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Society of Family Planning Clinical Recommendation: Medication management for early pregnancy loss★,☆,☆☆

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ABSTRACT

Early pregnancy loss (EPL) occurs in 15% to 20% of clinically recognized pregnancies. We recommend that patients experiencing EPL have equal access to all treatment options, including expectant, medication, and procedural management, when urgent treatment is not necessary (GRADE 1A). We recommend a patient-centered approach that uses shared decision-making to diagnose EPL through ultrasonography, serial quantitative hCG measurements, or symptoms (GRADE 1C). We suggest a shared decision-making approach for continuing expectant management of EPL up to 8 weeks after diagnosis in the absence of medical complications or symptoms requiring urgent intervention (GRADE 2C). We suggest against Rh testing and Rh-immunoglobulin administration before 12 weeks of gestation for patients undergoing medication management of EPL (GRADE 2B). We recommend a combined regimen of mifepristone with misoprostol for medication management of EPL (GRADE 1A), using mifepristone 200 mg orally followed 7 to 48 hours later by misoprostol 800 mcg vaginally or buccally (GRADE 2A). When used without mifepristone, we recommend misoprostol in two or more doses of 600 to 800 mcg sublingually or vaginally at intervals of at least 3 hours (GRADE 1B). We suggest ibuprofen 800 mg orally for pain control during medication management of EPL (GRADE 2A). Clinicians should offer all patients, but not require, in-person confirmation of completed EPL (GRADE 2B). We recommend against using endometrial thickness alone as a criterion for recommending additional intervention after medication management of EPL (GRADE 1B). We recommend institutions and clinicians make thorough efforts to obtain and maintain access to mifepristone in clinical settings where patients receive EPL care (GRADE 1C).

★ Disclaimer: This publication is designed as a resource to assist clinicians in providing family planning care. It should not be considered inclusive of all proper treatments or serve as the standard of care. It is not intended to substitute for the independent professional judgment of the treating clinician. Variations, taking into account individual circumstances, may be appropriate. This publication reflects the best available evidence at the time of publication, recognizing that continued research or major changes in the practice environment may impact future recommendations and should be evaluated for incorporation into care. Any updates to this document can be found at https://societyfp.org/clinical/clinical-guidance-library/. The Society and its contributors provide the information contained in this publication "as is" and without any representations or warranties, express or implied, of any kind, whether of accuracy, reliability, or otherwise.

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1. Background

1.1. Purpose

Early pregnancy loss (EPL), sometimes called miscarriage, spontaneous abortion, missed abortion, and early pregnancy failure, makes up 15% of all clinically recognized pregnancies [1]. Patients often present in the outpatient setting or emergency department (ED) with symptoms such as vaginal bleeding and cramping. However, with the increased availability of highly sensitive pregnancy tests and early ultrasonography, the diagnosis of EPL is often made before the onset of symptoms. Once diagnosed, a patient-centered approach should be used to counsel patients on their treatment options, including expectant management, procedural management via uterine aspiration, or medication management. All methods of EPL management have been found to be safe, effective, and accepted by patients [2]. Evidence demonstrates that patients offered their preferred management method through shared decision-making have higher satisfaction with care, improved quality of life scores, and better outcomes [3–6]. However, evidence suggests that patients may not be offered all options for EPL management depending on the practice setting; geographic location; state policies about abortion; and facility-, clinician-, and patient-level characteristics [7–11]. Standard gynecologic and emergency care should include access to prompt active management of EPL when indicated and desired by the patient. **We recommend that patients experiencing EPL have equal access to all available treatment options, including expectant, medication, and procedural management, when urgent treatment is not necessary (GRADE 1A) (Table 1).** Indications for urgent treatment may include but are not limited to hemorrhage and suspected intrauterine infection, which may necessitate prompt procedural management.

Medication management may be preferable to patients who prioritize control, predictability, privacy, or avoidance of procedural intervention during the pregnancy loss process [12]. Mifepristone followed by misoprostol is the most efficacious and cost-effective medication management regimen for EPL [13–18]. Despite mifepristone's excellent safety profile, it is highly regulated by the US Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategy (REMS) with patient- and clinician-directed requirements due to its use in abortion. At the time of publication of this guidance, mifepristone is subject to multiple abortion-targeted legal restrictions, which restrict access to the most evidence-based medication EPL regimen. Misoprostol-only regimens are also safe and effective for the treatment of EPL and should be offered when mifepristone is unavailable or restricted [19,20]. Even when EPL care is accessible, people may prefer to self-manage EPL, especially if they have experienced structural racism and stigma within the medical system. Although outside the original scope of this document, common self-managed approaches include sourcing mifepristone, misoprostol, or both outside the formal health care system or using herbal preparations to induce pregnancy expulsion [21].

Clinicians caring for pregnant people should be familiar with diagnostic considerations and patient-centered approaches to the management of EPL, as well as systemic and legal barriers that restrict access to safe and effective care. This Clinical Recommendation provides evidence-based guidance on outpatient medication management of EPL, including considerations for management in areas with abortion restrictions impacting access to medications used to manage EPL. It is based on a review of relevant literature, primarily including studies that assess EPL management outcomes but also including studies that address medication abortion when evidence is lacking for EPL, as they are managed similarly.

1.2. Definitions

EPL is a broad term that includes intrauterine pregnancies with findings that suggest the pregnancy may not progress or definitely will not progress, pregnancies with a gestational sac (GS) in the lower endometrial cavity or endocervical canal in the process of expulsion, residual pregnancy tissue or persistent GS, and complete passage of the GS without residual tissue. This document addresses medication management of EPL in which the complete passage of the GS has not yet occurred, including pregnancies concerning for and diagnostic of EPL (sometimes called "missed abortion") and EPL in progress. These recommendations do not specifically address incomplete EPL in which no GS is seen on ultrasonography (sometimes called retained products of conception [RPOC]). They also do not specifically address EPL with spontaneous passage of the GS prior to health care evaluation or expectant management of EPL with subsequent passage of the GS, although many of the treatment approaches, including indications for Rh testing, pain management, and confirmation of completed EPL, can also be employed in these clinical situations. EPL is most commonly defined as a pregnancy loss within the first 12 6/7 weeks of gestation [2,22,23]. However, there is no consensus on gestational duration in the definition of EPL in the literature, which can make comparing studies challenging. This document provides recommendations for medication management of EPL through 13 6/7 weeks of gestation.

