Review article

Review of medical abortion using mifepristone in combination with a prostaglandin analogue

Christian Fiala a,b,*, Kristina Gemzell-Danielsson b

a Gynmed Clinic, Mariahilferguertel 37, A-1150 Vienna, Austria
b Division for Obstetrics and Gynaecology, Department of Woman and Child Health, Karolinska Institutet, SE-17176 Stockholm, Sweden

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Abstract

Induced abortion is still a major health problem in the world and the most frequently performed intervention in obstetrics and gynecology with an estimated total of 46 million worldwide each year. Medical abortion with mifepristone and prostaglandin was first introduced in 1988 and is now approved in 31 countries. This combination of drugs has recently been included in the List of Essential Medicines by the World Health Organisation. The present review summarizes the development, physiology and the development of the currently used regimens.

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1. Introduction

1.1. Development of medical abortion during early pregnancy

Summary: The discovery of mifepristone has made a major improvement in medical abortion and is now available in 31 countries.

Inducing abortion of an unwanted pregnancy by administering drugs is not a new concept. Historic documents list an incredibly large number of drugs and other substances, which women have swallowed or inserted vaginally with the intention of inducing abortion of an unwanted pregnancy [1,2]. However, most of these drugs have been either ineffective as an abortifacient or dangerous to the health and/or even the life of the women.

The discovery of prostaglandins (PGs) has been an important step in the development of safer methods. The first studies were performed using intraamniotic injection of PG, which offered an advantage over hypertonic saline, the standard of that time [3]. However, these methods were only suitable for inducing abortion in the second trimester. Very quickly, a vaginally applicable PG was developed, which gave satisfying efficacy also during early pregnancy [4]. But the drawback of the PG analogues available at that time, i.e., associated pain and gastrointestinal side effects, were major obstacles for widespread use.

The turning point came when the French scientist Etienne-Emile Baulieu and colleagues from the French national institute INSERM and a group of colleagues at the French pharmaceutical company Roussel-Uclaf developed mifepristone or RU-486, as it was initially called [5]. The abortifacient potential of mifepristone was described for the first time in May 1982 [6]. This, together with a dose-finding study performed in Stockholm and Szeged in Hungary, indicated that mifepristone is a promising abortifacient drug with very few side effects [7]. However, it became clear that mifepristone had a maximal effectiveness <80% when used alone, which was not sufficiently effective to be used as an abortifacient drug in clinical routine. This low efficacy was confirmed by other studies [8–13]. The final breakthrough came with the discovery that mifepristone increased the sensitivity of the pregnant myometrium to PG, which allowed use of a reduced dose of PG [14]. The maximal effect of the sensitization was seen when the interval between mifepristone and the PG analogue was 36–48 h. This led to the development of a combined treatment using mifepristone followed by a PG analogue [12,14–16]. A protocol for medical abortion was developed from these findings, consisting of a single 600-mg oral dose of mifepristone (Europe) or repeated low doses of mifepristone.
(China), followed by an appropriate dose of a PG analogue 36–48 h later. The high efficacy in terminating early pregnancy and the low rate of side effects of this combined regimen were subsequently confirmed in several large multicenter studies [17–19].

Medical abortion was first approved in France in 1988 (up to 49 days of amenorrhoea), followed by approvals in the United Kingdom (1991) and Sweden (1992) (up to 63 days in both countries). Mifepristone has also been used in China since 1992. However, it was not until 1999/2000 that medical abortion with mifepristone and PG was approved in several other European countries and the United States. Today, mifepristone is marketed in 31 countries worldwide (Fig. 1). The approved protocol includes the association of 600-mg oral mifepristone with 400-μg oral misoprostol for use up to 49 days of gestation in all countries except the United Kingdom. In Sweden and Norway, the approved protocol also includes giving mifepristone 600 mg in association with gemeprost 1.0 mg vaginally for use up to 63 days of gestation. In the United Kingdom, gemeprost 1.0 mg following 600 mg of mifepristone up to 63 days of gestation is the only approved regimen. In China, a different protocol is used in most institutions, consisting of mifepristone 25-mg tablets taken twice daily for 3 days, followed by misoprostol 600 μg po for gestations up to 49 days or 800 μg vaginally in pregnancies between 50 and 63 days of gestation. However, various regimens with several days of ingestion of mifepristone are also used in China (Linan Cheng, personal communication 2005) [20].

According to the manufacturer, so far, more than 1.5 million women have been treated with mifepristone in Europe since it was first introduced in 1988 (Exelgyn, Paris). The close surveillance of the treatment allows confirmation of the very high safety of this regimen.

Furthermore, the World Health Organisation (WHO) has recently included the combination of mifepristone and misoprostol for this indication in the Essential Medicine List [21]. Since introduction of the method, research has largely focused on improving efficacy, defining the optimal type, dose and route of administration of the PG analogue. Many studies have also focused on finding the minimum effective dose of mifepristone needed to induce an abortion. An important reason for reducing the dosage of mifepristone has been the relatively high price: approximately 70 per box of three tablets in Europe and approximately US$270 per box in the United States.

However, the approved regimen has undergone only a few changes from the patients’ perspective since its first marketing in 1988, for instance, changing the PG from intramuscular sulprostone (Nalador) to vaginal gemeprost (Cervagem) or oral misoprostol (Cytotec).

Currently, mifepristone is the only antiprogesterone used clinically to any extent. Before mifepristone became available in the United States, a combined regimen of methotrexate (MTX) and a PG analogue was used and is still in use in Canada because mifepristone is not on the market there. So far, no randomized control trial (RCT) has been published, comparing MTX plus PG to mifepristone plus PG. Results of different studies show a lower efficacy for the regimen with MTX, as well as a longer duration until complete abortion and a higher incidence of continuing pregnancies [22]. MTX is also teratogenic. Therefore, WHO and other authorities do not recommend MTX for medical abortion of an intrauterine pregnancy.

2. Mifepristone

2.1. Mode of action

Summary: Mifepristone as well as its metabolites are antagonists to progesterone binding to its receptor.

Mifepristone is a 19-norsteroid substituted at the 11β position by a p-(dimethylamino)phenyl group. A hydrophobic 17α-substituent increases the binding affinity to the
 progesterone receptor (PR) [23]. A glycine at position 722 in the hormone-binding domain of human PR is critical for mifepristone binding [24]. Like progesterone, mifepristone enters the target cell and interacts with receptors that are largely loosely bound in the nucleus. No metabolization of mifepristone in target cells has been detected [25]. The steroid receptor–antagonist complex also binds tightly to progesterone response elements, but these DNA-bound receptors are transcriptionally inactive if progesterone is present. Mifepristone binds with high affinity to the PR. Its binding affinity for the PR is 2.5–5 times that of progesterone [26,27].

Mifepristone is regarded as an almost pure progesterone antagonist, but a slight agonistic action has been reported [13,28–30]. It has been suggested that in the absence of progesterone, the steroid receptor–mifepristone complex may be transcriptionally active on some genes, and mifepristone thus acts as a “partial agonist” [31]. When mifepristone is used to terminate pregnancy, one finds a failure to respond in about 1% of the women. It has been suggested that this may be due to a genetic variation in the PR [32].

Mifepristone also binds to the glucocorticoid receptor, with a binding affinity three times that of dexamethasone. To a lesser extent, it also binds to the androgen receptor but not to the estrogen or mineralocorticoid receptor.

Three metabolites of mifepristone have a lower affinity to the PR, ranging from 21% to 50%, relative to 100% for progesterone, or 9–21% compared to mifepristone [26,33,34]. The data on pharmacokinetics and binding affinity suggest that these metabolites may contribute to a significant extent (23–33%) to the antiprogestagenic effects of mifepristone. Thus, the biological actions of mifepristone seem to be induced by the combined pool of mifepristone plus its metabolites [34,35].

