

Review article

Continuing pregnancy after mifepristone and “reversal” of first-trimester medical abortion: a systematic review[☆]

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Abstract

Objective: We conducted a systematic review of the literature on the effectiveness of medical abortion “reversal” treatment. Since the usual care for women seeking to continue pregnancies after ingesting mifepristone is expectant management with fetal surveillance, we also performed a systematic review of continuing pregnancy after mifepristone alone.

Study design: We searched PubMed, CINAHL (*Cumulative Index to Nursing and Allied Health Literature*), Scopus and the Cochrane Library for articles published through March 2015 reporting the proportion of pregnancies continuing after treatment with either mifepristone alone or after an additional treatment following mifepristone aimed at reversing its effect.

Results: From 1115 articles retrieved, 1 study met inclusion criteria for abortion reversal, and 13 studies met criteria for continuing pregnancy after mifepristone alone. The one report of abortion reversal was a case series of 7 patients receiving varying doses of progesterone in oil intramuscularly or micronized progesterone orally or vaginally; 1 patient was lost to follow-up. The study was of poor quality and lacked clear information on patient selection. Four of six women continued the pregnancy to term [67%, 95% confidence interval (CI) 30–90%]. Assuming the lost patient aborted resulted in a continuing pregnancy proportion of 57% (95% CI 25–84%). The proportion of pregnancies continuing 1–2 weeks after mifepristone alone varied from 8% (95% CI 3–22%) to 46% (95% CI 37–56%). Continuing pregnancy was more common with lower mifepristone doses and advanced gestational age.

Conclusions: In the rare case that a woman changes her mind after starting medical abortion, evidence is insufficient to determine whether treatment with progesterone after mifepristone results in a higher proportion of continuing pregnancies compared to expectant management.

Implications: Legislation requiring physicians to inform patients about abortion reversal transforms an unproven therapy into law and represents legislative interference in the patient–physician relationship.

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Keywords: Medical abortion; Mifepristone; Reversal; Progesterone; Continuing pregnancy

[☆] Conflicts of interest: none.

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1. Introduction

First-trimester medical abortion involves the use of mifepristone followed by misoprostol, generally up to a gestational age of 63 days from last menstrual period [1,2]. Many women prefer medical abortion to surgical abortion

because they perceive it as less invasive and more private [3]. The proportion of all nonhospital abortions in the United States that were early medical abortions increased from 17% in 2008 to 23% in 2011 [4].

In early 2015, legislatures in Arizona and Arkansas passed laws requiring physicians providing abortion to inform women that if they choose to have a medical abortion and then decide not to complete the abortion, the effect of mifepristone may be reversed with specific treatment [5]. Treatment to reverse the effects of mifepristone is not considered an established practice by the American College of Obstetricians and Gynecologists (ACOG) [6] and was not described in a recent practice bulletin on first-trimester medical abortion issued by ACOG and the Society of Family Planning (SFP) [1].

The purpose of this study was to perform a systematic review of the literature on reversal of medical abortion that documented the proportion of pregnancies continuing after treatment. Since the usual care for women seeking to continue pregnancies after ingesting mifepristone is expectant management with fetal surveillance, we also performed a systematic review of continuing pregnancy after treatment with mifepristone alone.

2. Materials and methods

2.1. Systematic review of medical abortion reversal

In this review, we searched for reports of pharmacological methods (e.g., intramuscular injection of progesterone) to reverse the effects of mifepristone prior to administration of misoprostol (or any other prostaglandin) for first-trimester medical abortion. We anticipated few, if any, randomized controlled trials and therefore broadened our search to include cohort studies and case studies or case series; we excluded review articles, editorials and commentaries. The primary outcome was the proportion of women who carried their pregnancies to term after receiving treatment to reverse the effect of mifepristone.

We searched for studies published through March 31, 2015, using databases for PubMed, the CINAHL (*Cumulative Index to Nursing and Allied Health Literature*), Scopus and the Cochrane Library. We combined the following search terms as Medical Subject Headings (MeSH) and text words: induced abortion, steroidal abortifacient agents; mifepristone; Mifeprex; Mifegyne; RU-486; reverse; antidote; progesterone; progestin; first-trimester pregnancy (see [Box](#)).

