A New Medical Option for Termination of Pregnancy: Introducing Mifegymiso

CLEVE ZIEGLER, M.D. FRCS

JEWISH GENERAL HOSPITAL

MCGILL ANNUAL UPDATE IN FAMILY MEDICINE 2018

Conflicts of Interest:

- Advisory Board: Allergan, Abbvie, Bayer
- Speaker: Allergan, Abbvie , Bayer

Objectives:

- 1. Review the use of Mifepristone and Misoprostol for medical abortion
- 2. Overview of the present landscape in Quebec
- 3. Review the guidelines and recommendation of the College Des Medecins du Quebec

What is Medical Abortion?

- Termination of early intrauterine pregnancy < 8 weeks from LMP with medication rather than surgical evacuation
- Combination of Mifepristone and Misoprostol (M&M) has been used widely in China and France (1988) , Sweden and Great Britain (1992), and USA (2000) 2015 for pregnancy < 49 days from LMP
- 2015: Approved in Canada for pregnancy < 49 days
- 2017: Approved in Canada for pregnancy < 63 days
- 2017 (December): Available in Quebec

Canadian Landscape:

- 100,000 abortions/ year in Canada
- 25,000 Quebec
- 50% pregnancies unplanned
- 50% unplanned pregnancies are terminated
- 40% in women using contraception

Features of Medical vs. Surgical Abortion

Medical

- Effective (>95%) < 63 days
- Acceptable (63-96%)
- Avoid surgery
- Very early intervention
- May take days
- Significant cramps and bleeding
- Discrete and private
- Several visits for follow up
- D&C 1.6%
- FREE IN QUEBEC

Surgical

- Highly effective (>99%)
- Very acceptable (90-100%)
- Allows for sedation and analgesia
- 6 weeks +
- Takes minutes
- Negligible
- Clinic or hospital
- Few visits
- D&C 1%
- FREE IN QUEBEC

Comparison of Morbidity: Medical Vs. Surgical Abortion

Tableau 3 **Incidence (%) des événements indésirables associés aux ivg médicamenteuses et chirurgicales pratiquées à un âge gestationnel de 63 jours ou moins.**

	IVG MÉDICAMENTEUSE (n = 22 368)	IVG CHIRURGICALE (n = 20 251)	*P*
HÉMORRAGIE	15,6	2,1	< 0,001
AVORTEMENT INCOMPLET	6,7	1,6	< 0,001
(RÉ)ÉVACUATION PAR CHIRURGIE	5,9	1,8	< 0,001
INFECTION	1,7	1,7	0,85
LÉSION NÉCESSITANT UNE CHIRURGIE	0,03	0,60	< 0,001
MALADIE THROMBOEMBOLIQUE	0,08	0,08	0,90
MORBIDITÉ PSYCHIATRIQUE	0,009	0,005	0,62
DÉCÈS	0,009	0,020	0,35

N : population étudiée ; p : signification statistique.

Adapté de Niinimäki *et al.*, 2009.

Key Data: Medical vs. Surgical

Medical	Surgical
No need for subsequent Intervention: 95-98%	99%
Surgical Aspiration: 1.6%	1%
Ongoing Pregnancy: 0.5-0.9%	<< 1%
Infection: 0.18%	0.5%
Limits: < 63 days from LMP	20 weeks
Cost: None	None

