

Unintended pregnancy and early medical abortion

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To the man who always believed in me and inspired me to chase my dreams. You taught me that nothing is impossible, and your wisdom and strength continue to guide me every day. This book is for you, Dad.

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Background: Very early medical abortion (VEMA) is performed before the confirmation of intrauterine pregnancy (IUP) by ultrasound. Over the past 25 years, more women have sought abortions earlier in pregnancy. Concerns about VEMA's effectiveness and the risk of ectopic pregnancy (EPs) have resulted in inconsistent practices, multiple clinic visits, and limited access to care. While many countries adopted telemedicine abortion during COVID-19 to minimize in-person visits, Swedish regulations still required all women seeking medical abortion to attend in person for an examination and to receive mifepristone under clinical supervision.

Aim: The overall aim of this thesis was to increase the safety and accessibility of early medical abortion by expanding available knowledge and obtaining data to develop evidence-based guidelines.

Methods: This thesis comprises four studies using quantitative and qualitative methodologies. *Study I:* a retrospective case note review; *Study II:* a multicenter, multinational randomized controlled trial; *Study III:* a cohort study from the randomized controlled VEMA trial; *Study IV:* a qualitative study with semi-structured interviews.

Results: Complete abortion was defined as no ongoing pregnancy or need for further surgical intervention. In *Paper I*, the success rate of VEMA was 97.6% (660/676), and the number of ongoing pregnancies was (0.59%). The success rate was lower (93.1%) in pregnancy of unknown location compared to those with a probable intrauterine pregnancy (98.4%). Six cases of EPs (0.88%) required post-abortion treatment; in *Paper II*, the success rate was 95.2% (676/710) in the VEMA group and 95.3% (656/688) in the standard (delayed) treatment group, with a risk difference of only 0.1 (CI -2.3, 2.3). Ongoing pregnancy rates were higher (3.0% vs. 0.1%; RR 20.3, CI 2.74, 151), but surgical interventions were lower (1.8% vs. 4.5%; RR 0.41, CI 0.21, 0.77) in the early group. Ten cases of EPs (1.3%) were identified in the early group, and 6 cases (0.8%) in the standard group; *Paper III*, a decline in hCG level of $\geq 80\%$ was observed in $\geq 95\%$ of cases with complete abortion (533) 7 (+/- 2) days post-abortion, regardless of baseline hCG levels. Rising or insufficient decline ($< 80\%$) indicated ectopic and ongoing pregnancy; in *Paper IV* the participants found it easy to contact the abortion clinic but faced undesired waiting time, gynecological exams were appreciated by most but distressing for some. Telemedicine abortion and home administration of mifepristone were seen as good options in addition to in-person care.

Conclusion: This thesis confirms the efficacy and safety of VEMA, validates hCG monitoring as a reliable follow-up method after VEMA, and emphasizes patient satisfaction with in-person abortion care while highlighting the potential benefits of more flexible abortion services.

Keywords: medication abortion, very early medical abortion, human chorionic gonadotropin, medical abortion, ectopic pregnancy

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Sammanfattning på svenska

Bakgrund: Medicinsk abort med mifepriston och misoprostol, är den vanligaste metoden för abort i Sverige och står för 97 procent av alla aborter. Ungefär 35 550 aborter rapporterades till Socialstyrelsen under 2023. Andelen aborter som utförs före graviditetsvecka 7 har ökat stadigt och utgjorde 63 procent av alla aborter under 2023. Under och efter COVID-19 pandemin har många länder infört möjligheten att genomföra hela aborten hemma genom en telemedicinsk modell. I Sverige kvarstår dock regeln att kvinnor som söker medicinsk abort måste genomgå en fysisk undersökning och ta den första aborttablett (mifepriston) under övervakning på kliniken. Fler kvinnor söker abort i mycket tidig graviditet, ibland innan graviditet kan bekräftas i livmodern med vaginalt ultraljud. Det finns en farhåga för att mycket tidig medicinsk abort VEMA (Very Early Medical Abortion) kan vara mindre effektiv än behandling som initieras efter ultraljudsbekräftelse av graviditet. Det finns också en risk för utomkvedshavandeskap (ektopisk graviditet), vilket ytterligare komplicerar tidig behandling. Dessa faktorer har lett till inkonsekventa behandlingsprotokoll, upprepade besök på abortkliniker, onödiga, eller i vissa fall skadliga väntetider och försämrad tillgång till vård. Tidigare studier har visat motstridiga resultat gällande effektiviteten och därför ville vi undersöka om en mycket tidig abort är lika effektiv och säker som att avvakta.

Syfte: Det övergripande syftet med denna avhandling var att öka säkerheten och tillgängligheten för tidig medicinsk abort genom att bredda kunskapen och samla in data för att utveckla evidensbaserade riktlinjer.

Delarbete I: Denna retrospektiva studie bygger på en genomgång av medicinska journaler, från 682 kvinnor som genomgått tidig medicinsk abort, från två kliniker: GynMed-kliniken i Wien, Österrike och Sahlgrenska Universitetssjukhuset i Göteborg, Sverige. Syftet med denna studie var att utvärdera utfallet av mycket tidig medicinsk abort (VEMA), undersöka om metoden kan förbättra den tidiga diagnostiken och behandlingen av asymtomatisk ektopisk graviditet samt analysera mönstret för graviditetshormonet (hCG) nedgång efter en lyckad VEMA. Totalt 97,6 procent av kvinnorna genomgick en komplett abort. Endast 0,59 procent hade pågående graviditeter och 0,88 procent av deltagarna diagnostiserades med ektopisk graviditet. En genomsnittlig minskning av hCG-nivån med 93 procent noterades mellan dag 5 och 10 efter aborten.

Delarbete II: I VEMA studien inkluderades 1 504 kvinnor från 26 kliniker i nio länder. Deltagarna, som sökte abort randomiserades till antingen fördröjd abort eller

mycket tidig abort. Vid studiestart var alla deltagare högst sex veckor gravida och saknade symtom eller riskfaktorer för ektopisk graviditet. I båda grupperna genomgick över 95 procent av kvinnorna en komplett abort. I gruppen med fördröjd behandling var 4,5 procent ofullständiga behandlingar och behövde kompletteras med exeres, medan 0,1 procent av graviditeterna fortsatte. I den tidiga behandlingsgruppen behövde 1,8 procent genomgå exeres medan 3 procent av graviditeterna fortsatte. Totalt sett diagnostiserades cirka 1 procent av deltagarna med ektopisk graviditet.

Delarbete III: en kohort valdes ut från den randomiserade VEMA-studien. Syftet med den här studien var att undersöka om blodprov med hCG kan användas som ett verktyg för att öka säkerheten vid mycket tidig medicinsk abort VEMA och bedöma om hCG-minskning kan användas som en indikator på lyckad behandling. Över 95 procent av de med komplett abort (533) visade en minskning av hCG med minst 80 procent sju dagar efter aborten oavsett hur högt startvärdet var. En genomsnittlig minskning på 94 procent noterades vid lyckade aborter medan mindre minskning eller stigande hCG-nivåer signalerade ektopisk eller pågående graviditet.

Delarbete IV: en kvalitativ studie med semistrukturerade intervjuer med 20 kvinnor som sökte för tidig medicinsk abort genomfördes. Syftet med den här studien var att undersöka kvinnors erfarenheter av dagens abortvård med fysiska besök, väntetider och tillgång till vård, samt deras förslag på förbättringar och syn på en modell utan fysiska besök. Resultaten visade att det var enkelt att kontakta kliniken, men väntetider upplevdes som negativt. Gynekologisk undersökning inklusive ultraljud uppskattades av de flesta, men var stressande för vissa. Telemedicinsk abort och att ta mifepriston hemma ansågs vara bra alternativ till vård med fysiska besök.

Sammanfattning: Denna avhandling visar att mycket tidig medicinsk abort är effektiv och säker, även innan graviditeten bekräftats med ultraljud. Den bekräftar att hCG-uppföljning är en pålitlig metod samt lyfter fram att även om de flesta patienter är mycket nöjda med dagens abortvård i Sverige, finns ett tydligt intresse för och potentiella fördelar med att erbjuda mer flexibla vårdalternativ.

List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I.** Jar-Allah T, Hognert H, Köcher L, Berggren L, Fiala C, Milsom I and Gemzell-Danielsson K.
Detection of ectopic pregnancy and serum beta hCG levels in women undergoing very early medical abortion: a retrospective cohort study.
The European Journal of Contraception & Reproductive Health Care. 2022. Jan; 27:240–246
- II.** Brandell K, Jar-Allah T, Reynolds-Wright J, Kopp-Kallner H, Hognert H, Gyllenberg F, Kaislasuo J, Tamang A, Thuladhar H, Boerma, C, Schimanski K, Gibson G, Løkeland M, Teleman P, Bixo M, Kjaer M, Kallfa E, Heikinheimo O, Cameron S, Gemzell-Danielsson K.
A Randomized Trial of Very Early Medication Abortion
The New England Journal of Medicine (NEJM). 2024. Nov; 6:391:1685–1695
- III.** Jar-Allah T, Brandell K, Gyllenberg F, Kaislasuo J, Kopp-Kallner H, Heikinheimo O, Gemzell-Danielsson K Hognert H.
Change in hCG levels after very early medication abortion for pregnancy of unknown location and probable intrauterine pregnancy. *Submitted*
- IV.** Jar-Allah T, Edalat M, Nyman V, Milsom I, Gemzell-Danielsson K, Rydelius J, Hognert H.
Perspectives on Abortion Services, the Pre-abortion Visit, and Telemedicine Abortion: A Qualitative Study in Sweden.
Perspectives on Sexual and Reproductive Health. 2025. Jan; 0:1–9

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Abbreviations

AEs	Adverse events
CI	Confidence interval
D&C	Dilation and curettage
D&E	Dilation and evacuation
EMA	Early medical abortion
EP	Ectopic pregnancy
EPF	European Parliamentary Forum
EVA	Electric vacuum aspiration
FDA	U.S Food and Drug Administration
hCG	Human chorionic gonadotropin
IPPF	International Planned Parenthood Federation
IUD	Intrauterine device
IUP	Intrauterine pregnancy
LMP	Last menstrual period
MVA	Manual vacuum aspiration
NBoHW	National Board of Health and Welfare
PUL	Pregnancies of unknown location
RCT	Randomized controlled trial
SAEs	Serious adverse events
SRH	Sexual and reproductive health
VEMA	Very early medical abortion
WHO	World Health Organization
WoW	Women on Web
β-hCG	Beta-subunit of hCG

Introduction

Induced abortion, the voluntary termination of pregnancy, is an essential part of sexual and reproductive health (SRH). Although abortion is a common experience in women's reproductive lives, access is significantly shaped by varying legal, social, and economic factors. Unintended pregnancies, which may be mistimed, unwanted, and/or accompanied by feelings of uncertainty and ambivalence (1), often result in significant health, economic, and psychosocial impacts for women and their children and families (2). Current estimates indicate that nearly half (48%) of all pregnancies worldwide are unintended (correspond to 66 pregnancies/1000 women aged 15-49 years, with 61% of these ending in abortion, totaling approximately 73.3 million abortions each year (3). Comprehensive abortion care includes providing accurate information, managing the abortion procedure, and delivering post-abortion support. The World Health Organization (WHO) classified comprehensive abortion care as an essential health service during the COVID-19 pandemic in 2020 recognizing the importance of accessible abortion services (4).

Abortion is considered safe and effective when performed using methods recommended by the WHO guidelines (5). Adhering to these guidelines and using modern abortion methods helps keep the procedure safe, with minimal health risks (5, 6).

In this book, the terms "women", "individuals" and "persons" are used alternately to refer to individuals capable of pregnancy and childbirth. This includes cisgender women, transgender men, females, and those who identify as gender non-binary. Moreover "medication abortion" and "medical abortion" refer to termination of pregnancy by using pharmacological treatment.

Unintended pregnancy and abortion globally

The rate of abortion is often described as the annual number of abortions per 1000 women between 15-49 (or 15-44) years of age. The Global abortion rate remained consistent between 1990–1994 and 2015-2019 (39/1000 women). While the global annual rates of unintended pregnancy have declined since 1990 (from 79 to 64/1000) (3) (Figure 1).

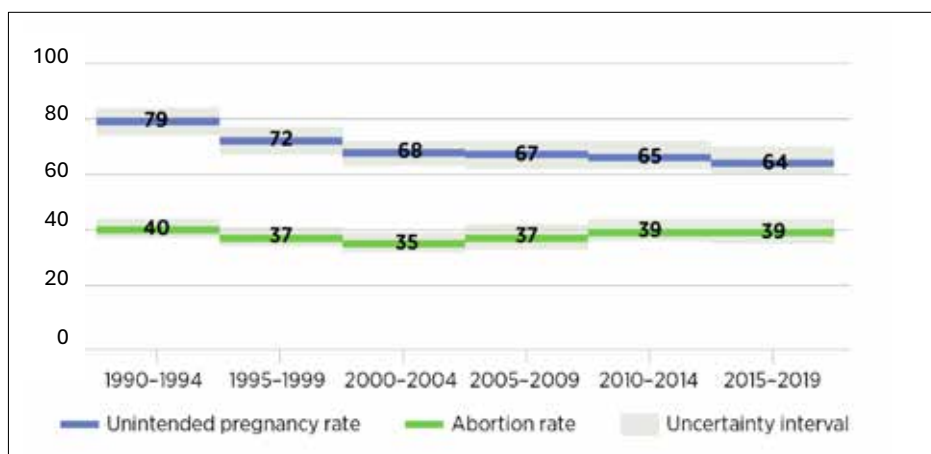


Figure 1. Global annual rates of unintended pregnancy and abortion per 1,000 women aged 15–49 years. Bearak J et al. *Lancet Glob Health* 2020; 8: e1152–61

Bearak J et al. highlighted the significant regional variations in abortion rates between 2015 and 2019, with West Asia and North Africa showing the highest abortion rates globally (53/1000 women), followed by Latin America and the Caribbean (3). In these regions, restricted access to contraception, limited reproductive healthcare, and social and legal barriers often lead to higher rates of unintended pregnancies and, consequently, more abortions (7). The abortion rate was the lowest in North America and Europe, about 17 per 1000 women (Figure 2). This low rate can largely be attributed to the availability of reproductive health services, comprehensive contraception access, and supportive policies that empower individuals to make informed reproductive choices. However, the U.S. abortion rate increased from 14.4 per 1,000 women in 2020 to 15.9 per 1,000 in 2023, reflecting changes after the 2022 Supreme Court ruling which ended federal abortion protections and allowed states to set their regulations (8).

