

Management of early pregnancy loss by reproductive endocrinologists: does access to mifepristone matter?

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Objective: To describe patterns and variations in the medical and procedural management of early pregnancy loss (EPL) among reproductive endocrinology and infertility specialists, with attention to mifepristone use.

Design: Cross-sectional.

Setting: Online survey.

Patients: Society for Reproductive Endocrinology and Infertility members.

Intervention: Not applicable.

Main Outcome Measure: Preferred management for EPL.

Results: Of 101 completed surveys (response rate: 12.2%), 70.3% of respondents reported diagnosing EPL at least once per week. Half (50.5%) of respondents preferred medical management compared with 27.7% who preferred procedural management and 21.8% who preferred expectant management. Approximately one-quarter (26.7%) of respondents offer mifepristone for medical management of EPL. The most common reason cited for not prescribing mifepristone was a lack of access to the medication. Mifepristone prescribers were more likely to work in a hospital or university setting than private practice. Increasing years in practice was also associated with mifepristone use. The use of mifepristone for EPL did not vary by the respondent's age, gender, prior abortion training, or practice region.

Conclusion: The most effective method of medical management uses both mifepristone and misoprostol. However, nearly three-quarters of reproductive endocrinology and infertility physicians do not offer mifepristone, which may be linked to access issues. (*F S Rep*® 2024;5:252–8. ©2024 by American Society for Reproductive Medicine.)

Key Words: Early pregnancy loss, mifepristone, miscarriage

Early pregnancy loss (EPL) occurs in approximately 10%–15% of all clinically recognized pregnancies (1). Accordingly, more than 1 million women in the United States experience EPL each year (2). Although pregnancy loss alone can be distressing, individuals who experience EPL while undergoing fertility treatment may experience even greater distress (3–5). Even as live birth rates after in vitro fertilization treatment improve, as many as 15% of in vitro

fertilization-induced pregnancies still result in EPL (6). Because most cases of EPL will occur before 10 weeks of gestation, often before a patient has established obstetric care, reproductive endocrinology and infertility (REI) specialists are expected to manage these cases.

Early pregnancy loss management options include expectant, medical, and procedural management. The American College of Obstetricians and Gynecologists emphasizes the

importance of patient preference when deciding on a treatment for EPL (7). Expectant management is the least effective option, associated with an increased risk of unplanned hospital admission and procedural evacuation (8). Medications taken to induce an abortion offer higher success rates than expectant management and avoid the risks of an invasive procedure, although they may not be appropriate for patients with infection, anemia, hemorrhage, or bleeding disorders. Medical management is not recommended for patients who are unable to follow up and confirm completion. Procedural evacuation, by contrast, is the most effective method of managing EPL, although some outpatient clinics may not be equipped to offer this service on-site or in a timely fashion (7).

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Until recently, medical management of EPL consisted exclusively of misoprostol, a prostaglandin E1 analogue. Results of multiple randomized control trials suggest that pretreatment for 24–48 hours with mifepristone, a progesterone receptor antagonist, is significantly more effective than misoprostol monotherapy (9, 10). Successful expulsion occurs in up to 83.8% of patients receiving the combination of mifepristone with misoprostol vs. 67.1% with misoprostol monotherapy, with fewer patients requiring procedural evacuation (11). Mifepristone's Food and Drug Administration (FDA) label indication for the termination of pregnancies up to 10 weeks gestational age, among other logistical barriers, limits the extent of uptake among physicians (12). Difficulty accessing mifepristone is primarily a result of the drug's inclusion in the FDA's Risk Evaluation and Mitigation Strategy (REMS) Program (12–14). Although the REMS program is designed to closely monitor medications that place patients at high risk for serious complications, mifepristone safety data continues to be reassuring (11, 15, 16). The REMS requirements limit the ability to prescribe mifepristone to certified providers who must submit a drug manufacturer's prescriber agreement form, attesting to their ability to determine the gestational age of a pregnancy, diagnose ectopic pregnancies, and perform or refer a patient for surgical management. Additionally, providers must ensure that patients sign specific agreement forms accepting the potential risks of medical management with mifepristone, as well as receive a copy of the form and a medication guide. The form must also be uploaded into the patient's medical record. Restrictions on where the medication may be stored and sold also exist.

