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Commentary

Mifepristone antagonization requires real studies to evaluate safety and efficacy

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The modern era of medical abortion treatment evolved with the development of mifepristone, a progesterone-receptor antagonist with an affinity for the receptor greater than progesterone itself [1]. Early studies of modern medical abortion regimens evaluated mifepristone alone, primarily at very early gestations. Continued research demonstrated that adding a prostaglandin analogue within a few days after mifepristone significantly improved the efficacy of the treatment [2]. The current FDA-approved regimen of mifepristone 200 mg with misoprostol treatment 24–48 h later is effective through 70 days gestation [3]. Ongoing pregnancy as a reason for treatment failure increases 10-fold from 0.3% at less than 49 days gestation to approximately 3% at 64–70 days' gestation [3–5]. While most women with an ongoing pregnancy opt for further treatment, such as surgical aspiration, some decide to continue the pregnancy. Recent UK data show that among 2673 women having a medical abortion from 9 to 10 weeks' gestation, 90 women had ongoing pregnancies after treatment of whom 9 (10%) opted to continue the pregnancy [6]. Thus, even following treatment, some women do change their mind.

The non-medical terms "abortion reversal," "medical abortion reversal" and "abortion pill reversal" have been used to describe a purported treatment first published as a case series in the Annals of Pharmacotherapy in December 2012 [7]. However, medical abortion cannot be "reversed," which would imply putting a pregnancy back in the uterus. Conceptually, the goal of progesterone proponents is mifepristone antagonization with high doses of progesterone; two small case reports and one large case series have been published about such treatment [7–9]. Commentaries in the American Journal of Obstetrics and Gynecology and New England Journal of Medicine have outlined the numerous scientific and ethical problems with these reports, including lack of control groups, no confirmation of mifepristone ingestion, failure to establish viability prior to progesterone treatment, and providing experimental treatment without patient consent or institutional review board oversight [10,11]. Within the reproductive rights community, some may even argue that mifepristone antagonization is conceptually impossible and potentially harmful to women.

We see a parallel issue in second trimester surgical abortion, with women requesting osmotic dilator removal in less than 1% of procedures [12]. Even when providers have reviewed all pregnancy options prior to dilator placement, counsel patients that dilator placement is the start of the procedure, and confirm with patients that they are absolutely clear in their decision before proceeding, a small minority of women do change their mind. The best information we have about what happens after dilator removal is a small case series of 12 women, which demonstrated pregnancy loss in 50% and complications in 66% of women [12]. Still, when requested, patient autonomy requires dilator removal.

What should we do for the small fraction of women who change their mind after taking mifepristone? Is recommending expectant management or progesterone treatment the better choice? To answer this question, we need to understand what happens when mifepristone is taken without misoprostol, if mifepristone antagonization with progesterone works (including the appropriate progesterone route, dose and duration) for all or just for specific gestational age ranges, and what safety concerns are present in both scenarios.

1. Trying to understand efficacy of mifepristone-only treatment

Two competing systematic reviews, both of which have inherent problems, attempted to establish the continuing pregnancy rate after mifepristone-only treatment to provide a base rate for comparison with attempted mifepristone antagonization [13,14].

First, Grossman et al [13] found 11 publications with 17 treatment groups meeting criteria to be included in the review. Continuing pregnancy rates ranged from 0 to 36% when patients were assessed generally 1–2 weeks after mifepristone ingestion. Overall, the review included 1092 women with an intrauterine pregnancy; continuing pregnancies occurred in 193 (18%) after mifepristone alone. Of note, all but one of the studies included women at 49 days gestation or less. Only six of the included studies clearly defined the outcome of continuing pregnancy as a viable pregnancy [15–20]. The other five studies appeared to consider retained nonviable gestations in the outcome of continuing pregnancies [21–25].

In 2017, Davenport, Delgado and colleagues [14] published a second review as a rebuttal to the review from Grossman et al. This review included 12 publications with 16 treatment groups; seven publications [15–20,25] had been considered acceptable for inclusion in the analysis by Grossman et al. These authors report a

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slightly lower combined continuing pregnancy rate of 13%. While this review excluded four studies that did not clearly define a continuing pregnancy as a viable pregnancy [18–21], it did include three reports of published meeting proceedings that were not peer-reviewed. Only one published study (by Vervest and Haspels [26]) in the Davenport et al review was not included in the Grossman et al review.

