Expanding uses for Mifepristone and Misoprostol

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Mifepristone, also known as "the abortion pill", was discovered by a French biochemist, Dr. Etienne Emile Baulieu.He discovered that it bound tightly to progesterone receptors and behaved as an antagonist. It was first approved for use in France in September 1988 and it was developed by Roussel-Uclaf, the sole manufacturer of the drug and holder of the patents. Since then it came to be known as RU-486. The US Food and Drug Administration (FDA) approved Mifepristone for use as an abortifacient on September 28, 2000[1].

Misoprostol is a synthetic analogue of PGE1. It was approved by the US FDA for the prevention of non-steroidal anti-inflammatory drug induced gastric ulcers. The action of misoprostol on the pregnant uterus was first described by Rabe et al in 1987, as they discovered it binds to the EP-2/EP-3 prostanoid receptors and induces effective uterine contraction.

MECHANISM OF ACTION[2]

Mifepristone	Misoprostol
Binding to the progesterone receptors in endometrium and decidua resulting in necrosis of the placenta.	Binding to myometrial cells causes strong myometrial contractions.
Softening of cervix and mild uterine contractions	Softening and dilatation of cervix.
Sensitizes uterus to prostaglandins	

Thus the use of these two drugs in conjunction with each other is physiological with action on three aspects of the pregnant uterus, i.e. the placenta, uterus and the cervix.

HOW THE COMBINATION IS USED

The US FDA approved regimen for termination of pregnancy involves three steps-

1. A visit to the clinician to discuss the procedure and its alternatives and to receive a 600 mg dose of Mifepristone .
2. A second visit two days later for an oral dose of 400 mcg of Misoprostol
3. A third visit on day 14 for a follow up visit.

   The FDA approved mifepristone for use 49 days after the first day of the last menstrual period.[1]

   Ways in which the regimen is adapted is as follows:

   a. ***Changing the dosage of the medications***- it has been found that 200 mg of mifepristone and 800 mcg of misoprostol orally or vaginally/ 200 mg mifepristone with 600mcg misoprostol (200mcg/3 tablets orally) is equally effective or more effective than using 600mg of mifepristone and 400mcg of misoprostol.[3]

   b. ***Eliminating the second visit***- At home administration of the second drug .Studies have shown at-home administration to be both safe and effective.[4]

c. ***Extending the time period for using mifepriston***e- Studies have found that mifepristone can be effective up to 63 days from the last menstrual period, dependant on the regimen used (buccal and / or vaginal administration of the prostaglandin allows the 63 day limit.[5]

d. Eliminating the follow up ultrasound visit- Some health centres allow women to take a blood test in place of a repeated ultrasound to determine if the medication abortion process was complete.[4]

EFFECTIVENESS AND SAFETY

Using the FDA approved regimenupto 49 daysgestation about 92% women complete their abortion without needing vacuum aspiration.[6] Evidence based alternative regimens have shown to have had success rates of upto 98%.[5]

Some women may begin bleeding after taking mifepristone, before taking misoprostol. For most the bleeding takes place within 4-5 hours after misoprostol.[7] Women are advised to take the misoprostol even though they begin bleeding, else it can result in an incomplete abortion.

The advantages of medical abortion over surgical methods of abortion are –

- Less invasive
- More privacy
- No anaesthesia or perforation risks as seen with curettage or manual vacuum aspiration.[2]

The most common side effects of using the mifepristone and misoprostol regimen are abdominal cramps, bleeding, dizziness, fatigue, nausea and vomiting.[8]

Complications of medical abortion are heavy bleeding, incomplete abortion and infection. Ectopic pregnancy may also be missed if sonography is not done prior to use of medication.

Contraindications to medical abortion using Mifepristone- Misoprostol include severe anaemia and suspected ectopic pregnancy.

ALTERNATIVE USES

Medical uses of Mifepristone have been identified in the treatment of breast cancer, Cushing's syndrome, endometriosis, glaucoma, meningioma, ovarian cancer, prostate cancer, depression and uterine fibroids.[1]

USES	DOSAGE
Fertility Regulation (currently in trial by WHO)	Postovulatory cyclical use 5-10 mg daily for 10 days, once a week and once a month.[9]
Emergency contraception	600 mg of mifepristone given within 72 hrs of unprotected intercourse has shown success rates comparable to Yuzpes regime.[10]
Cervical ripening before surgical abortion	Single dose of 50, 200 0r 600 mg given 30 to 60 hrs before surgery.[11]
Induction of labour	200 mg/ day for 2 days is under study followed by 100 -300 mcg misoprostol.[12]
Treatment of endometriosis	100 mg day / 3months or 50 mg / day for 6 months.[13]

Mifepristone- Misoprostol regimen can be used also for termination of pregnancy in the second trimester. The Cochrane Database Review 2011[14] analysed the medical methods for mid-trimester termination of pregnancy. The conclusion was that medical abortion in the second trimester using Mifepristone and Misoprostol appeared to have the highest efficacy and shortest abortion time

interval. Where mifepristone is not available, misoprostol is a reasonable alternative. The optimal route for administering misoprostol is vaginally, preferably using tablets at 3 hourly intervals. However in India, Mifepristone- misoprostol in not licensed for pregnancy termination in the second trimester.

Misoprostol can be used as first line management for incomplete abortions. Studies show that misoprostol is as effective as MVA at treating incomplete abortion at uterine size of <12 weeks.[15] In these studies, the acceptability of misoprostol appears higher than surgical techniques. Given the many practical advantages of misoprostol over MVA in low-resource settings, misoprostol should be more widely available for treatment of incomplete abortion in the developing world.

Misoprostol is used for induction of labour in Intrauterine fetal death.Intravaginal misoprostol at the dose of 100 micrograms every 12 hours appears to be a safe, effective, practical, and inexpensive new method for induction of labor in intrauterine fetal death.[16]

Misoprostol is effective in the treatment of postpartum hemorrhage. It can be administered sublingually, orally, vaginally, and rectally. Doses range from 200 to 1,000 mcg; the dose recommended by FIGO is 1,000 mcg administered rectally.[17] Higher peak levels and larger doses are associated with more side effects, including shivering, pyrexia, and diarrhea. Although misoprostol is widely used in the treatment of postpartum hemorrhage, it is not approved by the U.S. Food and Drug Administration for this indication.

Conclusions: Thus Mifepristone and misoprostol combination is very effective for pregnancy termination in the first and second trimester. Mifepristone by virtue of being a progesterone receptor antagonist has several potential uses which are being researched. Misoprostol is effective for labour induction and postpartum haemorrhage.

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