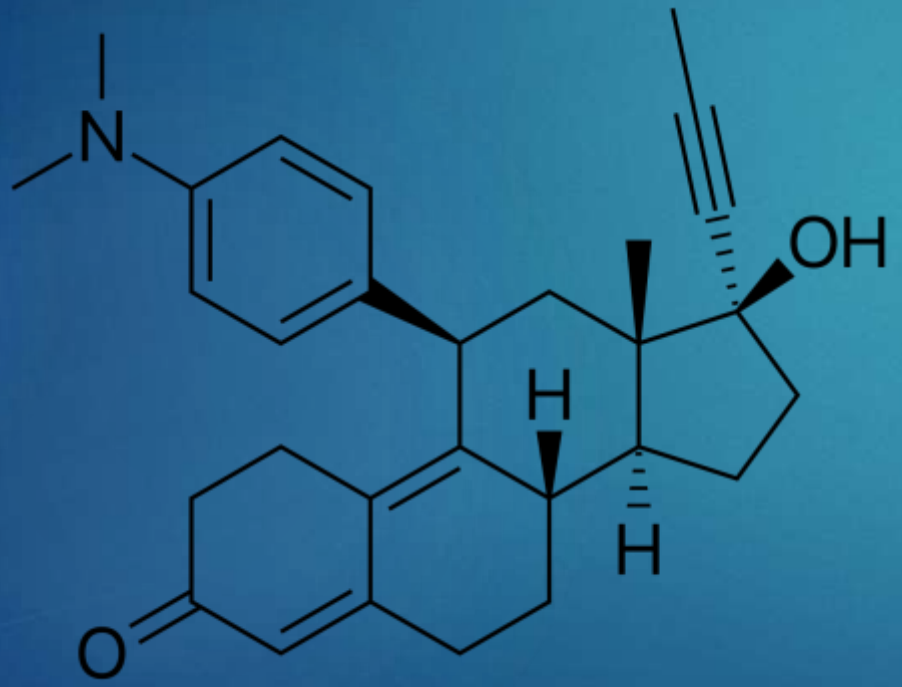
Mifegymiso


PrMifegymiso
Mifepristone tablet
Misoprostol tablets
For medical termination of pregnancy
Step 1: in the presence of your doctor or a member of the medical staff, swallow Mifepristone tablet with water.
Step 2: 24 to 48 hours after taking Mifepristone tablet, place all 4 Misoprostol tablets (as a single 800 mcg dose)

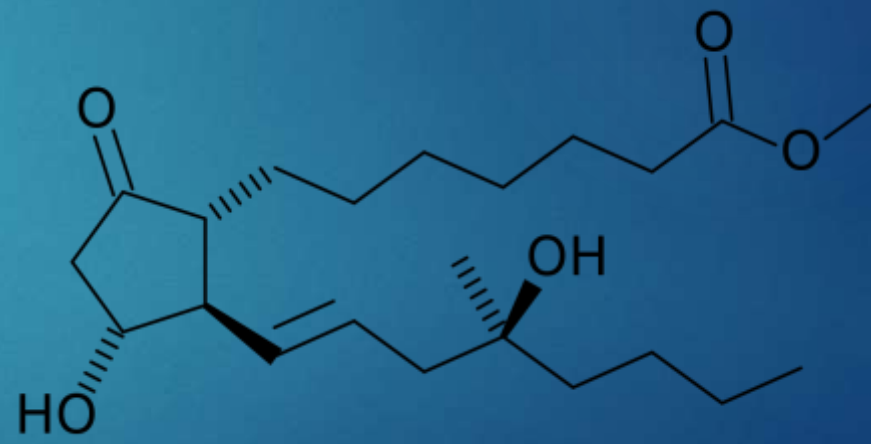
Mifegymiso: Mifepristone 200 mg+ Misoprostil 800 mcg

