

REVIEW

Medical termination of pregnancy in the early first trimester

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Abstract

Surgical abortion using vacuum aspiration or dilatation and curettage has been the method of choice for termination of pregnancy up to 63 days' gestation since the 1960s. Over the last three decades many studies have explored the use of medical methods for inducing abortion at these gestations. Earlier regimens assessed the systemic and intrauterine injection of prostaglandins. This was followed in the 1980s by the introduction of the anti-progesterone, mifepristone. Since its introduction, the uptake of medical abortion has been steadily increasing in countries where it has been available for routine use. Most current clinical protocols require the use of prostaglandins in combination with anti-progesterones or anti-metabolites. The safety, efficacy and acceptability of the medical regimen are now well established at all gestations of pregnancy. Provision of medical abortion increases the choice available to women, in particular those wishing to avoid surgery.

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Key message points

- The safety, efficacy and good patient acceptability of medical abortion up to 63 days' gestation is now well established.
- The provision of medical abortion offers additional choice to women, in particular those wishing to avoid surgery.
- Follow-up provides the opportunity to confirm successful abortion and identify possible complications. This is particularly essential for women who do not expel recognisable products of conception, to exclude risk of failed treatment and continuing pregnancy.

Introduction

It is estimated that approximately 26 million legal and 20 million illegal abortions are performed annually worldwide, resulting in an abortion rate of 35 per 1000 women aged 15-44 years.¹

Surgical abortion by vacuum aspiration or dilatation and curettage has been the method of choice since the 1960s.² However, since the introduction of mifepristone in the 1980s, the uptake of the medical regimen has been steadily increasing in countries where it has been available for routine use, and this has probably been one of the most significant developments in fertility control in recent years. This review explores both the historical aspects and the practical application of the medical regimen in the context of early medical abortion.

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Historical background

Over three decades ago, it was shown that the systemic or intrauterine injection of prostaglandins would induce abortion in over 90% of women in early pregnancy.^{3,4} In 1980, the scientists at Roussel-Uclaf (Romainville, France) discovered a C19 derivative of norethisterone with a modification at the 11-beta position. This was found to have high affinity for the progesterone receptor. The company's code for this drug was RU38486 (later shortened to RU486) and the generic name, mifepristone. This discovery began a new era in fertility control and has shaped much of our current practice. In 1982, the potential abortifacient effect of mifepristone was demonstrated and the compound was reported to interrupt the menstrual cycle and early pregnancy.⁵ This provoked a wave of publicity and protest from anti-abortion organisations, which has continued to this day. In 1988, France was the first country to license the use of mifepristone in combination with a prostaglandin analogue for termination of pregnancy up to 49 days' gestation. The regimen was licensed in China in the same year and, in 1991, mifepristone was approved by the United Kingdom Licensing Authority for use in Great Britain up to 63 days' gestation. In 1992, mifepristone was approved for use in Sweden, and was eventually approved by the United States Food and Drug Administration for use as an abortifacient in September 2000.⁶

Methods used for medical abortion

The three main categories of medical abortion are described in the following paragraphs.

Uterotonic compounds (prostaglandins)

Prostaglandins are naturally occurring fatty acids that are produced by many tissues in the body. Prostaglandins cause uterine contractions and result in softening and dilatation of the cervix.^{7,8} PGF₂α and PGE₂ were first investigated for medical abortion in the 1970s.⁹ Both cause powerful contractions of the smooth muscle in the myometrium at all stages of pregnancy. This contrasts with the relative uterine insensitivity to oxytocin in early pregnancy.^{7,10} Prostaglandins, however, also cause contractions in other areas of smooth muscle in the body (e.g. the intestinal wall) and hence may be associated with a high incidence of gastrointestinal side effects. The natural prostaglandins were gradually replaced with the prostaglandin analogues (gemeprost and misoprostol), which are more stable, relatively resistant to metabolism and, therefore, result in more prolonged action.⁶ The initial prostaglandin analogue used in France was sulprostone, a prostaglandin of the PGE₂ series, given by intramuscular injection.⁵ However, because of concerns about cardiovascular complications and reports of myocardial infarction, sulprostone was withdrawn from the market and is no longer in use.¹¹ Subsequently, the PGE₁ analogues (gemeprost and misoprostol) have been used for medical abortion.