After initial title and abstract screening, two reviewers (DG and KW) independently evaluated full-text articles to determine whether they met the inclusion criteria. For relevant studies, we recorded the number of women enrolled in the study (or included in the case series) and the number of continuing pregnancies. We then calculated the percentage of continuing pregnancies and 95% Wilson Score confidence intervals (CIs) for women receiving reversal therapy.

Box

List of PubMed search terms used in a systematic review of studies on the efficacy of medical abortion reversal

Search	
(1)	“Abortifacient Agents, Steroidal”[mesh] or “Mifepristone” [mesh] or mifepristone or mifegyne or mifeprex or “r 38486” or r38486 or r-38486 or “ru 38486” or “ru 486” or ru486 or ru-486 or ru38486 or “zk 98296” or zk98296 or zk-98296
(2)	“Abortion, Induced”[mesh] or abort* or terminat*
(3)	(“Pregnancy”[mesh] or pregnan* and (“first trimester”) or (week*)) or “Pregnancy Trimester, First”[mesh] or “early pregnancy”
(4)	revers* or antidote or “Progesterone”[mesh] or progesterone or “progestins”[mesh] or progestin* #1 AND #2 AND #3 AND #4 AND (“0001/01/01”[PDAT]: “2015/03/31”[PDAT]) AND “humans”[MeSH Terms]

2.2. Systematic review of continuing pregnancies following the use of mifepristone alone for first-trimester medical abortion

We reviewed cohort studies and randomized controlled trials that used mifepristone alone during the first trimester of pregnancy to induce abortion, which we identified through a search of the same four databases and using the same search strategy, excluding the reversal terms. We also searched the reference lists of relevant publications for additional studies. We excluded studies that only reported medical abortion failure after mifepristone alone and did not specify the number of continuing pregnancies. We calculated the proportion of pregnancies continuing at the time of the follow-up visit after treatment with mifepristone alone and 95% Wilson Score CIs. Because the mifepristone regimens were not uniform, metaanalysis could not be performed.

3. Results

3.1. Systematic review of medical abortion reversal

Of the 319 unduplicated titles identified in our search, one article met our inclusion criteria ([Fig. 1](#)). This article was a case series by Delgado and Davenport [7] of seven women who received progesterone treatment after taking mifepristone for medical abortion at 7–11 weeks gestation. The mifepristone dosage was not noted. One patient was lost to follow-up. Of the six patients with follow-up data, four continued the pregnancy and delivered at term with no apparent congenital malformations; two patients aborted the pregnancy within 3 days of taking mifepristone. The progesterone regimen varied from progesterone in oil 200 mg intramuscularly daily to twice per week, sometimes followed by oral micronized progesterone, to micronized

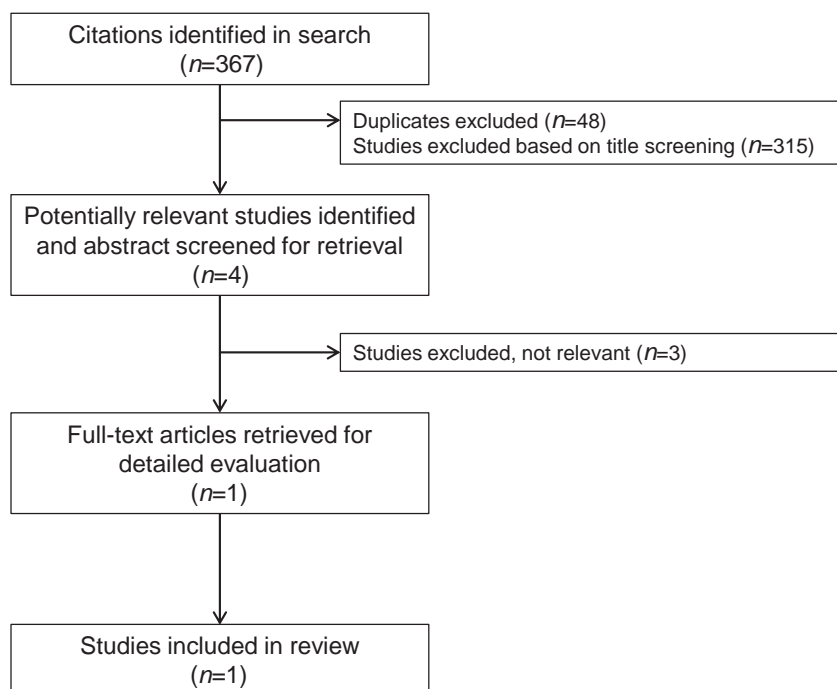


Fig. 1. Summary of study selection process for medical abortion reversal.