Given these restrictions and limitations in continuing education and practice settings, fertility specialists' management of EPL may vary widely. We thus conducted a national survey examining variations in EPL management, with attention to the provision of combination mifepristone and misoprostol medical management.

MATERIALS AND METHODS

Study participants

We conducted a cross-sectional survey examining variations in EPL management among REI specialists nationwide via the Society for Reproductive Endocrinology and Infertility (SREI). The SREI is a professional organization for board-certified REI physicians that promotes research and education by regularly conducting surveys among members. The SREI solicits and gives preference to member-submitted surveys with the potential "to elucidate practice patterns, knowledge, and/or attitudes relevant to optimizing patient care and/or training in the field of REI."

Survey development

Survey questions were designed to characterize EPL management preferences and variations by provider demographic and practice characteristics. Survey items asked respondents how frequently they encountered EPL, their preferred methods of EPL management, and the methods they offered,

with specific attention to their provision of mifepristone when offering medical management of EPL. The treatment options included expectant management, medication with misoprostol alone, medication with mifepristone and misoprostol, office-based procedures, and operating room-based procedures. The medication route and dosing were not specified. The different procedural options were solely based on procedure location. No additional explanation was provided. We additionally queried provider attitudes regarding why they preferred certain management modalities and barriers to not offering treatment modalities. We reviewed literature from studies conducted among similar populations to understand the potential barriers or reasons influencing treatment decisions for EPL (12, 13, 17–21). The second half of the survey collected respondent sociodemographics (e.g., provider age, sex, race/ethnicity, years in practice) and practice characteristics such as practice type (e.g., solo private practice, group practice, university-affiliated, hospital-based, other), region (e.g., Northeast, Southwest, West, Southeast, Midwest, non-United States), and setting (e.g., urban, suburban, rural). With respect to its possible influence on the provision of procedural management of EPL, we asked respondents whether they received abortion training during residency (22).

TABLE 1

The Society for Reproductive Endocrinology and Infertility physician respondent characteristics.

Characteristic	Mean (±SD)	n (%)
Age (y)	52.4 (±9.85)	
Years in practice	18.6 (±10.6)	
Gender identity		
Man		49 (49.5)
Woman		50 (50.5)
Race/ethnicity		
NH Asian/PI		8 (8.0)
Hispanic		3 (3.0)
NH White		83 (84)
NH other		1 (1.0)
Prefer not to answer		4 (4.0)
Abortion training		
Yes		87 (87.9)
No		12 (12.1)
Practice region		
Northeast		32 (32.3)
Southwest		11 (11.1)
West		26 (26.3)
Southeast		15 (15.2)
Midwest		14 (14.1)
Non-United States		1 (1.0)
Practice setting		
Urban		51 (51.5)
Suburban		48 (48.5)
Practice type		
Solo private		7 (7.1)
Group		43 (43.4)
Hospital		6 (6.1)
University		41 (41.4)
Other		2 (2.0)

NH = non-Hispanic; PI = Pacific Islander.

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Recruitment and data collection

We distributed the online survey to 826 SREI members from March 1st to June 30th, 2022, using REDCap, a secure web-based survey platform (23, 24). Survey invitations included a brief study description, a reminder of its voluntary nature, and a web link to the anonymous survey. No follow-up invitations were sent, and no compensation was provided. This study was designated as exempt from human subject review by the University of Southern California's Institutional Review Board.

Statistical analysis

We summarized demographics, practice characteristics, available and preferred treatments, and barriers to providing a specific treatment option using descriptive characteristics. We conducted bivariate analyses (e.g., Chi-square tests) where appropriate to examine factors linked to variations in EPL management at a significance level of $P < .05$. We included associated factors in a bivariate multivariable logistic regression model to determine those factors independently associated with providing mifepristone for medication management in EPL.

