Clinical Management of Medical Abortion Beyond 12 Gestational Weeks

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Cover illustration: Promoting autonomy by Johanna Rydelius

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To Frank and Ines

Abstract

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Background: Abortion beyond 12 gestational weeks (GWs) constitutes a minor part of the total number of abortions globally and access is often restricted due to legal frameworks or lack of necessary resources. In Sweden around 5% of abortions are conducted after 12 GWs. A regimen with mifepristone followed by repeat doses of misoprostol is recommended for medical abortion beyond 12 GWs. With an induction-to-abortion interval around 5–8 h the regimen is suitable for day-care. Placement of an intra-uterine device (IUD) is recommended as soon as possible post-abortion but the optimum timing of insertion after a medical abortion beyond 12 GWs has not been determined.

Aims: The overall aim of this thesis was to increase the knowledge about the clinical management of medical abortion beyond 12 GWs. A specific aim was to investigate the impact of the coronavirus disease 2019 (COVID-19) pandemic on abortion numbers in Sweden and explore reasons for the findings.

Material and methods: Paper I was a mixed-methods study with a convergent parallel design. Data regarding the number of abortions during and before the COVID-19 pandemic was collected from the National Board of Health and Welfare. Qualitative data was collected from semi-structured interviews. Paper II was a multicentre, randomised controlled trial (RCT) in which the effects of home compared with hospital administration of the first misoprostol dose for abortion beyond 12 GWs was studied. Paper III was a multicentre RCT in which the effects of IUD-insertion within 48 h compared with after 2–4 weeks was studied. Paper IV was a descriptive cross-sectional study in which data regarding pain, measured by visual analogue scale (VAS), and analgesic treatment was retrieved from the RCT in Paper II.

Results: Paper I: The total number of abortions did not change significantly during the study period compared with the years before the pandemic. Interview themes

were *meeting with abortion care* and *the impact of the COVID-19 pandemic on the abortion decision*. Paper II: 156/220 (70.9%) of the participants who administered the first misoprostol dose at home completed the treatment as a day-care procedure compared with 99/215 (46.0%) for those who administered the first dose at the hospital (difference 24.9 percentage points (pp), 95% CI 15.4 to 34.3; p <0.0001). Paper III: After 6 months 34/67 (50.7%) of the participants in the group with IUD-insertion within 48 h were using an IUD, compared with 48/67 (71.6%) of the participants in the group with insertion after 2–4 weeks (difference 20.9 pp, 95% CI 4.4 to 35.9; p=0.021). Paper IV: The participants reported a mean VAS of 39.1 (SD 34.4) at fetal expulsion and a maximum pain score during the abortion of VAS 65.4 (SD 28.6). A total 266/425 (62.6%), 163/425 (38.4%) and 86/425 (20.2%) of the participants received an oral opioid, a paracervical block (PCB) or an opioid injection respectively. The largest decrease in VAS was achieved with administration of a PCB preceded by an oral or an injectable opioid or by both an oral and an injectable opioid.

Conclusions: The abortion numbers in Sweden were not critically affected by the COVID-19 pandemic and, despite pandemic-related factors that influenced the abortion decision-making, abortion-seeking persons did not hesitate to proceed with the abortion. Home-administration of the first misoprostol dose in medical abortion after 12 GWs significantly increased the proportion of day-care procedures, with maintained safety and patient acceptability. Promoting day-care protocols for medical abortion beyond 12 GWs, with support from tertiary care levels, could lead to increased access also in regions with low admission possibilities. IUD-insertion within 48 h after medical abortion beyond 12 GWs resulted in higher expulsion rates and was less advantageous in terms of IUD-use after 6 months when compared with insertion after 2–4 weeks. Persons having a medical abortion beyond 12 GWs reported severe pain and most often required extra analgesia in addition to non-steroidal anti-inflammatory drugs and paracetamol. An oral opioid was the most common analgesia, but a PCB was associated with a larger reduction of VAS when administered after onset of pain.

Keywords: Medical abortion, abortion beyond 12 gestational weeks, day-care, intra-uterine device, pain management.

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Sammanfattning på svenska

Bakgrund: Abort efter 12 graviditetsveckor (GV) utgör en mindre andel av det totala antalet aborter i världen. Risken för abortrelaterade komplikationer anses vara högre jämfört med efter en abort tidigare under graviditeten. I Sverige utförs runt 5% av alla aborter efter 12 veckor. Globalt är tillgängligheten till abortvård efter 12 GV sämre än för en abort i tidig graviditet, bland annat pga. legala begränsningar.

En abort efter 12 GV kan utföras med kirurgisk eller medicinsk metod. Den rekommenderade medicinska metoden med mifepriston följt av upprepade doser av misoprostol har visats vara effektiv, säker och väl tolererad av patienter.

För att undvika att en ny oönskad graviditet uppkommer rekommenderas ett effektivt preventivmedel, som tex en spiral, så snart som möjligt efter aborten. Kunskap kring det optimala tillfället för spiralinsättning efter en abort efter 12 GV saknas.

Syfte med avhandlingen: Att öka kunskapen om den kliniska handläggningen av personer som genomgår en medicinsk abort efter 12 GV. En särskild frågeställning berörde COVID-19 pandemins påverkan på abortsökande patienter.

Metod: I delarbete I inhämtades data från Socialstyrelsen och Graviditetsregistret över det totala antalet aborter och födslar under COVID-19 pandemin, och för jämförelse även från föregående år. Intervjuer genomfördes med abortsökande personer under motsvarande tidsperiod av pandemin.

I delarbete II undersöktes hur andelen dagvårdsbehandlingar (<9 tim) påverkas om den första dosen misoprostol tas i hemmet vid abort efter 12 GV. Studiedeltagarna lottades till att antingen ta den första misoprostoldosen hemma eller efter ankomst till den gynekologiska avdelningen 2 timmar senare. Andelen dagvårdade studiedeltagare, total vårdtid, upplevd deltagarnöjdhet och abortrelaterade komplikationer mättes. I delarbete IV användes samma kohort av studiedeltagare till att närmare analysera den upplevda smärtan under aborten. Smärta mättes på en visuell analog skala (VAS) 0–100 mm. Effektivitet av given smärtbehandling undersöktes också.
I delarbete III undersöktes hur spiralanvändning 6 månader efter en abort efter 12 GV påverkades av tidpunkten för insättning. Studiedeltagarna lottades till att antingen få en spiral insatt inom 48 tim efter aborten eller vid ett återbesök 2–4

veckor senare. Andelen spiralanvändare efter 6 månader, andel som kom till sitt insättningsbesök och spiralutstötningsfrekvens mättes.

Resultat: I delarbete I sågs ingen förändring i antalet aborter eller födslar i Sverige under den första pandemivågen 2020, jämfört med föregående år. Andelen aborter efter 12 GV förblev också opåverkad. I analysen av intervjuerna med de abortsökande framkom två teman: *mötet med abortvård under COVID-19 pandemin* och *pandemins påverkan på abortbeslutet*. Studiedeltagarna uttryckte att de inte tvekade att söka abortvård och att det var enkelt att få en tid för bedömning på abortmottagningen. Det framkom att pandemin i sig inte påverkade deras beslut att utföra en abort men att faktorer sekundära till pandemin delvis influerade deras beslut.

I delarbete II lottades 457 abortsökande under åren 2019–2022 till att ta den första misoprostoldosen hemma eller efter ankomst till sjukhus. Efter exkludering av ett antal patienter ingick 220 deltagare i hem-gruppen och 215 i sjukhus-gruppen. I hem-gruppen genomförde 156/220 (70,9%) av studiedeltagarna behandlingen som dagvård, jämfört med 99/215 (46,0%) för de som fick den första dosen på sjukhus (differens 24,9 procentenheter (pe), 95% konfidensintervall (KI) 15,4 till 34,3; p <0,0001). Deltagarna i hem-gruppen tillbringade också kortare tid på sjukhus; 10,3 (standarddeviation (SD) 10,8) tim jämfört med 13,1 (SD 12,5) tim i sjukhusgruppen (differens -2,8 tim, 95% KI -5,0 till -0,6; p=0,014). Studiedeltagarna uppvisade hög nöjdhet med behandlingen och fler personer i hem-gruppen föredrog sin tilldelade behandling jämfört med sjukhus-gruppen. Det fanns ingen skillnad i andelen komplikationer mellan grupperna. Riklig vaginal blödning var den vanligaste komplikationen och 1% av studiedeltagarna fick en blodtransfusion. Nio personer aborterade utanför sjukhus.

I delarbete III lottades 179 personer under åren 2019–2022 till antingen tidig (inom 48 tim) eller sen (2–4 veckor) insättning av spiral efter en abort efter 12 GV. Efter exkludering ingick 67 studiedeltagare i varje grupp (tidig eller sen insättning). Rekrytering till studien avslutades i förtid då en interimsanalys visade en spiralutstötningsfrekvens >20% i gruppen med tidig insättning. Efter 6 månader uppgav 34/67 (50,7%) av de med tidig insättning att de använde spiral jämfört med 48/67 (71,6%) i gruppen med sen insättning, (differens 20,9 pe, 95% KI 4,4 till 35,9; p=0,021). Totalt kom 69/77 (89,6%) i den tidiga gruppen till sitt insättningsbesök jämfört med 56/78 (71,8%) i den sena gruppen. Spiralutstötning var dock vanligare

i den tidiga gruppen och 22/73 (30,1%) av studiedeltagarna rapporterade utstötning jämfört med 2/70 (2,9%) i den sena gruppen.

I delarbete IV utfördes analyser av upplevd smärta och smärtbehandling på 425 studiedeltagare från studie II. Medel-VAS vid utstötning av fostret var 39,1 (SD 34,4) men den maximala smärtan uppgavs till medel 65.4 (SD 28,6). Studiedeltagare som inte genomgått en vaginal förlossning samt de med graviditetslängd >126 graviditetsdagar (=18 GV) skattade sin smärta under aborten signifikant högre än de som genomgått vaginal förlossning och de med kortare graviditetslängd. Majoriteten av studiedeltagarna, 357/392 (91,1%), var nöjda med sin smärtbehandling. Den vanligaste smärtbehandlingen var en opioidtablett som användes av 266/425 (62,6%) av studiedeltagarna. Totalt 163/425 (38,4%) erhöll paracervicalblockad (PCB) och 86/425 (20,2%) en opioidinjektion under aborten. Administration av PCB, där en opioidtablett eller en opioidinjektion eller både en opioidtablett och opioidinjektion givits till studiedeltagaren tidigare under aborten, var den metod som uppvisade den största minskningen av VAS.

Slutsats: Sammanfattningsvis förändrades inte aborttalen under COVID-19 pandemin i Sverige. Abortsökande personer tvekade inte att genomföra abort men pandemin påverkade till viss del deras beslutsfattande kring aborten. Att ta den första misoprostoldosen i hemmet ökar andelen patienter som genomför en medicinsk abort efter 12 GV som en dagvårdsbehandling, med bibehållen säkerhet och hög patientnöjdhet. Dagvård är en åtgärd som skulle kunna öka den globala tillgängligheten till abort efter 12 GV. Spiralinsättning inom 48 tim efter en medicinsk abort efter 12 GV innebär ökad utstötningsfrekvens och leder till minskad spiralanvändning efter 6 månader. Personer som genomgår en medicinsk abort efter 12 GV skattar smärtan som svår och de allra flesta behöver extra smärtlindring. En opioidtablett är en vanlig smärtlindrande metod, men administrering av PCB ger sannolikt en bättre smärtlindrande effekt.

List of papers

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

I. Rydelius J, Edalat M, Nyman V, Jar-Allah T, Milsom I, Hognert H. Influence of the COVID-19 pandemic on abortions and births in Sweden: a mixed-methods study. *BMJ Open*. 2022;12:e054076

II. Rydelius J, Hognert H, Kopp-Kallner H, Brandell K, Romell J, Zetterström K, Teleman P, Gemzell-Danielsson K. First dose of misoprostol administration at home or in hospital for medical abortion between 12-22 gestational weeks in Sweden (PRIMA): a multicentre, open-label, randomised controlled trial (published correction appears in Lancet 2024 Sep 14;404(10457):1018, in Lancet 2024 Nov 30;404(10468):2164, and in Lancet 2025 Jan 4;405(10472):32. *Lancet*. 2024;404(10455):864-873

III. Hogmark S, Rydelius J, Envall N, Teleman P, Gemzell-Danielsson K, Kopp Kallner H. Placement of an intrauterine device within 48 hours after second-trimester medical abortion: a randomized controlled trial. *Am J Obstet Gynecol*. 2024;231(5)

IV. Rydelius J, Kopp Kallner H, Karlsson O, Hognert H, Gemzell-Danielsson K. Pain management for medical abortion beyond 12 weeks of gestation – a cross-sectional study in Sweden. Under revision 250318

Contents

Abbreviations

AE(s)	Adverse event(s)
BMI	Body mass index
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRF(s)	Case report form(s)
D&E	Dilatation and evacuation
EDA	Epidural analgesia
GCP	Good clinical practice
GD(s)	Gestational day(s)
GW(s)	Gestational week(s)
IM	Intramuscular
IQR	Interquartile range
ITT	Intention-to-treat
IUD	Intrauterine device
IV	Intravenous
IV-PCA	Intravenous patient-controlled analgesia
LARC	Long-acting reversible contraception
LNG-IUD	Levonorgestrel-releasing intrauterine device
mITT	Modified intention-to-treat
NBoHW	National Board of Health and Welfare
NICE	The National Institute for Health and Care Excellence
NSAID(s)	Non-steroidal anti-inflammatory drug(s)
PCB	Paracervical block
PP	Per protocol
Q1; Q3	First quartile; third quartile
RCT	Randomised controlled trial
Rh	Rhesus
RR	Relative risk
SAE	Serious adverse event
SD	Standard deviation
STC	Systematic text condensation
TENS	Transcutaneous electrical nerve stimulation
VAS	Visual analogue scale
WHO	World Health Organization

Introduction

Language clarifications

Throughout the thesis, the noun "person" is used to apply an including language when referring to the pregnant individual who is opting for or having had an abortion. In a few paragraphs, when specific statistics or articles are cited, the noun "woman" is used. The term abortion refers to induced abortion, as in voluntary termination of pregnancy in contrast to spontaneous abortion or miscarriage.

Abortion beyond 12 gestational weeks

It has become more common to state the exact gestational age interval when referring to an abortion conducted later in pregnancy. For abortions beyond 12 or 13 completed gestational weeks (GWs) the term second trimester abortion has traditionally been widely used. The second trimester of pregnancy is usually defined as the interval between 13 and 28 GWs. However, trials and guidelines about second trimester abortions do not always include all GWs from 13 to 28. In this thesis, when applicable, the exact gestational age interval will be referred to, otherwise "second trimester" will be used.

For abortions beyond 12 GWs both medical and surgical methods are available. Medical abortion refers to termination of pregnancy by using pharmacological treatment, and surgical abortion to a procedure using transcervical techniques. This thesis will focus on the medical methods, but the surgical methods are also covered below.

Reasons for abortions beyond 12 gestational weeks

Pregnant persons seek abortion services for a variety of reasons, and globally the most frequently cited causes are socioeconomic concerns including limiting childbearing.[1] For abortions beyond 12 GWs the indications seem to be as diverse, dependent on the setting and are often a combination of many factors that together ultimately lead to an abortion later in pregnancy. Nevertheless, a few points differ for abortions in later compared with earlier pregnancy.

External barriers

Legal restrictions are common reasons for low access to abortion beyond 12 GWs, but could also explain why an abortion occurs beyond 12 GWs. A general ban for abortions will cause delays for the abortion-seeking person to find available abortion care outside of the local community, and consequently some pregnancies are prolonged beyond 12 GWs. It is also common with legal restrictions for abortions above a certain gestational age limit, or a necessity of obtaining special permission, which could further complicate the pathway to abortion.

Despite being legal in a specific setting, it does not necessarily mean that abortion care beyond 12 GWs is readily available. In settings with more liberal abortion laws there are many examples of barriers potentially delaying abortion care to later in pregnancy: a need for initial referral to another centre, lack of access to certain services (such as surgical abortion or abortion care at later gestation), conscientious objection, increasing travel distances, financial barriers (abortion being more expensive later in pregnancy), mandatory assessments, multiple approvals or waiting periods between the consultation and the procedure are common.[2-4]

Fetal indication

Fetal indications, such as prenatal diagnosis of genetic disorders or structural abnormalities, usually constitute a considerable proportion of abortions beyond 12 GWs, especially above 20 GWs. In Sweden the proportion of abortions that are conducted because of a fetal indication is approximately 70% among persons applying for abortion beyond 18 GWs.[5] In the UK the proportions are 13% and 29% for abortions between 13–19 GWs and ≥20 GWs respectively.[6] Global rates are however difficult to estimate. There is a lack of reporting on indications to abortion registers and management of fetal disabilities are very diverse. With the rapid growth of prenatal screening programs, the number of abortions conducted due to fetal impairment will probably increase.