Clinicians should use patient-centered language and individualized counseling to improve patient-clinician communication. In a survey of English-speaking patients in the US being treated for first-trimester pregnancy loss, the terms "miscarriage" and "early pregnancy loss" were preferred by patients and provided the most clarity; patient preferences varied by ethnicity and history of abortion [24]. Additionally, patients experiencing EPL value clear communication and emotional sensitivity during diagnosis and management [12,25]. The term "early pregnancy loss" may not translate into other languages and culture may influence terminology preference. While outside the original scope of this document, we do not recommend qualifiers such as "elective," "therapeutic," or "medically necessary" when referring to pregnancy loss or abortion care, as these terms further perpetuate abortion stigma [26]. Additionally, the Society of Family Planning (SFP) supports the use of language as outlined in *A lexicon for first-trimester ultrasound: Society of Radiologists in Ultra sound consensus conference recommendations* [23].

Table 1
Key for GRADE recommendations[a]

Symbol	Meaning
1	Strong recommendation
2	Weaker recommendation
A	High-quality evidence
B	Moderate quality evidence
C	Low-quality evidence, clinical experience, or expert consensus
Best practice	A recommendation in which either (1) there is an enormous amount of indirect evidence that clearly justifies a strong recommendation, direct evidence would be challenging and an inefficient use of time and resources to bring together and carefully summarize, or (2) a recommendation to the contrary would be unethical

[a] Society of Family Planning Clinical Recommendations use a modified GRADE system. The GRADE system is described in several publications, with a comprehensive set of articles in the Journal of Clinical Epidemiology (J Clin Epidemiology, [2011] 64:383–394, 64:395–400, 64:401–406, 64:407–415, 64:1277–1282, 64:1283–1293, 64:1294–1302, 64:1303–1312, 64:1311–1316, [2013] 66:140–150, 66: 151–157, 66:158–172, 66:173–183, 66:719–725, 66:726–735).

1.3. Epidemiology

EPL is a common occurrence and affects nearly 1 million pregnancy-capable people each year in the US [27]. An estimated 15% to 20% of pregnancies end in EPL, although it is difficult to estimate the true incidence of EPL as many pregnancy losses occur before clinical recognition or outside the health care system [1,28–30]. Recent evidence from private insurance claims demonstrates that approximately 10.2% of US patients with an EPL diagnosis received medication management; however, the proportion of patients who were offered or received their preferred management option regardless of insurance status or type has not been reported [7].

2. Clinical questions

Diagnosis

2.1. How can clinicians diagnose early pregnancy loss?

Clinicians can use several modalities to diagnose EPL. Clinicians should approach the diagnosis of EPL using a shared decision-making model. Shared decision-making is a patient-centered approach to health care where patients are not only educated about the risks and benefits of each option, but their preferences also guide decision-making around testing and management [31].

When available, ultrasonography can serve as a primary method for diagnosing EPL. Guidelines from the Society of Radiologists in Ultrasound are frequently cited but promote exceptionally conservative ultrasonographic diagnostic criteria for EPL with the stated goal of 100% specificity for diagnosis. These criteria prioritize maintaining a potentially ongoing pregnancy without consideration of the clinical context or patient preference. The American College of Obstetricians and Gynecologists (ACOG) endorses the diagnostic criteria from the Society of Radiologists in Ultrasound (SRU) as reasonable parameters while recognizing the limitations of the guidelines [2]. For example, the SRU guidelines suggest diagnosing EPL when there is a crown-rump length of 7 mm and no embryonic cardiac motion, despite evidence that a 5.3 mm threshold gave 100% diagnostic certainty [32]. Similarly, an empty GS with a mean-sac diameter of 25 mm was also recommended as a diagnostic threshold for EPL, despite research showing that 21 mm was adequate for diagnostic certainty [32]. Strict adherence to these criteria could lead to a delay in diagnosis by up to 2 weeks in some cases to achieve 100% diagnostic certainty of EPL, without regard for the needs or preferences of the pregnant person [33]. While a definitive diagnosis of an EPL might be prioritized by some patients, other patients may prioritize expedited pregnancy resolution, such as those who desire future pregnancy in the short term or those experiencing an undesired pregnancy [34].

While many clinicians might prefer ultrasonography for diagnosing EPL, serial measurement of quantitative serum human chorionic gonadotropin (hCG) can help expedite diagnosis for people without access to ultrasonography or when ultrasonography is not initially definitive. In a prospective study of people with intrauterine pregnancies of uncertain prognosis by ultrasonography presenting for pain or vaginal bleeding, serum quantitative hCG measurements at the time of presentation were compared to the same measure 48 hours later. A quantitative hCG ratio of less than 1.1 had 100% diagnostic certainty for EPL, allowing for diagnosis sooner than a repeat ultrasonography in 7 to 14 days [35]. In situations where ultrasonography diagnosis is unclear, serial quantitative hCG measurements can prevent a delay in diagnosis. Additionally, serial quantitative hCG measurements can preclude the need for an in-person evaluation for EPL.

Although “no-test” protocols for the initiation of medication abortion have been recently established and safely employed, similar “no-test” protocols for the diagnosis and management of EPL have yet to be established. To increase access to EPL treatment, symptomatic patients who do not desire diagnostic certainty can also be offered treatment for EPL without the need for ultrasonography or blood work when clinically appropriate and legally permissable. While any bleeding at all in early pregnancy is not indicative of a loss, data from two community-based cohort studies analyzed as part of a systematic review found that heavy bleeding, longer duration of bleeding, and heavy bleeding accompanied by pain were associated with increased risk of pregnancy loss [36–38]. Similar to how the resolution of nausea and vomiting can clinically signal medication abortion completion, the absence or loss of nausea in the setting of bleeding confers a greater risk of EPL [36,39,40]. Like protocols proven safe for “no-test” telemedicine abortion [41,42], symptom-based EPL diagnosis should include screening for risk factors for ectopic pregnancy or gestational duration uncertainties (e.g., history of ectopic pregnancy, unilateral pelvic pain, history of tubal damage, irregular menses) and recommend ultrasonography, serum quantitative hCG measurements, in-person evaluation, or some combination of these interventions as appropraite. However, more research is needed to determine which combinations of symptoms and symptom duration could be reliably used to diagnose EPL without the need for further testing. **We recommend a patient-centered approach that uses shared decision-making to diagnose EPL through ultrasonography, serial quantitative hCG measurements, or symptoms, depending on the patient’s desire for a definitive diagnosis (GRADE 1C).**

To improve access to medication management for EPL, clinicians should advocate for increased access to and acceptability of all diagnostic approaches. Clinicians should consider how to incorporate EPL diagnosis and treatment into a telemedicine workflow for their practices. Clinicians can evaluate patients with pain or bleeding in early pregnancy who desire a more definitive diagnosis using serial serum quantitative hCG measurements, avoiding the need for an in-person exam. Clinicians can then offer a telemedicine consultation to review the results and prescribe or dispense the medications. For patients who do not desire a definitive diagnosis, a telemedicine consultation could be employed to review symptoms highly suggestive of EPL and prescribe or dispense medications in lieu of an ultrasonography or blood work.

