Update on Miscarriage

November 25 2021
Victoria BC

Konia Trouton, Clinical Professor, UBC
Medical Director, Vancouver Island Women's Clinic

Objectives

- Triage early pregnancy loss
- Apply appropriate management of miscarriage for outpatients
- Describe appropriate use of cytogenetic analysis in pregnancy loss
- Propose RhIG as needed

Faculty/Presenter Disclosure

- **Faculty:** Konia Trouton
- **Relationships with commercial interests:** *none*
- **Grants/Research Support**: *Bayer*
- **Speakers Bureau/Honoraria:** *Bayer, Merck, Organon, Searchlight*
- **Consulting Fees:** *Searchlight, Celopharma*(Linepharma)*

Mitigating Potential Bias

- Generic names will be used in the presentation
- Reference will be made to literature and research that is published in the peer reviewed literature
- No Linepharma sponsored research will be discussed (there is none)

Defining miscarriage

Evidence may be one or more of the following;

1. Non rising HCG from early lab work
   - HCG plateau about 8-10 weeks, ***so not always reliable***
2. Sac with no embryo on ultrasound (**ANEMBRYONIC**)
   - Sac needs to be 30mm on transabdominal US, or 20mm on transvaginal
3. Embryo with no heartbeat on ultrasound (**FETAL DEMISE**)
   - Embryo needs to be over 5mm to see this (over 6 week 5days)

NOTE: HCG needs to be **at least 1500** for TRANSVAGINAL US (**better if over 2500**)

Types and Options

Type of miscarriage

A. Incomplete
   - Retained products of conception (RPOC), after some bleeding

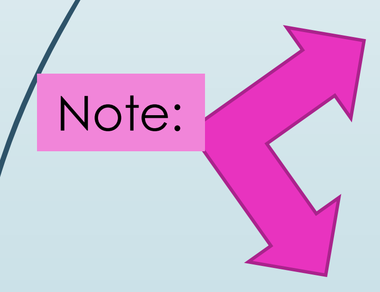
B. Missed
   - Fetal demise (60-70%)
   - Anembryonic (30-40%)

Type of management

1. Expectant (Wait & Watch)
2. Medical Management
3. Surgical Aspiration (D&SC)

Expectant Management

- If wait 2 weeks from diagnosis,
  - 84% of those with RPOC or **<u>incomplete</u>** will complete without intervention
  - 72% with **<u>fetal demise</u>** will pass without intervention
  - 66% of those with **<u>anembryonic</u>** pregnancy



Medical Management for **MISSED** >> Misoprostol only

prostaglandin E1

misoprostol (Cytotec®)

Use of Misoprostol is **OFF LABEL** in Canada

Rx: **800mcg** (4x200mcg) pv or sl, **repeated 4-24 hours later** if minimal bleeding

Use NSAID and acetaminophen for pain relief

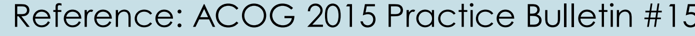
FU: HCG (drop over 80%) or ultrasound a week later

