MIFEPRISTONE plus MISOPROSTOL
for medical termination of PREGNANCY
An effective and safe option
Foreword

The continued demand for abortion services reflects the unmet need for avoiding unwanted pregnancies.

Unsafe abortions have always been a hazard to the lives of women. The fact that safe abortions save lives has been proven time and again across all cultures and countries. The provision of safe abortion services therefore assumes an importance which extends beyond simply doing the MTP.

Despite the availability of medication abortion since 2002 there is a felt need to disseminate the optimal uses of this safe and effective technology. Most providers fail to use this technology because of fears which are not necessarily grounded in facts. It is hoped that publications like these as this will dispel such fears.

FOGSI remains committed to making abortions safer and this commitment is reflected in the support of the office bearers and past chairperson of the MTP committee in making this publication a reality. Many thanks to Dr. C.N. Purandare, Dr. Sanjay Gupte, Dr. Shirish Patwardhan, Dr. P.K. Shah, Dr. Nozer Sherier, Dr. Hrishikesh Pai.

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Medical Abortion: An Update

Introduction
Unsafe abortion is still a major health problem in the world. Of the 6.4 million abortions performed in India in 2002 and 2003, 56% or 3.6 million were unsafe (Abortion Assessment Project I, 2004). Induced abortion is the most frequently performed intervention in obstetrics and gynaecology, with an estimated total of 46 million abortions globally each year.¹

Medical abortion with mifepristone and prostaglandin was first introduced in 1988 and is now approved in 31 countries. Since the introduction of this method, research has largely focused on improving its efficacy, and defining the optimal type, dose and route of administration of the prostaglandin 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. This booklet will help you understand the evolution and concerns of medical abortion over time.

Evolution of Medical Abortion
Inducing abortion by administering drugs is not a new concept. Historic documents list an incredibly large number of drugs, tablets, decoctions and other substances like papaya, abrus precatorius, etc., which women have swallowed with the intention of inducing abortion. 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. This has led to a perception amongst the lay people that medication abortion may not be very efficacious. This is a patently wrong perception and the safety and efficacy of the modern drugs should be emphasized during counselling.

Discovery of Prostaglandins
This was an important step in the development of safer methods. The first studies were performed using an intra-amniotic injection of prostaglandin. However, these methods were only suitable for inducing abortion in the second trimester. Very quickly, a vaginally-applicable prostaglandin
was developed, which was also efficacious during early pregnancy. But the drawbacks of the prostaglandin analogues available at that time, i.e., associated pain and gastrointestinal side effects, were major obstacles for widespread use.

However besides the above problems, myocardial infarction attributed to coronary spasm induced by sulprostone and the disadvantages of gemeprost (being unstable at room temperature, difficult to store and transport, expensive and only available in a limited number of countries), led to the substitution of sulprostone and gemeprost by the safer drug - misoprostol

**Misoprostol**

Misoprostol is a synthetic prostaglandin E₁. Misoprostol acts on the cervix to efface (soften) and the uterus to contract. It also inhibits gastric acid secretion in humans.

**Mode of action of misoprostol**

Misoprostol causes myometrial contractions by interacting with specific receptors on myometrial cells. This interaction results in a change in calcium concentrations, thereby initiating muscle contraction. By interacting with prostaglandin receptors, misoprostol causes the cervix to soften and the uterus to contract, resulting in the expulsion of the uterine contents.

**Pharmacokinetics of oral and vaginal misoprostol**

Misoprostol is extensively absorbed and is readily metabolized to the free acid, which is the biologically active form and is responsible for its clinical activity.

Following oral administration, the plasma misoprostol levels increased rapidly, with a peak at 30 minutes, declined rapidly by 120 minutes, and remained low thereafter.

In contrast, after vaginal administration, the plasma concentration gradually increased, reaching maximum levels after 70–80 minutes and slowly declined, with detectable levels present after 6 hours. Vaginal misoprostol was present in the circulation longer than oral misoprostol and, hence, its duration of stimulation of the uterus exceeds that of oral misoprostol.

