Worldwide, approximately 26 million legal and 20 million illegal abortions are performed annually; this has resulted in an abortion rate of 35 per 1,000 women aged 15-44 years.

Since the 1960s, surgical abortion by vacuum aspiration or dilatation and curettage has been a method for performing abortion. The use of the medical abortion by mifepristone in the 1980s has changed the aspect of traditional abortion performed. The use of medical abortion or mifepristonone has been increasing in countries where this product has been available. This review examines the historical issues and the use of medical regimen.

History of Medical Termination of pregnancy: From past till present

In the late 1960s, systemic or intrauterine injection of prostaglandins has been shown to induce abortion over 90% of women in their early pregnancy. The scientists at Roussel-Uclaf (Romainville, France) discovered a C19 derivative of norethisterone with a modification at the 11-beta position in 1980. It was found to have a high affinity for the progesterone receptor. The company’s code for this drug was RU38486 (later known as RU486) and the generic name, mifepristone. This discovery has marked a new era in fertility control and has been the beginning of the new era for the modern practice. In 1982, the effects of mifepristone were shown to have interrupted the menstrual cycle and early pregnancy. This has created controversy among parties concerned about the drug’s performance, which has continued to this day. France was the first country in the world to license the use of mifepristone in combination with a prostaglandin analogue for termination of pregnancy up to 49 days gestation in 1988. This drug 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 of gestational age. Mifepristone was approved for use in Sweden in 1992, and was then licensed by the United States Food and Drug Administration for use as an abortifacient in September 2000.

Methods used for Medical Termination of pregnancy

The medical abortion can be elaborated in three main categories as follows:

Anti-progesterones (Mifepristone)

Progestrone antagonists are synthetic steroids that bind to the progesterone receptor and prevent endogenous progesterone from exerting its effect. Mifepristone binds to the progesterone receptor with an affinity five times greater than that of progesterone, 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 of mifepristone involves an effect on the decidua, myometrium and a ripening effect on the cervix. Also, it prevents progesterone’s decidualisation effect on the endometrium. Mifepristone has been reported to have an increase in uterine contractility 24-36 hours after its administration, and a five-fold increase in the sensitivity to exogenous prostaglandins when administered in the first trimester of pregnancy or early stage of pregnancy.

Mifepristone was initially used as a single agent for abortion with 60-80% effectiveness. Its failure rates increased as gestation was found in combination with prostaglandins, and this forms the mainstay of most current regimens used in clinical practice of obstetrics.

Anti-metabolites (Methotrexate)

Methotrexate inhibits dihydrofolate reductase, the enzyme which is necessary for purine and pyrimidine synthesis. Its effect on pregnancy appears to be predominantly on the rapidly dividing cytrophoblast. Methotrexate has been effective for the treatment of gestational trophoblastic disease or molar pregnancy. However, since 1993, there has been a renewed interest, particularly in the USA, in the use of methotrexate for medical termination of pregnancy.

Successful use of methotrextate in combination with the prostaglandin analogue, misoprostol, has been reported. Creinin et al. reported a randomized trial comparing the administration of misoprostol (800µg 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 methotrextate (p-value = 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 far higher when used up to 49 days gestation and decreased when used at higher gestations.

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

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

**Uterotonic compounds (prostaglandins)**

Prostaglandins, which are natural fatty acids that are produced by many tissues in the body, cause uterine contractions and result in softening and dilatation of the cervix. PGF2α and PGE2 were first tested for medical abortion in the 1970s. 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. 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 such as abdominal cramps, nausea and vomiting. The natural prostaglandins were gradually replaced with the prostaglandin analogues (gemeprost and misoprostol), which are much more stable, relatively resistant to metabolism and, therefore, result in more prolonged action. The initial prostaglandin analogue used in France was sulprostone, a primitive type of prostaglandin of the PGE2 series, given by intramuscular injection. However, because of concerns about cardiovascular complications and reports of myocardial infarction, sulprostone was removed from the market and is no longer in use anywhere else. Subsequently, the PGE1 analogues (gemeprost and misoprostol) have been used for medical termination of pregnancy.

Although abortion can be induced with prostaglandins alone, the dose required produces a high incidence of side effects as mentioned. This makes prostaglandins unsuitable for use as sole agents in abortion induction. As a consequent, most current clinical protocols use prostaglandins in rather lower doses in combination with anti-progesterones or anti-metabolites.

