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FAMILY PLANNING (A BURKE, SECTION EDITOR)

Recent Advances in the Medical Management of Early Pregnancy Loss

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Abstract

Purpose of Review To provide an update on advances in medical management of early pregnancy loss, including the addition of mifepristone pretreatment to existing regimens.

Recent Findings The utilization of misoprostol for medical management of early pregnancy loss has been studied extensively and is established as a safe and effective treatment. Two recent randomized controlled trials have demonstrated that the addition of mifepristone pretreatment significantly increases the effectiveness of misoprostol and a large body of data demonstrate the excellent safety profile of mifepristone. However, the Food and Drug Administration Risk Evaluation and Mitigation Strategy restrictions impose a major barrier to mifepristone use.

Summary The addition of mifepristone to existing misoprostol regimens has significantly improved the effectiveness and patient-centered benefits of medical management of early pregnancy loss. Mifepristone restrictions need to be removed in order to decrease the barriers to women obtaining evidence-based care.

Keywords Early pregnancy loss · EPL · Miscarriage · Early pregnancy failure · Mifepristone · Misoprostol

Introduction

Early pregnancy loss (EPL), defined as a nonviable intrauterine pregnancy up to 13 weeks of gestation [1], is the most common complication in pregnancy affecting up to 20% of clinically diagnosed pregnancies [2, 3]. Approximately 1 in 4 women will experience an EPL in her lifetime, affecting approximately 1 million women in the USA every year [4, 5]. Current treatment options for women diagnosed with an EPL are expectant care, medical management, or surgical evacuation [6]. Until the 1990s, surgical aspiration was the standard treatment, as it is a predictable and definitive option for EPL management [6–8]. However, surgical treatment is invasive and carries anesthetic and surgical risks. Expectant and medical management have been shown to be safe alternatives in women without signs of hemodynamic instability, infection, molar pregnancy, or ectopic pregnancy. The majority of EPLs will pass spontaneously with complete expulsion of all gestational tissue within 6 weeks [1, 9]. Expectant management, or observation until spontaneous passage of pregnancy tissue, is often slow and unpredictable, but allows women to avoid a procedure and is often perceived as a more "natural option" [10]. The use of medical management is increasing and provides women with an active, less invasive, patient-centered treatment option [11–14].

This article will highlight advances in medical management of EPL with a focus on the improved effectiveness of adding mifepristone pretreatment to existing misoprostol regimens, discuss barriers to the utilization and implementation of mifepristone in clinical settings, and acknowledge gaps in knowledge with recommendations for future research.

Medical Management of EPL with Misoprostol

Medical treatment is often used as an alternative to uterine aspiration of nonviable pregnancies. Advantages to medical management include controlled timing of management and expedited expulsion of pregnancy tissue. Compared with expectant care, medical management has been shown to decrease the time to expulsion and increase rates of a complete

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EPL with avoidance of surgical intervention [15]. Contraindications to medical management include infection, severe anemia, hemorrhage, or bleeding disorders; in these clinical scenarios, uterine aspiration is preferred [1].

Multiple drugs (misoprostol, mifepristone, gemeprost, dinoprostone, and methotrexate) have been studied for medical management of EPL [10]. The drug most frequently investigated and currently used is misoprostol. Misoprostol is a synthetic prostaglandin E1 analogue that is currently approved by the Food and Drug Administration (FDA) of the USA for the management of gastric ulcer disease. It is commonly used in obstetrics and gynecology for a variety of indications, including induction of labor, cervical ripening, and treatment of obstetric hemorrhage. It is also widely used in combination with mifepristone for medical abortion.

There is no consensus on the best route and dose of misoprostol administration [16]. In a 2019 Cochrane review on medical treatment for early fetal death, different doses and administration routes were compared in order to detect which regimen most often induces a complete EPL with the fewest side effects [17•]. This review included 43 randomized clinical trials involving 4966 women with nonviable pregnancies at less than 24 weeks gestation. There were similar rates of effectiveness in completing EPL at less than 13 weeks when looking at trials that studied various routes of misoprostol administration. Specifically, there was little difference when comparing vaginal and sublingual misoprostol or oral and vaginal misoprostol routes.

