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Priority Updates from the Research Literature from the Family Physicians Inquiries Network

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Early pregnancy loss: Pretreat with mifepristone?

Yes. While medical management of early pregnancy loss with misoprostol frequently results in treatment failure, pretreating with mifepristone can increase efficacy.

PRACTICE CHANGER

Pretreat patients with oral mifepristone prior to using vaginal misoprostol to increase the efficacy of medical management of early pregnancy loss over that with misoprostol alone.

STRENGTH OF RECOMMENDATION

B: Based on a single, well-executed, randomized controlled trial.[1]

Schreiber CA, Creinin MD, Atrio J, et al. Mifepristone pretreatment for the medical management of early pregnancy loss. *N Engl J Med.* 2018;378:2161-2170.

ILLUSTRATIVE CASE

Jenny is a 29-year-old G2P1001 woman who presents to your clinic for a missed period. Her last menstrual period was about 10 weeks ago. She is found to have a positive pregnancy test in the office. On examination, her uterus is nontender and consistent in size with gestation of 7 weeks. She denies any bleeding or cramping. On ultrasound, you see a gestational sac measuring 28 mm and no embryo. You confirm early pregnancy loss. Jenny is sad about this diagnosis. She does not wish to proceed with expectant management and is hopeful to avoid a surgical procedure. How do you counsel her regarding medical management?

Early pregnancy loss or first trimester miscarriage is estimated to occur in about 1 million women in the United States annually and is the most common complication of early pregnancy.[2,3] Early pregnancy loss is defined as a nonviable, intrauterine pregnancy with either an empty gestational sac or a gestational sac containing an embryo or fetus without fetal heart activity within the first 12 weeks 6 days of gestation.[4]

Once early pregnancy loss is confirmed by ultrasound, expectant management with no intervention is an acceptable treatment option. Women generally prefer active management, either medically or with surgical evacuation.[5,6] Misoprostol 800 mcg administered vaginally or orally has been the accepted medication regimen for medical management.[5] However, failure rates with misoprostol have been reported to be as high as 40%, particularly among women with a closed cervical os, who then require repeat dosing of misoprostol or surgical evacuation.[6]

STUDY SUMMARY

Mifepristone before misoprostol improves efficacy for early pregnancy loss

The PreFaiR (Comparative Effectiveness of Pregnancy Failure Management Regimens) study was a randomized trial that took place at 3 US centers. The study was designed to assess the safety and efficacy of pretreatment with oral mifepristone prior to use of vaginal misoprostol for the medical management of early pregnancy loss.[1]

Three hundred women, ≥ 18 years and undergoing medical management for early pregnancy loss, were randomized to receive misoprostol 800 mcg vaginally alone or mife-

pristone 200 mg orally followed by misoprostol 800 mcg vaginally 24 hours later.

Inclusion and exclusion criteria. Women who showed a nonviable intrauterine pregnancy at 5 to 12 weeks' gestation by ultrasound were eligible for the study. Exclusion criteria included incomplete or inevitable abortion, contraindications to either study drug, viable or ectopic pregnancy, hemoglobin < 9.5 g/dL, current use of anticoagulants or the presence of a clotting disorder, and pregnancy with an intrauterine device in place.

Outcomes. The primary outcome was gestational sac expulsion by the first follow-up visit and no additional interventions within 30 days of treatment. Secondary outcomes included acceptability of treatment, adverse events, and clinical characteristics associated with successful expulsion.

Demographics. The mean age of the study participants in both groups was ~30 years, and there was a similar percentage of participants by self-reported race and ethnicity in both groups (~44% black, ~35% white, and ~25% Hispanic). The majority of participants in both groups were at 6 to 8 weeks' gestation and had been pregnant at least 3 times.

Results. Researchers were able to evaluate 297 women at the initial follow-up. Of the women who received mifepristone and misoprostol, 83.8% (124 of 148 women; 95% confidence interval [CI], 76.8-89.3) had complete expulsion within 1 to 3 days, compared to 67.1% (100 of 149 women; 95% CI, 59-74.6) in the misoprostol alone group. The number needed to treat with mifepristone and misoprostol to achieve complete expulsion at the first follow-up visit was 6. The percentage of patients receiving uterine aspiration was lower in the mifepristone and misoprostol group (8.8%) than in the misoprostol alone group (23.5%; relative risk = 0.37; 95% CI, 0.21-0.68). There were no significant differences in adverse events including bleeding intensity, pelvic infection, or pain.