2.2. Uterine contractility

Summary: Mifepristone reverses the action of progesterone in pregnancy. It increases uterine contractility, but most importantly, it sensitizes the myometrium to PGs.

During early human pregnancy, uterine contractility is suppressed. Csapo et al. [36] showed that lutectomy before the luteoplacental shift, and the subsequent decrease in plasma progesterone resulted in increased uterine contractions and spontaneous abortion. It was proposed that the degree of uterine activity during pregnancy is regulated by the balance between the intrinsic suppressor, progesterone and the stimulant PG F2α (PGF2α) [37]. Progesterone suppresses uterine contractions by inducing hyperpolarization of the cell membrane, which makes the myocytes less sensitive to electrical stimulation. Furthermore, progesterone induces inhibition of gap-junction formation, which counteracts coordinated uterine contractions. In addition, progesterone also has effects on the cervix and the decidua.

Treatment with mifepristone counteracts these effects of progesterone. Mifepristone reverses the hyperpolarization of the cell membrane and the progesterone-induced inhibition in gap-junction formation [38]. Following treatment with mifepristone, there is also an increase in decidual PG release and a reduced activity of PG dehydrogenase [39].

Of decisive importance for the use of mifepristone was the discovery made in 1985 when the combined effect of mifepristone and a PG analogue on uterine contractility was investigated in early pregnancy (Fig. 2) [14]. The authors showed that mifepristone increases uterine contractility and sensitizes the myometrium to PG. The maximum effect was achieved when PGs were administered 36–48 h after mifepristone and the dose of PGs could be five times lower than used without mifepristone, thus reducing side effects [16]. This effect of mifepristone could also be observed in the nonpregnant uterus [40,41]. However, no effect on cervical priming was observed in nonpregnant women in another study [42].

2.3. Pharmacokinetics

Summary: Oral absorption of mifepristone is rapid with a half-life of 20–40 h.

When mifepristone is administered orally, absorption is rapid with peak concentrations after 1–3 h, irrespective of dose. Following oral administration of a single dose of 600 mg, the peak plasma concentration of 2.5 μmol/l occurs approximately 90 min after ingestion [27,43,44]. Thereafter, concentrations decrease slowly with an elimination half-life of 20–40 h. Although the absorption of mifepristone per os is high (about 70%) its bioavailability is reduced to about 40% due to first-pass metabolism by the liver [13].

Absorption following vaginal application has been shown to be insufficient for any clinical effect [45].

In serum, mifepristone binds to α1-acid glycoprotein (AAG), but it does not bind to transcortin or sexual hormone-binding globulin [26,27]. The presence of AAG in the human may partly explain the differences in pharmacokinetic behavior of mifepristone between the human and other mammalian species [46]. The binding capacity of AAG is saturated by 2.5-μM/l mifepristone, which leads to nonlinear

![Fig. 2. Uterine contractility after PG without (A) and with pretreatment of mifepristone (B) [adapted from Contraception 1985;32:45–51].](image-url)
kinetic behavior. Doses of mifepristone exceeding 100 mg do not lead to higher plasma levels [47,48]. Furthermore, there is no difference in serum profiles between men, nonpregnant and pregnant women, or between morning and evening administration of the drug [13,49]. When the concentration of mifepristone exceeds the binding capacity of AAG, it becomes more susceptible to metabolism. Thus, the serum concentrations of the metabolites increase as a function of the oral dose of mifepristone. Three metabolites of mifepristone have been identified [34,47]. Mifepristone undergoes demethylation to give the monodemethylated (RU 42,633) and didemethylated (RU 42,848) derivatives, as well as hydroxylation of the propynyl group (RU 42,698). In contrast to didemethylated (RU 42,848) derivatives, as well as hydroxylation to give the monodemethylated (RU 42,633) and faeces via the billiary system (90%) [46].

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2.4. Regimens

Summary: Mifepristone and the PG analogue act synergistically. The efficacy of various regimens depends on the dose of mifepristone and the interval to PG administration, as well as the dose, type and route of administration of the PG.

Efficacy is also dependent on the duration of pregnancy. Beyond 49 days of gestation, oral misoprostol is not sufficiently effective. The bioavailability of misoprostol can be increased by vaginal or sublingual administration, avoiding first-pass metabolism by the liver. Medical abortion can be achieved by using either mifepristone or a PG analogue alone [5,17,50]. However, efficacy is low for sole use for mifepristone, ranging from 60% to 80% [5,17,50]. With repeated doses of gemeprost alone, a success rate of around 95% could be reached and with misoprostol alone up to 90% with an appropriate regimen. Disadvantages of PG analogues are, however, the high rates of pain and gastrointestinal side effects associated with use of the high doses needed [12,22].

The combined regimen offers a higher efficacy with a low rate of side effects. Mifepristone and the PG analogue act in synergy, as has been mentioned previously [14]. Consequently, a change in the available dose or potency of one drug or in the type, route of administration and interval after mifepristone of the PG analogue will impact on the necessary dose of the other and upon the subsequent efficacy and incidence of side effects. A pictorial comparison to a balance is valid, where reducing one side leads to an increase on the other side.

The challenge of medical abortion, therefore, is to find the best balance between both drugs involved or, in other words, to find a balance between high efficacy and good tolerance. Economic considerations are also important, especially for developing countries, where medical abortion could help to reduce the terrible consequences of unsafe abortions [53,54]. Research is still ongoing to finding the optimal dose of mifepristone as well as the optimal type, dose, route of administration of PG and the shortest possible interval between both drugs.

Prior to the first marketing in France, dose-finding studies were performed under the auspices of Roussel-Uclaf for termination of pregnancy using mifepristone alone. At doses of 200–800 mg, efficacy was shown to be dose-related in the range of 63–87%. No increase in efficacy could be observed with doses above 600 mg or with repeated doses [5,17,50].

These data led to the first registered regimen of a single oral dose of 600 mg of mifepristone followed by a PG analogue. Repeated dose of mifepristone followed by a PG analogue has also been shown to be effective and are widely used in China. The clinical advantages of a single-dose regimen outweigh the slightly higher efficacy of a repeated low-dose regimen [55,56]. The single dose is still the approved regimen in all countries where mifepristone is registered, except in China.

When medical abortion was first introduced, the main concern was to find a highly effective regimen and, hence, the dosage of mifepristone and the PG may have tended to be higher than necessary. More recently, research has focused on two aspects:

- Reducing dose of mifepristone
- Reducing side effects of the method

Reducing side effects means optimizing dose, route of administration and regimen of the PG analogue. This will be discussed in the following section.

The use of a reduced dosage of mifepristone (200 mg) combined with either 600 or 800 μg of misoprostol given vaginally or orally or gemeprost vaginally has been investigated in several small trials with the number of patients ranging from 100 to 220. The results showed an efficacy above 90% [57–61]. This led the way for WHO to perform two large multicenter, multinational RCTs with gestations up to 56 days [62,63]. The first study found a similar efficacy of around 94% for 200 and 600 mg of mifepristone when followed by gemeprost 1 mg. The other study compared gemeprost 0.5–1 mg in association with 200 mg of mifepristone and found a similar efficacy of 91.7% and 92.9%, respectively.

Another large, double-blind randomized trial with pregnancies up to 63 days compared 0.5 mg gemeprost with 800 μg misoprostol vaginally after 200 mg mifepristone and found an efficacy of 96.2% vs. 98.7% [64].

