the time of the consultation. Gestational age was confirmed with ultrasound in 78.9% of the cases (107).

4.1.2.2 Study 2.

In this study 83.7% of the women stated that they were less than seven weeks pregnant at the time they consulted the doctor online; the remaining 16.3% were seven to nine weeks pregnant at the time of the online consultation (108).

4.1.3 Gestational age of more than 9 weeks.

The study of Brazilian women calculated the actual gestational age at the time of the medical abortion and found that 67.4% of the women had a gestation of 9 weeks or less, 23.1% of the women had a gestational age of 10, 11 and 12 weeks and 9.5% of the women had a gestational age of 13 weeks or more, when performing the medical abortion. Of the women, 83.7% reported confirmation the gestational age of the pregnancy with an ultrasound scan (109).

4.1.4 Complaints and symptoms of a possible complication.

4.1.4.1 Study 2.

In this study 24.9% of the women reported a visit to the doctor or a hospital for a perceived complication after the medical abortion. Of these women more than half (56.9%) had a surgical intervention. There was a large difference in frequency of doctors visits after the medical abortion in the different regions. Women in Western Europe (22.2%), Latin America and the Caribbean (29.0%), Asia/Oceania (24.0%) and Eastern Europe (25.7%) were more likely to visit a doctor or a hospital than women in the Middle East and Africa (16.7 and 17.2%, respectively)(108).

Data about the type of complaints that lead women to visit a local doctor or hospital, were not collected in this study.

4.1.4.2 Study 3.

This study analyzed the data on women living in Brazil and found that 42.2% of them reported having had no signs of a complication before going to a doctor to confirm the completeness of the abortion (109).

Of the women who had a surgical intervention after the medical abortion, only 12.5% reported heavy bleeding, which would have justified an intervention.

Of the women, 10.9% reported having pain that continued several days after the abortion, 3.1% reported having fever and/or abnormal discharge, 21.9% reported having more pain or cramps than they had expected, and 9.4% thought they had not enough bleeding or pain (109). These types of complaints do not always require a surgical intervention (Table 2).

	total	< 9 weeks	10, 11, 12 weeks	> 13 weeks	p-value
type of complaint	n=64	N=40	n=11	n=13	
no complaints (%)	27 (42.2)	16 (40.0)	5 (45.5)	6 (46.1)	0.94
continuing pain (%)	7 (10.9)	5 (12.5)	1 (9.1)	1 (7.7)	0.88
heavy bleeding (%)	8 (12.5)	6 (15)	0	2 (15.3)	0.44
fever/vaginal discharge (%)	2 (3.1)	1 (2.5)	1 (9.1)	0	0,43
more pain/bleeding than expected (%)	14 (21.9)	8 (20.0)	3 (27.3)	3 (23.1)	0.9
not enough bleeding/cramps (%)	6 (9.4)	4 (10.0)	1 (9.1)	1 (7.7)	0.97

Table 2: Complaints leading to surgical intervention

4.1.5 Factors influencing surgical intervention rate.

4.1.5.1 Study 1: Effects of Follow up.

The first evaluation of the services provided by Women on Web showed that a follow up of 54.8% was accompanied by a surgical intervention rate after using the medical abortion of 13.6%. After improving follow-up rates to 77.6% the surgical intervention rate dropped to 6.8% (107).

4.1.5.2 Study 2: Effects of Location.

The second study examined the effect of different geographical locations on on surgical intervention rate and showed a wide variety between regions from 4.7% in the Middle-East, 5.8% in Western Europe, 6.1% in Africa and 11.0% in Asia and Oceania up to 14.4% in Latin America and the Caribbean and 14.8% in Eastern Europe (p=0.000) (Table 3). The surgical intervention rate was also higher (16.4%) in the gestational group of 7 to 9 weeks than in the gestational group of less than 7 weeks (11.7%) (108).

	total	Surgical (%)	No surgical (%)	p-Value
Worldwide	2323	289 (12.4)	2034 (87.6)	0.00
Western Europe	362	21 (5.8)	341 (94.2)	
Eastern Europe	1342	199 (14.8)	1143 (85.2)	
Middle East	127	6 (4.7)	121 (95.3)	
Africa	33	2 (6.1)	31 (93.9)	
Asia/Oceania	146	16 (11.0)	130 (90.0)	
Latin America/Caribbean	313	45 (14.4)	268 (85.6)	