Medical Management- **INCOMPLETE**

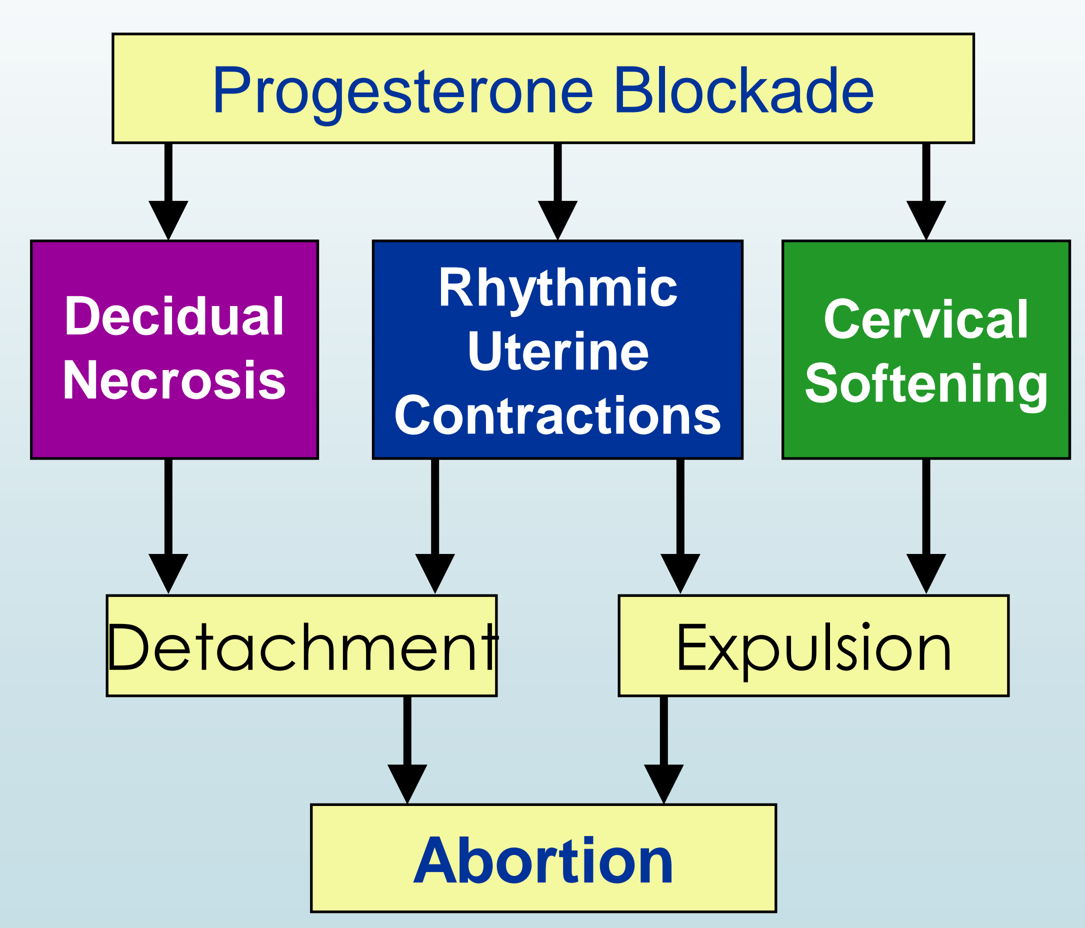
- Incomplete (started **bleeding**)
  - **600mcg** misoprostol PV comparable to aspiration (WHO)