A large case report (2000 consecutive abortions up to 63 days of amenorrhea) showed that 200 mg of mifepristone followed by 800 μg of misoprostol vaginally gave an efficacy of 97.5% [65]. The high efficacy of this regimen has been confirmed in several other studies [64,66–69]. This regimen has since become widely used in some countries (Finland, Sweden, United Kingdom, United States). It is also recommended by several clinical guidelines for pregnancies up to 63 days [WHO guidance, Royal College of Obstetricians and Gynaecologists (RCOG) clinical guidelines and National Abortion Federation recommendations] [70–72].
The above studies were carried out using either gemeprost or misoprostol. 800 μg vaginally for gestations <63 days. Only a few studies have been done in a developed country setting with a reduced dosage of 200 mg of mifepristone and 400 μg misoprostol given orally [73–75]. Misoprostol 400 μg po is also the approved and the standard dose for pregnancies up to 49 days of gestation. However, efficacy for gestations up to 49 days was around 90% in all three studies.

The WHO study found no difference in efficacy between 200 and 600 mg of mifepristone. But some aspects make the results of the WHO study difficult to interpret: ultrasound was not done on a routine basis, neither before nor after treatment; gestational age was estimated on Last Menstrual Period (LMP) and clinical examination; most of the centers had no prior experience with medical abortion and efficacy by center ranged from 77% to 100% among the 50–100 cases performed in a routine clinical setting and efficacy for gestations up to 49 days was around 90% in all three studies.

Shannon et al. [75] excluded 12 patients (3.3%) after the treatment because they needed additional misoprostol at or after follow-up. No information is given as to how many of these patients needed curettage, which would have classified the cases as failures [75].

Schaff et al. [74] conducted a large randomized trial comparing the same regimen as the two abovementioned studies, 200 mg mifepristone followed by 400 μg misoprostol po vs. 800 μg given vaginally in gestations up to 63 days. However, Schaff et al. prematurely stopped the arm with the 400-μg oral misoprostol regimen because they judged the success rate too low: 84% overall and 89% in gestations up to 49 days. The group using the higher dose of vaginal misoprostol had an overall success rate of 96% and 97% in gestations up to 49 days [74].

A direct comparison in an RCT has not been done between the approved regimen of 600-mg mifepristone followed by either 400 μg of misoprostol po or 1-mg gemeprost vaginally and 200-mg mifepristone followed by 800 μg of misoprostol vaginally.

A further reduction of mifepristone to 50 mg has also been studied in gestations up to 56 days. The result shows the interdependency of both drugs: when one drug is given in a sufficient dose, it can counteract a reduction of the other drug. Efficacy was 89.8% in combination with the standard dose of gemeprost 1 mg but fell to 84.7% with a reduced dose of gemeprost of 0.5 mg [63].

Unfortunately, the published recommendations on regimens differ from each other and from the approved regimen (Table 1). The situation is further complicated by the fact that mifepristone is approved for medical abortion with different gestational age limits in different countries. Also, these limits are not respected in the same manner in all countries. As a result, there is some confusion among clinicians as to which regimen is optimal and approved to use.

### 3. Prostaglandin analogues in medical abortion

Summary: E₁ PG analogues like misoprostol or gemeprost have become the standard of care because of better tolerability and higher uterine specificity, as compared to other PG analogues. Today, misoprostol has replaced gemeprost due to a lower rate of side effects and costs.

When medical abortion was introduced in France in 1988, in most cases, sulprostone, a PG E₂ derivative, was given intramuscularly 36 to 48 h after the administration of 600 mg of mifepristone. Providers applied different doses of sulprostone ranging from 125 to 1000 μg [17]. Less often, gemeprost, a PG E₁, was used intravaginally in a dose of 1 mg [17,76,77]. Gemeprost had been available as a vaginal pessary, licensed for induction of second trimester termination of pregnancy.

In the following years, myocardial infarction attributed to coronary spasm induced by sulprostone occurred in three
patients among the 60,000 women treated with medical abortion [77]. One of them, a 30-year-old multiparous woman who smoked heavily, died due to the infarct [78]. At least one of these three patients had received a dose of sulprostone higher than the recommended dose of 250 μg [17]. The suspicion that sulprostone had caused the myocardial infarction is further substantiated by a similar report without pretreatment of mifepristone [79].

Following these severe reactions, sulprostone for intramuscular injection was withdrawn from the market and misoprostol 400 μg po was used instead from 1992 onwards after several studies suggested similar efficacy [77,80,81]. Since introduction of an E1 PG analogue (gemeprost or misoprostol) in association with mifepristone for termination of pregnancy, no cases of myocardial infarct have been reported. Also, the rate of less severe side effects has diminished, as compared to the rate associated with use of sulprostone.

After the three cases of cardiovascular adverse events, a contraindication was added to the product label for Mifegyne/ Mifeprax for women over 35 years of age who smoke. This contraindication was added, although the cardiovascular incidences were associated with use of an E2 PG and not with misoprostol or gemeprost, both E1 derivatives. The contraindication was later changed to a warning. However, the product information for misoprostol does not include any reference to age or smoking habits of patients when being used as a continuous therapy for gastric ulcer.

Gemeprost has been widely used in early medical abortion. It is easily available in many countries, and gynecologists have a long experience with the drug as it is approved for vaginal application in second-trimester abortion. However, it has several disadvantages compared to misoprostol:

- It is only available as 1-mg pessary for vaginal use.
- The available pessary contains an unnecessarily high dose of PG for very early medical abortion, with dose-related side effects.
- It is unstable at room temperature, which makes it difficult to store and transport.
- It is expensive.
- It is only available in a limited number of countries, in contrast to misoprostol.

These aspects have led to the substitution of gemeprost by misoprostol over the last few years [64].

3.1. Misoprostol

Summary: Misoprostol is the PG analogue of choice for medical abortion. It is a well-known and thoroughly studied drug. It is well tolerated and has few, but dose-dependent, side effects.

Misoprostol (15-deoxy-16-hydroxy-16-methyl PG E1) is a PG E1 analogue, developed in 1973 by Searle for the treatment and prevention of gastric ulcer. It received its first marketing authorization in 1985 and is now approved in more than 80 countries, mostly under the brand name of Cytotec (Fig. 3, world map on the approval of misoprostol). It is supplied in tablets containing 200 μg of misoprostol for oral use. A 100-μg form is available in some countries.

Treatment and prevention of gastric ulcer is still the only licensed indication for misoprostol, with the exception of the recently approved Gymiso in France and a 25-μg vaginal suppository for induction of labor available in Brazil and Egypt (www.misoprostol.org).

Misoprostol has several advantages over other PGs on the market:

- It has limited effect on the bronchi or blood vessels at the licensed doses used for abortion.
- It can be stored at room temperature for many years.
- The oral tablets are effective when administered orally, vaginally, sublingually or rectally.
- It is inexpensive.
- The only side effects of note are diarrhoea and shivering, both of which are dose-dependent and self-limiting.

The use of misoprostol has been extensively studied in the field of reproductive health and it is widely recommended for treatment of missed and incomplete miscarriages, induction of abortion and cervical preparation before uterine instrumentation [51,82]. Misoprostol is also used in late pregnancy for induction of labor and prophylaxis and treatment of postpartum hemorrhage.

However, the manufacturer and holder of the patent for misoprostol, Searle (now incorporated into Pfizer), has never applied for licenses for any of the reproductive health indications, despite the abundant literature on its safe and effective use in that field. The reason is probably an effort to avoid potentially damaging discussions about the drug’s use for inducing abortion [83].

Despite the lack of an approved indication, misoprostol is specifically mentioned as the PG of choice in the marketing authorization for mifepristone in European countries except the United Kingdom and together with gemeprost in Sweden and Norway. The Food and Drug Administration (FDA) in the United States granted a license for mifepristone in 2000, and the recommended abortion regimen specifies misoprostol as the PG of choice [84]. This has resulted in the unique situation where misoprostol is approved in many countries as part of an abortion regimen but does not hold a registration for abortion in its own right. To reflect this, the FDA has recently changed the labelling of misoprostol so that it is no longer “contraindicated in pregnancy” but, rather, that it “should not be taken by pregnant women to reduce the risk of ulcers induced by nonsteroidal anti-inflammatory drugs” (NSAIDs) [85]. This move followed the change of the French registration of misoprostol, which now lists pregnancy as a contraindication except in the case of an induced abortion.

