

RCT

Potential PURL Review Form

PURL Jam Version

PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL [to be completed by PURLs Project Manager]

- A. Citation: Schreiber CA, Creinin MD, Atrio J, Sonalkar S, Ratcliffe SJ, Barnhart KT. Mifepristone Pretreatment for the Medical Management of Early Pregnancy Loss. N Engl J Med. 2018 Jun 7;378(23):2161-2170. doi: 10.1056/NEJMoa1715726. PubMed PMID: 29874535
- B. Link to PubMed Abstract: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29874535>
- C. First date published study available to readers: 6/7/2018
- D. PubMed ID: 29874535
- E. Nominated By: Emily White VanGompel
- F. Institutional Affiliation of Nominator: University of Chicago, NorthShore
- G. Date Nominated: 6/8/2018
- H. Identified Through: NEJM
- I. PURLs Editor Reviewing Nominated Potential PURL: Dean Seehusen
- J. Nomination Decision Date: 6/9/2018
- K. Potential PURL Review Form (PPRF) Type: RCT
- L. Assigned Potential PURL Reviewer: David Moss
- M. Reviewer Affiliation: Nellis Air Force Base
- N. 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:

We randomly assigned 300 women who had an anembryonic gestation or in whom embryonic or fetal death was confirmed to receive pretreatment with 200 mg of mifepristone, administered orally, followed by 800 µg of misoprostol, administered vaginally (mifepristone-pretreatment group), or 800 µg of misoprostol alone, administered vaginally (misoprostol-alone group). Participants returned 1 to 4 days after misoprostol use for evaluation, including ultrasound examination, by an investigator who was unaware of the treatment-group assignments. Women in whom the gestational sac was not expelled were offered expectant management, a second dose of misoprostol, or uterine aspiration. We followed all participants for 30 days after randomization. Our primary outcome was gestational sac expulsion with one dose of misoprostol by the first follow-up visit and no additional intervention within 30 days after treatment.

RESULTS:

Complete expulsion after one dose of misoprostol occurred in 124 of 148 women (83.8%; 95% confidence interval [CI], 76.8 to 89.3) in the mifepristone-pretreatment group and in 100 of 149

women (67.1%; 95% CI, 59.0 to 74.6) in the misoprostol-alone group (relative risk, 1.25; 95% CI, 1.09 to 1.43). Uterine aspiration was performed less frequently in the mifepristone-pretreatment group than in the misoprostol-alone group (8.8% vs. 23.5%; relative risk, 0.37; 95% CI, 0.21 to 0.68). Bleeding that resulted in blood transfusion occurred in 2.0% of the women in the mifepristone-pretreatment group and in 0.7% of the women in the misoprostol-alone group (P=0.31); pelvic infection was diagnosed in 1.3% of the women in each group.

CONCLUSIONS:

Pretreatment with mifepristone followed by treatment with misoprostol resulted in a higher likelihood of successful management of first-trimester pregnancy loss than treatment with misoprostol alone. (Funded by the National Institute of Child Health and Human Development; PreFaiR ClinicalTrials.gov number, NCT02012491 .).

O. Pending PURL Review Date: 1/17/2019

SECTION 2: Critical Appraisal of Validity [to be completed by the Potential PURL Reviewer]

- A. Number of patients starting each arm of the study?
Experimental (mifepristone pre-treatment): 149
Control (misoprostol alone): 151
- B. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)
Inclusion: Healthy females over the age of 18, determined to have a non-viable intrauterine pregnancy identified by ultrasound.
Exclusion: Incomplete or inevitable abortion as identified by ultrasound, viable or ectopic pregnancy, pregnancy with IUD, hemoglobin <9.5 g/dL, known clotting defects or on anticoagulation, contraindication to misoprostol or mifepristone, did not desire to participate in the study.
Demographics: Participants averaged 30 years old, include a variety of race or ethnic groups, as well as a variety of education levels.
Setting: Women were recruited over a three year span (May2014-Apr2017); clinical setting and geographic location not discussed in the article.
- C. Intervention(s) being investigated?
Management of anembryonic gestation and embryonic or fetal death in women in clinically stable condition who have a closed cervical os
- D. Comparison treatment(s), placebo, or nothing?
Pre-treatment with mifepristone followed by treatment with misoprostol compared to misoprostol use alone
- E. Length of follow-up? (Note specified end points, e.g., death, cure, etc.)
Initial follow up (at least 24 hours but not more than four days), eight day follow up, thirty day follow up
- F. What outcome measures are used? List all that assess effectiveness.
Primary outcome: Gestational sac expulsion by the first follow-up appointment without additional intervention within 30 days.