Misoprostol-based regimens have shown high rates of effectiveness in management of EPL [6, 11, 15, 18]. Different doses of misoprostol have been used ranging from 100 up to 800 μg per dose; 800 μg is the most commonly tested dose [19]. In a randomized controlled trial by Zhang et al. [11], women with first trimester pregnancy loss underwent medical management with misoprostol or surgical management. The success rate, defined as complete expulsion of pregnancy tissue, after one dose of 800 μg of vaginal misoprostol was found to be 71% by day 3 [11]. This success rate increased to 84% after an additional dose of 800 μg of vaginal misoprostol was administered, if needed [11]. Additionally, the study found differences in effectiveness rates for incomplete abortion compared with missed abortion (93% versus 81%, respectively). Based on the results of this study, it is currently recommended to use 800 μg of vaginal misoprostol for the initial medical treatment of early pregnancy loss [1].

The Addition of Mifepristone

Medical management of EPL with misoprostol is a safe and effective option. However, recent literature has shown superior efficacy with mifepristone pretreatment to existing misoprostol regimens [1, 17•, 20•]. Mifepristone is a 19-nor steroid that blocks progesterone receptors and acts by priming the myometrium and cervix for prostaglandin activity and increasing uterine contractility [21–25]. At the level of the endometrium, mifepristone also restricts the invasion of trophoblastic tissue [26] and disrupts progesterone-mediated trophoblast-decidua interactions [23, 24, 27]. The combination of mifepristone 200 mg with misoprostol 800 μg has been extensively studied for medical termination of pregnancy with effectiveness rates that exceed 95% in women up to 10 weeks gestation [25, 28–31].

EPL treatment with both mifepristone and misoprostol was explored in an important study by Trinder et al. [6] known as the MIST trial. This study compared expectant, medical, and surgical management in women with an early fetal demise or incomplete EPL. Their primary outcome was to evaluate infection risk and complication rates. Women undergoing medical management of EPL were pretreated with a single dose of mifepristone 200 mg orally followed by a single dose of misoprostol 800 μg vaginally 24–48 h later. Study findings demonstrated overall low infection rates and low complication rates for medical management. Results demonstrated that 36% of women undergoing medical management of EPL failed medical management, defined as needing an unplanned surgical curettage. Surgical curettage was performed for any evidence of echogenicity on ultrasound after initial misoprostol administration, which may have contributed to the high rates of surgical intervention [6].

Although early studies were unclear about the advantage of using mifepristone in the management of EPL [32], a recent randomized controlled trial demonstrated that a combined mifepristone-misoprostol regimen was more effective than using misoprostol alone [33••]. This clinical trial included 300 women diagnosed with an anembryonic pregnancy or embryonic/fetal demise less than 13 weeks gestation. The study participants received either pretreatment with 200 mg of oral mifepristone, followed by 800 μg of vaginal misoprostol 24 h later, or 800 μg of vaginal misoprostol alone. At approximately 3 days after patients' self-administered misoprostol, the rate of complete expulsion of the gestational sac without additional surgical or medical intervention was 67% with misoprostol alone compared with 84% with mifepristone pretreatment followed by misoprostol (RR 1.25, 95% CI 1.09–1.43). By day 8, treatment effectiveness in the mifepristone pretreatment group remained higher than the misoprostol alone group (87.8 versus 71.1%). By day 30, effectiveness increased to 91% in the mifepristone pretreatment group with two doses of misoprostol. The absolute risk reduction for needing a surgical aspiration in the mifepristone pretreatment group was 14.7% (95% CI 6.5–22.9). Only 9% of the mifepristone pretreatment group required uterine aspiration compared with 24% of the misoprostol alone group (RR 0.37; 95% CI 0.21–0.68). Side effects and serious adverse events were similar and infrequent between the two treatment groups [33••].

Another recently published trial compared the efficacy of a combined mifepristone-misoprostol regimen with misoprostol alone for treatment of EPL [34••]. This randomized, double-blind placebo-controlled trial included 92 women with EPL up to 12 weeks gestation. Participants were randomized to initially receive either mifepristone 200 mg or a placebo. After 48 h, all participants were given 800 μg of vaginal misoprostol. If no expulsion occurred within 4 h, repeat doses of 400 μg of misoprostol were given orally at 3-h intervals. Women up to 9 weeks gestation were able to receive up to two additional doses of misoprostol as needed, and women greater than 9 weeks gestation could receive up to 4 additional doses as needed. This study found that mifepristone pretreatment significantly improved the complete abortion rate (86.7 vs 57.8%, $p = 0.009$) and decreased the need for surgical evacuation (13.3 vs 42.4%, $p = 0.002$). The average number of additional required misoprostol doses was 0.68 vs 1.91 ($p < 0.001$) in the mifepristone pretreatment group compared with the placebo group, respectively. This study further demonstrated that the use of mifepristone prior to misoprostol in EPL has superior efficacy to misoprostol alone.

