MMM: USING MISOPROSTOL, MIFEPRISTONE, AND METHOTREXATE FOR EARLY PREGNANCY LOSS AND TERMINATION

FMF November 11, 2017
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OBJECTIVES

- Choosing appropriate spontaneous abortion patient for treating with misoprostol
- In early abortions (spontaneous/induced), describe the risks and side effects of
  - Misoprostol
  - Mifepristone
  - Methotrexate
- Safely use protocols for treating early ectopic pregnancies (and PUL) with methotrexate
OUTLINE

- 4 common clinical scenarios
- Ensuring correct diagnosis
- Treatment options
- Treatment side effects
- Treatment success rates
- Managing failure
1) **Alice**

- Alice (29 y o, G1,P0) presents with a missed abortion, 10 weeks by dates. She had gone to ER as she was spotting. **US reports 30mm sac with no embryo**
2) BELL

- Bella (40 y o, G3P2) presents with bleeding at 14 weeks from LMP. Ultrasound shows fetal demise. Fetus is 20mm in length (8+ week size). Rh negative.
3) **Candice**

- Candice (18 y o, G1) presents with unplanned pregnancy that she wants to abort. She is 6 weeks from LMP and HCG levels are 45000. Ultrasound is booked in 2 weeks time.
4) ERICA

- Erica comes to you to get her depo provera dose but she is 2 weeks late to receive it. You do a urine pregnancy test which is faintly positive.
VALUE OF THE ULTRASOUND

- Transvaginal
  - Discriminatory value
  - bHCG must be over 1500-2000 to see anything

- Transabdominal
  - Discriminatory value 2500-3000

- Ultrasound for anembryonic/demise (missed)
  - 20mm sac and no yolk
  - 30mm sac and no embryo
  - No fetal heart beat (CRL> ~4mm)
**Blood Tests**

- **Rh factor**
  - CBS – all cases, SOGC – only above 7 weeks
  - Up to 72 hours from end of pregnancy (passing)

- **CBC**
  - Baseline if women anemic
  - If heavy or prolonged bleeding (over 10 days)

- **HCG levels (Quantitative)**
  - Used for diagnosis and for follow/up than serial ultrasound
ESTABLISHING EARLY PREGNANCY VALUE OF $\beta$-hCG

- > 25 mIU by 7 days after **implantation** in 98%
- doubles q 1.3-2 days (32-48 hours) up to 6 weeks
- rise slower until peak at 9-10 weeks
- if rise < 50% over 48 hours
  ⇒ pregnancy abnormal (99+%)  
- if falls > 50% over 48 hours, >80% 1 week  
  ⇒ pregnancy gone (99+%)
ASSESSMENT ALSO INCLUDES....

- No bleeding/clotting disorder
- No allergy to misoprostol
- Adequate liver & kidney function (methotrexate)
- No long Q-T interval/Adrenal insufficiency (mifepristone)
- No contraindications to NSAIDs
- CONSENT and understanding of treatment
1) **Anembryonic Pregnancy**

- Alice (29 y o, G1,P0) presents with a missed abortion, 10 weeks by dates. She had gone to ER as she was spotting. US reports 30mm sac with no embryo
2) **Fetal demise**

- Bella (40 y o, G3P2) presents with bleeding at 14 weeks from LMP. Ultrasound shows fetal demise. Fetus is 20mm in length (8+ week size).
- Rh negative.
3) **UNPLANNED EARLY PREGNANCY**

- Candice (18 y o, G1) presents with unplanned pregnancy that she wants to abort. She is 6 weeks from LMP and HCG levels are 45000. Ultrasound is booked in 2 weeks time.
4) PUL OR ECTOPIC PREGNANCY

- Erica comes to you to get her depo provera dose but she is 2 weeks late to receive it. You do a urine pregnancy test which is faintly positive. An ultrasound shows nothing in the uterus or adnexae
Misoprostol
Mechanism of Action

- Misoprostol – a prostaglandin analogue of PGE$_1$
  - Stimulates uterine contraction
  - Softens the cervix
  - Also GI effects: nausea, diarrhoea

- Expulsion of products of conception

- THIS IS OFF LICENSE USE
From Zieman et al Obstet Gynecol 1993
MISOPROSTOL
WHAT WOMEN EXPERIENCE

- Nausea ~ 30%
- Diarrhea ~ 30%
- Chills – transient, < 24 hours ~ 10%
- Fever- transient, < 24 hours ~ 10%
- If buccal, burning, itchy throat ~ <5%

- ....Very small chance of teratogenicity
BEST PUBLISHED REGIMES

- For failed pregnancy;
  - 800mcg vaginally with second insertion of 800mcg 1-3 days later if no expulsion. Evaluate on day 8 and consider surgery if incomplete

- For abortion when NO methotrexate or mifepristone available;
  - 800mcg sublingual or vaginal 800 mcg with subsequent doses every 3-12 hours for maximum or 3 doses. Vaginal better than sublingual in nulliparous
  - 15% risk of ONGOING pregnancy...

Ref: WHO updates June 2012 – “Safe abortion: technical and policy guidelines for health systems” and Ipas website (supported by WHO)
TREATMENT OUTCOME (SA)

Medication (misoprostol)  | success | failure |
---------------------------|---------|---------|
Fetal demise               | 0.878   | ~12%    |
Anembryonic                | 0.807   | ~20%    |
Incomplete                 | 0.933   | ~7%     |


RCT of ~500 women in each group
Mifepristone (Mifegymiso)

- Mifepristone 200mg oral + Misoprostol 800mcg (buccal, pv) 24-48 hours later
- SOGC, Celopharma and NAF: have on-line training modules
- Check with pharmacist or company for availability
Courses

December 21, 2016 to December 21, 2017
1:40 PM - 11:57 AM

Accredited Medical Abortion Training Program

Info

Training program modules

1. Overview of medical abortion in Canada
2. Pre-abortion care
Welcome to Canada’s online community for health professionals certified to provide Mifepristone.