From a health equity perspective, clinicians should advocate against health system policies and protocols that require ultrasonography as the only diagnostic modality for EPL and protocols that only use the most conservative ultrasonography criteria. Even in states with severely restrictive abortion laws, there are no current laws in any state that specifically dictate the diagnostic criteria for EPL. Clinicians should, therefore, resist policies and protocols that attempt to conflate abortion regulation with EPL diagnosis requirements. People experiencing EPL have varied and nuanced priorities, and the decision to actively manage EPL should take into account the likelihood of EPL based on clinical characteristics together with the patient’s individual needs and desires.

Management

2.2. What is the recommended time between diagnosis and initiating medication management?

In the absence of medical complications or symptoms requiring emergent intervention, patients should have access to prompt active management options after EPL diagnosis. Clinicians should not require patients to undergo a period of expectant management before they offer medication or procedural management, although patients may prefer expectant management for a variety of reasons including

preference for avoiding medical interventions. For many patients, the decision between expectant and medication management for EPL depends on the importance of timing of resolution [12]. In qualitative studies of patients' experiences with EPL treatment, some people selected expectant management because they needed time to process the diagnosis or consider their options before initiating treatment [25]. Some individuals valued a rapid resolution, as medication management provided control and predictability over the process, and quicker return to personal and professional obligations [5,12].

Evidence demonstrates expectant management of EPL for 6 to 8 weeks after diagnosis is safe; however, varying lengths of follow-up time and ultrasonography criteria for incomplete EPL make interpretation of this evidence challenging [43–48]. One observational study found that 81% of all patients who chose expectant management had a complete EPL by approximately 7 weeks after EPL diagnosis. However, completion rates were higher for patients experiencing incomplete EPL (91%) compared to embryonic demise (76%) or anembryonic pregnancy (66%) [43]. Limited data exist that detail the risk of complications of prolonged retention of a GS after EPL is diagnosed; however, data suggest that the risk of infection with expectant management is similar to that of medication management [44]. Although an increased risk of disseminated intravascular coagulation can be seen in the prolonged retention of a demised fetus in the second and third trimesters [49], a lack of data about this risk in the first trimester provide an area for continued research.

We suggest a shared decision-making approach for continuing expectant management of EPL up to 8 weeks after diagnosis in the absence of medical complications or symptoms requiring urgent intervention (GRADE 2C). Medically stable patients who select expectant management should be counseled that they may decide to change to medication or procedural management at any point during expectant management. Clinicians should use a shared decision-making approach to consider the patient's needs and preferences as well as external demands when counseling a patient about management options.

2.3. Are Rh testing and Rh-immunoglobulin administration in Rh-negative patients required during medication management of early pregnancy loss?

The *Society of Family Planning committee consensus document on Rh testing in early pregnancy* does not recommend Rh testing or Rh-immunoglobulin administration for pregnancies before 12 weeks of gestation undergoing abortion or pregnancy loss [50]. This recommendation is based on a review of historical literature as well as new studies that use flow cytometry to quantify the amount of fetal-maternal hemorrhage that occurs during pregnancy termination [51,52]. A large clinical trial including over 500 patients undergoing either medication or procedural induced abortion before 12 0/7 weeks of gestation again confirmed that neither increased the risk for Rh sensitization above the risk of sensitization in an ongoing pregnancy. This trial did not include patients with EPL but did include patients who had bleeding. Three participants had pretreatment circulating fetal red blood cells that were above the estimated threshold for Rh sensitization; the volume of circulating fetal red blood cells in two of these participants went down below the threshold after medication abortion [53].

Overall, evidence for the need for Rh immunoglobulin in EPL is scarce and derived from abortion studies. The implications of EPL compared to abortion on Rh sensitization are unclear, as are the implications for prolonged retention of products of conception after EPL diagnosis. However, given the available evidence, the likelihood of these factors increasing the volume of fetal-maternal hemorrhage to the degree needed for Rh sensitization is very low. We reaffirm the appropriateness of SFP's guidance, and **we suggest against Rh testing and Rh-immunoglobulin administration before 12 weeks of gestation for patients undergoing medication management of EPL (GRADE 2B).** Although not recommended, Rh testing and Rh-immunoglobulin administration may be considered at patient request as part of a shared decision-making process, discussing the patient's future fertility desires in the context of existing data.

This recommendation is also in line with recommendations from ACOG [54], the National Abortion Federation [55], the World Health Organization [20], and the Planned Parenthood Federation of America's Medical Standards and Guidelines. SFP continues to recommend Rh-immunoglobulin administration of 100 mcg (500 IU) dose for Rh-negative patients with pregnancies from 13 0/7 to 18 6/7 weeks of gestation [50].

2.4. What medications are safe and effective for medication management of early pregnancy loss?

Mifepristone with misoprostol

Although mifepristone has been available and studied for the management of EPL in Western Europe for over 20 years [56,57], the increased efficacy of adding mifepristone to a misoprostol-only regimen has only recently been widely accepted domestically based on new well-designed randomized controlled trials (RCTs) (Table 2). Chu et al. [14] published a large placebo-controlled trial that found mifepristone 200 mcg taken 2 days before misoprostol 800 mcg decreased treatment failure (defined as failure to expel the GS by 7 days) from 24% to 17% (p = 0.04). Schreiber et al. [13] found that pretreatment with mifepristone 200 mg orally before misoprostol 800 mcg vaginally increased the likelihood of GS expulsion within 1 to 4 days from 67% for misoprostol alone to 84%. An RCT in the Netherlands ended early on the advice of an independent data safety monitoring board, finding that mifepristone 600 mg orally followed by up to three doses of misoprostol 400 mcg orally was more effective than placebo plus misoprostol for the completion of EPL after 1 week of expectant management (risk ratio 1.35, 95% CI 1.16–1.56) [58]. A dose of mifepristone 600 mg orally was not found to be more effective than mifepristone 200 mg when followed by misoprostol [59]. These RCTs did not include the use of buccal misoprostol, but FDA labeling of mifepristone for pregnancy termination is based on buccal administration of misoprostol; thus, it can be extrapolated that buccal administration of misoprostol for EPL management is also acceptable [60].