The addition of mifepristone to a medical management regimen, and its resultant improvement in effectiveness, is likely to lead to a reduction in treatment costs. Costs would be lowered by reducing additional office visits, ultrasonographic examinations, and aspiration procedures, and the inconvenience of multiple visits for both the patients and providers would be reduced as well. In a cost-effectiveness analysis of surgical versus medical management of EPL, surgical evacuation by manual vacuum aspiration (MVA) was found to be less expensive when compared with medical management using 800 μg of misoprostol alone [35]. These findings were due to the increased costs associated with failed medical management, such as the need for a repeat uterine aspiration, an additional ultrasound, and more office visits. However, in a cost analysis performed using a hypothetical decision model comparing costs of usual care (expectant management and surgical evacuation in an operating room) with expanded care (usual care with the additional options of medical treatment with misoprostol and surgical evacuation in an office setting), expanding women's treatment options for early pregnancy loss were shown to lower direct medical expenditures [36]. A cost-effectiveness analysis of mifepristone pretreatment with misoprostol is currently in progress, and preliminary results demonstrate that pretreatment with mifepristone is less expensive and more effective than misoprostol alone for management of EPL [37].

Overall, recent literature demonstrates that mifepristone pretreatment is significantly more effective than misoprostol alone in achieving EPL treatment success and supports the use of this regimen as the new standard of care for medical management [38]. These findings are consistent with the demonstrated efficacy and safety of the mifepristone-misoprostol regimen for medical abortion [39, 40]. Based on this evidence, the American College of Obstetricians and Gynecologists (ACOG) guidelines were updated in 2018 to include the recommendation to consider providing a dose of mifepristone 200 mg orally, if available, 24 h before misoprostol administration for medical management of early pregnancy loss [1].

Barriers to Mifepristone Use/Implementation

Medical treatment for EPL has been gaining popularity as a noninvasive alternative management option. This is evident in the Schreiber et al. trial, where 42% of eligible women chose to undergo medical management of their EPL [33••]. If almost half of women with an EPL choose medical management, it is important to accommodate patient treatment preferences and offer the most effective medical regimen in a timely manner. However, the availability of mifepristone for medical treatment of EPL has proven challenging.

In September 2000, mifepristone was approved by the FDA for use in the USA. Due to limited US clinical trial data at that time, the FDA imposed a Risk Evaluation and Mitigation Strategy (REMS) restriction on mifepristone [41]. REMS restrictions are intended for drugs that have been shown to have serious adverse effects. This regulation requires (1) mifepristone to be directly dispensed to a patient by or under the supervision of a certified prescriber in a medical setting, (2) certified health care providers to demonstrate competency in diagnosing early pregnancy, and (3) each patient to be given a FDA-approved medication guide and signed patient agreement [42]. In 2016, the FDA approved an updated label for mifepristone to include the more effective dosing regimen that brought the drug's label up-to-date with the evidence-based practice [42]. However, despite accumulated research showing limited risks associated with mifepristone use, this update did not remove the REMS restriction. Since approval, over 3.7 million women have used mifepristone for medical-induced abortion in the USA [41]. After nearly 20 years of research and actual use, mifepristone has been shown to be extremely safe and effective with the majority of side effects being mild and severe adverse events only occurring in less than 0.5% of patients [43].

The REMS restrictions place a burden on women's healthcare providers. The requirements for mifepristone prevent prescription sales in retail pharmacies, which require clinicians to have mifepristone available in the office. The administrative hurdles of certification and maintenance of drug inventories may discourage clinicians from providing the most effective options for medical treatment of EPL. This can lead to delayed treatment and increases cost, inconvenience, and unnecessary medical or surgical risks for women presenting for EPL management. Women should have access to FDA-approved medications that have been repeatedly proven to be safe and effective. The evidence supports a better

approach for women who want medical management for EPL. To provide better care for the more than half a million US women with EPL each year, availability of mifepristone should be ensured.

Future Research

Although strong evidence supports the use of mifepristone in addition to misoprostol for the management of EPL, additional research is needed to create strong patient-centered clinical guidelines.