RESULTS

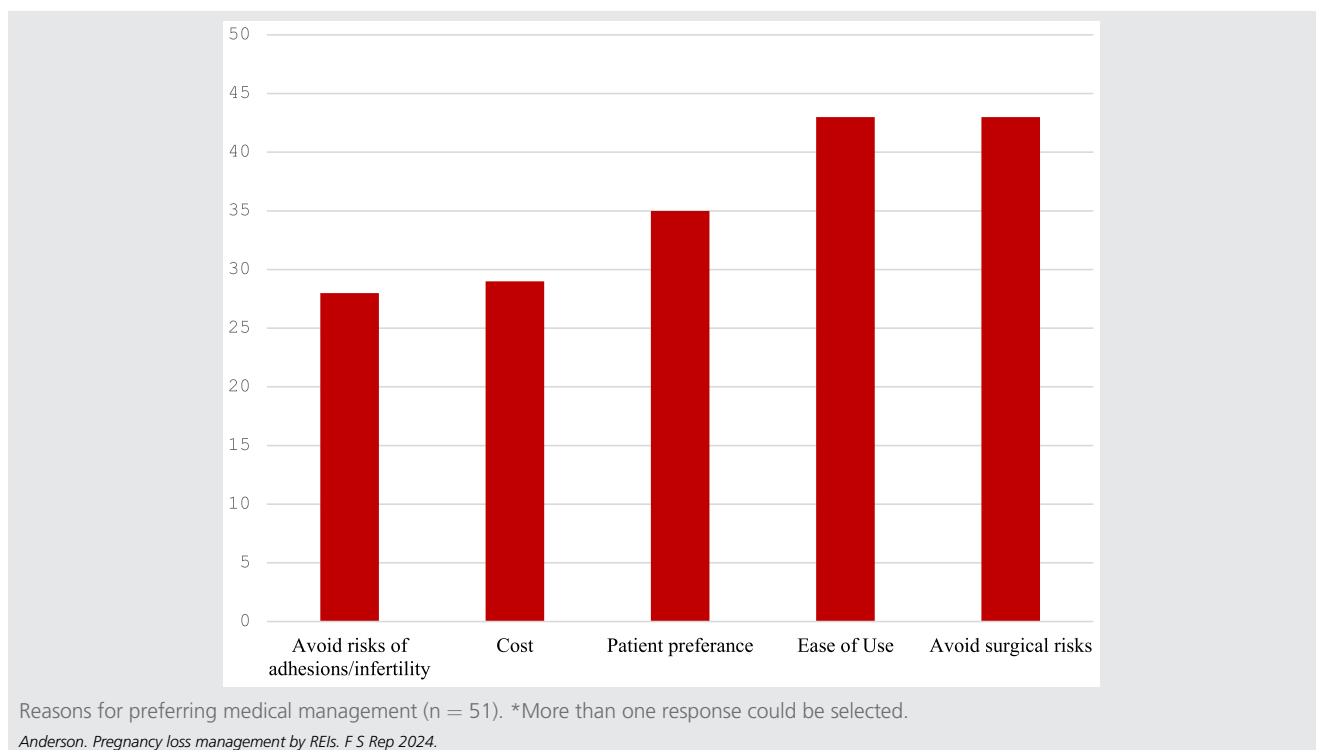
We received 101 completed surveys, yielding a response rate of 12.2% ($n = 101/826$). Two respondents did not complete the survey questions regarding demographic or practice

characteristics. Respondents were, on average, 52.4 (± 9.8) years old and, in practice 18.6 (± 10.6) years. Approximately half (51.0%) were women; 84% identified as non-Hispanic White. Over half (50.5%) of respondents worked in private practice, and slightly less than half (47.5%) were in a practice affiliated with a university or hospital. Respondents worked in suburban (48.5%) and urban (51.5%) settings; none reported working in a rural setting. Most providers practiced in the Northeast (32.3%) and Western (26.3%) United States. Most respondents received abortion training during residency (87.9%) (Table 1).