In the United Kingdom, the RCOG recommends misoprostol for the induction of abortion in association with mifepristone, as done in France by the relevant health authority Agence Nationale d’Accréditation et d’Évaluation en Santé (ANAES), and the British National Formulary has added a paragraph stating, “misoprostol is given by mouth or by vaginal administration to induce medical abortion (unlicensed indication)” [71,86,87].

In Sweden and Norway, it is specified in the summary of product characteristics (SmPC) for Mifegyne/Mifeprex that misoprostol 400 µg po should be given for termination of pregnancy of up to 49 days of amenorrhoea or gemeprost 1-mg pessary up to 63 days. Only in 2004 has the first presentation of misoprostol been specifically approved for medical abortion. So far, it is only available in France under the brand name of Gymiso.

3.2. Pharmacokinetics misoprostol

Summary: Misoprostol is rapidly absorbed after oral or sublingual intake and has a short half-life of 20–40 min. Plasma levels increase more slowly following vaginal or buccal administration. Sublingual, vaginal and buccal administration results in a longer-lasting elevation in plasma levels compared to oral misoprostol. The effect seems to be shorter-lasting for sublingual than vaginal misoprostol. The latter routes lead to regular uterine contractions in contrast to oral administration.

Misoprostol is rapidly and almost completely absorbed after oral administration. It is converted by the liver passage to its pharmacologically active metabolite, misoprostol free acid. Plasma concentrations of misoprostol acid peak in approximately 12 min and decline rapidly thereafter with a terminal half-life of 20–40 min. The bioavailability of misoprostol is decreased by concomitant ingestion of antacids or food, delaying plasma peak to 20 and 64 min, respectively. However, there is a high variability of plasma levels of misoprostol acid between and within studies (product information of Cytotec) [88,89].

Misoprostol is primarily metabolized in the liver, and less than 1% of its active metabolite is excreted in urine. Misoprostol has no known drug interactions and does not induce the hepatic cytochrome P-450 enzyme system.

This very short pharmacokinetic and, therefore, short clinical effectiveness has stimulated research into ways to prolong its activity. One way has been to evaluate different routes of application. Although misoprostol 200-µg tablets are approved for oral use only, vaginal, sublingual, buccal and rectal application have been shown to be possible and even clinically superior in some cases. Pharmacokinetic studies have shown that the peak concentration is highest after sublingual administration [90], whereas vaginal administration has the advantage of a prolonged time to peak concentration and a slower decrease, as compared to oral administration (Fig. 4) [89–93]. One problem with vaginal application, however, is the great individual variation of absorption. While the misoprostol from the tablets is mostly very well absorbed, the tablets do not fully dissolve in many cases. Remnants of the tablets can therefore be found in the vagina several hours after application. This might pose a risk for prosecution in countries where abortion is illegal [91].

![Fig. 4. Mean plasma concentrations of misoprostol acid over time with oral and vaginal administration](image-url) [modified from Obstet Gynecol 1997; 90:88–92].
Furthermore, most women prefer the oral route to vaginal application [94–96].

A few clinical studies have been published using repeated dose of misoprostol after 4–6 h. So far, there is no published study on plasma misoprostol levels beyond 6 h of administration or after repeated doses.

Another approach could be the use of an oral slow-release misoprostol. Previous studies had shown high rates of side effects due to the PG analogues used at that time [97,98]. Recently, a new misoprostol slow-release formula for oral use has been described [99].

Pharmacokinetics and uterine contractility have shown promising results [100,101]. So far, no clinical studies of this agent for medical abortion have been published.

### 3.3. Misoprostol alone

Summary: Misoprostol alone can induce an abortion, although it is associated with more side effects and a longer induction-to-abortion interval as when combined with mifepristone.

The effectiveness and safety of medical abortion using a combination of mifepristone and misoprostol have been well established. However, many women live in countries where they have no easy access to legal abortion [53,54]. Unfortunately, mifepristone is not available in these and other countries (Fig. 1, world map of availability of mifepristone). Very quickly, women and physicians in these countries have realized that misoprostol can be used alone to induce abortion. The use of misoprostol for this indication has been facilitated by the drug’s wide availability and low cost. The frequent use of misoprostol for the induction of abortion in some countries has been reported to contribute to an observed decrease in the complications from unsafe abortion [102]. The resulting increased demand for a misoprostol-alone regimen has prompted research to find the regimen with the highest efficacy and the lowest rate of side effects. Different doses, dosage intervals and route of administration have been evaluated (www.misoprostol.org) [103]. However, available data suggest that the effectiveness of misoprostol alone is lower than that seen with the sequential use of mifepristone and misoprostol, even when misoprostol is administered vaginally [103]. Furthermore, the procedure takes longer, requires higher doses of misoprostol and, thus, causes more side effects, such as painful uterine contractions, diarrhea and fever.

### 3.4. Doses and route of administration of misoprostol

Summary: The pharmacokinetics of the approved oral application with short-lasting elevation in plasma levels and weak effect on uterine contractility led to the evaluation of other off-label routes, which proved to have a longer-lasting and more pronounced effect on uterine contractility.

An oral dose of 400 μg of misoprostol, in combination with 600 mg mifepristone, is effective for termination of pregnancy of up to 49 days of gestation and is associated with an acceptable level of PG-related side effects. However, the success rate of this regimen declines with increasing gestational age and has unacceptable failure rates above 49 days [63,69,104]. The rate of complete abortion with this regimen was shown to be 92%, 83% and 77% for gestational age of less than 49, 50–56 and 57–63 days, respectively [105]. Another study found similar rates with 89%, 81% and 65%, respectively [74]. Therefore, studies were undertaken to determine if alternative regimens would improve the efficacy of the regimen for medical abortion of pregnancies longer than 49 days of gestation. Efficacy of 800-μg misoprostol given orally as a single or divided dose after mifepristone to women with pregnancy of up to 56 days of gestation resulted in a sufficiently high level of efficacy (95% and 92% for the single and divided dosage, respectively) [59]. However, side effects were common.

This led to the evaluation of vaginal, sublingual and buccal routes for administration of misoprostol, even though the misoprostol 200-μg tablets are intended and approved for oral use only. Studies on the route of administration and the dose of misoprostol are a major topic in recent and current research. This activity reflects the need for an improved regimen. A slow-release formulation may offer advantages over the currently available formulation of misoprostol.

#### 3.4.1. Vaginal application

Summary: Misoprostol given vaginally leads to longer-lasting elevations in plasma levels and to the development of regular uterine contractions as compared to oral application. This route of administration has shown clinical benefit and has become the standard of care for gestational age above 49 days of amenorrhea.

The vaginal route of administration of misoprostol has been shown to be more potent in medical abortion, compared to oral application. Treatment with 800-μg misoprostol orally resulted in a significantly higher rate of side effects, compared to the same dose applied vaginally and in more continuing pregnancies in pregnancies up to 63 days of gestation [106]. This has been confirmed in a large number of case series reports. The complete abortion rate in up to 63 days of gestation achieved by using mifepristone, followed by 800 μg of vaginal misoprostol administered 48 h later, was 95–98% [64–67,107].

Furthermore, three randomized comparative trials were carried out, which compared mifepristone followed by 800 μg misoprostol given orally or vaginally for termination of pregnancy of up to 63 days of gestation. They showed a complete abortion rate of only 87–90% in the oral group, compared to 95–97% in the vaginal group. Also, the number of continuing pregnancies was higher following oral treatment, while the incidence of side effects was significantly lower following vaginal treatment [69,108,109].

