Letters to the Editor

Risks of and Indications for Mifepristone for Medication Abortion

Original Article: Mifepristone and Misoprostol for Early Pregnancy Loss and Medication Abortion

Issue Date: April 15, 2021

See additional reader comments at: https://www.aafp.org/afp/2021/0415/p473.html

To the Editor: We believe more information should be offered about the risks and indications for mifepristone (Mifeprex) for medication abortion. Tables 1 and 2 in the article emphasize the need for a careful history, physical examination, and important laboratory studies to determine eligibility. However, the authors do not emphasize in-person visits, stating, "Telehealth has been shown to be a safe and effective model for providing medication abortion...." This statement oversimplifies the referenced study,[1] which says that "...each participant had ... pre-treatment laboratory tests and ultrasound...." The American College of Obstetricians and Gynecologists reports that approximately one-half of women inaccurately recall the date of their most recent menstrual period; therefore, the estimated gestational age in the first trimester is adjusted in 40% of pregnancies after ultrasonography.[2] Without ultrasound visualization to determine an intrauterine pregnancy, it is difficult to diagnose or rule out an early ectopic pregnancy. Telehealth evaluation should not replace an adequate physical examination with vital signs, a speculum, bimanual examination, ultrasonography (for location, dating, and viability), and appropriate laboratory studies, including beta human chorionic gonadotropin, hemoglobin, and Rh status.

The overall complication rate of medication abortion after an appropriate in-person evaluation is 5.2%, based on a large study,[3] and the risks of adverse events increase with advancing gestational age. These risks and concerns for diversion and misuse were why the U.S. Food and Drug Administration (FDA) implemented an in-person dispensing requirement. Of the 2,660 unique U.S.-only codable adverse event reports submitted for mifepristone between 2000 and 2016, 73% were classified as severe, 20% were life-threatening, and 0.75% resulted in death. Morbidity was primarily attributed to retained products of conception and hemorrhage, for which women with a gestational age greater than 49 days are at the highest risk. There were 1,639 bleeding events, including 466 life-threatening events, 642 severe events, and 106 moderate events; an additional 424 reports of bleeding were uncodable because of insufficient information. A total of 75 patients had ectopic pregnancies, with 25 presenting with ruptured ectopic pregnancies.[4] We would encourage a more detailed review of the risks of mifepristone. Physicians must anticipate and be prepared to manage complications and adverse events that patients experience with mifepristone, especially if there are increasing numbers of medication abortions without an office visit, ultrasonography, and appropriate ancillary studies.

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This series is coordinated by Kenny Lin, MD, MPH, deputy editor.

In Reply: Several important studies have been published on this topic recently. We appreciate the opportunity to share more information on the safety and effectiveness of providing mifepristone without in-person testing or ultrasonography. In a cohort study of 54,142 women in Great Britain, the rate of serious adverse events in 18,435 women who had a no-test telemedicine abortion between April and June 2020 (0.04%) was no different than in patients who received traditional in-person care (P = .56).[1] In another

study, family physicians in the United States successfully provided medication abortion to more than 500 women using an asynchronous telehealth platform, with 90% meeting criteria for no-test abortion care.[2]

On April 12, 2021, the FDA announced its intention "...to exercise enforcement discretion with respect to the in-person dispensing requirement of the Mifepristone REMS Program, ...during the COVID-19 public health emergency" as a "...result of a thorough scientific review by experts within FDA's Center for Drug Evaluation and Research (CDER), who evaluated relevant information, including available clinical outcomes data and adverse event reports."[3]

Mifepristone is one of the most carefully studied medications that has been brought to market. Although the article by Aultman, et al., describes the breakdown of the types of reported adverse events, it does not include the denominator of mifepristone use since FDA approval in 2000.[4] Over the past 20 years, mifepristone has been used for medication abortion by more than 2.75 million people, and there have been only 24 deaths, meaning that the risk of death is less than one in 100,000.[4] Similarly, in considering the overall 5.2% complication rate after medication abortion reported by Upadhyay, et al., it is important to note that 94% of the documented complications were minor issues; the rate of major complications was 0.31 per 100 abortions. These rates of complications are far lower than rates associated with term delivery and indicate that mifepristone is safer than over-the-counter acetaminophen, which causes 500 deaths per year in the United States.[5,6]

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Weight-Based Levothyroxine Dosage Adjustment for Hypothyroidism

