Nos. 22A901, 22A902

IN THE

Supreme Court of the United States

U.S. FOOD AND DRUG ADMINISTRATION, ET AL.,
and
DANCO LABORATORIES, LLC,

Applicants,

v.

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.

Respondents.

To the Honorable Samuel A. Alito, Justice of the Supreme Court of the United States and Circuit Justice for the Fifth Circuit

APPENDIX TO RESPONDENTS' OPPOSITION TO APPLICATION TO STAY OR VACATE INJUNCTION PENDING APPEAL

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EARLY PREGNANCY TERMINATION WITH MIFEPRISTONE AND MISOPROSTOL IN THE UNITED STATES

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ABSTRACT

Background Mifepristone and a prostaglandin have been used successfully to terminate pregnancy in Europe and China. We report the results of a large U.S. study of mifepristone and misoprostol in women with pregnancies of up to nine weeks' duration.

Methods We administered 600 mg of mifepristone and then 400 μg of misoprostol two days later to 2121 women seeking termination of their pregnancies at 17 centers. The women were observed for four hours after the administration of misoprostol and returned on day 15 for final assessment.

Results Two thousand fifteen women completed the final assessment. Among them, pregnancy was terminated in 762 of the 827 women pregnant for ≤49 days (92 percent), 563 of the 678 women pregnant for 50 to 56 days (83 percent), and 395 of the 510 women pregnant for 57 to 63 days (77 percent) ($P<0.001$). Termination occurred within 4 hours after the administration of misoprostol in 49 percent of the women and within 24 hours in 75 percent. Failures, defined as cases requiring surgical intervention for medical reasons or because the patient requested it, the abortion was incomplete, or the pregnancy was ongoing, increased with increasing duration of pregnancy. The largest increase was in failures representing ongoing pregnancy, which increased from 1 percent in the ≤49-days group to 9 percent in the 57-to-63-days group ($P<0.001$). Abdominal pain, nausea, vomiting, diarrhea, and vaginal bleeding also increased with advancing gestational age. Two percent of the women in the ≤49-days group, as compared with 4 percent in each of the other two groups, were hospitalized, underwent surgical intervention, and received intravenous fluids ($P=0.008$).

Conclusions This mifepristone–misoprostol regimen is effective in terminating pregnancies, especially in women with pregnancies of 49 days' duration or less. (N Engl J Med 1998;338:1241-7.)

THE antiprogestin mifepristone (RU 486) causes abortion by competitively blocking progesterone receptors.[1-3] For maximal effectiveness, a prostaglandin should be given 48 hours after mifepristone.[1,3,4] The rates of termination of pregnancies 49 days old or less are similar, ranging from 96 to 99 percent, whether mifepristone is used with gemeprost or misoprostol, both prostaglandin E_1 compounds.[1,3,5-7] Gemeprost is expensive, requires refrigeration, and is not widely available, but misoprostol is inexpensive, stable at room temperature, and obtainable in many countries, including the United States.

Many American women do not have access to abortion,[8] and in developing countries up to 200,000 women die annually of complications after illegal abortions.[9] The availability of medical abortion in the United States and elsewhere could lead to greater access to safer abortion services. We conducted a multicenter trial of mifepristone and misoprostol to determine whether this combination could be used to terminate pregnancies of up to 63 days' duration.

METHODS

Participating Centers

From September 1994 to September 1995, we enrolled 2121 women, each with a documented pregnancy of 63 days' duration or less, requesting termination of pregnancy. Women with liver, respiratory, renal, adrenal, or cardiovascular disease, thromboembolism, hypertension, anemia, insulin-dependent diabetes mellitus, coagulopathy, or known allergy to prostaglandins were excluded, as were women less than 18 years of age or those more than 35 years of age who smoked more than 10 cigarettes per day and had another cardiovascular risk factor. Women were also excluded if they had in situ intrauterine devices, were breast-feed-

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The principal investigators and centers participating in the study are listed in the Appendix.

ing, were receiving anticoagulation or long-term glucocorticoid therapy, had adnexal masses, had ectopic pregnancies, or had signs or symptoms suggesting they might abort spontaneously. All the women agreed to undergo surgical termination of pregnancy if the medical method failed. Among the 2121 women, 915 were enrolled at eight Planned Parenthood clinics, 538 at four university-hospital clinics, and 668 at five free-standing abortion clinics. The protocol was approved by the human investigational review board at each participating institution, and all the women gave informed consent.

Study Design

Pregnancy was measured from the first day of the last menstrual period according to menstrual history, pelvic examination, and vaginal ultrasonography. On the basis of the investigator's final assessment of these three measures, the women were assigned to the following arbitrarily defined gestational-age groups: the ≤49-days group (859 women); the 50-to-56-days group (722); and the 57-to-63-days group (540).

Three clinic visits were scheduled. At visit 1 (day 1), the women were assessed clinically and took 600 mg of mifepristone orally. At visit 2 (day 3), they took 400 μg of misoprostol orally unless a complete abortion had already occurred. After taking misoprostol, the women were monitored for four hours for adverse events, such as nausea, vomiting, diarrhea, and abdominal pain. These events were rated by the women and recorded as mild (felt but easily tolerated), moderate (uncomfortable enough to interfere with usual activity), or severe (incapacitating, preventing usual activity). Vaginal bleeding was recorded on a diary card and rated by each woman on days 1 through 15 of the study as spotting (less than normal menstrual bleeding), normal (similar to normal menstrual bleeding), or heavy (more than normal menstrual flow). During this period, the women were also monitored for expulsion of the conceptus. At visit 3 (day 15), the treatment outcome was assessed.

Efficacy was defined as the termination of pregnancy with complete expulsion of the conceptus without the need for a surgical procedure. The need for a surgical procedure (either vacuum aspiration or dilation and curettage) constituted a failure, and such a procedure was performed at any time if the investigator believed there was a threat to a woman's health (medically indicated), at a woman's request, or at the end of the study for an ongoing pregnancy or incomplete abortion. Follow-up was extended beyond visit 3 if there was uncertainty about the completeness of the abortion or if bleeding persisted.

A total of 106 women were excluded from the efficacy analysis because they did not return for visit 3. Evidence suggesting a successful outcome was available for 92 of these women, and evidence of failure for 1. The remaining 13 women were lost to follow up; 5 had continuing pregnancies when last seen at visit 2. The analyses of efficacy therefore included 2015 women.

Statistical Analysis

Statistical analysis was performed with the use of Statistical Analysis System software (SAS Institute, Cary, N.C.). One-way analysis of variance and Kruskal–Wallis tests were used to compare mean values in the gestational-age groups, and Pearson's chi-square tests were used to compare the distributions of categorical variables. Fisher's exact test was used to compare rates in the gestational-age groups. Stepwise logistic-regression analysis was used to evaluate the relation between success or failure and various base-line patient characteristics; the significance level required for a variable to stay in the model was 0.10. All statistical tests were two-tailed.

RESULTS

There were 859 women in the ≤49-days group, 722 in the 50-to-56-days group, and 540 in the 57-to-63-days group. The three groups were similar with respect to age (mean, 27 years; range, 18 to 45), gravidity, parity, number of spontaneous or previous elective abortions, and ethnic or racial distribution (white, 71 percent; black, 15 percent; Hispanic, 9 percent; Asian, 5 percent). Seventy-three percent of the women had had previous pregnancies, 51 percent elective abortions, and 15 percent spontaneous abortions.

Efficacy

Among the 2015 women who returned for the third visit, the rates of pregnancy termination were 92 percent in the ≤49-days group, 83 percent in the 50-to-56-days group, and 77 percent in the 57-to-63-days group ($P<0.001$) (Table 1). Of the 59 women who did not receive misoprostol, 56 had termination of their pregnancies after mifepristone alone. In the remaining three women, it subsequently became apparent that their pregnancies had not been terminated after mifepristone and they should have been given misoprostol; they later underwent surgical termination. The rate of termination after mifepristone alone also decreased significantly with increasing gestational age, from 5 percent to 0.8 percent (Table 1).