These RCT protocols include a range from 24 to 48 hours waiting period between mifepristone and misoprostol, likely based on optimal and FDA-approved protocols for medication abortion. The RCT by Schreiber et al. showed that despite instructions to take misoprostol at 24 hours after mifepristone, 15% of participants used misoprostol between 0 and 6 hours, and 20% used misoprostol between 7 and 20 hours later [13]. This study not only showed that using misoprostol 7 to 20 hours after mifepristone was slightly more efficacious than 20 to 48 hours, but it also highlights the desire of participants to use misoprostol at differing time periods [67]. Additional research should explore optimal timing regimens for misoprostol after mifepristone for both efficacy and patient satisfaction.

Several systematic reviews and meta-analyses have approached the topic of the effectiveness of misoprostol alone versus pretreatment with mifepristone. A 2021 Cochrane review included seven RCTs with a total of 1,812 patients and concluded that mifepristone with misoprostol is more effective than misoprostol alone (RR 0.89 [0.79, 0.97]) [48]. A systematic review and meta-analysis in 2019 included 46 trials of moderate quality and found a combined regimen of mifepristone and misoprostol was more effective than misoprostol alone (RR 1.49, 95% CI: 1.09–2.03) [62]. Few studies have concluded that mifepristone did not improve outcomes, and those

Table 2
Selected literature comparing mifepristone and misoprostol to misoprostol alone for management of early pregnancy loss

First author, year of publication, country	Participants in primary outcome analysis (*n*)	Diagnostic and gestational duration inclusion criteria	Study type	Mifepristone + misoprostol medication regimen	Misoprostol alone medication regimen	Primary outcome result	Notes
Hamel, 2021, the Netherlands [58]	344	Nonviable intrauterine pregnancy between 6 and 14 wk of gestation, who had been managed expectantly for at least 1 wk[a]	RCT	Mifepristone 600 mg PO + misoprostol 400 μg PO × 2 doses 4 h apart, 36–48 h after mifepristone	Placebo identical to mifepristone PO + misoprostol 400 μg PO × 2 doses 4 h apart, 36–48 h after mifepristone	Misoprostol alone group had a higher risk of total endometrial thickness >15 mm by US 6–8 wk after treatment start: RR 1.35 (95% CI 1.16–1.56)	Secondary outcome: requiring additional medication or procedural intervention: $p < 0.0001$ favoring mifepristone arm
Chu, 2020, United Kingdom [14]	696	Nonviable pregnancy with the presence of a GS up to 14 wk of gestation	RCT	Mifepristone 200 mg PO + misoprostol 800 μg PV, PO, or SL 2 d after mifepristone	Placebo identical to mifepristone PO + misoprostol 800 μg PV, PO, or SL 2 d after mifepristone	Mifepristone group had a reduced risk of failure to pass GS by US 7 d after randomization: RR 0.73 (95% CI 0.54–0.99)	Secondary outcome: Surgical intervention to resolve EPL: RR 0.71 (95% CI 0.53–0.95) with decreased risk in the mifepristone group
Schreiber, 2018, United States [13]	297	Nonviable pregnancy between 5 and 12 completed wk of gestation	RCT	Mifepristone 200 mg PO + misoprostol 800 μg PV 24 h after mifepristone	Misoprostol 800 μg PV	Increased success of GS expulsion within 1–4 d and no additional intervention within 30 d: RR 1.25 (95% CI 1.09–1.43)	Uterine aspiration was less frequent in the mifepristone group: RR 0.37 (0.21, 0.68)
Stockheim, 2006, Isreal [61]	115	Blighted ovum or missed abortion with a crown-rump length compatible with up to 9 wk of gestation	RCT	Mifepristone 600 mg PO + PRN misoprostol 400 μg PO, 2 doses 3 h apart 48 h later if persistent GS	Misoprostol 400 μg PO, 2 doses 3 h apart. PRN repeat the same regimen 48 h later if persistent GS	No procedural intervention needed, more common in the misoprostol alone group: RR 1.47 (95% CI 0.61–3.55)	Concluded mifepristone added to misoprostol does not increase the success of EPL management
Ghosh, 2021, various [48]	1,812	RCTs comparing mifepristone + misoprostol to misoprostol alone for early miscarriage treatment at 14 wk of gestation or less diagnosed by US or clinically	Meta-analysis	Various mifepristone + misoprostol regimens	Various misoprostol alone regimens	Mifepristone + misoprostol more likely to complete miscarriage than misoprostol alone, based on clinical findings or US: RR 0.87 (95% CI 0.79–0.97)	Need for unplanned procedure is more common in misoprostol alone groups: RR 1.55 (95% CI 1.22–1.96)
Al Wattar, 2019, various [62]	3,949	RCTs comparing two or more treatments for first-trimester miscarriage less than 14 wk of gestation	Meta-analysis	Various mifepristone + misoprostol regimens	Various misoprostol alone regimens	Complete evacuation of products of conception defined clinically or on US as an empty uterine cavity without the need for further treatment: RR 1.43 (0.87, 2.36)	Inconsistency in treatment regimens hinders interpretation
van den Berg, 2015, various [63]	n/a	RCTs and nonrandomized trials reporting on the added value of mifepristone to nonsurgical treatment regimens for EPL	Systematic review	Various mifepristone + misoprostol regimens	Various misoprostol alone regimens	n/a	Conclusion: Success of mifepristone + misoprostol regimens ranges from 52% to 95%. Evidence is insufficient to determine mifepristone + misoprostol is superior to misoprostol alone
Friedman, 2024, Isreal [64]	999	Anembryonic gestation or embryonic death with US consistent with 12 wk of gestation or less following SRU Criteria for EPL, 2016–2023	Retrospective cohort	Mifepristone 200 mg PO + misoprostol 800 μg PV 48 h later. Additional dose misoprostol 800 μg PV offered in 1 wk if incomplete	Misoprostol 800 μg PV. Additional dose misoprostol 800 μg PV offered in 1 wk if incomplete	Any surgical intervention: RR 0.66 0.44, 0.97. Includes patients electing for aspiration over expectant management when endometrial strip >15 mm after second dose of misoprostol	Misoprostol alone used from 2016 to 2022. Medical center protocol changed to mifepristone + misoprostol May 2022
van den Berg, 2014, the Netherlands [65]	301	Presence of a nonviable pregnancy before 14 wk of gestation and "an indication for medical treatment" who had been managed expectantly for at least 1 wk, 2008–2013	Retrospective cohort	Mifepristone 200 mg PO + misoprostol 800 μg PV 36 h later + 800 μg misoprostol PV PRN no bleeding 24 h later	Misoprostol 800 μg PV x 2 doses 24 h apart	Complete expulsion as judged by the treating physician using any criteria. 44.6% in misoprostol alone and 64.1% in mifepristone + misoprostol ($p < 0.01$)	

