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Original Research Article

Early pregnancy loss medical management in clinical practice☆,☆☆,☆☆☆

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ABSTRACT

Objectives: This study aimed to review clinical practice outcomes of early pregnancy loss (EPL) medical management using mifepristone and misoprostol outside of a clinical trial setting.
Study design: In this retrospective cohort study, we reviewed a deidentified database of patients who received mifepristone-misoprostol for EPL from May 2018 to May 2021 at our academic center–based clinic, which was a study site for a multicenter mifepristone-misoprostol EPL trial completed in March 2018. All patients received mifepristone 200 mg orally and misoprostol 800 mcg vaginally or buccally, with clinic follow-up typically scheduled within 1 week. The primary outcome was successful medical management, defined as management without the need for aspiration, and the secondary outcomes included additional interventions and indications, follow-up ultrasonography findings, and adverse events requiring treatment.
Results: We treated 90 patients with a median ultrasound-measured gestational size of 49 (range 30–80) days and median time from mifepristone to misoprostol of 24 (range 8–66) hours. Follow-up was completed in clinic by 80 (88.9%), completed remotely by five (5.6%), and not completed by five (5.6%) patients. Overall, 76 (95% CI 82.9%–96.0%) of 85 patients (89.4%) with follow-up were successfully managed without uterine aspiration. Eighty patients had initial follow-up ultrasonography interpreted as gestational sac expulsion; seven (8.8%) of these ultimately underwent aspiration, including one patient who had a previously undiagnosed cesarean scar ectopic pregnancy. Two patients had significant safety outcomes: one pelvic infection and one blood transfusion during aspiration in the patient with a cesarean scar ectopic pregnancy.
Conclusions: Outside of a clinical trial setting, medical management of EPL with mifepristone and misoprostol remains effective and safe.
Implications: Medical management of EPL with mifepristone and misoprostol is effective and safe outside of a clinical trial setting. A standardized protocol based on the best available clinical trial evidence can be used in clinical practice for the medical management of EPL.

1. Introduction

Early pregnancy loss (EPL) occurs in 10% to 20% of recognized pregnancies [1] and includes anembryonic gestation, embryonic demise (< 10 weeks), fetal demise (≥10 weeks), inevitable abortion, and incomplete abortion [2]. Following diagnosis, options include expectant management, uterine aspiration, and medical management. The Comparative Effectiveness of Pregnancy Failure Management Regimens (PreFaiR) trial, conducted at the University of Pennsylvania, the University of California (UC), Davis, and the Albert Einstein College of Medicine between May 2014 and April 2017, established a higher likelihood of successful management of EPL with mifepristone followed by misoprostol than misoprostol alone [3]. While the use of mifepristone and misoprostol for the management of EPL is "off-label" from indications approved by the United States Food and Drug Administration, this combined treatment regimen for EPL is recommended by the American College of Obstetricians and Gynecologists and the World Health Organization [4,5]. Subsequent

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studies have confirmed the superiority of the combined treatment compared to misoprostol alone [6,7].

At our institution, we enacted an EPL medical management protocol using the regimen validated by the PreFaiR trial as soon as the study was completed. Because management and outcomes of individual cases may vary in clinical practice outside of a trial setting, we aimed to review our initial outcomes using mifepristone and misoprostol for EPL management.

2. Materials and methods

We reviewed a deidentified clinical database of patients who received mifepristone for a diagnosis of EPL through 11 completed weeks' gestation in our institution's Complex Family Planning (CFP) clinic from May 2018 to May 2021. We chose the initiation of the 3-year time frame as 1 year after completion of the PreFaiR trial. All care was provided by a CFP specialist or by an obstetrics and gynecology resident or CFP fellow under their supervision. The clinic's standard operating procedure included physician dispensing of mifepristone 200 mg for oral use in the office or at home. Physicians prescribed misoprostol 200 mcg #4 and pain medications for patient pickup at the pharmacy in the clinic building. Patients were counseled primarily to use the misoprostol vaginally approximately 24 hours later, although alternative misoprostol routes could be discussed by physicians per their judgment. We typically scheduled patients for in-office follow-up 3 to 7 days after mifepristone, at which time we performed transvaginal ultrasonography to evaluate for gestational sac expulsion; patients with a persistent gestational sac were offered a second dose of misoprostol, aspiration, or expectant management. Further follow-up was scheduled, if needed, at the physician's discretion. Patients unable to attend an in-person follow-up or who were deemed more appropriate for follow-up with serum human chorionic gonadotropin levels (e.g., difficult ultrasonography due to anatomy) were contacted by scheduled telephone communication and laboratory testing. For patients who did not attend scheduled in-person follow-up, physicians attempted to contact them by phone or electronic medical record messaging and assessed their outcomes remotely [8]. We did not make changes to our protocol due to the coronavirus disease 2019 pandemic.