The rates of incomplete abortion were 8 percent in the 50-to-56-days group and 7 percent in the 57-to-63-days group, as compared with 5 percent in the ≤49-days group (Table 1). The failures for all other reasons were significantly higher in both the 50-to-56- and 57-to-63-days groups than in the ≤49-days group. The largest increase was in failures representing ongoing pregnancy, which rose from 1 percent in the ≤49-days group to 9 percent in the 57-to-63-days group. Ninety percent of the surgical terminations performed for medical reasons were for vaginal bleeding. A patient's request was the reason least often cited for surgical termination.

Although the study design called for analysis according to the three discrete gestational-age groups, there was in fact a steady decline in the frequency of termination of pregnancy with increasing duration of gestation (Fig. 1). Logistic-regression analysis indicated that the rates decreased with increasing gestational age, from more than 95 percent before day 40 to less than 90 percent after day 47 and to less than 80 percent after day 59. The only other factor that was related to outcome was the number of previous elective abortions (Fig. 1); the termination rates were higher for women with no previous abortions than for those with previous abortions. The differences in rates were less than 2 percent up to day 35, 2 to 3 percent from days 36 to 42, 3 to 4 percent from days 43 to 48, 4 to 6 percent from days 49 to 55, and 6 to 10 percent from days 56 to 63. The outcomes were unrelated to other base-line characteristics, including age, race, body weight, gravidity, and previous spontaneous abortions.

TABLE 1. RESULTS OF MIFEPRISTONE AND MISOPROSTOL IN WOMEN SEEKING TERMINATION OF PREGNANCY.

OUTCOME	PREGNANT ≤49 DAYS (N=827)	PREGNANT 50 TO 56 DAYS (N=678)	PREGNANT 57 TO 63 DAYS (N=510)
	number (percent [95% confidence interval])		
Success	762 (92 [90–94])	563 (83 [80–86])*	395 (77 [74–81])*†
After mifepristone alone	40 (5)	12 (2)‡	4 (0.8)*
Failure (need for surgical intervention)			
Medical indication for intervention	13 (2)	26 (4)‡	21 (4)‡
Patient's request for intervention	5 (0.6)	13 (2)	
Incomplete abortion	39 (5)	51 (8)‡	12 (2)‡
Ongoing pregnancy	8 (1)	25 (4)*	36 (7)
			46 (9)*§
Total	65 (8)	115 (17)*	115 (23)*†

*P<0.001 for the comparison with the ≤49-days group.

†P=0.02 for the comparison with the 50-to-56-days group.

‡0.001≤P<0.03 for the comparison with the ≤49-days group.

§P<0.001 for the comparison with the 50-to-56-days group.

Complete expulsion of the conceptus occurred before the administration of misoprostol in 76 women (4 percent). This group included the 56 women who received only mifepristone and an additional 20 women who received misoprostol because their expulsion status was considered uncertain at the beginning of visit 2. It was subsequently determined that these 20 women had had complete expulsions before they took misoprostol. During the four hours of observation after the administration of misoprostol, 49 percent of the women expelled the conceptus, and during the fifth hour an additional 11 percent expelled the conceptus. By 24 hours after misoprostol administration, 75 percent of the women had expelled the conceptus (Fig. 2).

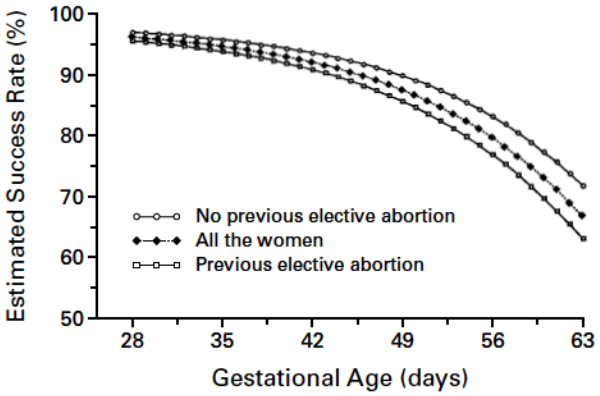

Figure 1. Logistic-Regression Analysis of the Predicted Probability of Successful Pregnancy Termination, According to the Duration of Pregnancy for All the Women and for the Women Who Had and Those Who Had Not Had Previous Elective Abortions.

Vaginal Bleeding

Vaginal bleeding is a natural consequence of the abortion process, and it occurred in all the women whose pregnancies were terminated medically. The median duration of bleeding or spotting was 13 days in the ≤49-days group and 15 days in the other two groups (P<0.001). The proportions of women who reported heavy bleeding did not differ significantly in the three groups, were highest on day 3, and then decreased steadily. By day 15, 77 percent of all reported bleeding was considered spotting (Fig. 3). Nine percent of the women reported some type of bleeding after 30 days, and 1 percent after 60 days.

Excessive bleeding necessitated blood transfusions in four women and accounted for 25 of 27 hospitalizations (including emergency-room visits), 56 of 59 surgical interventions, and 22 of 49 administrations of intravenous fluid. Hospitalizations, surgical interventions, and intravenous-fluid administration were reported for 2 percent of the women in the ≤49-days group and for 4 percent of those in each of the other groups (P=0.008). Bleeding was managed by the administration of uterotonic agents, such as oxytocin, methylergonovine, or vasopressin, in 41 women (5 percent) in the ≤49-days group, 50 (7 percent) in the 50-to-56-days group, and 55 (10 percent) in the 57-to-63-days group (P<0.001).

Other Adverse Events

Almost all the women (99 percent) reported at least one adverse event during the study period (Ta-

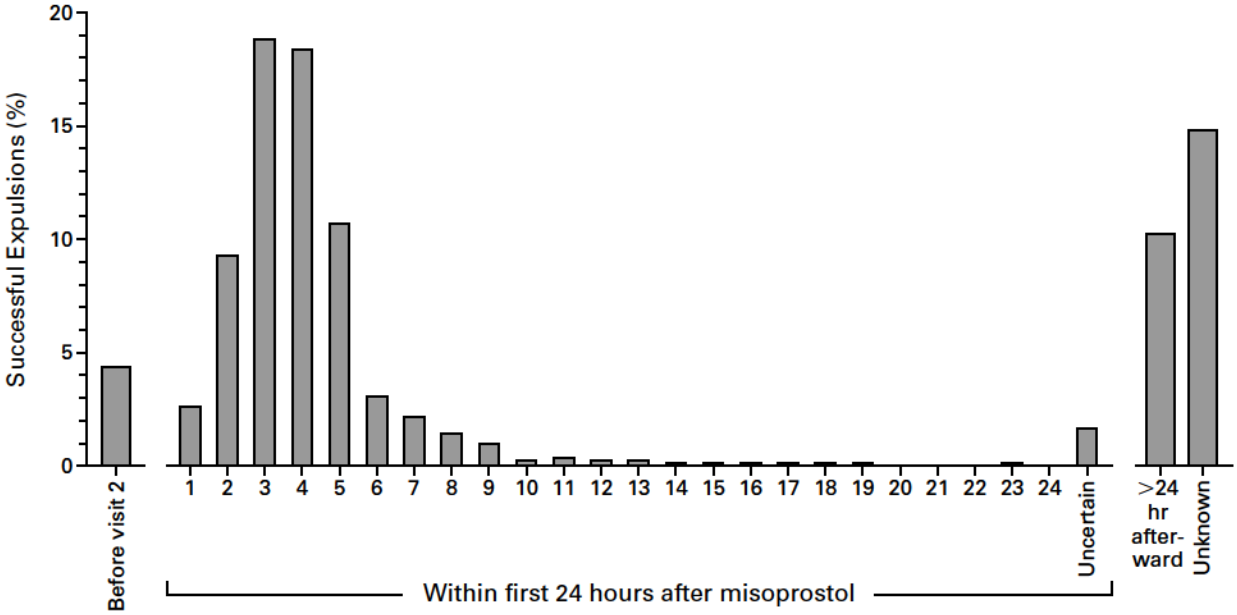

Figure 2. Times of Expulsion of the Conceptuses in 1720 Women with Successful Termination of Their Pregnancies.
The women received mifepristone at visit 1 and misoprostol two days later (visit 2). "Uncertain" indicates that expulsion occurred within the first 24 hours after misoprostol was given, but the exact time was not known. "Unknown" indicates that expulsion occurred more than 24 hours after misoprostol was given, but the exact time was not known.

ble 2). Nearly all had abdominal pain; its overall incidence did not differ among the three groups. However, 53 percent of the women in the 50-to-56-days group and 54 percent in the 57-to-63-days group had abdominal pain reported as severe, as compared with 43 percent in the ≤49-days group ($P<0.001$). Sixty-eight percent of the women received at least one medication for abdominal pain (usually acetaminophen), and 29 percent also received opiates (usually acetaminophen with hydrocodone or codeine). The women in the 50-to-56- and 57-to-63-days groups received significantly more analgesia and opiates than the women in the ≤49-days group ($P<0.001$). Abdominal pain resulted in one hospitalization and was the reason for two medically indicated surgical interventions.