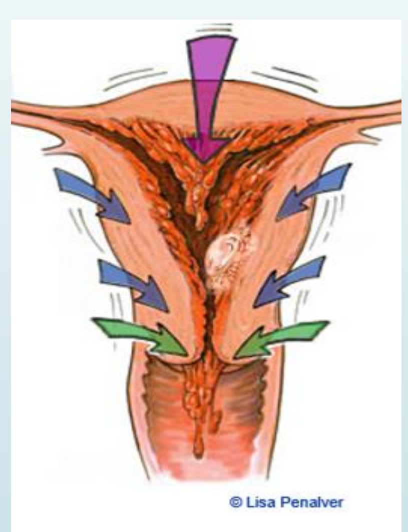
  One dose only

  Follow up with HCG or ultrasound a week later


Reference: ACOG 2015 Practice Bulletin #150

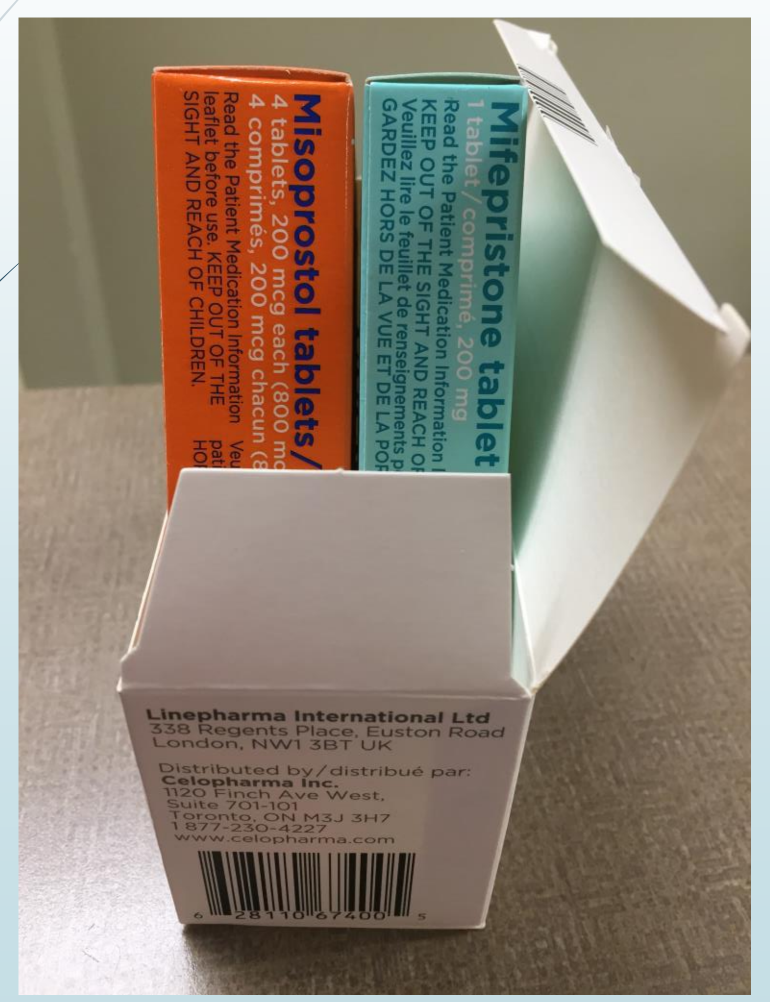
Mifepristone: would it be useful?