Original Article: Hypothyroidism: Diagnosis and Treatment

Issue Date: May 15, 2021

See additional reader comments at: https://www.aafp.org/afp/2021/0515/p605.html

To the Editor: Dr. Wilson and colleagues' excellent article provided a recommendation for the starting dosage of levothyroxine to treat overt hypothyroidism. In nonpregnant patients younger than 60 years with no cardiac disease, mental changes, hypothermia, or stupor, the article recommended initiating a levothyroxine dosage of 1.5 to 1.8 mcg per kg per day. The references cited for that dosage recommended different amounts, including 1.6 mcg per kg per day, 1.6 to 1.8 mcg per kg per day, and 1.6 mcg per kg per day for an average-sized man or woman.[1,2]

Current guidelines recommend a levothyroxine dosage of 1.6 mcg per kg per day based on ideal body weight or lean body mass instead of actual body weight.[3,4] Ideal body weight can be calculated as the weight for height that would generate a body mass index of 24 to 25 kg per m^2. Lean body mass is a better predictor of the dosage requirement than actual body weight.[5] Without this clarification, some patients may receive a dosage of levothyroxine that is too high.

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In Reply: We thank Dr. Muncie for the opportunity to clarify the starting dosage of levothyroxine in patients with overt hypothyroidism. The need for a dosing adjustment

based on weight is clinically relevant because of the high prevalence of obesity among adults in the United States.

Although a starting dosage of 1.6 to 1.8 mcg per kg per day can be appropriate in patients with a body mass index of less than 26 kg per m^2, weight-based dosing of levothyroxine may inappropriately overdose patients who are overweight and obese.[1,2] A lower starting dosage may help bring patients' thyroid-stimulating hormone (TSH) levels into normal range more quickly. Currently, there is no clear, high-level guideline on how to best adjust the starting dosage in patients with a body mass index greater than 30 kg per m^2. Strategies include using the ideal body weight or considering the body mass index as a coefficient. Monitoring TSH levels every six to eight weeks and adjusting levothyroxine dosages until the TSH reaches goal are critical to avoid iatrogenic hyperthyroidism or underreplacement. As noted in the article, it is important to regularly monitor the TSH level until it is in the normal range, then make future adjustments based on symptoms or periodic testing.

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Family Physicians Should Treat Pregnant Patients With Hypothyroidism

Original Article: Hypothyroidism: Diagnosis and Treatment

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See additional reader comments at: https://www.aafp.org/afp/2021/0515/p605.html

To the Editor: The article by Dr. Wilson and colleagues included many useful evidence-based pearls. However, the authors' assertion that endocrinology referral is routinely indicated for pregnant persons with preexisting hypothyroidism is not supported by their cited references.

The authors state that "The lower and upper limits of normal TSH [thyroid-stimulating hormone] drift downward during pregnancy, which, with geographic and ethnic variation, supports the recommendation to include endocrinology referral in managing pregnant patients with hypothyroidism." The guideline cited for this sentence does not include language about endocrinology referral.[1] One reference for Figure 2 and Table 9 in the article includes a mention of specialty; that reference is to a previous *American Family Physician* article on hypothyroidism,[2] which referenced a 2004 study that concluded: "the prevention of hypothyroidism and its possible adverse effects on the fetus and pregnancy…requires the combined efforts of primary care physicians, endocrinologists, obstetricians, and the women themselves."[3] A 2017 guideline, by the same lead author, is cited in the current article and includes no mention of specialty.[4]

Beneficial patient-oriented outcomes result from appropriate TSH monitoring and levothyroxine dosing, not from the specialty of the clinicians performing those tasks. Family physicians can adjust levothyroxine dosing during pregnancy, even if doing so optimally includes identifying "population-based trimester-specific reference ranges for serum TSH…through assessment of local population data."[4] The American College of Obstetricians and Gynecologists 2020 guideline on thyroid disease in pregnancy recommends maintaining the TSH between "the lower limit of the reference range and 2.5 milliunits/L," and does not mention a need for routine endocrinology referral.[5]

The evidence base does not support the routine referral of pregnant persons with preexisting hypothyroidism to an endocrinologist. It is fully within a family physician's scope of practice to independently treat most pregnant patients with hypothyroidism.

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Editor's Note: Dr. Middleton is an assistant medical editor for *AFP*.