But, when used alone for medical abortion, a higher dose of misoprostol was required causing severe gastrointestinal side effects like cramps, nausea, vomiting and diarrhoea.

**The Turning Point (Discovery of Mifepristone)**

**Mode of action of mifepristone**

Mifepristone is an anti-progesterone drug; thereby, it inhibits the activity of progesterone and results in termination of
pregnancy. The anti-progestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. It inhibits the activity of endogenous or exogenous progesterone, thereby causing termination of pregnancy.

Doses of 1 mg/kg or greater of mifepristone have been shown to antagonize the endometrial and myometrial effects of progesterone in women. Receptor-mifepristone complex inhibits transcription, resulting in the down-regulation of progesterone-dependent genes, with decidual necrosis and detachment of the products of conception.

However, it became clear that mifepristone had a maximal effectiveness of 80% when used alone, which was not sufficiently effective to be used as an abortifacient drug in clinical routine.

The final breakthrough came with the discovery that mifepristone increased the sensitivity of the pregnant myometrium to prostaglandins, which allowed use of a reduced dose of prostaglandin. This led to the development of a combined treatment using mifepristone followed by misoprostol.

In very simple terms mifepristone is used to detach the pregnancy and misoprostol to expel it.

Approval of Medical Abortion

Medical abortion was first approved in France in 1988, followed by approvals in the UK (1991) and Sweden (1992). Medical abortion was approved in India in 2002.

The MTP act allows the use of medication abortion up to 49 days of gestation. This is conditional to the provider following the MTP act in its entirety including filling Form C and the MTP register.

Day 1 : Mifepristone 200 mg orally
       Inj. Anti-D to Rh - negative patient

Day 3 : Misoprostol 400 μg vaginally or orally

Day 14 : Follow-up visit to assess for completion of abortion preferably clinically or by ultrasonography if indicated.

Combipack of Mifepristone & Misoprostol has been approved for use up to 63 days from LMP by Drug Controller Authority of India.

Regime – 49 to 63 days

Day 1 : Mifepristone 200 mg orally.
       Inj. Anti-D to Rh negative patient
Day 14: Follow-up visit for clinical assessment

As per the MTP Act, Medical methods for termination of pregnancy not exceeding seven weeks, may be prescribed by a registered medical practitioner (as defined in the act) as prescribed under Section 2 (d) and Rule 3, having access to a place approved by the Government under Section 4 (b) & Rule 5 of MTP Rules. RMP should display a certificate to this effect from the owner of the approved place.

Besides the above mentioned regimen the following regimens are also practised.

1. US FDA approved-regimen 2000
   
   The regimen is approved for up to 49 days of gestation.
   
   Day 1: Mifepristone 600 mg orally
   
   Day 3: Misoprostol 400 μg orally
   
   Day 14: Follow-up visit to assess for completion of abortion clinically, by ultrasonography, or by documenting a significant decrease in serum beta-hCG levels.

Surgical termination is recommended if a viable pregnancy is detected at this time by ultrasonography, because the pregnancy may continue and there is a risk of foetal malformation.

2. Regimen recommended by Royal College Of Obstetrics and Gynaecology (RCOG), World Health Organization (WHO)

   The regimen is recommended for up to 63 days of gestation.
   
   Day 1: Mifepristone 200 mg orally
   
   Day 3: Misoprostol 800 μg vaginally

   For women at 49–63 days of gestation, if abortion has not occurred 4 hours after administration of misoprostol, a second dose of misoprostol 400 μg may be administered vaginally or orally.

   Day 14: Follow-up visit to assess for completion of abortion clinically, by ultrasonography or by documenting a significant decrease in serum beta-hCG levels.

Surgical termination is recommended if a viable pregnancy is detected at follow up, because the pregnancy may continue and there is a risk of foetal malformation.
Counseling

It may be appropriate to say that patient perception to medication abortion depends to a very large extent on the counseling. Counseling should be adequate, non judgmental and confidential. It should cover at least the following talking points and also address all doubts that the patient may have.

