KATHMANDU

25-28 MARCH 2019 / KATHMANDU, NEPAL

19TH GENERAL MEMBERSHIP MEETING OF THE REPRODUCTIVE HEALTH SUPPLIES COALITION

Safe Abortion Supplies Workstream

Co-leads:
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Welcome and intros

Selected SAS achievements since our last meeting:

- 4 SAS led webinars
  - Safe Abortion Supplies Workstream Planning Webinar (Dec 2017)
  - Combi-pack updates from WHO and Concept Foundation (Jul 2018)
  - IPPF Medical Abortion Commodities Database (Oct 2018)
  - Combi-pack Commercial Distribution Landscape Assessment (Feb 2019)

- One grant awarded to Mann Consulting for combi-pack distribution landscape assessment
- Social media campaign for Safe Abortion Day (Sept 28)
- Innovation grant awarded to Gynuity Health Projects

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Increasing access to mifepristone: Paving the path for registration and commercialization for additional indications

Gynuity Health Projects

With contributions from:
Jennifer Blum, Ayisha Diop and Laura Frye

CONTEXT

- # of countries with mifepristone increasing; yet in places with restrictive abortion laws, “access” remains challenging
- Persistent commodity gap in restrictive climates due to multiple barriers: registration, distribution, commercialization, demand creation – innovative market strategies are needed!
- Four clinical indications of interest: missed abortion, intra-uterine fetal death, cervical ripening, and second trimester abortion
- All are legal in most settings; meaning drug registration would not pose the same problems as most existing labeled products (1st tri abortion)
- It is possible: in France, Mifegyne® is already labeled for cervical ripening prior to IUD insertion and cervical/intra-uterine surgery

OBJECTIVES	ACTIVITIES
To engage the RHSC community, commercial entities, and SMOs to identify market gaps & potential bottlenecks & assess interest in registration and commercialization of mife for new indications	• Create tool to guide interviews with pharma and SMOs on perceived barriers to registration • Conduct interviews with partners • Share project findings
*To increase **awareness** of and information on mifepristone's non-controversial (e.g. non elective first trimester abortion) indications*	• Develop briefing document on uses of mife • Assemble available clinical data for use to register a product • Disseminate via RHSC Webinar
To assess country-level opportunities to register mifepristone for new indications	• Conduct landscape analysis with key stakeholders • Write report of country-level findings • Disseminate landscape findings

INTERVIEWS WITH PHARMA, SMOS & IMPLEMENTING AGENCIES – WHAT WE'VE LEARNED

- Interviews conducted with: MSI, PSI, Danco, Linepharma, Naari, IPPF, DKT, Concept Foundation
- High interest in exploring labeling other indications for mifepristone; although mixed knowledge about the available level of evidence to support one or more of these indications and/or what is actually needed to get an additional labeled indication
- Most agencies had had internal discussions on this topic; but indicated that they either have insufficient time (human resources) or are unsure of next steps; e.g. how best to dedicate resources and/or how exactly to move forward
- Interest in pooled procurement for low volume regions but questions about feasibility/implementation

INTERVIEWS WITH PHARMA, SMOS & IMPLEMENTING AGENCIES – WHAT WE'VE LEARNED

What indications are most widely known?

- incomplete abortion, missed abortion, second trimester abortion, IUFD
- Some interest in menstrual regulation

Which are considered most promising?

- No consensus: incomplete abortion, cervical ripening, second trimester abortion, IUFD
- One respondent mentioned that a mife product for new indication, not in combi-pack, might be more successful in registration (and could be used with registered/country-level available misoprostol)

INTERVIEWS WITH PHARMA, SMOS & IMPLEMENTING AGENCIES – WHAT WE'VE LEARNED

Why do it?

- Political barriers making access to formal registration and availability of these products for induced abortion difficult
- Small market, hard to interest local distributors in politically sensitive use, manufacturers currently don't see mife as a profitable product

Where should efforts focus?

- Where donors support us
- In West Africa
- In South America

The future…

MIfepristone's Multiple RH Uses: An Overlooked Opportunity to Expand Access

Mifepristone's Multiple RH Indications:

An overlooked opportunity for expanding access

Mifepristone is an antiprogestin that 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. 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.

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.

WHAT ARE MIFEPRISTONE'S ALTERNATIVE INDICATIONS?

- EARLY PREGNANCY LOSS
- CERVICAL RIPENING
- INTRA-UTERINE FETAL DEATH
- SECOND TRIMESTER ABORTION

In countries where there are highly restricted legal indications for abortion and/or where opposition to abortion on request impacts 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.