In our own re-evaluation of the peer-reviewed studies included in both reviews, only seven studies clearly define continuing viable pregnancy rates after mifepristone alone (Table 1). We excluded non-peer-reviewed meeting proceedings, three studies that considered an increasing hCG as evidence of continuing pregnancy as this could represent viable or non-viable gestations [21,24,25], and two studies without any definition of continuing pregnancies in the text [22,23]. The studies in Table 1 include 550 women who received a wide range of mifepristone dosing, the majority (n = 468, 88%) of whom were enrolled in studies with an upper gestational age limit of 49 days or less. Among the four studies using a single mifepristone dose, only one had a study arm with 200 mg, the dose used in contemporary clinical practice. The continuing pregnancy rate was higher with 200 mg (7/30 [23%, 95% confidence interval 8–38%]) than 600 mg (29/420 [7%, 95% confidence interval 4–9%]), p = .006 (Fisher exact test) [17–20]. However, the number of women (n = 30) is too little for this statistical comparison to be considered precise [17].

2. Trying to understand harm

Because we have inadequate data to determine the continuing pregnancy rate after mifepristone alone, we cannot be certain if mifepristone antagonization is effective. Some argue that since progesterone might be effective, is there any harm in offering such treatment to the rare patient who does change her mind? We do not know that answer either. Whereas the first two published case series included only eight women at 10 weeks or less gestation [7,8], a single large series analyzed 547 women treated in various ways by 325 different providers with "high-dose" progesterone, including progesterone in oil intramuscularly, micronized progesterone orally, micronized progesterone capsules administered vaginally, compounded micronized progesterone vaginal suppositories, progesterone vaginal gel, and progesterone vaginal suppositories [9]. The authors reported continuing pregnancy in 261 (48%) but did not report any adverse events, side effects, or details of what happened to the approximately 50% of women for whom the treatment did not "work."

In contrast, mifepristone-only studies for abortion did report complications, including hemorrhage and transfusion [15,16,26]. Among eight studies that used a single dose of mifepristone 200 mg or 600 mg, no cases of hemorrhage or transfusion occurred, though these studies were limited to women 49 days gestation or less [17–20,22–25]. Since medical abortion is available through 70 days [3], what are the risks when mifepristone is used without misoprostol beyond 49 days? These unanswered questions underscore that the published case series of progesterone use for mifepristone antagonization are reports and not clinical trials.

3. Laws based on no science

Unfortunately, in the absence of rigorous evaluations, some lawmakers are using case reports as medical gospel and passing laws stipulating mifepristone antagonization as fact. These laws mandate that women who receive mifepristone be informed that it may be possible to reverse the effects of mifepristone if they change their minds. In 2015, Arkansas implemented the first mandatory abortion reversal counseling. Other states that soon followed included Arizona (later repealed in 2016), South Dakota, Utah, and Idaho. In 2019, Arkansas updated its law to clarify the information provided to patients, and four states (Oklahoma, Kentucky, Nebraska, and North Dakota) enacted new laws. Kansas also passed such a law that the governor vetoed. A federal judge recently blocked the North Dakota law following a lawsuit from plaintiffs that included the American Medical Association. The judge's decision acknowledged that compelling counseling based on the State's viewpoint without credible scientific evidence that the treatment was effective interfered with health care providers' first-amendment rights. Similarly, when Louisiana was considering such a law in 2017, a Louisiana Department of Health report in April 2017 found "neither sufficient evidence nor a scientific basis to conclude that the effects of an abortion induced with drugs or chemicals can be reversed" [27]. Still, states continue to introduce bills to create similar laws. These laws interfere with our duty to counsel women about both efficacy and safety, and put providers in the position of counseling about uproven assurances without any mention of potential harms. In 2015 and reiterated in August 2017, the American Congress of Obstetricians and Gynecologists publicly opposed laws mandating reversal information as lacking scientific standing [28].