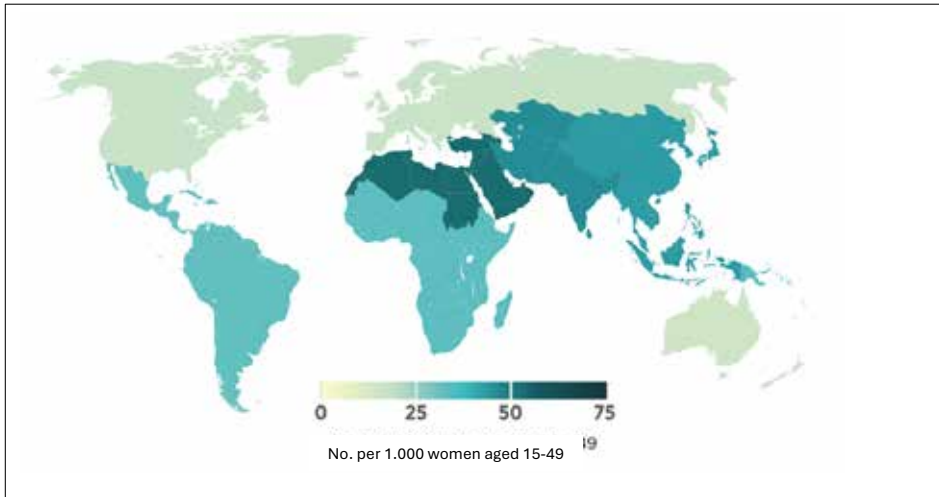


Figure 2. Abortion rates by 1000 women per region 2015-2019. Gutmatcher institute 2022

WHO defines unsafe abortion as a pregnancy termination carried out by an untrained individual or in conditions lacking basic medical standards. Abortions performed under proper medical conditions and by qualified personnel are considered safe, with a minimal risk for serious complications or mortality (9, 10). Unsafe abortions often arise due to restrictive laws and cultural taboos. Global data from 61 countries from 2010 to 2014 showed there were 55.7 million annual abortions worldwide and 45% of all induced abortions were unsafe. Over half of all unsafe abortions took place in Asia, primarily in South and Central Asia, while in Latin America and Africa, roughly 75% were unsafe. Among these, 17.1 million (around 31%) were deemed less safe, and 8 million (approximately 14%) were in the least safe category (11). Less safe abortion means that it meets only one of the two safety criteria: either a recommended method is used, but the provider is not fully qualified, or a qualified provider performs the abortion without using a fully approved method. The least safe category means neither a safe method nor a qualified provider is involved. These abortions carry the highest risk of complications and often occur in unregulated environments with informal setting as in private homes, increasing the likelihood of severe complications, including mortality. Unsafe abortion is higher in developing countries with restrictive abortion laws, where access to safe and legal abortion services is either highly restricted or entirely unavailable (12) (Figure 3).

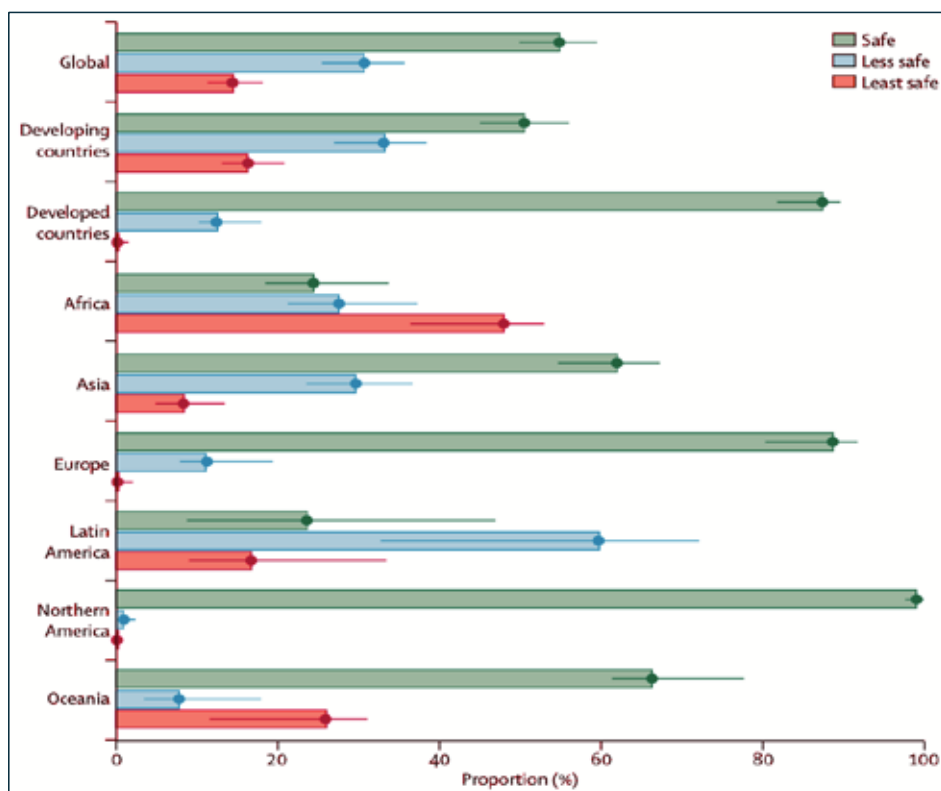


Figure 3. Distribution of abortion safety categories worldwide and by region. Gnatar et al. *Lancet* 2017; 390: 2372–81

In 2012, an estimated 7 million women in developing countries received hospital treatment for complications from unsafe abortions (13), such as incomplete abortion, infection, hemorrhage, and damage to the uterus and genital tract (14). The treatment rate was 6.9 per 1,000 women aged 15–44. Rates varied by region, from 5.3 in Latin America and the Caribbean to 8.2 in Asia. Over the past few decades, more than 60 countries have liberalized abortion laws to support reproductive autonomy and enhance access to safe abortion services recognizing that restrictive abortion policies negatively impact women's lives (Figure 4). In contrast, only four countries have moved to restrict the legality of abortion in recent years, including the United States (US), Poland, Nicaragua, and El Salvador. Still, about 40% of women of reproductive age worldwide live in countries where abortion laws are restrictive and limiting access to safe and legal abortion services (Figure 5) (15).

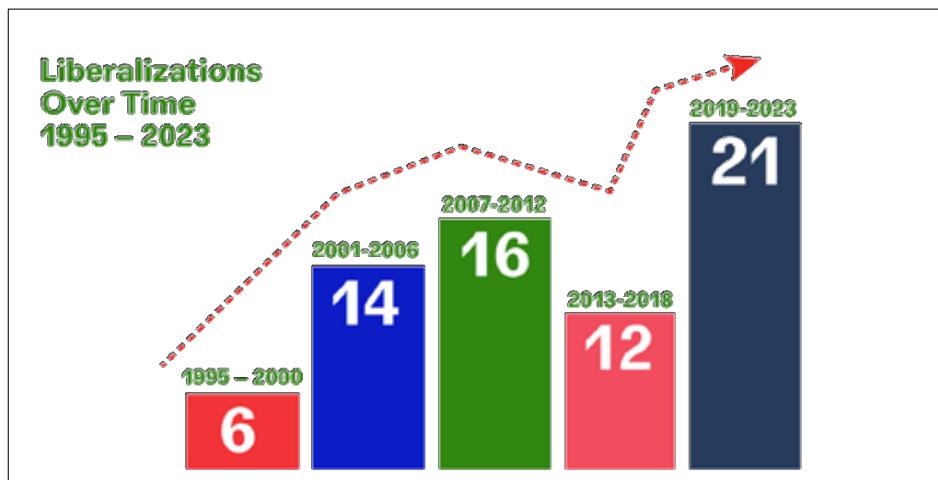


Figure 4. The number of countries liberalizing their abortion laws per time period. 7 countries liberalized more than once in the past 30 years (Argentina, Benin, Central African Republic, Chad, Colombia, Rwanda, and Thailand). Center for Reproductive Rights. August 2023

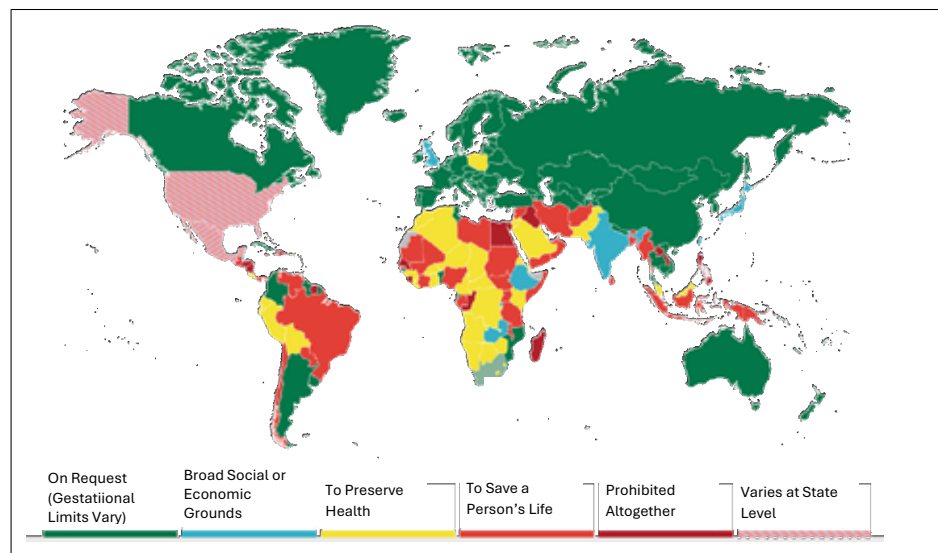


Figure 5. World Abortion Laws Map. Center for Reproductive rights. August 2023

Abortion policies in Europe

European countries have consistently progressed in implementing more liberal abortion laws and eliminating barriers that restrict access to abortion care. Nearly all European nations now permit abortion on request or broad social grounds, especially in the first trimester. Forty-two out of 47 countries in Europe, have legalized abortion on request, allowing individuals to make autonomous decisions about pregnancy termination without requiring specific justifications (16). Countries with progressive abortion laws also ensure that access remains legal to protect the health or life of pregnant persons.

Recently, some countries have introduced changes to improve access to abortion services and eliminate mandatory requirements. For example, Spain permitted girls aged 16 and 17 to access abortion without needing parental consent, and Malta changed the strict anti-abortion law to permit abortion when a woman's life is at risk. In March 2024, the French parliament voted to make abortion a constitutional right.

However, there are still challenges and barriers to abortion access in Europe such as mandatory waiting periods, (as in Germany, Hungary, and Italy), mandatory counseling which often includes biased, anti-abortion messaging to influence persons' decisions, and short legal time limits for abortion. Moreover, third-party authorization requirements, such as parental consent for minors or committee approvals are considered to be an obstacle to timely and safe abortion care. The European Abortion Policies Atlas was developed by the European Parliamentary Forum for Sexual and Reproductive Rights (EPF) and the International Planned Parenthood Federation European Network (IPPF EN), as a tool to provide a detailed analysis of abortion laws and accessibility across Europe. The Atlas ranks countries based on their abortion policies, highlighting both progressive and restrictive measures (17) (Figure 6).



Figure 6. The European Abortion Policies Atlas. Countries with high rank have progressive abortion policies. Countries with low ranks have restrictive policies. Sept 2021. Dark green most progressive (85-94%), green (71-84%), yellow (61-67%), orange (58-60%), and red most restrictive (0-16%) (European Parliamentary Forum EPF)

Abortion in Sweden

In Sweden, women are legally allowed to request an abortion until the 18th week of pregnancy, according to our current abortion law which dates from 1975. After the 18th week, the National Board of Health and Welfare (NBoHW) can permit an abortion if there are certain reasons and if the fetus is assessed not to be viable outside the uterus. Presently, the legal advice from the NBoHW allows permission for abortion until week 21 plus six days for a viable fetus. In 2023, approximately 36,000 induced abortions (18 per 1,000 women aged 15 to 44) were reported to the NBoHW. Abortions are most common in the 25 to 34 age group. Abortions among teenagers (15-19 years) declined from 25/1000 in 2006 to 8,5/1000 in 2023 (Figure 7). One explanation could be the increased prescription of long-acting contraceptives, such as hormonal intrauterine devices (IUDs), and contraceptive implants. Since 2017, contraception has been free for women under 21. All regions offer subventions for contraceptives to young women, meaning that contraceptives are either free or significantly reduced in cost until the age of 26. In Sweden, medical abortion can be used for all weeks of gestation, from very early to week 21+ 6 days. While in surgical abortion the upper time limit for vacuum aspiration is generally at week 12 of gestation.