Although abortion can be induced with prostaglandins alone, the dose required results in a high incidence of side effects making prostaglandins unsuitable for use as sole agents to induce abortion. Consequently, most current clinical protocols use prostaglandins in lower doses in combination with anti-progesterones or anti-metabolites.

Anti-progesterones (mifepristone)

Progesterone antagonists are synthetic steroids that bind to the progesterone receptor and prevent endogenous progesterone from exerting its effect.¹²⁻¹⁶ Mifepristone binds to the progesterone receptor with an affinity five times greater than that of progesterone,⁷ thus denying endogenous progesterone access to the receptor. Mifepristone has some agonist as well as antagonist properties and is also a potent antagonist of cortisol by binding to the glucocorticoid receptor.

The mechanism by which mifepristone seems to act involves an effect on the decidua, myometrium and a ripening effect on the cervix.^{5,7,13,16} It also prevents progesterone's decidualisation effect on the endometrium. It has been reported that mifepristone results in an increase in uterine contractility 24-36 h after its administration, and a five-fold increase in the sensitivity to exogenous prostaglandins when administered in the first trimester of pregnancy.^{7,10,16}

Mifepristone was initially used as a single agent for abortion. However, the effectiveness was reported to be 60-80% and the failure rates increased as gestation increased.^{5,17} Subsequently, a more effective application was found in combination with prostaglandins, and this forms the mainstay of most current regimens used in clinical practice.^{18,19}

Anti-metabolites (methotrexate)

Methotrexate inhibits dihydrofolate reductase, the enzyme necessary for purine and pyrimidine synthesis. Its effect on pregnancy appears to be predominantly on the rapidly dividing cytotrophoblast.^{20,21} Methotrexate has been shown to be effective for the treatment of gestational trophoblastic disease.²²⁻²⁵ However, since 1993, there has been a renewed interest, particularly in the USA, in the use of methotrexate for medical abortion.^{6,21} Studies have reported the successful use of methotrexate in combination with the prostaglandin analogue, misoprostol.²⁶⁻²⁸ Creinin *et al.*²⁹ reported a randomised trial comparing the administration of misoprostol (800 µg vaginally) 3 and 7 days after intramuscular methotrexate administration. The study showed that the regimen was more effective when misoprostol was given 7 days (complete abortion 98%) rather than 3 days (complete abortion 83%) after methotrexate ($p = 0.03$) and concluded that the protocol would be an effective alternative to surgery or to medical abortion using mifepristone in combination with prostaglandin analogues. The efficacy of the regimen has been reported to be higher when used up to 49 days' gestation and decreased when used at higher gestations.²¹

Methotrexate is potentially teratogenic and there have been several reports of limb reduction defects in fetuses following its use.³⁰ The toxicity of methotrexate is dose dependent and can affect rapidly dividing cells in the body including the lining of the gastrointestinal tract, bone marrow and pulmonary interstitium.²¹ This is more likely to occur at doses higher than those used for medical abortion. Nonetheless, serious complications have been reported with low-dose methotrexate.^{21,31,32} A further drawback of the regimen is that the induction to abortion interval can be several days or weeks.³⁰ The use of methotrexate in this context has been relatively restricted to places where mifepristone is either unavailable or unaffordable.²

Mifepristone in combination with prostaglandin analogues remains the standard regimen used for early medical abortion and will be the focus for the remainder of this review.

Type of prostaglandin

The most commonly used prostaglandins are the PGE1 analogues, gemeprost and misoprostol.² The conventional prostaglandin analogue used for medical abortion is gemeprost. A 1 mg pessary costs approximately £20 and is unstable at room temperature. Studies have demonstrated that the PGE1 analogue, misoprostol, is an effective alternative to gemeprost.³³ Misoprostol is cheap (£1 per dose) and, unlike gemeprost, does not require specific storage conditions.

