Significant Adverse Events and Outcomes After Medical Abortion

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OBJECTIVE: To analyze rates of significant adverse events and outcomes in women having a medical abortion at Planned Parenthood health centers in 2009 and 2010 and to identify changes in the rates of adverse events and outcomes between the 2 years.

METHODS: In this database review we analyzed data from Planned Parenthood affiliates that provided medical abortion in 2009 and 2010 almost exclusively using an evidence-based buccal misoprostol regimen. We evaluated the incidence of six clinically significant adverse events (hospital admission, blood transfusion, emergency department treatment, intravenous antibiotics administration, infection, and death) and two significant outcomes (ongoing pregnancy and ectopic pregnancy diagnosed after medical abortion treatment was initiated). We calculated an overall rate as well as rates for each event and identified changes between the 2 years.

RESULTS: Among 233,805 medical abortions provided in 2009 and 2010, significant adverse events or outcomes were reported in 1,530 cases (0.65%). There was no statistically significant difference in overall rates between years. The most common significant outcome was ongoing intrauterine pregnancy (0.50%); significant adverse events occurred in 0.16% of cases. One patient death occurred as a result of an undiagnosed ectopic pregnancy. Only rates for emergency department treatment and blood transfusion differed by year and were slightly higher in 2010.

CONCLUSION: Review of this large data set reinforces the safety of the evidence-based medical abortion regimen.

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LEVEL OF EVIDENCE: III

First-trimester abortion with medications rather than surgery is widely used throughout the world, primarily using a combination of mifepristone and misoprostol. Extensive experience with medical abortion has proven it to be highly effective and safe.[1–6] Like with surgical abortion, complications with medical abortion are relatively infrequent. The low probability of clinically significant adverse events and outcomes and varying protocols make it difficult to estimate these rates without a very large patient population.

Planned Parenthood is a large, multisite provider of women's health care whose health centers have offered medical abortion as an option since 2001.[6] Most Planned Parenthood affiliates (accredited by the Planned Parenthood Federation of America) operate several health centers; some health centers within one affiliate may offer medical abortion services, whereas others may not. At Planned Parenthood health centers that offer medical abortion, this option is available up to and including 63 days of gestation (assuming that state regulations do not restrict health care providers to the U.S. Food and Drug Administration [FDA]–approved regimen).

All Planned Parenthood affiliates are required to follow the Planned Parenthood Federation of America Manual of Medical Standards and Guidelines as a condition of accreditation. The 2009 and 2010 guidelines outlined three acceptable medical abortion regimens using mifepristone and misoprostol (Table 1)

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Table 1. Medical Abortion Regimens Provided at Planned Parenthood Health Centers in 2009 and 2010*

Regimen†	Gestational Limit (Up to and Including)	Mifepristone	Misoprostol	
			Days After Mifepristone	Dosage
FDA-approved	49 d	Three 200-mg tablets, orally, in office	2 (only if needed)	Two 200-microgram tablets, orally, in office
Evidence-based, oral misoprostol	49 d	One 200-mg tablet, orally, in office	1	Four 200-microgram tablets (split into two doses over 2 h), orally, at home
Evidence-based, buccal misoprostol	63 d	One 200-mg tablet, orally, in office	1 or 2	Four 200-microgram tablets, bucally, at home

FDA, U.S. Food and Drug Administration.
* Follow-up appointment scheduled within 2 weeks of mifepristone ingestion for all regimens.
† All medical abortion regimens required that patients start a course of antibiotics on the day mifepristone was administered. Patients received 100 mg doxycycline orally twice a day for 7 days; if a patient was allergic to doxycycline, acceptable alternatives included 1 g azithromycin orally, 500 mg erythromycin base orally four times a day for 7 days, 800 mg erythromycin ethylsuccinate orally four times a day for 7 days, 300 mg ofloxacin twice a day for 7 days, or 500 mg levofloxacin orally once a day for 7 days.
Data from Planned Parenthood. *Manual of Medical Standards and Guidelines*. New York (NY); 2009 and 2010 (unpublished document).

including the FDA-approved regimen and two evidence-based regimens. All three regimens required that patients start a course of antibiotics the day they took mifepristone and that a follow-up appointment be scheduled within 2 weeks of mifepristone (Planned Parenthood Federation of America Manual of Medical Standards and Guidelines, 2009 and 2010). Planned Parenthood Federation of America internal data from affiliate surveys indicate that at least 99% of the medical abortions performed during 2009 and 2010 followed the evidence-based buccal regimen.