Medical abortion is the most common abortion method, accounting for 97 percent of all abortions (18). Medical abortion is done by using a combination treatment of mifepristone and misoprostol. The proportion of abortions performed before week 7 of pregnancy have increased since the early 1990s, reaching 63 percent in 2023, and nearly 94 percent of abortions in 2023 took place before week 12 (Figure 8). The current Swedish abortion act mandates abortions to be conducted in authorized healthcare facilities by qualified medical practitioners.

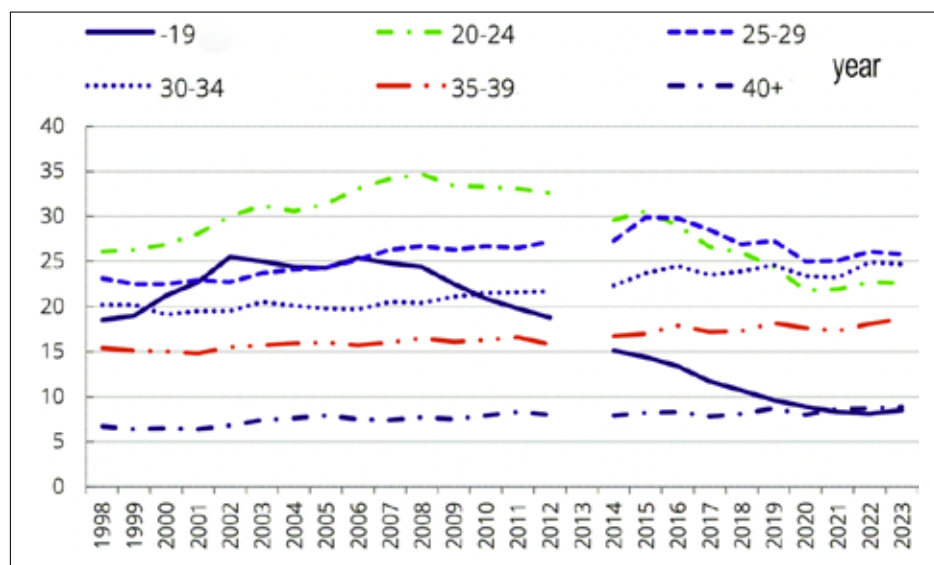


Figure 7. Number of abortions in Sweden per 1,000 women by age, 1998–2023. Swedish National Board of Health and Welfare. May, 2024

All women seeking medical abortion in Sweden are required to attend in person for examination and to have mifepristone administered within the clinic. Abortion services in Sweden are mainly available at specialized gynecological departments and clinics, both public and private, rather than being offered at primary-care facilities (19). However, a recently published report by The Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) confirms that offering mifepristone home administration does not compromise the treatment's safety or effectiveness of treatment (20, 21). Consultation visits typically last around 60 minutes and include a medical history review, an ultrasound scan, a gynecological/pelvic examination and screening for sexually transmitted infections (STIs). Medical doctors or certified abortion care midwives conduct this visit (19). Self-administration of misoprostol treatment at home was initially permitted until the

9th week of pregnancy in 2004 and was later extended to the 10th week. (22). However, WHO now recommends it can be done throughout 12+0 weeks of pregnancy (5). Medical abortion including home treatment with misoprostol is now widely recognized as highly effective, safe, and well-tolerated by women (5, 23-26).

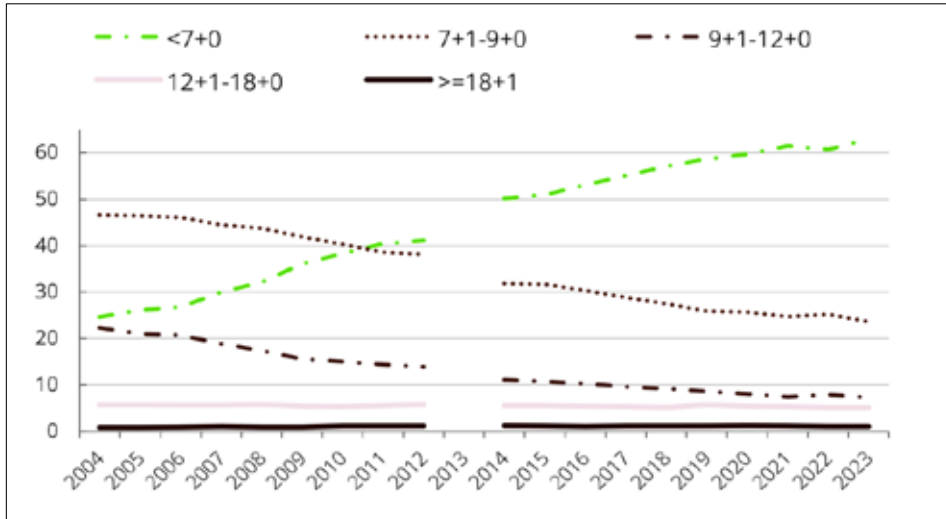


Figure 8. Percentage of abortion according to gestational length 2004-2023. Swedish National Board of Health and Welfare. May, 2024. Data for 2013 is missing due to a pause in data collection. Information on gestational length is missing for 2.8% of abortions in 2020

History of abortion methods

Various contraception and abortion methods have roots stretching back to ancient civilizations, with historical evidence indicating that different methods were used to terminate pregnancies. Riddle, J. M. (1992) provided a comprehensive look at the history of contraception and abortion including techniques and tools used by ancient civilizations such as Egypt, Greece, and Romans (27). Flemming R, explored Roman medical practices, including abortion, and discusses how early Roman medical texts documented various methods of terminating pregnancies (28). Multiple methods were used in ancient times to induce abortion, including herbal medicines, sharp instruments to pierce the uterus, and the use of mercury (29).

The rise of Christianity introduced more public control over sexual practices, accompanied by increased disapproval of abortion. Discussions on abortion

techniques became less common, and physicians gradually stepped back from providing these services. Before the 18th century, abortion and contraception were predominantly part of a “women’s culture,” with midwives playing central roles in providing family planning and abortion services. This role often subjected them to discrimination, with many midwives being accused of witchcraft for their involvement in reproductive healthcare. While, in Islam’s early teaching, there is information that abortion is prohibited after ensoulment (the soul enters the fetus) (30). The 20th century saw significant advancements in abortion methods to increase the safety and effectiveness (29).

Surgical abortion

The World Health Organization (WHO) defines surgical abortion as a procedure using transcervical techniques to terminate a pregnancy. These methods include vacuum aspiration (VA) for first-trimester abortion and dilation and evacuation (D&E) for second-trimester abortion. VA is performed using either electrical or manual methods. The procedure removes uterine contents through a plastic or metal cannula attached to a vacuum source. In electric vacuum aspiration (EVA), an electric pump creates the suction, while manual vacuum aspiration (MVA) uses a 60 ml hand-operated aspirator (often called a syringe) to create the vacuum. MVA devices support plastic cannula sizes ranging from 4 to 12 mm, whereas EVA suction tubing accommodates up to 16 mm cannula (5). Aspiration abortion can be used up to about 12-14 weeks of gestation and generally has a lower complication rate than sharp curettage (also known as dilation and curettage (D&C)). Compared to D&C, aspiration abortion carries a reduced risk of bleeding and uterine perforation (31). D&C is outdated and should not be used according to the WHO (2022).

The use of VA in abortion can be traced back to Russian physician S. G. Bykov, who, in the mid-1920s, became the first in medical literature to describe vacuum suction as a method for inducing abortion (32). In 1958, Chinese physicians were the first to document the use of electrical suction for abortion in medical literature. In the 1960s, Yugoslavian physician Franc Novak further refined VA device. By 1968, this innovative approach gained traction in the United States, with physicians such as Robert Hall adopting electrical vacuum aspiration as a safer, more efficient alternative to the traditional D&C method (30, 32). VA can be done by using general anesthesia or local techniques such as paracervical blockage. Cervical priming agents, like misoprostol or mifepristone may be given a few hours or days before VA to minimize the risk of cervix and uterine laceration, incomplete abortion and reduce

the time needed for the procedure (33). Complications from surgical abortion in the first trimester using VA are very rare. Bleeding requiring transfusion occurs in about 0–1% of cases, while infections occur in 0–2% of all cases. Cervical lacerations occur in 0.02–3.3% of cases, primarily when mechanical dilation is required in nulliparous, advanced gestation, and inexperienced provider (34).

Medical abortion

Medical or medication abortion is the most common method both in Sweden and globally. It is a combination of the progesterone receptor antagonist mifepristone and a prostaglandin (PG) analogue. Prostaglandin analogues are a Swedish innovation developed during the 1980ies. The PG analogue is usually administrated 24–48 hours after mifepristone.

Historical development of mifepristone in medical abortion

Mifepristone (RU-486) was first synthesized in 1980 by a team led by Étienne-Émile Baulieu at the French pharmaceutical company Roussel-Uclaf. The drug was named after the company (RU for Roussel-Uclaf) and the batch number (486). Initial clinical trials in the early 1980s showed that RU-486 was not highly effective on its own to induce abortion. A key breakthrough in mifepristone's use came in 1985 when researchers at the WHO collaborating center in Human Reproduction at Karolinska Institutet demonstrated its enhanced effect on uterine contractility when combined with a prostaglandin analog during early pregnancy (35). It was first approved in France and China in 1988 for use as a medical abortion drug up to seven weeks of gestation. After its approval in France, mifepristone gained acceptance across Europe, especially in countries where abortion was legal and widely accessible as the UK 1991, and Sweden in 1992 (up to 63 days) (36). The U.S. Food and Drug Administration (FDA) approved mifepristone for limited use in 2000 (37).

Initial studies in France and the European, British, and Swedish market authorization included a higher dose of mifepristone (600 mg) for medical abortion. However, later research found that 200 mg was as effective when followed by a prostaglandin analogue (37–39). The lower dose makes the procedure more affordable and accessible without compromising safety or effectiveness. In 2005, the WHO included mifepristone on its list of essential medicines, reaffirming it as an effective and important tool for reproductive health when used in combination with misoprostol for medical abortion (26). In 2013, a controlled clinical trial at Columbia University

confirmed that mifepristone's home administration is safe and acceptable (40), and a recently published report by The Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) also found offering home administration of mifepristone could promote autonomy without compromising safety or efficacy (20). During the COVID-19 pandemic, many countries introduced temporary policies to allow home administration of medical abortion pills, including mifepristone, which was later extended and made permanent in 2022 (Figure 9). Mifepristone is registered and approved as an abortion medicine in only about 100 countries (41).

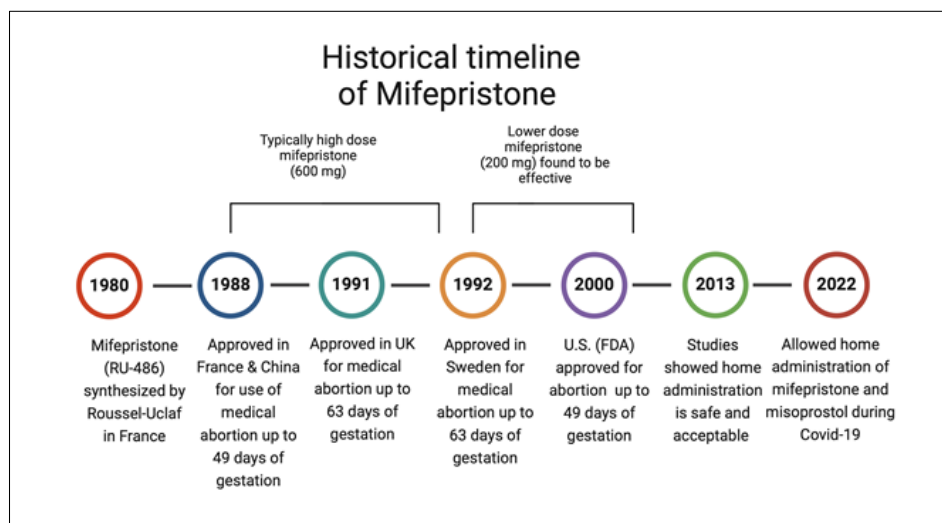


Figure 9. Historical development of mifepristone in medical abortion. Created by BioRebder.com, by Tagrid Jar-Allah

Mechanism and route of administration

Mifepristone acts as a progesterone receptor antagonist, blocking progesterone's effects, which is essential for maintaining early pregnancy. It is rapidly absorbed following oral administration, with an approximate half-life of 30 hours (37). Moreover, mifepristone binds to the progesterone receptor with high affinity (2.5-5 times greater than progesterone) (42). This action disrupts progesterone's suppression of uterine contractions, which increases uterine contractility, makes the uterine muscle cells more responsive to stimulation (especially by prostaglandins), softens the cervix, and detaches the decidua.

Misoprostol, a prostaglandin E1 analog, activates smooth muscle contractions in the uterus by binding to prostaglandin receptors in myometrial cells. This binding increases intracellular calcium, promoting muscle contraction. Misoprostol also plays a crucial role in cervical ripening, promoting collagen degradation and softening cervical tissue (26). In 1985, research demonstrated that combining mifepristone with a prostaglandin analogue significantly enhanced its effect on uterine contractility during early pregnancy (35).