Baird *et al.*³⁴ reported a randomised trial that compared misoprostol 600 µg given orally to gemeprost 0.5 mg administered vaginally, both after receiving mifepristone 200 mg orally. The study showed similar efficacy for the two regimens although the continuing pregnancy rates were higher in the misoprostol group and, in particular, for women between 49 and 63 days' gestation. The same group subsequently reported a trial that compared misoprostol 800 µg given vaginally to gemeprost 0.5 mg administered vaginally after mifepristone 200 mg orally.³³ This study showed that the complete abortion rate was higher with misoprostol and the continuing pregnancy rates lower compared to gemeprost. Both differences were statistically significant. The incidence of side effects was similar for women in the two groups. The former study adopted a lower dose of misoprostol (600 µg) and used the oral route of administration, which might explain the lower efficacy noted with misoprostol for that group.

Dose

The Cochrane Database reviewed seven randomised trials comparing mifepristone in doses of 200 to 600 mg.² Of these, four trials were included in a meta-analysis. The review showed similar efficacy for the two regimens and concluded that the dose of mifepristone can be lowered to 200 mg without significantly decreasing efficacy. A multicentre trial conducted by the World Health Organization assessed the effect of further reducing the dose of mifepristone.³⁵ This study showed that women receiving 50 mg mifepristone were 1.6 times more likely to experience failed treatment compared to those receiving 200 mg. A further study assessed the efficacy of a dose of 100 mg mifepristone and suggested that this may be an adequate dose.³⁶ Nonetheless, this was a single-centre, small study and further research is required to evaluate this dose before it can be recommended for use in routine practice.

Studies have reported that the dose of gemeprost could be reduced from 1 to 0.5 mg without a significant reduction in efficacy, while reducing the incidence of prostaglandin-related side effects.^{33,37}

Misoprostol has been used in doses of 400-800 µg in combination with mifepristone. In France, where the use of mifepristone was described first, the standard regimen involves the use of mifepristone 600 mg followed by misoprostol 400 µg orally in a single dose.^{38,39} Two large French trials assessed the regimen and reported success rates of 95-97% at 49 days' gestation.^{38,39} The second French study³⁹ included women up to 63 days' gestation. The standard regimen was followed by an additional dose of misoprostol 200 µg for women who did not abort within 3 h of the initial dose. The authors concluded that the use of a second dose of misoprostol did not improve efficacy in comparison with historical data from regimens that used only a single dose of misoprostol. Spitz *et al.*⁴⁰ reported that the efficacy of the medical regimen decreased as gestation increased for women up to 63 days' gestation. However, the regimen used included mifepristone 600 mg followed by a single dose of misoprostol 400 µg given orally. Ashok *et al.*⁴¹ reported a review of 2000 women undergoing medical abortion up to 63 days' gestation using mifepristone 200 mg

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followed by a single dose of misoprostol 800 µg given vaginally: the complete abortion rate was 97.5%. However, it was noted that efficacy significantly decreased at gestations ≥49 days. Following the review, the regimen was modified to offer a second dose of misoprostol 400 µg to women who had not aborted within 4 h of the initial dose.⁴² There was no difference in the complete abortion rate with the modified regimen (79.9%). A significant finding, however, was that with the modified two-dose regimen, gestation ceased to have an effect on the overall efficacy and there was a significant reduction in the continuing pregnancy rates. This, nonetheless, was not a randomised study and these findings would need further evaluation, preferably in the context of a randomised trial.

Route of misoprostol administration

The earlier medical abortion protocols used misoprostol in doses of 400 µg administered orally.^{38,39} El-Refaey *et al.*⁴³ reported a randomised trial that compared vaginal to oral administration of misoprostol 800 µg following mifepristone 600 mg in the context of medical abortion up to 63 days' gestation and showed superior efficacy and lower side effects with the vaginal route of administration. Zieman *et al.*⁴⁴ reported on the absorption kinetics of misoprostol with oral and vaginal administration. The study showed that the systemic bioavailability of vaginally administered misoprostol was three times higher than that with the oral route of administration. Peak plasma levels were slightly lower but were achieved more slowly and sustained for up to 4 h. This may explain the higher efficacy and lower side effects noted with vaginal administration compared to the oral route of administration of misoprostol.