(*continued on next page*)

Table 2 (*continued*)

First author, year of publication, country	Participants in primary outcome analysis (*n*)	Diagnostic and gestational duration inclusion criteria	Study type	Mifepristone + misoprostol medication regimen	Misoprostol alone medication regimen	Primary outcome result	Notes
Dunford, 2018, Australia [66]	281	Anembryonic pregnancy, missed miscarriage, or incomplete miscarriage at 13 wk gestation or less electing medical management, 2010–2013	Retrospective cohort	Mifepristone 200 mg PO + misoprostol 400 μg PO × 2 doses 48 h later	Misoprostol 600 μg or 800 μg PO × 2 doses, 3 h apart	Persistent GS or endometrial stripe <15 mm 7–10 d after treatment: 44% in misoprostol alone and 27% in mifepristone + misoprostol ($p = 0.012$)	Misoprostol alone used from 2010 to 2011. Mifepristone introduced in late 2011 and adopted at different rates by providers
Benson, 2024, United States [8]	31,977 (Insurance claims database)	ICD-10 codes consistent with EPL + prescription of misoprostol with or without mifepristone, 2015–2022	Retrospective cohort	Mifepristone + misoprostol ($n = 975$)	Misoprostol alone ($n = 31,002$)	Procedural management after medication management: aOR 0.71 (95% CI, 0.57–0.87) with mifepristone group having reduced odds of procedure	Exploratory outcome: ED visits related to EPL 7.9% in misoprostol alone and 3.5% in mifepristone + misoprostol ($p < .001$)

aOR, adjusted odds ratio; CI, confidence interval; ED, emergency department; EPL, early pregnancy loss; GS, gestational sac; ICD-10, International Classification of Diseases, Tenth Revision; PO, per oral; PV, per vagina; RCT, randomized controlled trial; RR, risk ratio; SL, sublingual; SRU, Society of Radiologists in Ultrasound; US, ultrasonography.
Inclusion criteria, regimens, and outcomes maintain the study authors' language in order to maintain the intention of the original study.
[a] Diagnostic criteria for EPL: ultrasonography describing a crown-rump length ≥6 mm and no cardiac activity, or a crown-rump length <6 mm and no embryonic growth at least 1 week later, or a gestational sac with the absent embryonic pole for at least 1 week.

that did not demonstrate improved outcomes did not use the most efficacious mifepristone and misoprostol regimens [61]. However, a 2015 systematic review that included five RCTs and 11 non-randomized trials concluded that available evidence was not conclusive in favor of either mifepristone plus misoprostol or misoprostol alone [63]. It can be difficult to compare treatment efficacy findings from published studies of medication management of EPL because of variations in gestational duration, doses of medications, the timing of combinations or series of medications (e.g., mifepristone followed by misoprostol), route of administration (including oral, vaginal, sublingual, and buccal), the definition of treatment success, and follow-up periods.

Many observational and retrospective studies have also concluded that mifepristone added to a misoprostol-based regimen is safe and more effective than the use of misoprostol alone [8,64–66,68,69]. Reported success rates of mifepristone and misoprostol for EPL management range from 61% to 95%, again likely due to variations in treatment protocols [70–72]. **We recommend a combined regimen of mifepristone with misoprostol over misoprostol alone for medication management of EPL (GRADE 1A). We suggest the use of a combination of mifepristone 200 mg orally followed 7 to 48 hours later by misoprostol 800 mcg vaginally or buccally for medication management of EPL (GRADE 2A).** Sublingual and oral administration of misoprostol are also safe and effective but less preferred because they are associated with a greater likelihood of nausea, vomiting, and diarrhea [73].

Multiple cost-effectiveness analyses have found a combination regimen of mifepristone and misoprostol versus misoprostol alone to be cost-effective [15–18]. Reductions in cost are especially marked in scenarios where multiple doses of misoprostol or multiple follow-up appointments are necessary and when procedural management under anesthesia in the operating room is the alternative treatment if medication management is unsuccessful [15]. The use of mifepristone with misoprostol reduces ED utilization after treatment compared to misoprostol alone [8]. Factors such as uterine size less than 9 weeks of gestation, serum progesterone greater than 10 nmol/L, prior minor symptoms (e.g., light bleeding), higher body mass index, and no prior uterine curettages may be associated with a higher likelihood of successful EPL management with mifepristone and misoprostol [74,75].

Misoprostol alone

Studies of misoprostol alone for the management of EPL report efficacy that has varied widely, from 11% to 90.5% [48,76–79]. Variations in treatment regimens are likely responsible for this large range and, again, can make direct comparisons difficult. A recent meta-analysis concluded that dosing strategies of misoprostol 600 mcg sublingually or 800 mcg vaginally are optimal when compared with lower doses (e.g., 200–400 mcg), and a Cochrane review concluded higher doses (600–800 mcg) administered vaginally were more effective than lower doses [78,80]. The International Federation of Obstetrics and Gynecology recommends misoprostol alone for first-line treatment of EPL in doses of 800 mcg vaginally or 600 mcg sublingually every three hours for two doses [81]. ACOG recommends misoprostol 800 mcg vaginally with a second dose if needed no sooner than 3 hours and typically within 7 days if there is no response to the first dose [2]. One RCT comparing misoprostol 600 to 800 mcg vaginally found the higher dose to be significantly more effective [82]. Another found misoprostol 400 mcg versus 800 mcg vaginally to be equivalent and concluded that misoprostol 400 mcg doses should be used [83]. Additional retrospective and observational studies support the use of misoprostol 800 mcg vaginally and 600 mcg sublingually [84–90]. One retrospective cohort study did not find any difference between regimens of two doses of misoprostol 600 and 800 mcg vaginally 24 hours apart [79].