Planned Parenthood Federation of America has a centralized reporting mechanism for significant adverse events and outcomes after medical abortion, which allows a large number of patient outcomes to be assessed through routine reporting. The primary objective of this study was to analyze rates of significant adverse events and outcomes in women having a medical abortion at Planned Parenthood health centers in 2009 and 2010. We also sought to identify changes in the rates of adverse events and outcomes between the 2 years, overall and separately for each event or outcome.

METHODS

This analysis includes data obtained from Planned Parenthood affiliates that provided medical abortion from January 1, 2009, through December 31, 2010. The total number of medical and surgical abortions provided by Planned Parenthood affiliates is collected by the Planned Parenthood Federation of America national office through quarterly and annual summary reports. Abortion in the first trimester is defined as occurring through the 12th week of pregnancy. This study was approved by Allendale investigational review board.

Planned Parenthood health center staff are trained in accurate and complete reporting of significant adverse events and outcomes after medical abortion, and such reporting is centralized through the Planned Parenthood Federation of America national office. Since 2005, the Planned Parenthood Federation of America accreditation process has included auditing to verify that significant adverse events and outcomes related to the use of mifepristone for medical abortion are reported as required. In accordance with the mifepristone prescribing information, Planned Parenthood Federation of America reports all significant adverse events and outcomes to Danco Laboratories, the U.S. distributor of mifepristone, which in turn reports them to the FDA.

Planned Parenthood health center staff collect information about significant adverse events and outcomes after medical abortion from different sources including routine follow-up visits, reports from clinicians providing care at hospital inpatient units or emergency departments, or voluntary reports by patients. The 2009 and 2010 Planned Parenthood Federation of America Manual of Medical Standards and Guidelines included requirements to emphasize the importance of the follow-up visit to all patients, and staff members were required to make three attempts (two in writing) to reach patients who did not return for follow-up. Despite substantial effort to follow up with patients, complete information on the proportion of women who did not return for follow-up as well as any complications they may have experienced is not available.

During the study period, protocols for providing medical abortion and reporting significant adverse

events and outcomes remained consistent, with the exception that beginning in July 2010, affiliates had the ability to submit reports through a secure web-based system in addition to submitting reports by fax. We analyzed reports of significant adverse events and outcomes after medical abortion, and rates were evaluated for both years together as well as individually for 2009 and 2010. We excluded 2010 data from one affiliate (that had reported only two cases of adverse events or outcomes) which as of September 2010 was no longer a member of Planned Parenthood Federation of America. Because delays in reporting adverse events and outcomes are common, we could not be certain that all adverse events and outcomes that may have occurred at this affiliate during the first 9 months of 2010 had been adequately reported.

Per the Danco Laboratories Mifepristone Prescriber's Agreement, "adverse events, such as hospitalization, blood transfusion, ongoing pregnancy, or other major complications after the use of Mifeprex and misoprostol must be reported to Danco Laboratories."[7] In this report, we evaluate six clinically significant adverse events (hospital admission, blood transfusion, emergency department treatment, intravenous antibiotics administration, infection requiring treatment with intravenous antibiotics or admission to the hospital, and death) and two significant outcomes (ongoing intrauterine pregnancy and ectopic pregnancy diagnosed after medical abortion treatment was initiated) after medical abortion. In this analysis, blood transfusion is binary (whether or not blood products were administered) because not all reports included the specific components or amount.

The Planned Parenthood Federation of America Manual of Medical Standards and Guidelines defined ongoing pregnancy as "a living, viable pregnancy that is growing. For example, the ultrasound scan shows a fetal pole with cardiac activity or a gestational sac that has grown appropriately since mifepristone was given" (Planned Parenthood Federation of America Manual of Medical Standards and Guidelines, 2009 and 2010). The Planned Parenthood Federation of America Manual of Medical Standards and Guidelines permitted use of a repeat dose of misoprostol when the initial follow-up evaluation demonstrated an ongoing pregnancy up to and including 63 days of gestation. In this analysis, if a repeat dose of misoprostol was successful, the case was not included as an ongoing pregnancy.

Categories of significant adverse events and outcomes are not mutually exclusive; in some cases, one problem could be counted as more than one event or outcome. For example, if a patient with a serious infection was admitted to the hospital and treated with intravenous antibiotics, this case would be counted in each of the three outcome categories.

We calculated 95% exact binomial confidence intervals for rates and used Fisher's exact test to test the statistical significance of differences in proportions. Two-sided P values of $<.05$ were considered to be indication of statistical significance. All calculations were performed using Stata SE 11.