Also had planned assessments of the treatment outcomes at the day 8 and 30 time points. Secondary outcomes included adverse effects, acceptability of treatment, and assessment of clinical characteristics associated with complete gestational sac expulsion.

- G. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CU, p-values, etc.

Treatment success at first follow-up appointment occurred in 124 of 148 women (83.8%; 95% confidence interval [CI], 76.8 to 89.3) in the mifepristone-pretreatment group; treatment success in the misoprostol alone group occurred in 100 of 149 women (67.1%; 95% CI, 59.0 to 74.6). Absolute difference in the rate of treatment success was 16.7 percentage points [95% CI, 7.1 to 26.3]; relative risk of expulsion with one dose of misoprostol, 1.25 [95% CI 1.09 to 1.43]. The number needed to pretreat with mifepristone to attain an additional outcome of treatment success by the first follow-up was six.

- H. What are the adverse effects of intervention compared with no intervention?

There were no significant between-group differences in rates of serious adverse events (bleeding resulting in blood transfusion, pelvic infection, nausea, diarrhea, etc.).

- I. The study addresses an appropriate and clearly focused question.
(select one) Well covered

Comments:

- J. Random allocation to comparison groups:
(select one) Well covered

Comments:

- K. Concealed allocation to comparison groups:
(select one) Well covered

Comments:

- L. Subjects and investigators kept "blind" to comparison group allocation:
(select one) Well covered

Comments: No placebo for group was included since the primary outcome was assessed by an investigator who was unaware of the treatment-group assignments.

- M. Comparison groups are similar at the start of the trial:
(select one) Well covered

Comments:

- N. Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential sources of bias. (select one) Well covered

Comments:

- O. Were all relevant outcomes measured in a standardized, valid, and reliable way?
(select one) Well covered

Comments:

- P. Are patient oriented outcomes included? If yes, what are they?

The primary outcome is gestational sac expulsion by the first follow up appointment. This is a patient oriented outcome. The authors also collected data on prespecified secondary outcomes which included acceptability of treatment (an overall assessment of the treatment, would participants use medical management if they had another early pregnancy loss, “would you recommend this method of treatment to a friend?”). These secondary outcomes are also patient oriented.

- Q. What percent dropped out, and were lost to follow up? Could this bias the results? How?
Two patients were lost to follow-up and one patient was determined to be ineligible after randomization. These are unlikely to bias the results since this represents a very small proportion of the study participants.
- R. Was there an intention-to-treat analysis? If not, could this bias the results? How?
Yes, intention-to-treatment analysis was used. The authors indicate they use a preplanned modified intention-to-treat principle to assess the primary outcome.
- S. If a multi-site study, are results comparable for all sites?
The authors do not comment on whether or not participants were recruited from multiple sites.
- T. Is the funding for the trial a potential source of bias? If yes, what measures were taken to ensure scientific integrity?
Mifepristone was purchased from the manufacturer (Danco Laboratories) at a research price for use in the trial and was dispensed at the trial sites.
- U. To which patients might the finding apply? Include patients in the study and other patients to whom the findings may be generalized.
The trial population was diverse with respect to sociodemographic status and pregnancy diagnosis which supports the generalizability of the study results.
- V. In what care settings might the finding apply, or not apply?
It is unclear if the findings directly apply to a military medical center since this information was not included in the characteristics of participants at baseline.
- W. To which clinicians or policy makers might the finding be relevant?
Clinicians in primary care, emergency medicine, and OB/GYN practices who diagnosis and treat spontaneous abortions.

SECTION 3: Review of Secondary Literature

[to be completed by the Potential PURL Reviewer]

[to be revised by the Pending PURL Reviewer as needed]

Citation Instructions:

For up-to-date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS on editor & current year as publication year.

Example: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: <http://www.uptodate.com>. {Insert

date modified if given.} Accesses February 12, 2009. [whatever date PPRF reviewer did their search.]

For DynaMed, use the following style:

Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at <http://www.DynamicMedical.com>. Last updated February 4, 2009. {Insert date modified if given.} Accessed June 5, 2009. {search date}

A. DynaMed excerpts

Medication and dosing regimens for [first-trimester medical abortion](#):

- For medical abortion of pregnancy up to 70 days gestation, use mifepristone 200 mg orally, then 24-48 hours later misoprostol 800 micrograms buccally.
- For medication regimen for pregnancies between 9 and 12 weeks gestation (63-84 days), consider mifepristone 200 mg orally followed by misoprostol 800 mcg vaginally 24-48 hours later ([Strong recommendation](#)). Additional misoprostol 400 mcg may be administered vaginally or sublingually every 3 hours for up to 4 additional doses until the products of conception are expelled ([Strong recommendation](#)).