For this analysis, we extracted relevant demographic and obstetric information (e.g., age, gravidity, parity, ultrasound-measured gestational age, and EPL diagnosis), date, time, and route of misoprostol administration based on physician documentation of patient report and follow-up visit(s) information, including ultrasonography findings (e.g., presence of gestational sac and endometrial thickness). For each variable, those with missing data were not included in the calculation; where applicable, a percentage of those with missing data was calculated. The primary outcome was successful medical management, defined as management without the need for aspiration, with secondary outcomes including additional interventions and indications, follow-up ultrasonography findings, and adverse events requiring treatment (e.g., hospitalization, blood transfusion, and antibiotics). We used Mann-Whitney U testing to compare endometrial thickness at follow-up in patients with and without a "thickened" endometrium as determined subjectively by clinicians. Our institutional review board deemed the study exempt. This cohort study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [9].

3. Results

Between May 2018 and May 2021, we treated 90 patients with mifepristone and misoprostol for early pregnancy loss. The median ultrasound gestational size was 49 (range 30–80) days with two patients (2.2%) at > 70 days; further demographic information is included in Table 1. The median time from mifepristone to misoprostol was 24 (range 8–66) hours. Although our protocol stipulated vaginal misoprostol administration, seven (7.8%) had no documented route, and four (4.4%) used misoprostol buccally; the reasons for buccal administration were recorded as patient preference (n = 2), vaginal bleeding present (n = 1), and unknown (n = 1).

Table 1
Characteristics of patients who received mifepristone and misoprostol for early pregnancy loss at a California university clinic from May 2018 to May 2021 (N = 90)

Characteristics	Values
Age (years), mean ± SD	33 ± 6.1
Gestational size (d)[a], n (%)	
≤42	14 (16)
43–49	32 (35)
50–56	21 (23)
57–63	15 (16)
64–70	6 (7)
> 70	2 (2)
Diagnosis, n (%)	
Anembryonic pregnancy	34 (38)
Embryonic demise[b]	52 (58)
Fetal demise[b]	4 (4)

[a] Based on ultrasound examination measurement.
[b] Embryonic demise: < 70 d; fetal demise: ≥70 d.

Figure 1 shows the follow-up flow and outcomes for our cohort. Eighty-five patients (94.4%) had follow-up, with 80 (88.9%) in clinic at a median of 6 (range 1–20) days following mifepristone, and 5 (5.6%) remote. Follow-up was not completed by five patients (5.6%). Of the patients who completed in-person follow-up, 17 (21.3%) had more than one postmedication visit. Seventy-six (95% CI 82.9%–96.0%) of the 85 patients (89.4%) with follow-up underwent successful medical management, 71 (83.5%; 95% CI 75.6%–91.4%) with one misoprostol dose and five (5.9%; 95% CI 0.9%–10.9%) with two misoprostol doses. Nine (95% CI 4.0%–17.1%) patients (10.6%) had a uterine aspiration after initial treatment, three more than 30 days after mifepristone use. Indications recorded for aspirations were persistent or heavy bleeding (n = 4), thickened endometrium or concern for retained products without associated bleeding concerns (n = 2), and persistent gestational sac (n = 2); one patient had no clearly documented indication. One patient with an embryonic demise measuring 49 days' gestation had follow-up ultrasonography after initial medical management with a persistent gestational sac and new findings concerning for cesarean scar ectopic pregnancy (CSEP); an aspiration was performed in the operating room with associated hemorrhage requiring blood transfusion and uterine balloon tamponade. Of note, three (95% CI 0%–7.5%) of the 80 patients (3.8%) who had clinic follow-up had tissue noted within the cervical canal on ultrasonography and had removal with ring forceps; one of these patients had an aspiration on day 18 post-mifepristone for new-onset heavy bleeding.

Almost all (78 [97.5%]; 95% CI 94.1%–100%) of the 80 patients who received a follow-up postmedication ultrasound examination had findings interpreted as gestational sac expulsion. Seven (90%, 95% CI 2.6%–15.3%) of these 78 patients ultimately underwent an aspiration. Pathologic examination demonstrated villi for all but one, which showed chronic endometritis.