Table 3: Geographical location of the women undergoing a surgical intervention after the medical abortion

4.1.5.3 Study 3: Effects of Gestational age.

This study looked at the effects of gestational age at the time of the medical abortion on the surgical intervention rate and the number of ongoing pregnancies and found that 20.9% of the women reported having undergone a surgical

intervention after using the medication. When divided into gestational groups, 19.3% (95% CI 14.5–25.2) of the women with a gestational age of 9 weeks or less, 15.5% (95% CI 8.9–25.7) of the women with a gestational age of 10, 11 or 12 weeks and 44.8% (95% CI 28.4–62.5) of the women with a gestational age of 13 weeks or more, underwent a surgical intervention. The difference between the groups was statistically significant (p=0.006) (109) (Table 4).

	total	9 weeks or less	10, 11, 12 weeks	13 weeks or more	p-Value
outcome	n=307	N=207	n=71	n=29	
complete (%) (95% CI)	236 (76.9) (71.7-81.4)	163 (78.7) (72.4-84.0)	59 (83.1) (72.0-90.6)	14 (48.3) (29.9-67.1)	
ongoing pregnancy(%;) (95% CI)	7 (2.3) (1.1-4.6)	4 (1.9) (0.8-4.9)	1 (1.4) (0.3-7.6)	2 (6.9) (1.9-22.0)	0.22
surgical intervention (%) (95% CI)	64 (20.9) (16.5-25.9)	40 (19.3) (14.5-25.2)	11 (15.5) (8.9-25.7)	13 (44.8) (28.4-62.5)	0.006

Table 4: Outcome in different gestations

4.1.5.4 Study 5: Effects of total misoprostol doses after a gestational age of 12 weeks.

This study retrospectively analyzed the data of 115 Brazilian women who carried out a second trimester medical abortion (after 12 weeks of gestation). The outcome of the medical abortion measured in terms of ongoing pregnancy and surgical intervention rates with regards to the three different dosages of misoprostol (1200 mcg, 1600 mcg and 2400 mcg) was analyzed (Table 5). The outcome was not significantly different for the misoprostol dose used.

In the 1200 mcg group, a surgical intervention was performed in 30,8% of the women and 2,6% had an ongoing pregnancy. In the 1600 mcg group, 15,4% of the women required a surgical intervention and 7,7% had an ongoing pregnancy. Among women that used a dose of 2400 mcg misoprostol, 28% required a surgical intervention and 8% of the women had an ongoing pregnancy. The reported differences in surgical intervention rates between prescribed dosages of misoprostol were not significant (p=0.367).

	total	1200 mcg	1600 mcg	2400 mcg	p-value
outcome	N=115	N=39	n=26	n=50	
ongoing pregnancy(%)	7 (6.1%)	1 (2,6%)	2 (7,7%)	4 (8,0%)	0.52
surgical intervention (%)	30 (26,1%)	12 (30,8%)	4 (15,4%)	14 (28,0%)	0.37

Table 5: Differences in effectiveness between 1200 mcg, 1600 mcg and 2400 mcg misoprostol.

4.1.6 Ongoing pregnancy rates.

4.1.6.1 Study 1 and 2.

The first study showed an ongoing pregnancy rate of 1.1% (92). The second study found an ongoing pregnancy rate of 0.9%, which is comparable to the first study (107, 108).

4.1.6.2 Study 3 and 5.

Of the women with a pregnancy of 9 weeks or less at the time of the medical abortion, 1.9% (95% confidence interval of 0.8-4.9], women reported an ongoing pregnancy and 1.4% of the women with a pregnancy of 10, 11 or 12 weeks (95%

CI 0.3–7.6) reported an ongoing pregnancy. These rates fall within the same range as the first and second study (109) (Table 4).

The ongoing pregnancy rate was higher in the gestational age group of 13 weeks or more at the time of the medical abortion among women using 6 tablets of misoprostol. In this group 2 of 29 women (6.9%; 95% CI 1.9–22.0) reported a continuing pregnancy.