Maternal indication

Abortion due to maternal indications, when the person carrying the pregnancy is at risk of falling seriously ill, is a minor group. Common life-threatening conditions include early development of preeclampsia, newly diagnosed cancer, cardiopulmonary events or sepsis resulting from chorioamnionitis. Abortion of a

pregnancy resulting from a sex offence is another maternal indication and is possibly more common. Mental illness is often reported as a maternal indication for abortion, and persons with severe psychiatric disease is a group in which delays in seeking abortion care could be explained by their mental condition.

In one study from the Netherlands 1.5% of abortions between 22–27 GWs were due to maternal disease. In the UK 0.4% of abortions beyond 13 GWs were undertaken because of a life-threatening risk to the mother.[6, 7]

Other reasons

Even in countries with liberal laws and easy access to services for abortion beyond 12 GWs some non-medical reasons for delaying the abortion persist. Frequently reported motives for seeking abortion care later in pregnancy are delays in recognising pregnancy, because of lack of pregnancy symptoms or continuous use of contraceptives, and delays in taking a pregnancy test. Some persons seeking abortion experience ambivalence concerning the pregnancy and postpone the abortion-decision, both before and after the first consultation, leading to abortion later in pregnancy.[2, 3]

The global perspective

In 2015–2019 73.3 million abortions were reported world-wide each year, corresponding to an abortion rate of 39 per 1000 women (aged 15–49 years) (see Figure 1).[8] A safe abortion is defined as a procedure conducted with a method recommended by the World Health Organization (WHO) and by a provider with necessary skills. Global estimates demonstrate that 45% (2010–2014) of all abortions are unsafe and 97% take place in low-income countries.[9] Between 4.7% and 13.2% of all maternal deaths are believed to be caused by unsafe abortions.[10] As a consequence of legal restrictions a higher proportion of abortions beyond 12 GWs are unsafe, and the proportion of morbidity and mortality due to unsafe abortion is higher for abortions later in pregnancy.[11]

It is difficult to obtain data on the global number of abortions beyond 12 GWs and often statistical sources are non-existent because of legal restrictions. Proportions have been estimated to be around 10–15% of all abortions.[12] There has been a shift towards abortions occurring earlier in pregnancy since the 1980s. Possible

explanations are increased awareness as well as increasing availability of medical abortion.

Multiple factors, such as the availability of drugs and equipment, capacity to administer pain control, abortion provider skills, client preference, cultural considerations and local regulation, influence the choice between a surgical or medical procedure being conducted for abortions beyond 12 GWs in a given setting.

Globally very diverse legal frameworks and local restrains in access result in different proportion of abortions conducted beyond 12 GWs. In the section below a few examples are presented, but to make a complete global overview is not the purpose of this thesis.

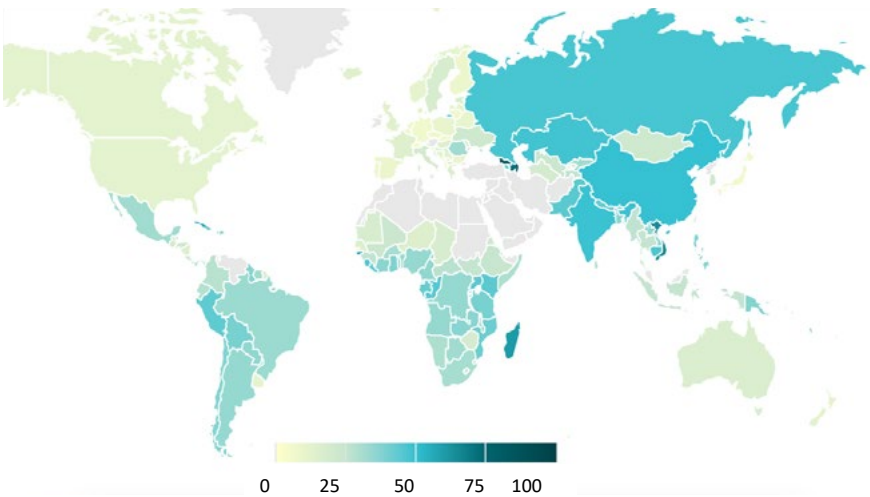

Figure 1. *Abortion Incidence. Average annual number of abortions/1000 women (aged 15–49): 2015–2019. Source: Bearak J et al., Country-specific estimates of unintended pregnancy and abortion incidence: a global comparative analysis of levels in 2015–2019, BMJ Global Health. https://gh.bmj.com/content/7/3/e007151. Collected from https://data.guttmacher.org/countries/map?topics=405&dataset=data. 2024-12-20.*

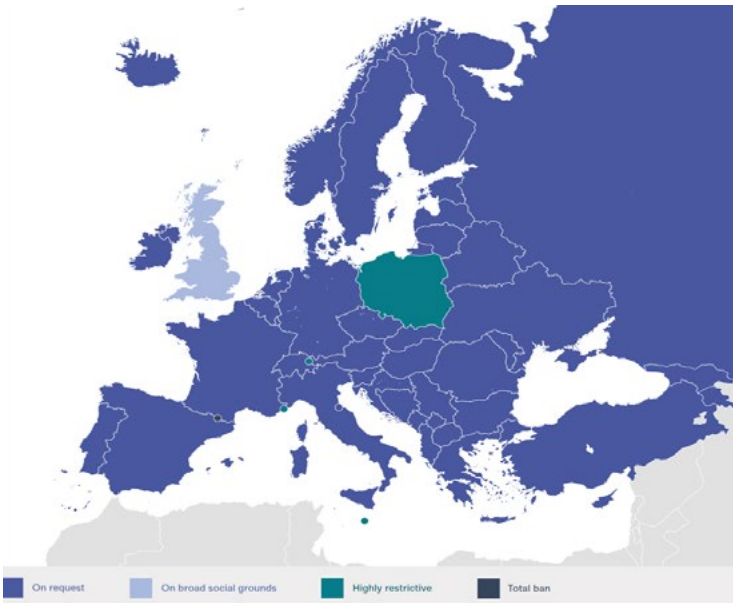

Figure 2. *European Abortion Laws: A Comparative Overview. Source: Center for Reproductive Rights. 2023-09-13. https://reproductiverights.org/wp-content/ uploads/2023/09/European-Abortion-Laws-A-Comparative-Overview-new-9-13-23.pdf. 2024-12-20.*

Europe

In Europe most countries allow abortion upon request or on broad social grounds until 12 GWs (see Figure 2). Beyond 12 GWs it is often permitted for maternal and fetal indications. Only Poland, Andorra, Monaco, Liechtenstein, Malta and San Marino still have highly restrictive abortion laws.[14]

The proportion of abortions beyond 13 GWs vary between 3% for Germany and Iceland to 7% in Italy and 15% in the Netherlands.[15] The higher numbers reported from the Netherlands could be explained by the influx of abortion-seeking persons traveling from other countries where they could not access an abortion beyond 12 GWs.[16]

The rates of surgical compared to medical abortion in Europe vary according to availability, local tradition and legal framework. In the UK around 80% and 74% of

abortions are performed with a surgical method if the abortion is conducted between 13–19 GWs or beyond 20 GWs respectively.[6]

In the Scandinavian countries the proportion of second trimester abortion is around 5%. In one recently published article the authors present the current trends for abortions later in pregnancy. The proportion of abortions after 12 or 13 GWs has decreased since the liberation of abortion laws in the 1970s but the proportion of abortions >19 GWs has increased over the study period (1984–2022) reaching around 1.6%. There seem to be a steady increase of second trimester abortions on fetal indications in all age groups, possibly due to improved screening methods.[17] The majority of abortions beyond 13 GWs are conducted by a medical method.[18]

North America

In the US the political landscape of abortion rights changed rapidly after June 2022 when "Roe versus Wade" from 1973 was overturned by the US supreme court. The decision in "Dobbs versus Jackson Women's Health Organization" eradicated the federal right to abortion. As of January 2025, thirteen states across the country have banned abortion with few exceptions. In addition, 28 states have implemented laws that restrict access based on gestational age. For updated information Guttmacher Institute provides an interactive map for US abortion policy and access.[19, 20]

Recent findings from Guttmacher Institute estimate an abortion rate of 15.9 per 1000 women in the US.[19] In general there is an increase of medical abortions with 63% of all clinician-provided abortions (excluding self-managed abortions outside the health care system and procedures conducted in states with total bans when medication was provided by mail) being medical in 2023, but there are no more recent estimates covering the proportions of medical second trimester abortion.[21] Before the Dobbs decision there was a trend with a decreasing number of abortions performed ≥13 GWs reaching 6.6% (2010–2021). Concerns are raised that due to the Dobbs decision more abortion-seeking persons will experience even further delays which will increase the proportion of abortions performed after 13 GWs. The majority of abortions beyond 12 GWs in the US are performed surgically.[22]

Abortion in Canada is legal throughout pregnancy as a medical procedure under protection by the federal Canada Health Act.[23] However, access to abortion beyond 12 GWs varies by region and many times due to ill-defined impressions of lethality or viability concepts.[24] In 2022 the total abortion rate was 12.3 per 1000 women (15–

44 years) and in 2020 13.2% of abortions were conducted after 12 GWs. There are no statistics on which abortion method is most commonly used after 12 GWs but medical procedures are widely available and constitute 40% of abortions for all GWs.[25]

Australia

In Australia there is no national data registration of abortions. The abortion rate is estimated to be 16 per 1000 women. Regional data from South Australia (2023) estimates that 10.5% of all abortions were conducted after 14 GWs, out of which 69% by a surgical method.[26]

Low- and middle-income countries

In many low-income countries access to abortions beyond 12 GWs is limited. This is partly due to the legal framework but other factors such as lack of skilled providers and recommended medications are also of importance. In most settings surgical options for abortions beyond 12 GWs are not available, and medical abortion continues to be the most common method. Obtaining universal data on the actual proportions of abortions after 12 GWs, and which procedures that are available is difficult. A few examples from low- and middle-income countries will be presented below.

In South Africa the abortion rate is 30 per 1000 women and 10% of all abortions are conducted beyond 13 GWs. Medical abortion is the predominant method, and surgical services are only available on a very limited basis.[27-29]

There has been a substantial progression of abortion rights in Latin-America with Argentina taking the lead in 2021 when the new abortion law was reinforced. It allows abortions on request through 14 GWs, and beyond if there is a threat to the pregnant person's life or in cases of rape. Before the introduction of the law the abortion rate was estimated to be 33 per 1000 women. The proportion of abortions beyond 14 GWs has been estimated to be around 20% in tertiary hospitals. The majority of abortions were by medical methods.[30] After 2021 Mexico and Colombia have decriminalized abortion as well, allowing the procedure up to 12 and 24 GWs respectively.[14]

In India abortion is legal for a broad range of indications up to 20 GWs. The abortion rate is estimated to be 48 per 1000 women. There is no official data, but approximation indicates that 81% are medical abortions, and 10–15% are performed during the second trimester. Even though the legal framework allows abortions in these gestational weeks, access is skewed and there are many obstacles to obtain an abortion later in pregnancy.[29, 31, 32]

In Nepal, abortion is legal upon request in the first trimester and up to 28 GWs under special circumstances such as rape, fetal anomaly and risk of severe maternal illness. Since legalisation in 2002, access to abortion care has been facilitated and maternal mortality due to abortion has decreased. Nevertheless, barriers to abortions beyond 13 GWs remain, particularly in remote areas. The abortion rate is 41 per 1000 women but only 48% of all abortions are managed by legal providers. There is a lack of official data on proportions of abortions induced after 13 GWs. Most second trimester abortions are conducted using medical regimens.[33]

The Swedish perspective

According to the Swedish Abortion Act from 1974 abortion is available upon request by the pregnant person until 18 GWs. Beyond 18 GWs the National Board of Health and Welfare (NBoHW) grants permission for abortions.[34] Since 2004 medical abortion with home use of misoprostol is available for abortions up to 10 GWs, but according to the Abortion Act mifepristone still has to be administered at the abortion clinic.[35]

Abortion statistics from Sweden are published by the NBoHW to which all clinics report on a yearly basis. During 2023, 35,548 abortions were conducted in Sweden which correlates to 18.4 abortions per 1000 women (15–44 years of age).

A total of 5.1% of all abortions were undertaken between 12 GWs and 1 gestational day (GD) and 18 GWs, and 1.0% from 18 GWs and 1 GD. The proportion of abortions beyond 12 GWs has remained stable since the 1990s (see Figure 3). In 2023, 78.3%, 20.2% and 1.6% of abortions after 18 GWs were conducted due to fetal, social or maternal reasons respectively.[36]

In 2023, 98.4% of abortions beyond 12 GWs were conducted by a medical method.[36] The Swedish guidelines for medical abortions >12 GWs adhere to the WHO

Abortion Care Guideline from 2022 in which the combined mifepristone-misoprostol regimen is recommended. A "loading dose" of misoprostol is administered followed by repeat lower doses of misoprostol. Dilatation and evacuation (D&E) is recommended as a surgical method, especially beyond 15 GWs.[35, 37]

All persons seeking abortion are required to attend an abortion clinic in person to receive mifepristone. During the day for misoprostol administration patients can be hospitalized or attend an outpatient ward with access to surgical service. Most medical abortions are provided by midwifes under supervision of gynecologists.

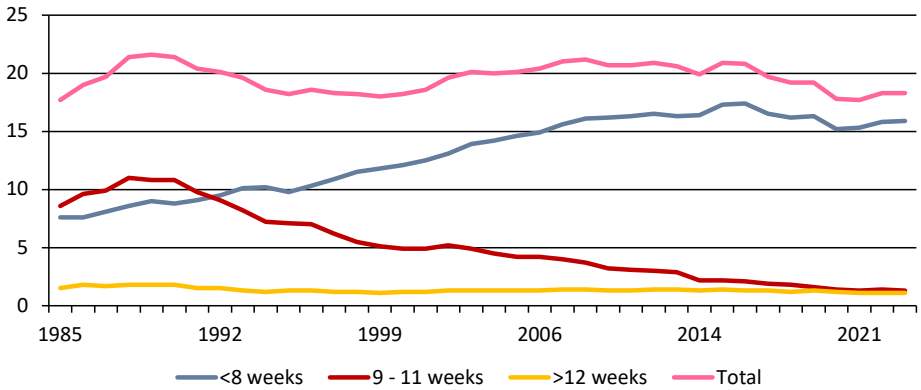

Figure 3. *Abortion rates (number/1000 women, 15–44) according to gestational age in Sweden 1985–2022. Source: Statistikdatabas för aborter. Swedish National Board of Health and Welfare. https://sdb.socialstyrelsen.se/if_abo/val.aspx. 2024-12-12.*

The coronavirus disease 19 pandemic and the effects on abortion care

During the coronavirus disease 2019 (COVID-19) pandemic the WHO underlined the importance of ensuring access to contraception and abortion to the full extent as permitted by the legal framework. They further recommended that if facility-based provision of abortion services would be disturbed, then telemedicine alternatives should be implemented.[37] Despite this recommendation, access to abortion care was restricted in many parts of the world, due to priorities in health services, lack of political will and as an effect of the lockdown.[38]

It is difficult to get a global overview of actions taken by politicians and healthcare authorities since abortion care regulations and services are very differently organized throughout the world. For healthcare in general several difficulties arose: travel restrictions, quarantine, fear of viral transmission, disruptions in supply chains, and reduced staff availability. There is one scoping review showing that the pandemic had broad impact on abortion services with declining coverage, interruptions in access (especially for surgical abortion), shortages in medical supplies and also indications that more persons opted for unsafe abortions.[39]

Figure 4. The COVID-19 virus. By Johanna Rydelius. 2024.

Globally there is evidence that countries with pre-pandemic severe restrictions were less likely to implement changes to abortion care to mitigate the impact of the pandemic compared to countries with more liberal policies.[38]

In Europe governments handled the challenge with abortion care during the pandemic very differently, from suspension of abortion services to lifting of regulations. In a few countries, for example Lithuania, Slovakia and Hungary, abortion was further restricted by declaring abortion a non-essential service and making surgical abortion very hard to access. In Poland a bill was passed to ban abortions on fetal indication.[38, 40, 41]

The pandemic was however also a trigger to update regulations. Several strategies were undertaken to facilitate access to abortion care despite lockdowns and reduced healthcare capacity: introduction of telemedicine options, introduction of medical abortion in countries where it was previously prohibited, allowing self-administration of abortion medication at home, postal delivery of mifepristone and misoprostol, changes in the requirement for ultrasound, extension of gestational limits for medical abortion and elimination of mandatory waiting periods.[38, 41]

There is no overview of how the abortion numbers and rates changed during the COVID-19 pandemic in Europe. In France there was a reduction in abortions during the first lockdown and this was suggested to be caused by a decline in conceptions.