With regards to route of administration of misoprostol, a Cochrane review found no significant difference in effectiveness between sublingual and vaginal administration in medication management of EPL. While no difference in safety and efficacy was found between sublingual and oral administration, sublingual administration was associated with less nausea, vomiting, and diarrhea, and greater treatment satisfaction than oral administration [78]. No difference was found in the effectiveness of misoprostol 800 mcg administered vaginally versus orally in one RCT, although vaginal misoprostol led to significantly shorter pregnancy expulsion times [91]. **We recommend misoprostol in two or more doses of 600 to 800 mcg sublingually or vaginally at intervals of at least 3 hours when used alone for medication management of EPL (GRADE 1B).** Planned intervals of up to 24 hours between misoprostol doses have been shown to be effective. Buccal administration of misoprostol alone for EPL has not been compared to other dosing routes, but given its success when used for medication abortion up to 13 6/7 weeks of gestation, it is reasonable to assume that buccal administration can also be used for EPL.

For medication abortion with misoprostol alone, moistening misoprostol tablets before vaginal administration may improve effectiveness [19]. However, neither moistening misoprostol tablets with saline before vaginal insertion nor the use of powdered misoprostol versus compact tablets has been shown to improve the effectiveness in resolving EPL [92,93]. Given the low risk associated with moistening misoprostol tablets and the potential benefits demonstrated in the medication abortion literature, it is reasonable to employ this approach in EPL management.

One study found that treatment success of a single dose of misoprostol may be predicted by serum quantitative hCG levels equal to or greater than 4000 mIU/ml [94], while another found that lower serum quantitative hCG levels may negatively affect the success of treatment [94,95]. Other predictors of success for misoprostol-only regimens may include light bleeding before misoprostol administration and higher gravidity and parity [95,96].

Alternate regimens

Alternative prostaglandin analogs. Early management regimens for EPL included various prostaglandin analogs, including PGE1 analogs (gemeprost and misoprostol), PGE2 analogs (sulprostone and dinoprostone), and the PGF2α analog carboprost [97–105]. The use of misoprostol eventually became favored among prostaglandin analogs for its low cost, versatility in multiple obstetric scenarios, choice of dosing routes, and shelf stability [73], and consequently is included in the World Health Organization's List of Essential Medicines [106]. However, in settings where misoprostol is not available and other prostaglandin analogs are, their use can be considered for the treatment of EPL with or without pretreatment with mifepristone. For example, vaginal dinoprostone alone for EPL management is effective, but it may not be as effective as vaginal misoprostol alone [78,107], and gemeprost has been successfully used with mifepristone for EPL [108].

Methotrexate. The efficacy of methotrexate, which is cytotoxic to trophoblastic tissue, with misoprostol has been well-established for abortion [109–111]; data are scarce on comparative efficacy and safety for EPL. In one small study with 21 participants experiencing EPL, methotrexate with misoprostol was found to be more effective than misoprostol alone [112]. However, because methotrexate targets rapidly dividing cells, this may not be as effective of a strategy in EPL as in abortion care. Data on methotrexate from abortion studies may not be relevant to EPL, and there is insufficient evidence to routinely recommend methotrexate for medication management of EPL.

Letrozole. Letrozole is an aromatase inhibitor that reduces the synthesis of estrogen. A recent RCT from China concluded that pretreatment with 3 days of letrozole 10 mg daily prior to vaginal misoprostol was noninferior to pretreatment with mifepristone to treat EPL, with efficacy at 42 days of follow-up of 97.8% and 97.2% in letrozole and mifepristone groups, respectively. Time to expulsion after misoprostol administration was shorter in the mifepristone group compared with the letrozole group (9 and 15 hours, respectively); this was in addition to the 3 days of letrozole treatment preceding misoprostol compared to the 24 to 48 hours required for mifepristone [113]. Two RCTs demonstrated that pretreatment with 3 days of letrozole 10 mg daily before oral or vaginal misoprostol improved rates of completed abortion compared to a placebo pretreatment [114,115]. Letrozole shows promise for an alternative to mifepristone pretreatment before misoprostol for EPL, although letrozole likely increases the time from diagnosis to pregnancy expulsion. Further studies are needed to demonstrate its efficacy in various settings and practice patterns.

2.5. What is the recommended pain management approach during medication management for EPL?

In a secondary analysis of an RCT comparing mifepristone plus misoprostol to misoprostol alone for the management of EPL, the mifepristone plus misoprostol group reported a higher severity of pain, but potentially a shorter duration of pain compared to the misoprostol alone group [116]. Although pain management in the setting of abortion is a topic of continued research, few, if any, studies have similarly explored pain management during the management of EPL. Studies of abortion often specifically exclude patients experiencing pregnancy loss from their study populations. Despite the lack of research specifically for EPL, pain management options can reasonably be guided by literature for abortion.

A Cochrane review of pain relief interventions for medication abortion with mifepristone and misoprostol through 13 6/7 weeks of gestation found ibuprofen to have the best evidence for pain management among evaluated studies, although optimal dosing and duration remained unclear [117]. One well-designed placebo-controlled trial found no difference in pain when oxycodone 10 mg versus ibuprofen 800 mg was given with the onset of abdominal pain following misoprostol for medication abortion [118].

In an RCT of people receiving pregabalin 300 mg before misoprostol in medication abortion, pregabalin did not decrease pain in comparison to the placebo but did reduce the need to coadminister ibuprofen or narcotics [119]. In a secondary analysis of real-time pain scores from that same study, participants reported pain scores reaching 5.5 out of 10, with over half of participants not having any pain 12 hours from misoprostol administration [120]. The median dosage of ibuprofen used was 1,600 mg total.