4. So, what do we do now?

Abortion providers can either continue to dismiss the concept of mifepristone antagonization or can work to help patients find answers. Choosing the latter option is a proactive stance towards

Table 1
Studies reporting the proportion of continuing viable pregnancies after mifepristone alone for medical abortion*

First author	Year published	Mifepristone dose	Duration of treatment	Number	Gestational age limit (days)	Follow-up (days after mifepristone)	Complete abortion	Continuing viable pregnancy rate
Kovacs [15]	1984	25 mg twice daily	4 days	18	42	14	12 (67%)	2 (11% [0–26%])
		50 mg twice daily	4 days	10	42	14	5 (50%)	1 (10% [0–29%])
		100 mg twice daily	4 days	8	42	14	5 (63%)	0
Cameron [16]†	1986	150 mg daily	4 days	20	56	14	12 (60%)	5 (25% [11–47%])
Vervest [26]	1985	100–200 mg daily	4 days	35	55	14	25 (71%)	0
		200 mg daily	4 days	9	56–70	14	3 (33%)	0
Maria [17]†	1988	200 mg	Single dose	30	49	7	19 (63%)	7 (23% [12–41%])
		600 mg	Single dose	174	49	7	147 (84%)	4 (2% [0.1–5%])
Maria [18]†	1988	600 mg	Single dose	149	42	7	131 (88%)	14 (9% [5–14%])
Carol [19]	1989	600 mg	Single dose	50	39	NR	40 (80%)	6 (12% [6–24%])
Ylikorkala [20]†	1989	600 mg	Single dose	47	43	14	33 (70%)	5 (11% [5–23%])

NR: not reported.
Data presented as n (%) or n (% [95% confidence interval]).
* All studies except Vervest et al [26] included in systematic review by Grossman et al [13]; all studies included in Davenport et al [14].
† Gestational age determination included ultrasound examination.

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providing evidence-based care to patients seeking medical abortion, especially to the very few who may change their mind.

If a woman uses mifepristone and then returns to the same provider's office 24 hours later stating she has changed her mind, what should that provider tell her? Is progesterone itself harmful – likely not based on widespread use within obstetrics. Does progesterone actually work for mifepristone antagonization – we don't know and can only tell our patient that the existing reports in the literature are inadequate to answer that question. Is NOT using misoprostol harmful, especially if the patient is beyond 49 days gestation – we also do not know that answer. If one believes that progesterone treatment cannot antagonize mifepristone, then the safety of not using misoprostol after starting a mifepristone-misoprostol regimen is the real question. Using progesterone for mifepristone antagonization means not using misoprostol as prescribed. Currently, the rare patient who changes her mind is potentially going to a website to get an experimental treatment rather than returning to the clinician providing her abortion services. The answers can only be found in properly conducted clinical trials that can inform evidence-based decision making and not in poorly conceived laws based on no science. For FDA approval, new treatments go through safety testing before efficacy testing. It is incumbent upon the medical community to conduct proper research on mifepristone antagonization that evaluates the efficacy and safety of providing progesterone and not using misoprostol.

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Conflicts of interest

Dr. Creinin is a consultant for Danco Laboratories to provide medical advice to clinicians who contact the company with questions related to mifepristone use.