In study 5, 2,6% of the women in the 1200 mcg group, had an ongoing pregnancy. Of the women in the 1600 mcg group, 7,7% had an ongoing pregnancy. Among the women who used a dose of 2400 mcg misoprostol, 8% had an ongoing pregnancy. The reported differences in the ongoing pregnancy rates between the prescribed dosages of misoprostol were not significant (p=0.516).

4.1.7 Acceptability.

4.1.7.1 Study 1.

The first study found that of 58.2% of the women were just grateful to be able to have the medical abortion, 30.9% felt stressed but found the experience acceptable, 9.8% had no specific feeling or did not want to share it, and 1.0% answered that if they had known before how stressful it would be they would not have done it (107).

4.1.7.2 Study 2.

This study found a similar acceptability rate among 1893 women. Of the women, 64.1% reported that they were grateful, 22.5% reported acceptable stress and 11.1% reported no specific feeling or did not want to share their feelings. Only 2.3% of the women reported the following: “if I had known before how stressful it would be, I would never have done it myself”.

This study found that 1.3% of the women who did not have a surgical intervention considered the abortion extremely stressful, compared to 8.6% of the women who received a surgical intervention after the abortion (p=0.000) (108).

4.1.7.3 Study 3.

At the time of the third study alterations had been made to the follow-up questionnaire. Women could choose between only 3 options: "I felt grateful", "I thought it was acceptable" or "It was not acceptable for me". No one reported that the process was unacceptable for her (109).

4.1.7.4 Testimonies posted on the website.

Some of the testimonies that have been posted on the WoW website by the women themselves, suggest that some of them experienced the medical abortion at home as a way of increasing their privacy and control.

"My experience at home was a lot better then in a clinic. I would never go back to a clinic again. All they care about is getting money off you, being an Irish person travelling over, we have to pay, whereas the British receive it for free a lot of the time through the NHS" (111).

"Was straight forward with the instructions and felt more relaxed in the comfort of my own home" (112).

Other women though described that they had experienced stress because of the abortion at home.

"Having to do this at home rather than in a hospital with medical care scared me and this made me angry with my government it didn't affect how I felt about having an abortion, we made that decision for the right reasons" (113).

" ……that I was alone in my room and if something happened to me and who could I ask for help. Thanks god, nothing happened to me during my abortion" (114).

4.2 STUDY 4: MIDWIFE PROVISION OF MEDICAL ABORTION.

In total 1180 women were included and randomly allocated to either a nurse midwife or gynecologist for counseling, examination including ultrasound, and a medical abortion service. The study found that the provision of medical abortions by midlevel providers is as effective and safe as the provision of medial abortion by a physician (Table 6). Patients were more positive about nurse midwife providing the abortion care than they were about physicians providing the service (Table 7). In addition nurse midwives less time in total on the consultation, which has an economical impact on the healthcare system (110).

Future Preference	Allocated to nurse midwife (N=534)	Allocated to physician (N=533)	CI	p-value
Midwife	200	108	0.118-0.225	<0.001
Physician	5	12	-0.003-0.030	0.06
Indifferent	271	320	0.033-0.152	<0.001
Missing	58	93	0.024-0.108	0.002

Table 6: Preference with regard to possible future abortions.

Outcome measure	Allocated to nurse midwife (%)	Allocated to physician (%)	Total (%)	CI
Efficacy	476/481 (99)	445/457 (97.4)	923/940 (98.2)	-0.002-0.036
Safety	453/473 (95.8)	414/443 (93.5)	867/916 (94.7)	-0.006-0.054
Acceptability	200/535 (37.4)	12/533 (2.3)	212/1068 (19.9)	0.308-0.394

Table 7: Overview of primary and secondary outcome measures

5 CONFLICT OF INTEREST.

My first encounter with the consequences of unsafe abortions took place when I followed my surgical internship in Guinea, Africa. Each day, a woman was hospitalized because of severe bleeding which were occasionally nearly fatal. The French doctor in the hospital actually performed abortions but I did not realize at the time what legal risks he took, nor did I realize that the women hospitalized with complications of botched abortions were caused by the illegality.