Mifegymiso: Mifepristone and Misoprostol

Mifepristone (RU-486) 200mg



Misoprostol 800 mcg



Mifepristone

200 mg dose

Rapid absorption

Peak serum levels 1-2 hours after administration

Metabolized by CYP P 450

Fecal excretion

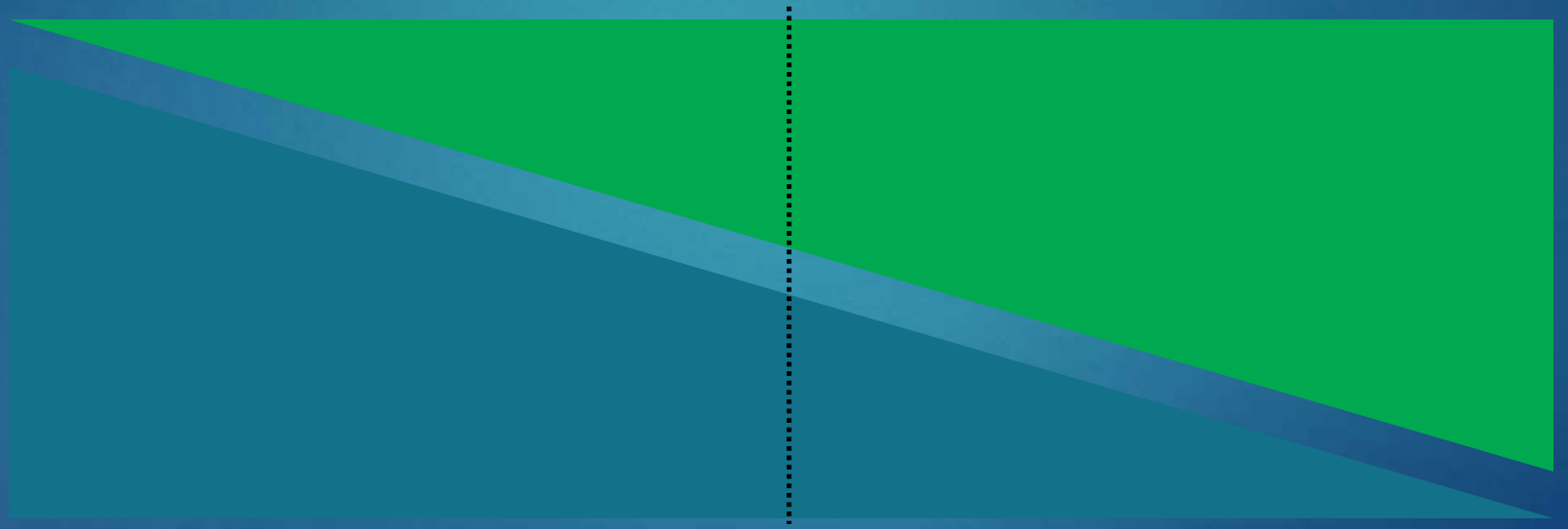
SPRMs: Agonistic vs. Antagonistic Effects

Onapristone
Mifepristone

Ulipristal acetate
Asoprisnil
Telapristone acetate
J 1042

Progesterone

R5020 (synthetic progestin)