The numbers returned to baseline during the second pandemic wave in the autumn of 2020.[42] In Germany statistics from the pandemic years indicate that there was no major change in abortion numbers and provision of abortion care was not impaired.[43] In the UK there was an increase of abortions during the first wave of the COVID-19 pandemic.[44]

In the US the COVID-19 pandemic placed hardships, in addition to barriers already existing, on abortion-seeking persons. Eleven states had categorized abortions as non-essential procedures by May 2020 resulting in 16% of clinics temporarily stopped providing abortion service in the beginning of the pandemic.[45] Temporary restraining orders, restriction to telehealth and unclear definitions of essential care created a confusing situation regarding access to abortion care.[46] But as a response to the pandemic many abortion providers also adjusted their policies to increase access, such as expanding gestational age limits and offering telemedicine options.[46, 47] It has been estimated that the number of abortions decreased by 14% during the COVID-19 pandemic. The decline was primarily driven by a decrease in surgical abortions by 31%. The rates of medical abortion were similar before and after the beginning of the pandemic.[48]

One of the highlighted issues during the pandemic was access to abortion care beyond 12 GWs. Delays in access, due to the pandemic, could result in abortions much later in pregnancy which in turn could result in that the abortion-seeking person exceeded the local abortion provider's gestational age limit and needed to travel even further away. There were reports about increasing travel distances for abortion-seeking persons and several difficulties such as quarantine measures when leaving the country or region or finding safe accommodation.[49, 50]

The COVID-19 pandemic and abortion care in Sweden

The first wave of the COVID-19 pandemic in Sweden begun in February 2020 and reached the highest peak during the second and third weeks of April. The Public Health Agency of Sweden did not issue any official lockdowns. Contact tracing, viral testing, hygiene recommendations, physical distancing and restriction of the number of persons allowed in gatherings were protective measures widely applied. The Swedish public healthcare system did not officially change their access policy but since staff was transferred to COVID-19 intensive care units, the actual availability did change.[51]

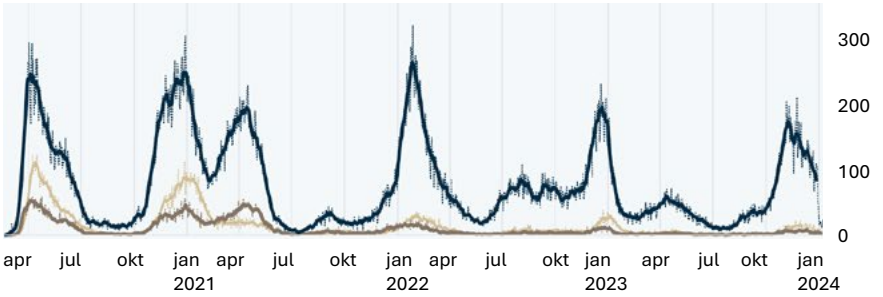

Figure 5. *The COVID-19 pandemic waves from April 2020 in Sweden. The lines show the median number of patients for 7 days. Admissions to hospital (black line), admissions to intensive care (brown line), deceased (yellow line). Source: The National Board of Health and Welfare. https://www.socialstyrelsen.se/statistik-och-data/statistik/alla-statistikamnen/lagesbild-covid-19-influensa-och-rs-statistik/tidigare-publicerad-statistik/. Updated 2024-01-18. 2024-12-10.*

The primary and secondary abortion care units provided services as usual during the COVID-19 pandemic. The NBoHW did not issue any changes of policy to facilitate access, such as expansion of telemedicine or self-administration of mifepristone at home.

Medical methods for abortion beyond 12 gestational weeks

When investigating different medical managements for abortion beyond 12 GWs most trials define the efficacy of the treatment in terms of success rates and induction-to-abortion intervals. The success rate is mostly defined as the proportion of individuals who complete the abortion (expulsion of fetus and placenta) without surgical intervention, usually within 24 hours. The induction-to-abortion interval is defined as the time (in hours or minutes) from administration of the first prostaglandin analogue dose until placental expulsion.

In this section of the thesis, the body of evidence behind the medical regimen for abortions beyond 12 GWs using mifepristone followed by repeat doses of misoprostol will be presented. This regimen is recommended by the WHO and The National Institute for Health and Care Excellence (NICE).[13, 52]

There are very few absolute contraindications to the combination of mifepristone and misoprostol. Allergic reaction to any of the drugs, porphyria, chronic adrenal failure and hemorrhagic (coagulation) disorders are contraindications usually specified. If the pregnant person is under treatment with prolonged corticosteroid therapy, has severe anemia or cardiovascular risk factors extra attention is needed.[53, 54]

Pre-misoprostol era

The first medical abortion methods were intra-amniotic hypertonic installations of saline or urea. They were effective but invasive and injection-to-abortion intervals were extensive.[55]

Ethacridine lactate (Rivanol) is a dye with antiseptic properties. Extra- or intra-amniotically installed it provokes chemical trauma to the fetal membranes and the decidua leading to secretion of endogenous prostaglandins with cervical priming and initiation of abortion. Rivanol-protocols are currently still in use in China and India. One systematic review from 2011 comparing Rivanol to misoprostol revealed that abortion failure rates were higher for Rivanol and the induction-to-abortion interval was shorter for misoprostol.[56]

Natural prostaglandins stimulate uterine contractility and cause cervical ripening. Dinoprostone (prostaglandin E_2) was in clinical practice before the introduction of misoprostol.[55, 57] Dinoprostone was administered vaginally and when given every third hour it resulted in a mean time to abortion of around 13 h.[58]

Prostaglandin analogues are better suitable for clinical use since they metabolize slower, have a prolonged action, are more selective for the myometrial cells and consequently have fewer gastrointestinal side effects.[59] The first prostaglandin $F_{2\alpha}$ analogue introduced for medical treatment was carboprost which was indicated for intra-amniotic or intramuscular (IM) use. When administered together with cervical dilators it was effective, but there were significant gastrointestinal side effects and a risk of cervical rupture. Carboprost IM every second hours resulted in a mean time to abortion of 16.5 h.[60]

Gemeprost was the first prostaglandin E_1 analogue to be introduced and was widely used in medical abortion in the UK and Sweden. Gemeprost is now replaced by another prostaglandin E_1 analogue, misoprostol. In one systematic review gemeprost was compared with misoprostol. The conclusion was that the two regimens were as

effective in achieving fetal expulsion but given the advantages of misoprostol, including its flexible routes of administration and lower cost, stability at room temperature and wide-spread accessibility, it has become the preferred prostaglandin analogue in medical abortion.[61]

Mifepristone

The synthetic compound (see Figure 6) was first synthesized in France in 1982 and approved for clinical use in abortion in 1988. The code name during the development was "RU-486". Mifepristone is an antagonist, binding strongly to progesterone and gluco-corticoid receptors. It is also an antagonist to the androgen receptor, but to a lesser extent. It is an orally active compound and the increase in plasma levels is linear up to doses of 100–200 mg. Above that it is non-linear, indicating that serum levels are not directly correlated to dose. Half-live of elimination is around 24–30 h.[13, 53, 62, 63]

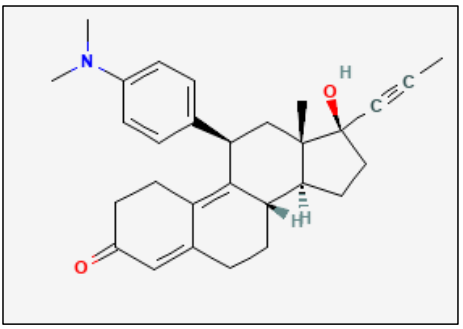

Figure 6. *The mifepristone molecule. National Center for Biotechnology Information (2024). PubChem Compound Summary for CID 55245, Mifepristone. Retrieved November 27, 2024 from https://pubchem.ncbi.nlm.nih.gov/compound/Mifepristone.*

Binding to the progesterone receptor results in decidual necrosis and detachment of the products of conception as well as cervical softening and dilatation. The binding disrupts the suppression of uterine contractions, normally caused by progesterone. The contractility of the pregnant uterus increases, and more importantly, the sensitisation of endogenous and exogenous prostaglandin is increased by five times with maximum effect on uterine contractility at 36–48 h. Mifepristone is not proven to be effective to induce abortion as a sole agent but needs to be combined with prostaglandins as discussed below. However, in around 0.2–2.5% of abortions beyond 12 GWs fetal expulsions occur following mifepristone alone.[59, 64-69]

Mifepristone is the only medication, when used as a sole agent, which is indicated for abortion. In most protocols for medical abortion beyond 12 GWs a 200 mg dose of mifepristone is recommended but the approved dose is 600 mg. The induction-to-abortion time as well as side effects do not differ between the doses. The lower dose

makes the procedure more affordable and, similar to medical abortion during the first trimester, 200 mg is the evidence based recommended dose.[13, 70]
Mifepristone is relatively expensive (around 70 USD for mifepristone 200 mg, in the US (2024)). Because of legal limitations and possible high costs, it is not always available globally. As of today it is registered and approved in 100 countries (see Figure 7).[71]

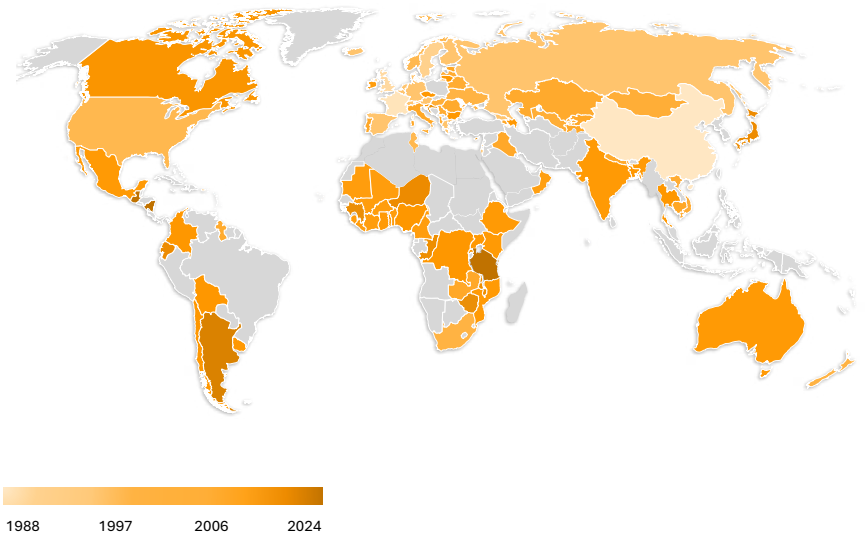

Figure 7. *Map of Mifepristone Approvals 2024. Source: Gynunity Health Projects. First published 2017-06-01. https://gynuity.org/assets/resources/map_mife_en.pdf. 2024-12-20.*

Even though the WHO emphasises that persons opting for medical abortion should be given the opportunity of self-administration of abortion medication, self-administration for mifepristone is not permitted to the same extent as misoprostol, and consequently not as well researched. However, in a recent systematic review the authors conclude that self-administration of mifepristone is effective, and that compliance did not differ compared to in-clinic administration. The majority of patients expressed a preference for home administration of mifepristone.[72]

Misoprostol

Misoprostol is a synthetic prostaglandin E_1 analogue (see Figure 8). It was developed in 1973 for treating gastric ulcers and is used off-label for abortions. Combipacks with mifepristone and misoprostol, and with abortion as an indication, are however available on the market in some countries. Misoprostol is supplied as pills containing 200 mcg or 400 mcg for oral use. The oral pill is effective in other routes of administration and the sublingual, buccal, vaginal and rectal (not used for abortion and with very limited effect) routes are common. Misoprostol is rapidly absorbed and has a half-life of 20–40 min.[73]

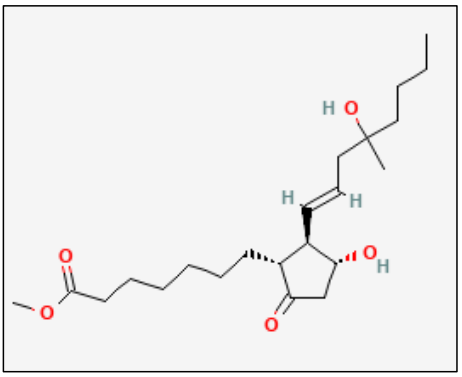

Figure 8. *The misoprostol molecule. National Center for Biotechnology Information (2024). PubChem Compound Summary for CID 5282381, Misoprostol. Retrieved November 27, 2024 from https://pubchem.ncbi.nlm.nih.gov/compound/Misoprostol.*

Prostaglandins and its analogues bind to prostaglandin receptors in myometrial cells and stimulate the myometrium to contract. In cervical tissue prostaglandins promote collagen degradation. Repeat administration cause both regular contractions and cervical ripening, which eventually will expel the detached pregnancy.[73, 74]

The pharmacokinetics and bioavailability for misoprostol differ depending on the mode of administration. If taken sublingually high peak plasma concentration is reached fast, and bioavailability is high. With vaginal administration the peak plasma level occurs later but the detectable plasma concentrations are maintained for a longer time. Side effects tend to be more frequent with sublingual compared with vaginal administration, but the former route is generally preferred by patients. The buccal route of administration has become common. The bioavailability is similar to that of vaginal administration, but side effects are potentially more common.[59, 73, 75-77]

Misoprostol is usually inexpensive (<1 USD per tablet, USA (2024)), can be stored at room temperature for long periods, and since it has other obstetric and gynecologic indications (such as post-partum hemorrhage) it is often available also for medical abortions.[59] It is currently more widely available than mifepristone (see Figure 9).

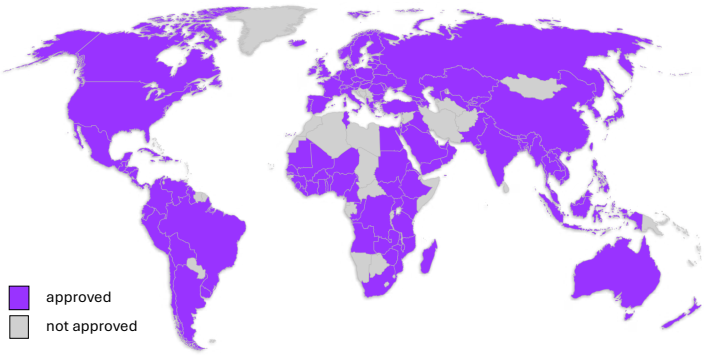

Figure 9. *Map of Misoprostol Approvals 2021. Source: Gynunity Health Projects. First published 2015-11-01. https://gynuity.org/assets/resources/mapmiso__en_2021-10-29-145231.pdf. 2024-12-20.*

Misoprostol is often self-administered, both by vaginal, buccal or sublingual routes. For first trimester abortions the concept of self-managed abortion (home abortion) with misoprostol is well established. In a Cochrane review from 2020 the authors conclude that effectiveness in achieving a successful abortion was the same between self-administered and provider-administered groups among persons having an abortion in the first trimester, and those who self-administered misoprostol were more satisfied and more likely to choose the option again.[78]

The first trial on misoprostol and abortion beyond 12 GWs was conducted in 1994 and it compared dinoprostone with misoprostol for abortions between 12 and 22 GWs. Similar success rates (within 24 h) and induction-to-abortion intervals for both groups were presented. Side effects were more common with dinoprostone, which also had a much higher cost per treatment.[79]

Mifepristone-misoprostol regimen

Medical abortion up until 7 GWs was first approved in France and China in 1988, and up until 9 GWs in the UK and Sweden in 1991 and 1992. Mifepristone together with a prostaglandin analogue was introduced for second trimester abortions in 1994 in Sweden and around 2000 in several other European countries.[59] Evidence for the benefits of the combination of mifepristone and other prostaglandin analogues for second trimester abortion was growing before the introduction of misoprostol. One

study showed that pretreatment with mifepristone 36–48 h before gemeprost resulted in a shorter induction-to-abortion interval (15.7 h to 6.6 h).[80]

There is robust evidence for the higher efficacy of the combined regimen compared to administering only misoprostol for medical abortion beyond 12 GWs. In a review from 2020 by Whitehouse et al. seven trials comparing regimens with misoprostol only to the combination of mifepristone and misoprostol were identified. Three of them were placebo controlled, and the median induction-to-abortion interval was between 7.5–10 h for the mifepristone group compared to 10.8–18.2 h in the placebo group. Success rates were also significantly higher with the combined regimen.[81-83]

Figure 10. *Self-administration of abortion medication. By Johanna Rydelius. 2024.*

Given these results as well as the results from the non-placebo controlled trials, the authors of the review conclude that higher rates of complete abortion at 24 h and a 5.9 h shorter mean time to pregnancy expulsion are achieved with the combination of mifepristone and misoprostol.[84]

Mifepristone-misoprostol dosing interval

Due to the pharmacokinetic properties of mifepristone, it takes at least 12 h before priming happens and the peak effect on uterine contractility occurs 36–48 h following administration. However, the proposed interval of 36–48 h between mifepristone and misoprostol poses problems in a clinical setting with the need for a repeat attendance to the hospital, a risk of ambivalence and of aborting outside the hospital after mifepristone only. Subsequently, there seem to be a need for a flexible dosing-gap.