The increased efficacy associated with use of vaginally administered misoprostol is likely due to a threefold increase in the bioavailability of the drug as well as prolonged exposure of the myometrium when administered by the vaginal route [89,90].
When the absorption kinetics of oral and vaginal treatment was compared, it was shown that the plasma levels of misoprostol were directly correlated with the effect on uterine tonus. Following administration of misoprostol, the initial increase in uterine tonus was faster and more pronounced after oral administration. However, following vaginal administration, all patients developed uterine contractions that increased continuously during the 4-h observation period and still seemed to increase at the end of recording (Fig. 4). This was not the case after oral treatment [91].

The half-life for misoprostol is about 20–40 min and should be the same following oral or vaginal administration. Thus, the difference in effect on uterine contractility most likely represents a difference in the rate of absorption and metabolism. With vaginal administration, the first-pass liver metabolism can be avoided, and plasma levels remain elevated for a longer period. Prolonged stimulation of the myometrium will result in development of uterine contractions [91].

So far, there are no published RCTs that evaluate a reduced dose of vaginal misoprostol, but such studies are ongoing. When 200 mg of mifepristone was followed by either 0.5 mg of gemeprost or 800 µg of misoprostol administered vaginally, the efficacy was higher with misoprostol [64].

As mentioned previously, there is currently no formulation of misoprostol 200 µg available for vaginal use. The only type of misoprostol designed for vaginal use is a 25-µg pessary for induction of labor, which is on the market in Brazil and Egypt. The widely used 200-µg tablets are approved for oral use only and not intended for vaginal application. However, a physician is allowed to use a drug in a way not specified in the approval (off-label) if supported by available evidence (EC Pharmaceutical Directive 65/65/EEC) [71,82]. The EC Pharmaceutical Directive 65/65/EEC specifically permits physicians to use “licensed medicines for indications or in doses or by routes of administration outside the recommendations given in the license.”

### 3.4.2. Sublingual administration

**Summary:** Sublingual administration leads to regular uterine contractions, similar to the vaginal route, but the effect may be shorter lasting. However, the prevalence of PG-related side effects was higher with this route of administration. The data on buccal use of misoprostol in medical abortion are limited to one study up to 56 days.

A drawback of vaginal administration of misoprostol is the fact that the tablets are licensed for oral use only. In addition, most women prefer to take the tablets by mouth [94–96].

Recently, sublingual administration of misoprostol has been described, and the effect of sublingual misoprostol on uterine contractility has been investigated [110–112]. The authors found regular uterine contractions in all subjects following sublingual and vaginal administration but not after oral administration (Fig. 5). The increase in uterine activity measured in Montevideo units following sublingual and vaginal administration, after 2 h and thereafter, was significantly higher than that seen following oral administration. The development of contractility measured after sublingual administration was very similar to that seen after vaginal administration but decreased faster at 4 h.

One inconvenience of sublingual administration is the unpleasant taste, and some women prefer to swallow the pills [112]. The effect of sublingual misoprostol may also be shorter-lasting than that of vaginal misoprostol, but it could be an alternative when vaginal administration is not acceptable [113]. Several studies report an efficacy similar to the vaginal route (96–99% for gestations up to 63 days) and high acceptability [114].

However, women receiving misoprostol sublingually were more likely to experience diarrhea (p < .01), shivering (p < .01) and unpleasant taste in the mouth (p < .01).

### 3.4.3. Buccal administration

**Summary:** Recently, buccal administration has been suggested as a new route of administration, but only two studies on this route of administration have been published so far [115,116]. A pharmacokinetic study showed that peak concentration of misoprostol after buccal administration is less pronounced, as compared to sublingual administration [115]. Also, side effects were less pronounced. After these promising results, buccal administration in early medical abortion was evaluated. In another study, the buccal and vaginal routes were compared in gestations up to 56 days. Women received mifepristone 200 mg po and were randomized to use 800 µg of misoprostol either buccally or vaginally 1–2 days later. Among 429 patients, the efficacy rate was 95% and 93% in the buccal and the vaginal group (p = .51), respectively. Nausea was the most commonly reported side effect, affecting 70% in the buccal group and 62% in the vaginal group. There were no differences in the satisfaction with the overall procedure between the buccal (92%) and the vaginal groups (95%).

### 3.4.4. Repeated doses

**Summary:** So far, there is insufficient evidence to give an evidence-based recommendation on repeated oral misoprostol in early gestational age.

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Fig. 5. Uterine activity in Montevideo Units induced by misoprostol given at different routes of administration [modified from Obstet Gynecol 1999; 93:275–80, Ann N Y Acad Sci 1959;75:813–30, Hum Reprod 2004; 19:81–4].
Mifepristone followed by repeated doses of misoprostol for termination of early pregnancy was investigated in several studies to determine if dividing the dose would increase the efficacy of medical abortion or reduce the amount and duration of bleeding whilst minimizing the level of side effects. This approach has been successful in the second trimester [117,118].

Different misoprostol regimens have been evaluated, which have included various dosages (200, 400, 600 or 800 µg), intervals between doses (3, 4, 6–8 or 24 h) and the number of doses given [66,68,69,77,108,119–122]. A recent study showed that 1 week of misoprostol 400 µg bid po following mifepristone did not significantly improve efficacy or bleeding patterns, compared to the standard single dose but increased side effects [69,109].

Similarly, the overall efficacy of the procedure was not increased by a single small second dose of misoprostol (200 µg) approximately 3 h after the first dose. It did, however, shorten the interval to expulsion [104,120].

In another study with 903 women, a larger second dose of misoprostol (400 µg) was given orally to those women who had not expelled the gestational sac within 3 h after the first dose. In this study the results showed an increase in efficacy from 95.4% to 98.5% and a reduction of treatment failures (ongoing pregnancy) from 1.5% to 0.1%, as compared to the standard single dose of misoprostol [120,123].

Another study with more than 1000 patients found a significant increase in efficacy after a second dose of 800 µg misoprostol given vaginally to those women with a persistent gestational sac on sonogram on Days 4–8, as compared to the single dose [74]. The increase in efficacy was more pronounced in the group receiving misoprostol orally (92% vs. 95%) and less pronounced in the group receiving vaginal misoprostol (96% vs. 98%).

A large case series report with 4132 patients compared single-dose treatment of misoprostol following mifepristone in the first 2000 women with giving a second dose of 400-µg misoprostol 4 h after the first dose to the subsequent 2132 women; both doses were given vaginally. Adding a second dose did not change the overall success rate of 97.8% but led to a significantly lower rate of ongoing pregnancies of 0.2% vs. 0.6% [68].

There is, so far, too little data on repeated doses of misoprostol after mifepristone in early medical abortion to make an evidence-based recommendation. Despite this, some providers use repeated doses either routinely for all patients or in those cases when expulsion or bleeding has not occurred after a certain number of hours.

The failure to detect a difference in the available studies should not be interpreted as evidence that repeated misoprostol does not improve effectiveness. However, the success rate of medical abortion is already very high, and any further improvement by giving a second dose would be small. Consequently, the trial could have been underpowered to detect a significant difference.

3.5. Misoprostol taken in the clinic or at home

Summary: Home use of misoprostol has been shown to be safe in gestations up to 63 days of amenorrhea and is therefore increasingly offered. However, the approved regimen stipulates taking misoprostol at the provider’s facility in most countries.

When medical abortion was first introduced in the late 80s and early 90s, patients were monitored closely. Providers had no experience, and the patients did not know what to expect. Patients remained under medical supervision in the clinic during the first few hours following administration of the PG. Consequently, the patients are required to attend more visits at the clinic (usually 3 or 4) for a medical abortion with mifepristone followed by misoprostol than for a vacuum aspiration. This requirement is frequently met with little understanding from the patients who expect a “natural” and “spontaneous abortion-like” process.