As compared with the ≤49-days group, the 50-to-56- and 57-to-63-days groups had significantly more nausea and vomiting, and diarrhea was more frequent in the 57-to-63-days group. The overall percentages of events reported as severe were 3 percent for diarrhea, 10 percent for vomiting, and 20 percent for nausea. Medications for these adverse events were taken by 1 percent, 4 percent, and 19 percent of the women, respectively, with no differences among the gestational-age groups. Severe vomiting resulted in one hospitalization and was the reason for one medically indicated surgical intervention.

In the four-hour observation period after the administration of misoprostol, the number of adverse events and the percentage classified as severe were similar to those reported during the entire study period. During these four hours, nausea ($P<0.001$) and vomiting ($P<0.001$) were significantly more frequent in the 50-to-56- and 57-to-63-days groups than in the ≤49-days group, and abdominal pain ($P=0.009$) and diarrhea ($P=0.006$) were more severe in the 57-to-63-days group.

The frequency of adverse events declined significantly with increasing gravidity and parity (Table 2). Nulliparous women received significantly more analgesia ($P<0.001$), opiate analgesia ($P<0.001$), and medications for nausea ($P<0.001$) and diarrhea ($P<0.001$) than parous women. Chronologic age was not consistently related to the frequency of adverse events.

Other adverse events reported included headache (32 percent); dizziness, encompassing light-headedness and faintness (12 percent); back pain and fatigue (9 percent each); fever, vaginitis, and viral infections (4 percent each); rigors and dyspepsia (3 percent each); and asthenia, leg pain, anxiety, insomnia, anemia, syncope, leukorrhea, and sinusitis (2 percent each). Endometritis occurred in 19 women; it was considered study-related in 10, in 1 of whom it was severe.

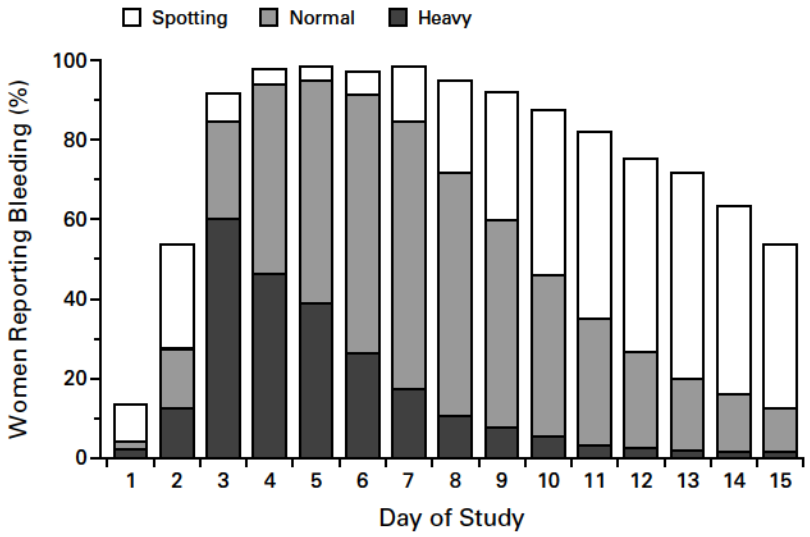

Figure 3. Types of Vaginal Bleeding as Recorded by the Women from Day 1 (Administration of Mifepristone) to Day 15.

The data are from 1506 women who did not undergo surgical termination of pregnancy and who recorded the types of bleeding they had from study day 1 to day 15 on menstrual-diary cards. Bleeding was characterized as spotting, as similar to normal menstrual bleeding (normal), or as heavier than normal menstrual bleeding (heavy).

TABLE 2. INCIDENCES OF ABDOMINAL PAIN, NAUSEA, VOMITING, AND DIARRHEA ACCORDING TO GESTATIONAL GROUP, GRAVIDITY, AND PARITY.

VARIABLE	NO. OF WOMEN	ABDOMINAL PAIN	NAUSEA	VOMITING	DIARRHEA
		number (percent)			
Gestational group					
≤49 days	859	827 (96)	528 (61)	222 (26)	174 (20)
50 to 56 days	722	704 (98)	512 (71)*	277 (38)*	169 (23)
57 to 63 days	540	529 (98)	388 (72)*	220 (41)*	142 (26)†
Gravidity					
1	568	555 (98)	395 (70)‡	236 (42)‡	148 (26)‡
2	527	519 (98)‡	378 (72)‡	205 (39)‡	131 (25)‡
≥3	1026	986 (96)	655 (64)	278 (27)	206 (20)
Parity					
0	1163	1143 (98)	827 (71)	473 (41)	295 (25)
1	449	432 (96)§	280 (62)§	132 (29)§	94 (21)
≥2	509	485 (95)§	321 (63)§	114 (22)§	96 (19)§

*P<0.001 for the comparison with the ≤49-days group (by Fisher's exact test).

†P=0.01 for the comparison with the ≤49-days group (by Fisher's exact test).

‡0.001≤P≤0.03 for the comparison with the women who had had three or more pregnancies (by Fisher's exact test).

§0.001≤P≤0.004 for the comparison with the women who had had no children (by Fisher's exact test).

DISCUSSION

In this large, multicenter U.S. trial, the success of medical termination of pregnancy decreased gradually with advancing gestational age. We confirmed the international experience that mifepristone and misoprostol can terminate pregnancies of up to 49 days' duration, although the success rate was lower than previously described.[7,10-12] As noted in other countries,[13] this lower success rate may be related to the lack of experience with medical abortion in the United States as well as to the design of our study. We considered the need for surgical intervention on day 15 as representing failure, but abortion might have occurred later.[13,14] Also, a surgical termination performed at the woman's request was classified as a failure instead of being excluded from the efficacy analysis.[10,12,13] Unexpectedly, success was also less frequent among women who had previous elective abortions. Although the reason is unknown, this factor could also have contributed to the differences, because 51 percent of the women in our study had had previous elective abortions, as compared with 25 to 27 percent in two British studies.[12,13]

Efficacy decreased after 49 days' gestation. A similar trend has previously been reported with misoprostol but not with gemeprost.[10-15] Thus, the lower success rates later in gestation are probably related to the prostaglandin component of the regimen. Such lower rates were not found when misoprostol was given by the vaginal route,[16,17] presumably because of greater tissue bioavailability.[18] Higher doses of oral misoprostol increase uterine contractility[19] and are also associated with improved results.[11,12,15] Efficacy is not, however, related to differences in the dose of mifepristone, and similarly good results have been reported with single doses as low as 200 mg.[11,14,20]

The incidence of adverse events rose with the duration of pregnancy.[7,10,13] These events included both subjective symptoms (abdominal pain, nausea, and vomiting) and more objective markers (hospitalizations and surgical interventions). The majority of hospitalizations and surgical interventions were for vaginal bleeding. With advancing pregnancy, the duration of bleeding increased, as did the administration of uterotonic drugs and intravenous fluids. Despite the increases in the numbers of failures and adverse events, the majority of the women in this study reported that they were satisfied with their medical abortions, regardless of whether the outcome was successful (Winikoff B, et al.: unpublished data).