- Vaginal bleeding may occur for up to 10-14 days. It usually resembles a heavy, prolonged menses. If at any time the patient feels that bleeding is excessive or she is passing clots she should report to the provider immediately.

- Occasionally the patient may see the products of conception on expulsion. She should be told that these usually look like a pinkish mass. She should be reassured that this is a part of the procedure and is not abnormal.

- 3 visits are usually essential for the procedure.

- In case of failure of the medical method (not very common) or retained products of conception or excessive hemorrhage the abortion may have to be completed surgically.

Post abortion contraception is vital in preventing another unwanted pregnancy.

Confirmation of pregnancy termination

Patients should be scheduled for and return for a follow-up visit at approximately 14 days after administration of mifepristone to confirm that the pregnancy is completely terminated and to assess the degree of bleeding. Vaginal bleeding is not evidence of the termination of pregnancy. Termination can be confirmed by clinical examination or an ultrasonographic scan. Lack of bleeding following treatment, however, usually indicates failure. Medical abortion failures should be managed with surgical termination.

It is important to stress here that at no point should ultrasound be considered as mandatory in the entire process of medication abortion. It is an aide which the clinician must use as indicated.

Efficacy of these regimens

True drug failure this is defined as the presence of cardiac activity 2 weeks following mifepristone and misoprostol administration. It occurs in < 1 % of women and the process should be completed surgically.

A study using 600 mg of mifepristone followed by 400 μg of misoprostol orally in women seeking termination of pregnancy for up to 49 days of gestation resulted in complete abortion in 92% of patients, with surgical abortion being required in 8% of
In the latter, the reasons for surgical abortion were incomplete abortion in 5%, and continuing pregnancy in 1%. While 0.6% of the patients requested an intervention, it was a medical indication in 2%. A consecutive case series of 2,000 women with pregnancies of up to 63 days of gestation and using 200 mg of mifepristone orally followed by 800 \( \mu \text{g} \) of misoprostol orally resulted in complete abortion in 97.5% of the patients. Surgical evacuation was required in 2.5% of the patients, with the reasons being incomplete abortion in 1.4%, missed abortion in 0.4% and continuing pregnancy in 0.6% of the patients.

**Birth Control**

Counselling for post abortion contraception forms as important a part of the procedure as the technology itself. The woman may conceive immediately after the abortion even prior to the next menstruation. It is therefore imperative that the patient adopt a method of contraception immediately after the abortion.

Birth control methods should be started as soon as it is determined that the pregnancy is terminated. Practically all methods of contraception can be used.

**Contraindications**

Abortion per se and medication abortion in particular are amongst the safest medical procedures. There are very few absolute contraindications to medical abortion. These include:

- Previous allergic reaction to one of the drugs involved
- Inherited porphyria
- Chronic adrenal failure
- Known or suspected ectopic pregnancy

**Caution is required when:**

- The woman is on long-term corticosteroid therapy (including those with severe, uncontrolled asthma)
- She has a haemorrhagic disorder
- She has severe anaemia
- She has pre-existing heart disease or cardiovascular risk factors (e.g., hypertension and smoking)
Special situations

Age
Neither adolescence nor older age (e.g., over 35 years) should be regarded as a contraindication to medical abortion.

Anaemia
This need not be regarded as a contraindication. However, anaemia detected at the time of abortion should be treated. Average blood loss in medical abortion may be more than that in surgical abortion, and the incidence of heavy bleeding may be higher.

Breastfeeding
It is likely that mifepristone passes into breast milk. Small amounts of misoprostol also enter breast milk soon after administration, but it is not known whether this could have any effect on the infant. As misoprostol levels decline rapidly, it has been recommended that misoprostol should be taken immediately after a feed and the next feed given after 4 hours in case of oral administration. After vaginal administration, misoprostol levels stay high for longer, and the feed should preferably be given more than 6 hours later. Unfortunately, the available data do not allow a precise recommendation on optimum timing.