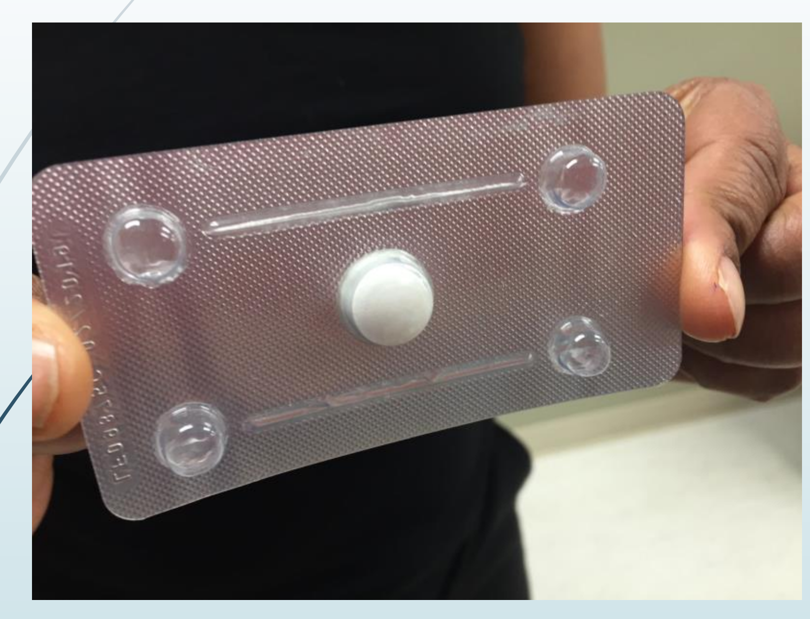


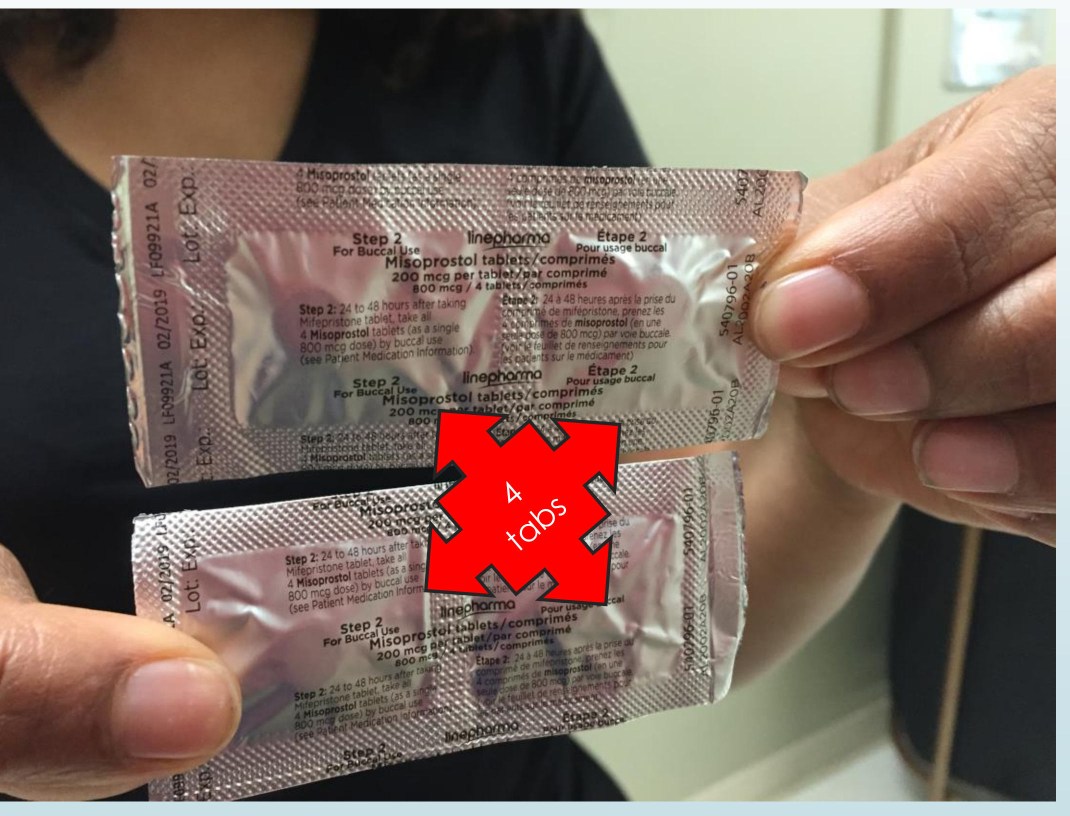
Is mifepristone available in Canada? **ONLY** in combination package

2 boxes inside. Mifepristone/Misoprostol. Only country where packed together.



Single mifepristone
4 tablets of misoprostol 24-48 hrs later





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

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

Findings in the NEJM Schreiber paper

WHO?

300 women

Anembyonic or demise (MISSED)……NOT RPOC

Not bleeding, **closed cervix**

WHAT?

200mg Mifepristone, then 800mcg misoprostol PV 24 hours later

Or

800 mcg misoprostol PV (one dose)

FOLLOW UP?

FU 1-4 days later for US evaluation

FU 30 days later with options of W&W, Miso, or ASPIRATION

Conclusions

Complete expulsion at 1-4 days

- 124 of 148 women (**83.8%;** 95% confidence interval [CI], 76.8 to 89.3) in the mifepristone-pretreatment
- 100 of 149 women (**67.1%;** 95% CI, 59.0 to 74.6) in the misoprostol-alone group

Complications

Uterine aspiration:

- was performed **less** (**8.8% vs. 23.5%)** in the mife-miso

Bleeding that resulted in blood transfusion

- occurred in **less** (**0.7% vs 2%**, but NS) in the mife-miso

Pelvic infection

- **1.3%** of the women in each group.

What is the US changed?

Recommendations and Conclusions

The following recommendation and conclusion are based on good and consistent scientific evidence (Level A):

- In patients for whom medical management of early pregnancy loss is indicated, initial treatment using 800 micrograms of vaginal misoprostol is recommended, with a repeat dose as needed. The addition of a dose of mifepristone (200 mg orally) 24 hours before misoprostol administration may significantly improve treatment efficacy and should be considered when mifepristone is available.

ACOG Practice Bulletin 200
November 2018

What is the cost?