Therefore, “home use of misoprostol” was studied in order to avoid the need for the second clinic visit [107,124]. These studies showed that home use is safe from a medical point of view and that patients can cope with the side effects of the treatment. Furthermore, it showed that a majority of patients prefer the privacy of their home environment in which to cope with the vaginal bleeding. These findings were later confirmed by several studies that included women undergoing termination of pregnancy of up to 63 days of gestation [66,67,125,126]. Home use of misoprostol has also been the standard of care with very good results in the French island of Guadeloupe since the early 90s [124]. When medical abortion was introduced in the United States in 2000, home use of misoprostol quickly became the standard of care [Mary Fjerstad, Planned Parenthood, Planned Parenthood of America (PPFA), personal communication].

In contrast, home use of misoprostol is still not offered to most women in Europe except for Sweden and Austria where it has been shown to be highly acceptable to women and their partners [127]. There are currently initiatives in France and the UK to offer home use of misoprostol [128,129].

4. Various aspects of medical abortion

4.1. Acceptance

Summary: It has been shown that a free choice of the available methods is highly important for the women. Up to 70% will choose medical abortion, provided they have the option.

Medical abortion is not a better method per se than vacuum aspiration. It is just another method with different characteristics [130]. Medical abortion has advantages and inconveniences. The choice of one or the other method depends not so much on medical criteria but, rather, on individual preference. An important factor determining choice of one or another of the methods is speed of access to treatment once the decision to have an abortion has been made [131].
There are some aspects that limit free choice and acceptance of medical abortion. For example, the number of visits required is still three in most clinics and sometimes four, depending on national regulations on abortion and obligatory waiting period (i.e., France, Germany). Also, women are asked to stay for several hours in the clinic following administration of the PG. Furthermore, some physicians are reluctant to start the treatment in very early pregnancy if they cannot detect fetal cardiac activity on ultrasound. Last, but not least, the reimbursement for medical abortion by the health insurance might be less than for surgical abortion, limiting free choice (i.e., Germany).

The uptake of medical abortion has been slow in most countries as a consequence of limited choice for the women [139]. It took about 10 years in France, Scotland and Sweden before 50% of all abortions in the first trimester were carried out using the medical method (Fig. 6). Studies also confirmed that around 50–70% of eligible women in early pregnancy will choose medical abortion if they have a truly free choice [94,132].

Positive examples of the introduction of medical abortion are given by Switzerland and Finland; in these countries, fast uptake reflects the flexible medical system, which offered women a free choice after a short introductory period. Training of health care providers has also been shown to be crucial for fast uptake. In order to give patients a free choice of medical or surgical abortion, doctors, midwives and nurses must feel comfortable with the methods and be well informed about all aspects of the treatment. Training of the health care providers is therefore essential when introducing medical abortion. Health care providers who are not actually engaged in performing medical abortion also need to be well informed in order to counsel and to refer their patients properly.

Why do women choose medical abortion when the surgical method works so well? The women themselves best answer this question. The following main reasons were given in different surveys [94,133,134]:

1. Avoiding surgery or general anaesthesia
2. Perceived to be safer
3. Perceived to be more natural
4. More privacy and autonomy
5. Less invasive

In most studies, between 80% and 95% of women who chose medical abortion found it acceptable and would choose the same method again if they need another abortion in the future. They would also recommend the method to other women who need an abortion [94,96,131,133,135]. This high rate of satisfaction was dependant on women being offered a truly free choice of method.

4.1.1. Long-term acceptability

Several studies evaluated the long-term acceptance and well-being of patients following medical abortion.

As regards psychological aspects, medical abortion was found to be as safe as surgical vacuum aspiration, mainly because abortion per se is associated with a high incidence of psychological benefit, whichever method is used [136]. Another study found that medical abortion is associated with the same low rate of short-term psychiatric morbidity as had previously been recorded following surgical methods [137].

Having a choice between the methods was considered very important and resulted in high levels of acceptability. No significant differences in general, reproductive or psychological health were found between women who had undergone medical abortion or vacuum aspiration 2 years previously [94,138,139].

4.2. Interval mifepristone–misoprostol

Summary: Mifepristone and the PG act in synergy. The optimal sensitization of the myometrium occurs after an interval of 36–48 h.

After it was discovered that mifepristone sensitizes the myometrium to PG analogues, research was initiated to determine the optimum time interval between administration of the two drugs. In the first study, an interval of 4 days was tried [14]. It was soon discovered that sensitization of the myometrium develops within 24 h. The sensitization further increases until 36–48 h after mifepristone, although this later increase was not statistically significant [16]. This finding led to the approved and widely recommended regimen with an interval of 36–48 h between mifepristone and misoprostol administration.

This finding was later confirmed by a study on the effect of mifepristone on cervical ripening, dilatation and softening. It was shown that the priming effect after 48 h is significantly more pronounced than after 24 h [140]. The study showed that women who received mifepristone 24 h before the operation had a significantly lower baseline cervical dilatation (7.5 mm vs. 8.3 mm; \( p = .05 \)) and required greater mechanical force to dilate the cervix (cumulative force to 9 mm: 37.7 vs. 23.4 N; \( p = .03 \)) than did women who received mifepristone 48 h before the operation.

Similarly, the mean interval from induction to expulsion in second trimester abortion was significantly shorter when PG was initiated 48 h (6:20 h) after mifepristone as compared to 24 h (7:25 h) [141].

Fig. 6. Percentage of medical abortions among first trimester abortions (Source: national statistics).
However, waiting for 2 days may be inconvenient for the women concerned as well as for the institution providing the treatment. Therefore, shorter intervals of 24 h and 6–8 h have been studied [67,108,142,143].

Efficacy has been high in all these studies, depending on the dose, route of administration and potency of the PG analogue used. Studies with either gemeprost 1 mg or 800 μg misoprostol given vaginally had a high (≥95%) success rate. The success rate was in the range of 90% when 400 μg of misoprostol was given orally.

A few pilot studies went even further by giving both drugs on the same day [122,144–147]. However, this led to a significant decrease in efficacy, which was confirmed by a small RCT showing an efficacy of only 50% after a first dose of 400 μg of misoprostol given orally the same day as mifepristone [148]. A high percentage of women needed a second dose of misoprostol for incomplete abortion in these studies, as compared to studies with a 2-day interval.

4.3. Evaluation of outcome of medical abortion

Summary: Training is required to correctly interpret an ultrasound picture or human chorionic gonadotropin (hCG) level at follow-up. Experienced centers can reduce the frequency of backup curettage for “incomplete abortion.” The most widely used definition of a successful medical abortion is the avoidance of a surgical intervention [5]. Treatment will result in complete abortion in the vast majority of patients (≥95%) [149]. However, a small percentage will experience incomplete abortion, missed abortion or continuing pregnancy.

The following methods are used for evaluating the outcome of treatment at follow-up:

- Visual verification of expulsion following intake of misoprostol
- History of clinical events (heavy or continuous bleeding and pain)
- Gynecological examination
- hCG in serum measured quantitatively
- hCG in urine, using a rapid test with a high cut-off value
- Ultrasound examination

One or several of the abovementioned criteria are used at the follow-up visit [150–155].

The large individual variation in the time to expulsion is a disadvantage of using verification of expulsion during the observation period after PG administration (Fig. 7).

The gestational age at the beginning of treatment has to be taken into consideration when discussing the diagnostic method used at follow-up. This is because an intrauterine pregnancy becomes difficult or even impossible to diagnose prior to 5 weeks gestation.

So far, no standard has been described for the evaluation of successful treatment and various methods are used in clinical practice [149]. Of particular note is that there are no accepted guidelines for interpretation of ultrasound findings at follow-up. This is an important aspect as some patients present with a thick endometrium even after successful expulsion and may be subjected to unnecessary curettage [156].