For abortions beyond 12 GWs immediate administration of misoprostol is inferior to a 24-or 48-h dosing interval. One trial compared simultaneous administration of mifepristone and misoprostol with an administration interval of 36–38 h. The induction-to-abortion interval was shorter (4.9 h vs 10.0 h) and the success rate was higher (100% vs 91.5%) in the 36–38 h group.[85] In another trial simultaneous

administration was compared with a 24-h interval and the induction time was shorter in the 24-h group (7.7 h vs 13.0 h).[4] In addition, a study comparing a 12-h interval to 24-h between mifepristone and misoprostol showed a shorter induction-to-abortion interval in the 24-h group.[86]

Evidence differs regarding variations of the mifepristone-misoprostol intervals (24 or 48 h). One trial comparing 24- to 48-h intervals between mifepristone and misoprostol presented no difference in success rate (95.8% for 24 h vs 93.6% for 48 h) or induction-to-abortion interval (8.6 h vs 8.7 h).[87] One comparable trial showed similar results.[88] However there are other trials favouring the longer interval with 48 h between mifepristone and misoprostol. In one randomised controlled trial (RCT) the induction-to-abortion interval was 7.2 h for the 48-h interval group compared with 8.5 h for the 24-h group. For the stratified analysis of abortions >12 GWs of a recently published RCT the mean induction-to-abortion interval was significantly shorter (5.4 h vs 7.1 h) for the 48-h interval group compared to the 24-h interval group, but success rates within 24 h were the same for both groups (98.5% and 98.1%).[89-91]

Vaginal, sublingual and buccal administration of misoprostol for the mifepristone-misoprostol regimen

In 1995 El-Refaey et al. conducted the first trial in which they compared two regimens of mifepristone and misoprostol: vaginal versus a combination of vaginal and oral misoprostol, for second trimester abortion. The mean time from administration to abortion was 6.4 h, and abortion was achieved in 97% of cases with no difference between groups.[92] When comparing the oral with the vaginal route it has later been shown that the latter is more effective and has less side effects but more participants prefer the oral route.[93, 94]

To maintain the advantageous effectivity of the vaginal route and to enhance privacy for patients for whom self-administration of vaginal misoprostol is not an option, there are several trials investigating the sublingual route. One trial compared a sublingual with a vaginal protocol: mifepristone followed by a loading dose (vaginal or sublingual) and subsequent 400 mcg every third hour. There was no difference between groups in success rate or induction-to-abortion time, which was between 5–6 h. The incidence of lethargy and hot flushes was higher for persons in the vaginal group while unpleasant taste was more common in the sublingual one, but acceptability was similar in both groups.[95] Mifepristone followed by 400 mcg of

misoprostol by sublingual administration has been compared with the oral route. The median induction-to-abortion interval was shorter in the sublingual group compared with the oral group; 5.5 h vs 7.5 h, but succession rates were the same. There was a higher incidence of fever in the sublingual group.[96]

The buccal route is also a potentially advantageous route of misoprostol administration, but for the mifepristone-misoprostol regimen data is more limited. In a prospective case series covering 120 abortions in which the participants administered mifepristone followed by 400 mcg of misoprostol buccally every third hour success rate was 96.7% after 15 h and the median induction-to-abortion interval was 10.3 h. Most participants reported on side effects but the absolute majority were satisfied with the treatment and route of administration.[97] In a RCT where buccal administration of misoprostol was studied with or without mifepristone the combined regimen had a median time to abortion of 8.6 h and 88.3% expulsed within 24 h. Side effects were very common, but acceptability was high with the buccal route.[83]

To further optimize management of abortion beyond 12 GWs there are trials in which an initial high dose of vaginal misoprostol, a "loading-dose" with 800 mcg, followed by repeat doses of oral administration are used. Two case series with this regimen showed high success rates >95% and a mean induction-to-abortion interval of around 7 h.[64, 98] There is one RCT in which the oral, vaginal and sublingual routes are compared after mifepristone and the vaginal loading dose was administered. The median duration to abortion was shorter in the vaginal (7.4 h) and sublingual (7.8 h) groups than in the oral group (9.5 h) and success rates were also lower with 89% in the oral group vs around 96% for the vaginal and sublingual groups. Satisfaction, side effects or pain scores did not differ.[99]

To summarize, it appears as if for abortions beyond 12 GWs a shorter interval than 48 h between mifepristone and misoprostol is associated with a higher risk of unsuccessful abortion and a longer induction-to-abortion interval. But to promote a certain flexibility in the clinical setting 24- and 36-h intervals are useful as well. Current international guidelines differ: the WHO recommends a 24–48 h interval, whereas the NICE guidelines recommend a 36–48 h interval.[13, 52] Regarding the route for misoprostol administration, sublingual and vaginal routes are most effective in achieving abortion, but side effects and patient preferences differ. The buccal route is less studied and the value of adding a vaginal loading dose is considered more uncertain.

Misoprostol-only regimen

Globally mifepristone is not always available, due to prices and legislation. The misoprostol-only regimen is effective but higher total doses are needed and the induction-to-abortion interval is longer.[59] For medical abortion beyond 12 GWs the WHO recommends repeat doses of 400 mcg misoprostol (vaginally, sublingually, buccally) every third hour when mifepristone is unavailable.[13] When reviewing trials conducted with the misoprostol-only regimen there are a number of factors affecting the induction-to-abortion time as well as the success rates. One trial compared different doses of misoprostol and gemeprost 1 mg vaginally every fourth hour. Misoprostol 400 mcg had the highest success rate at 48 h (92.5% vs 70.3% for misoprostol 200 mcg and 74.4% for gemeprost 1 mg).[100] Higher doses than 400 mcg of misoprostol was associated with higher incidence of side effects.[101] Other trials have investigated the interval between misoprostol doses. The shorter (3 or 6 h) intervals were more favorable.[102, 103] A few trials compared different routes of administration of misoprostol (oral, buccal, sublingual and vaginal) when used as a sole agent as well. In accordance with the mifepristone-misoprostol regimen the vaginal route seemed more favourable in achieving abortion completion, but had lower rate of satisfaction.[84]

Day-care for abortion beyond 12 gestational weeks

There is no international definition of day-care procedure. It is often referred to as a medical procedure that is more complex than an outpatient department visit but does not require overnight stay. In this thesis it is referred to as in-ward care during normal working hours. It is a form of service recognized as patient-centred and cost-efficient.

Before the introduction of the mifepristone and prostaglandin analogue regimens, it was common with hospitalization for a longer period, sometimes even for a few days for medical abortions beyond 12 GWs. This was due to both longer induction-to-abortion durations as well as the increased risk of complications and severe side effects. Legal limitations, such as the requirement for in-ward care for abortions, and use of guidelines based on surgical abortions, still make abortions beyond 12 GWs an in-ward routine in some settings.[65]

For the individual abortion-seeking person the possible advantages of day-care include extended contact with the immediate family, less time away from work, reduced waiting times and travel distances and less economic loss. Offering medical abortion as a day-care service in an outpatient clinic with access to surgical back-up

for abortions beyond 12 GWs would promote task-shifting between physicians and mid-level providers (such as midwives), make valuable resources available at tertiary care levels and consequently increase access. Health-care costs could possibly also be reduced. From a global perspective increased access to services for abortions beyond 12 GWs could potentially decrease the practice of unsafe abortion procedures also later in pregnancy.

Given the efficacy and safety of the mifepristone-misoprostol regimen with an approximate median of 6–7 h induction-to-abortion time makes the regimen suitable for managing abortions beyond 12 GWs as day-care procedures.[104] Already in 2004 in a case-series by Ashok et al. the authors reported that 74.3% of the patients aborted within 6 and 8 h, and that 72.4% were treated on a day-care basis. They did, however, not define day-care.[64]

There is one review investigating the feasibility of a hospital outpatient day procedure for medical abortions between 13 and 22 GWs. The authors used pooled primary data from six clinical studies (a total of 846 patients) where participants received mifepristone followed 24 h later by misoprostol 400 mcg at 3 h intervals. They defined day-service as 8 h and 47.4% of the participants had achieved abortion within this period. The authors further speculate that if the first dose of misoprostol would have been administered 2 h before admission day-care could have been expanded to 10 h allowing 62.2% to complete their abortion within day-care.[105] One prospective cohort trial from 2019 investigated whether day-care was feasible and safe for pregnant persons having abortions between 13–18 GWs. Participants took mifepristone 24–48 h before administration of misoprostol 400 mcg 2 h before admission to the hospital. Day-care was not clearly defined as it was dependent on staff availability. Almost 90% had a successful abortion without transfer for overnight care and the median induction-to-abortion time was 7.2 h. Three participants experienced an adverse event (AE), and one expelled the fetus after administration of mifepristone only.[65] Another similar cohort study from 2024 showed that 81.7% of the participants were treated within day-care (outpatient ward closed at 16.00 h) and the median induction-to-abortion time was 5 h. A total of 9.2% of participants (11/120) expelled the fetus before admission, 2 of them after mifepristone only and 9 after the first misoprostol dose. None experienced an AE.[68] One recent retrospective case review from the US reports clinical outcomes among persons receiving medical management with mifepristone and misoprostol (self-administered 2 h before admission) with surgical back-up if evacuation was not complete after working hours at 16.00 in the afternoon. Median time from

misoprostol to fetal expulsion was 6 h (active management of placental retention as in immediate removal and suction aspiration was performed). A total of 0.8% (3/359) expulsed after taking mifepristone, but none after misoprostol administration at home. All patients completed their abortion as day-care patients but 36.5% needed procedural evacuation to complete the procedure within 9 h.[66]

Considering previous findings, offering day-care for medical abortions beyond 12 GWs seems feasible. The WHO recommends task-sharing and emphasizes the involvement of mid-level providers for abortion care services in order to enhance staffing availability in day-care. Mid-level providers for medical abortions beyond 12 GWs is standard care in the UK as well as in Sweden. The safety and acceptability of administering the first dose of misoprostol at home, and the consequential outcome for day-care, needs however to be further explored.

Prolonged induction-to-abortion interval

Prolonged abortions >24 h are rare for medical abortion beyond 12 GWs. In a case series by Ashok et al. 3% needed to continue for 2–4 days.[64] A second dose of mifepristone is recommended after 15 h of misoprostol treatment, and a repeat set of misoprostol is initiated after 24 h. Following this treatment, there is no clear evidence on how to proceed. Amniotomy and mechanical dilatation (with balloon catheter or osmotic dilators) are methods frequently reported and often in combination with the continuous use of prostaglandin analogues or oxytocin.[35, 106, 107]

Pain during medical abortion beyond 12 gestational weeks

Medical abortion beyond 12 GWs is associated with more pain than surgical procedures performed under general anaesthesia.[108] Pain is caused by uterine cramping and is often reported as intense. The most severe pain is related to expulsion of the fetus and most persons undergoing the medical procedure require analgesia. Medical abortion at a later gestational age increases the intensity and duration of experienced pain and there is evidence suggesting that nulliparity and younger age (of the patient) predict a more demanding pain experience.[109-111]

There are different means of measuring physical pain intensity in health care. The visual analogue scale (VAS) is a very common tool to measure acute pain.[112-114] The VAS has a line on each side. On one side the patient indicates the level of pain ranging from "no pain" to "worst pain possible" and on the opposite side the line corresponds to a 100-mm scale (0–100) (see Figure 11). Severe pain is often defined as VAS ≥70, and mild pain as VAS ≤40. For acute pain the minimal clinically important reduction in VAS is estimated to around 10–30.[114-116] In clinical trials indirect measurements of pain are often reported, such as the need for analgesia and patient satisfaction with the different treatments.[105]

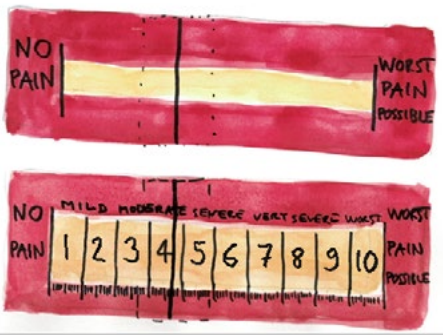

Figure 11. *The visual analogue scale (0–100 mm). Indicating a VAS of 47. By Johanna Rydelius. 2025.*

Pain is an important outcome in studies on medical abortion and is listed on the final core outcome set required for all abortion trials.[117]

Pain management

Pain management is an essential component of the quality of abortion care. As the pain experience for persons undergoing medical abortions beyond 12 GWs is likely to be more intense compared with earlier in pregnancy, a different strategy for pain management is often required. Thus, effective analgesia with the lowest risk of side effects or AEs for the person undergoing the abortion is desirable. There are few studies evaluating pain management for medical abortion later in pregnancy and the optimal regimen is yet not established.

Pain and analgesia are difficult topics to research. Pain involves both a sensory and emotional experience and many measures are subjective. The trials conducted on pain and analgesia for abortion later in pregnancy differ widely in settings, methods of measuring pain, analgesia used and which facilities that are accessible.

Common pain treatment in medical abortions beyond 12 GWs are paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, often with a combination of non-pharmaceutical methods such as transcutaneous electrical nerve stimulation (TENS) and heat packs. Other methods reported are paracervical block (PCB),

intravenous patient-controlled analgesia (IV-PCA) and epidural analgesia (EDA). [110, 118, 119]

When recommending a pain management strategy for abortions beyond 12 GWs, it must be considered that access to different analgesic methods is highly dependent on the setting. Both EDA and IV-PCA are reliant on specific equipment and anesthesiologists which might not be readily available in all abortion clinics.

The reported need for different types of pain medication is diverse, most likely due to the study population characteristics and availability in different medical settings.[110, 118, 119] The need for opioid administration has varied from less than 10% to more than 80%.[108, 111, 120, 121] In a study by Hamouda et al. only 2.5% received intramuscular morphine and 0.3% diclofenac rectally,[110] while in the trials conducted by Kemppainen et al. and Fiala et al. >80% and 90% of the participants were administered opioids respectively. [118, 119]

The WHO recommends NSAID to alleviate pain for medical abortion at any gestational age, and beyond 12 GWs it is suggested to add other methods such as anti-emetics and EDA.[13] Similarly the Swedish Society of Obstetrics and Gynecology recommends the combination of ibuprofen 600 mg (or any other NSAID) and paracetamol with/without an opioid with the first misoprostol dose and, if needed, an addition of opioids, PCB or EDA.[35] In a review from 2020, the authors conclude that persons having a medical abortion beyond 12 GWs should be offered either EDA plus a prophylactic NSAID medication or repeat doses of an appropriate parenteral opioid on predetermined times to minimize their pain.[122]

Three RCTs have investigated NSAIDs as analgesia for abortions beyond 12 GWs. In one trial celecoxib (a selective cox-2 inhibitor) was compared with placebo and the mean pain score was lower for the celecoxib-group.[123] In one trial primary administration of diclofenac (a NSAID) resulted in a lower median dose of required opioids compared with administration of paracetamol plus codein, but in another trial there was no difference between the groups receiving paracetamol, diclofenac or hyoscine n-butyl bromide (a muscle relaxant).[118, 124]

Two PCB studies have been identified. In one RCT PCB was compared with saline placebo when administered prophylactically. The proportion of persons reporting severe pain and the use of additional morphine did not differ between the groups.[120] In another trial both groups received pethidin (a short active morphine) and

butylscopolamin (a muscle relaxant) and, in addition, one group was administered a PCB after a cervical dilatation of 3 cm. There was no difference in median VAS scores or requirement of analgesics in the two groups.[125]

Two studies on antiemetics showed that persons administering metoclopramide in addition to an IV-PCA used less morphine compared with persons in the placebo group.[126, 127] When comparing pregabalin (an antiepileptic) with prazepam (an anxiolytic) as an adjuvant to patient-controlled EDA the mean pain score was lower in the antiepileptic group and fewer participants asked for a rescue dose.[128]

Three RCTs have investigated the effect of IV-PCA for medical abortion beyond 12 GWs, and results seem to favour use of fentanyl (an opioid) and tramadol with low mean pain scores and high satisfaction.[119, 129, 130] In two RCTs the use of EDA (with a combination of a local anesthetic drug and an opioid) resulted in low mean pain scores and were, compared to IV-PCA, even more favourable. Results indicate that an intermittent EDA protocol results in fewer side-effects compared with continuous epidural infusion.[131, 132]

Post-abortion contraception

Post-abortion contraception counselling is an important aspect of the abortion care program. In Sweden 45.5% of all women who had an abortion in 2023 had experienced a previous induced abortion.[36] One systematic review and meta-analysis from 2022 reports the prevalence of repeat abortion globally to be 31.3% with the highest number (42.2%) in Middle East and North Africa.[133] In Europe figures vary from 41% of women who had had at least one prior abortion in the UK, to 37% in Finland and 24% in Italy.[6, 15] One risk factor for repeat abortion is use of an ineffective contraception.[134] Persons having abortions beyond 12 GWs are considered at even higher risk of subsequent unwanted pregnancy and another abortion later in pregnancy.[135]

To decrease the number of repeat unplanned and unwanted pregnancies it is recommended that contraception counselling is offered at the same appointment as the abortion counselling. Many persons who have an abortion are interested in highly effective contraceptive methods and wish to leave their consultation with a selected contraceptive method.[136]

Studies show that ovulation can return just a few days after the initiation of an abortion <9 GWs, and 80% ovulate during their first menstrual cycle post-abortion.[137, 138] Recommencement of sexual intercourse can happen soon after the abortion. In one study 51% of the participants reported having had coitus within two weeks post-abortion.[139] In one trial investigating the use of an intrauterine device (IUD) after abortion, 42% of the participants who were planned for an IUD-insertion at 3–4 weeks after the abortion had already had unprotected intercourse.[140] Immediate initiation of any contraceptive is therefore usually desirable.