- For those who take it in the province they are insured in- no cost

  E.G. Person residing in BC needs mife/miso while in BC

- For those whose **health card is from another province-** **$270**

  E.G. Person residing in BC while at university, but with OHIP only

If you use it… **ON LABEL USE**

- Consenting woman
- Under **9 weeks** from LMP
- **Rh testing** and offer WinRho
- Hemoglobin over 100
- Support with **24/7 on-call**
- Ensure **follow up** in 7-14 days

Exclusion criteria

- IUD in situ
- Confirmed or suspected **ectopic pregnancy**
- Chronic adrenal failure
- **Hemorrhagic disorder** or currently on anticoagulant therapy
- Allergy to one of the medications
- Current long-term steroid use
- Inherited porphyria

Side effects of mifepristone and buccal misoprostol

Adverse Reaction	Number of Evaluable Women	Range of frequency (%)
Nausea	1,248	51-75%
Weakness	630	55-58%
Fever/chills	414	48%
Vomiting	1,248	37-48%
Headache	630	41-44%
Diarrhea	1,248	18-43%
Dizziness	630	39-41%

What is the range of cramping and bleeding?

No noticeable pain
light bleeding

Intense pain
heavy bleeding

When is miscarriage completed?

1. Ultrasound before and after
   - Pregnancy present
   - Pregnancy absent
2. HCG before and after* (*helpful* ***ONLY*** *if symptoms also gone*)
   - Drop of over 50% in 48 hours
   - Drop of over 80% in 7 days
3. Symptoms before and after
   - Nausea, breast tenderness, fatigue
   - Lots of bleeding, more than a period, and absence of symptoms
   - Pregnancy test negative at 1 month

When do we need surgical aspiration (suction curettage)?

- Persistant RPOC: 10-15% of those using medical management
- Those who prefer surgical management
- Those cases that cytogenetic evaluation indicated
- Those who are not eligible for medical management

Surgical Aspiration

- Risks reduced with pre-operative antibiotic use and use of sedation rather than general anesthesia
- Risks are low (under 1%) , but include Infection, perforation, cervical trauma, uterine synechia and anesthetic risks
- No evidence that return to fertility is any different with any approach to miscarriage or abortion care
- Can ovulate as soon as 7-8 days after management

When should cytogenetic analysis be ordered?

Where the etiology of the loss is needed-

1. When several losses. This may suggest an unbalanced chromosome complement especially if there is also a family history in previous generations or in other branches
2. To reduce recurrence (e.g. IVF)
3. Patient reassurance/compassionate reasons

Q: Will there be any change in clinical management with this information?

For some cases, the answer is yes:

- Where advanced maternal age limits the time left to become pregnant.
- Pregnancies that were achieved with donor sperm, IVF, other interventions.

Reference-"Overview of Chromosome Abnormalities in First Trimester Miscarriages: A Series of 1,011 Consecutive Chorionic Villi Sample Karyotypes"
Soler A, Morales C, Mademont-Soler I et al
Cytogenetic and Genome Research 2017;152:81-89

Chromosome	# of cases with trisomy
2	8
4	12
5	1
6	7
7	13
8	8
9	12
10	13
11	3
12	6
13	30
14	15
15	65
16	86
17	2
18	24
20	13
21	56
22	85
total	**459**

- **An abnormal karyotype was detected in 70%**
- Single autosome trisomy was the most common abnormality (64.5%)
- Followed by triploidy (13.1%)
- Monosomy X (10.4%)

How is this done?

- Cytogenetic analysis analyses chromosomes.
  - Use the CYTOGENETIC requisition when possible
- Chromosomes are prepared from LIVING, dividing cells so…
  - No formalin
  - As little bacteria contamination as possible, but moist with normal saline
  - No delays in transit to the cytogenetics lab (inside pathology dept)- VGH
  - Rinsed and separated by pathologist on site (Monday-Friday 8-4 usually)
  - No extreme temperature changes

Chromosome preparation

Fibroblast cells grown on glass slides.

1.

2. Colchicine (metaphase arrest)

3. Hypotonic solution;
4. Fixative.

5. Stain with trypsin, Giemsa.

6. Microscope Analysis.

7. Digital capture & karyotyping

8. Report written

Why is there sometimes no result?