Further research within the WHO network also refined the timing between administering mifepristone and misoprostol to enhance effectiveness and reduce side effects. Studies indicated that taking misoprostol 24 to 48 hours after mifepristone provides optimal results, with a higher efficacy rate and reduced likelihood of incomplete abortion (5). The flexible guidelines allow for the buccal, sublingual, or vaginal routes of misoprostol administration. Many studies compared these routes to provide the best balance of efficacy and comfort.

- **Oral Route:** Swallowing misoprostol leads to rapid absorption and significant first-pass metabolism reaches peak plasma levels within 30 minutes but declines sharply by 120 minutes (43). Oral administration has lower bioavailability compared to buccal, sublingual, and vaginal administration (26) (Figure 10) and higher rates of side effects such as gastrointestinal side effects, fever, and dizziness.
- **Buccal Route:** Misoprostol is placed between the cheek and gum for 30 minutes before swallowing any remaining fragments. Buccal administration results in similar bioavailability as the vaginal route, with slower absorption and lower peak levels but sustained elevation in misoprostol free acid compared to oral administration. This route avoids rapid spikes in concentration, offering a steadier absorption rate and potentially fewer gastrointestinal side effects (44).
- **Vaginal Route:** Vaginal administration of misoprostol results in plasma levels of free misoprostol acid similar to the buccal route but is better tolerated compared with oral, buccal, and sublingual administration (45). Misoprostol acid typically reaches peak plasma concentrations within 30 to 90 minutes (46) and lasts for around 4 to 5 hours (37, 46) (Figure 10). WHO guidelines still recommend this route when feasible, particularly in clinical settings.

- **Sublingual Route:** Sublingual administration under the tongue has, pharmacokinetics similar to merging oral and vaginal profiles but the elevated plasma levels are shorter-lasting. Due to the high peak plasma level, the prevalence of side effects is higher with this route of administration compared with the vaginal route (44).
- **Rectal Route:** This has primarily been studied for its role in managing postpartum hemorrhage and the third stage of labor, but it has also been evaluated in the context of abortion (47). Research indicates that rectal misoprostol reaches its peak earlier and declines more rapidly compared to oral or vaginal routes, resulting in lower peak plasma concentrations but fewer gastrointestinal side effects such as nausea and diarrhea basically due to very low bioavailability and very minor effects on uterine contractility (46). This route has no clinical indication.

Buccal, sublingual and vaginal administration results in a longer-lasting elevation in plasma concentration and thus higher bioavailability compared to oral intake of misoprostol (26). This translates into pronounced effects on uterine contractility. The route of administration depends on the indication. In medical abortion sublingual and buccal routes are sometimes preferred over the vaginal route due to fear of discovering remnants of tablets on forced vaginal examination. However, the vaginal route is associated with less gastrointestinal side effects. (44, 48).

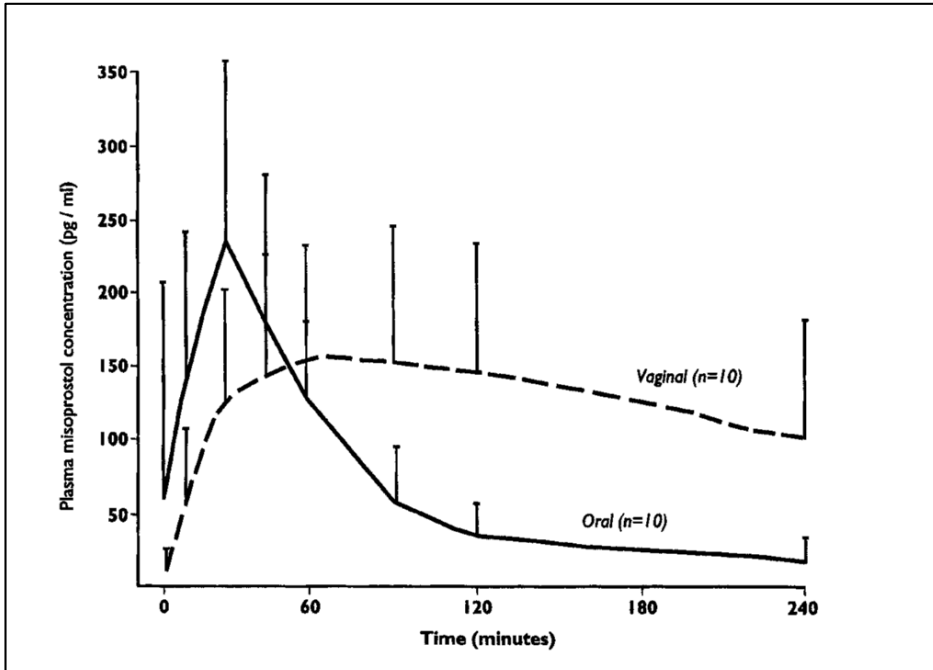


Figure 10. Mean plasma concentrations of misoprostol acid across time with oral (solid line) and vaginal (dotted line) administration. Error bars represent 1 SD. Newhall et al. *Am J Obstet Gynecol* 2000;183:S44-S53

WHO recommendation about medical abortion

Medical abortion by using mifepristone and misoprostol was recommended as a safe, effective option in 2003 global guidelines (49). The WHO recommends a combination treatment of 200 mg of mifepristone orally and 800 micrograms of misoprostol 24-48 hours later (buccal, sublingual, or vaginal). An additional 400 micrograms of misoprostol may be used 3 hours later to increase the effectiveness (5). Research confirming the safety and acceptability of misoprostol home administration dates back to the late 1990s, with several studies supporting these findings (38, 50). Misoprostol-only regimens (repeat doses) can be used as an alternative method when mifepristone is unavailable. The combined method is more effective with less side effects. A systematic review of 38 trials with 12,829 women undergoing misoprostol-only abortions up to 13 weeks of gestation found that 22% required surgical intervention. Higher initial doses and non-oral administration methods (vaginal, sublingual, or buccal) significantly reduced the likelihood of needing surgical evacuation (51). Another alternative regimen for areas with restricted mifepristone access is using a 10 mg daily dose of letrozole for three days,

followed by 800 micrograms of misoprostol. Medical abortion can be administered at any stage of gestation depending on the legal limit but dosing of the drugs needs to be adjusted according to the gestational age (6). The risk for ongoing pregnancy after medical abortion in women with pregnancies up to 9 weeks of gestation by using mifepristone and misoprostol (buccally, sublingually or vaginally), is very low around 1% (25). Complications from medical abortion are rare, hemorrhage requiring transfusion, and serious infection are seen in only 0.01-0.5% (25, 44). The most common complication is the need for surgical intervention due to retained tissue, ongoing pregnancy, pain, or prolonged bleeding. Complication rates depend on gestational age (52).

Human chorionic gonadotropin (hCG) is an important indicator of early pregnancy (53-55). Urine pregnancy tests, which measure hCG, are commonly used in both home and clinical settings to confirm pregnancy with nearly 100% sensitivity and specificity at hCG concentrations of 25 IU/mL (56). The WHO supports the use of home pregnancy tests as a reliable follow-up method after medical abortion, promoting its role in self-managed abortion care up to 12 weeks, as part of the WHO guideline on self-care intervention (57). Studies showed that self-testing for pregnancy after abortion is both highly acceptable and effective to confirm the success of medical abortion (58-60).

Self-managed abortion

Self-managed abortion (SMA) or self-induced abortion usually refers to the process of ending a pregnancy outside the formal healthcare system, usually without direct medical supervision. This is frequently done by obtaining and using medications, such as mifepristone and misoprostol, which are recommended by the WHO for safe and effective medical abortion up to 12 weeks of pregnancy. Some studies referred to self-managed by using other methods to end pregnancy involving the use of herbs, other medications, or physical procedures (61). The self-management approach has been described by the WHO abortion guidelines as management of the abortion process in whole or partially including one or all steps of abortion (self-assessment for illegibility and determination of gestational age, self-intake of abortion pills and self-assessment of abortion success) (5).

Persons use SMA for various reasons such as barriers to accessing clinical abortion services and a desire for greater privacy. Access challenges include legal restrictions, high costs, distance from healthcare facilities, and sometimes lack of health care

providers in certain areas. Some persons prefer SMA which allows them to manage the abortion in a familiar and private setting and to enhance the feeling of autonomy, empowerment and control over their reproductive health (62).

Very early medical abortion

Very early medical abortion (VEMA) refers to a medical abortion performed before the pregnancy is confirmed on an ultrasound scan. Over the past 25 years, there has been a noticeable decrease in the gestational age at which induced abortions are performed. This trend aligns with changes such as the legalization of abortion without mandatory waiting periods or two-doctor signatures. This has led to an increase in women seeking abortions during very early gestation (63). Transvaginal sonography continues to be the preferred method for determining gestational age in many countries (64, 65).

However, the ultrasound findings traditionally recognized as definitive for confirming an intrauterine pregnancy (IUP), a yolk sac or fetal structure, with or without cardiac activity (66) is not consistently visible in women seeking abortions at early stages of pregnancy (≤ 6 weeks amenorrhea) (67-70). A pregnancy of unknown location (PUL) means to a positive pregnancy test without evidence of an IUP on ultrasound. On the other hand, the WHO guidelines recommend against routine ultrasound and do not include any specific recommendation for abortion with non-confirmed IUP (5).

VEMA can notably reduce pain and bleeding and possibly hold substantial benefits for women, both psychologically and medically. Although there is limited data on abortions before the sixth week of pregnancy, emerging indications suggest that earlier abortions generally tend to be safer (31). In addition, encouraging early presentation for abortion may also provide the chance to detect and address ectopic pregnancy (EP) at an early stage of pregnancy. However, there are concerns that VEMA may be less effective compared to abortion when an ultrasound scan confirms an IUP, and there is also the risk of EPs (71, 72).

This has resulted in inconsistent treatment protocols, repeated clinic visits, unnecessary or potentially harmful waiting periods, and restricted access to services. Most doctors require confirmation of an IUP by ultrasound such as a yolk sac or fetal structure (73) in clinical praxis as well as in clinical trials of medical abortion. Some clinics measure the beta-subunit of hCG (β -hCG) routinely when uncertainty exists

about confirming an intrauterine pregnancy. The discriminatory β -hCG level indicates the point at which ultrasonographic findings are expected to be visible, whereas the threshold β -hCG level represents the minimum serum concentration at which features like a gestational sac or fetal pole can be detected (74). However, hCG's dynamic nature and significant individual variation make it challenging to establish the precise discriminatory and threshold levels for visualizing a normal IUP via ultrasound (74-76). Serial hCG measurements have been found to be essential for evaluating PUL location and guiding clinical management (77).

There are some observational studies about VEMA before confirmation of IU pregnancy, showing treatment efficacy rates between 85% and 100% (70-72, 78-80). However, these studies vary in design, and these inconsistencies make direct comparisons challenging and highlight the need for standardized approaches for a better understanding of treatment outcomes in such cases.

Telemedicine

Telemedicine refers to the provision of healthcare services remotely using telecommunication technologies. It enables healthcare providers to deliver consultations, diagnoses, treatments, and follow-ups without requiring an in-person visit. The WHO defines telemedicine as “the delivery of healthcare services, where distance is a critical factor, by all healthcare professionals using information and communication technologies (ICTs) for the exchange of valid information for the diagnosis, treatment, prevention of diseases and injuries, research and evaluation, and continuing education of healthcare providers” (81). Telemedicine programs are generally divided into two categories: synchronous and asynchronous.

1. Synchronous telemedicine represents real-time interaction between patients and healthcare providers through live video calls, using devices such as smartphones, tablets, or computers. These virtual appointments require a reliable internet connection and may need an app to connect with the healthcare provider.
2. Asynchronous telemedicine does not require simultaneous interaction. Instead, patients send relevant health data, such as images, videos, or readings from wearable devices, which healthcare providers review later. This allows flexibility in managing health information over time without needing immediate responses (82).

Both methods enhance patient access to care and offer different advantages depending on the specific healthcare need. Telemedicine expands access to healthcare and medical information and is found to be cost-effective and safe (83).

The start of telemedicine abortion

Women on Web (WoW) was founded in 2005 by Rebecca Gomperts, the same physician who founded Women on Waves in 1999. Women on Web provides access to safe medical abortions via telemedicine outside the conventional healthcare system (84, 85). The organization initially offered online consultations and (mail) delivery of abortion pills to women in countries where abortion is restricted worldwide (86). Later on, the service expanded to geographically challenging areas with shortage of abortion clinics. In 2018, Dr. Gomperts also launched Aid Access. This similar telemedicine service provides abortion pills to women in the United States, especially in states with restrictive abortion laws. WoW had a significant rise in demand for its services during the COVID-19 pandemic, where lockdowns limited access to in-clinic abortions. In France, WOW service expanded, with demand increasing from 60 consultations in March to 128 in April 2020 (87). Both organizations have played critical roles in ensuring access to safe abortion services during the pandemic, and their telemedicine platforms have become even more vital in overcoming barriers to care (87).

Further development of telemedicine abortion under COVID-19

During the COVID-19 pandemic, several countries implemented telemedicine abortion services to ensure access to safe abortion while minimizing in-person visits and reducing the risk of virus transmission. Telemedicine abortion involves consulting with a healthcare provider remotely, typically through a phone or video call, and then receiving abortion medications, mifepristone, and misoprostol by mail. However, in addition to the mail-order option, many countries offered the flexibility to pick up the medications at a pharmacy or hospital/clinic. In the UK, this change started in March 2020, permitting women to receive both mifepristone and misoprostol after a teleconsultation, a policy initially set up for the pandemic period which was then extended and became permanent in 2022 (88-90). Similarly, in 2020, the FDA temporarily removed the requirement for in-person dispensing of mifepristone, allowing telemedicine and mail delivery to ensure safe access to abortion services while reducing COVID-19 exposure risks. This policy became

permanent in December 2021 after evidence of its safety and effectiveness (39). By 2022, the WHO had recognized telemedicine, when accessible, as a reliable and safe method for self-administered abortion care (5). Studies during and after the pandemic found telemedicine abortion to be highly effective, with minimal complications and many patients appreciate the privacy and convenience it offers (91-97).

