Contraception

Contraception 92 (2015) 203–205

Commentary

Off-label indications for mifepristone in gynecology and obstetrics

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Received 29 May 2015; revised 24 June 2015; accepted 25 June 2015

The 15th anniversary of the registration of mifepristone in the United States (US) provides an opportunity to reflect on its history, its contribution to women's reproductive health and to consider its promising future as a therapeutic agent. Mifepristone was first approved by the Food and Drug Administration (FDA) as part of a medical regimen to induce abortion in the early first trimester, and most recently in 2012, it was registered in a different formulation as an antiglucocorticoid for the treatment of Cushing's syndrome [1]. Furthermore, years of scientific research have demonstrated the utility of mifepristone for a variety of off-label obstetric and gynecologic indications. Evidence-based alternative use of registered drugs for indications other than those on their approved labels is commonplace in the US and allowable under FDA policy [2,3]. There are numerous examples of registered drugs that are widely used off-label safely and effectively for obstetric and gynecologic conditions, such as misoprostol to induce cervical ripening and uterine contractions, methotrexate to treat ectopic pregnancy, and magnesium sulfate as a treatment for preeclampsia.

Mifepristone is now used in the management of second-trimester pregnancy terminations, both as part of nonsurgical uterine evacuation regimens, as well as for cervical preparation prior to surgical dilation and extraction (D&E) procedures. Second-trimester medical abortion is increasingly utilized around the world, replacing surgical methods that are predominantly offered in higher-level secondary or tertiary level facilities and require providers with specialized training. Now that instillation methods are considered obsolete due to high rates of serious adverse events, the World Health Organization recommends second-trimester medical induction with either mifepristone–misoprostol regimens or misoprostol alone (when mifepristone is not available), as do other global health authorities, such as The International Federation of Gynecology and Obstetrics, Royal College of Obstetrics and Gynaecologists (RCOG) and American College of Obstetricians and Gynecologists [4–7]. Pretreatment with mifepristone increases the complete expulsion rate of misoprostol alone from approximately 70% to more than 90% and decreases time to expulsion by up to 50% in second-trimester inductions. Furthermore, adding mifepristone to the prostaglandin-only regimen requires fewer repeated misoprostol doses, thereby reducing side effects [8–10] and improving the patient experience overall.

Similar to medical induction with a live fetus, the combined regimen of mifepristone and misoprostol is also proving highly effective for labor induction after intrauterine fetal demise in the second and third trimesters [11] and can reduce expulsion time by nearly four hours (from 16 to 10 hours) in comparison to misoprostol alone [12,13]. Timely evacuation can alleviate emotional distress and reduce the possibility of developing rare complications due to delayed care, such as infection, hemorrhage and disseminated intravascular coagulopathy [14,15]. Despite the absence of large prospective randomized controlled trials, the combined mifepristone–prostaglandin regimen is currently recommended as first-line treatment for late intrauterine death and stillbirth by RCOG [16].

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http://dx.doi.org/10.1016/j.contraception.2015.06.021

Mifepristone has been tested as an adjunct to osmotic dilators for cervical preparation prior to D&E to maximize safety and decrease the patient burden associated with multiday procedures [17,18]. Recent data show modest, yet promising, results that the addition of mifepristone to osmotic dilators alone may shorten the total procedure time and improve cervical dilation, thereby facilitating the procedure and enhancing provider satisfaction with the preparation [19]. Cervical preparation with a combination of mifepristone, osmotic dilators and misoprostol may reduce the number of osmotic dilators needed and shorten the number of pretreatment visits required when compared to osmotic dilators and misoprostol only [20]. While this area of investigation is relatively new, it is possible that mifepristone will have an adjunctive role in combination with osmotic dilators in the provision of D&Es performed later in gestation.

The evidence base for mifepristone in obstetrics and gynecology includes its use as a cervical priming agent and for induction of labor at term [21–23]. One randomized controlled trial demonstrated that women who received mifepristone were twice as likely to present a ripe cervix and/or go into labor within 48 hours when compared to placebo. The infants born to women exposed to mifepristone had slightly lower Apgar scores at 1 min, but that difference was mitigated at 5 and 10 min [21]. Even though these research findings are encouraging, pharmaceutical companies remain reluctant to register mifepristone for this indication due to liability concerns around its use with a live fetus and wanted baby.

Early pregnancy loss (EPL), specifically anembryonic gestation and embryonic/fetal demise, is another potential off-label therapeutic application of mifepristone. Misoprostol alone is recommended as an alternative to suction curettage for active management of first-trimester EPL in the US [24]; many European countries use mifepristone and misoprostol to induce tissue expulsion for early pregnancy demise [25]. To date, the published literature shows much variation in efficacy of mifepristone–misoprostol regimens, which ranges from 65 to 95% [26–31]. It is likely that the discrepancies are attributable to small sample sizes, the type of pregnancy failure (anembryonic gestation vs. embryonic fetal death), women presenting with or without bleeding, misoprostol dose, the timing of the follow-up visit and criteria used to define success. Research is ongoing to determine the clinical advantage of using mifepristone and misoprostol together for treatment of missed abortion.

Clinicians around the world, and especially in the US, may be largely unaware of the advantage conferred by using mifepristone for indications other than early first-trimester abortion. As we see with numerous other drugs, off-label use for new indications is often incorporated into clinical practice in advance of, or without, a label change. For example, antidepressants are not approved by the FDA as a treatment for neuropathic pain; nevertheless they are now considered a first-line treatment option [32]. The benefits to a drug manufacturer of updating the label in accordance with the current evidence may be outweighed by the very costly and laborious process required, particularly when off-label use is legal and there is no competing product on the market.

But American women's access to mifepristone has become restricted. Several US states have passed laws requiring mifepristone to be used strictly in accordance with the label, despite the fact that off-label regimens for first-trimester medical abortion are more effective and less expensive and result in fewer side effects. In those states, off-label use for second-trimester medical abortion, labor induction and cervical preparation as described above are also prohibited. How can we ensure continued access to the benefits of mifepristone for the women who reside in those states and in other states that may follow suit? A label change would improve access for women, and facilitate use commensurate with the current evidence. Alternatively, the registration of additional mifepristone products, possibly for other indications, could broaden mifepristone use in the US.

Mifepristone facilitates uterine evacuation in a variety of clinical conditions and is therefore important for women's health. As the barriers to access and evidence-based use multiply, it may be time, 15 years later, to address unnecessary restrictions on use by expanding indications formally through a label change.

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