Only after I followed my abortion training and worked as a ships doctor with Greenpeace in South America, where I came across many women who severely suffered as a result of the lack of access to safe, legal abortion, I realized the health impact of illegal abortion. These women and their stories inspired me to start Women on Waves. On a ship, abortion pills can be provided safely and legally to women with unwanted pregnancies, outside the territorial waters of countries where abortion is illegal. At the invitation of local women's organizations, Women on Waves set sail to Ireland (2001), Poland (2003), Portugal (2004), Spain (2008) and Morocco (2012). These campaigns generated enormous public interest. As a result of the media attention, women from all over the world started emailing for help. These stories were so desperate that I decided it should be possible to help them. As an abortion can be carried out by using pills, it can be sent by mail. And so I initiated the Women on Web service.

The Women on Web database is unique as it is at present the only existing database with information about women who carry out a medical abortion by themselves in countries where there is no access to abortion services. The studies presented in this thesis only examined pieces of the information at hand. There is so much more information that is worthwhile exploring.

6 DISCUSSION.

The studies included in this thesis show that medical abortion can be safely and effectively be provided by midlevel healthcare personnel and administered by women themselves when they are provided with accurate information.

Task shifting in medical abortion in high resource settings in which assessment of the duration of pregnancy through ultrasound is part of the protocol is highly effective. The study is of importance for low resource settings as well as ultrasound is becoming more and more available. The study in Sweden was the first where no pre-examination was performed before allocating the women to a doctor or nurse midwife and the complete abortion treatment was done by the nurse midwives. Nurse midwives spent less time on the consultations resulting in a potential economic impact on the healthcare system.

The main arguments against the use of email or an online consultation form (store and forward telemedicine) is the lack of control on false answers.

Other studies reporting on the use of telemedicine for providing medical abortions, describe the use of real time video conferencing. One study in the US reports the provision of medical abortion via telemedicine at clinics where trained staff is present but no physician. Clinical staff uploaded the patient's medical history and ultrasound image for review by the physician at a distance. The physician also had a consultation with the woman in question via video teleconference. If the woman was eligible for medical abortion, the doctor entered a password that remotely unlocked a drawer in front of the woman containing the medical abortion tablets. The doctor observed how the woman swallowed the mifepristone and gave her some final instructions via the video teleconference (115, 116).

In a Canadian study, women consulted a physician and counselor via videoconferencing in order to be screened, receive information, and give consent. The women went to a local laboratory for HCG tests at the initial screening, on the day they took the medication and one week later (3 tests). If

their HCG level was more than 5000 mIU/mL, she underwent an ultrasound. The medications were couriered or a prescription was faxed to a local pharmacy. Because mifepristone is not available in Canada, the women received methotrexate (50 mg/m2 orally) and misoprostol (800 mcg vaginally which was repeated twice 4–12 hours later). Women were given a follow-up videoconferencing appointment to discuss the outcome of the medical abortion. If their HCG level had fallen by 80% in the first week, women were informed that the abortion is complete and that further follow-up was not necessary. If additional medication, surgery, or further blood tests was necessary, this was arranged by the clinic (117).

Although real-time video conferencing can asses whether the person on the other side is indeed a woman and not a man, it cannot check whether the person's true identity. Furthermore, unless the doctor watches the woman swallowing the medicines - like they did in a study in the US- , there is not guarantee that the woman in question will actually use the medicines provided by mail as described in a study in Canada (115, 116, 117).

Furthermore research has shown that the average deception detection rate is only 54% in a normal population and that lie detection performance is not reliable (118).

Another argument against telemedical abortion provision is that the absence of a physical examination makes it impossible to confirm the duration of the pregnancy. The study in the US study tackled this problem by the performance of ultrasound examination in the women by clinical staff. During the study in Canada, the HCG levels were assessed at a local laboratory one week before the medical abortion, and at the day the medical abortion was carried out (115, 116, 117).

It is true to say that the doctor working for the Women on Web service cannot confirm the gestational age. Although women are also advised to have an ultrasound to establish the duration of the pregnancy and to exclude an ectopic pregnancy, review of the evidence suggests that ultrasound scanning is not

necessary for early medical abortion (84). If women have no access to ultrasound facilities they can estimate the duration of their pregnancy based on the last menstrual period. Research has shown that nine in ten women are able to estimate their gestation age by their last menstrual period at a sufficient level of accuracy to carry out a medical abortion themselves. A woman's own estimate of pregnancy duration has been shown to be approximately 19 days shorter than ultrasound estimates (119).