Aim

The overall aim of this thesis was to increase the safety and accessibility of early medical abortion (EMA) by expanding available knowledge and obtaining data to develop evidence-based guidelines.

The specific aims were:

Paper I

- To evaluate the effectiveness of VEMA and assess its potential to improve early diagnosis and treatment of asymptomatic ectopic pregnancy (EP).
- To examine the correlation between serum hCG levels and ultrasound findings, as well as the pattern of hCG decline following successful VEMA.

Paper II

- To investigate the effectiveness and safety of VEMA in a multicenter, multinational, randomized, controlled, non-inferiority trial in women undergoing medical abortion with or without a confirmed intrauterine pregnancy by ultrasound.

Paper III

- To investigate if plasma/serum-hCG can be used as a monitoring instrument to increase the safety of VEMA in pregnancies of unknown location (PUL) and probable intrauterine pregnancy (IUP).
- To examine serum/plasma-hCG dynamics in VEMA, and to assess hCG decline as an indicator of treatment success.

Paper IV

- To assess women's experiences with the current in-person abortion care model, focusing on in-person consultations and the impact of access to abortion services and related waiting times.
- To investigate women's suggestions for improvements to medical abortion care and their perspectives on an alternative abortion care model without in-person consultations.

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Patients and Methods

The thesis includes both quantitative and qualitative study methodology. Table 1 shows an overview of patients and methods of all four studies. Paper I is a retrospective case note review of medical records, Paper II is a multicenter, multinational, randomized, controlled, non-inferiority trial, Paper III is a cohort of patients from the RCT on VEMA, and Paper IV is a qualitative study with semi-structured interviews.

Table 1: Overview of Patients and Methods

	Paper I	Paper II	Paper III	Paper IV
Setting	Retrospective cohort	Randomized controlled non-inferiority trial	Prospective cohort from the VEMA trial	Qualitative semi-structured interviews
Data source and sites	GynMed Clinic in Vienna, Austria, and Sahlgrenska University Hospital, Gothenburg, Sweden	26 sites, 9 countries. Sweden, Nepal, Australia, New Zealand, Norway, Denmark, Finland, Scotland, Austria	26 sites, 9 countries. Sweden, Nepal, Australia, New Zealand, Norway, Denmark, Finland, Scotland, Austria	Sahlgrenska University Hospital, Gothenburg, Sweden
Gestational age	≤49 days (7 weeks)	≤42 days (6 weeks)	≤42 days (6 weeks)	≤70 days (10 weeks)
Number of patients	682	1504	717	20
Outcome	Rates of successful medical abortion & ectopic pregnancies Baseline hCG-level and decline after abortion	Complete abortion with no ongoing IUP and no need for surgical intervention within 30 days after treatment	Baseline hCG level and decline after medical abortion in four groups: Complete abortion (no need for surgical or medical intervention), ectopic, ongoing pregnancy, and incomplete abortion	Experience of the current abortion care. Suggestions for improving medical abortion care. Views on an abortion care model without the in-person appointment and examination
Statistical method	Descriptive statistics and tests for comparisons between groups. SPSS statistics (version 24)	Non-inferiority to estimate the efficacy of VEMA by modified intention to treat (mITT) analysis and strict ITT-analysis approach. R version 3.3	Descriptive statistics and tests for comparisons between groups. SPSS statistics (version 29)	Systematic text-condensation, according to Malterud
Study protocol	Vienna 2004-2014 Gothenburg 2012-2013	March 2019 to April 2023	March 2019 to April 2023	March and April 2003

Paper I

Study Design

This retrospective study involved a review of medical records from early medical abortion cases. Data were obtained from two sites: GynMed Clinic in Vienna, Austria (2004–2014), and Sahlgrenska University Hospital in Gothenburg, Sweden (2012–2013). Patients were categorized into two groups according to their ultrasound findings: pregnancies of unknown location (PUL), with empty uterine cavity, and probable intrauterine pregnancy (IUP), identified as a sac-like structure without a yolk sac or embryonic pole (66). Mifepristone was administered, and a blood sample was collected to determine the baseline β -hCG. This was followed by self-administered misoprostol 24–48 hours later. In Gothenburg, β -hCG levels were rechecked 5–10 days post-mifepristone; if the level fell $\geq 80\%$ from the baseline level, abortion was considered complete for asymptomatic patients. Additional follow-up was conducted to exclude EP for unchanged or elevated β -hCG levels. In Austria, follow-up included a scheduled ultrasound examination seven days post-abortion, and, when needed, β -hCG levels were confirmed with a semiquantitative urine or serum test.

Population

The study included persons seeking EMA with gestational ages of $\leq 7+0$ weeks (49 days) based on LMP without confirmed IUP by ultrasound. Exclusion criteria are outlined in Figure 11.

Outcomes

The primary outcome was to evaluate the outcome of the VEMA protocol and its potential to improve early diagnosis and treatment of asymptomatic EP. The secondary outcomes included the identification of β -hCG reference levels related to ultrasound findings at very early gestation without confirmation of intrauterine pregnancy (IUP). Furthermore, the decline in β -hCG levels was measured approximately one week after a successful VEMA. Successful abortion was defined as the absence of an ongoing pregnancy or the need for further surgical intervention up to 42 days after abortion treatment.

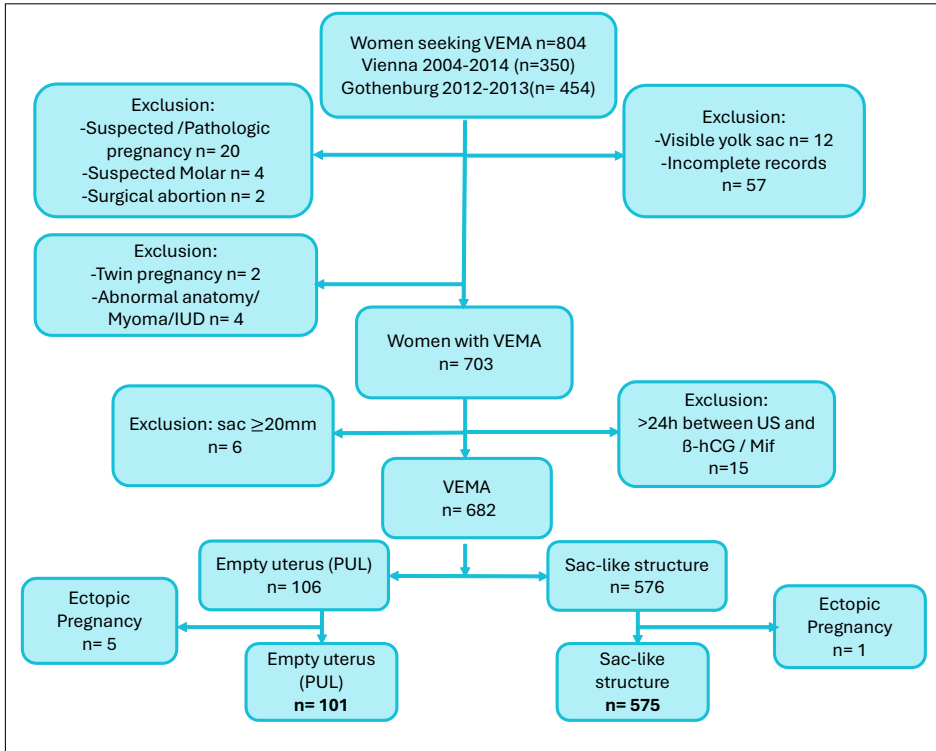


Figure 11. Flowchart for patient selection in Paper I

Statistical Analysis

Descriptive statistics were applied for categorical variables (counts, percentages) and continuous variables (mean $\pm$ SD or median and range). The student's t-test and Chi-square test compared baseline characteristics between groups. Independent t-tests compared β -hCG levels and gestational age between PUL and probable IUP groups, while the Kruskal-Wallis test assessed β -hCG levels across different sac-size categories. A p-value of <0.05 indicated statistical significance. All analyses were conducted using SPSS version 24.

Paper II

Study Design

This study is an international, randomized, controlled, and non-inferiority trial across nine countries and 26 trial sites from March 2019 to April 2023 (Figure 12). Participants were randomly allocated into either the intervention group (early start)

or the standard care group (delayed start) through block randomization with varying block sizes, stratified by trial center, in a 1:1 ratio. In the early start group, medical abortion was initiated on the day of or the day after enrollment. Treatment was delayed for the standard care group until a repeat ultrasound on trial day 7 (+/- 2 days) confirmed an IUP. If no IUP was visible, a third ultrasound was conducted on trial day 14 (+/- 2 days). Cases without confirmed IUP at this stage were classified as pathological pregnancies. Participants diagnosed with pathological pregnancies at any point during the study received treatment according to local clinical guidelines and were monitored for outcomes and adverse events (AEs). All participants received the WHO's recommended protocol for medical abortion: 200 mg of oral mifepristone, followed by 800 µg of misoprostol administered vaginally, sublingually, or buccally 24–48 hours later, as per local practice (5). For both study groups, serum or plasma hCG levels were measured during pre-abortion visits. The early start group had their treatment outcome assessed by hCG measurements taken at mifepristone intake and again on day 7. A successful treatment outcome was defined by an hCG decline of $\geq 80\%$ from the baseline level. Additional clinical evaluations were conducted if complications or signs of ongoing pregnancy were noted. Participants were followed up for four weeks after the abortion via telephone or in-person consultations. If participants could not be reached, their medical records were reviewed to obtain follow-up data.



Figure 12. Countries with the number of sites, participated in VEMA randomized trial. Created with mapchart.net, by Tagrid Jar-Allah

Population

Eligible patients for inclusion were those seeking medical abortion with an estimated gestational age of ≤ 42 days according to LMP, and without a confirmed IUP on transvaginal ultrasound (Figure 13). The non-confirmed IUP included PUL or probable IUP (66). Eligibility criteria were participants ≥ 18 years old, fluent in English or the local language. Exclusion criteria were any symptoms or indications of pathological pregnancy (such as bleeding or abdominal pain), risk factors for EP such as a previous EP or the presence of an intrauterine device (IUD) in situ, or any contraindications to medical abortion (Figure 13).

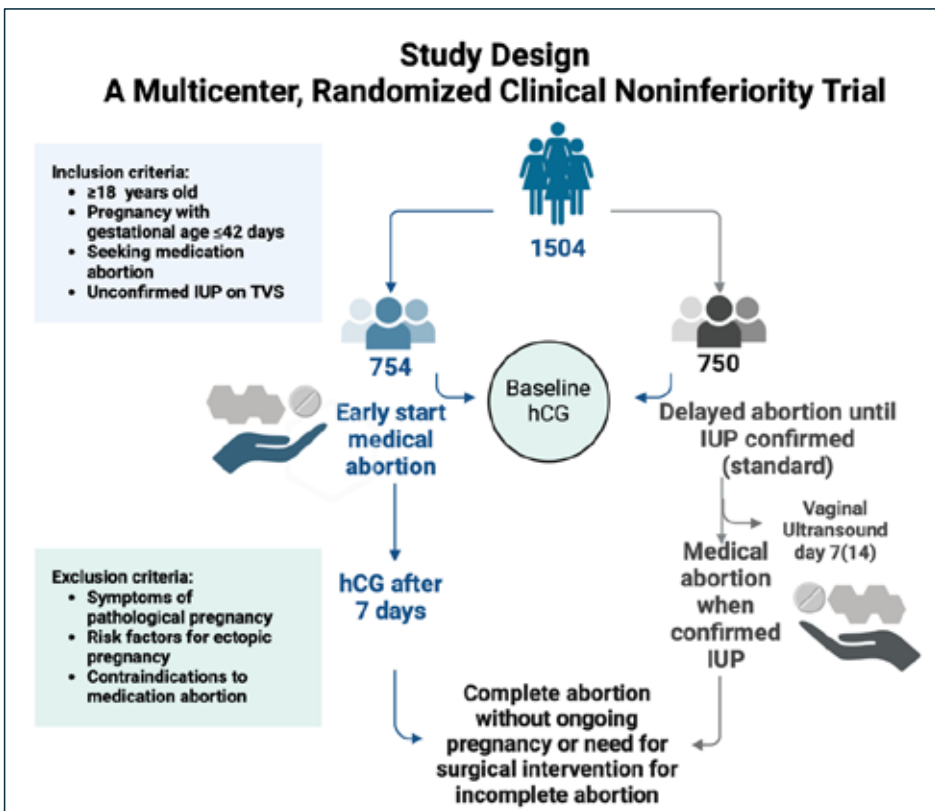


Figure 13. Study design Paper II. Created by BioRebder.com, by Tagrid Jar-Allah

Outcomes

The primary outcome was the efficacy of medical abortion, which was measured by complete abortion without ongoing intrauterine pregnancy (IUP) and no requirement for surgical intervention for incomplete abortion within 30 days of treatment. Comprehensive data on all ectopic pregnancies, including rupture status and treatment type, were gathered. Secondary outcomes include: the rate of incomplete abortion, additional medical treatment required for incomplete abortion, antibiotic-treated infections, unscheduled clinic visits or contacts, bleeding duration, maximum pain, satisfaction with treatment, and preferences and recommendations for treatment type (early or standard).