Long-acting reversible contraception

Long-acting reversible contraception (LARC) includes a copper-IUD, a levonorgestrel-releasing intrauterine device (LNG-IUD) and a contraceptive implant. Starting with a LARC instead of oral contraceptives post-abortion is associated with fewer unwanted pregnancies.[141-143] Providing an IUD as part of the integrated abortion care system also resulted in decreased rates of subsequent unintended pregnancies, compared with referral to primary care for insertion of an IUD.[144] In Sweden LARCs are the recommended first choices of contraceptives after an abortion.[35]

A possible disadvantage with medical abortion compared with surgical abortion has been the standard practice of delayed insertion of a LARC. Delaying initiation of a LARC to a follow-up visit may result in lower uptake and higher risk of leaving persons without contraception when ovulation returns.[145, 146]

Contraceptive implant post-abortion

Concerning placement of the contraceptive implant at the time of surgical abortion the procedure is uncomplicated and continuation rates are as high as for persons who receive the implant unrelated to an abortion.[147] For initiation of an implant after a medical abortion current research affirms the safety of insertion on the same day as mifepristone. There is no difference in abortion efficacy compared with the implant being inserted at a follow-up visit. More persons use the implant 6 months post-abortion and fewer subsequent unintended pregnancies are reported.[148, 149]

Figure 12. *Insertion position of contraceptive implant. By Johanna Rydelius. 2024.*

Intrauterine device post-abortion

The risk of expulsion (because of the dilated cervix), pelvic infection and uterine perforation when placing an IUD directly after a surgical abortion has been debated. It does however appear as if placement of an IUD at the end of a surgical abortion in the first trimester does not result in higher rates of expulsion, perforation or infection. Regarding insertion after abortion later in pregnancy the risk of expulsion seems higher. Early insertion however increases utilization rates and prevents subsequent unintended pregnancies, mainly because persons scheduled for later IUD insertion do not show up.[150, 151]

According to Swedish guidelines, the vast majority of abortions >12 GWs are medical and conducted in-clinic. If a patient requests an IUD post-abortion, insertion is most often undertaken at an appointment after discharge.[36]

International guidelines recommend IUD-insertion after a medical abortion as soon as the abortion is complete. Completion is traditionally defined as presenting a negative pregnancy test a few weeks post-abortion. Alternative strategies are based on clinical or ultrasonographic signs of abortion completion.[13, 52]

The risk with immediate insertion after medical abortion is foremost early expulsion due to contractions in the uterus and an open cervix. Expulsions have for instance been shown to be more common after immediate compared with delayed insertion following normal full-term delivery.[52, 152] The risks of infection and uterine perforation are unclear. Previous research has focused on both IUD insertion after medical abortion early in pregnancy as well as beyond 12 GWs. One systematic review from 2020 summarizes that IUDs should be placed “as soon as possible”, but the optimum timing is still to be defined.[153] Three trials assessed IUD insertion following medical abortion ≤9 GWs. There were no clear risks of higher expulsion rates, more infections or perforations when early insertion was compared with insertion at a follow-up visit. Fewer persons attended the delayed IUD placement appointment.[140, 154-156]

Immediate IUD-insertion after a medical abortion beyond 12 GWs is however less studied. In a review from 2020, one trial was identified and in 2021 another trial was published. In a RCT by Korjamo et al. same-day placement of a LNG-IUD was compared with placement after 2–4 weeks. Higher expulsion rates were observed in the immediate insertion group.[157] In a RCT by Constant et al. placement of a copper-IUD prior to discharge was compared with placement after 3 weeks. Significantly more persons in the early insertion group expulsed their IUD, but utilization was higher in this group after 6 months. This was due to the low attendance for insertion in the delayed group.[158]

Figure 13. *Position of an intrauterine device inside the uterus. By Johanna Rydelius. 2024.*

Surgical methods for abortion beyond 12 gestational weeks

D&E has been the most common surgical technique for abortion in the second trimester since the 1970-ties. Older techniques often referred to in the literature are hysterotomy and hysterectomy. Vacuum aspiration can be used for abortions performed up until 15 GWs.[159]

After adequate dilatation is completed the surgeon (commonly a gynecologist) inserts a specialized forceps into the uterus via the cervix. Fetal and placental extraction is achieved intact or in fragments. A suction is used to aspire the amniotic fluid and remaining tissue. It is usually a fast procedure, with operative times around 10–20 min. But the total time from administration of adjunctive medication and dilators is substantially longer, often with a duration over several days. D&E is considered a safe procedure when performed by a skilled provider and complications are rare.[66, 159, 160] One disadvantage is however the potential distress experienced by the provider dealing with the fetus at more advanced gestations.[161]

Cervical preparation

Cervical preparation is considered important to prevent complications and to facilitate the procedure. Inadequate cervical dilatation is associated with a more challenging procedure and with more complications. Dilatation is achieved by using osmotic dilators, usually laminaria or Dilapan-S. Laminaria is a thin stick composed of seaweed that dilates 2–3 times their size. Dilapan-S is a small rod that is made of a synthetic material and absorbs fluid gradually and exerts its maximum effect a bit faster than laminaria (4–6 h vs 12–24 h).[59, 162]

It has become more common to administer adjunctive medications to aid in cervical preparation, and usually mifepristone and/or misoprostol are used. One RCT compared overnight osmotic dilators alone with dilators plus misoprostol and dilators plus mifepristone for two groups of patients (16–18 GWs and 19–23 GWs). There were no differences in operative times and for D&E performed after 19 GWs the mifepristone group was considered less difficult.[163] When comparing two days with dilators with mifepristone and one set of dilators before D&E between 19 and 24 GWs the regimens had similar operative times and no difference in ease of the procedure was reported but the mifepristone group experienced more pain.[164]

There are also studies investigating the use of pharmacologic agents alone, without dilators. One RCT compared mifepristone and misoprostol to osmotic dilators with the same combination of drugs or dilators with misoprostol only. The regimen without dilators required more mechanical dilatation during the procedure but there was no difference in patient satisfaction.[165] Using the combination of overnight mifepristone and preprocedural misoprostol alone seems safe, effective and preferred by the patients, and is recommended up to 18 GWs.

Since D&E is undertaken under general anesthesia pain control is focused on the preprocedural pain with laminaria insertion. Pain scores following insertion of osmotic dilators can reach high levels on a VAS. PCB appears to effectively reduce pain in these situations.[166] In a systematic review from 2020 the authors conclude that general anesthesia is effective as pain control for D&E and that there is no additional benefit from adjuvant therapy.[122]

Prophylactic treatment: Rhesus and antibiotics

The risk of Rhesus (Rh) immunization specifically for abortions after 12 GWs has not been investigated. Currently, all guidelines recommend Rh prophylaxis after an abortion beyond 12 GWs as for any term pregnancy.[13, 54]

A prophylactic dose of antibiotics is usually included in guidelines for D&E. For medical abortion there are no randomised studies investigating the need for prophylactic antibiotics and the WHO recommends against it.[13, 54] It should however be considered during a prolonged procedure if membranes have broken.[106]

Feticide

To avoid fetal survival after the abortion and legal issues concerning registration of the patient as a mother, providers in some settings induce fetal demise before both medical and surgical abortions after 20–22 GWs. Feticide is accomplished by intra-amniotic injection of digoxin or intracardiac potassium chloride. Digoxin has high efficacy and a low complication rate and is easier to use than potassium.[162]

In some countries, for example in Sweden, it is not common with feticide. In case of gasping or reflex movements after fetal expulsion it is important to separate reflexes, that can be present after fetal expulsion well before this time, from signs of potential viability. Local guidelines recommend fetal palliation such as wrapping with a warm cover.[54, 167]

Complications related to abortions beyond 12 gestational weeks

It has been estimated that around two thirds of all serious abortion-related complications occur during the second trimester and complication rates are in general higher compared with abortions during the first trimester. It has also been reported that the risk of maternal death due to complications from abortion increases exponentially for each additional week of gestation.[12, 168]

A serious adverse event (SAE) is usually referred to as hemorrhage requiring a blood transfusion, the need for surgical intervention or re-hospitalization, severe organ injury or infections requiring antibiotics intravenously. In a review from 2020 the

overall SAE rate was estimated to 1.7% for medical abortion beyond 12 GWs using misoprostol with or without mifepristone.[84] In a retrospective analysis from the US from 2015 the rate of major complications following surgical second trimester procedure was estimated to 0.4%.[169]

Comparison of medical and surgical abortion methods is difficult, often due to the existing preference of the abortion clinic or larger setting in which the trial is performed. In one RCT from 2004, 18 persons opting for second trimester abortion were allocated to D&E or to medical abortion with the mifepristone-misoprostol regimen. The authors found that pain and AEs were more common for medical abortion.[170] There are no larger or more recent RCTs covering this topic and consequently the complication rates for both methods originate from retrospective case series and summarizing reviews of them. Two retrospective cohort studies from the US (2020) and Ethiopia (2024) compared complication rates between D&E and medical abortion with the mifepristone-misoprostol regimen. Overall, few AEs were reported. In the American study 1/75 (1.3%) and 7/81 (8.6%) AEs were reported for D&E and medical abortion. In the Ethiopian study 6/63 (9.5%) AEs were reported for D&E compared with 5/162 (3.1%) for the medical method.[171, 172]

Bleeding

Excessive bleeding can occur both during surgical and medical abortion. A review of case series showed an incidence of around 0.09–0.6% for D&E, and <1% for the mifepristone-misoprostol regimen.[160] A case series by Ashok et al. showed that 0.7% of the persons who had a medical abortion beyond 13 GWs needed a blood transfusion.[64] In a case series on medical abortions between 13 and 28 GWs from 2023 1.7% required a blood transfusion.[67]

Post-abortion surgical procedure

A post-abortion surgical procedure due to bleeding is less likely to occur after D&E, as compared with a medical abortion, and in different case series the proportion of patients requiring a repeat surgical intervention for incomplete abortion varies between 0.05% to 1%.[160]

In many protocols for medical abortion beyond 12 GWs, such as the Swedish guidelines, it is specified that surgical evacuation post-abortion should be on indication only.[35] The most common reasons for surgical intervention are failure to

expel the placenta, heavy bleeding after fetal expulsion and retained products of conception (often after discharge from the hospital). The surgical evacuation rates are diverse, probably due to local practice, and seem to decrease over time. In a Danish national cohort study the proportion of surgical evacuations declined from 64% in 2006 to 26% in 2017, and the rates varied substantially between hospitals.[173] In a case series by Ashok et al. the surgical evacuation rate was 8.1%. More recent reviews present rates as low as 0.6–5%, but there are also studies where the rate is around 20%.[4, 64, 65, 67, 68, 83, 86, 87] In conclusion the surgical evacuation rate immediately after a medical abortion varies greatly, possibly due to different interpretations of the need for an evacuation.

Organ injury

Regarding organ injuries after abortion beyond 12 GWs there is a risk of uterine perforation during D&E or vacuum aspiration following an unsuccessful medical abortion. For D&E it is relatively uncommon (0.2–0.5%) and for medical abortion there are few reported events. In contrast to perforations during first trimester surgical abortions, perforations during D&E are more strongly associated with bowel injury and hemorrhage. Cervical laceration is also rare and occurs predominantly after D&E (0.1–1%), whereas none has been reported for medical abortion with the mifepristone-misoprostol regimen.[160]

Uterine rupture following abortion beyond 12 GWs is a topic of concern. Even though it can occur after D&E it is predominantly a complication after misoprostol treatment for patients with a previous uterine scare, usually after a caesarean section. It is a rare event and seldom captured in studies but can result in life-threatening hemorrhage and potentially a hysterectomy. In a review from 2023 the authors compared patients, with or without a previous uterine scar, having an abortion with the mifepristone-misoprostol regimen (12–28 GWs). In the group with a prior scar a uterine rupture risk of 10/874 (1.1%) was found, compared with 2/6244 (0.01%) in the group without a scar. There is no consensus on how to clinically manage cases with previous uterine surgery and the WHO recommends increased monitoring.[13, 174]

Infections

For post-abortion infections (diagnosed among cases with follow-up), the incidence of mild infection following a D&E (with antibiotic prophylaxis) is 0.8–2% and 0.05–0.4% of the patients require hospitalization.[160] For medical abortion the rates are

around 2.6–6% for patients requiring antibiotics and the risk of infection seems higher after second trimester abortions compared with after first trimester abortions.[64, 175, 176]

Side effects

Gastro-intestinal side effects from mifepristone are frequent and vaginal bleeding and cramping, before administration of misoprostol, can occur.[177] Common side effects from misoprostol include nausea, vomiting, diarrhoea, fever and chills.[53, 65]

Long term complications

There have been concerns regarding cervical incompetence following cervical dilatation during D&E, potentially leading to miscarriage and preterm birth in future pregnancies. One case review found neither an increased risk of second trimester spontaneous abortion nor preterm birth after D&E. For 5 (5.2%) of the 96 documented pregnancies after D&E a prophylactic cerclage was however placed in the second trimester.[178] Concerning intra-uterine adhesions following abortion there is one review highlighting the very scarce evidence of this complication. The second trimester abortion cases in the review were treated with outdated prostaglandin regimens followed by sharp curettage.[179]

Regarding other potential long term complications for medical abortion beyond 12 GWs there is one large case review suggesting no increased risks of preterm birth, low birth weight or placental complications in subsequent pregnancies, further underlining the long-term safety of the procedure.[180]

Aims of the thesis

The overall aim of this thesis was to increase the knowledge about the clinical management of medical abortion beyond 12 GWs.

The specific aims were:

Paper I

- To investigate if the number of abortions and ongoing pregnancies changed during the first pandemic wave of COVID-19 in 2020 compared with the years prior to the pandemic.
- To explore possible reasons for the quantitative findings.

Paper II

- To investigate the impact of home administration of the first dose of misoprostol before admission on the proportion of persons undergoing a medical abortion beyond 12 GWs as a day-care procedure.
- To investigate satisfaction, success and complication rates for the same persons undergoing a medical abortion beyond 12 GWs.

Paper III

- To investigate if the effectiveness and safety of IUD-insertion within 48 h after medical abortion beyond 12 GWs is superior compared with delayed insertion.

Paper IV

- To describe the pain experienced by persons undergoing a medical abortion beyond 12 GWs.
- To investigate predicting factors of intense pain, administrative pattern and effectivity of different analgesics commonly used.

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Patients and methods

This thesis includes both quantitative and qualitative study methodology. An overview of patients and methods is presented in Table 1. Paper I is a mixed-methods study with a convergent parallel design, with the purpose of using qualitative data, collected from semi-structured interviews, to illustrate quantitative findings. Papers II and III are multicentre, randomised controlled trials. Paper IV is a descriptive cross-sectional study analysing data from secondary outcomes in Paper II.