One drawback of this method of pregnancy termination is the inconvenience of the four-hour clinic stay after the administration of misoprostol. In its favor is the fact that many adverse events, including those rated as severe, occurred during this period, as did almost half the expulsions, and some women may prefer to be in the clinic during these events. Moreover, in the women with pregnancies of longer duration, the majority of the hospitalizations or surgical interventions occurred on day 3, whereas in the women with pregnancies of shorter duration, these events were evenly distributed throughout the 15-day study period. Thus, the four-hour visit may be most appropriate for women with pregnancies of longer duration. Nonetheless, on the basis of the results of a small study, mifepristone combined with home application of vaginal misoprostol is a safe alternative in women with pregnancies of up to 56 days' duration.[17]

Careful medical follow-up is essential to ensure that surgical termination is performed in cases of failed medical abortion. In this study, 5 percent of the women did not return for final confirmation of the outcomes of their pregnancies, and five of these women had continuing pregnancies when last seen at visit 2. The ultimate outcome of these pregnancies is unknown, despite our repeated attempts to contact the women. In other studies, the loss to follow-up has ranged from 3 to 11 percent.[5-7,10,12,21] Although mifepristone is not teratogenic in rats, mice, or monkeys,[22,23] skull deformities attributed to uterine contractions occurred in rabbits.[24] Misoprostol, on the other hand, has been reported to be teratogenic in humans.[25,26]

Recently, other methods of medical abortion have been evaluated. Oral misoprostol alone is not effective.[19,27] The efficacy of vaginal misoprostol in the first trimester varies widely, from 47 to 94 percent,[28,29] but it is highly effective in the second trimester.[30] Success rates with methotrexate and vaginal misoprostol range from 83 to 98 percent.[31-35] As compared with mifepristone, this latter regimen has the advantage of being an effective treatment for ectopic pregnancy.[36] However, misoprostol has to be given three to seven days after methotrexate, delaying the abortion process.[35] Unlike mifepristone, methotrexate is cytotoxic to proliferating trophoblast tissue, and persisting pregnancies may represent a greater teratogenic risk.[28,32,33,35]

In conclusion, the regimen of mifepristone and misoprostol is safe and effective for women seeking medical abortions of pregnancies of 49 days' duration or less. With longer durations of pregnancy, the regimen is less effective and the incidence of adverse events is higher.

We are indebted to Dr. Elof Johansson for his helpful advice and continuing support; to Dr. Brigid M. O'Connor, Dr. Charlotte Ellertson, Dr. Beverly Winikoff, and Ms. Batya Elul for their contributions to the data analysis; to Mr. Evan Read for preparation of the figures; and to Mr. Peter Conlon and Ms. Irina Shmerlin for preparation of the manuscript.

APPENDIX

The participating principal investigators and their associated centers are listed below (at the investigator's request, Planned Parenthood of Greater Boston is listed by center only):

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Self-Managed Medication Abortion: Implications for Clinical Practice

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Abstract

Medication abortion represents more than 50 percent of abortions in the United States (US). Since its approval in the US in 2000, the Food and Drug Administration (FDA) has progressively relaxed the prescribing requirements such that currently, no office visit, in-person dispensing, or ultrasound is required. Obtaining medication for abortion online without medical supervision or evaluation is also possible. This article reviews the complications of medication abortion by examining major studies and delineates the risks specific to self-managed abortion to inform clinicians in caring for women.

Summary: Medication abortion has become the most common abortion method in the United States. This document provides a detailed history of the relaxation requirements on medication abortion and reviews the major studies on medication abortion complications including a discussion of their limitations. Finally, the paper delineates the ease of access to medication abortion without a health care provider and the risks associated with self-managed abortion. This paper is intended to provide information for clinicians who likely will be encountering increasing number of patients with such complications.

Keywords

Abortion, Abortion complications, Gynecology, Obstetrical care, Roe v. Wade, Women's reproductive health, Women's reproductive issues, Medication Abortion, Chemical Abortion, Mifepristone, Misoprostol

Introduction

Medication abortion, approved in the United States (US) in 2000, now represents more than 50 percent of abortions in the US (Guttmacher Institute 2022a). It is accomplished with two medications: oral mifepristone, an anti-progesterone and buccal misoprostol, a uterotonic one to two days later. Bleeding usually lasts nine to sixteen days, and 8 percent of women bleed longer than thirty days ("Mifeprex Prescribing Information Revised 3/2016" 2016). The most common adverse events (AEs) are retained tissue and hemorrhage without transfusion, both of which can require surgical intervention. Other AEs include infection, hemorrhage requiring transfusion, ongoing pregnancy, and ectopic pregnancy.

Mifepristone is regulated under the Risk Evaluation and Mitigation Strategies (REMS), a drug safety program that the Food and Drug

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Administration (FDA) requires for certain medications with serious safety concerns to help ensure that the benefits outweigh the risks (Food and Drug Administration 2021b). The initial REMS required that the prescriber had to be a physician, the patient had to have three office visits, the medications had to be dispensed in certain health care facilities, and the physician had to be able to provide surgical intervention if needed, as well as ensure access to a hospital for resuscitation and transfusion if necessary (Food and Drug Administration 2011; US Government Accountability Office 2018; Center for Drug Evaluation and Research 2016). The physician was also required to report all serious AEs. These measures are no longer required; in many states, abortion can be obtained legally via telemedicine (Guttmacher Institute 2022b).

With the overturn of Roe v. Wade on June 24, 2022 (Supreme Court of the United States 2022), some states are enacting bans or restrictions on abortion, and women may increasingly turn to self-managed abortion with pills obtained online. The objective of this article is to review the complications of medication abortion by examination of significant studies and to delineate the risks specific to self-managed abortion to inform clinicians in caring for women who present with complications.

Pharmacology of Mifepristone

Mifepristone is a selective progesterone receptor modulator that binds to the progesterone receptor in the uterus with a higher affinity than progesterone but does not activate the receptor, thus acting as an anti-progesterone (ACOG 2020). It directly blocks the progesterone production by the corpus luteum and also blocks the decidual response to progesterone, resulting in fetal death. Other actions of mifepristone on the pregnant uterus include cervical softening, increased uterine contractility, and sensitivity to prostaglandins (ACOG 2020). Mifepristone interferes with the ability of the spiral arteries to contract, which is the primary method of hemostasis after the placenta separates from the decidua. At higher doses, mifepristone has anti-glucocorticoid activity (Autry and Wadhwa 2022). It blocks cortisol receptors in central and peripheral tissues. The drug was initially developed to treat Cushing's disease (Department of Health and Human Services et al. 2006).

Mifepristone use in medication abortion has been associated with infection, specifically *Clostridium sordellii (C. sordellii)*. Nine of the twenty-four US deaths after medication abortion (as of 2018) were from sepsis, five of which were from *C. sordellii* (Aultman et al. 2021). Four women died in California after medication abortion from 2003 to 2005 from *C. sordellii* sepsis. In response, the "Emerging Clostridial Diseases" workshop was held by the Department of Health and Human Services, the Center for Disease Control and Prevention, the FDA, and the National Institutes of Health (Department of Health and Human Services et al. 2006). This workshop discussed how mifepristone's anti-progesterone activity on the pregnant uterus predisposes it to infection. It was delineated that cervical ripening, decidual ischemia, and necrosis of the products of conception enable the decidua to become a favorable nidus for infection by the anaerobic bacteria, *C. sordellii* (Department of Health and Human Services et al. 2006, 107). It was also proposed that the anti-glucocorticoid activity of mifepristone impairs the functioning of the pregnant uterus' innate immune system, also predisposing to *C. sordellii* (Department of Health and Human Services et al. 2006, 107). These mechanisms are further delineated in peer-reviewed literature. (Aronoff et al. 2008; Miech 2005).