- Sometimes the loss has occurred earlier, no living cells available.
- Cells can die in transit.
- Sometimes they are contaminated with bacteria.
- Sometimes there is maternal decidua-

  Is a 46,XX results from mother or female fetus?

Tissue culture and chromosome preparation is labour intensive and requires skill.

When is it better to test the couple?

- General rule: Order karyotype analysis on peripheral blood lymphocytes for both members of a couple who have experienced **two or more** spontaneous pregnancy losses (**on the 3rd SA**)

- Chromosome translocations occur in the general population at ~1/600.

- Any couple undertaking **IVF or donor sperm** insemination or ICSI or other
  - Both members of a couple should have karyotype analysis
  - Blood karyotype is relatively simple, inexpensive and fast when compared to IVF.
  - IVF couples are often of later age, may have less time

VIWC services

- Fax all relevant information (all or any HCG, US and Rh status)
  - Fax: 250 480 7339
- Call private line to see when we can book them (NOT FOR PATIENTS)
  - Private number for clinicians; **250 480 7377**
- Nurse educator will call, and next day, physician will see them
- On-call number will be provided **778 265 4111**
- Medical management and FU OR surgical aspiration will be organized
- **WinRho will be given as needed**

**** VIWC is accredited by the BC College as a limited LAB to test and treat**

WinRho (Rh Immune Globulin)

- COVID presented obstacles to access
- SOGC is reviewing information and guidelines
- Canadian blood services not updated in decades
- WHO indicates only to test and offer <u>where Rh negative is prevalent</u>
- Royal College UK says <u>not to test</u> or offer for SA <u>under 12 weeks</u>
- Netherlands since 2002 only tests and treats <u>over 10 week SA</u>
- Hollenbach et all in Contraception Journal 2019 that fetal cells only detected by the flow cytometry method with 17 – 18 week terminations, not before (D&SC up to that point are do not provoke isoimmunization)

Summary of Recommendations

	ACOG[1–5] (2006, 2012, 2015, 2016, 2017)	SOGC[6] (2003)	RCOG[7–9] (2010, 2011, 2014)	RANZCOG[10–12] (2013, 2015)
Complete or incomplete <12 wk	Yes	Yes	No	Yes
Threatened <12 wk	NS[a]	Yes	NS[a]	No
Threatened >12 wk	Yes	Yes	Yes	Yes
Ectopic pregnancy	Yes	Yes	Yes	Yes
Invasive intrauterine procedures[b]	Yes	Yes	Yes	Yes
Antepartum hemorrhage	Yes	Yes	Yes	Yes
Abdominal trauma	Yes	Yes	Yes	Yes
External cephalic version	Yes	Yes	Yes	Yes
Molar pregnancy	Yes	Yes	Yes	Yes
Defer, if complete mole	No	Yes	Yes	No
Stillbirth	Yes	NS	Yes	NS

Sperling 2018

Informed consent to decline testing & treatment- (*from AnnuaSOGC 2021*)

01

< 8 weeks do not need testing or treatment

02

8-10 weeks discuss options

03

> 10 weeks suggest testing & treatment

What should we do about Rh negative?

Test RhIG eligibility for all in early pregnancy

Do the test at the **Hospital**, not Life Labs

If under 8 weeks by fetal size (CRL 14m), and miscarrying, ***can*** offer
If over 8 weeks, and miscarrying, ***should*** offer

Do not stress if you miss the 72 hour window to administer

RhIG lasts about 3 weeks, and re-checking antibody levels can be done

Trying again- the EAGER trial

- Multi-center study of 1000 women given no particular advice;

- Those (76.7%) tried within 3 months and became pregnant;
- 53.2% had a baby

- Those (23.4%) waited over 3 months before trying
- 36.1% had a baby

And if not trying again….

- LARC is the best option
  - IUD can be inserted with surgical aspiration
    - Or when bleeding subsides after use of medication
  - Implant (Nexplanon) is now available as of September 2020
    - Can be inserted with aspiration
    - Can be inserted same day as Mifepristone

Questions?