RESULTS

As of December 31, 2010, Planned Parenthood Federation of America included 85 independent affiliates operating 810 health centers in 49 states and the District of Columbia; 39% (324) of health centers provided abortion care, and nearly all of these (97.8% [317]) offered medical abortion. In 2009, 314,772 first-trimester abortions were provided by Planned Parenthood Federation of America affiliates, 35% of which were medical abortions. In 2010, medical abortion comprised 38% of the 320,991 first-trimester abortions. Overall, in 2009 and 2010, medical abortion comprised 37% of all first-trimester abortions provided by Planned Parenthood health centers.

Among the 233,805 medical abortions provided at Planned Parenthood health centers in 2009 and 2010, significant adverse events or outcomes were reported in 1,530 (0.65%) cases. There was no statistically significant difference in overall rates between years ($P=.29$). Rates for each significant adverse event and outcome are shown in Table 2. A clinically significant adverse event occurred in 0.16% of cases; this rate did not differ by year. A clinically significant outcome occurred in 0.5% of cases (with no difference by year). Of importance is the rarity of an undiagnosed ectopic pregnancy, which occurred at a rate of 0.7 per 10,000 medical abortions. The most common significant adverse event or outcome after medical abortion during the study period, ongoing intrauterine pregnancy, was reported in 0.50% of cases for both years combined. Among 1,158 ongoing intrauterine pregnancies, 1,095 (94.6%) were known to be terminated surgically, and 63 (5.4%) were either lost to follow-up or patients indicated that they would continue or were considering continuing the pregnancy.

The only adverse event rates that differed in statistical significance in bivariate models between 2009 and 2010 were emergency department treatment (0.07% [n=87] compared with 0.12% [n=151], respectively, $P=.001$) and blood transfusion (0.04% [n=42] compared with 0.06% [n=72], respectively, $P=.024$). There was one death, as a result of an undiagnosed ectopic pregnancy, for a mortality rate of 0.4 per 100,000 over the 2-year study period.

Table 2. Rates of Significant Adverse Events and Outcomes After Medical Abortion, 2009 and 2010*

Event	No. of Cases	Rate (%)†	95% Confidence Interval	P‡
All significant adverse events and outcomes				
Any significant adverse event or outcome	1,530	0.65	0.62–0.69	.293
2009	706	0.63	0.59–0.68	
2010	824	0.67	0.62–0.72	
Significant adverse events				
Any significant adverse event	385	0.16	0.15–0.18	.092
2009	166	0.15	0.13–0.17	
2010	219	0.18	0.16–0.20	
Emergency department treatment	238	0.10	0.09–0.11	.001
2009	87	0.07	0.06–0.10	
2010	151	0.12	0.10–0.14	
Hospital admission	135	0.06	0.05–0.07	.343
2009	70	0.06	0.05–0.08	
2010	65	0.05	0.04–0.07	
Transfusion§	114	0.05	0.04–0.06	.024
2009	42	0.04	0.03–0.05	
2010	72	0.06	0.05–0.07	
Intravenous antibiotics	57	0.02	0.02–0.03	.292
2009	23	0.02	0.01–0.03	
2010	34	0.03	0.02–0.04	
Infection	37	0.016	0.011–0.021	.254
2009	14	0.013	0.001–0.021	
2010	23	0.019	0.001–0.028	
Significant outcomes				
Any significant outcome	1,174	0.50	0.47–0.53	.953
2009	556	0.50	0.46–0.54	
2010	618	0.50	0.46–0.54	
Ongoing intrauterine pregnancy	1,158	0.50	0.47–0.52	.929
2009	548	0.49	0.45–0.54	
2010	610	0.50	0.46–0.54	
Ectopic pregnancy	16	0.007	0.004–0.011	1.00
2009	8	0.007	0.003–0.014	
2010	8	0.007	0.003–0.013	

* Events are not mutually exclusive.
† Denominator is all medical abortions; n=111,022 in 2009, n=122,783 in 2010, and N=233,805 for 2009 and 2010 combined.
‡ Difference between 2009 and 2010 rates.
§ Transfusion is any blood product transfusion, regardless of the number of units.

DISCUSSION

As the largest provider of abortion care in the United States, Planned Parenthood Federation of America is in a unique position to provide reliable, large-scale data on the efficacy and safety of abortion procedures. The data presented here reinforce the infrequency of clinically significant adverse events and outcomes after medical abortion. The vast majority (99.34%) of medical abortions provided at Planned Parenthood health centers in 2009 and 2010 were completed with no known complications. Clinically significant adverse outcomes were rare, occurring at a rate of 16 per 10,000 medical abortions. The most common significant adverse event or outcome reported was ongoing intrauterine pregnancy, occurring in 0.5% of all medical abortion procedures.