In an RCT of people undergoing medication abortion with mifepristone and misoprostol through 10 0/7 weeks of gestation, dronabinol, a synthetic cannabinoid, did not reduce maximum pain when compared to placebo [121]. However, it is important to note that dronabinol is not indicated for pain management. **We suggest ibuprofen 800 mg orally for pain control in medication management of EPL (GRADE 2A). The use of other nonsteroidal anti-inflammatory drugs and opioids in this setting is not supported by the EPL literature but may be reasonable on an individual basis.**

More research is needed to develop alternative pain management strategies for EPL and medication abortion.

2.6. What are the optimal approaches to confirm completed EPL after medication management?

All patients who receive medication management of EPL should be offered follow-up to confirm completed EPL. Depending on whether a fetus was visible sonographically at EPL diagnosis, the medication regimen used, and the time to follow-up assessment, up to 9% to 29% of patients may not have expelled all pregnancy tissue, and some of these patients may need or desire further intervention [13]. There are various safe approaches to ensuring complete passage of the pregnancy tissue. Options for follow-up include in-person or virtual evaluation by telemedicine and can also include a confirmatory ultrasonography or hCG testing via blood or urine [2]. Any confirmatory evaluation and testing should consider patient needs and goals; no one approach will work for all patients. **We suggest clinicians offer all patients confirmation of completed EPL, but in-person evaluation should not be required (GRADE 2B).**

When desired, in-person follow-up visits with ultrasonography most commonly take place 1 to 2 weeks following medication management [2]. The goal of an ultrasonography should be to confirm the passage of the GS. There is no need to demonstrate a completely empty uterine cavity or use a cutoff for endometrial thickness. In a large, pooled analysis of 2,208 individuals who underwent medication abortion, there was no endometrial thickness threshold that had a positive predictive value of greater than 25% for needing subsequent procedural intervention [122]. While many recommendations regarding confirmation of successful medication management of EPL are extrapolated from the medication abortion literature, one randomized trial did evaluate ultrasonography findings of 80 patients with EPL who were treated with up to two doses of misoprostol [123]. This study found no clear relationship between endometrial thickness and the need for procedural intervention. Additionally, a prospective observational study of 44 patients who underwent medication management of EPL found no relationship between the size of remaining intrauterine contents and duration of pain or bleeding following EPL [124]. For patients who have an evaluation that demonstrates incomplete EPL, also called residual or RPOC, management options may include procedural intervention (i.e., uterine aspiration), repeat medication management, or expectant management. Decisions regarding subsequent or repeat intervention should consider the patient's clinical status and employ shared decision-making. **We recommend against using endometrial thickness alone as a criterion for recommending additional intervention after medication management of EPL (GRADE 1B).**

Telemedicine may also be used for follow-up of medication management of EPL. Chen et al. [125] used synchronous video visits to assess patient symptoms and concerns and recommended in-person follow-up only if needed. They demonstrated a similar loss to follow-up rate and complication rate as similar visits for telemedicine follow-up of medication abortion, which is well-supported by the literature. Telephone follow-up to assess symptoms at 1 week, with subsequent at-home high-sensitivity urine hCG testing at 4 weeks after treatment, may be an acceptable approach, as in the case of medication abortion [126]. Telephone or telemedicine evaluation typically includes a series of questions regarding the severity and duration of bleeding and cramping [127,128]. It also includes questions regarding whether the patient feels treatment was successful, as studies support that when the patient and clinician think a medication abortion has been successful, they are correct 96% to 99% of the time [127,129]. Data regarding the ability of patients and clinicians to predict successful treatment of EPL are limited, but the probability of a correct assessment is likely lower given the less predictable trajectory of symptoms following EPL compared with medication abortion. One prospective cohort study of 197 patients with EPL found that the resolution of bleeding within 2 weeks of medication management indicated successful treatment and that the odds of RPOC were increased sixfold if bleeding persisted past 2 weeks [130]. If either the patient or the clinician feels that management may not be complete or there are other concerns, an in-person evaluation should be offered.

Testing of hCG levels, either by blood or urine, is often used to confirm complete EPL when ultrasonography is not desired or feasible. Unlike the predictable serum quantitative hCG trends seen following medication abortion, there is significantly more variability seen in serum quantitative hCG values following EPL [131]. In a planned secondary analysis of an RCT comparing EPL management with mifepristone and misoprostol to misoprostol alone, EPL treatment success was associated with a greater decline in serum quantitative hCG, but there was no threshold for percentage decrease that could predict successful treatment [132]. While there is no clear consensus regarding absolute serum quantitative hCG levels or threshold for change in serum quantitative hCG level that confirms successful medication management, a substantial decrease in serum quantitative hCG level can suggest successful completion of EPL. Similarly, thresholds for expected time to a negative urine hCG test are not clearly defined in the setting of medication management of EPL, and any use of urine hCG testing to monitor completion of EPL should also consider clinical course and symptoms.

Any follow-up should consider patient needs and preferences, with follow-up visits or evaluation offered but not required; treatment should not be withheld on account of a patient's ability to follow up in person or amenability to undergo subsequent ultrasound or lab testing.

Health equity and access

2.7. What are important factors to consider to increase access to medication management of EPL?

Even in settings where mifepristone is available, patients face barriers to accessing medication management of EPL, including systemic racism, institutional limitations, cost, clinician practices, abortion-related stigma, and the politicization of reproductive health care. Besides variations in medications offered for medication management of EPL, studies suggest that patients may not be offered all management options depending on the clinical setting in which they present. A recent observational study of insurance claims of people seeking EPL care found that patients presenting to the ED were less likely to receive medication management than people presenting to outpatient clinics (5.4% vs. 11.2%, respectively) and less likely to receive active management overall [7]. Prior research has found that patients presenting to the ED for EPL care are more likely to be young, Black, and without insurance or insured through Medicaid [7,25]. Additionally, patients presenting to the ED were less likely to be satisfied with their care and more likely to meet the criteria for posttraumatic stress disorder [25]. However, integrating medication management of EPL in the ED setting has been proposed and studied as a feasible approach to increasing access to high-quality EPL management [133]. Understanding disparities in pregnancy loss care is an essential step toward providing equitable, patient-centered care to all patients experiencing EPL and allows clinicians, institutions, and policymakers to create initiatives that improve early pregnancy care.