Statistical Analysis

The study required an estimated 1,360 participants to show non-inferiority of early treatment compared to standard treatment with 90% power, assuming an efficacy of 97% in both groups based on prior findings. (98). The non-inferiority margin was set at 3%, with a two-sided 95% confidence interval (CI) for comparison. The sample size was increased to 1,500 to account for an anticipated 10% loss to follow-up, including cases with pathological pregnancies. Analyses were conducted using R version 3.3 and STATA version 17.25.

A strict intention-to-treat (ITT) analysis included participants with intrauterine pathological pregnancies to reduce selection bias. Sensitivity analyses used modified ITT (mITT) and per protocol approaches. Multivariate logistic regression adjusted for country and ultrasound findings on the ITT population, and secondary outcomes were assessed in the mITT population. For detailed information about the statistical analysis, please see the main article of this study (99).

Paper III

Study Design

This study used a prospective cohort from the randomized controlled VEMA trial. Serum or plasma hCG levels were measured at the time of mifepristone intake (day one) and repeated on day seven (5-9 days was acceptable). The hCG levels were analyzed using the immunoassay method applied in each participating country (Figure 12) and categorized into four main groups: Abbot Architect, Roche Cobas Elecsys, Siemens Atellica, and additional methods. Treatment success was defined

as a $\geq 80\%$ decrease in hCG levels by day seven. Additional clinical assessments were performed for patients with hCG decline $< 80\%$ and for those with any signs or symptoms of complications or ongoing pregnancy.

Population

Overall, 741 participants were randomized to VEMA and formed the study cohort for this analysis. Eligibility required an estimated gestational age of ≤ 42 days, according to the LMP, and without confirmed IUP by ultrasound. Non-confirmed IUP cases were classified into two categories: PUL and probable IUP (66). All eligible participants received medical abortion according to the WHO-recommended protocol, with treatment beginning either on the same day of enrollment or the following day. A total of 25 participants were excluded: 19 due to missing primary outcomes, two with suspected spontaneous abortions, one case of molar pregnancy, and two cases of suspected EP that were later confirmed as IUP (Figure 1 in Paper III).

Outcomes

The primary outcome was to assess the change in serum/plasma hCG levels from baseline to 5-9 days post-abortion across four outcome categories: complete abortion, EP, ongoing pregnancy, and incomplete abortion. Secondary outcomes included examining variations in baseline hCG levels and the decline in serum/plasma hCG levels following complete abortion across different countries. Furthermore, the study aimed to evaluate hCG changes 5-9 days post-abortion in two subgroups: PUL and probable intrauterine pregnancies (IUP).

Definitions of outcome groups:

- **Complete abortion:** No additional medical or surgical intervention within 30 days.
- **Ongoing pregnancy:** Confirmed IUP post-medical abortion.
- **Incomplete abortion:** Presence of retained conception products or missed abortion following medical abortion. Participants sought medical care due to symptoms requiring further evaluation and management, such as repeated administration of mifepristone and/or misoprostol, surgical intervention, or expectant management.
- **Ectopic pregnancy:** Patients undergoing medical, surgical, or conservative management for EP.

Statistical Analysis

Continuous variables were summarized as means ($\pm$ standard deviation) or medians (interquartile range), depending on their distribution. Categorical variables were expressed as frequencies and percentages. The Independent-Samples Kruskal-Wallis test was applied to compare baseline serum/plasma hCG levels and hCG changes across the four outcome groups. Dunn's pairwise tests were performed for group comparisons. Differences in hCG changes between PUL and probable IUP groups were analyzed using the independent t-test. Statistical significance was set at a p-value of <0.05 . Data analyses were conducted using SPSS version 29.

Paper IV

Study Design

This qualitative study used semi-structured interviews to examine women's experiences and opinions on consultation visits before medical abortion and on abortion care services, specifically the telemedicine options. An interview guide was developed (see supplementary appendix Paper IV) with questions about the study participants' experiences and perspectives. Interviews were conducted by a midwife who was not involved in the participants' care. All interviews took place between March and April 2023.

Population

The study sample consisted of twenty women who sought early medical abortion, at the Department of Obstetrics and Gynecology, Sahlgrenska University Hospital (SU) in Gothenburg. Eligible participants included women aged 18 or older who attended abortion counseling with gestational age up to 10 weeks, based on LMP or TVS, and who spoke Swedish or English. All women were considering medical abortion, with misoprostol administered either at home or in the clinic (Figure 14).

Outcomes

The outcome was a description of (1) women's experiences with the current abortion care model, including in-person consultations, with gynecological examinations, and ultrasound scans, as well as their perspectives on accessing services and associated waiting times; (2) women's suggestions for enhancing medical abortion

care; and (3) explore women's views on an abortion care model that excludes in-person appointments and examinations.

Statistical Analysis

Data were analyzed using systematic text condensation (STC) as described by Malterud et al. (100) is a descriptive approach that emphasizes participants' expressed experiences rather than underlying meanings. The analysis involved four steps: 1) initial reading to identify general themes; (2) the first two authors then coded the data, identifying meaning units and subcodes; 3) these codes were condensed and reduced into synthesized themes; and (4) final themes were generated, with translated participant quotes and verified by all authors to maintain original meaning. The text used participant numbers to protect privacy (Figure 14).

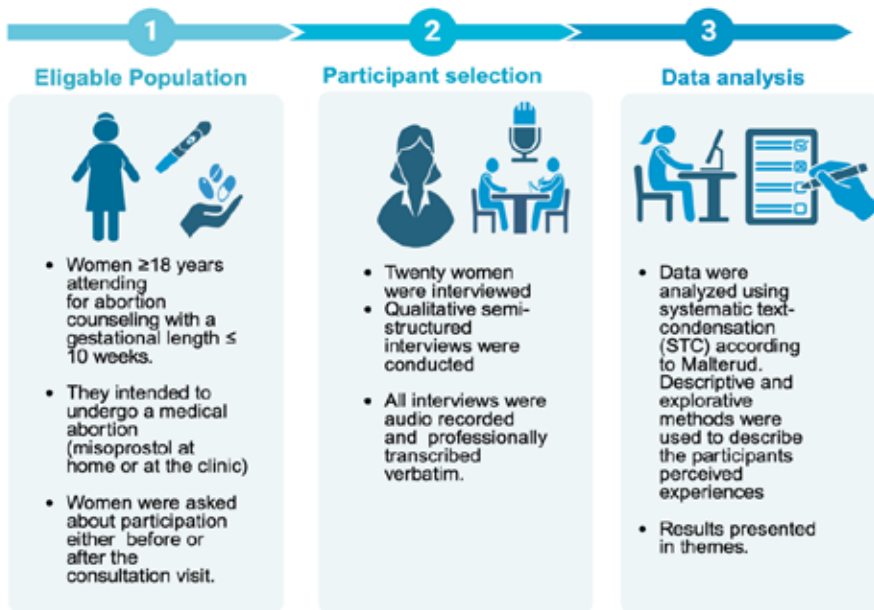


Figure 14. Method and Population of Paper IV. Created by BioRebder.com, by Tagrid Jar-Allah

Ethical approval and ethical considerations

Paper I

Ethical approval was obtained by the Regional Ethics Committee in Stockholm.

Original application (2015/2103-31; 16th September 2015)

Amendment (2015/2103-32; 9th December 2015)

In this retrospective study, while individual informed consent was not obtained due to the nature of data collection, women were generally informed about the use of their information for quality research and had the option to block their data from being used. We prioritized the protection of participant confidentiality so that only authorized researchers had access to patient records to ensure data security. All data were anonymized using key codes, which replaced personal identifiers and were stored separately from the data to maintain anonymity and confidentiality.

Papers II & III

Ethical approval was obtained by the Regional Ethics Committee in Stockholm.

Original application (2017/1622-31; 18th October 2017)

Amendment I (2019/050-63; 2ed January 2020)

Amendment II (2021/034-87; 1st July 2021)

Amendment III (2022/04920-02; 29th September 2022)

The trial protocol received approval from the local ethics committees at each trial site or in each participating country (see supplementary appendix Paper II).

This RCT was conducted in strict adherence to the protocol, Good Clinical Practice (GCP), the Declaration of Helsinki, and relevant regulatory requirements. The investigators prioritized sensitivity and guaranteed complete confidentiality throughout the study because abortion can be considered a sensitive topic. The use of (mifepristone and misoprostol) is well-documented as safe and well-tolerated, with minimal contraindications, and medical abortion is considered a safe procedure. Although there is a theoretical risk of undiagnosed EP when initiating treatment before confirming IUP, treatment exposure itself has no risk of rupture of EP. Participants were thoroughly informed about potential risks related to EP, and the signs and symptoms requiring clinic contact, and their right to withdraw at any point of the study.

Paper IV

Ethical approval was obtained by the Regional Ethics Committee in Uppsala (2023-00091-01; 15th February 2023).

The personal nature of abortion was acknowledged, and potential impacts on participant integrity were considered. As in Papers II and III, women were informed about the study and provided oral and written consent, with the right to withdraw at any time without explaining the reasons or risking affecting their care. Data were coded to prevent potential identification and accessible only to the first and second authors.

Results

This section provides a summary of the most significant findings from all four papers. While the methodologies used across these studies vary, they share key overlapping outcomes. The main results of this thesis are highlighted and organized by the findings below.

Efficacy of VEMA

The overall efficacy of VEMA was high across both the retrospective study and the RCT (**Paper I and II**) (Figure 15). Complete abortion was defined as no ongoing pregnancy or need for further surgical intervention in both studies. In (**Paper I**), a success rate of 97.6% was observed (660 out of 676 cases), and only 2.4% resulted in unsuccessful outcomes. The unsuccessful outcomes included incomplete abortions requiring vacuum aspiration because of an incomplete abortion (0.89%), bleeding requiring interventions with vacuum aspiration (0.15%), diagnostic laparoscopy (0.30%), and infections (0.29%). The number of ongoing pregnancies (0.59%) was very low (Figure 16a). Among women with PUL, the success rate was lower (93.1%) compared to those with a probable IUP (98.4%) ($P<0.001$).

The RCT (**Paper II**) reinforced these findings, demonstrating success rates of 95.2% (676/710) in the early start group and 95.3% (656/688) in the standard treatment group, with a risk difference of only 0.1 (CI -2.3, 2.3), confirming the non-inferiority of early treatment compared to standard (delayed) treatment. The sensitivity analysis for the m-ITT population also showed similar outcomes, reinforcing the robustness of the primary analysis. The adjusted and unadjusted risk differences remained within the non-inferiority margin, supporting the efficacy of the VEMA protocol. While ongoing pregnancy rates were higher in the early group (3.0% vs. 0.1%; RR 20.3, CI 2.74, 151) (Figure 16a), surgical interventions for incomplete abortions were lower in the early group (1.8% vs. 4.5%; RR 0.41, CI 0.21, 0.77) (Figure 16b).

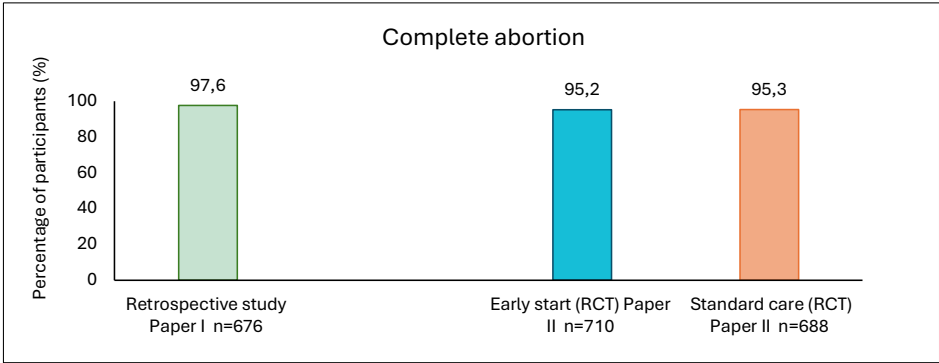


Figure 15. Complete abortion in VEMA was 97.6% in the retrospective study (Paper I) and 95.2% in the early start and 95.3% in the delayed start (standard) in the RCT (Paper II).