- Exchange tips, resources, and best practices
- Gain feedback from experts
- Locate pharmacies in your region

To become a member, please fill in the Registration Form

Access to this site is restricted to certified Mifepristone providers.
For more information, visit our About page.
Mifepristone Mechanism of Action

- Competitive progesterone receptor antagonist
- Softens cervix
- Primes uterus for misoprostol (24-72 hours)
- Non-teratogenic
Clinical Practice Guidelines

Search Guidelines

Medical Abortion (Replaces No. 184, Nov. 2006)

332 - Published April 2016

Full Guideline

Download

Please follow the link to access the English copy of the Medical Abortion that was published in the April 2016 Issue of the JOGC.
Indication: Termination of a developing intra-uterine pregnancy with a gestational age up to nine weeks (63 days) as measured from the first day of the last menstrual period.

Language changed from physicians to ‘health professionals’

Pharmacists can dispense directly to patients

No mandatory training - "health care professionals should have the appropriate knowledge."

The requirement to register with the manufacturer prior to prescribing or dispensing has been removed.

Informed consent must be discussed but signed consent not required
Current Health Canada Approval November 7, 2017

- **Health professionals** are required to do the following prior to prescribing MIFEGYMISO:
  - Provide the patient with the current Patient Medication Information and a completed Patient Information Card
  - Exclude ectopic pregnancy and confirm gestational age by ultrasound
  - Counsel on the effects and risks
  - Ensure that patients have access to emergency medical care in the 14 days following administration of mifepristone; and,
  - Schedule a follow-up 7 to 14 days after patients take mifepristone to confirm complete pregnancy termination and monitor for side effects.
EVIDENCE-BASED REGIME

- Health Canada vs SOGC
- 9 weeks vs 10 weeks gestation
- Baseline mandatory US vs US when needed
- Follow-up either HCG or US
WHAT TO EXPECT

- Rare mild SE from mifepristone
- Same SE from misoprostol (nausea, vomiting, diarrhea, fever, chills)
- Bleeding and cramps
- 99.5% successful in stopping pregnancy BUT about 4% have D&C for bleeding/RPOC/delayed
METHOTREXATE
MECHANISM OF ACTION

- Antimetabolite
  - Folic acid antagonist
- Affects rapidly growing cells (like trophoblast)
- 85% effective as a single agent
- VERY teratogenic
- Used alone for ectopic, with miso for MA

THIS IS OFF LICENSE USE IN PREGNANCY
BEST PUBLISHED REGIME

- Start with pregnancy no more than 49 days from LMP, i.e. CRL 9mm on day of injection
- Methotrexate 50mg/m² either IM or oral
- Misoprostol 800mcg vaginally, buccal or sublingual (NOT oral) every 4-12 hours starting 1-6 days later
- More side effects with non-vaginal route

- Ref: Medical methods for first trimester abortion, the Cochrane Collaboration 2010
TREATMENT SUCCESS  (NO SURGERY)

- Methotrexate/one dose miso 0.73 (0.94 at 1 m)
- Methotrexate/3 doses miso 0.80 (0.95 at 1 m)
- Mifepristone/ one dose miso 0.93 (0.97 at 1 m)

Serious complications with mife/miso & mtx/miso
  - Excess bleeding 0.0005  Infection 0.0008

Success with vacuum aspiration 0.99
No complications 0.99
  - Excess bleeding 0.0003  Infection 0.0097

Ref. Limacher et al, Early abortion in Ontario: Options and Costs JOGC February 2006
Methotrexate/Misoprostol vs. Mifepristone/Misoprostol

By 4 weeks both have 96% success, but methotrexate much slower and ongoing pregnancy 0.4% vs 0%.
More miso used with MTX + more side effects
COPING WITH SYMPTOMS/FEARS

- Prepare her for the symptoms/bleeding
- Analgesics and anti-emetics (Gravol PO and PR, ibuprofen, T#3, oxycodone)
- Follow-up appointment (?telemedicine)
- 24 hour phone
FOLLOWING YOUR PATIENT

- Administer medication, then...
  - HCG
  - Ultrasound
  - Suction D&C

- Cytogenetics
1) ANEMBRYONIC PREGNANCY

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2) **Fetal Demise**

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**FOLLOW-UP**

- **Ultrasound:** sac or no sac (RPOC should diagnosed clinically)
- **HCG:** complete if >80% drop in 1 week or >50% drop in 2 days
- **For incomplete PUL,** weekly HCG until <10
- **For incomplete IUP,** offer choices
ECTOPIC PREGNANCIES

- MTX alone for HCG 2000-5000
- MTX with MISO or MIFE with MISO for PUL (HCG<2000)
- High risk or low risk?
  - Previous ectopic
  - IUD in place
  - Hx severe PID
WHAT ABOUT TREATMENT FAILURE?

- Viable pregnancies: 0.5% MIFE/MISO, 1% MTX/MISO
  Choices: Surgery/repeat meds
- Non-viable pregnancies: intact sac or incomplete (retained products of conception)
  Choices: Wait and see/surgery/more meds
OTHER CONSIDERATIONS

- Women’s emotional well being is linked to *her* choice and *her* timing of the process.

- Expressing sadness for the loss

- Spiritual considerations

And ...

- Contraception.

Ovulate as soon as 8 days after bleeding starts!
RESOURCES

- Willow Clinic www.willowclinic.ca
- CAPS www.caps-cpca.ubc.ca/
- National Abortion Federation http://www.prochoice.org/education/cme
- http://www.medicationabortion.com/
- SOGC guidelines https://sogc.org/