Several studies have used serial measurement of hCG to evaluate outcome at follow-up. However, there are large variations in the hCG value at the beginning of the treatment. This makes it difficult to interpret the value at follow-up without knowledge of the initial value [150]. A long duration may be necessary to make sure most patients with successful abortion have a serum hCG below a threshold. Using a urinary test with a cutoff at 1000 mIU/mL at 2 weeks following first-trimester surgical abortion has been...
described (i.e., Duo test, Veda Lab, France) [151]. A urinary test with a cutoff value of 500 mIU/mL is used at the Karolinska University Hospital to verify expulsion at 3 weeks after medical abortion [157].

Most authors have therefore reported the result at follow-up as percentage of the initial value. One study used a cutoff level at follow-up for successful abortion as 30% of the initial value; in another study, a cutoff value of 40% of the initial level was recommended [158,159]. A much faster decline has been described: 60–70.5% 24 h following misoprostol administration and 99.4% on Day 14 [153,154].

The need for further evaluation had been clearly expressed, but even the current clinical guidelines do not mention a method for verifying expulsion, nor do they give criteria for the interpretation of the findings [70,71,86,151].

The follow-up visit takes place 1–3 weeks following the treatment, depending on the provider. The time interval between treatment and follow-up has an impact on the findings at ultrasound, hCG levels and gynecological examination. The need for another follow-up visit will also be influenced by the time interval. The delay until follow up may also change acceptability of the method. No study has been published so far evaluating these aspects. It could be assumed that women would prefer to know the final diagnosis after a shorter rather than longer interval and prefer fewer follow-up visits.

4.4. Safety

Summary: Medical abortion with mifepristone and a suitable PG analogue is a very safe abortion method.

Prior to approval of mifepristone, Roussel-Uclaf conducted a comprehensive toxicology program, demonstrating its safety. One and 6 months of treatments in rats and monkeys revealed no true toxicity [33].

The safety for single use in humans was confirmed by a large study of 16,173 cases of medical abortion [17]. Safety in long-term use has been established in several studies for other indications including myoma, endometriosis, breast cancer or meningioma [160–164].

4.5. Teratogenicity

Summary: There are insufficient data to evaluate the teratogenetic potential of medical abortion. Available evidence suggests some risk.

In general terms, it is difficult to evaluate the teratogenetic risk of a substance that is highly abortifacient. However, studies in rodents using subabortive doses of mifepristone showed no anomaly. Also, no teratogenetic effects were found in studies with rabbits that received mifepristone combined with progesterone to counteract the abortifacient effect [33].

Another important source of information are records from women who carried their pregnancy to term after a failed medical abortion (Exelgyn, Paris, 2005). A total of 161 cases of continuing pregnancy following failed medical abortion have been reported out of an estimated 1.5 million procedures performed between 1987 and 2005 in countries where Exelgyn holds marketing authorization. In 58 of these cases, mifepristone was used alone as the women refused to proceed with the treatment. The remaining women took one of the available PGs: misoprostol (65), sulprostone (4), gemeprost (13) or unspecified (21) (Exelgyn 2005) [165]. However, these reports are voluntary and done at the initiative of the treating physician. There is no way to reliably calculate the total number of deliveries after failed medical abortion.

In total, 14 cases of malformations were reported out of the reported 161 known deliveries.

The teratogenetic risk of misoprostol has been evaluated recently by analyzing animal model evidence, cases reported by the drug manufacturer and the scientific literature [166]. Several studies on this aspect come from Brazil. There, authors found an association between birth defects and in utero exposure to misoprostol, which could be explained by uterine contraction and bleeding induced by misoprostol. Many of the cases with central nervous system anomalies were noted to have some or all of the features of Möbius syndrome. Möbius syndrome is a rare condition characterized by the loss of function of the motor cranial nerves and is said to be associated with fetal misoprostol exposure.

4.6. Infection after medical abortion

Summary: Very few infections following medical abortion have been reported so far. However, a small number of fatal septic shock following infection with a rare bacteria have been reported from North America since the method was introduced there in 2000. So far, no final conclusion has been reached as to the casual link with details of the treatment.

The frequency of infection following aspiration in the first trimester is reported to be as high as 10% but depends strongly on the regional prevalence of sexually transmitted diseases and gestational age at the time of intervention [71]. However, most studies on this topic are from the 1980s. Recently, registered side effects of 56,000 abortions performed between 1980 and 1994 in Denmark were analyzed. Bleeding, infections or reevacuation were recorded in 5% of all cases and did not change over time [167]. In the United Kingdom, prophylactic antibiotic treatment is recommended in order to reduce the frequency of infections [71]. However, this approach to the prevention of infections depends not only on the prevalence but varies also by country. For instance, routine antibiotic prophylactic treatment is given in the United Kingdom, whereas in Scandinavian countries and in China, it is given only on a case-by-case basis with obvious advantages but larger short-term costs.

The literature on infection following medical abortion has recently been reviewed and the overall rate was estimated to be 0.92% [168]. An unexpected finding was the high rate of possible infection in the studies from the United Kingdom (10 times higher as compared to studies from other countries). It was suggested that a difference in diagnostic criteria might be the underlying reason, as the
United Kingdom also reported suspected infection. Excluding the data from United Kingdom, the overall infection rate fell to 0.28%. Also, no difference was found between different regimens and routes of administration of the PG.

Recently, a total of five fatal cases of septicaemia during medical abortion have been reported from North America out of an estimated 450,000 cases of medical abortion carried out since approval in 2000 [169–171]. In all four cases, as well as in a fifth death in Canada in 2002, a septicaemia with the bacteria Clostridium sordellii was the cause of death [171]. No explanation for these fatal events has been found. So far, no causation between septic shock and mifepristone and misoprostol has been shown. Death with the same bacteria have been reported following spontaneous abortion as well as postpartum [172]. Clostridium sordellii is sensitive to common antibiotics such as metronidazole. No such case has been reported from Europe with an estimated number of patients treated with medical abortion of more than 1.5 million for more than 15 years.

Recently, another two death cases were reported in association with medical abortion [173]. However, one of these cases has later been confirmed to be unrelated to medical abortion and the one case is still under investigation at the time of submission of this paper [FDA, Mifeprrox (mifepristone) Information April 10, 2006 Update. http://www.fda.gov/cder/drug/infopage/mifepristone].

4.7. Pain treatment in medical abortion

Summary: Avoiding or sufficiently treating pain is of very high importance for the patients. Usual strategies should be applied including prophylactic treatment.

Abdominal pain is one of the most common adverse effects of medical abortion [105,109]. Women are much more likely to experience pain during medical abortion than with surgical abortion under general anaesthesia [131]. The pain is most pronounced following the administration of the PG (misoprostol or gemeprost). Consequently, pain remains a decisive factor influencing women’s choice of method.

Despite the fact that pain experienced during medical abortion causes significant distress, it has been uncommonly studied. There are no studies that directly compare different analgesic regimens or prophylactic medication for pain relief at the time of medical abortion with mifepristone and misoprostol. However, a placebo-controlled, randomized trial evaluated the relative efficacies of ibuprofen or acetaminophen with codeine as prophylaxis in the context of early medical abortion with MTX and misoprostol [174]. The agents were taken as prophylaxis at the time of misoprostol administration, prior to the onset of pain. Severe pain scores were reported by almost a quarter of women, and there were no significant differences in pain scores between treatment groups (placebo, ibuprofen or acetaminophen with codeine). Those women who were given acetaminophen with codeine as prophylaxis reported taking fewer of the same medication in the days following PG administration.

In another nonconcurrent cohort study in early medical abortion, the use of opiate analgesia was shown to be lower when prophylactic acetaminophen was given compared to a control group without prophylactic treatment [175].

4.7.1. NSAID in medical abortion

Summary: The product information contains a recommendation against the use of NSAIDs. However, this is not based on evidence, and several studies suggest that NSAIDs should be an integral part of pain treatment.

