PROGRAM BRIEF

MIFEPRISTONE'S MULTIPLE RH INDICATIONS: AN OVERLOOKED OPPORTUNITY FOR EXPANDING ACCESS

When evidence supports safe and effective use of a medication or device, women should be given a choice of options for their care, and this applies to treatments involving mifepristone. Often mifepristone represents a non-invasive treatment alternative which may make it especially attractive to health systems as well as to women.

Mifepristone is an antiprogestin which blocks the activity of the hormone progesterone which is needed to maintain a pregnancy. Mifepristone also plays a role in softening and dilating the cervix and can be used to achieve cervical priming for medical procedures.[1] It is most commonly known for its use in combination with the drug misoprostol to induce a medical abortion.

Although the number of countries with access to mifepristone grows every year, the medication is still not available in many places. In others, it is officially registered but unobtainable due to a variety of stigma and market-related barriers. As a result, populations that could benefit, including women and girls, the young and disenfranchised, rural and remote populations, are not able to access this safe, effective medication.

Additional Mifepristone Indications

- **Treatment of early pregnancy loss**
- **Treatment of intra-uterine fetal death**
- **Second trimester abortion**
- **Cervical preparation**

One strategy to increase availability and market sustainability of mifepristone is to register it for additional indications. Several of these "uncontroversial" indications are legal in most jurisdictions and could provide an entry point for the medication to be listed on national drug registries, stocked in hospitals and other health care facilities, and integrated into health care systems.

In countries where there are highly restricted legal indications for abortion and/or where opposition to abortion on request impacts drug registration regulatory processes, focusing on other indications may eliminate some hurdles to product registration.

Additionally, in the face of constrained health care budgets, medications that address multiple indications may be more appealing for purchase by health systems.

Ultimately, each labeled indication for a single pill mifepristone (200 mg) has the potential to appeal to different stakeholders and expand the marketability of this medication.

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Early Pregnancy Loss

EXPLANATION OF INDICATION

Early pregnancy loss occurs in 15-20% of all recognized pregnancies. One type of early pregnancy loss is a "missed abortion" wherein a non-viable pregnancy is retained. This includes anembryonic gestations and cases of embryonic or early fetal demise. Treatment may be sought to expel the pregnancy and, in many contexts, this involves expectant management or either curettage or vacuum aspiration which require trained providers, special equipment, sterile conditions, and often anesthesia. Using medications for uterine evacuation is an attractive alternative. A large body of evidence supports the use of misoprostol for missed abortion [2-9] new evidence on the use of mifepristone for this indication has recently emerged.

SUMMARY OF EVIDENCE

- Some small early studies included mifepristone, with or without misoprostol, for management of missed abortion with mixed results.[10-26] These studies highlighted issues around consistent case definition.[27,28]
- A large randomized-controlled trial published in the New England Journal of Medicine reports that pretreatment with mifepristone prior to misoprostol for management of early pregnancy loss resulted in complete expulsion for significantly more participants compared to misoprostol alone[29] and a recently completed randomized-controlled trial on missed abortion showed that pre-treatment with mifepristone results in needing fewer misoprostol doses.[30]
- The current evidence supports the same regimen of mifepristone and misoprostol contained in a combi-pack.

NOTE: There is a large ongoing trial in the UK on this topic: https://www.medscinet.net/mifemiso/

Late Intrauterine Fetal Demise (IUFD)

EXPLANATION OF INDICATION

Late intrauterine fetal demise (IUFD) arises when a fetus is no longer alive but has yet to be expelled from the uterus. Timely evacuation is necessary to avoid developing life-threatening maternal coagulopathies or serious infections and to reduce emotional distress.[31-33] Options for IUFD management include: expectant management, which may increase risk of infection and be less appealing to a woman; surgical management, which requires specialized skill that may not be readily available in some settings; and medical management, which is most effective when mifepristone is used.

SUMMARY OF EVIDENCE

- RCOG, NICE, and WHO guidelines all recommend the use of mifepristone in IUFD management.[34-36]
- Mifepristone alone has been found to induce labor after IUFD in approximately 61-67% of women.[37-39]
- When mifepristone is combined with a prostaglandin, efficacy rates improve.[40-49]
- Several recent studies have demonstrated that when comparing misoprostol alone to mifepristone and misoprostol combined, the latter results in faster time to expulsion.[50-55]
- The current evidence supports the same regimen of mifepristone and misoprostol contained in a combi-pack.

Second Trimester Medical Abortion

EXPLANATION OF INDICATION

Second trimester abortion generally refers to abortions occurring in 12-24 week gestations. Abortions in this period are done for a number of reasons including patient choice, to save the life of the mother, for fetal defects, and in cases of rape and/or incest.[56] According to the WHO Global Abortion Policies Project, while abortion on request is legal in 50 countries, 80 countries legally permit abortion in the case of fetal impairment and 115 countries allow it to save the life of a pregnant person.[58] These conditions often arise or are only identified in the second trimester and medical abortion may play a key role as the technical skill required for second trimester surgical abortion may not always be available. Women may also prefer a medical method over a surgical procedure.