Fig. 16a

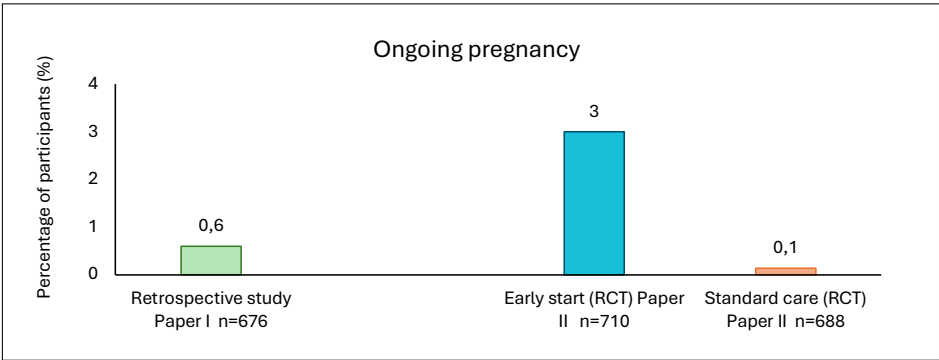


Fig. 16b

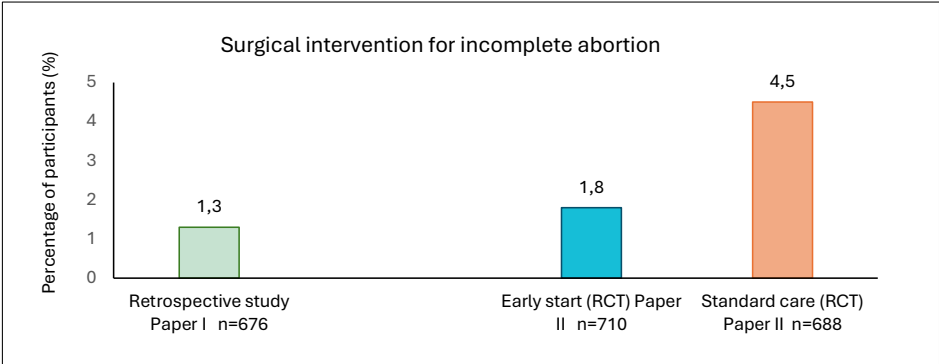


Figure 16a-b. Ongoing pregnancy and surgical intervention for incomplete abortion in the retrospective study (Paper I) and early and delayed start (standard) in the RCT (Paper II).

Safety of VEMA

The safety of VEMA was assessed by analyzing the occurrence and management of ectopic pregnancy cases (EPs), adverse events (AEs) (**Paper I and II**), and serious adverse events (SAEs) (**Paper II**). The findings of these studies indicate that ectopic pregnancies are relatively rare among asymptomatic women seeking early abortion. In **Paper I**, six cases of EPs (0,88%) required post-abortion treatment, accounting for 5/106 (4.7%) in the group with an empty uterine cavity and 1/576 (0.2%) in the group with an intrauterine sac-like structure. All cases were confirmed surgically. Most cases were asymptomatic, with four detected due to rising hCG levels approximately seven days after initiating treatment. Only one woman required emergency medical attention due to abdominal pain and underwent a laparoscopic salpingectomy due to an unruptured EP two days after a visit to the emergency department. **Paper II** demonstrated a low incidence of EPs, with 10 cases (1.3%) in the early start group and 6 cases (0.8%) in the standard group, including two cases with a pregnancy with an IUD in situ (protocol violation one in the early and one in the standard group) (Figure 17). These cases were treated with methotrexate administration, surgical intervention, or conservatively. Only one case in the early start group involved a ruptured EP, which occurred 25 days post-abortion and was treated with acute laparoscopic surgery and blood transfusion. This patient did not return for the planned follow-up visit. The timeframe from the initial administration of abortion treatment to the identification and management of EPs varied. In the retrospective study (**Paper I**), most cases were detected approximately within seven to ten days. In the RCT (**Paper II**), treatment for EPs occurred typically between four to twelve days post-abortion, while in the standard group, between two to 14 days after inclusion in the study (pre-abortion). In **Paper II**, 15/737 (2.0%) participants in the early start group and 35/718 (4.9%) in the standard group reported at least one AE (bleeding, pain, infection, and allergy), indicating a statistically significant difference ($p=0.003$). While SAEs which included conditions requiring hospitalization (≥ 24 hours) and/or hemorrhage demanding blood transfusion, were reported in 12/737 (1.6%) of the early start group and 5/718 (0.7%) of the standard group ($p=0.10$). Conditions requiring hospitalization included blood transfusion, inpatient-treated infection, and surgical operation (laparoscopy, laparotomy, and inpatient uterine aspiration).

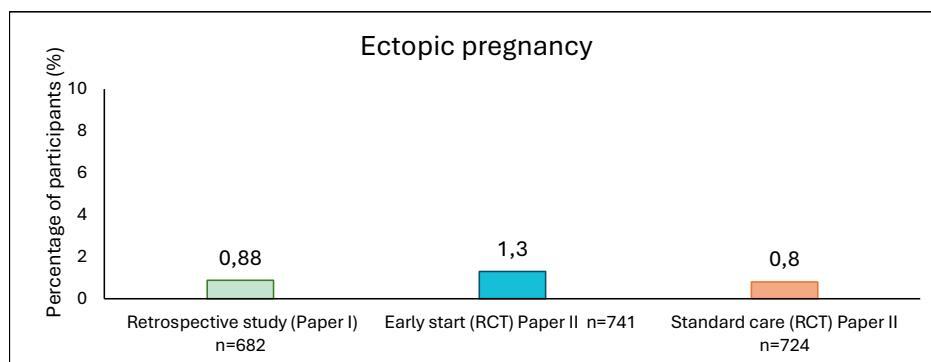


Figure 17. Ectopic pregnancy rates in the retrospective study (Paper I) and early and delayed start (standard) in the RCT (Paper II).

The decline of hCG after complete medical abortion

The decline in plasma/serum hCG levels post-abortion is a key indicator for assessing the success of medical abortion. In **Paper I**, 660 women (97.6%) experienced a successful medical abortion without the need for surgical intervention or the presence of ongoing pregnancy with a mean decline of hCG level by 93% (CI: 91.7-94.2) between 5-10 days after abortion treatment. A decline of $\geq 90\%$ in baseline hCG was found in 87% of cases. These findings were further confirmed through a prospective analysis in **Paper III**. This study strengthened the observation that a hCG decline of $\geq 80\%$ was observed in $\geq 95\%$ of patients 5-9 days after treatment, with consistent patterns across all countries participating in the study (Table 2, **Paper III**). Data from women with complete abortions without ongoing pregnancy or need for further surgical or medical intervention after abortion, and who returned for follow-up visits between 5- and 9 days post-abortion, provided further significant insights into the pattern of hCG decline. The proportion of patients with an hCG decline of $\geq 80\%$ increased from 75% on day 5 to 97% on day 7, with most data available on day 7 (Figure 3, **Paper III**). For details on results, see **Paper III**

The change of hCG after medical abortion in different outcomes

The post-abortion dynamics of hCG levels varied significantly among different outcomes, including ectopic pregnancies, ongoing pregnancies, and incomplete abortions.

Ectopic pregnancy: In **Paper I**, out of six cases of EPs (0,88%), four showed a median increase in hCG levels of 83%, (IQR 184) within 5–10 days post-abortion, while only one case demonstrated a decline (by 40%) from the baseline hCG level. One patient had only a single hCG value available. **Paper III** reported ten patients with EPs (1,3%): eight patients returned for follow-up within 6–8 days; most patients showed a substantial median increase, while one exhibited a decline (by 20%) from the baseline hCG level. Two patients had only one hCG value available for assessment (Supplemental Figure 2, **Paper III**).

Ongoing pregnancy: In **Paper III**, 21 cases (2.9%) of ongoing pregnancies were identified following medical abortion. Of these, 18 cases returned for follow-up within 5 to 9 days post-abortion. Analysis of hCG levels revealed a general pattern of significant increases during this period (Supplemental Figure 3, **Paper III**).

Incomplete abortion: In 29 cases (4%) of incomplete abortions, hCG levels were measured within 5 to 9 days post-abortion. The overall change in hCG levels showed a wide range, with some cases experiencing increases, others showing minimal or no decline, and a few demonstrating more substantial decreases (Supplemental Figure 4, **Paper III**).

Overall, the hCG dynamics showed clear distinctions when comparing ectopic, ongoing, and incomplete abortion cases to complete abortion cases (Figure 5, **Paper III**).

Key findings Paper IV

This section summarizes the main findings from **Paper IV**. Figure 18 illustrates the themes that captured the participants' experiences before the first visit, during the pre-abortion examination, and their views on alternative abortion services.

Ease of contact and undesired waiting time

Participants generally found it easy to contact the abortion clinic, eased by clear and comprehensive online information and efficient booking services. However, many women faced undesired waiting periods for their appointments, leading to emotional and physical challenges. The waiting period was often difficult due to physical symptoms such as nausea, vomiting, and cramps, and emotional stress. Concerns about advancing gestational age sometimes strengthened the emotional discomfort.

Feelings about the pre-abortion examination

Most participants valued the thoroughness of the pre-abortion gynecological examination including ultrasound examination, considering it as an essential part of their care. However, for some, it was a source of discomfort or distress. Additionally, viewing the ultrasound screen evoked different reactions. While some avoided looking to prevent emotional distress, others felt curious but were cautious about how it might affect their abortion experience.

Opinions on different options of abortion services

Participants expressed varied views on taking mifepristone at home or in the clinic. While some felt safer taking mifepristone in the clinic due to the presence of healthcare professionals, others preferred the convenience of home administration for better flexibility, even if this option is not currently allowed. Moreover, they felt that having the option to receive the pill by mail and self-administer it at home would offer greater flexibility, allowing them to schedule the procedure around their personal and professional responsibilities. Telemedicine was viewed positively as a complement to in-person visits, and it was seen as a valuable choice, especially for those who wished to avoid the hospital setting or found multiple clinic visits troublesome. Participants appreciated telemedicine for reducing waiting times and enabling self-management of the abortion process, though there were some concerns about complications and undetected ectopic pregnancies. Overall, participants valued having choices between in-clinic and telemedicine services, emphasizing that these options enhanced autonomy and control over their care.

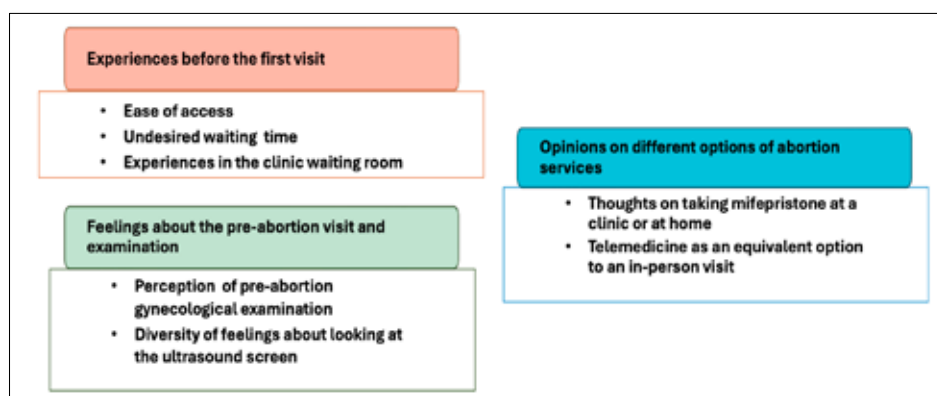


Figure 18. Results Paper IV, Themes

Discussion

Comparison of study findings

This thesis combines evidence from retrospective and prospective studies to evaluate VEMA comprehensively. **Paper II** (RCT) confirms findings from previous observational studies, demonstrating the efficacy and safety of VEMA for women with PUL and probable IUP. The retrospective study, **Paper I** reported a high success rate of 97.6%, consistent with the 95.2% success rate observed in the early start group of the RCT. Importantly, the RCT provided more robust evidence, confirming the non-inferiority of early treatment with unconfirmed IUP compared to delayed (standard) treatment with confirmed IUP. More recent observational studies focusing solely on PULs have reported lower efficacy for early treatment compared to delayed treatment (78, 79). However, the early start group showed higher rates of ongoing pregnancy (3.0% vs. 0.1%), whereas the standard treatment group had higher surgical intervention rates (1.8% vs. 4.5%). Subgroup analysis in the RCT indicated that efficacy may vary between PUL and cases with sac-like structure (probable IUP), with slightly better outcomes for standard treatment in the PUL subgroup. These findings align with findings in **Paper I**, which have shown that treatment success may depend on baseline ultrasound findings. Additionally, both the retrospective and RCT studies highlighted the importance of hCG monitoring (7 days post-abortion), with consistent results showing a decline of $\geq 80\%$ as a reliable marker for successful abortion. We found, as in previous studies (78, 80, 98), that early diagnosis of EP was possible regardless of whether abortion treatment was initiated promptly or delayed. This finding underscores the importance of follow-up protocols using serial hCG measurements and ultrasound examination when it is indicated to ensure timely detection and management of ectopic pregnancies.

Early and very early medical abortions trends in Sweden: Opportunities for improvements

In Sweden, medical abortion is the predominant method of termination, accounting for 97% of all abortions. Over recent decades, there has been a significant increase in the number of abortions carried out before the 7th week of pregnancy reaching 63% in 2023 (18). Several factors contribute to this trend toward earlier abortions, including improved access to abortion services, advancements in ultrasound technology enabling earlier confirmation of IUP, and greater public awareness about

reproductive health. Despite these developments, a limitation in Sweden's abortion reporting system is evident. The current categorization by the NBoHW groups all abortions occurring before the 7th week of pregnancy without specifying the exact gestational age in days. This broad classification obscures the ability to distinguish between pregnancies in very early stages before confirmation of IUP versus those closer to 6–7 weeks of gestational with confirmed IUP. This gap in data presents a challenge for understanding the true prevalence of VEMA which might be very high. Historically, protocols for medical abortion in Sweden varied, with some requiring women to return for additional ultrasound examinations to confirm an IUP before starting medical abortion. However, our VEMA studies, including an RCT trial (Paper II) and the retrospective study (Paper I), have demonstrated the safety and feasibility of initiating abortion treatment before IUP confirmation. These findings provide a strong basis for standardizing care practices to expand access to treatment earlier in pregnancy. With the integration of VEMA into clinical practice, the proportion of women receiving treatment before 6 weeks (a gestational age with a high probability for confirmation of IUP) is expected to rise. This approach not only reduces delays in care but also empowers women with more flexible and patient-centered options for early abortion. To ensure that VEMA's impact is fully realized and to support ongoing improvements in abortion care, adjustments to the reporting system are needed. Introducing more detailed data on gestational age would enable better tracking of very early abortion trends, and strengthen the evidence base for policy and practice.