Continuing Pregnancy after administration (failure of medication abortion)

Mifepristone
Mifepristone is indicated for use in the termination of pregnancy (through 49 days of pregnancy) and has no other approved indication for use during pregnancy.

Patients who have an ongoing pregnancy at the last visit have a risk of foetal malformation resulting from the treatment. Surgical termination is recommended to manage medical abortion treatment failures.

Misoprostol
Several reports in the literature indicate that prostaglandins, including misoprostol, may have teratogenic effects in human beings. Skull defects, cranial nerve palsies, delayed growth and psychomotor development, facial malformation and limb defects have all been reported after exposure during the first trimester.

Insulin-dependent diabetes or thyroid disorder
There is no evidence that medical abortion causes particular problems in women with these disorders. However, mifepristone has been shown to alter insulin sensitivity in vitro.
and these effects may or may not be reflected in blood sugar and insulin levels.

**Multiple pregnancy (current gestation)**

There is no evidence that the failure rate of medical abortion is increased or that a different dosage regimen is required in the case of a multiple pregnancy.

**Obesity**

There is no evidence that the failure rate of medical abortion is increased or that a different dosage regimen is required in obese women.

**Bronchial asthma** – Mifepristone & Misoprostol can be used

**Previous caesarean section**

There is evidence from one study that the safety and efficacy of early medical abortion are unaffected by previous caesarean section.

**Smoking**

There is no evidence of interaction between the risks of smoking and medical abortion. However, smoking contributes to cardiovascular risk and this factor should be considered when assessing a woman’s overall suitability for medical abortion.

**Uterine malformations, congenital and acquired; previous cervical surgery**

There is no evidence that these represent contraindications.
A KAP study on Medication Abortion in India revealed that although the technology was taken up quickly and used widely there were some practitioners who were not offering women this option due to certain questions/doubts which were not necessarily grounded in fact. It was thought then that having a peer to peer education and experience sharing network would encourage more physicians to expand their services and provide it in a scientifically correct manner.

The MAPnet project was set up as a joint effort of FOGSI and Ipas piloted at the Navi Mumbai and Sholapur societies.

Its objectives were:

- Equip members of the network with training, guidelines, protocol to enable them to offer quality medical abortion care to their clients.
- Provide members with patient information material, take away and site signage to help them counsel their clients and enable the women to make informed choices.
- Share experiences among members in providing medical abortion service.
- Ensure women have an option of quality medical abortion care.
- Document their service delivery experience and disseminate it to other interested providers and stakeholders.

The network has the potential to enhance the base of accessibility of medication abortion services under a small clinical setup. It also offers a vital platform for including private doctors. Considering that the pilot project achieved its objectives the intervention is now being scaled up to include 10 districts in state clusters across the country.
FAQ’s

Some of the issues which needed to be addressed are given below. There are of course more questions than one can outline but we hope that the following will be helpful:

1. **Is the interval between the administration of mifepristone and the prostaglandin crucial?**

   The licensed and most commonly used interval of 36–48 hours corresponds to the time when the uterus is most sensitive to prostaglandin after priming with mifepristone; hence, the therapeutic dose can be reduced to the minimum. It has been shown recently, however, that the interval can be shortened to 24 hours or lengthened to 72 hours, without loss of efficacy, when mifepristone is used in combination with 800 μg of vaginally-administered misoprostol. If misoprostol is given as an oral dose of 400 μg, the interval of 36–48 hours should be adhered to. Other time intervals are currently being studied.

2. **What pain relief should be available to women during medical abortion?**

   Pain is caused both by the abortion process and as a side effect of the prostaglandin. It is most likely to be felt in the few hours after administration of the prostaglandin, when the gestational sac/embryo is being expelled from the uterus. Healthcare providers should make adequate analgesia easily available to all women who request it during medical abortion. Examples of commonly used preparations are paracetamol 500–1,000 mg, or non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen 200 mg. In cases of severe pain, codeine 30–40 mg may be added to either of the above-mentioned treatments.