Nearly all (98.0%, $n = 99$) agreed on the importance of REI specialists considering the potential and variable impact of EPL treatment methods on assisted reproductive outcomes. Most (70.3%, $n = 71$) respondents diagnose EPL at least once per week. Expectant management was offered as an option for management by 94.1% ($n = 95$) of respondents, followed by misoprostol monotherapy (77.2%, $n = 78$) and outpatient surgery (74.3%, $n = 75$). Far fewer (26.7%, $n = 27$) respondents offered medical management with the combination of mifepristone and misoprostol; less than half (46.5%, $n = 47$) offered in-office procedural management.

Medical management with misoprostol was the preferred form of treatment identified by 47.7% ($n = 48$) of respondents, whereas the combination of mifepristone and misoprostol was preferred by 2.8% ($n = 3$) of respondents. The most common reasons for preferring medical management included ease of use, avoiding surgical risk, patient preference, and the desire to avoid the risk of adhesions (Fig. 1). Respondents ($n = 74$)

FIGURE 1



who reported not using mifepristone noted difficulty accessing the drug (59.5%) and a lack of familiarity with the drug (23.1%). Examining factors independently linked to providing mifepristone using multivariable logistic regression, we noted the association of provider affiliation with a hospital (adjusted odds ratio [aOR] 18.1; 95% confidence interval [CI]: 2.4–134.2) or university (aOR 7.2; 95% CI: 2.3–22.7) compared with private practice. Increasing years in practice may be also associated with an increased provision of mifepristone (aOR 1.1; 95% CI: 1.0–1.1). Respondent age, gender, prior abortion training, or practice region were not associated with mifepristone provision (Table 2). Procedural management was preferred by 27.7% (n = 28) of respondents, with the most common reasons including the availability of tissue for chromosome analysis, patient preference, and faster treatment time (Fig. 2). Procedural evacuation in the OR was preferred by 17.8% (n = 18), and in-office evacuation was preferred by 9.9% (n = 10). Practicing in a suburban versus urban setting may be linked to the provision of procedural evacuation in the office ($P=.06$).

DISCUSSION

Our findings suggest that of the REI specialists surveyed, most manage EPL frequently and prefer medical over procedural or

expectant management. Only a quarter (26.7%) of respondents use the most effective medical regimen, which includes mifepristone, and just 2.8% prefer this treatment option. The primary reason mifepristone is not used among REI specialists is the inability to access the medication, as cited by more than half (67.7%) of respondents. Unfortunately, the medication is targeted because of to the FDA label indication for termination of pregnancy (25). Mifepristone is not FDA-approved for EPL. In January 2023, the American College of Obstetricians and Gynecologists and 70 other women's health organizations, including the American Society for Reproductive Medicine, submitted a citizen's petition to the FDA and drug manufacturers, requesting that EPL be included as an indication (7). In 2023, several updates were made to the REMS policy for mifepristone. The medication can now be prescribed via telemedicine, and retail pharmacies were added to the list of those that can store and dispense the medication. Pharmacies need to become certified and can distribute the medication in person or through the mail. Providers electing to prescribe the medications via pharmacies must send a copy of their certification to each pharmacy where they prescribe (7). Although the REMS policy was modified, the medication is still limited to the states where it remains legal. In 2022, a survey of 350 obstetricians and gynecologists found