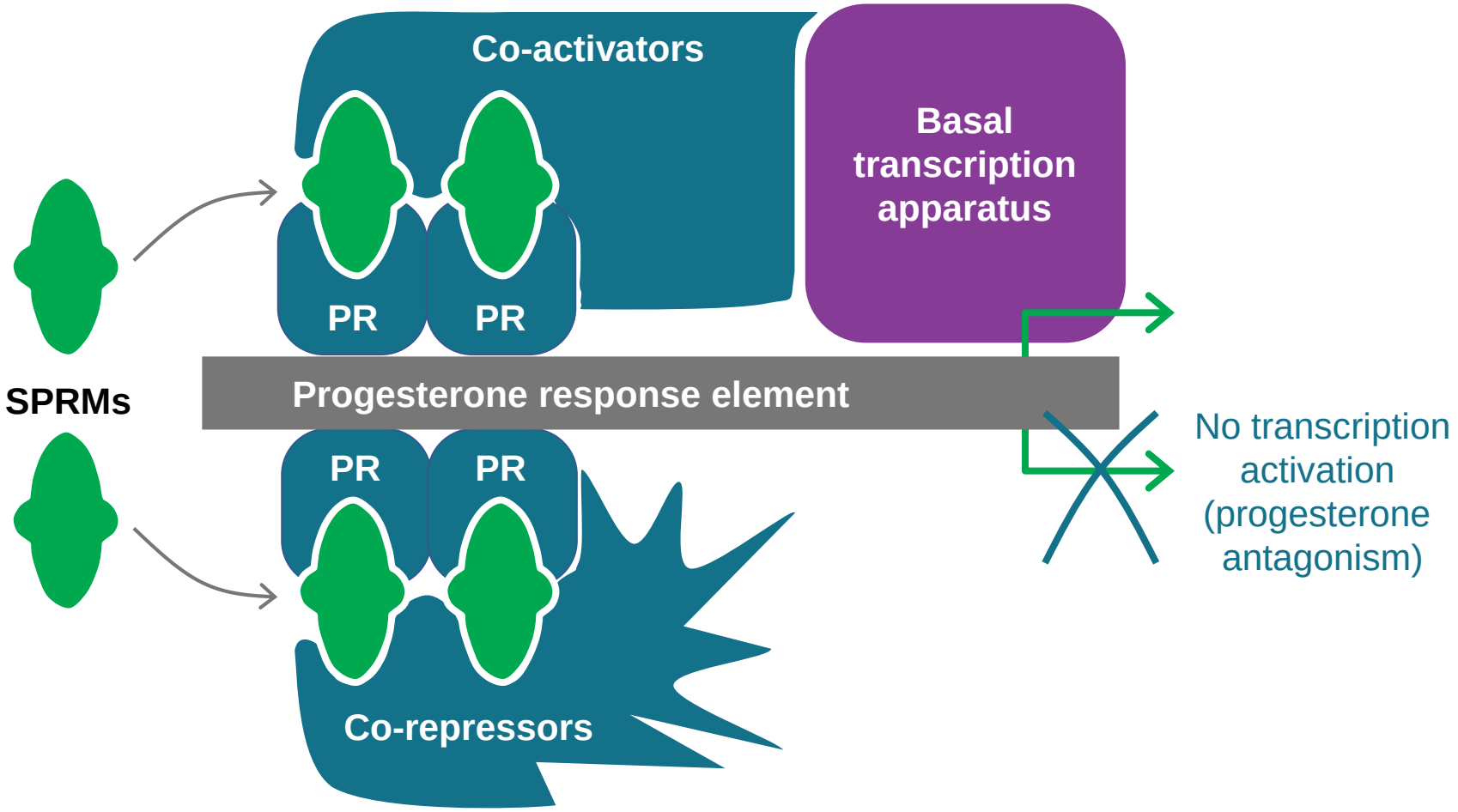


Mesoprogestins

Antagonists

Agonists

SPRMs Act as Progesterone Agonists or Antagonists Depending on the Target Tissue



Chabbert-Buffet N, et al. *Hum Reprod Update* 2005;11:293-307
Madauss KP, et al. *Mol Endocrinol* 2007;21:1066-81
Spitz IM. *Curr Opin Investig Drugs* 2006;7:882-90