Implications for clinical practice

We found that VEMA before confirmation of IUP is an effective and safe method which offers women the opportunity to access treatment earlier in pregnancy. The selection of patients suitable for VEMA is crucial. It should include those with a known LMP, no signs or symptoms of pathological pregnancy, and no risk factors for EP, such as a history of EP or a current pregnancy with an IUD in situ. Clear instructions about follow-up care and information about EP must be provided to ensure women understand the potentially serious consequences of an undetected EP. It is important to inform women about the benefits and the possible risks of choosing VEMA, particularly regarding the slightly increased risk of ongoing pregnancy. Shared decision-making, supported by comprehensive counseling, empowers women to make informed choices that align with their preferences and circumstances. The timing of treatment appears to play a role in optimizing outcomes. Data suggest that initiating VEMA around 5+1 weeks of gestation could

enhance efficacy versus treatment starting at 4 weeks. However, the difference is minor and may not be of clinical significance as long as the treatment outcome is assessed.

The timing of follow-up visits is also essential. A decline in serum hCG levels of 50% within 48–72 hours post-misoprostol or 80% within 7 days of mifepristone has been used to indicate a complete abortion (78). The analysis of our data shows that follow-up 7 days post-treatment can reliably confirm abortion success and exclude ectopic pregnancies when hCG declines $\geq 80\%$ of the baseline value (**Paper I and III**). Earlier follow-ups on days 4–5 may be feasible, particularly in settings where waiting times are challenging, but further investigation is still required to explore whether earlier follow-up can provide comparable safety. Due to the limited number of participants attending follow-up on days 4 and 5 in Paper III, definitive conclusions about earlier follow-up timing cannot be drawn.

In addition to hCG decline, clinical symptoms such as continuous vaginal bleeding and pain are very important. These symptoms may signal incomplete abortion or other complications as infection that require further evaluation and intervention. This highlights the critical need to integrate patient-reported symptoms and clinical assessment into the follow-up strategy.

Impact on global abortion policies

The implications of VEMA are particularly significant in restrictive legal settings, such as U.S. states where abortions are prohibited after six weeks of gestation (when detecting embryonic cardiac activity) (101). VEMA provides a critical option for women seeking early abortion care in these regions, demonstrating its effectiveness and safety before an IUP can be confirmed on ultrasound.

By confirming the feasibility and safety of VEMA, this thesis supports international calls for the removal of unnecessary barriers to early abortion care. This aligns with WHO recommendations that emphasize timely access to abortion as a cornerstone of reproductive health (14). These findings highlight the potential of VEMA to advance the de-medicalization of abortion, by shifting early abortion care away from the clinical requirements, such as mandatory confirmation of IUP on ultrasounds. Instead, relying on patients' history, biochemical marker (hCG) and patient-reported outcomes. There is a broad trend of de-medicalization of abortion by reducing unnecessary clinical interventions and shifting care to less medicalized, more patient-

centered approaches. VEMA exemplifies this shift, offering a safe, effective, and patient-centered alternative that reduces dependency on traditional clinical medical care and empowers women to manage their reproductive health with greater autonomy.

Although this thesis primarily evaluates VEMA application, the findings contribute to broader discussions about telemedicine in abortion care. They strengthen the case for telemedicine with less medicalized protocols, such as initiating abortion treatment before ultrasound confirmation of IUP. This not only enhances accessibility but also makes abortion care more inclusive, flexible, and responsive to women's needs.

Women's perspectives on abortion care in Sweden

The participants in our study **Paper IV**, largely report being satisfied with the quality of abortion services, highlighting the supportive and professional approach of healthcare providers. However, our study shows several aspects of the current system that may need improvement, particularly regarding waiting times and the flexibility of care options.

While many participants appreciated the easy contact with the abortion clinic and scheduled pre-abortion visits, the waiting period for in-clinic appointments caused significant emotional distress and physical discomfort, especially when experiencing pregnancy symptoms. Research has consistently shown the importance of reducing waiting times and timely access to care, which aligns with international guidelines advocating for patient-centered and efficient abortion services (102, 103).

The required ultrasound and gynecological examinations were often seen as a valuable health check, particularly since routine gynecological care is not common in Sweden. However, some participants found these procedures to be uncomfortable. Previous studies showed while some women find value in the information provided by ultrasounds, others may perceive them as emotionally challenging (104-107). A more flexible approach, as in telemedicine abortion where such procedures are conducted only when clinically necessary, could help to consider individual preferences while maintaining safe care practices.

Participants found telemedicine abortion as a promising alternative to in-person model. It offers flexibility, reduces waiting times, and empowers women by allowing

them greater autonomy in their care decisions. Many participants recognized telemedicine as an important complement, particularly for those unable to attend in-person consultations due to logistical or personal barriers. Previous studies affirm the safety, efficiency, and person-centered nature of telemedicine abortion (92, 94, 108-110).

Another key area of concern is the mandatory in-clinic administration of mifepristone. While some women felt reassured by taking the medication under the supervision of healthcare providers, others expressed preference for the option to take mifepristone at home. Allowing home administration could further enhance autonomy and convenience, without compromising the safety or efficacy of the procedure, as confirmed by recent Swedish and international research (20, 88, 111).

Methodological considerations

It is essential to address the consistency and variability in defining complete or successful abortion. In **Papers I and II**, we used a definition of successful or complete abortion as the absence of ongoing IUP pregnancy and no need for surgical intervention 30 days following medical abortion following abortion (112). This aligns with many studies that evaluate medical abortion outcomes, where success is similarly defined as achieving complete expulsion without the need for surgery (48, 113-115). In **Paper III**, we expanded this definition to include the absence of ongoing IUP pregnancy and no need for surgical or extra medical intervention 30 days following medical abortion, which still fits within the general understanding of complete abortion described in the literature. This expanded definition was adopted to address cases where participants might experience symptoms related to retained products of conception or missed abortion, necessitating contact with healthcare providers. Such cases may require further treatment, including repeated medical intervention with mifepristone and/or misoprostol. By this definition, we aimed for a more comprehensive assessment of abortion outcomes in comparison with hCG dynamics pre- and post-abortion.

There was a variation in follow-up duration between the studies. **Paper I** was extended to 42 days, while **Papers II and III** were limited to 30 days. Based on clinical experience, a 30-day follow-up may be insufficient to identify all cases of retained products of conception that require additional medical intervention with mifepristone or, in some cases, surgical management. A longer follow-up period, such as 42 days, may provide a more comprehensive understanding of the full range

of outcomes and complications, particularly for identifying delayed cases of incomplete abortion.

In **Paper IV**, we interviewed women who sought EMA at the abortion clinic within the Department of Obstetrics and Gynecology at Sahlgrenska University Hospital in Gothenburg, Sweden. Broader recruitment strategies may be used to increase diversity in future studies and to get wider opinions. Online platforms like Facebook, Instagram, or other social forums could be considered for recruiting participants. This would allow for the inclusion of women from different geographical areas and backgrounds.

Strengths and limitations

This thesis benefits from a comprehensive approach, combining data from a large multinational RCT (**Paper II**) and a large retrospective study (**Paper I**). The inclusion of diverse populations across nine countries enhances the generalizability of the findings. Additionally, the analysis of hCG dynamics offers valuable insights into the safe management of very early abortions (**Paper I and III**).

A significant strength of **Paper IV** is that it is the first study to explore women's experiences with accessing pre-abortion appointments, undergoing pelvic and ultrasound examinations, and their perspectives on telemedicine abortion within the context of a liberal abortion policy in Sweden. To our knowledge, no prior research has specifically investigated Swedish women's views on current abortion service options, with a particular focus on the potential provision of telemedicine and intake of mifepristone at home.

The limitations of **Paper I** come from its retrospective design. However, the results were confirmed and consistent with findings from the RCT, reinforcing the reliability and validity of the outcomes. Patient exclusions occurred due to incomplete data. Additionally, follow-up protocols differed between Austria and Sweden, with Gothenburg routinely conducting a second hCG test one-week post-mifepristone, while in Vienna, hCG was only performed if deemed necessary by the treating physician. These differences may introduce potential bias to the findings.

The limitation of **Papers II and III** is the relatively short follow-up time of 30 days post-abortion. While this duration aligns with many standard protocols, it may not capture all late-presenting cases of retained products of conception that might need

additional surgical interventions. However, it is crucial to balance the follow-up duration with the risk of losing patients to follow-up. Extending the follow-up period increases the likelihood of patients not responding to follow-up inquiries, which can compromise the completeness of the data. In the randomized study, the four-week follow-up period was specifically chosen to achieve this balance, ensuring a high follow-up rate while minimizing the risk of loss to follow-up. This underscores the importance of carefully selecting follow-up durations in study designs to maintain both data integrity and patient participation.

Paper IV The study' depend on selected participants who were seeking abortion care in a specific clinic which may limit the diversity of the participant pool. This might affect the generalizability of the findings to broader populations who may seek abortion care in different settings or under other circumstances. Since the study only included women who attended in-person consultations and received mifepristone at the clinic, it did not capture the experiences of women who experienced telemedicine abortions which is still not allowed in Sweden.

Conclusions

This thesis demonstrates that very early medical abortion (VEMA) is an effective and safe option for women seeking abortion care before confirmation of an intrauterine pregnancy with ultrasound. Across retrospective and randomized controlled studies, VEMA achieved high success rates, with success defined as the absence of ongoing pregnancy and no need for further surgical intervention. In **Paper I**, the success rate was 97.6%, while the RCT in **Paper II** confirmed the non-inferiority of early treatment compared to delayed treatment, with success rates exceeding 95%, across 26 trial sites in nine countries. The studies also highlighted the slightly higher rate of ongoing pregnancies in the early treatment group compared to the delayed group, balanced by a reduced need for surgical interventions. These findings establish VEMA as a valuable option for earlier access to abortion care without compromising safety.

The studies also showed that a follow-up protocol by measuring hCG levels seven days post-abortion provides a reliable indicator of successful abortion and ensures safe care. A decline of $\geq 80\%$ in hCG levels can accurately exclude ectopic and ongoing pregnancies and most cases of incomplete abortion, regardless of variations in baseline hCG levels or the laboratory method used for analysis **Paper III**. This finding underscores the generalizability of hCG monitoring as a cornerstone of post-abortion care, as long as the same assay is used pre- and post-abortion.

Reducing waiting times, allowing home administration of mifepristone, and offering telemedicine options are important considerations to enhance abortion care in Sweden **Paper IV**. Such measures would improve access and provide a more individualized care experience. These adjustments would help Swedish abortion care to align with international best practices while maintaining its high standards of safety and support.

Future perspectives

Sweden is known for its high standards in abortion care, providing safe and accessible services. However, further research and innovation in specific areas could help advance both clinical practice and policy, ensuring continued progress in this field. The following areas highlight key priorities for future research and development:

- **Telemedicine for Early Medical Abortion (EMA):** The COVID-19 pandemic significantly transformed abortion healthcare worldwide, with many countries adopting telemedicine services to ensure continued access. Numerous studies have demonstrated the safety and effectiveness of telemedicine for EMA. However, in Sweden, there is a lack of published data on this approach. Focused studies are needed to validate its safety and efficacy in the Swedish context. Such research would provide critical insights into integrating telemedicine into standard (in-person) abortion care, expanding patient access and autonomy while addressing barriers such as geographic distance and clinic availability.
- **Safety of Home-Based Abortion Between 10–12 Weeks:** While SMA is recommended by the WHO for gestational age up to 12 weeks. There are limited studies about the safety of home-based medical abortion >10 weeks of gestation (24). While in Sweden currently requires abortions between 10 and 12 weeks to be conducted in clinical settings. Research is needed to assess the feasibility and outcomes of home-based abortion within this gestational window. Such evidence would be crucial for expanding telemedicine services in the future and aligning with WHO recommendations for self-managed abortion (5).
- **Innovative Home-Based Monitoring Tools:** The development of quantitative urine hCG tests capable of measuring hormone levels accurately could revolutionize abortion follow-up care. Enabling women to monitor hCG levels at home and communicate results to healthcare providers via web-based platforms (like 1177) or telephone consultations, before and after medical abortion to evaluate the decline of hCG would minimize visits to health care services. These tools could enhance safety by confirming successful abortion and excluding ectopic or ongoing pregnancies. Such innovations would integrate easily into VEMA

and eventually into telemedicine models, increasing confidence and convenience for patients.

- **Impact on Long-Acting Reversible Contraception (LARC) Use:** One challenge of telemedicine abortion is the potential decrease in contraception utilization (116) , especially LARC such as subdermal contraceptive implants (e.g., Nexplanon), which are often inserted on the same day mifepristone is administered in clinical settings (117). Future research should explore strategies to maintain LARC services within telemedicine models to ensure contraceptive use without disruption.
- **Patient Experiences on Telemedicine:** Understanding women's experiences and perspectives is important for assessing the acceptability of telemedicine abortion service in Sweden when it will be provided. Qualitative studies focusing on patient satisfaction and experience will provide valuable insights to tailor telemedicine services in the future to meet patients' needs and preferences.

By addressing these areas, Sweden can advance its abortion care framework to remain in the lead of evidence-based and patient-centered practices. Integrating innovative technologies and aligning with international recommendations will ensure that abortion care continues to prioritize safety, accessibility, and the autonomy of women.

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