**Type of prostaglandins**

The most well known prostaglandins are the PGE1 analogues, gemeprost and misoprostol. Gemeprost is one of the conventional prostaglandin analogues used for medical abortion. A 1 mg pessary of gemeprost costs approximately 800 Baht and requires specific room storage temperature. Moreover, there have been reports that the PGE1 analogue, misoprostol, is an effective alternative to gemeprost. Misoprostol is cheap (40 Baht per dose), and unlike gemeprost, it can be stored at room temperature.

Baird et al., reported a randomized 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 authors subsequently reported a trial that compared misoprostol 800 µg given vaginally to gemeprost 0.5 mg given vaginally after mifepristone 200 mg orally. This study showed that the complete abortion rate was higher with misoprostol and the continuing pregnancy rates lower compared to gemeprost. Statistically significant differences were shown in both groups. The incidence of side effects was similar for women in the both groups. The former study adopted a lower dose of misoprostol (600 µg) administered orally, which might explain the lower efficacy noted with misoprostol for that group.

**Dose**

The Cochrane Database thoroughly reviewed seven randomized trials comparing mifepristone in doses from 200 to 600 mg. Four trials of these seven 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 multi-centre study trial conducted by the World Health Organization (WHO) assessed the effect of further reducing the dose of mifepristone revealed that pregnant women in an early stage of pregnancy receiving 50 mg mifepristone were 1.6 times more likely to experience treatment failure compared to those receiving 200 mg. A further study assessed the effect of a further reduction in the dose of mifepristone which investigated the efficacy of a dose of 100 mg mifepristone and suggested that this may be an proper and adequate dose. Nonetheless, this was a single-centre, small study and further research is required to assess this dose before it can be recommended for use in routine practice of obstetrics. Some studies have reported that the dose of gemeprost could be reduced from 1 to 0.5 mg without a significant reduction in efficacy, which reduced the incidence of prostaglandin related side effects, particularly gastrointestinal adverse effects.

Misoprostol has been used in doses of 400-800 µg in combination with mifepristone. In France, the usage of mifepristone was prescribed first, the standard regimen involves the use of mifepristone 600 mg followed by misoprostol 400 µg orally in a single dose. The success rates of 95-97% at 49 days of gestational age was reported by the two large French trials. These French studies included women in clinical trial up to 63 days of gestational age. The standard regimen was followed by an additional dose of misoprostol 200 µg for women who did not abort within 3 hours 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 reported that the efficacy of the medical regimen decreased as the gestational age increased for women up to 63 days of
gestational age. However, the regimen used included mifepristone 600 mg followed by a single dose of misoprostol 400 µg given orally. Ashok et al reported a review of 2,000 women undergoing medical termination of pregnancy up to 63 days gestation using mifepristone 200 mg 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. The regimen was modified following the review to offer a second dose of misoprostol 400 µg to women who had not aborted within 4 hours of the initial dose. It was found that 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. However, it was not a randomised study and would need a strong and sound study, such as a randomized clinical trial.

**Route of Misoprostol administration**

The first generation of the misoprostol was in doses of 400 µg given orally. El-Rafaey et al., reported the superior efficacy and lower side effects of mifepristone 600 mg given by the vaginal route for medical abortion up to 63 days compared to the oral administration of misoprostol 800 µg. Zieman et al reported that in terms of the abortion kinetics of misoprostol by vaginal route, the systemic bioavailability of vaginally administered misoprostol was three times higher than that of the oral routing.

Peak plasma levels were slightly lower, but were achieved more slowly and sustained for up to 4 hours. This may explain the higher efficacy and lower side effects noted with vaginal routing compared to the oral route of the misoprostol.

Studies have evaluated the feasibility of the sublingual route of misoprostol administration in the context of medical termination of pregnancy in doses of 600-800 µg. The sublingual route was reported to be an effective alternative to the vaginal route of administration with good patient acceptability. The sublingual route offers additional choice to women as well as avoiding the inconvenience of vaginal administration and the first-pass liver effect associated with oral administration. Tang et al 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 termination of Pregnancy**

Side effects of the medical termination of pregnancy include the prostaglandin-related side effects of nausea, vomiting, diarrhoea, abdominal pain, shivering and fever. These side effects are dose-related and are much more profound with the oral and sublingual routes compared to the vaginal route of administration. Excessive bleeding at the time of abortion is rare; however, there is more observed blood loss with medical abortion when compared to surgical abortion. Blood transfusion has been reported to be required in 0.1-0.2% of women undergoing medical abortion up to 63 days of gestational age.