TABLE 2

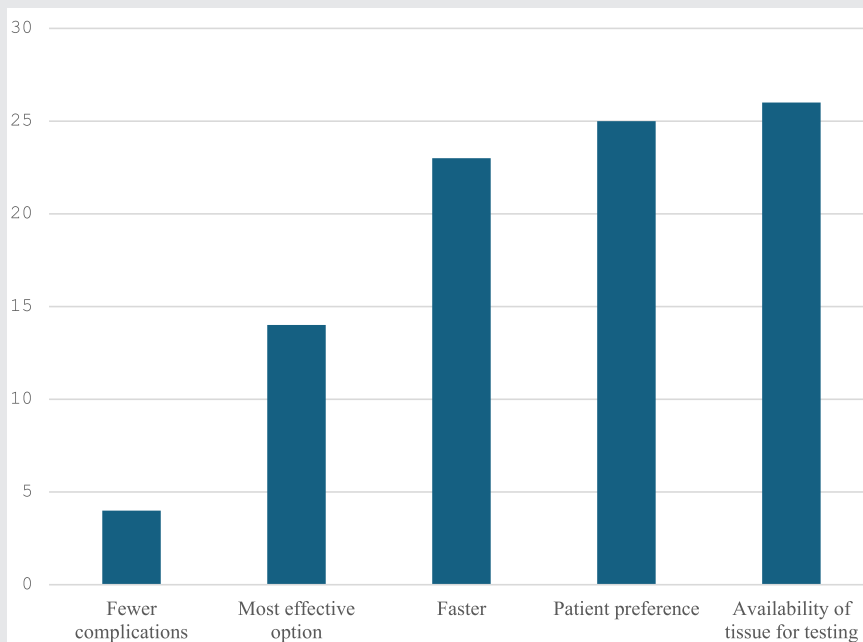
Respondent characteristics associated with the provision of combination mifepristone-misoprostol and in-office dilation and curettage for early pregnancy loss.

	Combination mifepristone-misoprostol use for early pregnancy loss			In-office dilation and curettage for early pregnancy loss		
	Yes (n = 27)	No (n = 72)	P value	Yes (n = 45)	No (n = 54)	P value
Age (y) (mean)	55.1	51.4	.10	51.7	52.9	.56
Years in practice (mean)	22.3	17.3	.03	18.5	18.8	.89
Gender identity			.28			
Men	11	38		19	30	
Women	16	34		26	24	
Race/ethnicity			.75			.09
NH Asian/PI	3	5		2	6	
Hispanic	1	2		1	2	
NH White	23	60		42	41	
NH other	0	1		0	1	
Prefer not to answer	0	4		0	4	
Abortion training			.85			.39
Yes	24	63		41	46	
No	3	9		4	8	
Current region			.41			.56
Northeast	10	22		15	17	
Southwest	1	10		3	8	
West	8	18		11	15	
Southeast	6	9		9	6	
Midwest	2	12		7	7	
Non-United States	0	1		0	1	
Setting			.16			.05
Urban	17	34		28	23	
Suburban	10	38		17	31	
Practice Type			.002			.06
Solo private	1	6		2	5	
Group	4	39		15	28	
Hospital	4	2		5	1	
University	17	24		21	20	
Other	1	1		2	0	

NH = non-Hispanic; PI = Pacific Islander.

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FIGURE 2



Reasons for preferring surgical management (n = 28). *More than one response could be selected.

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variations in EPL management by clinician state of residence. Clinicians from states with more restrictive abortion policies were less likely to offer mifepristone and office-based management than clinicians from more supportive states (33.2% vs. 51.3%; $P = .001$) (26). Because our data collection occurred before the Dobbs decision, recent REMS modifications, and numerous state-level policy changes, the restrictions limiting providers from utilizing specific treatments may have changed. At the time of writing, mifepristone is legal at the federal level, but attempts to ban the medication continue (27).

An additional reason for 29.3% of providers not prescribing mifepristone was unfamiliarity with the medication for EPL management. Following the previously discussed Schreiber et al. (11) study, an evaluation of 711 women with missed abortion before 14 weeks reported a failure rate of 17% for patients randomized to combination mifepristone and misoprostol vs. 24% with placebo followed by misoprostol (RR 0.73, 95% CI 0.54–0.99; $P = .04$). The need for procedural intervention was similarly improved with mifepristone-misoprostol vs. placebo-misoprostol (17% vs. 25%, $P = .02$) (10). In the Triple M randomized control trial, women with missed abortions diagnosed at 6–12 weeks were randomized to receive mifepristone and misoprostol or placebo and misoprostol and evaluated 6–8 weeks later. Similarly, the success rate of 79.1% after mifepristone and misoprostol was superior to 58.7% with placebo and misoprostol ($P < .0001$, RR 1.35, 95% CI 1.16–1.56) (9). A secondary analysis of several studies found the inclusion of mifepristone to be more cost-effective as well (28, 29).