Table 1. *Overview of patients and methods. IUD = Intrauterine device.*

	Paper I	Paper II	Paper III	Paper IV
Design	Mixed-methods study	Open-label, randomised, multicentre trial	Open-label, randomised, multicentre trial	Descriptive cross-sectional study
Setting	Sahlgrenska University Hospital, Gothenburg, Sweden	6 abortion clinics in Sweden	8 abortion clinics in Sweden	6 abortion clinics in Sweden
Data source	Quantitative data: Swedish National Board of Health and Welfare and the Swedish Pregnancy Register. Qualitative data: semi-structured interviews	Clinical case report form	Clinical case report form	Clinical case report form
Participants	Quantitative: All abortions and births/1000 women (15–44) years in Sweden. Qualitative:15 participants aiming for surgical or medical abortion	457 randomised participants having a medical abortion > 12 gestational weeks	179 randomised participants having a medical abortion > 12 gestational weeks and opting for an IUD post-abortion	425 participants having a medical abortion > 12 gestational weeks and for whom pain data was registered
Gestational age	0–153 gestational days	85–153 gestational days	85–153 gestational days	85–153 gestational days
Study period	Quantitative: January 2018–March 2021. Qualitative: June 2020	January 2019–December 2022	January 2019–June 2022	January 2019–December 2022
Intervention		Misoprostol administration at home (2 h before admission) vs in hospital after admission	IUD-insertion within 48 h vs after 2–4 weeks	
Statistical method	Quantitative: All abortions and births were reported Qualitative: Systematic text-condensation according to Malterud	Fisher's exact test, Matel-Haenszel x^2 linear-by-linear test, independent t-test	Mann-Whitney U-test, chi-square, Fisher's exact test	T-test, ANCOVA model, Tukey-Kramer multiple comparison adjustment
Software		SAS 9.4	SPSS 29.0	SAS 9.4
Outcome	Number of abortions and births during the study period vs the years prior to pandemic Themes and subthemes identified from interviews	Primary: completing abortion treatment as day-care patient	Primary: IUD-use after 6 months in both groups	Primary: pain at pre-determined time points

Paper I

Study design

In this convergent parallel mixed-methods study quantitative and qualitative strands of the research is performed independently but collected concurrently. The purpose of the design is to use qualitative data to illustrate quantitative findings. Quantitative data, as in total number of abortions and births in Sweden during the study period and the years prior to the pandemic, were collected from the Swedish NBoHW and the Swedish Pregnancy Register respectively. All abortion clinics in Sweden report yearly to the abortion register at the Swedish NBoWH and in 2020 97.9% of all births were registered in the Swedish Pregnancy Register.[181]

Qualitative data was collected using semi-structured (one-to-one) including interviews, according to Berg and Lundgren.[182] An interview guide containing demographic questions and two open-ended questions about the experience of seeking abortion care and of being pregnant during the COVID-19 pandemic was developed. Interviews were conducted by a midwife, who was working at the clinic but not involved in the informants' care, at their first visit to the clinic. The interviews were recorded and transcribed verbatim.

Population

Data on all abortions and births in Sweden during the first wave of the COVID-19 pandemic in Sweden, and for comparison, abortions from January 2018–March 2020 and births from January 2018–March 2021, were included for the quantitative part of the study.

Abortion-seeking persons who attended the abortion clinic, at Sahlgrenska University Hospital, Gothenburg, Sweden, during the pandemic were asked to participate in the qualitative part of the study. Inclusion criteria were Swedish- or English-speaking persons >18 years of age. Individuals with severe mental illness were excluded. Considerations were made to include persons of different ages and with pregnancies of different gestational ages.

Outcomes

The outcomes were total number of abortions and ongoing pregnancies before and after the first pandemic wave of COVID-19 in Sweden and reasons for the findings.

Statistical analysis

Quarterly numbers of abortions/1000 women (aged 15–44 years) conducted during January to March and April to June 2020 were compared with the same periods during 2018 and 2019. Percentages of abortions in different gestational weeks (grouped into <7 GWs, 7–9 GWs, 9–12 GWs, 12–18 GWs and >18 GWs) and different abortion methods used (surgical, medical in-hospital and medical home abortion) were also compared. To detect any effect on ongoing pregnancies the number of births/1000 women (aged 15–44 years) was also compared on a quarterly basis for January 2018 to March 2021.

The conducted interviews were analysed by systematic text condensation (STC) according to Malterud. STC is a thematic method of cross-case analysis aiming to describe the informants' experiences as expressed by themselves, rather than exploring underlying meanings (see Figure 14). The method involves describing differences and highlighting variations in the phenomenon being studied.[183]

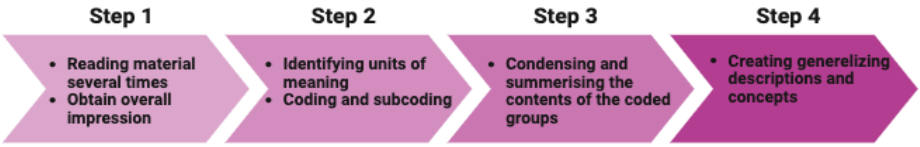

Figure 14. *The four-step procedure of systematic text condensation as described by Malterud. Created with Biorender.com. 2025-01-13.*

Paper II

Study design

This trial is a multicentre, open-label, randomised controlled trial conducted in 6 hospitals in Sweden.

At the first visit to the abortion clinic a physical examination was performed. If eligible, the abortion-seeking persons were randomly assigned either to home treatment of misoprostol (intervention group) or to hospital treatment (control group).

After assignment, all participants took 200 mg of mifepristone at the abortion clinic. Between 24–48 h later the participants in the intervention group administered the first dose of misoprostol (800 mcg) vaginally at home, together with pain medication, and went to the hospital 2 hours later. The participants in the control group self-

administered the first dose of misoprostol directly after admission to the hospital ward. After admission the participants followed the same mifepristone-misoprostol regimen with repeat doses of misoprostol (400 mcg) every third hour until abortion.

After fetal and placental abortion, the participants were observed in hospital for a minimum of one hour. Before discharge they filled in a questionnaire about satisfaction with the treatment, side-effects experienced, and an assessment of the maximum pain experienced during the abortion.

A follow-up was conducted within 2–4 weeks and the survey included questions about extra visits, complications after discharge, use of contraception and satisfaction with the abortion treatment.

Population

Abortion-seeking persons were included if they were aged ≥18 years and carried a singleton pregnancy of 85–153 gestational days (GDs). Exclusion criteria were being unable to communicate in Swedish or English, carrying a non-viable pregnancy or a fetus with a malformation that was judged as having a potential effect on the time to abortion, having a contraindication to medical abortion or a pre-existing health condition which could complicate the abortion procedure.

Outcomes

The primary outcome was completion of the medical abortion as a day-care procedure (defined as <9 h from admission to discharge). Secondary outcomes were time spent in hospital, induction-to-abortion interval, success rate at 24 h, number of doses of misoprostol used, satisfaction with the abortion procedure, acceptability and pain assessed on predetermined time points. Safety outcomes were AEs, SAEs, surgical interventions and abortion before admission.

Statistical analysis

With a power of 90% a sample size of 784 was required to demonstrate an increase in proportion of day-care procedures from 70% in the control group to 80% in the intervention group using a two-sided test with an alpha of 0.05. To compensate for loss to follow-up the sample size was increased to 896. The sample size calculation

suffered from lack of data on how many medical abortions beyond 12 GWs that are being conducted as day-care procedures.

All randomised participants, except for those who withdrew consent and those who did not have an abortion, were included in the intention-to-treat (ITT) population. The per-protocol (PP) population included all participants in the ITT-population except for those who crossed over to the other treatment group and those who were found in retrospect to not fulfil inclusion criteria but still were included. The analysis of the primary outcome was performed on the ITT- and PP-populations, and all other analyses were done on the ITT-population. In the safety assessment, any differences in the number of AEs, SAEs and abortions before admission were noted. The safety population was defined as all participants except for those who did not take mifepristone and one participant who was included twice.

Paper III

Study design

This trial is part of a larger multicentre, open-label, randomised, clinical trial including abortion-seeking persons stratified into three gestational age categories (≤9 GWs+0 GDs, 9 GWs+1 GD to ≤12 GWs+0 GDs, and >12 GWs). They were recruited at 8 abortion clinics in Sweden and inclusion was made before the abortion, at the first visit to the clinic. Participants were allocated to IUD-insertion within 48 h after completed abortion (intervention) or IUD-insertion at a follow-up visit 2–4 weeks after the abortion (control).

The participants could choose from 4 types of IUDs: copper-IUD (NOVA T 380™), LNG-IUD 52 mg (Mirena®), LNG-IUD 19.5 mg (Kyleena®) and LNG-IUD 13.5 mg (Jaydess®). All IUDs were provided by Bayer GmBH, Leverkusen, Germany, and at no cost for the participant.

After randomisation the participants pursued the medical abortion with the regimen for abortion beyond 12 GWs as recommended by the Swedish Society of Obstetrics and Gynecology (based on the WHO guidelines). Abortion was defined as complete after expulsion of the fetus and placenta and cessation of heavy bleeding.

Participants in the intervention group had the IUD inserted before discharge from the ward or returned within 48 h for placement. In the control group the participants had

an appointment scheduled for later IUD-insertion. Participants were asked to indicate pain before insertion, at placement of the tenaculum, at sounding, at placement of the IUD and before leaving the clinic. Healthcare providers were asked to rate the easiness of IUD-placement.

Follow-up was conducted by phone call or e-mail at 3, 6 and 12 months after intake of mifepristone. In case of inconsistency or incomplete data, patient records were examined to gain clarity. Information regarding expulsion was limited to self-assessed complete expulsion because no clinical examination was scheduled. Acceptability with timing of IUD-placement and satisfaction with their contraceptive was assessed.

Population

Eligibility criteria were being ≥18 years of age, requesting medical abortion and opting for an IUD after the abortion and a gestational age of 85–153 GDs. Exclusion criteria were contraindications for medical abortion or IUD-use (previously known abnormal uterine cavity, history of breast cancer (for LNG-IUD)), inability to comply with follow-up in Swedish and abortion-related complications (septic abortion, bleeding >1000 ml or uterine atony).

Outcomes

The primary outcome was self-reported use of an IUD 6 months after the abortion. Secondary outcomes were uptake and expulsion of IUD, reasons for nonplacement, pain at placement, AEs, SAEs, participant acceptability and subsequent pregnancies and abortions.

Statistical analysis

With a power of 90% and an alpha of 0.05 a total of 240 individuals needed to be randomised based on a hypothesis of 80% IUD-use in the intervention group and 60% in the control group after 6 months. The proportion of IUD-use mainly depends on attendance to the IUD-insertion appointment, and data concerning attendance was not available for this gestational age group. The sample size was furthermore increased from 109 to 120 participants in each group to compensate for loss to follow-up and an approximated 3–5% of participants needing a vacuum aspiration.

An interim analysis was performed when 50% of the participants had been recruited. The predefined decision was to stop inclusion in case of expulsion >20% or acceptability <50% within 3 months in any of the groups. Inclusion continued during this evaluation period.

A modified intention-to-treat (mITT) analysis was used for the main analysis including all randomly assigned participants with medical abortion, except if they withdrew consent. For the primary outcome a sensitivity analysis was performed on the mITT-population according to best- and worst-cases scenarios. A PP-analysis was also conducted for the primary outcome and for IUD-expulsion. Participants with no IUD-placement and insertion outside the allocated time window or during surgery were included in the mITT population but excluded for the PP-population. Missing data were not imputed, and analysis included the full data set based on observed outcomes.

Paper IV

Study design

This trial is a descriptive cross-sectional study. Data describing pain and analgesic methods used during the abortion was collected from clinical case report forms (CRFs) from the RCT reported in Paper II.

The participants from the RCT took pain medication (paracetamol and NSAID) together with the first dose of misoprostol which was administered either at home or after hospital admission. The allocation was according to the randomisation conducted as part of the study protocol for Paper II.

After admission all participants adhered to the mifepristone-misoprostol regimen until abortion. Paracetamol and NSAID were administered every 8 hours. When required, opioids, heat pack, TENS, PCB or EDA, were offered. Pain during the abortion was assessed using VAS. VAS score was recorded in the CRF at fetal expulsion, before any additional analgesia was given and 30 minutes after administration of analgesia. If any additional analgesia was administered, it was recorded in the CRF as well. Before discharge the participants assessed maximum pain during the abortion, satisfaction with the abortion and the pain treatment.

Population

The participants in Paper IV were included or excluded according to the same criteria as in Paper II. If abortion occurred before admission the participants were excluded from analysis in paper IV since they did not receive any pain treatment that could be evaluated.

Outcomes

The primary outcome was pain assessed with VAS by the study participants at pre-determined time points: at fetal expulsion and the maximum pain during the abortion.

Secondary outcomes were pain severity correlated to predetermined baseline characteristics and to the induction-to-abortion interval, administered pain treatment during the abortion and their effectiveness in alleviating pain (measured as a reduction of VAS score between before and 30 min after administration of pain medication) and the satisfaction with the different analgesic treatments.

Statistical analysis

Since Paper IV is a descriptive study, no power-calculation was performed. All participants from Paper II who were admitted to the inpatient unit (time upon arrival recorded) were part of the total analysed population in Paper IV. The primary variable VAS was analysed as a continuous variable.

Ethical approvals and considerations

Abortion can be apprehended as a profound personal matter and throughout all the studies the investigators showed consideration and guaranteed full confidentiality to the study participants. They were able to withdraw from participation in the studies at any point without having to explain their decision and without any negative effect on their abortion care. The eligible persons were informed both orally and in written before they gave written consent. Confidentiality was guaranteed and data was coded and stored separately in approved and locked storages.

The two RCTs were conducted in compliance with the protocols, good clinical practice (GCP), Helsinki declaration and the applicable regulatory requirements.

Paper I

Ethical approval was obtained from the Regional Ethical Review Authority in Stockholm.

Original application (2020-02661, 27 May 2020).

To share experiences about abortion could possibly be apprehended as very private and there was a risk that the participants could have felt that their integrity was affected. The interview consisted of open questions which enabled the participants to choose what they were willing to share. All data was coded and at the time of the analysis there was no possibility to link the information to a specific person, except for the author who also conducted the interviews.

Paper II and IV

Ethical approval was obtained from the Regional Ethical Review Authority in Stockholm.

Original application (2017/2312-31/2, 20 December 2017)
Amendment 1 (2021-000404, 24 February 2021)
Amendment 2 (2024-01710-02, 4 April 2024)

Additionally, the trial obtained approval from the Swedish Medical Products Agency (5.1-2018-20568, 9 May 2018).

Administering the first dose of misoprostol at home could potentially lead to abortion before admission to the hospital. It has previously been shown that there is a small risk of abortion outside the hospital after administering mifepristone, before misoprostol, and the intervention in this trial could further add to that risk. The study participants were informed about this risk and advised to seek care urgently and transport themselves to the hospital without hesitation if affected by heavy bleeding and/or severe pain.

Paper III

Ethical approval was obtained from the Regional Ethical Review Authority in Stockholm.

Original application (2016/1685-31/1, 7 October 2016)
Amendment 1 (2018/48-32, 12 January 2018)
Amendment 2 (2018/962-32, 14 May 2018)
Amendment 3 (2019-03183, 20 June 2019)
Amendment 4 (2020-02925, 3 July 2020)
Amendment 5 (2021-02625, 7 June 2021)

Additionally, approval was obtained from the Medical Products Agency (5.1-2018-6719, 17 April 2018 and 5.1-2018-38966, 18 May 2018).

IUD-use in general and after abortions beyond 12 GWs is safe and user satisfaction has been reported as high and with few side-effects, but the optimal time of insertion is uncertain. The participants were informed of the higher risk of IUD-expulsion. To further ensure safety an interim analysis was conducted when half of the participants were enrolled.

The LNG-IUDs were provided for free, which is not standard care in Sweden where the price usually lies around 90 USD (December 2024) per IUD. This advantage for the patient could have affected the eligible persons to enrol solely to obtain the IUD for free.

Results

Paper I

Number of abortions and births

The number of abortions/1000 women (15–44 years) did not change during the first two quartiles of 2020, compared with the same quartiles in 2018 and 2019. Neither did the number of births change during the fourth quartile of 2020 and the first quartile of 2021. For the whole years of 2018, 2019 and 2020 the total number of abortions/1000 women was 19.2, 19.2 and 18.3 respectively.

The proportion of surgical abortions declined from 6.3% and 5.2% during the first two quartiles of 2019 to 5.1% and 3.5% during 2020. There was no change in which GW the abortions were conducted.

Interviews

Forty women were asked to participate whereof 17 accepted, but 2 declined before the interviews. The final study sample consisted of 15 informants.

Two themes were identified: *meeting with abortion care during the COVID-19 pandemic* and *the impact of the pandemic on the abortion decision*.

From the theme concerning meeting with abortion care two subthemes emerged: *availability,* and *fear of being infected by the virus or infecting others*. The participants did not hesitate to seek care and reported that it was easy to book an appointment at the abortion clinic. A fear of not being welcome or lack of space for inpatient care was however expressed.

From the theme about the impact on the abortion decision three subthemes were identified: *to catch COVID-19 during pregnancy, feelings of loneliness and isolation,* and *social aspects*. The participants said that they did not plan a pregnancy during the pandemic, and that they would have dreaded contracting COVID-19, both for their own and the baby's health. The participants missed having a supportive person accompanying them to the abortion clinic, and home abortion was preferred. Lastly, they stated that the pandemic did not influence their decision to seek abortion care but factors such as unstable work and income, and concerns about sufficient

maternal healthcare during the pandemic influenced their decision. For examples of quotes see Figure 15.