It has been suggested that women prefer the oral route of administration and value having additional choice.⁴⁵⁻⁴⁷ Studies have since evaluated the feasibility of the sublingual route of misoprostol administration in the context of medical abortion in doses of 600-800 µg.⁴⁸⁻⁵² The sublingual route was reported to be an effective alternative to the vaginal route of administration with good patient acceptability. The prevalence of prostaglandin-related side effects, however, was higher. The sublingual route offers additional choice to women, while avoiding the inconvenience of vaginal administration and the first-pass liver effect associated with oral administration. Tang *et al.*⁵³ compared the pharmacokinetics of the sublingual, oral and vaginal routes of misoprostol administration. Sublingual administration achieved the highest peak serum concentrations, while the time to peak concentration was higher for the sublingual and oral routes compared to the vaginal route. The area under the curve was significantly higher with the sublingual route compared to the oral and vaginal routes of administration. This may explain the higher prevalence of side effects noted with sublingual administration. Further research is needed to assess the optimal dose of misoprostol in the context of medical abortion using the sublingual route of administration.

Side effects and complications of medical abortion

Side effects of the medical regimen include the prostaglandin-related side effects of nausea, vomiting, diarrhoea, abdominal pain, shivering and fever.^{2,9} These side effects are dose-dependent and are more profound with the oral and sublingual routes compared to the vaginal route of administration.^{43,48,49,51,52} Excessive bleeding at the time of abortion is rare; however, there is more observed blood loss with medical abortion when compared to surgical abortion.² Blood transfusion has been reported to be required in 0.1-0.2% of women undergoing medical abortion up to 63 days' gestation.^{40,42,54}

Post-abortion genital tract infection of varying degrees of severity, including pelvic inflammatory disease, is estimated to occur in up to 10% of cases.⁵⁵ The risk is reduced when prophylactic antibiotics are given or when lower genital tract infection has been excluded by bacteriological screening.

Medical regimens carry a small risk of failure to terminate the pregnancy, thus necessitating surgical intervention. In a series of 4132 cases undergoing medical abortion using mifepristone in combination with misoprostol the surgical evacuation rate was 2.3%.⁴² Indications for surgery included: continuing pregnancy (0.3%), missed abortion (0.3%) and incomplete abortion (1.6%). A further series of 3161 women undergoing medical abortion using mifepristone and gemeprost reported a surgical evacuation rate of 3.6%.⁵⁴ Of these, 1.4% had continuing pregnancy while 2.2% had incomplete abortion.

Both anti-progesterones and prostaglandins have contraindications to their use including: allergy to mifepristone or prostaglandins, adrenal insufficiency, severe asthma, porphyria, breastfeeding, history of cardiovascular disease and women over the age of 35 years who are heavy smokers.⁵⁶

The safety of misoprostol has been documented in doses up to 1600 µg per day.⁵⁷ Misoprostol is, however, potentially teratogenic and there have been reports of congenital anomalies associated with its use in the first trimester of pregnancy, and where the pregnancy subsequently continues. These are usually related to vascular disruption possibly related to uterine contractions and include limb defects, skull defects, facial malformations and cranial nerve palsies.^{9,58} Despite the extensive evidence supporting misoprostol's use in this context and its wide uptake, this remains an off-licence application for the product. Women should, therefore, be carefully counselled about this and the potential complications related to its use.