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

Medical termination of pregnancy has a small risk of failure to terminate the pregnancy, thus necessitating surgical intervention. In a series of 4,132 cases undergoing medical abortion using mifepristone in combination with misoprostol the surgical evacuation rate was 2.3%. Indications for surgery included: continuing pregnancy (0.3%), missed abortion (0.3%) and incomplete abortion (1.6%). A further series of 3,161 women undergoing medical abortion using mifepristone and gemeprost reported a surgical evacuation rate of 3.6%. Of these, 1.4% had continuing pregnancy while 2.2% had incomplete abortion.

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

The safety of misoprostol has been documented in doses up to 1,600 µg per day. 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. 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.

**Acceptability**

The medical termination of pregnancy offers additional choice to pregnant women. Reasons given by women who like the regimen include: autonomy, more privacy, less invasiveness and greater Naturalness than surgery. Frequently reported disadvantages include: abdominal cramp or pain, duration of bleeding, number of visits and the time waiting to know if the treatment has been successful. There has been increasing number of medical termination of pregnancy in many countries,
such as 56% in France, 59% in Scotland, 51% in Sweden and 14% in England and Wales.

Winikoff reported in her review on the acceptability of the medical termination of pregnancy in an early stage of pregnancy that in most trials which offered women a choice between medical and surgical methods, 60-70% of women chose medical methods. Moreover, 88-97% of women expressed their satisfaction with the medical abortion. This assessment was carried out on a self-selected population that has chosen this method for abortion.

**Analgesia requirements**

The most common adverse effect of medical termination of pregnancy is abdominal pain or cramping, especially among women of younger age, higher gestation and longer induction of abortion interval who need more analgesia than the other groups of women. On the other hand women with a previous live birth(s) were less likely to use analgesia. Use of analgesia does not seem to be affected by the route of misoprostol administration used. Among 4,343 women undergoing medical abortion up to 22 weeks’ gestation 72% used analgesia and the majority of them (97%) used oral analgesia and only 2.3% demanded intramuscular opiates. Westhoff et al reported that women who were given analgesia when having medical abortion were more likely to use the drug than those women who received a prescription. Moreover, women with prescription of analgesia have a higher use than those who used analgesia on demand. Role of analgesia use and its effects on women’s acceptability is another issue of attention for future evaluation in different settings in the context of a clinical randomized trial.

**Home administration of Misoprostol**

Medical termination of pregnancy at home provides the process of abortion to occur in a privacy and familiar environment. Moreover, the inconvenience of additional visits to the hospital has been solved, which renders the major cost-saving issues for health service provision.

Medical termination of pregnancy seems to have gained high attention and acceptability in the USA as the procedure allows women to have it in their home environment. However, the assessment of medical abortion should be done on a randomized trial basis. Although there were reports concerning this matter from USA, in other settings, the UK for instance, there were no such studies or the acceptability of home medical abortion. A report from a multicentre, questionnaire survey sponsored by the Family Planning Association (FPA) surveyed women’s views on home administration of misoprostol for medical abortion, especially women’s perceived acceptability and perceived ability to cope with the process at home. Seventy one percent 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 done home abortion had that choice been available. However, 64% indicated that they would prefer to have an abortion in hospital. This can imply that medical abortion at home is acceptable to women who currently have hospital-based medical abortion. Still, the medical abortion at home needs further assessment plus follow-up in different settings.

**Follow-up**

It seems that the medical termination of pregnancy does not need a follow-up of the procedure. However, medical termination of pregnancy requires a follow-up after the procedure to ensure the successfully complete abortion as well as checking some possible complications that might occur following the procedure. Complete abortion is usually confirmed through identifying the products of conception or by carrying out a transvaginal ultrasound of the uterus. The requirement for follow-up is within 2 weeks of abortion. Some suggested that with simple instruction and advice about detecting complications women can do it without a follow-up visit. However, follow-up is still very essential and necessary for women who do not expel recognizable products of conception and to exclude the risk of failed treatment and continuing pregnancy.

**Future directions**

It is likely that the efficacy, safety and acceptability of the medical abortion has been established. However, further research is needed to establish the optimal dose of misoprostol in relation to different routes of administration, as well as the role of the preemptive analgesia and its effect on women’s acceptability. Moreover, research needs to closely investigate the feasibility and acceptability of home medical abortion among women in different settings, especially in the low-resource countries, which might radically change the provision of abortion services and might have important cost implications as well.

**REFERENCES**

7. The efficacy and tolerance of mifepristone and prostaglandin in termination of pregnancy of less than 63 days gestation; UK Multicentre Study – final results. Contraception 1997;55:1-5.