Above all, when evidence supports safe and effective use, women should be given a choice of methods for their care, and this choice may include treatment with mifepristone. Often mifepristone represents a non-invasive alternative which may make it especially attractive not only to women, but to health systems.

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

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Early Pregnancy Loss

EXPLANATION OF INDICATION

An early pregnancy loss is the loss of an intrauterine pregnancy in the first trimester and occurs in 15-20% of all recognized pregnancies. Treatment may be sought in the case of incomplete abortion (when products of conception are partially expelled from the uterus) or missed abortion (when products are not expelled but the pregnancy is no longer growing). In many contexts treatment involves either curettage or vacuum aspiration which requires trained providers, special equipment, sterile conditions, and often anesthesia. Medications for uterine evacuation is an attractive alternative. A large body of evidence supports the use of misoprostol for early pregnancy loss[33–35] but the use of mifepristone for this indication is emerging.

SUMMARY OF EVIDENCE

- Some small early studies included mifepristone for management of early pregnancy loss[36–41] with mixed results. These studies highlighted issues around consistent case definition.
- A large RCT 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.[42]
- A recently completed randomized-controlled trial on missed abortion showed that pre-treatment with mifepristone results in fewer side effects when compared to misoprostol alone.[17]

Cervical Ripening/Preparation

EXPLANATION OF INDICATION

Prior to a surgical abortion, the cervix can be ripened, or prepared, 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. Cervical ripening is also used prior to other obstetric procedures but current evidence around mifepristone use for cervical ripening relates to abortion.

SUMMARY OF EVIDENCE

- A 2010 Cochrane review includes mifepristone as an effective method of cervical preparation for first trimester abortion.[16]
- 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.[30]
- Women prefer mifepristone to osmotic dilators for second trimester cervical preparation and reported less pain.[31]
- When using mifepristone and misoprostol as pretreatment to dilators after 19 weeks, fewer dilators are necessary.[32]

Intrauterine Fetal Demise (IUFD)

EXPLANATION OF INDICATION

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 and to reduce emotional distress.[23,4] 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

- Mifepristone alone has been found to induce labor after IUFD in approximately 63-66% of women.[5–7]
- When mifepristone is combined with a prostaglandin, efficacy rates improve.[8–14]
- A review of literature done by WHO to inform their 2018 guidelines showed that women treated with a combination of mifepristone and misoprostol had higher rates of complete abortion within 24 hours and a shorter expulsion time than those treated with misoprostol alone.[15]
- A recent RCT comparing misoprostol alone to misoprostol with mifepristone reports that mifepristone conferred a faster time to expulsion.[16,17]
- RCOG, NICE, and WHO guidelines all recommend the use of mifepristone in IUFD management.

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.[18] 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 the woman or pregnant person.[19] These conditions often arise or are identified in the second trimester and medical abortion may play a particularly key role as the technical skill required for second trimester surgical abortion may not always be available.

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.[20–23]
- 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.[24–27]
- The WHO and RCOG recommend mifepristone-misoprostol for abortion in the second trimester.[28,29]

Indication	Recommendations in International Guidelines	Existing products with this indication in label?
Early Pregnancy Failure	WHO: Misoprostol is the recommended treatment for incomplete abortion and there is no mention of mifepristone for this indication in the guidelines. NICE: Do not offer mifepristone as a treatment for missed or incomplete miscarriage (2012)	Mifegyne® (Exelgyn, France): Labour induction in foetal death in utero. In patients where prostaglandin or oxytocin cannot be used. Mediprist ® (Acme, India): To induce labour in cases where the foetus has died in the womb and where it is not possible to use other medical treatments (prostaglandin or oxytocin.
Cervical Ripening/Preparation	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)	
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 E_2 or misoprostol. (NICE clinical guideline 70, 2013)	Mifegyne® (Exelgyn, France): Softening and dilatation of the cervix uteri prior to surgical termination of pregnancy during the first trimester. Mediprist ® (Acme, India): For softening and opening the cervix before surgical termination of pregnancy during the first trimester.
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)	NO

NEXT STEPS

- Finish and disseminate briefing document on mife for other uses (in draft form)
- Conduct country-level assessments
- Webinar in the early summer to share findings

MA Commodities Panel

- Eleni Han, CHAI
- Hans Vermer, Concept Foundation
  - *Questions by Nathalie Kapp*

- Brian McKenna, RHSC
- Dr. Moazzam Ali, World Health Organizations
  - *Questions by Jennifer Blum*

Updates and plans for coming year

- Opportunity for member groups to provide updates on their work in this area
- Review of workplan, make any additions, amendments, plans forward

Thank you

Any questions?