progesterone administered vaginally. Therapy was continued for up to 5 months. The publication provides limited details, but it appears that, in at least five cases, a living embryo was documented prior to initiating progesterone treatment. The authors did not report how many women presented seeking medical abortion reversal after taking mifepristone and were found to have already aborted and therefore excluded from treatment. The dates during which cases were collected are not specified, and it is unclear if all women treated were included in the case series. Based on the four continuing pregnancies and excluding the patient lost to follow-up, the proportion of pregnancies continuing after this therapy was 67% (95% CI 30–90%). If we assume that the patient lost to follow-up had an abortion, the continuing pregnancy proportion was 57% (95% CI 25–84%).

3.2. Systematic review of continuing pregnancies following the use of mifepristone alone for first-trimester medical abortion

Our search retrieved 1115 unduplicated articles, and 13 studies in 11 publications met our inclusion criteria (one publication was an English-language article that included two relevant studies performed in China, and one publication provided complete information on two relevant mifepristone dosages) (Fig. 2) [8–18]. Women were generally assessed 1–2 weeks after mifepristone and those with a continuing pregnancy at that time underwent surgical abortion. Table 1 shows for each study the mifepristone regimen used, the gestational age limit, when the follow-up visit occurred, the proportion of pregnancies that had a complete abortion after

mifepristone alone and the proportion of pregnancies that were continuing at the follow-up visit. The continuing pregnancy proportions ranged from 8% to 46% with the different regimens.

4. Discussion

We found only one small case series that evaluated a treatment aimed at reversing the effects of mifepristone. The proportion of pregnancies that continued after this treatment was 57–67%, but the 95% CI of this estimate was wide, ranging from 25% to 90% [7]. The study was of poor quality with few details.

Due to the limited information in the article [7], one cannot directly compare the results of this single small series to the continuing pregnancy rate after mifepristone alone, which was as high as 46% in one of the clinical trials [15]. In the report by Delgado and Davenport [7], women presented 7–48 h after mifepristone ingestion, and, except for two cases, the patient had a live embryo at the time of treatment. In order to calculate the proportion of women with a continuing pregnancy seeking this treatment, which would be comparable to the proportion of continuing pregnancies after mifepristone alone, one must know how many women requested treatment and were found to already have an embryonic demise or incomplete abortion. It is reasonable to suppose that women who have an ongoing pregnancy 1–2 days after mifepristone are more likely to have pregnancies that continue to term with no further treatment. It is also possible that some of the continuing pregnancies noted 1–2