Of course there is the risk of women underreporting their gestational age to access help. Although WoW only intends to provide medical abortions up to 9 weeks of pregnancy, a woman may acknowledge being pregnant for more than 12 weeks, after already having obtained the package containing the medicines. For this reason, the website warns of an increased risk of complications if the gestational age is higher than 9 weeks.

Worldwide the majority of abortions are induced in the first trimester of pregnancy. Only 10-15% of abortions take place in the second trimester. The provision of medical abortions in more advanced stages of the pregnancy has the potential to decrease the number of major complications (even if incorrect dosages of misoprostol are being used) (120, 121, 122).

In case of an intentional or unintentional error in dates and the gestational age is in fact higher than the woman claims, research has shown that a medical abortion is still safe and effective until the end of the first trimester and also in the second trimester (120, 121, 123, 124, 125, 126, 127, 128).

A limitation to all four studies that examined the outcome of the telemedical service, is the overall low follow up rates and which may implicate that some serious complications were missed. Another limitation is the information being based on self-reporting which may lead to inaccuracies, such as incorrect reporting on the duration of the pregnancy or a bias towards selective reporting which cannot be excluded.

In all four telemedical studies the surgical intervention rates are higher than usually reported with regards to medical abortion (5). However, other studies in

outpatient settings that have a lower follow-up rate found a higher vacuum aspiration rate as well (128, 129). A possible explanation is that women who experience problems after the abortion are more likely to come for follow-up visits or fill out follow-up forms compared to the women who had no problems or did not use the medication.

Geographical differences in surgical intervention rates might be explained by cultural reasons. Women from the Middle East for instance avoid healthcare professionals because they cannot present with a miscarriage in case they are unmarried and are, therefore, not supposed to be pregnant at all. The low rate of healthcare visits in Africa may be due to the lack of care providers and the high cost of healthcare (108).

We found that geographical cultural and political differences also correspond with demographic characteristics of women who completed the online consultation. For example average rates of contraceptive usage the Philippines is 41% to 50% (130). On the other hand in Ireland contraceptives are widely available and accessible and 64.8% of people aged 18-49 use contraceptives (131, 132). Our analyses found that more women from the Philippines reported that the unwanted pregnancy was caused because they did not use contraceptives compared to women from the Ireland (70.5% vs 41.5%).

Another factor which may explain the higher surgical intervention rates can be the advice to women to obtain an ultrasound scan 10 day after using the medication. In many countries an incomplete miscarriage (abortion) is still traditionally followed by surgical curettage even though current standards imply that surgical intervention is not needed if the woman has no complaints (5). This is also suggested by our findings that 40% of the woman who underwent a surgical intervention after the medical abortion did not have any signs or symptoms of a complication. Only 12.5% of the women who had a surgical intervention after the medical abortion reported heavy bleeding justifying the intervention (109).

In our studies we found that the surgical intervention rate in the gestational age up to 12 week (18.3%) in Brazil is comparable to the reported surgical intervention rate of women with pregnancies up to 9 weeks. The risk of a surgical intervention or ongoing pregnancy after home medical abortion tends to increase only after 12 weeks of pregnancy (108, 109).

The high surgical intervention rate in the second trimester abortions (44.8%) in our studies can only partially be explained by the lack of a sufficient amount of misoprostol to complete the maximum 4 additional doses advised by the WHO in case if the abortion was not induced after the second dose of misoprostol was taken (5). As in other studies, Rose et al. reported an average surgical intervention rate of 8.3% in women who had had a medical abortion at a duration of pregnancy of 13–20 weeks and showed that the proportion of women who has an successful abortion increased from 40% after two doses of misoprostol to 96% after five doses (121, 126).

Indeed our study found that the number of surgical interventions that was performed among women using a dose of 1600 mcg misoprostol (15,4%) was half of the number observed in the group of women who took 1200 mcg misoprostol (30,8%). However 4 extra doses of misoprostol (a total of 2400 mcg) did not result in a lower surgical intervention rate (28%). Furthermore higher ongoing pregnancy rates were found in the groups that used higher doses of misoprostol (2.6% vs 8%), although these differences were not significant.

On the other hand when our data are compared to the findings of a study done in Finland, there seems to be little difference in the effectiveness of mifepristone/misoprostol between home administration and administration at a clinic in the second trimester of pregnancy (128). This should be confirmed in larger studies.