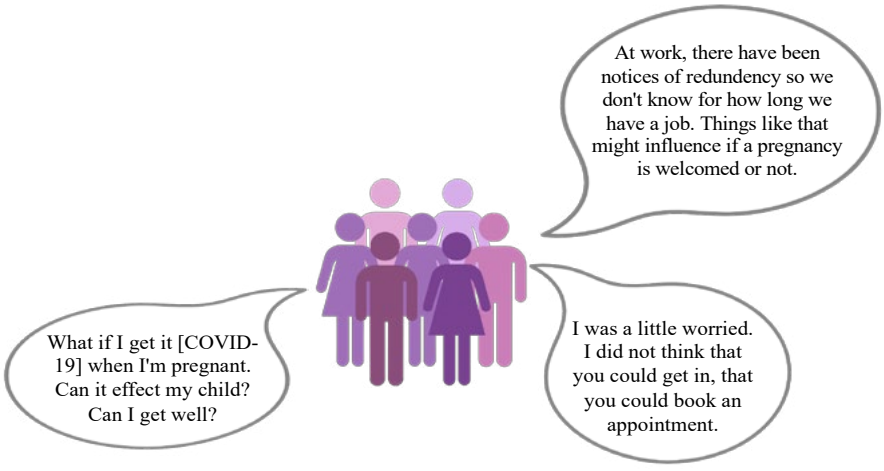

Figure 15. *Verbatim quotes by participants 4, 16 and 17. Created with Biorender.com. 2025-01-13.*

Paper II

Between January 2019, and December 2022, 457 persons were randomised, and 20 were subsequently excluded, see Figure 16. Two participants were excluded due to unknown outcome and the ITT-population consisted of 220 participants in the intervention group and 215 in the control group. Six participants were excluded from the PP-population. The safety analysis population consisted of 444 participants.

After directions from the Data and Safety Monitoring Board the study was halted at 51% of the planned sample size. The reason for premature closure was slow recruitment.

Primary outcome results are presented in Table 2. Mean time spent in hospital was significantly shorter in the intervention group compared with the control group: 10.3 (standard deviation (SD) 10.8) h and 13.1 (SD 12.5) h (difference -2.8, 95% CI -5.0 to -0.6; p=0.014), respectively. There was no difference in the induction-to-abortion interval between groups. For the intervention and control group a mean time of 525 (SD 517) min and 533 (SD 563) min from the first dose of misoprostol until

placental expulsion was reported (difference 7.9, 95% CI -110.5 to 94.7, p=0.88). The corresponding median induction-to-abortion interval reported in hours was 6.5 (Q1 4.7; Q3 8.8) h for the intervention group and 6.4 (Q1 4.8; Q3 9.5) h for the control group.

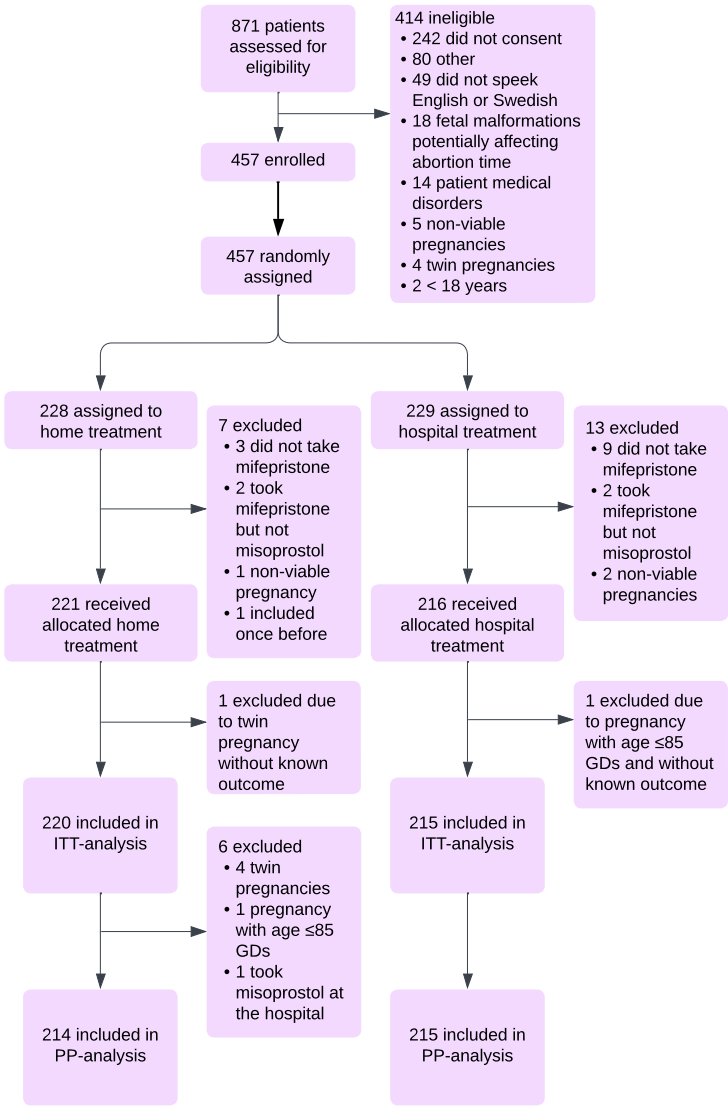

Figure 16: *Trial profile, flow of participants. Other = long distance to hospital, not a Swedish resident and family logistics. ITT = Intention-to-treat. PP = Per protocol. GD = gestational day.*

The level of satisfaction with the medical abortion treatment was high and did not differ between the groups. In the intervention group a significantly higher proportion of the participants preferred their allocated administration: 155/200 (77.5%) compared with 92/188 (48.9%) in the control group (difference -26.4 percentage points (pp), 95% CI -36.1 to -16.7; p <0.0001).

The effect of background characteristics, such as maternal age, BMI, parity and gestational age, on the primary outcome was calculated. The gestational age <126 days (=18 GWs) (relative risk (RR) 2.3, 1.5 to 3.6; p=0.002) and a previous vaginal birth (RR 1.6, 1.4 to 1.9 p <0.0001) were associated with completing the abortion within the range of day-care while it was not possible to detect an association with BMI or maternal age.

Table 2. *Primary outcome for the intention-to-treat (ITT)- and per protocol (PP)-population.*

	Treated as day-care			
	Intervention (home)	Control (hospital)	Difference between groups. Percentage points (95% CI)	P-value
ITT-population	N=220	N=215		
	156 (70.9%)	99 (46.0%)	24.9 (15.4–34.3)	<0.0001
PP-population	N=214	N=215		
	151 (70.6%)	99 (46.0%)	24.5 (15.0–34.0)	<0.0001

In total 47/224 (21%) of the participants in the intervention group were affected by an AE from the time of mifepristone administration until the follow-up, compared to 50/220 (22.7%) in the control group. The most frequent AE was vaginal hemorrhage (defined as ≥500 ml) during the hospital stay or after discharge and 1.4% of the participants received a blood transfusion. A post-abortion infection affected 5% of the participants and 1% required intravenous (IV) antibiotics.

In total 6/224 (2.7%) participants in the intervention group and 6/220 (2.7%) in the control group experienced a SAE. Nine participants aborted before admission to the hospital, 7/444 (1.6%) aborted after taking mifepristone only, and 2/220 (0.9%) after the first dose of misoprostol. Of those who aborted after mifepristone there were 2 SAEs while none of the abortions after misoprostol before hospital admission was reported as a SAE.

Paper III

From January 2019 to June 2022, 179 persons were randomly assigned to either insert the IUD within 48 h post-abortion or after 2–4 weeks, see Figure 17. Six participants in the intervention group and 8 in the control group were excluded before abortion and after some participants were lost to follow-up or withdrew consent the mITT population for the primary outcome analysis consisted of 67 participants in each group.

The interim analysis revealed an expulsion rate of >20% in the intervention group which resulted in a premature termination of recruitment.

For the mITT-population 34/67 (50.7%) of the participants in the intervention group were using an IUD after 6 months compared with 48/67 (71.6%) in the control group (difference 20.9 pp, 95% CI 4.4 to 35.9; $p<0.021$). For the PP-population 27/48 (56.3%) and 42/47 (89.4%) were using an IUD in the intervention compared with the control group, respectively ($p<0.001$). The sensitivity analysis with imputation of the results with best-and worst-case scenarios confirmed the robustness of the result.

The proportion of participants who attended the IUD-placement visit differed between groups; 69/77 (89.6%) vs 56/78 (71.8%) for the intervention and control group respectively, ($p=0.008$). More participants in the intervention group reported on IUD expulsion within 6 months compared with the control group; 22/73 (30.1%) vs 2/70 (2.9%) (difference 27.3 pp, 95% CI 15.6 to 38.8; $p=0.001$). Of the 22 participants in the intervention group who had an expulsion 18 (81.8%) were not using an IUD at 6 months post-abortion, whereas both participants in the control group had an IUD inserted again. There was no difference in expulsion based on IUD type. There were no significant differences in the participants' preference for the time of placement. Participants in the intervention group reported higher mean VAS pain scores compared with the control group before the IUD insertion and during the placement of the tenaculum.

Few AEs, such as unscheduled visits within 3 months due to signs of infection or heavy bleeding, were reported in the safety analysis. One person in the intervention group experienced a SAE with bleeding, but this was judged as unrelated to the intervention. There were 9 and 6 reported subsequent pregnancies in the intervention and control group respectively.

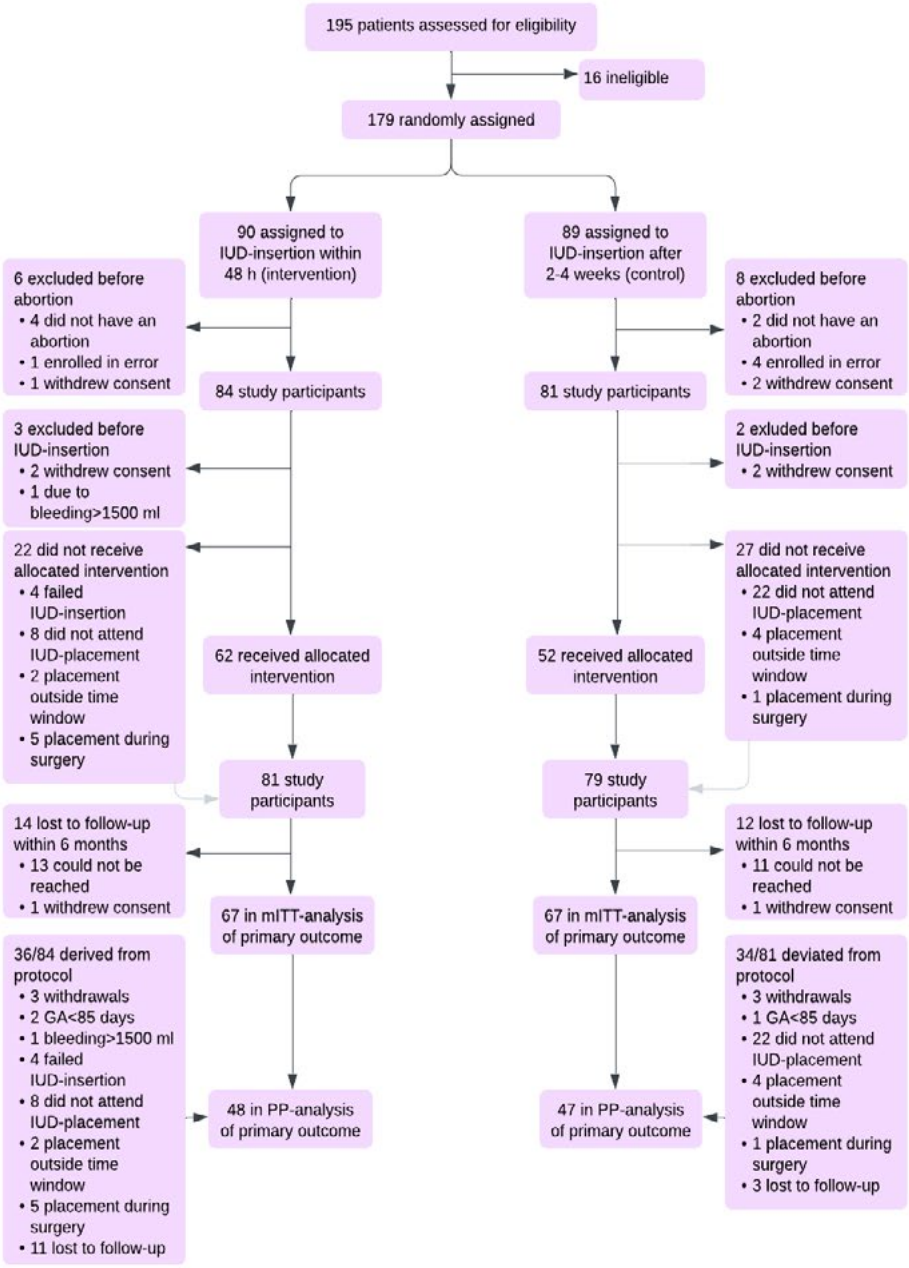

Figure 17. *Participant flowchart in Paper III. IUD = Intrauterine device. mITT = Modified intention-to-treat. PP = Per protocol. GD = Gestational day.*

Paper IV

In the RCT in Paper II 457 participants were enrolled, and out of these 437 proceeded with the abortion. For Paper IV another 12 participants were excluded after the abortion (1 duplex and 1 pregnancy under the gestational age limit with no known outcome, 8 aborted before admission, 2 had inconclusive registration of pain medication). The analysed population included 425 individuals.

Primary outcome results are presented in Table 3. Participants with no previous vaginal birth had a significantly higher maximum VAS with a mean of 72.7 vs 56.7 for those who had given birth vaginally (difference 16.0, 95% CI 10.6 to 21.4; p<0.0001). The participants pregnant with a gestational age >126 GDs (=18 GWs) had a significantly higher maximum VAS with a mean of 74.3 vs 64.1 for those pregnant with a gestational age <126 GDs (difference 10.2, 95% CI 1.9 to 18.5; p=0.016).

Table 3. *Primary and selected secondary outcomes of paper IV.*

	N=425
VAS at abortion. Mean (SD)	39.1 (34.4) n=312
Maximum VAS. Mean (SD)	65.4 (28.6) n=405
Satisfied with pain treatment (yes/no) Yes No	 357 (91.1%) n=392 35 (8.9%) n=392
Number of participants who received extra pain treatment	352 (82.8%)
Number of participants who received an oral opioid	266 (62.6%)
Number of participants who received an opioid injection	86 (20.2%)
Number of participants who received a PCB	163 (38.4%)
No extra pain relief	73 (17.2%)
Other*	124 (29.2%)

Other = heat pack, diazepam, nitrous oxide, ketobimedone or transcutaneous electrical nerve stimulation (TENS). VAS = Visual analogue scale (0–100 mm). PCB = Paracervical block. SD = Standard deviation.

The majority of the participants were satisfied with their pain relief (Table 3). The 35 participants who were dissatisfied with the pain treatment conducted the abortion

at a significantly higher gestational age with a mean of 113.2 GDs vs 106.5 GDs (difference 6.7, 95% CI 0.7 to 12.7; p=0.03) and a higher proportion had not given birth vaginally 77.1% vs 51.5% (difference 25.6 pp, 95% CI 9.2 to 42; p=0.0053).

The most common pain methods during the abortion are presented in Table 3. A total of 88/425 (20.7%) participants used an oral opioid, 24/425 (5.6%) a PCB and 5/425 (1.2%) an injectable opioid as their only additional analgesia, respectively.

The change in VAS after the first administration (without any preceding administrations of analgesia) of an oral opioid (n=186), a PCB (n=65) and an injectable opioid (n=22) was significantly different overall (p<0.001), and between an oral opioid and a PCB (p<0.001), and between an injectable opioid and a PCB (p=0.007). Administration of a PCB preceded by an oral or an injectable opioid, or by both an oral and an injectable opioid, generated the largest decrease in VAS with a mean change of -48.3 (SD 25.6), -50.4 (SD 30.2) and -63.3 (SD 35.1) respectively.

Discussion

Methodological considerations

To describe the informants' experiences as expressed by themselves a thematic analysis was performed on the data collected from semi-structured interviews in Paper I. Thematic analysis focuses on identifying and interpreting patterns or themes within the qualitative data.[184] It would have been possible to use qualitative content analysis that focuses on systematically identifying patterns, themes, and meanings within the content, but thematic analysis was deemed suitable as it is a more flexible method.

Pre-understanding refers to prior knowledge, experiences and assumptions a researcher brings into their study. In thematic analysis the researcher is the instrument for collecting and interpretating data, and his/her pre-understanding always influence the analysis.[185] To maintain research integrity, it is customary to include a section about reflexivity in the paper. During the analysis of the interviews all authors reflected on their own pre-understanding, and how we potentially could have influenced the outcomes unintentionally, but no structured team-reflexivity discussion was conducted. Neither was a member reflection session done. It is possible that the selected themes from the interviews could have been interpreted differently or that the results could have been perceived as more transparent and ethical if the pre-understanding of the group would have been appraised in a more constructive way.

In clinical trials for which the purpose is to establish a causal relationship between an exposure and an outcome the randomised controlled design is considered gold standard. Several potential biases can be mastered by using this methodology. Both Paper II and III are RCTs in which randomisation was used to remove selection bias and equalise possible confounding factors.

Blinding can reduce performance and detection bias in clinical trials. Neither of the trials in Paper II and III were blinded. In Paper II it was judged as too complicated producing placebo pills for misoprostol and for Paper III blinding for IUD-insertion for participants and health care professionals was not deemed as feasible.