B. DynaMed citation/access date

Induced abortion. Elliot M. Levine, MD. In: DynaMed [database online]. Available at: www.DynamicMedical.com Last Updated: Jan2019. Accessed: 2/20/19.

C. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)

The DynaMed article recommends pretreatment with mifepristone for induced abortions prior to treatment with misoprostol. The article provides other medical treatment options but indicates they have a lower success rate.

D. UpToDate excerpts

Treatment options

- Mifepristone pretreatment followed by misoprostol – The most effective, and thus preferred, option for treating first trimester pregnancy failure (up to 13 weeks gestation) involves pretreatment with the progesterone antagonist mifepristone followed by misoprostol [28,34]. A trial including 300 women with anembryonic gestation or embryonic or fetal death between 5 and 12 completed weeks of gestation reported that mifepristone pretreatment followed by misoprostol therapy, compared with misoprostol alone, resulted in higher rates of complete expulsion by an average of three days post-treatment (84 versus 67 percent) and lower rates of surgical uterine aspiration (9 versus 24 percent) [35]. Rates of bleeding that required transfusion and pelvic infection were similar between the groups. Women with an absent gestational sac, open cervical os, or both were excluded from the study because of the known high efficacy of misoprostol alone in this group (approximately 90 percent) [36].

- E. UpToDate citation/ Always use Basow DS as editor & current year as publication year. Access date Title. Author. In: UpToDate [database online]. Available at: <http://www.uptodate.com>. Last updated: . Accessed

Basow DS, 2019. Date accessed: 02/20/2019. Spontaneous abortion: Management. Togas Tulandi, MD, MHCM; MHaya Al-Fozan, MD. In: UpToDate [database online]. Available at: <https://www.uptodate.com>. 09/18/2018.

- F. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)
The UpToDate article recommends pretreatment with mifepristone before treatment with misoprostol for early pregnancy loss.
- G. Other excerpts (USPSTF; other guidelines; etc.)
N/A
- H. Citations for other excerpts
N/A
- I. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)
N/A

SECTION 4: Conclusions

[to be completed by the Potential PURL Reviewer]

[to be revised by the Pending PURL Reviewer as needed]

- A. **Validity:** Are the findings scientifically valid? Yes
- B. If **A** was coded “Other, explain or No”, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?
- C. **Relevance:** Is the topic relevant to the practice of family medicine and primary care practice, including outpatient, inpatient, obstetrics, emergency and long-term care? Are the patients being studied sufficiently similar to patients cared for in family medicine and primary care in the US such that results can be generalized?
Yes
- D. If **C** was coded “Other, explain or No”, please provide an explanation.
- E. **Practice changing potential:** If the findings of the study are both valid and relevant, are they not a currently widely accepted recommendation among family physicians and primary care clinicians for whom the recommendation is relevant to their patient care? Or are the findings likely to be a meaningful variation regarding awareness and acceptance of the recommendation?

Yes

F. If **E** was coded as “Yes”, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

G. Applicability to a Family Medical Care Setting:

Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc.), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, education or counseling a patient; or creating a system for implementing an intervention? Yes

H. Please explain your answer to **G**.

For physicians who provide treatment for early pregnancy loss, it would be reasonable to consider pretreatment with mifepristone prior to misoprostol for improved rate of gestational sac expulsion.

I. Immediacy of Implementation:

Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug, or other essentials available on the market? Other, explain

J. If **I** was coded “Other, explain or No”, please explain why.

Mifepristone is not easily available in all communities. This may present a barrier for some health systems.

K. Clinically meaningful outcomes or patient oriented outcomes:

Do the expected benefits outweigh the expected harms? Are the outcomes patient oriented (as opposed to disease oriented)? Are the measured outcomes, if true, clinically meaningful from a patient perspective?

Yes

L. If **K** was coded “Other, explain or No”, please explain why.

M. In your opinion, is this a pending PURL? Yes

1. Valid: Strong internal scientific validity; the findings appear to be true.
2. Relevant: Relevant to the practice of family medicine.
3. Practice Changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.
4. Applicability in medical setting.
5. Immediacy of implementation

N. Comments on your response for question M.

I believe this article meets the above criteria and should be included in practices that manage early pregnancy loss. The availability of mifepristone may present a barrier to immediate implementation.