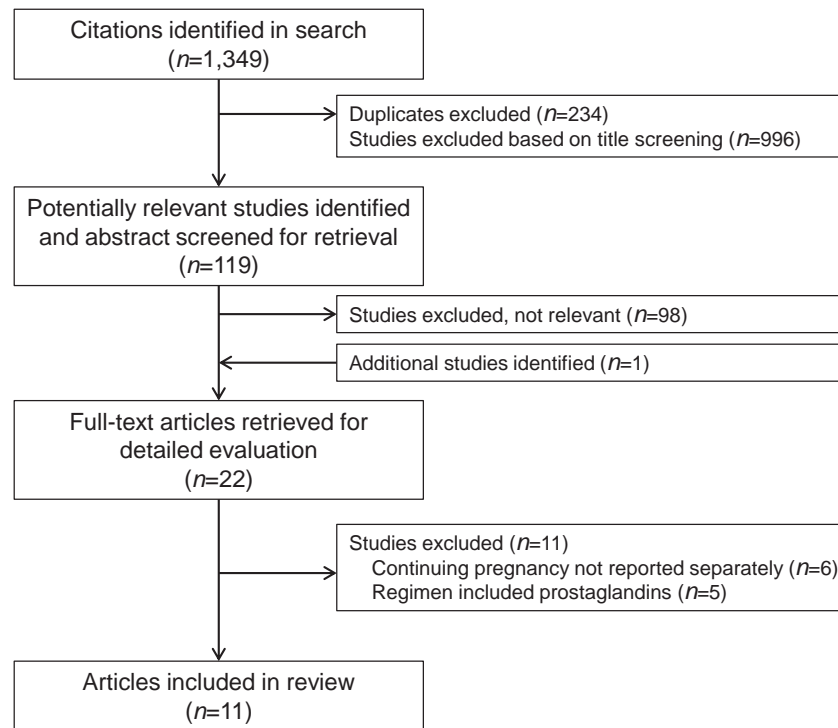


Fig. 2. Summary of study selection process for continuing pregnancy following administration of mifepristone alone for medical abortion.

weeks after treatment in the studies of mifepristone alone may have aborted if the period of follow-up were longer.

Although the dose of mifepristone was not noted in the report by Delgado and Davenport [7], women likely received 200 mg, which is the dosage recommended by ACOG and SFP and most often used by providers in the US [1,19]. Most of the studies of mifepristone alone used a higher dose, and the one study that compared 600 mg to 200 mg found a higher proportion of continuing pregnancies with 200 mg

[18]. In addition, none of the studies of mifepristone alone included women pregnant beyond 56 days, while the report by Delgado and Davenport [7] included women up to 11 weeks gestation. In the first trimester, the risk of continuing pregnancy after medical abortion increases as gestational age advances [15,20].

Progesterone is used for other indications during pregnancy. Injections of 17 α -hydroxyprogesterone caproate or administration of vaginal progesterone suppositories or

Table 1

Studies reporting the proportion of women with continuing pregnancies following administration of mifepristone alone for medical abortion

Study	Mifepristone oral dose	N	Gestational age limit	Follow-up visit (number of days after mifepristone)	Complete abortion	Continuing pregnancy at follow-up visit (%; 95% CI)
Birgerson 1988 [9]	10, 25 or 50 mg twice daily for 7 days	153	49 days	8–10 days	67%	27% (20–34%)
Cameron 1986 [8]	150 mg daily for 4 days	20	56 days	14 days	60%	25% (11–47%)
Carol 1989 [17]	600 mg (single dose)	50	39 days	NS	80%	12% (6–24%)
Grimes 1988 [10]	600 mg (single dose)	50	49 days	14 days	88%	10% (4–21%)
Kovacs 1984 [11]	25–100 mg twice daily for 4 days	36 ^a	42 days	14 days	61%	8% (3–22%)
Maria 1988a [16]	600 mg (single dose)	149 ^a	42 days	7 days	88%	9% (6–15%)
Maria 1988b [18]	600 mg (single dose)	174	49 days	7 days	84%	11% (8–17%)
Maria 1988b [18]	200 mg (single dose)	30	49 days	7 days	63%	23% (12–41%)
Somell 1990 [12]	600 mg (single dose)	70	42 days	7 days	80%	17% (10–28%)
Swahn 1989 [13]	25 mg twice daily for 4 days	14	49 days	14 days	57%	36% (16–61%)
Ylikorkala 1989 [14]	600 mg (single dose)	47 ^b	43 days	14 days	70%	11% (5–23%)
Zheng 1989 [15]	600 mg (single dose)	204	42 days	7 days	65%	31% (25–38%)
Zheng 1989 [15]	600 mg (single dose)	95	49 days	7 days	53%	46% (37–56%)

NS, not specified.

^a One additional participant was later found to have an ectopic and is excluded from the total here.

^b Three additional participants had a missed abortion at time of treatment and are excluded from the total here.

gel may be used for prevention of preterm birth among women at high risk of early delivery, generally weekly from 16 weeks to 36 weeks gestation [21]. Progesterone supplementation is also used with assisted reproductive technologies that involve treatment with a gonadotropin-releasing hormone (GnRH) analog, agonist or antagonist, which may interrupt the normal functioning of the corpus luteum [22]. Progesterone in oil injections or vaginal suppositories or gel may be used for this purpose, but treatment is generally stopped after 9–12 weeks gestation, by which time the trophoblast is the primary source of progesterone. Progesterone is not associated with an increased risk of congenital anomalies, including genital abnormalities. Adverse events associated with progesterone injections include injection site swelling or irritation [23], as well as the potential of allergies to the yam, soy or peanut used in manufacturing or compounding the medication [21].