3. **Are there any undesirable effects due to the drugs used for medical abortion?**

   The treatment procedure is designed to induce the vaginal bleeding and uterine cramping necessary to produce an abortion. Nearly all of the women who receive mifepristone...
and misoprostol will report adverse reactions, and many can be expected to report more than one such reaction. These are as follows:

a) Gastrointestinal side effects like diarrhoea, abdominal pain, nausea, flatulence, dyspepsia, headache, vomiting and constipation

b) Shivering
c) Hyperthermia
d) Dizziness
e) Pain due to uterine contractions
f) Severe genital bleeding
g) Shock
h) Pelvic pain
i) Uterine rupture (requiring surgical repair, hysterectomy, and/or salpingo-oophorectomy)

4. Is there a risk of overdosage with mifepristone and misoprostol?

**Mifepristone**

No serious adverse reactions were reported in tolerance studies in healthy non-pregnant women where mifepristone was administered in single doses greater than threefold of 600 mg (1,800 mg) for termination of pregnancy. If a patient ingests a massive overdose, she should be observed closely for signs of adrenal failure.

The oral acute lethal dose of mifepristone in the mouse, rat and dog is greater than 1,000 mg/kg.

**Misoprostol**

Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnoea, abdominal pain, diarrhoea, fever, palpitations, hypotension, or bradycardia. Symptoms should be treated with supportive therapy. It is not known if misoprostol acid is dialysable. However, because misoprostol is metabolized like a fatty acid, it is unlikely that dialysis would be an appropriate treatment for overdosage.

5. Are there any warnings and precautions to be taken during and after medical abortion?

a) Anti-D IgG (250 IU before 20 weeks of gestation and 500 IU thereafter) should be given, by injection into the deltoid muscle, to all non-sensitized RhD-negative women within 72 hours following abortion, whether by surgical or medical methods.
b) Facilities of emergency curettage and intravenous fluids should be provided, or reliably arranged for through other providers.

c) Confirm that there is no suspicion of ectopic pregnancy, check that the patient is not anaemic, and rule out other contraindications to the administered drugs.

d) Educate the patient on what to expect (pain, bleeding, passage of products and so on) and what to report and when.

e) Give the patient clear instructions on what to do and whom to call in the event of an emergency.

Women value being offered a choice of abortion methods and, ideally, such choices should be available within comprehensive abortion services. Medical abortion using a combination of mifepristone and misoprostol represents a safe, effective and acceptable alternative for women.

8. If a woman has an incomplete abortion, is it necessary to evacuate the uterus surgically?

On average, vaginal bleeding gradually diminishes over about two weeks after a medical abortion, but in individual cases spotting can last up to 45 days. Generally, bleeding after medical abortion lasts longer than after vacuum aspiration. If the woman is well, neither prolonged bleeding nor the presence of tissue in the uterus (as detected by ultrasound) is an indication for surgical intervention. Remaining products of conception will be expelled during subsequent vaginal bleeding.

**Surgical evacuation of the uterus may be carried out:**

i) On the woman’s request

ii) If the bleeding is heavy or prolonged or causes anaemia

iii) If there is evidence of infection, Antibiotic treatment should be initiated prior to surgery

9. Which methods of contraception can a woman use after medical abortion?

- Combined oral contraceptive pills can be started on the day that misoprostol is administered, when expulsion usually occurs. It does NOT affect complete abortion rates, side-effects and duration of bleeding

- Progestogen-only methods are commonly associated with breakthrough bleeding, which may be confused with an incomplete abortion.
• Depot-medroxyprogesterone injections and implants are often associated with amenorrhoea, or irregular bleeding, which may make it difficult to determine whether pregnancy has been terminated. It may therefore be preferable to start using these methods only after it has been confirmed that the pregnancy has been terminated.

• Sterilization and insertion of an intrauterine device should be deferred until confirmation that the abortion is complete.

• Barrier methods can be used as soon as sexual intercourse is resumed, preferably when bleeding has stopped.

• Methods of natural family planning can be resumed only after the return of regular cycles.

References
4. Adapted from WHO 2006: Frequently asked clinical questions about medical abortion.