Ongoing pregnancy is reportable to Danco Laboratories per the Mifepristone Prescriber's Agreement. Because it is the efficacy metric for medical abortion, data on ongoing intrauterine pregnancy should be reported and reviewed. However, ongoing intrauterine pregnancy is not a complication that is related to the safety of medical abortion the same way serious infection or blood transfusion is. The risk associated with ongoing pregnancy is tied to the potential teratogenicity of misoprostol.[8,9] Continuing pregnancy is of clinical significance only if it is unrecognized through follow-up and the patient does not have a surgical abortion.

Although we present data for ongoing pregnancy rates, we are unable to assess an overall "failure rate" for the 2-year reporting period. Treatment failure encompasses all reasons for a dilation and curettage,

including incomplete abortion. Although incomplete abortion managed outside the Planned Parenthood health center is reportable when it is tied to an adverse event (ie, treatment in the emergency department or hospital), incomplete abortion managed at the health center is not. Therefore, we have data only on rates of surgical evacuation for ongoing pregnancy.

Ectopic pregnancy diagnosed after medical abortion treatment was initiated was extremely rare with a rate even lower than the likelihood of maternal death during delivery.[10] Our study includes only ectopic pregnancies that were diagnosed after the medical abortion regimen had begun, not those diagnosed during the initial screening process. One death occurred during the study period as a result of an undiagnosed ectopic pregnancy.

The overall rate for all clinically significant adverse events and outcomes combined did not differ between 2009 and 2010 nor did the rate for most of these events differ by year. Exceptions were emergency department treatment and blood transfusion, both of which were higher in 2010 than in 2009. Because each health center has different local resources available, and patients may travel from more rural areas to some health centers, emergency department treatment may be related to where the original service was provided. Patients who drove for several hours to a health center to obtain care might be more likely to need emergency department treatment for a complication because of less access to a health center for any urgent issue. We do not have any data regarding locale of patients to compare whether emergency department treatment or blood transfusion is related to distance from home to the health center.

The findings in this article are of timely significance because some states in the United States have passed or are considering legislation to restrict mifepristone and misoprostol use to the FDA-approved regimen. The largest U.S. trial of mifepristone and misoprostol using the FDA-approved regimen through 49 days of gestation showed an ongoing pregnancy rate of 1% among 827 women.[11] The 92% efficacy rate of the FDA-approved regimen[11,12] is lower than the 96% efficacy rate for the evidence-based regimen using buccal misoprostol through 63 days of gestation.[13] This current large database analysis reinforces the low ongoing pregnancy rate when using one 200-mg mifepristone tablet and buccal misoprostol.

Potential limitations to this analysis should be considered. The data analyzed in this article are those reported to or received by Planned Parenthood Federation of America; we cannot exclude the possibility that some clinically significant adverse events or outcomes were not included. Some patients may have experienced a significant adverse event or outcome but did not follow up after their medical abortion. Additionally, despite intensive efforts at training affiliate and national office staff in procedures for reporting significant adverse events and outcomes, there remains the potential for human error and omission in the reporting process. Additionally, because experiencing, treating, and reporting an adverse event is subjective, an event may not always reflect the severity of the condition, but rather the concern of the patient. Similarly, treatments with blood products and intravenous antibiotics for the same condition may vary substantially among physicians or institutions.

The last potential limitation to consider is the lack of information available about women who did not experience a significant adverse event or outcome. Detailed information about patient age and gestational age (but no other demographic information) is collected through the Planned Parenthood Federation of America reporting system only for those women with significant adverse events or outcomes after medical abortion. Therefore, we are unable to analyze rates of significant adverse events and outcomes based on patient age, gestational age, or other demographic variables or to identify the exact regimens used in the 232,275 medical abortions with no reported complications. Despite these potential limitations, the findings in this study confirm that evidence-based medical abortion is highly effective and extremely safe.

The FDA allows and encourages off-label use of registered products when existing medical evidence supports such use.[14] The data presented in this article contribute to existing information in the medical literature; all of this evidence, taken together, does not support legislation restricting providers to use of the FDA-approved regimen. Every woman deserves factual medical information whenever she is faced with a decision of whether to terminate her pregnancy.[15] Mandating the FDA-approved regimen, without a scientific basis, does not protect patients from unsafe abortion; it only limits access to safe and effective medical abortion for women desiring a pregnancy termination. This review of Planned Parenthood Federation of America's medical abortion data confirms the safety and efficacy of medical abortion and should be taken into consideration both by clinicians and legislators when considering policy and protocols related to abortion.

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