Most women report a sense of relief following abortion while many report complex emotional feelings in the 2-3 weeks immediately afterwards, which subsequently settle. However, it should be noted that there is an increased risk of psychological morbidity following abortion overall, and it has been reported that about 1% of women will have a psychiatric admission in the 4 years after abortion.⁵⁹⁻⁶⁴

Acceptability

The provision of medical abortion offers additional choice to women. Reasons given by women in favour of the regimen include: autonomy, more privacy, less invasiveness and greater 'naturalness' than surgery.⁶⁵ Frequently mentioned drawbacks include: abdominal pain, duration of bleeding, number of visits and the time waiting to know if the treatment has been successful.⁶⁵ The percentage of women choosing medical abortion is progressively increasing in countries where it has been in routine use and is about 56% in France, 59% in Scotland, 51% in Sweden, although only 14% in England and Wales.⁶⁶⁻⁶⁸

In a review on the acceptability of medical abortion in early pregnancy, Winikoff⁶⁵ reported that in most trials which offered women a choice between medical and surgical methods, 60-70% of women chose medical methods. There has also been high reported acceptability among women who have undergone medical abortion, with 88-97% of participants expressing satisfaction.⁶⁹ This assessment was, however, conducted on a self-selected population that had chosen this method for abortion and this needs to be taken into consideration when interpreting the findings.

Analgesia requirements

Abdominal pain is one of the most common adverse effects of medical abortion.^{18,19,40,70-72} Analgesia requirements have been reported to be higher in women of younger age, higher gestation and longer induction to abortion interval, while women with a previous live birth(s) were less likely to use analgesia.^{71,73} Analgesia use does not seem to be affected by the route of misoprostol administration used.^{43,73} In a series of 4343 women undergoing medical abortion up to 22 weeks' gestation 72% used analgesia. Of these, the majority (97%) used oral analgesia and only 2.3% required intramuscular opiates.⁷³ Westhoff *et al.*⁷² reported that women undergoing medical abortion and who were given analgesia supplies were more likely to use them compared to those given a prescription. In turn, the latter group had higher analgesia use compared to those asked to use analgesia only as required. The role of pre-emptive analgesia use and its effect on women's acceptability needs to be evaluated in different settings and preferably in the context of a randomised trial.

Home administration of misoprostol

The provision of medical abortion at home allows the procedure to be carried out in the privacy of a familiar environment and avoids the inconvenience of an additional visit to the hospital. It might also have major cost-saving implications for health service provision.

Studies from the USA have reported high efficacy and acceptability of medical abortion in home settings⁷⁴⁻⁷⁸ and home care is becoming the standard in the USA. However, home medical abortion is yet to be evaluated in the context of a randomised trial. Despite the reported research from the USA, it would be insufficient to extrapolate these findings to UK settings and, to date, there have been no studies evaluating the feasibility or acceptability of home medical abortion in the UK. A multicentre, questionnaire survey sponsored by the fpa (Family Planning Association) assessed women's views on home administration of misoprostol for medical abortion, and, in particular, their perceived acceptability and perceived ability to cope with the process at home.⁷⁹ A total of 71% of women said there was nothing that happened during abortion in hospital that they would have been unable to cope with at home, while 36% said they would have opted to undergo home abortion, had that choice been available. However, 64% indicated that they would prefer to undergo abortion in hospital, suggesting that medical abortion at home is acceptable to women who currently undergo hospital-based medical abortion in UK settings. These findings need to be further evaluated in different settings.

Follow-up

The main reason for follow-up after medical abortion is to confirm successful abortion and to identify possible complications following the procedure. Abortion is usually confirmed through identifying the products of conception or by carrying out a transvaginal ultrasound of the uterus. Follow-up is usually offered within 2 weeks of abortion.^{55,80} It has been suggested, however, that giving women simple instructions and advice about detecting complications would be a suitable alternative to follow-up, with little evidence that mandatory follow-up visits detect conditions that women could not learn to recognise themselves.^{81,82} Follow-up, however, remains essential for women who do not expel recognisable products of conception, to exclude the risk of failed treatment and continuing pregnancy.

Future directions

The efficacy, safety and acceptability of the medical regimen for abortion is now well established.^{40,42,54,83-85} Further research is needed to identify the optimal dose of misoprostol in relation to the different routes of administration, and the role of pre-emptive analgesia and its effect on women's acceptability. Research on the feasibility and acceptability of home medical abortion is also awaited. This could radically change the provision of abortion services and might have important cost implications.

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