References

[1] Heikinheimo O, Kontula K, Croxatto H, Spitz I, Luukkainen T, Lähteenmäki P. Plasma concentrations and receptor binding of RU 486 and its metabolites in humans. J Steroid Biochem 1987;26:279–84.
[2] Bygdeman M, Swahn ML. Progesterone receptor blockage. Effect on uterine contractility and early pregnancy. Contraception 1985;32:45–51.
[3] Mifeprex® label. Danco Laboratories, LLC. March, 2016. Available at <https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf>. Accessed 02.08.19.
[4] Spitz IM, Bardin CW, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United States. N Engl J Med 1998;338:1241–7.
[5] Chen MJ, Creinin MD. Mifepristone with buccal misoprostol for medical abortion: a systematic review. Obstet Gynecol 2015;126:12–21.
[6] Hsia JK, Lohr PA, Taylor J, Creinin MD. Medical abortion with mifepristone and vaginal misoprostol between 64 and 70 days' gestation. Contraception 2019;100:178–81.
[7] Delgado G, Davenport ML. Progesterone use to reverse the effects of mifepristone. Ann Pharmacother 2012;46. e36.
[8] Garratt D, Turner JV. Progesterone for preventing pregnancy termination after initiation of medical abortion with mifepristone. Eur J Contracept Reprod Health Care 2017;22:472–5.
[9] Delgado G, Condly SJ, Davenport M, Tinnakornsrisuphap T, Mack J, Khauv V, et al. A case series detailing the successful reversal of the effects of mifepristone using progesterone. Issues Law Med 2018;33:3–13.
[10] Bhatti KZ, Nguyen AT, Stuart GS. Medical abortion reversal: science and politics meet. Am J Obstet Gynecol 2018;218:315.e1–6.
[11] Grossman D, White K. Abortion, "reversal" - legislating without Evidence. N Engl J Med 2018;379:1491–3.
[12] Mark K, Merchant RM, Hu K. Pregnancy outcomes after removal of osmotic dilators in patients who presented for second-trimester abortion. Contraception 2019;99:285–7.
[13] Grossman D, White K, Harris L, Reeves M, Blumenthal PD, Winikoff B, et al. Continuing pregnancy after mifepristone and "reversal" of first-trimester medical abortion: a systematic review. Contraception 2015;92:206–11.
[14] Davenport ML, Delgado G, Harrison MP, Khauv V. Embryo survival after mifepristone: A systematic review of the literature. Issues Law Med 2017;32:3–18.
[15] Kovacs L, Sas M, Resch BA, Ugocsai G, Swahn ML, Bygdeman M, et al. Termination of very early pregnancy by RU 486 — an antiprogestational compound. Contraception 1984;29:399–410.
[16] Cameron IT, Michie AF, Baird DT. Therapeutic abortion in early pregnancy with antiprogestogen RU486 alone or in combination with prostaglandin analogue (gemeprost). Contraception 1986;34:459–68.
[17] Maria B, Chaneac M, Stampf F, Ulmann A. Early pregnancy interruption using an antiprogesterone steroid: mifepristone (RU 486). J Gynecol Obstet Biol Reprod (Paris) 1988;17:1089–94.
[18] Maria B, Stampf F, Goepp A, Ulmann A. Termination of early pregnancy by a single dose of mifepristone (RU 486), a progesterone antagonist. Eur J Obstet Gynecol Reprod Biol 1988;28:249–55.
[19] Carol W, Klinger G. Experiences with the antigestagen mifepristone (RU 486) in the interruption of early pregnancy. Zentralbl Gynakol 1989;111:1325–8.
[20] Ylikorkala O, Alfthan H, Kääriäinen M, Rapeli T, Lähteenmäki P. Outpatient therapeutic abortion with mifepristone. Obstet Gynecol 1989;74:653–7.
[21] Birgerson L, Odlind V. The antiprogestational agent RU 486 as an abortifacient in early human pregnancy: a comparison of three dose regimens. Contraception 1988;38:391–400.
[22] Grimes DA, Mishell DR, Shoupe D, Lacarra M. Early abortion with a single dose of the antiprogestin RU-486. Am J Obstet Gynecol 1988;158:1307–12.
[23] Swahn ML, Ugocsai G, Bygdeman M, Kovacs L, Belsey EM, Van Look PF. Effect of oral prostaglandin E2 on uterine contractility and outcome of treatment in women receiving RU 486 (mifepristone) for termination of early pregnancy. Hum Reprod 1989;4:21–8.
[24] Zheng SR. RU 486 (mifepristone): clinical trials in China. Acta Obstet Gynecol Scand Suppl 1989;149:19–23.
[25] Somell C, Olund A. Induction of abortion in early pregnancy with mifepristone. Gynecol Obstet Invest 1990;29:13–5.
[26] Vervest HA, Haspels AA. Preliminary results with antiprogesterone RU-486 (mifepristone) for interruption of early pregnancy. Fertil Steril 1985;44:627–32.
[27] Robinson D, Zapata A. Legislative Report on 2016 House Concurrent Resolution 87: Study Related to Whether the Effects of an Abortion Induced with Drugs or Chemicals Can Be Reversed. Louisiana Department of Public Health, April 12, 2017. Available at <http://ldh.la.gov/assets/docs/LegisReports/HCR87RS20161.pdf>. Accessed 02.08.19.
[28] American Congress of Obstetricians and Gynecologists. Facts Are Important: Medication Abortion "Reversal" Is Not Supported by Science, August 2017. Available at <https://www.acog.org/-/media/Departments/Government-Relations-and-Outreach/FactsAreImportantMedicationAbortionReversal.pdf?dmc=1&ts=20180206T1955451745>. Accessed 02.08.19.

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