Although a few women having an medical abortion will need hospital care because of complications (heavy bleeding, infection), the decision to actually seek medical services in these situations might be hindered by fear of being

reported and prosecuted. Hesitation to seek care increases the health risks and may lead to permanent disability or death (133).

Furthermore the quality of local post abortion care can be very poor and the use of outdated methods like D&C can cause complications and future fertility problems (134, 135).

The studies in this thesis show that acceptability and outcome of medical abortion carried out up to 9 weeks of pregnancy is similar whether provided by doctors or nurses midwives or through telemedicine (107, 108, 109, 110). Other prospective cohort studies similarly showed that there are no differences in acceptability between home-based and clinic-based medical abortion across countries (122, 136).

A study in Sweden found that women experienced greater autonomy with home medical abortion and that it increased their privacy and control (137, 138). This was also reported by women who used the WoW service (111, 112). Another study showed that acceptability of home medical abortion is also high in later gestational ages. Of the women with 64 to 70 days gestation, 88.3% found the procedure acceptable (139).

Of course the circumstances of doing a medical abortion after obtaining it via telemedicine in a country where there is no other alternative available cannot be compared to a medical abortion provided by a midwife in a country where abortion is legal and accessible. Additional stress factors are: the difficulty finding a solution and the doubt whether the service is legitimate as there are a lot of websites that send fake medicines or no medicines at all. After having verified the reliability of the service and filling out the online consultation, there is the stress of waiting for the package to arrive followed by the stress of having the medical abortion at home. Despite all this, our research found that the medical abortion at home provided via telemedicine was highly acceptable for the women in question who reported appreciation for the privacy and control.

Although medical abortion provided by telemedicine has the potential to circumvent all possible logistical, financial and legal barriers to access safe

abortions services, the service suffered some setbacks. Customs in Ireland, Brazil and Poland started to confiscate packages containing the medical abortion medication. In Brazil this even resulted in the prosecution of a woman and while she eventually won the court case, this must have been an awful experience for her (140).

Although states are under the positive obligation to respect the right to health by refraining from limiting access to contraceptives and other means of maintaining sexual and reproductive health, it will be hard to enforce this obligation (141, 142).

Another challenge to ensure accurate information about medical abortion is the censorship imposed by the companies that mediate access to internet. Exemplary is Google's AdWords for example, does not allow abortion related advertisements to be published in certain countries (143).

Similarly Facebook removed an image with information about the use of misoprostol to induce a safe abortion in January 2012. Only after extensive media coverage did they allowed the image to be posted again (144).

Changing the public perception of the safety of medical abortion by women themselves, remains a challenge as well. An example is the headline of the article in the Daily Telegraph of 18 July 2008 in reaction to the publication of the first article on medical abortion via telemedicine in the BJOG which stated: "Women risk health by using abortion websites"(145).

Most abortion laws originate from the time when surgical abortion was the only safe and effective abortion method available. The availability of medical abortion has had a dramatic impact on the circumstances in which women can have abortions. Unfortunately the scientific findings about the safety and acceptability of medical abortion at home are not yet reflected in regulations and practice of medical abortion care in most countries around the world. For example, although according to the text of the Dutch abortion law a general physician should be able to provide medical abortions up to pregnancies of 6.5 weeks, in reality the health inspection states that to do so outside a registered

clinic would be illegal and actively discourages general physicians to provide medical abortions in their practices (146).

A desirable future scenario would be for medical abortion to follow the same path with regards to availability as emergency contraceptives did in the past years. Initially these were only available on prescription, but dedicated EC products are now registered and available over the counter in more than 50 countries (147, 148).

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" The right to health imposes three types of obligations on States: the obligations to respect, to protect and to fulfill. The obligation to respect requires States to avoid measures that could prevent the enjoyment of the right. Therefore, States are under the obligation to respect the right to health by, inter alia, refraining from (i) denying or limiting equal access for all persons to preventive, curative and palliative health services; (ii) prohibiting or impeding traditional preventive care, healing practices and medicines; v) limiting access to contraceptives and other means of maintaining sexual and reproductive health; and (vi) censoring, withholding or intentionally misrepresenting health related information, including sexual education and information, as well as from preventing people's participation in health-related matters."

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