In nine (95% CI 4.4%–18.6%) of the 78 patients (11.5%) with gestational sac expulsion on ultrasonography, clinicians subjectively interpreted "thickened" endometrium at the initial follow-up. The median endometrial thickness for these nine patients was 16.0 mm (interquartile range 15.2–17.4 mm) and for the other 69 patients was 9.0 mm (interquartile range 7.9–11.9 mm; $p < 0.001$). Most (8 [89%]) patients with thickened endometrium had an additional follow-up visit, including five who received a second dose of misoprostol. Four of the nine patients had an aspiration, including one at initial follow-up due to desire for same-day intrauterine device insertion, one after

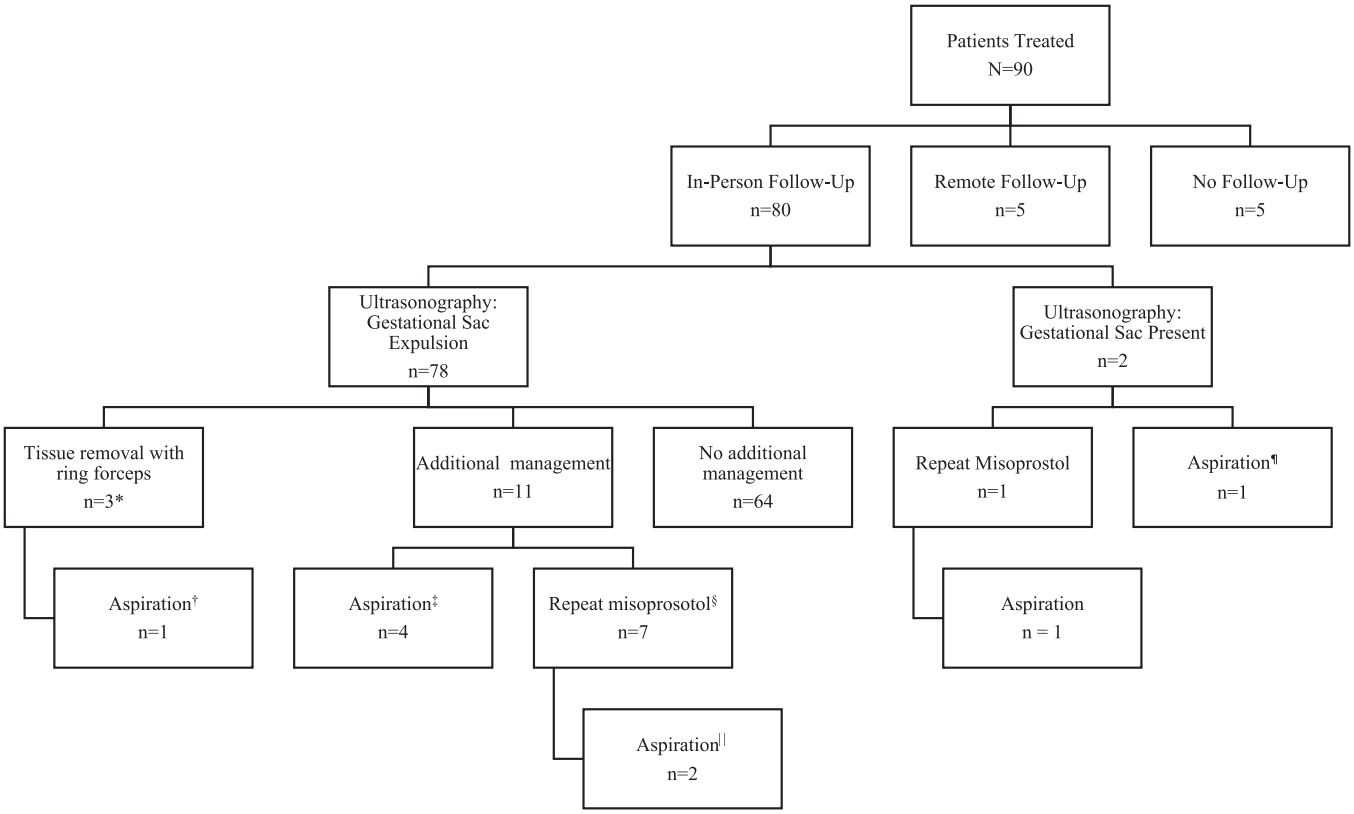

Fig. 1. Flow of follow-up and treatment outcomes for patients who received mifepristone and misoprostol for early pregnancy loss at a California University clinic from May 2018 to May 2021. *Ultrasonography performed after tissue removal. †Performed for new-onset heavy bleeding on day 18 postmifepristone. ‡Performed for "thickened endometrium" and desired intrauterine device placement (n = 1), "thickened endometrium" expectantly managed with procedure at 44 and 94 days postmifepristone for continued bleeding (n = 2), and persistent heterogenous structure in cervical canal expectantly managed with procedure at 44 days postmifepristone for continued bleeding (n = 1). §Performed for "thickened endometrium" (n = 5), increased bleeding 6 days after mifepristone in setting of upcoming unrelated medical procedure (n = 1), and uncertain indication (n = 1). ||Performed for persistent "thickened endometrium" (n = 1) and uncertain indication (n = 1). ¶Performed for suspected cesarean scar ectopic pregnancy on postmedication ultrasound imaging.

a second dose of misoprostol due to persistent thickened endometrium, and two (at 44 and 94 days after mifepristone) who did not receive additional misoprostol but had continued bleeding.