To minimise the risk of random error in data it is important to achieve a sufficient study population which is normally done thorough a sample size calculation. For Paper II the sample size calculation was performed on the primary outcome and did not target potential AEs which would have necessitated a larger population. Even though the final ITT-population did not reach the pre-defined sample size, it was possible to show a significant difference between the groups, most probably due to underestimation of the magnitude of the difference between the two treatment options. Since gestational age affected the proportion of day-care procedures it would have been relevant to use a stratification variable to achieve an even distribution of participants with different gestational lengths. No such calculation was performed which is a limitation for interpretation of the results.

For Paper III the sample size calculation was made for the complete RCT (all gestational lengths) on the primary outcome and not on the risk of expulsion. Expulsion of an IUD is a relatively rare event. In studies conducted prior to Paper III it was estimated to be around 10–15% for first trimester abortions and 3.6–18.1% for abortions beyond 12 GWs, depending on timing of insertion.[153] In this trial the aim was foremost effectiveness, independent of expulsion or not, which is why power was based on IUD-use.

One limitation of RCTs is the study protocol, with strict inclusion and exclusion criteria and a well-defined procedure, which often differ from the real-life clinical setting and reduces the generalisability of the results. For paper II the proportion of participants having an abortion due to fetal indication was lower than expected in this setting, and non-Swedish or non-English speaking persons and minors were excluded, which lowers the generalisability. In Paper III it may be difficult to draw conclusions on the effectiveness of the intervention concerning further use in the future since it is dependent on adherence to a contraceptive which possibly is higher in a RCT-population. On the other hand, the risk of expulsion is a highly generalisable outcome that is not dependent on adherence. IUDs were furthermore provided for free during the trial, potentially impacting the generalisability to standard care situations.

An alternative approach would have been to answer the research questions about day-care treatment and IUD-use post-abortion by conducting register-based cohort studies. With this methodology it is possible to collect more data and over a longer period, which would have made it possible to identify more rare AEs. Cohort studies are potentially more cost efficient, less ethically complex and results usually reflect

standard care. But for abortion care and IUD-use in Sweden there are no such national registers containing the data required to answer the research questions.

In Paper IV a cross-sectional cohort design is used. Cross-sectional cohort studies are also considered fast and inexpensive to conduct. They are advantageous for generating a hypothesis but the ability to establish causal inference is restricted. To investigate the generalisability of the results about satisfaction of the pain treatment a separate analysis of the 35 participants who were not satisfied was made. It was not possible to analyse the pain experience among the participants who aborted before admission since VAS was not reported and they were often taken care of in another department in which the post-abortion survey was not always available.

Clinical implications for abortion beyond 12 gestational weeks

The COVID-19 pandemic

When analysing the yearly abortion numbers reported to the NBoHW after the COVID-19 pandemic the small decrease in 2021 with 17.8 abortions per 1000 women compared to 19.2 in 2019, 18.3 in 2020, 18.5 in 2022 and 18.4 in 2023 could be interpreted as an effect of the pandemic. There is one study from Skåne in Southern Sweden, in which numbers from a local register were analysed, showing that there was a small decline in abortions among persons >24 years of age and an increase in abortions for persons <25 during the pandemic.[186] But when looking at the quarterly number of abortions/1000 women, from the NBoHW (2018–2023), it becomes evident that the effect of the pandemic was very minor (Figure 18).

Even though the actual number of abortions was not critically affected there are however studies indicating that the pandemic did influence the pregnant persons decision-making in relation to the abortion.[187]

Another consequence of the pandemic was that the necessity of administering mifepristone in a health care facility was criticised and in February 2025 the Swedish government received a report regarding a modernised Abortion Act. One of the proposals suggests that the requirement of an abortion to be performed/initiated in a medical facility should be removed.

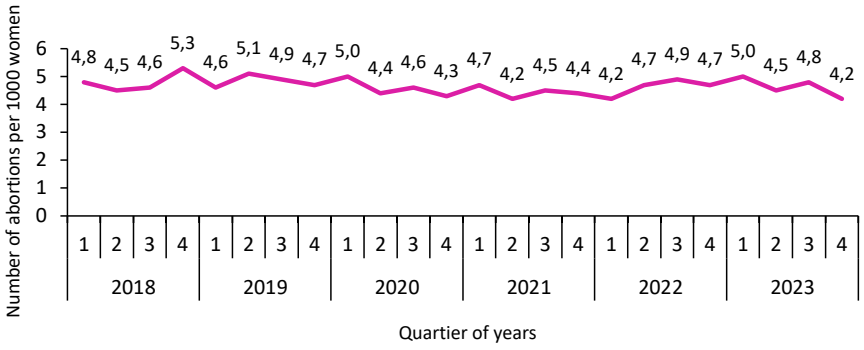

Figure 18. *Abortion rates in quarterly numbers (number/1000 women, 15–44) 2018–2023. Source: Statistikdatabas för aborter. Swedish National Board of Health and Welfare. Communication 2025-01-20.*

Day-care

Providing day-care, on an outpatient ward with access to surgical back-up or an inpatient ward staffed with midlevel abortion providers could pose several benefits, both for the individual abortion-seeking person as well as for the healthcare system. It entails less time away from home and work and less economic loss for the individual. Administering the first dose of misoprostol at home could also enhance greater autonomy. For the health care system promoting day-care could increase access, particularly in regions with limited admission possibilities.

In Paper II robust evidence for the increase in the proportion of day-care procedures and shorter hospital stays if the first dose of misoprostol is administered at home is presented. The results support findings from previous studies conducted on the mifepristone-misoprostol regimen. With a median induction-to-abortion time of around 5–7 h, which is similar to the results in Paper II, day-care seems to be achieved in 60–80% of the cases if day-care is defined as approximately 8–10 h and ward closes around 16.00–17.00. In a retrospective cohort study undertaken in the US all cases were managed within day-care but one third of the participants underwent surgical evacuation to complete the procedure within 9 h. This strategy is however not recommended in international guidelines.[13, 64-66, 105]

Patient acceptability and possibilities to provide sufficient pain management are important aspects when implementing a day-care protocol. Pain treatment is discussed below. In Paper II both groups reported high treatment satisfaction. The participants in the home-administration group showed a significantly higher preference for their allocated treatment. This difference might be due to having to spend less time in hospital and the increased autonomy of self-management. The results are in line with a previous study showing patient satisfaction >95% and >70% rating their pain experience as acceptable/very acceptable when conducting an abortion beyond 13 GWs in an outpatient day-care setting.[65]

Safety

Providing medical abortion beyond 12 GWs, and especially in a day-care setting, requires knowledge about safety outcomes for the medical regimen implemented. Previous studies on the mifepristone-misoprostol regimen have shown low risks of severe bleeding, severe infections and organ injuries. The need for post-abortion surgical interventions, such as vacuum aspiration due to bleeding or retained placenta is hard to estimate in a global context due to varying local practice.[4, 64, 65, 67, 68, 83, 86, 87, 175, 176]

In Paper II, 1% of the participants required a blood transfusion due to heavy bleeding, 1% required IV antibiotics and 7.4% underwent a post-abortion surgical intervention. In the trials with day-care protocols around 1% of participants experienced heavy bleeding or severe symptoms of infection and 1.4–5% had a vacuum aspiration after the abortion, which supports the generalisability of the results in Paper II.[65, 68, 105]

One important aspect with home-administration of misoprostol is the potential risk of abortion and bleeding before admission. It is previously known from cohort studies and RCTs that 0.2–2.5% of the patients experience abortion during the interval between mifepristone and misoprostol treatment, before admission.[59, 64-69] In Paper II 7/444 (1.6%) participants aborted following mifepristone which is in line with these numbers.

Concerning the risk of aborting during the period from misoprostol administration to admission previous evidence is scarce and inconsistent. Few events have been reported so far. In a retrospective analysis from the US (2024) and a prospective cohort from Nepal (2019) none aborted before admission after the first misoprostol dose. In a pooled analysis with data from Tunisia, Vietnam, Uzbekistan, Ukraine and

Armenia, a total of 19/846 (2.2%) experienced fetal expulsion within 3 h after the first misoprostol dose, but their admission status was not reported clearly. In Paper II, it was a rare event with 2/224 (0.9%) participants experiencing abortion after misoprostol but before admission. On the contrary, in a prospective cohort from Nepal (2024), 8/120 (6.7%) aborted after the first misoprostol dose before admission, which is a considerably higher number. The authors describe that arrival at the day-care unit was delayed in half of the cases. For Paper II the participants were instructed to seek care immediately in case of severe pain/and or bleeding. [65, 66, 68, 105]

Given the uncertainty of the topic the importance of providing the patients with reliable information and timely admission routines is stressed. A pooled analysis of the number of abortions prior admission after the first misoprostol dose is suggested to further analyse the risk.

Pain

As has been reported in earlier studies and in results from Paper IV pain during a medical abortion beyond 12 GWs is rated as severe although satisfaction with the pain treatment is high. Nulliparity and having the abortion at a later gestational age correlated to a higher maximum pain which is similar to previous findings.[109-111] One possible explanation for the high satisfaction despite high VAS levels could be that, besides receiving effective and timely analgesia, pain is a multifactorial experience and that other components such as emotional stress is being cared for by the staff, and that these measures increase the total rating of satisfaction.

Existing studies on pain management in abortion beyond 12 GWs are few and show great heterogenicity of what is offered as analgesia as well as what is effective as pain relief. In Paper IV oral and parenteral opioids and PCB were almost exclusively used as “on-demand” analgesia. The WHO recommends use of EDA, but the guideline review does not include any studies at all on the effectiveness of oral opioids for medical abortions beyond 12 GWs.[13] The discrepancy between recommendations and local use could probably be explained by lack of high-quality trials and possibly a setting with a somewhat restricted access to more resource-intensive anaesthesiologic care such as EDA.

In Paper IV pain was reduced to the highest degree by PCB alone or PCB preceded by an opioid. These results contrast with previous trials in which PCB was not superior to placebo in terms of mean decrease in VAS or less additional analgesia

used. It is however difficult to compare with previous trials since protocols differed widely. Results from Paper IV are descriptive but it is suggested that they better reflect clinical care since the PCB is administered after onset of pain, in contrast to prophylactically. It is possible that the analgesic effect will cease if the PCB is administered too early during the abortion procedure.[120, 125]

For the trials investigating the feasibility of day-care for abortions beyond 12 GWs pain experience and analgesia requirements are important outcomes. Around 70–80% of the participants report that their overall pain was acceptable or highly acceptable. The reported use of additional analgesia varies widely. Which analgesic methods that were administered is not sufficiently reported but NSAIDs seem to be the most commonly provided drugs.[65, 68, 105]

Contraception

The initial higher uptake of IUDs following early placement after a medical abortion beyond 12 GWs compared with later placement did not compensate for the high expulsion rate and explains why utilisation of IUD after 6 months was not superior for the early-insertion group (Paper III). The contrasting low versus high expulsion rates after early IUD-insertion following a first trimester medical abortion and vaginal delivery respectively, indicate an association between IUD-expulsions and gestational length.[156, 188] The precise mechanisms explaining these findings could be the continuation of uterine contractions and more prominent cervical dilation after an abortion later in pregnancy, but exact dilation at the time of insertion has not been reported.

The findings of higher expulsion rates in the early-insertion group in Paper III align with results from previous RCTs. Both Constant et al. and Korjamo et al. reported higher expulsion rates in the immediate insertion group: 20/55 (36%) vs 8/57 (14%) for the later insertion group, and 5/27 (18.5%) for the immediate insertion vs 1/28 (3.6%) for later insertion. But in contrast to the results in Paper III continuation rates were higher for immediate compared with later insertion. Constant et al. reported that at the end of the 6-week follow-up period 40/55 (73%) in the immediate group vs 23/57 (40%) in the late group were using an IUD. Korjamo et al. report higher proportion of IUD-use after early insertion (measured after 1 year): 15/27 (55.6%) vs 7/28 (25.0%) for later insertion.[157, 158, 189]

It is also worth addressing that even though expulsion rates are higher if insertion of the IUD occurs early after a medical abortion beyond 12 GWs, continuation rates can increase if protocols for contraception post-abortion allows a certain flexibility in timing of IUD-insertion.

Conclusions and wider implications

- During the first period of the COVID-19 pandemic in Sweden the number of abortions and ongoing pregnancies remained stable. (Paper I) When examining quarterly numbers of abortions between 2018 and 2023 after the end of the pandemic we conclude that the overall abortion numbers were not critically affected by the COVID-19 pandemic.

- Abortion-seeking persons did not hesitate to proceed with the abortion due to the COVID-19 pandemic. There were however pandemic-related factors, such as concerns about being pregnant or giving birth during a pandemic and an insecure work or economic situation, that seem to have influenced their abortion decision-making. (Paper I)

- Home-administration of the first misoprostol dose increases the proportion of persons having a medical abortion after 12 GWs as a day-care procedure. (Paper II)

- The mifepristone-misoprostol regimen for abortions beyond 12 GWs, when applied in a day-care setting is safe, effective and well-tolerated by patients. (Paper II)

- Day-care protocols for medical abortion beyond 12 GWs, with support from tertiary care levels, could spare valuable resources for hospitals and promote task shifting. An expansion of day-care medical procedures could further increase access of this abortion service to regions with limited admission possibilities as well as in settings with complicated legal frameworks.

- Home-administration of misoprostol for abortion beyond 12 GWs is preferred by patients and represents one measure that could enhance autonomy and expand choice for this group of abortion-seeking persons. (Paper II)

- IUD-insertion within 48 h after medical abortion conducted beyond 12 GWs is less advantageous in terms of IUD-use after 6 months when compared with insertion after 2–4 weeks. (Paper III)

- Expulsion rates are high when the IUD is inserted within 48 h post-abortion, and this approach may be used in selected individuals only after counselling on the risk of expulsion. It is however important to acknowledge that delaying

placement of an IUD post-abortion comes with a substantial risk of non-attendance at the appointment for placement, and consequently a lower IUD-user rate. (Paper III)

- Persons undergoing a medical abortion beyond 12 GWs report severe pain and most often require extra analgesia in addition to NSAID and paracetamol. A higher maximum VAS during the abortion is associated with having an abortion at a higher gestational age and nulliparity. (Paper IV)

- An oral opioid is often provided as pain management during medical abortion beyond 12 GWs, but reduction of VAS measured after its administration is minor. PCB is an analgesic method well adapted for day-care and low-resource settings. Administration of a PCB after onset of pain was associated with the largest reduction of VAS. (Paper IV)

Future perspectives

The global political landscape of abortion rights is a field with rapid alterations, creating sometimes uncomprehensible legal situations for abortion-seeking persons and providers. Given these turbulent times promoting easier access and self-management for abortions and especially beyond 12 GWs is more important than ever.

One measure to increase access for abortions beyond 12 GWs is to promote telemedicine for later gestations as well. For first trimester abortions growing evidence supports the feasibility of telemedicine protocols without physical contact, ultrasonographic measure of gestational length or in-clinic administration of abortion medication, as compared with standard care.[190] For abortion care beyond 12 GWs only a few trials have documented outcomes from out-of-clinic care, and they are all retrospective cohort studies undertaken in settings where access to abortion is restrained. In one study from Brazil abortion was provided by telemedicine to 29 abortion-seeking persons beyond 13 GWs. Half of the abortions were completed by medication outside the hospital. Almost 45% required surgical intervention but only half of the interventions were undertaken due to self-reported symptoms such as bleeding, and the high evacuation-rate might reflect local practice rather than the necessity of a surgical intervention.[191] In another cohort from South America the results from self-managed abortions beyond 13 GWs are reported. The success rate was 76%, and, for those with complete post-abortion data, 4% experienced delayed expulsion of the placenta and 4% heavy vaginal bleeding.[192] Further research on telemedicine options, for parts of or the whole procedure, for abortions after 12 GWs is appraised.

Promoting day-care and self-management for abortion requires offering abortion-seeking persons effective and acceptable pain management. Existing guidelines do not cover outpatient care with mid-level abortion providers for abortions beyond 12 GWs.[13] In Paper IV the use of PCB was described as an effective analgesic method, and future research on low-resource pain treatments for this specific group of patients is endorsed.

The ideal timing of IUD-insertion after an abortion conducted beyond 12 GWs is still unclear. According to paper III and other studies insertion a couple of weeks after the abortion decreased the rate of attendance, but immediate insertion increases the

risk of expulsion. In Paper III the median time from completed abortion to IUD-placement was 3 hours in the early-insertion group. Results from the same RCT but analysed for abortions ≤9 GWs showed less expulsions after early insertion of IUD but median time between abortion and insertion was 42 h. The optimal timing of IUD-insertion for persons opting for IUD-use after an abortion later in pregnancy should be further investigated.[156]

In the Swedish context, home-administration of mifepristone is most likely to be permitted soon and consequently telemedicine options for abortion care in Sweden can expand. Further research about telemedicine and its effect on access, self-management, autonomy and perhaps even for abortions later in pregnancy in Sweden is warranted.

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