Of note, the previous studies primarily examined naturally conceived pregnancies rather than those using assisted reproductive technology (ART) treatment. Differences in early pregnancies occurring with ART treatment may impact the effectiveness of medical management. Mifepristone is primarily an antagonist at progesterone receptors, but it can display agonist activity in the absence of progesterone. When used for EPL, it causes decidual necrosis and detachment of the pregnancy (30). Typically, the corpus luteum maintains an early pregnancy via progesterone production until 7–8 weeks gestation, at which point the placenta becomes the primary source of hormone production. Pregnancies conceived with ART can vary from having 1 corpus luteum, to multiple, or none, depending on the cycle type (31). Exogenous progesterone supplementation is generally provided, but the formulation, route of administration, and duration vary by practice. When EPL occurs without a corpus luteum before the luteal-placenta shift, then mifepristone may not be as effective because of a lack of progesterone receptors. Furthermore, it may not be required after discontinuing exogenous progesterone. When more than 1 corpus luteum is produced and the progesterone level is higher than expected, additional mifepristone may be warranted. Previous studies have reported an increased failure rate with expectant management when progesterone is low, with at least 1 study also reporting a decrease in the effectiveness of mifepristone when progesterone is low (32–34). A recent case series of 9 patients explored the use of mifepristone-misoprostol for the treatment of EPL in pregnancies conceived using ART. Investigators reported that 8 out of 9 patients had successful management with the medications,

although one required a dilatation and curettage. Importantly, that study only included 1 patient with a programmed frozen embryo transfer where no corpus luteum would be expected (35). Further evaluation of the medical management of EPL in ART-induced pregnancies is needed, although barriers to access among REI specialists should continue to be an area of focus.

Procedural management is the most effective and expedient treatment for EPL, preferred by only 27.7% (n = 28) of providers. Reasons for preferring procedural management include the availability of tissue for cytogenetic analysis, patient preference, and speed of treatment. Almost all (94%) respondents offer procedural management in the OR, but less than half (46.5%) offer office-based procedures. In-office manual vacuum aspiration is well accepted by patients, has a faster time to completion, and is more cost-effective than operating room-based procedures (36–38). Prior abortion training has been associated with the provision of office-based procedures in prior studies, although this association was not observed in the present study, it is difficult to assess as most (n = 88, 87.9%) respondents had prior abortion training (22, 39). Importantly, a lack of training could impact future providers because state-level restrictions on abortion have limited training opportunities for an estimated 44.8% of obstetrician and gynecologist residents (40).

With respect to study limitations, our data are limited by a low response rate. However, respondent characteristics in this study were comparable to those of a study reporting on the demographics and practice characteristics of 370 SREI members, which included 48.4% women, 45% working in private practice, 47% working in a hospital or university-based practice, 50% with 20+ years in practice, and 55% were 51 years or older (41). Additionally, we did not assess whether clinical factors of the miscarriage impacted treatment decisions. The presence of bleeding or cramping, specification as anembryonic or early fetal demise, and diagnosis of a missed abortion or incomplete abortion may impact treatment decisions.

CONCLUSIONS

Endocrinology and infertility physicians frequently diagnose and manage EPL. Medical management is the most popular method of EPL management among REI providers because of its minimal risks and ease of use. However, <30% of those surveyed have adopted the most effective regimen that combines mifepristone with misoprostol. Only 2.8% (n = 3) of respondents reported this to be their preferred regimen, likely because of barriers to accessing mifepristone.

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CRedit Authorship Contribution Statement

Zachary S. Anderson: Writing – review & editing, Writing – original draft, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation,

Conceptualization. **Richard J. Paulson:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Conceptualization. **Brian T. Nguyen:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of Interests

Z.S.A. has nothing to disclose. R.J.P. is the Editor-in-Chief for F&S Reports and was not involved in the editorial review or the decision to publish this article. B.T.N. is on the research advisory boards of Sebela Pharmaceuticals and Myovant Sciences, the products of which are unrelated to the subject of this research.

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