Significant safety outcomes were noted in only two patients: one pelvic infection treated with inpatient intravenous antibiotics and one blood transfusion in the patient with a CSEP.

4. Discussion

This analysis of 90 patients who received EPL medical management with mifepristone and misoprostol as routine clinical care provides evidence of the safety and efficacy of a trial-validated medication regimen. Our institutional protocol closely mirrors the PreFaiR trial protocol [3]; however, it is important to note that in clinical practice, subjective decisions by the clinician are not limited by trial protocol. Our primary outcome, the rate of successful management with medication, was 89.4%. Our overall aspiration rate was 10.6%, with a rate of 6.7% within 30 days of treatment. Notably, the 91.2% success rate in the mifepristone-misoprostol treatment arm of the PreFaiR Trial (n = 149) was similar to our rate but was defined by management with medication alone within 30 days [3]. In our cohort, three of nine aspirations occurred after day 30, showing that limiting outcome analyses to 30 days may not be long enough when evaluating the treatment of EPL. Similarly, low rates of serious adverse events were found in our review compared to the trial. Our one case of CSEP is a reminder to clinicians that a persistent sac following medical management in a patient with a prior cesarean delivery can be an indicator of abnormal implantation.

Seven patients (9.0%) who initially had follow-up ultrasonography showing gestational sac expulsion ultimately underwent an aspiration. Information on patients who required aspiration after ultrasonography showing gestational sac expulsion was not reported in PreFaiR [3]. In medication abortion literature, this rate is much lower (1.6%) [10]. This information is valuable for patient counseling and further supports that medication management of EPL and abortion, despite the use of the same medications, does not have the same outcomes.

In patients with EPL, endometrial thickness at follow-up is not an accurate predictor of the need for future surgical intervention [11]. We found that outside of a rigid research protocol, independent physician decision-making with input from patients about their preferences can result in additional interventions or follow-up for subjectively thickened endometrium even when ultrasonography demonstrates gestational sac expulsion. A 2011 publication described EPL medical management outcomes in clinical practice at the University of Pittsburgh in 123 patients who received the same mifepristone-misoprostol regimen [12]. Postmedication management follow-up ultrasonography was performed by generalist obstetrician-gynecologists, specialty obstetrician-gynecologists, and radiologists with success defined as gestational sac expulsion and endometrial thickness ≤30 mm. Overall, 21 patients (17.1%) had aspiration, of whom 13 (76.5%) were due primarily to ultrasound findings other than a persistent gestational sac. Comparatively, in our patient population, 10.6% of patients had aspiration of whom only one (11.1%) had an aspiration due to thickened endometrium without other indications. As clinicians gain more experience with providing this treatment in practice outside of a research setting, it will be important for them to understand that the desire to ensure a good outcome in patients with subjectively thickened endometrium does not require aspiration.

We describe an infrequent but important occurrence of removing tissue from the cervical os, which occurred in the original National Institutes of Health comparative trial of misoprostol and vacuum aspiration [13] and PreFaiR trials (MD Creinin, personal communication, March 21, 2023) but was not a reported outcome. Clinicians should remember to consider a pelvic examination if ultrasound or history indicates possible retained tissue in the cervix, as removal with ring forceps may expedite successful completion without additional medical or procedural treatment.

The strengths of this study include the consistent use of a standardized operating procedure for the medical management of EPL at our institution. However, even with a protocol in place, minor variations in practice exist. For example, we found that additional follow-up at physician discretion occurred even when ultrasonography was interpreted as showing gestational sac expulsion, which is typically unnecessary in some cases. The limitations of our study include possible information bias, as data were extracted from the electronic medical record and was dependent on physician documentation of patient report for some variables (e.g., route and timing of misoprostol use). Selection bias is possible, as physicians may have offered medical management differentially based on their assessment of its safety and likelihood of success in individual patients. In addition, care was provided by or under the supervision of the CFP faculty at a single facility experienced with EPL medication management and may not be generalizable to all clinical settings. Practically, at our institution, this occurs because mifepristone is provided through our specialty clinic. Given that mifepristone premedication is the primary modifiable factor in the successful treatment of EPL, any clinician opting to provide this care could obtain access to mifepristone and successfully utilize this evidence-based regimen [14].

Overall, medical management of EPL with mifepristone and misoprostol is effective and safe outside of a clinical trial setting. Our findings are important for clinicians as they translate guidance into clinical practice since findings from a rigorous clinical trial may not always reflect outcomes outside of a trial. A standardized protocol guided by the best available clinical trial evidence can be used in clinical practice for medical management of EPL.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.contraception.2023.110134.

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