Pharmacology of Misoprostol

Misoprostol is a prostaglandin E1 analog approved by the FDA for gastric ulcer prevention for those on long-term nonsteroidal anti-inflammatory drugs. Misoprostol inhibits gastric acid secretion and protects the mucosa. It also causes uterine contractions. Misoprostol is widely used in obstetrics for cervical ripening,

labor induction, and control of postpartum hemorrhage. Side effects of misoprostol include diarrhea, abdominal pain, nausea, flatulence, headache, dyspepsia, vomiting, and constipation (Pfizer 2021). Misoprostol is a known teratogen associated with Mobius sequence, terminal transverse limb defects, and other malformations. These malformations have been attributed to the common mechanism of fetal vascular disruption (Vauzelle et al. 2013).

The FDA and Medication Abortion

Understanding the history of the FDA's decisions toward progressively fewer requirements on medication abortion is essential, as it has provided the path to less physician involvement and increasing ease of obtaining this REMS-restricted medication. Medication abortion with mifepristone and misoprostol was initially approved in the US in September 2000 under restricted distribution regulations (Center for Drug Evaluation and Research 2000). The dosing regimen was mifepristone 600 mg orally, followed two days later by misoprostol 400 mcg orally. It was approved for up to forty-nine days of gestation, and there were three required office visits (days one, three, and fourteen). The prescriber had to be a licensed physician who could accurately assess the duration of pregnancy, diagnose ectopic pregnancies, and provide surgical intervention if necessary (or have made plans to provide such care through other qualified physicians). The prescribing physician had to ensure patient access to medical facilities equipped to provide blood transfusion and resuscitation if necessary. The medications had to be dispensed in a clinic, medical office, or hospital. The physician was required to sign and return the prescriber agreement form. Additionally, the abortion provider had to report any hospitalization, transfusion, serious event, or ongoing pregnancy (US Government Accountability Office 2018, 7). In 2011, the FDA instituted REMS, which incorporated the 2000 requirements (FDA 2011).

In 2016, the prescribing requirements were modified significantly. The approval was extended to seventy days gestation, only one office visit was required (a follow-up visit on days seven to fourteen), and the prescriber no longer had to be a physician. The dose of mifepristone was decreased to 200 mg, misoprostol was increased to 800 mcg, and the misoprostol route was changed from oral to buccal. A repeat dose of misoprostol could be given if the pregnancy was not expelled. At the same time that the prescribing requirements were relaxed, the AE reporting requirements were eliminated except for the requirement to report death (US Government Accountability Office 2018, 8).

In July 2020, a federal judge suspended the requirement for in-person dispensing during COVID-19 (American College of Obstetricians and Gynecologists et al., v. Food and Drug Administration et al. 2020). This requirement was overturned by the US Supreme Court in January 2021 (Supreme Court of the US 2021). In April 2021, after the American College of Obstetricians and Gynecologists (ACOG) advocated for women to receive medication abortion without in-person assessment, the FDA replied that they would not enforce any in-person requirements (Woodcock 2021). The April 2021 letter from FDA to ACOG documented a low rate of reported AEs, ignoring that reporting of AEs (except death) was no longer required. The FDA also identified four publications with relevant clinical outcomes and concluded that, although there were limitations in study designs, the findings did not appear to show an increase in serious safety concerns with modification of the in-person requirement. In December 2021, the FDA removed the requirement to dispense medication abortion pills in a healthcare setting, allowing for mail-order medication abortion (FDA 2021a). Table 1 summarizes the progression of relaxed restrictions on medication abortion. States may have further restrictions, but the FDA does not require an office visit, ultrasound, or physician. Although the prescriber must be able to assess pregnancy duration and diagnose ectopic pregnancy accurately, no visit or ultrasound is required.

Table 1. Changes in FDA Requirements for Medication Abortion.

	2000	2016	2020	2021
Gestational Age (GA)	49 days	70 days	70 days	70 days
Number of Office Visits	3	1	0	0
Prescriber	Physician	Healthcare Provider	Healthcare Provider	Healthcare Provider
Dispensing Location	Health care facility	Health care facility	Health care facility	Certified Pharmacy
Reporting Requirements	All serious events	Death	Death	Death

The FDA Adverse Event Reporting System (FAERS) is a mechanism for reporting adverse medication events. Anyone can submit an Adverse Event Report (AER) to the FDA for a medication. The database is available online ("FDA Adverse Event Reporting System"). When medication abortion was first approved, the prescriber was required to report any hospitalization, transfusion, serious AE, or ongoing pregnancy (Center for Drug Evaluation and Research 2000; FDA 2011). When the REMS were relaxed in 2016, the prescriber was no longer required to report AEs except death (US Government Accountability Office 2018, 8).

Although the FAERS is a database of AEs, it is not a comprehensive list of all AEs. Even when reporting was required, the only obligate reporter was the prescriber. Complications are often treated by someone other than the abortion provider. Aultman et al. was a study of the AERs submitted to the FDA for medication abortion, and in that study, less than 40 percent of the D&Cs for complications were performed by the abortion provider (Aultman et al. 2021).

One study demonstrated that even when reporting was required, not all AEs known to the abortion provider appeared in FAERS (Cirucci, Aultman and Harrison 2021). Cleland et al. published a study of medication abortion complications in 2013 and based their data on the AERs that Planned Parenthood reported to the manufacturer, Danco Laboratories (Danco) who then submitted them to the FDA. Cleland stated, "In accordance with the mifepristone prescribing information, Planned Parenthood Federation of America reports all significant adverse events and outcomes to Danco Laboratories, the US distributor of mifepristone, which in turn reports them to the FDA" (Cleland et al. 2013). Cirucci et al. reported discrepancies between the AEs that Planned Parenthood reported in 2009 and 2010 (according to Cleland et al.) and those on the FAERS online dashboard. According to Cleland et al., Planned Parenthood reported 1530 AERs/cases to Danco for 2009 and 2010, yet only 664 AERs are listed on the FAERS dashboard for that period. The FAERS should have more AERs than Planned Parenthood reported since Planned Parenthood performs only 37 percent of US abortions (Abortion Care Network 2020). This discrepancy demonstrates that even the known AEs that were supposedly reported do not all show up in the FAERS. Cirucci et al. conclude, "These discrepancies, and the fact that since 2016, reporting AEs other than deaths is no longer required, demonstrate that the FAERS is inadequate to evaluate the safety of mifepristone" (Cirucci, Aultman and Harrison 2021).

According to the FDA, from September 2000 to December 2018, out of 3.7 million medication abortions in the US, there were only 4,195 with any AE, including non-severe AEs (Food and Drug Administration 2018), a 0.11 percent complication rate. Even a conservative 2 percent complication rate would

generate 74,000 AEs, raising concern that less than 6 percent of actual AEs are included in the FAERS.

Complications of Medication Abortion

As physicians, we often look not to government databases but to peer-reviewed studies. There are a plethora of studies evaluating medication abortion. Several significant studies will be examined here. Many assert the safety of medication abortion, and a detailed evaluation of these studies is helpful.

Chen et al. in 2015 did a systematic review of 20 studies (n = 33,846) and provided results that seemed to support the safety of medication abortion (Chen and Creinin 2015). Chen et al. reported an efficacy rate of 96.7 percent up to sixty-three days gestation (n = 33,514) and 93.1 percent from sixty-four to seventy days (n = 332). The ongoing pregnancy rate was 0.8 percent up to sixty-three days gestation and 2.9 percent from sixty-four to seventy days. Transfusions (0.03%–0.6%) and hospitalizations (0.04%–0.9%) were uncommon. Emergency room (ER) visits occurred in 2.9 percent to 3.7 percent of patients, and surgical evacuation (other than for ongoing pregnancy) occurred in 1.8 percent to 4.2 percent. In Chen's review, 76 percent of the data was from two retrospective studies. One of these (n = 13,373) did not evaluate ER visits (Gatter, Cleland and Nucatola 2015), and the other study (n = 11,155) did not evaluate ER visits or hospitalizations (Goldstone, Michelson and Williamson 2012). The loss to follow-up in these two studies was 15.5 percent and 16 percent, respectively.