Access to mifepristone remains inequitable because of the politicization of reproductive health care, as evidenced by medically unnecessary FDA requirements, state-level restrictions, and federal decisions. Since its approval by the FDA in 2000, mifepristone has been used by over 5 million people in the US to safely manage

medication abortion and EPL [60,134]. Despite its excellent safety profile, the use of mifepristone has been regulated by the FDA REMS since FDA approval. REMS places several restrictions on mifepristone distribution and use, including clinician certification with the drug distributor and a patient agreement form. In the wake of the COVID-19 pandemic, the FDA halted enforcement of an in-person dispensing requirement, which allowed for telemedicine and mail distribution of the medication in some states. In January 2023, the FDA permanently removed the in-person dispensing requirement and added a pharmacy certification process, which allows certified retail pharmacies to dispense mifepristone with a prescription from a clinician [135,136].

Recent restrictions on the provision of mifepristone have been the cause of alarm regarding continued access to this important medication [137,138]. After the 2022 US Supreme Court's decision in *Dobbs v Jackson Women's Health Organization* removing the constitutional right to abortion, the availability of mifepristone for medication management of EPL may depend on the interpretation of state laws and perceived risks associated with prescribing it. Even in states where abortion is legal, the availability of mifepristone depends on clinicians and retailers being willing to complete REMS certification and feeling confident in their knowledge of special conditions placed on mifepristone use, as reproductive health clinicians report uncertainty and logistical barriers related to REMS requirements [139,140]. Other barriers to the use of mifepristone include resistance from institutional leadership and no prior experience with mifepristone use [139,140].

Whether from clinicians' lack of knowledge or barriers to use, the mifepristone–misoprostol regimen remains underutilized for the management of EPL. In a study of commercial insurance claims of adults in the US receiving medication management of EPL in 2020, 2.5% of patients received mifepristone plus misoprostol in 2020, while 97.5% received misoprostol alone [139,141]. These studies highlight the need for continued clinician education and support for clinicians and institutions in obtaining and providing mifepristone. Advocacy for mifepristone is an essential part of evidence-based and equity-informed EPL care, as barriers disproportionately burden communities already facing structural barriers to care, including people of color and those living long distances from a health care professional or facility [136]. **We recommend institutions and clinicians make thorough efforts to obtain and maintain access to mifepristone in clinical settings where patients receive EPL care (GRADE 1C).**

Resources exist to help clinicians and administrators acquire mifepristone for clinic and inpatient use as well as to generally implement high-quality EPL care [142–145]. Evidence shows that interdisciplinary training can also be beneficial in improving access to appropriate, patient-centered EPL management [146].

3. Conclusions and recommendations

Please see Table 1 for a key to interpreting GRADE.

- We recommend that patients experiencing EPL have equal access to all available treatment options, including expectant, medication, and procedural management, when urgent treatment is not necessary (GRADE 1A).
- We recommend a patient-centered approach that uses shared decision-making to diagnose EPL through ultrasonography, serial quantitative hCG measurements, or symptoms, depending on the patient's desire for a definitive diagnosis (GRADE 1C).
- We suggest a shared decision-making approach for continuing expectant management of EPL up to 8 weeks after diagnosis in the absence of medical complications or symptoms requiring urgent intervention (GRADE 2C). Medically stable patients who select expectant management should be counseled that they may decide to change to medication or procedural management at any point during expectant management.
- We suggest against Rh testing and Rh-immunoglobulin administration before 12 weeks of gestation for patients undergoing medication management of EPL (GRADE 2B).
- We recommend a combined regimen of mifepristone with misoprostol over misoprostol alone for medication management of EPL (GRADE 1A).
- We suggest the use of a combination of mifepristone 200 mg orally followed 7 to 48 hours later by misoprostol 800 mcg vaginally or buccally for medication management of EPL (GRADE 2A).
- We recommend misoprostol in two or more doses of 600 to 800 mcg sublingually or vaginally at intervals of at least 3 hours when used alone for medication management of EPL (GRADE 1B).
- We suggest ibuprofen 800 mg orally for pain control in medication management of EPL (GRADE 2A). The use of other nonsteroidal anti-inflammatory drugs and opioids in this setting is not supported by the EPL literature but may be reasonable on an individual basis.
- We suggest clinicians offer all patients confirmation of completed EPL, but in-person evaluation should not be required (GRADE 2B).
- We recommend against using endometrial thickness alone as a criterion for recommending additional intervention after medication management of EPL (GRADE 1B).
- We recommend institutions and clinicians make thorough efforts to obtain and maintain access to mifepristone in clinical settings where patients receive EPL care (GRADE 1C).

4. Recommendations for future research

We recommend that further research on medication management of EPL include:

- Development of safe and effective minimal intervention or "no-test" protocols for diagnosing and treating EPL with medications.
- Development of safe and effective telemedicine approaches to diagnosing and treating EPL with medications.
- Well-designed RCTs comparing alternatives to mifepristone (e.g., methotrexate, letrozole) that may increase the effectiveness of medication management of EPL compared to misoprostol alone.
- Optimal timing of misoprostol after mifepristone for EPL for both efficacy and patient satisfaction.
- Understanding disparities in EPL care: More research is needed to determine the influence of patient, clinician, social, and legal factors that may affect differences in EPL management patterns and reflect patient preferences or clinician biases.
- Barriers and accessibility to high-quality medication EPL management, particularly using mifepristone.
- Optimal pain management regimens for medication management of EPL.

5. Sources

A series of clinical questions was developed by the Society of Family Planning's Clinical Affairs Committee and was addressed by the authors in a narrative review. We searched the PubMed program of the National Library of Medicine and the Cochrane Library of Cochrane Reviews to identify relevant articles published between 2003 and June 2023. Search terms included, but were not limited to, EPL, diagnosis, diagnostic criteria, ultrasonography, miscarriage, hCG trends, and completed abortion. The search was restricted to articles published in the English language. We also reviewed guidelines published by organizations or institutions, such as the US Centers for Disease Control and Prevention, ACOG, and SFP, as well as relevant product labels. We located additional studies by

reviewing references of identified articles. When reliable research was not available, expert opinion from family planning clinicians was used.

6. Intended audience

This Clinical Recommendation is intended for Society of Family Planning members, family planning and reproductive health service clinicians, family planning and reproductive health researchers, consumers of family planning care, and policymakers.

Authorship

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