However, the evidence supporting the use of progesterone early in pregnancy after GnRH treatment or to prevent preterm birth is not directly applicable to the situation after mifepristone treatment. Mifepristone blocks the progesterone receptor with a higher affinity than progesterone itself [24]. Women treated with mifepristone for abortion have normal pregnancies with high progesterone levels, and it is not clear that adding more progesterone would counteract the effect of the receptor blockade. A recent randomized controlled trial found that insertion of an etonogestrel contraceptive implant, a very potent progestin, immediately after ingestion of mifepristone did not reduce the effectiveness of the medical abortion regimen compared to delayed insertion after abortion completion [25], confirming the findings of a previous pilot study [26]. In addition, the duration of treatment that women received in the report by Delgado and Davenport [7] was more consistent with preterm labor prevention (albeit with an unproven regimen). It also far exceeded the expected duration of action of mifepristone since the drug is undetectable in humans 10 days after ingestion of a 200-mg dose [27].

The evidence to date does not suggest an elevated risk of congenital malformations after mifepristone administration alone. A recent prospective study from France reported on 46 pregnancies exposed to mifepristone only [28]. Two major malformations occurred among 38 continuing pregnancies (5.3%), which, based on these small numbers, does not appear to be significantly elevated above the expected proportion of about 3%. While more prospective data are needed, information about the low risk of congenital malformations after mifepristone exposure should be given to women who decide to continue a pregnancy after taking the drug.

The clinical use and new state laws concerning abortion “reversal” raise serious ethical concerns. The limited data on mifepristone reversal grew out of the anecdotal experiences of physicians who performed experimental treatment on pregnant women, without usual research safeguards. Delgado and Davenport [7] do not report that their study

had an ethics board or institutional review board (IRB) approval. Case reports involving retrospective analysis of three or fewer cases do not generally require IRB oversight, although institutions or journals may require IRB review to determine that the report is exempt. While Delgado and Davenport [7] published their findings as a “case report,” their study is clearly “research” as defined in federal policy. Federal regulations define research as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge [29].” The report clearly extends into the realm of research, whether measured by its prospective nature, the number of patients on which it reports, its attempt to assess a specific new treatment regimen or the suggestion that the data produced be used to guide treatment of other women. In recognition of the report’s limitations, Delgado and Davenport [7] themselves called for further clinical trials before routine use of their protocol. The new laws in Arizona and Arkansas have now bypassed the research process, in effect making all women who undergo this treatment subjects in an uncontrolled, unmonitored experiment.

Providing evidence-based care is part of how physicians meet their beneficence-based obligations to patients, and therefore, it is a *moral* as well as a clinical mandate to base care on accepted scientific fact. The new laws compel physicians to say things that may contradict their clinical knowledge and judgment. Some physicians will not be able to do so in good conscience; they may feel that suggesting unproven treatment or suggesting that a woman can begin an abortion with uncertainty about her decision contradicts their duty to do no harm.

Women rarely change their minds after beginning a medical abortion. According to reports that physicians are required to submit to the drug’s manufacturer, between 2000 and 2012, less than 0.004% of women taking mifepristone in the US later chose to continue the pregnancy (personal communication, Danco Laboratories). In such a case, a woman should be counseled that there is a reasonable chance (10–45%) that the pregnancy will continue. We found no credible evidence that using medication after ingestion of mifepristone is better than expectant management in assuring a continuing pregnancy; suggesting otherwise is scientifically untenable. Legislative interference in the patient–physician relationship is unwarranted and dangerous [30]. In the case of recent Arizona and Arkansas laws, this interference transforms an unproven therapy into law, bases law on methodologically flawed research and in effect turns unethical experimentation on pregnant women into legislative mandate. These features of mifepristone reversal represent an affront to responsible research conduct and to the ethical practice of medicine.

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