Another systematic review, performed by Raymond et al. (Raymond et al. 2013), included 87 trials and 120 trial groups (n = 45,528). Raymond et al. reported efficacy of 95.2 percent, ongoing pregnancy of 1.1 percent, transfusion of 0.1 percent, and hospitalization of 0.3 percent (1.1% in the largest study). Only seven studies in this systematic review had more than 1,000 patients; the largest study had 4132 patients. The studies had various doses and routes of medication. Overall, 4.8 percent of women required surgical completion.

Ireland et al. performed a retrospective cohort study comparing medical abortion (n = 13,221) to surgical abortion (n = 16,925) (Ireland, Gatter and Chen 2015). For medical abortions, Ireland et al. reported an efficacy of 99.6 percent, based on the 0.4 percent ongoing pregnancy rate, but excluding the 2.2 percent of cases that required surgical aspiration. The reported rate of major complications was low (0.007%), as was persistent pain, bleeding, or both (1.8%). Ireland et al. reported the risk of any AEs as 2.2 percent. There was a 15.9 percent loss to follow-up rate, and those lost to follow-up were not excluded but were assumed to have had an uncomplicated complete abortion. Medication abortion had four times the risk of failure compared to surgical abortion and the ongoing pregnancy rate increased by 50 percent for each week of gestational age (GA).

Cleland et al. analyzed all Planned Parenthood medication abortions from 2009 to 2010 (n = 233,805) (Cleland et al. 2013). Eight specific AEs were evaluated and the study reported low rates of complications: ER treatment (0.10%), hospital admission (0.06%), transfusion (0.05%), intravenous (IV) antibiotics (0.02%), infection requiring IV antibiotics or admission (0.016%), ongoing pregnancy (0.50%), ectopic pregnancy (0.007%), and death (one death: 0.0004%). Cleland et al. reported an overall complication rate of 0.65 percent but did not evaluate retained products of conception, hemorrhage without transfusion, or incomplete abortion if treated at the clinic. Cleland et al. state that the data are only those reported to or received by Planned Parenthood and did not provide the percentage of patients lost to follow-up.

International studies show a different picture of the frequency of complications. Carlsson et al. reported on all induced abortions at Skaraborg Hospital, Sweden from 2008 to 2015 (n = 4945) (Carlsson, Breding

and Larsson 2018). Of these, 74.7 percent were medication abortions before twelve weeks. All patients had a pre-abortion evaluation consisting of a visit with a gynecologist at the clinic, a pelvic exam, vaginal ultrasound, and screening for infection. For medical abortion under twelve weeks, the rate of incomplete abortion was 4.1 percent, and the overall complication rate was 7.3 percent. Interestingly, the complication rate doubled from 4.2 percent to 8.2 percent during the study period.

Niinimaki et al. evaluated all abortions in Finland from 2000 to 2006 (n = 42,619) to estimate the immediate AEs and safety of medical versus surgical abortion (Niinimaki et al. 2009). Using high-quality data from the National Health Registry, this study included all abortions in Finland for up to sixty-three days and followed them for six weeks post-abortion. Niinimaki et al. found that hemorrhage occurred in 15.6 percent of those who had medication abortion compared to 2.1 percent of those who had a surgical abortion. Niinimaki et al. did not define hemorrhage but included all reported hemorrhages. The Society of Family Planning notes that hemorrhage after abortion has been variably defined (with definitions including more than 250 ml blood loss, more than 500 ml blood loss, requiring hospitalization, and requiring transfusion) and suggests that a clinically relevant definition would include both a clinical response and/or bleeding greater than 500 ml (Kerns and Steinauer 2013). Niinimaki et al. note that since medical abortion is associated with bleeding lasting approximately two weeks, the high rate of consultation for bleeding is not surprising. They suggest that uterine bleeding requiring surgical evacuation probably better reflects the severity of bleeding after pregnancy termination. Niinimaki et al. found that surgical re-evacuation was required in 5.9 percent and 1.8 percent for medication and surgical abortion, respectively. Incomplete abortion occurred in 6.7 percent of those who had a medication abortion compared to 1.6 percent of those who had a surgical abortion. The risk of infection was 1.7 percent for both. The study found that 20 percent of women who had a medication abortion suffered a complication compared to 5.6 percent of those who had a surgical abortion, almost four times the risk of complications.

Other studies confirm that medication abortion has higher complication rates than surgical abortion. Upadhyay et al. showed that first-trimester medication abortion had nearly six times the risk of complications compared to surgical aspiration (Upadhyay et al. 2015). In Ireland et al., medication abortion had four times the risk of failure compared to surgical abortion (Ireland, Gatter and Chen 2015). Studnicki et al. showed that medication abortion is more than twice as likely to result in an abortion-related ER visit (Studnicki et al. 2021).

A register-based cohort study by Mentula et al. demonstrated that risks of medication abortion increase with increasing GA (Mentula et al. 2011). The study evaluated 18,248 cases of medication abortion in Finland between 2003 and 2006. A surgical evacuation was required in 7.9 percent of first-trimester abortions compared to 38.5 percent of second-trimester abortions. Infection occurred in 1.9 percent of those who underwent a medication abortion in the first trimester compared to 4.0 percent in the second trimester.

Telemedicine Abortion

Telemedicine is the delivery of healthcare services by healthcare professionals utilizing telecommunications technology (Endler et al. 2019; Galle et al. 2021). One of the advantages of telemedicine is increased access; patients who live remotely or cannot obtain transportation can access care from home, which is particularly important in underserved populations. The increased access must be balanced with privacy issues and the lack of a physical exam and in-person face-to-face interaction. Although an evaluation of the literature on telemedicine, in general, is beyond the scope of this article, some significant studies on telemedicine abortion will be presented.

Endler et al. performed a systematic review of telemedicine abortion, which consisted of

31,223 medication abortions (Endler et al. 2019). For pregnancies of ten weeks or less GA, ongoing pregnancy rates ranged from 0 percent to 1.9 percent (1.3% to 2.3% over ten weeks). Complete abortion (self-assessed) was reported in 93.8% to 96.4%, and surgical evacuation was required in 0.9 percent to 19.3 percent (8.5% to 20.9% over ten weeks). Blood transfusion occurred in 0% to 0.7% and hospitalization occurred in 0.07 percent to 2.8 percent. In this systematic review, most studies were descriptive, and there were no randomized controlled trials. Most outcomes were self-reported, and all study groups were high-to-middle income and therefore not necessarily applicable to all socioeconomic groups. Endler et al. concluded that "success rate and safety outcomes are similar to those reported in the literature for in-person abortion care, and surgical evacuation rates are higher." However, they admitted that due to high heterogeneity, the evidence must be interpreted with caution (Endler et al. 2019). The loss to follow-up was 5 percent to 57 percent, and the authors rated the evidence's quality as low.

Grossman et al. documented a retrospective cohort study in Iowa and compared all medication abortions performed by telemedicine or in-person at a clinic system in Iowa from July 1, 2008 to July 30, 2015 (Grossman and Grindlay 2017). The telemedicine patients were evaluated by clinic staff, including a focused physical exam, hemoglobin, and ultrasound, and they later met with a physician off-site via video. The study evaluated hospital admissions, surgery (not including vacuum aspiration), blood transfusion, ER treatment, and death. The data was obtained from the AERs that Planned Parenthood submitted to Danco, any self-reported events, and a low-response rate ER survey. Grossman et al. reported 49 clinically significant AEs out of 19,170 medical abortions. The complication rate for telemedicine abortions (n = 8765) was 0.18 percent and that for in-person abortions (n = 10,405) was 0.32 percent. Some significant AEs were excluded from the study, including incomplete abortions if treated at a clinic, ongoing pregnancies, nonserious events treated as an outpatient, and ectopic pregnancies captured by another category. A lower complication rate for telemedicine abortion than in-person does not seem plausible. The data was based on the AERs submitted to the FDA, required for only certain complications at the time of the study. Importantly, all patients in the telemedicine group had an exam and ultrasound, not necessarily replicating other telemedicine protocols.