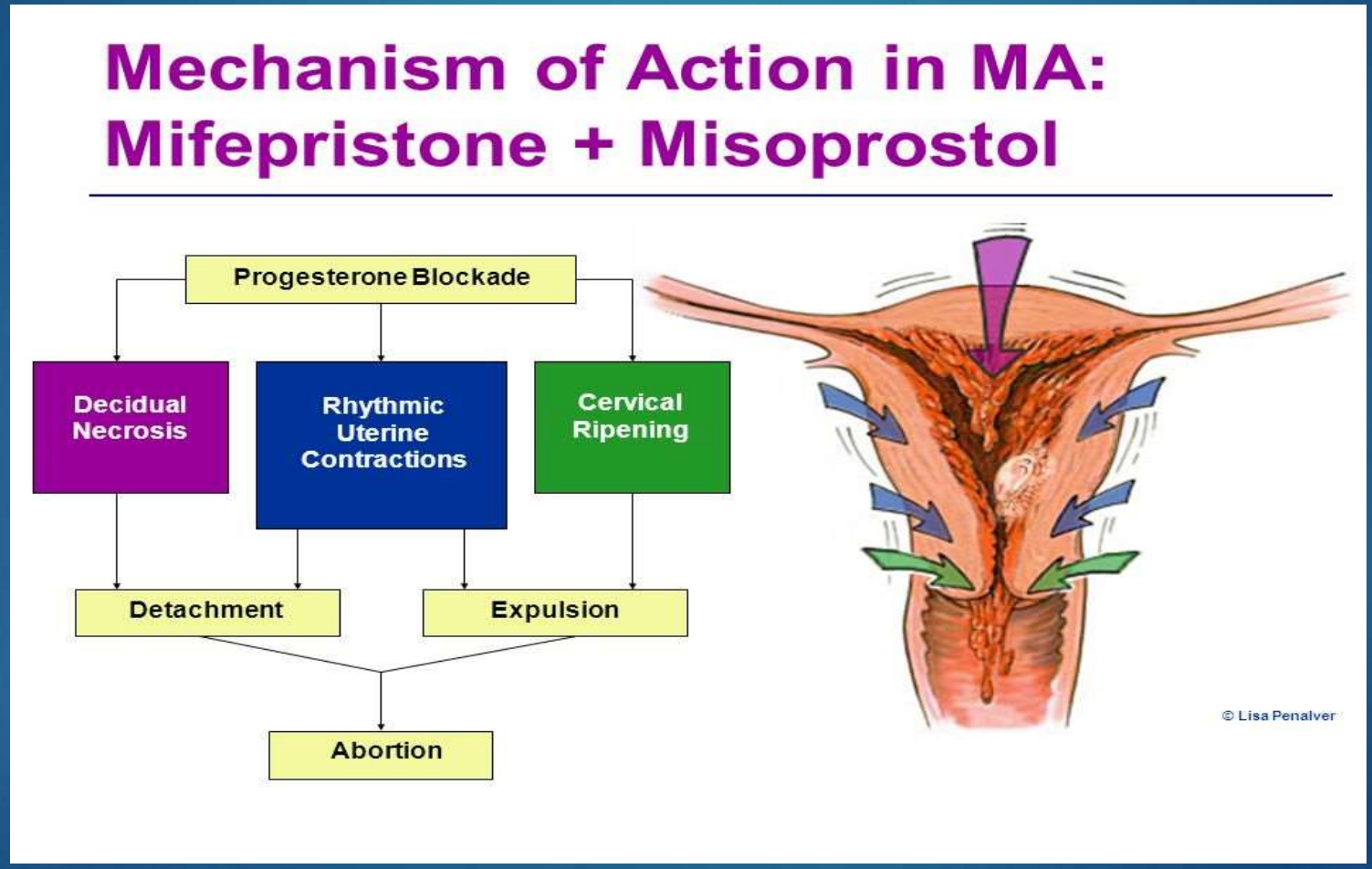
Misoprostol

What is misoprostol? How does misoprostol work?