Management of pain during medical abortion has been hampered by recommendations that NSAIDs should not be given to women, at least until the follow-up visit 8–12 days after mifepristone administration. Currently, the United Kingdom data sheet advises, “as they could affect the efficacy of the treatment NSAIDs, including aspirin, should be avoided until pregnancy termination is complete. For termination of pregnancy of up to 63 days of gestation, NSAIDs should not be given at least until the follow-up visit 8–12 days after mifepristone administration.” This recommendation is based on “theoretical” considerations.

So to be precise, NSAIDs are effective inhibitors of PG biosynthesis. NSAIDs can significantly prolong the induction-to-abortion interval for abortion methods depending on increased endogenous PG production, such as intrauterine instillation of hypertonic saline or Rivanol [176]. Furthermore, dysmenorrhea, believed to be caused by increased levels of PG, can be treated effectively by NSAIDs [177,178].

So far, there is no evidence that concurrent use of NSAIDs results in a reduction of efficacy of medical abortion. NSAIDs inhibit endogenous PG synthesis and should not influence the effect of exogenous PGs on uterine contractility.

A study has shown that indomethacin given together with mifepristone led to a marked reduction in the ability of the decidual to generate PGE2, but had no negative impact on uterine activity [39]. NSAIDs given together with exogenous PG do not appear to influence the effect of PG with regard to uterine contractility or cervical ripening [39,179,180]. NSAIDs also do not affect the efficacy of medical abortion using either MTX or mifepristone followed by misoprostol [181,182].

4.8. Contraindications

Summary: Mifepristone and misoprostol are both very safe drugs and have only a few contraindications.

The combination treatment of mifepristone and misoprostol has relatively few contraindications and is well tolerated when used according to the recommendations (SmPC) [50]. The contraindications are the following:

- Allergic reactions to one of the drugs
- Chronic adrenal failure
- Severe asthma not controlled by therapy
- Coagulation disorder
- Suspected extra uterine pregnancy
- Porphyria
- Pregnancy beyond the approved gestational limit
Precautions:

- Long-term systemic corticosteroid therapy
- Renal failure, liver failure and malnutrition (in the absence of specific studies, the treatment should be avoided in these cases)
- As a precaution, breastfeeding women should not be treated or discharge the breast milk for 2–3 days
- An intrauterine device in place should be removed before uterine contractions are initiated

Also, the contraindications of the PG analogue used have to be observed, even when the risk of cardiovascular incidences has greatly been reduced with the use of E1 analogues.

4.9. Postabortion bleeding

Summary: Uterine bleeding is an inherent aspect of abortion, and the amount is correlated with gestational age. Provisions have to be made for a small percentage of women experiencing very heavy bleeding with the need for emergency curettage.

Women undergoing medical abortion observe the blood loss and also perceive it to be heavier than women undergoing surgical abortion with vacuum aspiration [131]. Two studies compared the blood loss with surgical abortion and found significantly more bleeding in medical abortion but no significant change in hemoglobin levels [183,184]. Also, clinical measures showed no significant difference in blood loss between surgical and medical abortion in another large study [185].

Starting oral contraceptive pills immediately after medical abortion had no impact on the total amount of blood loss nor on the efficacy of medical abortion in several studies [186–188].

4.10. Gestational age limits

Summary: Medical abortion is effective throughout pregnancy. However, the dosage of the PG needs to be adapted according to the gestational age.

Mifepristone is effective as long as it can antagonize progesterone [189]. By definition, it is therefore effective during the entire pregnancy.

The first study published with use of mifepristone alone consisted of 11 patients with a pregnancy of up to 8 weeks gestation [6]. The failure rate of 2/11 was attributed by the authors to the high concentration of progesterone in the more advanced pregnancies. Similarly, a later study with mifepristone alone confirmed a negative correlation between high levels of hCG and efficacy [11]. The following studies were then done in gestations below 7 weeks [7,190]. Another study was published using mifepristone alone and included more advanced pregnancies up to 10 weeks of gestation [191]. The findings confirmed the drop in efficacy in pregnancies above 7 weeks of gestation: 80% complete abortion in pregnancies below 7 weeks vs. 33% above 7 weeks of gestation.

The gestational limit of 7 weeks was utilized in the following studies even when a PG analogue was added [14]. This regimen received marketing authorization in France in 1988 [5]. The gestational age limit was confirmed when studies showed a reduction in effectiveness of mifepristone in association with sulprostone or oral misoprostol with increasing gestational age. Also, psychological factors were considered, specifically the stress for the patients of seeing a fetus in case of an advanced pregnancy (a fetus is not visible before 6 1/2 weeks gestation). The psychological aspect has been confirmed by another study that found seeing the fetus was associated with more intrusive events (nightmares, flashbacks, unwanted thoughts related to the experience) [139].

Preliminary studies were also undertaken in the United Kingdom. Drawing on the benefit of the experience in France, the United Kingdom studies increased the limits of experience and investigated the use of mifepristone and gemeprost for termination of pregnancy of up to 56 and then 63 days of gestation [18,192,193]. These studies led to the approval of mifepristone in combination with gemeprost in the United Kingdom for use for termination of pregnancy up to 63 days of gestation in 1991. Using gemeprost did not lead to a loss in efficacy with increasing gestational age.

In the following year, mifepristone in association with gemeprost was also approved in Sweden for termination of pregnancy of up to 63 days of gestation. Sweden had previously participated in the WHO studies and had played a crucial role in the development of the method. Therefore, the 63-day gestational age limit of these studies had been the basis of the approval in Sweden.

As soon as the efficacy of medical abortion was established for termination of early pregnancy, studies were undertaken at later gestations [194–196]. These studies showed that mifepristone followed by repeated doses of PG is also highly effective. Based on these findings, mifepristone was approved for termination of pregnancy beyond the first trimester in France and Sweden in 1992 and in the United Kingdom in 1995.

Medical abortion with mifepristone and PG after the first trimester is now recommended in several guidelines and has become the standard of care [70,71].

Interestingly, the interval between 9 and 12 weeks of gestation has only recently been studied with encouraging results, provided that the PG is given repeatedly [197,198]. However, use of mifepristone and PG for termination of pregnancy between 9 and 12 of weeks gestation is not a registered indication in any country, even though it is recommended in the abovementioned guidelines.

Medical abortion is also highly effective in late gestation and has even become standard of care in some countries [70,71,157,199,200].

4.11. Rhesus factor

Summary: Insufficient evidence exists so far to judge the need for giving Rhesus (Rh) immunoglobulins to Rh-negative women.
The introduction of Rh immune globulin for prevention of Rh-immunization was a milestone in obstetrics. It is therefore not surprising that Rh-immunoprophylaxis was applied to all pregnancies, regardless of gestational age.

However, gestational age at termination of pregnancy has been declining over the last decades due to advances in abortion technology. The introduction of medical abortion has given women the option of having an abortion at an even earlier gestational age. In a number of cases, no fetal pole is visible on ultrasound, and the question arises: at which gestational age does the risk for Rh-immunization begin? Only few studies have specifically investigated gestations below 12 weeks, and these did not give a precise answer [201]. There is no study on Rh immunization following medical abortion.

A few review articles have been published; however, the conclusions differ [202–204]. Further studies are needed to clarify the necessity for Rh-prophylaxis for abortion procedures, especially for medical abortion, in very early gestations.

5. Outlook

It seems important to continue the search to find further improvements to the method. Possible future research activities could include the following:

- Reduction in bleeding
- Improving pain treatment
- Evaluating the need for Rh prophylaxis in a clinical study
- Allowing women themselves to verify successful abortion using a urinary hCG test
- Dose-finding studies with slow-release misoprostol and development of a regimen for medical abortion.

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