Raymond et al. reported on the Gynuity TelAbortion study (Raymond et al. 2019; Gynuity). Each patient had a videoconference with a healthcare provider, lab testing, and an ultrasound before an abortion. Pills were sent via mail, and the patients had a follow-up visit with a healthcare provider by phone or video. There were 433 screenings, of which 268 had a telemedicine evaluation, and 248 were sent packages of pills. There were fifty eight (23.4%) with unknown outcomes and two patients who chose not to take the pills. Of the remaining 188 with known outcomes, 6 percent required surgical completion. Despite a known outcome in only 190 patients, the authors claimed a "meaningful follow-up" in 217 patients. Of these, two (1%) had a serious AE (one a seizure after aspiration and one a hemoglobin of 6.3 g/dl requiring transfusion). The authors "judged that neither event would have been averted had the abortion medications been provided in person" (Raymond et al. 2019). Sixteen (7%) other patients went to the ER. Of those who were Rh-negative, 31 percent did not receive Rh D Immune globulin. The authors concluded, "This direct-to-patient telemedicine abortion service was safe, effective, efficient, and satisfactory" (Raymond et al. 2019). Again, the pre-abortion testing, including ultrasound, does not necessarily replicate other telemedicine abortion protocols.

There is a range of protocols for telemedicine abortion. In both Raymond's and Grossman's studies, all women had an ultrasound. A woman who gets blood work and an ultrasound locally and then meets with a physician via video has more safety measures

than a woman who only has a video visit without additional evaluation. These issues are particularly pertinent with the push toward medication abortion without ultrasound to determine pregnancy location or GA (Schmidt-Hansen 2020; Goldberg et al. 2022). The FDA requires the provider to be able to assess the duration of pregnancy and diagnose ectopic pregnancy yet requires no in-person visit (Woodcock 2021; FDA 2021a).

Self-Managed Abortion

Another way women can access abortion is by ordering pills online without medical supervision. In this article, telemedicine abortion has been used to refer to abortion pills obtained with remote interaction with a healthcare provider, either by video or phone. The term "self-managed abortion" will be used in this article to refer to obtaining abortion pills online, by mail, or by other means without any oversight by a health care provider and is distinguished from telemedicine abortion.

How to Obtain Abortion Pills for Self-Managed Abortion

Obtaining abortion pills online is easy and accessible even in states where telemedicine is restricted. "Plan C" has a website that says, "A safe, at-home abortion is here," and guides the person through the process, with different options tailored for each state ("A Safe at-home abortion is here"). The site provides four categories to obtain abortion pills: (1) telehealth, (2) online pharmacies, (3) mail forwarding for states in which telehealth is restricted, and (4) in-person. The first of these options, telehealth, sends the person to Aid Access (and sometimes other options depending on the state), a website that provides an online consult for abortion pills by mail. Dutch physician Rebecca Gomperts founded Aid Access (Aid Access). After determining that Aid Access caused the introduction into interstate commerce of misbranded and unapproved drugs, the FDA in 2019 requested Gomperts to "immediately cease causing the introduction of these violative drugs into US commerce" (FDA 2019). Gomperts' lawyer responded, "When US women seeking to terminate their pregnancies consult Dr. Gomperts, she will not turn them away" (Hearn Law PLC 2019). On her website, Gomperts wrote that she would not be deterred and would continue to provide abortion services (Gomperts 2019). Aid Access continues to provide abortion pills by mail.

Aiken et al. published a retrospective evaluation of the safety and effectiveness of self-managed abortion obtained via Aid Access (Aiken et al. 2022). The dataset (n = 4,583) included all the US residents who were sent abortion medications between March 20, 2018 and March 20, 2019. Four weeks after receipt of the medications, users were invited to report their abortion outcomes using an online evaluation tool or via email. Among 4,583 who received abortion pills, 3,186 (69.5%) provided follow-up information. Of these, 2,797 (88%) took the medication. Of those who took the medication, 96.4% terminated their pregnancy without surgical intervention, 1.0 percent reported treatment for any serious AE, 0.6 percent reported receiving a blood transfusion, and 0.5 percent reported receiving IV antibiotics. The authors reported that one of the study's limitations is that outcomes were self-reported and noted that the follow-up rate was 70 percent. They note that this follow-up rate is "on par with or better than many clinical studies since most outcomes are only recorded if patients decide to follow up with the clinic" (Aiken et al. 2022).

The second option in Plan C, online pharmacies, provides a list of five online pharmacies and the cost and lead time to get pills. "Shoppers" can put the pills in their shopping cart on these sites, similar to purchasing a book on Amazon. Option three provides several "creative ways" to access pills in states where telehealth is restricted, including mail forwarding, picking up in neighboring states, and general delivery in a neighboring state. Regarding mail forwarding for women in Texas, the website states, "You live in a state that restricts access to abortion, but alternate routes of access may still be possible.

People in your state are getting abortion pills by mail and having medically-safe abortions at home by using: Aid Access, Online pharmacies, Mail forwarding, Pickup in Mexico" ("The Plan C Guide to Abortion Pills: How to get abortion pill access by mail in Texas"). The fourth option provides a list of in-person clinics and abortion providers. The pills for medication abortion are accessible to anyone who may want to obtain them.

Complications With Self-Managed Abortion

In addition to the previously discussed risks of medication abortion, providers should be aware of additional concerns with women obtaining pills online without medical consultation. The issues of estimated GA, ectopic pregnancy, Rh incompatibility, access to care for complications, informed consent, and forced abortion are issues that must be forefront as self-managed medication abortion increases.

Estimation of GA

In self-managed medication abortion, the GA is typically determined by a woman's self-reported date of last menstrual period (LMP) (Aid Access). Accurate determination of GA is essential because risks of medication abortion increase with increasing GA (Mentula et al. 2011; Bartlett et al. 2004). In Mentula et al., surgical evacuation was required in 7.9% of first trimester abortions and 38.5% of second trimester abortions. Infection occurred in 1.9% of first trimester abortions and 4.0% of second trimester abortions (Mentula et al. 2011). Bartlett et al. evaluated risk factors for induced abortion-related mortality in the US and found that, "Women whose abortions were performed in the second trimester (at or after 13 weeks of gestation) had abortion-related mortality rates greater than women whose abortions were performed in the first 8 weeks of pregnancy (RR at 13–15 weeks, 14.7 [95% CI 6.2, 34.7]; RR at 16–20 weeks, 29.5 [95% CI 12.9, 67.4]; RR at or after 21 weeks, 76.6 [95% CI 32.5, 180.8]). If women who had abortions after 8 weeks of gestation had obtained abortions during the first 8 weeks of pregnancy, when risk is lowest, 87% of deaths likely could have been prevented." (Bartlett et al. 2004). Currently, medication abortion is approved up to seventy days gestation. In the first trimester, ultrasound is the most accurate method to determine GA (ACOG 2017a). In one study, 40 percent of women had their due date adjusted because of a discrepancy of more than five days in dating by ultrasound compared to dating by LMP (Bennett et al. 2004). Without an ultrasound to determine GA, medication abortion might inadvertently occur beyond the seventy-day limit, with subsequent potential for significant complications. Although ACOG states that an ultrasound is the most accurate method to determine GA, their Practice Bulletin on medication abortion states that no ultrasound or clinical examination is required for women with regular menstrual cycles, a certain LMP within the past fifty-six days, and no signs, symptoms, or risk factors for ectopic pregnancy (ACOG 2020). In a study in India on the safety of providing abortion pills without a prescription, 27.5 percent of women who presented to the hospital had consumed abortion pills beyond the approved GA of nine weeks, and 17.5 percent had consumed the pills after twelve weeks (Nivedita and Shanthini 2015).