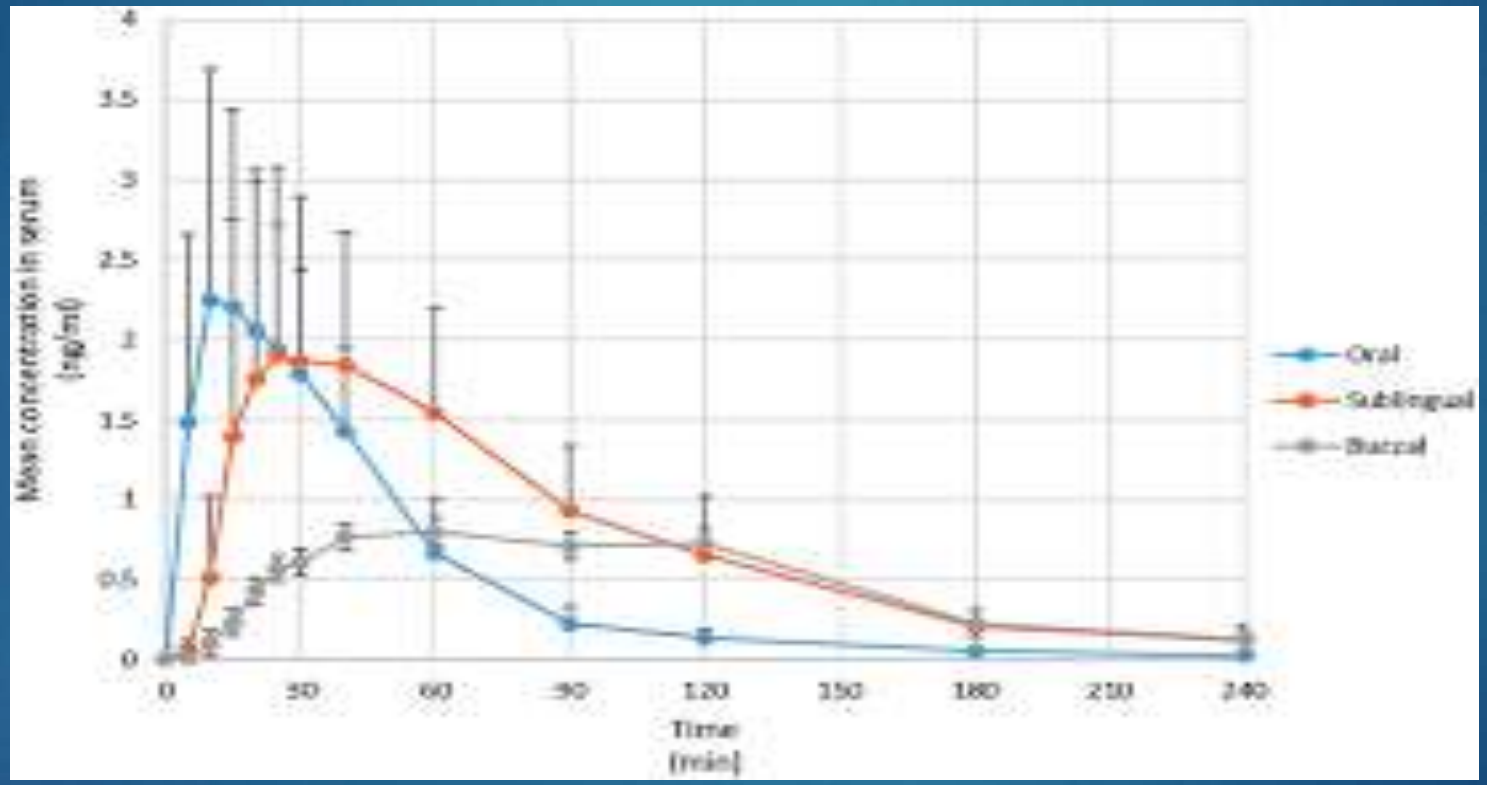
- Prostaglandin E1 analogue, approved for prevention and treatment of gastric ulcers
- Drug causes contractions of smooth muscles of the uterus -> empties the uterus
- Drug can soften the cervix -> increases dilation for interuterine procedures, facilitates expulsions

International Consortium for Medical Abortion

Mechanism of Action: M&M



Misoprostol: Pharmacokinetics



Protocol for Administration:

- Oral administration of Mifepristone 200 mg (single pill) followed by administration of 800 mcg Misoprostol 24-48 hours later
- Misoprostol: Buccal administration 4 pills , maintain between cheek and gums for 30 minutes, swallow remaining fragments with water
- Analgesics
- RH immune globulin prn
- IMPORTANT TO ENSURE FOLLOW UP 7-14 DAYS LATER TO ENSURE COMPLETED PREGNANCY TERMINATION

Side effects:

Frequent (10%)

- GI :(nausea, diarrhea, vomiting , abdominal pain
- NRO: Headache
- GYN: cramps, bleeding
- GEN: fever, chills, dizziness, fatigue

Rare (1%)

- GI: cramping
- GYN: prolonged bleeding, mastalgia
- ID: Endometritis

L'INTERRUPTION VOLONTAIRE DE GROSSESSE PRATIQUÉE À L'AIDE DE LA PILULE ABORTIVE

Directives cliniques

Décembre 2017

COLLÈGE DES MÉDECINS DU QUÉBEC

INESSS
LE SAVOIR PREND FORME

L'interruption volontaire de grossesse pratiquée à l'aide du Mifegymiso[MC]

(comprimé de mifépristone et comprimés de misoprostol)

Efficacité, innocuité, organisation des soins et considérations économiques

Février 2017

Une production de l'Institut national d'excellence en santé et en services sociaux

État des connaissances rédigé par
Geneviève Martin

Avec la collaboration de
Julien Baril, Cédric Jehanno et Marie-Claude Aubin

CMQ Guidelines for Use

Ainsi, parce qu'il doit tenir compte de ses compétences, de ses capacités et de ses limites dans l'exercice de sa profession[8], le médecin qui envisage de dispenser des soins relatifs à une interruption de grossesse, qu'elle soit médicale ou chirurgicale, doit :