WHAT'S NEW

A high-quality RCT demonstrates improved efficacy

Prior studies that have looked at combined mifepristone and misoprostol treatment for early pregnancy loss had heterogeneity in outcome definitions and study designs leading to variable reports of effectiveness.[1,5] This is the first high-quality, randomized trial to demonstrate the safety and efficacy of oral mifepristone pretreatment prior to misoprostol vaginal administration in the medical management of early pregnancy loss.

CAVEATS

Would a placebo group—or other forms of misoprostol—change the results?

The study did not include a placebo group; however, an investigator who was blinded to the treatment group allocation determined the primary outcome, and the lack of placebo did not introduce bias related to the outcomes.

Intravaginal misoprostol was used in this study, rather than oral, rectal, buccal, or sublingual misoprostol.[7] It is not clear from this study if the results of pretreatment with mifepristone would be different if misoprostol was administered via one of these other routes.

CHALLENGES TO IMPLEMENTATION

FDA restrictions limit availability of mifepristone

The main challenge to implementation is the availability of mifepristone. Mifepristone was approved by the US Food and Drug Administration in 2000. The approval included Risk Evaluation and Mitigation Strategy (REMS) restrictions, stipulating that a health provider be specially certified for prescribing; dispensing must occur in clinics, medical offices, or hospitals; and patients must sign a patient agreement form prior to obtaining the agent.[8] JFP

This is the first high-quality, randomized trial to demonstrate the safety and efficacy of oral mifepristone Tx prior to vaginal misoprostol administration in the medical management of early pregnancy loss.

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breast cancer findings, many clinicians look to alternative, nonoral dosage forms to improve the safety profile.

Safety of nonoral estrogen therapy. Administration of nonoral estrogen is associated with avoidance of hepatic first-pass metabolism and a resulting lower impact on hepatic proteins. Thus, data indicate a potentially lower risk for venous thromboembolic events with transdermal estrogen compared to oral estrogen.[1] Since the publication of the results of the WHI trials, prescribing patterns in the United States indicate a general decline in the proportion of oral hormones, while transdermal prescription volume has remained steady, and the use of vaginal formulations has increased.[2]

Topical estrogen formulations. Transdermal or topical delivery of estrogen can be achieved through various formulations, including patches, gels, and a spray. While patches are simple to use, some women display hypersensitivity to the adhesive. Use of gel and spray formulations avoids exposure to adhesives, but these pose a risk of transfer of hormonal ingredients that are not covered by a patch. This risk is amplified by the relative accessibility of the product-specific application sites, which include the arms or thighs. Each manufacturer recommends careful handwashing after handling the product, a specific drying time before the user covers the site with clothing, and avoidance of contact with the application site for a prescribed period of time, usually at least 1 to 2 hours.[3-6]

Our patient. This case illustrates the importance of discussing the risk of medication transfer to both humans and animals when prescribing individualized hormone therapy. While the Evamist prescribing information specifically addresses the risk of unintentional medication transfer to children, it does not discuss other contact risks.[6] In the literature, there have been a limited number of reports on the adverse effects from transdermal or topical human medication transfer to pets. Notably, the American Pet Products Association estimates that in the United States, approximately 90 million dogs and 94 million cats are owned as a pet in 67% of households.[7]

All members of a patient's household—including pets—may be subject to unintentional secondary exposure to topical estrogen formulations and thus, experience adverse effects.

THE TAKEAWAY

Use of HRT, including transdermal or topical estrogen formulations, is common. Given the large number of companion animals in the United States, physicians should consider that all members of a patient's household—including pets—may be subject to unintentional secondary exposure to topical estrogen formulations and that they may experience adverse effects. This presents an opportunity for patient education, which can have a larger impact on *all* occupants of the home. JFP

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