Ectopic Pregnancy

Ectopic pregnancies represent 2 percent of all reported pregnancies and 2.7 percent of pregnancy-reported deaths. Half of the women with ectopic pregnancies do not have risk factors (ACOG 2018). Ectopic pregnancy is a contraindication for medication abortion. Administration of medication for abortion without confirmation of pregnancy location has ended in undiagnosed and ruptured ectopic pregnancies (Aultman et al. 2021; Wang et al. 2021). Two of the 24 deaths from medication abortion in the US since 2000 resulted from ruptured ectopic pregnancies (Food and Drug Administration 2018).

Without an ultrasound to determine pregnancy location before administering mifepristone and misoprostol, ectopic pregnancies may be missed. Further, symptoms of ectopic pregnancy such as bleeding and pain can be easily attributed to the abortion process. Medication abortion without ultrasound is increasingly promoted (Schmidt-Hansen et al. 2020; Goldberg et al. 2022). Administering medications for abortion without confirmation of pregnancy location and GA is inconsistent with good medical practice, and bad outcomes have resulted (Gary and Harrison 2006; Food and Drug Administration 2018; Wang et al. 2021; Aultman et al. 2021). In the two papers categorizing the FDA AERs up to February 2019, there were a total of ninety-two ectopic pregnancies (Gary and Harrison 2006; Aultman et al. 2021). Gary and Harrison detail seventeen ectopic pregnancies, eleven of which were ruptured, one of which resulted in death (Gary and Harrison 2006). Aultman et al. detail seventy-five ectopic pregnancies, at least twenty six of which were ruptured (twenty-five rupture status is not given), one of which resulted in death (Aultman et al. 2021). If a woman attempting a self-managed abortion has an ectopic pregnancy, the lack of physician involvement can be catastrophic.

Rh Incompatibility

In North America, approximately 15 percent of women are Rh-negative (ACOG 2017b). ACOG states, "Rh D immune globulin should be given to Rh D-negative women who have pregnancy termination, either medical or surgical" (ACOG 2017b). In another ACOG bulletin, ACOG states that Rh testing is recommended before medication abortion, but if testing and Rh D immunoglobulin are unavailable or would significantly delay the abortion, shared decision-making is recommended (ACOG 2020). In untreated iso-immunized infants, 14 percent are stillborn, and half suffer neonatal death or brain injury (Zipursky and Paul 2011). Rh D immune globulin has decreased isoimmunization from 13 to 16 percent to 0.5 to 1.8 percent in a subsequent pregnancy (ACOG 2017b). As noted previously, in one telemedicine abortion study, 31 percent of Rh-negative women did not receive Rh D Immune globulin. For self-managed abortion, it is unclear how Rh-negative women will receive Rh D Immune globulin

Access to Medical Care for Complications

The FDA mandates that the prescriber be able to provide surgical intervention in cases of incomplete abortion or severe bleeding or have made plans to provide such care through others and also must assure patient access to medical facilities equipped to provide blood transfusions and resuscitation if necessary (Center for Drug Evaluation and Research 2016; Danco Laboratories 2016). If a woman obtains an abortion by pills online, it is unclear who will care for any complications and what will be her recourse if she does not have close access to an ER. It is essential that women who undergo medication abortion, whether self-managed or not, have access to emergency care.

Informed Consent

Physicians are responsible for providing informed consent for any medical treatment or intervention. Patients have the right to understand the risks, benefits, pros, and cons. The National Academies of Science 2018 Report on The Safety and Quality of Abortion Care in the US says, "Thus, when women seek an abortion, they should have the opportunity to discuss their questions and concerns and receive support in their decision making" (National Academies of Science, Engineering, & Medicine 2018, 46). ACOG states that "Meeting the ethical obligations of informed consent requires that an obstetrician–gynecologist gives the patient adequate, accurate, and understandable information and requires that the patient has the ability to understand and reason through this information and is free to ask questions and to make an intentional and voluntary choice, which

may include refusal of care or treatment" (ACOG 2021). ACOG also recommends shared decision-making which is a "patient-centered, individualized approach to the informed consent process that involves discussion of the benefits and risks of available treatment options in the context of a patient's values and priorities." Unlike telemedicine, where a physician and patient can discuss the risks and benefits of a given intervention, there is no such interaction when pills are obtained online.

Forced Abortion

One concern with online abortion is that the medication may be obtained by someone other than the patient. The covert use of abortion pills in a woman's food or drink has been documented even before the relaxation of restrictions. In 2007 in Wisconsin, Manishkumar Patel spiked his girlfriend's smoothie with mifepristone and was sentenced to twenty-two years in prison ("Wisconsin man spikes mistress's drink with abortion drug, gets 22 years in prison" 2018). In 2014, Scott Bollig in Kansas purchased pills on the internet and put them in his girlfriend's pancake, resulting in the unborn child's death ("Man accused of killing fetus with 'abortion pancake'" 2014). In 2017, Dr. Sikander Imran in Virginia put mifepristone in his girlfriend's tea, resulting in the death of the fetus. He pled guilty to fetal homicide ("Doctor sentenced for spiking girlfriend's drink to induce abortion" 2018; McBride 2017). In 2018, Jeffrey Smith in Wisconsin tried to kill his unborn child by putting mifepristone in his girlfriend's water bottle and was later convicted of attempted first-degree intentional homicide of an unborn child and sentenced to twenty years in prison (Siewert 2022). When these situations occurred, mifepristone was required to be dispensed in specific healthcare settings (clinics, medical offices, hospitals) under the supervision of a certified prescriber (FDA 2011, 2; Center for Drug Evaluation and Research, 2016, 3). Dispensing in a healthcare setting is no longer required (FDA 2021a), even for legal medication abortion.

Forced abortion is common among trafficked women. In Lederer's survey of 2014 human trafficking survivors, 55.2 percent of them had at least one abortion, 29.7 percent had multiple abortions, and 52.9 percent had one or more abortions partly or wholly forced on them (Lederer and Wetzel 2014). One victim reported that "in most of [my six abortions,] I was under serious pressure from my pimps to abort the babies" (Lederer and Wetzel 2014). Another trafficking victim reported seventeen abortions and indicated that at least some were forced on her. With the ability to obtain abortion pills online, traffickers can more easily accomplish forced abortions on their victims. Healthcare providers are one of the few professionals with whom trafficked women and girls are likely to interact and are uniquely positioned to identify and provide care for these victims (Dovydaitis 2010). As self-managed abortion becomes accessible, we must be aware of the increased possibility of forced abortions and look for ways to protect women.

Clinical and Ethical Implications

We are in an unprecedented time in the US. With the recent overturn of Roe v. Wade, some states seek to become abortion sanctuaries and are increasing access; other states are enacting abortion bans and restrictions. We can expect that women will increasingly access abortion pills online in states where abortion is restricted. These women may present to our offices and ERs, and it is essential to be aware of the medical implications as well as the personal situations that factor into their decisions.

Our ethical responsibility is to be vigilant of these complications and to care for women. We must continue to provide services to provide a safety net and to care for those with at-risk pregnancies. Black women are particularly at risk since the abortion rate is highest in black women (21.2 abortions per 1,000 women) than in White (6.3 per 1,000), Hispanic (10.9 per 1,000), or other races (11.9 per 1,000) (Kortsmit et al. 2021).

According to the latest CDC Abortion Surveillance Report, 38.4 percent of reported abortions were in Black women (Kortsmit et al. 2021), yet the population percentage is only 13.6 percent (US Census Bureau 2021).

In an ideal world, no one would get an abortion. However, we do not live in an ideal world, and women will continue to obtain abortions. It is essential to be aware of the complications germane to self-managed abortion so that we can provide the best care.

Conclusion

Any medical intervention or procedure has risks. It is our responsibility as physicians to advise our patients of risks and discuss options. We must work to minimize the risks and promote the best outcome. Finally, when we care for pregnant women, we have two patients: the mother and her baby. When a woman chooses to end her baby's life, our responsibility remains to care for the woman. Currently, in the US, the FDA has reduced safety measures even where abortion is legal. In places where it is not, women will continue to access pills online and through creative means. Both of these scenarios raise concerns about increasing harm to women. Access and availability must never supersede safety and care for women. Nevertheless, we will continue to care and advocate for our patients and manage their complications when they occur.

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