The optimal interval between mifepristone pretreatment and misoprostol administration needs to be further evaluated. In the Schreiber et al. trial [33••], participants were directed to wait 24 h after taking mifepristone before self-administering vaginal misoprostol. However, almost half of the participants in the mifepristone pretreatment group administered the misoprostol prior to 24 h [33••]. The average interval between mifepristone and misoprostol administration was 12 h (SD 7.3), and the rate of treatment success among participants who did not wait the full 24 h was 79.7%, compared with 86.9% among those who waited the complete 24 h. Comparable to prior studies demonstrating the efficacy of simultaneous administration of mifepristone and misoprostol for first trimester medical abortions [29], this EPL treatment regimen may offer similar flexibility. In order to improve patient-centered counseling, future studies are needed to evaluate the effectiveness of simultaneous administration in EPL management.

A 2019 systematic review and network meta-analysis looked at 46 randomized trials of women with first trimester EPL (< 14 weeks gestation) in order to evaluate the effectiveness and safety of EPL management options [20•]. The included trials studying medical management of EPL contained regimens of either misoprostol alone or mifepristone plus misoprostol with various routes and doses of medications. The authors concluded that although the addition of mifepristone seems to improve the effectiveness of misoprostol, more evidence is needed to address the inconsistencies between direct and indirect evidence. This is clear when comparing outcomes between two different regimens in the recent trials evaluating the effectiveness of pretreatment with mifepristone. In the Sinha et al. trial [34••], providers administered vaginal misoprostol 48 h after mifepristone pretreatment. Overall treatment success was found in 86.7% of participants; however, the study protocol included the option for additional doses of oral misoprostol if treatment success did not occur in the first 4 h. Treatment success within 4 h of the first dose of vaginal misoprostol was found to be significantly higher in the mifepristone group (66% vs 11%, $p < 0.001$). Since participants in the Sinha et al. trial [34••] received an additional dose of misoprostol if they did not expel their pregnancy within 4 h, it is hard to directly compare treatment success of this regimen used to the regimen used in the Schreiber et al. trial [33••], as participants were first evaluated on day 3 after misoprostol administration with no additional doses of misoprostol prior to that evaluation.

The follow-up of women undergoing medical management of EPL should be focused on optimizing the patient's experience. Although it is expected that most women will complete their EPL within 72 h after using mifepristone pretreatment with misoprostol [33••], a longer evaluation interval may allow women to completely pass the pregnancy and avoid unnecessary interventions. By day 30, 88% of participants in the trial by Schreiber et al. [33••] were treated successfully with only one dose of misoprostol after pretreatment with mifepristone. Various clinical or diagnostic parameters can be used to confirm successful medical management of EPL in the clinical setting. Similar to expectant management follow up, sonographic criteria involves the absence of a previously visualized gestational sac [11]. Clinical symptoms can also be used to inform success of medical management of EPL. After medical abortion, women and clinicians have been found to be able to predict pregnancy expulsion, with a positive predictive value of 95–99% [44, 45]. The need for subsequent ultrasounds to assess for retained products of conception is unnecessary in an asymptomatic patient with previously confirmed expulsion of the gestational sac.

In various clinical or remote settings, the use of patient-reported symptoms, serial b-hCG (beta human chorionic gonadotropin) testing, and telephone follow-up to confirm complete pregnancy expulsion have been studied. Similar studies are needed to be performed to examine the various methods of follow up for women receiving medical management with mifepristone followed by misoprostol.

Conclusion

EPL is a common complication in pregnancy, and advances in medical management can be impactful to many women. Misoprostol has been shown to be an effective and acceptable option for management of EPL. However, recent studies have demonstrated the superiority of mifepristone pretreatment to standard misoprostol regimens and should be considered as the new standard of care for medical management of EPL. The continued REMS restrictions enforced on mifepristone impose administrative burdens on providers. Although these burdens are surmountable at a practice level, the challenges inherent in overcoming them will continue to impede patients' access to obtaining the most effective option for medical treatment of induced abortion and EPL. Finally, although recent advances in the medical management of EPL strongly support the use of mifepristone pretreatment, further research is needed to evaluate the optimal interval between mifepristone and misoprostol administration, the most effective route and dose

of misoprostol, and the safest and most acceptable follow-up option for women treated with this new effective regimen.

Compliance with Ethical Standards

Conflict of Interest CAS is a consultant for Danco Laboratories, LLC. The Department of Obstetrics and Gynecology, University of Pennsylvania, receives contraceptive research funding from the NIH, the Society of Family Planning, Bayer, Daré, FHI360, Medicines360, and Sebela. In addition, Dr. Schreiber has a patent 62/777,369 pending.

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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