- avoir suivi une formation initiale et s'assurer de posséder toutes les ressources afin d'évaluer les risques, les bénéfices et autres facteurs pouvant déterminer si la pilule abortive est une option appropriée pour la patiente. Cette formation en IVG aura été acquise lors du parcours universitaire de la formation médicale (p. ex., résidence pour les obstétriciens-gynécologues ou durant un stage en centre de planification familiale) ou par des activités de formation reconnues (p. ex., stage accrédité en IVG et en échographie de datation reconnu par le Collège).
- acquérir des connaissances sur l'IVG pratiquée à l'aide de la pilule abortive par toute formation qui respecte les obligations déontologiques[9] et les normes en matière de développement professionnel continu des médecins[10].

CMQ Guidelines: Ultrasound

Plus spécifiquement, l'échographie vise à :

- déterminer plus précisément la durée gestationnelle;
- préciser la localisation de la grossesse;
- exclure la possibilité d'une grossesse extra-utérine[13];
- faire ressortir des particularités qui nécessitent une exploration ou un suivi.

CMQ Guidelines: Follow up

La patiente doit se présenter à la visite de suivi 7 à 14 jours après la prise de mifépristone (MIFÉ).

Ce suivi aura pour objectifs de :

- confirmer que l'avortement est complet;
- rechercher la présence de complications;
- répondre aux différentes questions;
- rediscuter des plans en matière de contraception.

CMQ Guidelines for Follow Up

- US for confirmation of evacuation of pregnancy
- Serum hcg: Reduction of > 80% is associated with complete abortion
- < 80% requires US for confirmation

Annexe I

Fiche de renseignements

NOM DE LA PATIENTE : _____

DG : _____ jours en date du : _____

NOM DU MÉDICAMENT : _____

PRISE DE LA MÉDICATION

- Mifépristone : _____ (Date) _____ (Heure)
- Misoprostol : _____ (Date) _____ (Heure)

RENDEZ-VOUS DE SUIVI :

Dr _____ Endroit : _____

Prévu pour le : _____

POUR JOINDRE VOTRE MÉDECIN PRESCRIPTEUR ET RESPONSABLE DES SOINS :

_____

POUR JOINDRE LE MÉDECIN QUI ACCEPTE D'ASSURER VOTRE SUIVI DANS VOTRE RÉGION :

_____

POUR JOINDRE INFO-SANTÉ :

Faites le **811**

POUR TOUTE URGENCE QUI REQUIERT DES SOINS IMMÉDIATS :

Urgence majeure : faites le **911**

POUR UNE CONSULTATION À L'URGENCE, VOUS RENDRE À :

_____

Role of Antibiotic Prophylaxis?

- Used fairly systematically in surgical TOP with reduction on infectious morbidity
- Doxycycline 200 mg p.o. single dose
- No date for medical TOP
- NNT: 2,500

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 7, 2018 VOL. 378 NO. 23

Mifepristone Pretreatment for the Medical Management of Early Pregnancy Loss

Courtney A. Schreiber, M.D., M.P.H., Mitchell D. Creinin, M.D., Jessica Atrio, M.D., Sarita Sonalkar, M.D., M.P.H., Sarah J. Ratcliffe, Ph.D., and Kurt T. Barnhart, M.D., M.S.C.E.

ABSTRACT

BACKGROUND

Medical management of early pregnancy loss is an alternative to uterine aspiration, but standard medical treatment with misoprostol commonly results in treatment failure. We compared the efficacy and safety of pretreatment with mifepristone followed by treatment with misoprostol with the efficacy and safety of misoprostol use alone for the management of early pregnancy loss.

METHODS

From the Pregnancy Early Access Center (PEACE), Division of Family Planning (C.A.S., S.S.), Department of Obstetrics and Gynecology (C.A.S., S.S., K.T.B.), University of Pennsylvania, Philadelphia; the Department of Public Health Sciences, University of Virginia, Charlottesville (S.J.R.); the Department of Obstetrics

Primary Outcome: Gestational Sac Expulsion by First Follow up Visit

Table 2. Clinical Outcomes among Women Who Received Medical Treatment for Early Pregnancy Loss.