SUMMARY OF EVIDENCE

- Significant evidence shows that a combination of mifepristone and misoprostol is superior to misoprostol alone for medical abortion in the second trimester. [59-62]
- Recommended regimens of mifepristone and misoprostol are highly effective and well tolerated, and associated with shorter times to abortion success compared to misoprostol alone and complications are rare.
- Recent analyses have also posited that the method can be offered as an outpatient day service, which could improve quality of care and prove more cost-effective to women and health care systems.[63-66]
- The World Health Organization and RCOG recommend mifepristone-misoprostol for abortion in the second trimester.[34,67]

Cervical Preparation

EXPLANATION OF INDICATION

Prior to a surgical abortion, the cervix can be prepared or softened, to make the procedure safer, shorter, and easier. Cervical preparation is of particular importance at later gestations. Osmotic dilators, misoprostol, and mifepristone, alone or in combination are all options for cervical preparation. While cervical preparation is also used prior to other obstetric procedures current evidence around mifepristone relates to abortion.

SUMMARY OF EVIDENCE

- A 2010 Cochrane review includes mifepristone as an effective method of cervical preparation for surgical first trimester abortion.[68]
- A 2010 Cochrane review found that while adding mifepristone to misoprostol improved cervical dilation in second trimester abortion, it increased procedure time and the frequency of pre-procedural expulsions compared to misoprostol alone.[69]
- A large three-armed RCT in 2015 concluded "Despite no difference in operative time, adjunctive mifepristone facilitates later dilation and evacuation compared with osmotic dilators alone and is better tolerated than misoprostol.[70]
- Women prefer mifepristone to osmotic dilators for second trimester cervical preparation and reported less pain.[71]
- When using mifepristone with osmotic dilators the day prior to D&E after 19 weeks with pre-procedure misoprostol, fewer dilators are necessary.[72]

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Indication	Recommendations in International Guidelines
Early Pregnancy Loss	NICE: Do not offer mifepristone as a treatment for missed or incomplete miscarriage. (Ectopic Pregnancy and Miscarriage: diagnosis and initial management NG126, 2012) WHO: Misoprostol is the recommended treatment for incomplete abortion and inevitable abortion. There is no mention of mifepristone for early pregnancy loss. (Medical Management of Abortion 2018; Management of Complications of Pregnancy & Childbirth 2017)
IUFD	WHO: Medical management of IUFD includes the use of mifepristone in combination with misoprostol (recommended) or misoprostol alone (alternate). (Medical Management of Abortion 2018) RCOG: A combination of mifepristone and a prostaglandin preparation is recommended as the first-line treatment for late intrauterine death and stillbirth for women with unscarred uteruses. For women with a history of lower segment cesarean sections, mifepristone can be used alone. (Greentop Guidelines 55, 2010) NICE: If a woman who has had a late IUFD chooses to proceed with induction of labour, mifepristone should be used, followed by vaginal prostaglandin E2 or misoprostol. (NICE clinical guideline 70, 2013)
2nd Trimester medical abortion	WHO: For medical management of induced abortion ≥12 weeks gestation…We suggest the use of 200 mg mifepristone administered orally, followed 1–2 days later by repeat doses of 400 µg misoprostol administered vaginally, sublingually or buccally every 3 hours. (Medical Management of Abortion 2018) FIGO: >13 weeks, If mifepristone is available (preferable), follow the regimen prescribed for mifepristone + misoprostol. 200 mg mifepristone followed 36-48 hours later by repeat doses of 400 µg miso pv, sl or bucc. There is no maximum dose of misoprostol recommended. RCOG: Medical abortion regimens using 200 mg oral mifepristone and misoprostol are effective and appropriate at any gestation. (Clinical Guideline #7, 2011)
Cervical preparation prior to surgical abortion	WHO: Cervical preparation before surgical abortion ≤12-14 weeks recommendations include administration of mifepristone 200 mg Oral 24–48 hours prior to the procedure. (WHO 2014) RCOG: Guidelines state that mifepristone 200 mg is effective for cervical preparation and is a licensed regimen but the recommended medical method up to 14 weeks is misoprostol. (Clinical Guideline #7, 2011)

OTHER

A Cochrane review in 2009 on mifepristone for labor induction concluded that there was insufficient evidence and since that time a few small studies have been published suggesting the mifepristone is effective for this indication.[73] However, due to the nascent nature of this area, and the unlikelihood that it would be included among "uncontroversial indications" we are not including mifepristone for labor induction in this review.

While mifepristone is also used for other indications like emergency contraception, uterine fibroids, and management of Cushing's disease, the tablet does not contain the same dose and thus not addressed in this brief. Additional indications are currently being explored (refractory depression, alcoholism) but also use a tablet that does not contain the same dose.

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220 East 42nd Street, Suite 710, New York, NY 10017
Phone: 1 (212) 448-1230
gynuity.org
pubinfo@gynuity.org

Support for this project was funded by PATH in its capacity as the Secretariat of the Reproductive Health Supplies Coalition. The views expressed by the authors do not necessarily reflect the views of the Reproductive Health Supplies Coalition or PATH.