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In Reply: We are grateful for Dr. Middleton's letter stating the reasons why family physicians could and should feel comfortable treating pregnant patients with hypothyroidism.

Having independently treated pregnant patients with preexisting hypothyroidism, we think this type of patient care in otherwise low-risk patients is within the scope of family physician practice, and we did not intend to construe referral as a mandate. For example, less experienced or comfortable family physicians may refer a couple or few patients, then feel comfortable assuming full care responsibilities after that. However, we are aware of the reduction in the number of family physicians delivering babies[1] and did not want to further dissuade readers who may be more comfortable comanaging hypothyroidism in prenatal patients with our endocrinology colleagues.

We hope the clarifications made to the article online reflect the data and our clinical reasoning while remaining aware and respectful of the wide range of practice, skills, and comfort of our family physician colleagues.

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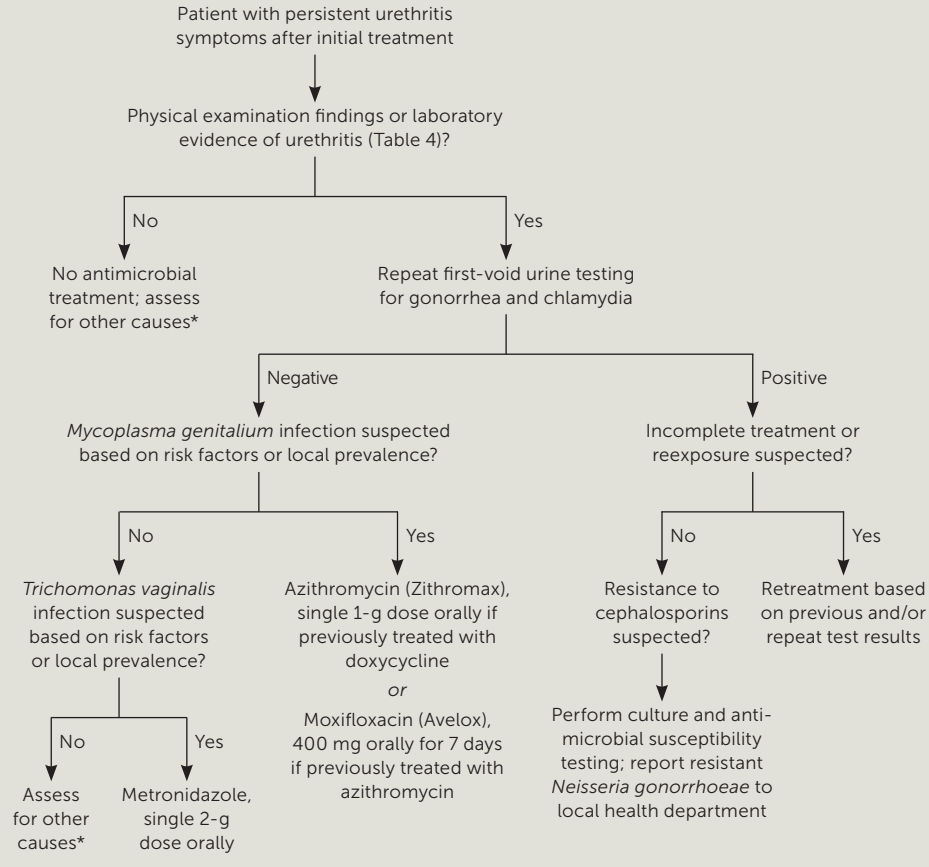
Correction

Error in algorithm. In the article, "Urethritis: Rapid Evidence Review," (May 1, 2021, p. 553) the next steps in Figure 1 (page 556) after "*Trichomonas vaginalis* infection suspected based on risk factors or local prevalence?" were inadvertently switched. The next step after Yes should have been "Metronidazole single 2-g dose orally". The next step after No should have been "Assess for other causes*". The online version of this article has been corrected and the corrected Figure 1 is reprinted below. ■

FIGURE 1



*—For all patients with persistent urethritis symptoms, consider:
- Workup for chronic prostatitis/chronic pelvic pain syndrome
- Obtaining a urethral specimen for herpes simplex virus culture
- Consulting a urologist, an infectious disease specialist, or an experienced colleague

Evaluation of patients with persistent urethritis symptoms after initial treatment.

Information from reference 21.