Outcome	Mifepristone-Pretreatment Group (N=148)	Misoprostol-Alone Group (N=149)	Relative Risk (95% CI)*
	number (percent)		
Gestational sac expulsion by the first follow-up visit: treatment success†	124 (83.8)	100 (67.1)	1.25 (1.09–1.43)‡
Gestational sac expulsion by the second follow-up visit at day 8	132 (89.2)	111 (74.5)	1.20 (1.07–1.33)
With 1 dose of misoprostol	130 (87.8)	106 (71.1)	
With 2 doses of misoprostol	2 (1.4)	5 (3.4)	
Gestational sac expulsion by the 30-day telephone call	135 (91.2)	113 (75.8)	1.20 (1.08–1.33)
With 1 dose of misoprostol	130 (87.8)	106 (71.1)	
With 2 doses of misoprostol	5 (3.4)	7 (4.7)	
Uterine aspiration§	13 (8.8)	35 (23.5)	0.37 (0.21–0.68)

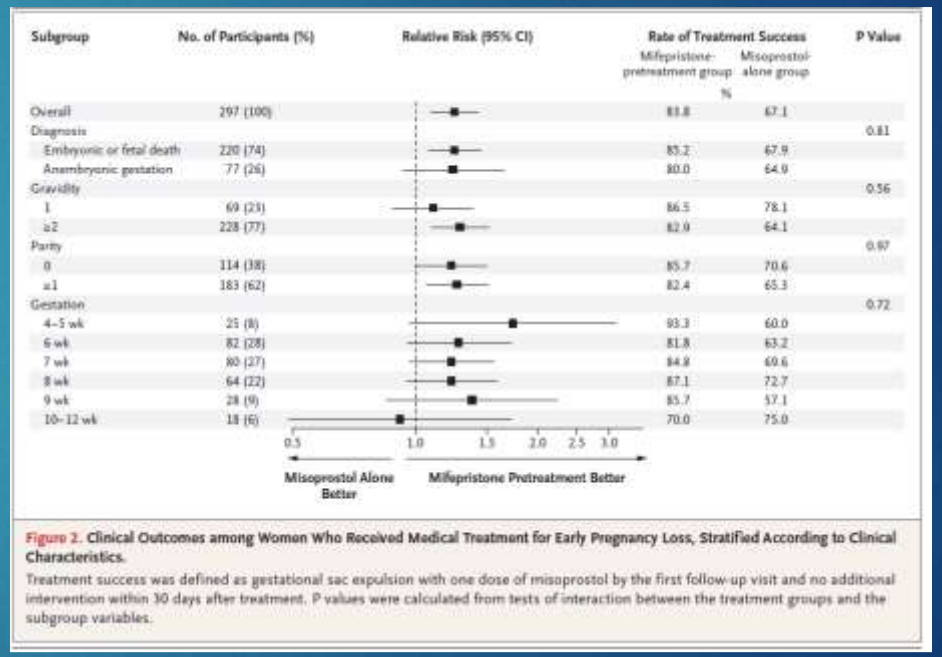


Figure 2. Clinical Outcomes among Women Who Received Medical Treatment for Early Pregnancy Loss, Stratified According to Clinical Characteristics.

Treatment success was defined as gestational sac expulsion with one dose of misoprostol by the first follow-up visit and no additional intervention within 30 days after treatment. P values were calculated from tests of interaction between the treatment groups and the subgroup variables.

Initiation of Contraception

- Rapid return of ovulation 20.6 +/- 5.1 days
- As early as 8 days post abortion
- Can initiate hormonal contraception same or following day as administration of Misoprostol
- Barrier methods can be used immediately
- IUD/IUS insertion with conformation of successful TOP

Conclusions:

- Combination of Mifepristone and Misoprostol provide an effective option for early medical abortion
- Evaluate for contraindications prior to use
- Patient counselling is essential
- Accurate determination of gestational age is essential, preferable by ultrasound
- Follow up must be assured to confirm successful termination of pregnancy