Deaths and Severe Adverse Events after the use of Mifepristone as an Abortifacient from September 2000 to February 2019

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ABSTRACT: *Objectives:* Primary: Analyze the Adverse Events (AEs) reported to the Food and Drug Administration (FDA) after use of mifepristone as an abortifacient. Secondary: Analyze maternal intent after ongoing pregnancy and investigate hemorrhage after mifepristone alone.

***Methods*: Adverse Event Reports (AERs) for mifepristone used as an abortifacient, submitted to the FDA from September 2000 to February 2019, were analyzed using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAEv3).**

***Results*: The FDA provided 6158 pages of AERs. Duplicates, non-US, or AERs previously published (Gary, 2006) were excluded. Of the remaining, there were 3197 unique, US-only AERs of which there were 537 (16.80%) with insufficient information to determine clinical severity, leaving 2660 (83.20%) Codable US AERs (Figure 1). Of these, 20 were Deaths, 529 were Life-threatening, 1957 were Severe, 151 were Moderate, and 3 were Mild.**

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The deaths included: 9 (45.00%) sepsis, 4 (20.00%) drug toxicity/ overdose, 1 (5.00%) ruptured ectopic pregnancy, 1 (5.00%) hemorrhage, 3 (15.00%) possible homicides, 1 (5.00%) suicide, 1 (5.00%) unknown (Table 1).

Retained products of conception and hemorrhage caused most morbidity. There were 75 ectopic pregnancies, including 26 ruptured ectopics (includes one death).

There were 2243 surgeries including 2146 (95.68%) D&Cs of which only 853 (39.75%) were performed by abortion providers.

Of 452 patients with ongoing pregnancies, 102 (22.57%) chose to keep their baby, 148 (32.74%) had terminations, 1 (0.22%) miscarried, and 201 (44.47%) had unknown outcomes.

Hemorrhage occurred more often in those who took mifepristone and misoprostol (51.44%) than in those who took mifepristone alone (22.41%).

***Conclusions*: Significant morbidity and mortality have occurred following the use of mifepristone as an abortifacient. A pre-abortion ultrasound should be required to rule out ectopic pregnancy and confirm gestational age. The FDA AER system is inadequate and significantly underestimates the adverse events from mifepristone.**

A mandatory registry of ongoing pregnancies is essential considering the number of ongoing pregnancies especially considering the known teratogenicity of misoprostol.

At the very least, the FDA should reinstate the original 2011 REMS and strengthen the reporting requirements.

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***Keywords*: Mifepristone, Mifeprex, RU-486, Misoprostol, Abortifacient, Medical Abortion, Abortion Pill, Medical Abortion Complications, No touch abortion, DIY Abortion, Self-Administered Abortion, Adverse Events, Adverse Event Reports, Post-marketing Surveillance, FAERS, Drug Safety, Emergency Medicine, FDA, REMS, Risk Evaluation Mitigation Strategy.**

Introduction

The application for mifepristone (RU-486, RU-38486, Mifeprex) as an abortifacient was submitted to the Food and Drug Administration (FDA) in 1996 by the Population Council, which was given the manufacturing and distribution rights from Roussel Uclaf. [1] The Population Council partnered with Danco Laboratories, newly created in 1995, and gave them the manufacturing, marketing, and distribution rights. The FDA approved mifepristone in September 2000 under restricted distribution regulations (Subpart H) due to the FDA's conclusion that restrictions "on the distribution and use of mifepristone are needed to ensure safe use of this product."[2]

Included in these restrictions was the requirement that all serious Adverse Events (AEs), after the use of mifepristone as an abortifacient, be reported to the FDA by Danco as part of post-marketing surveillance. According to the FDA,[3] the purpose of such post-marketing surveillance includes identification of potential risks recognized after the time of approval, identification of unexpected deaths, causal attribution of AEs based on the product's known pharmacological action, and AEs for which a Risk Evaluation Mitigation Strategy (REMS) is intended to mitigate the risk.

In 2006, in response to the deaths of 4 women from a rare bacterial sepsis from *Clostridium sordellii (C. sordellii)*, the FDA and CDC convened a workshop, during which mifepristone alteration of the immune system was detailed, and they concluded that such alteration could lead to impaired ability to respond to *C. sordellii* toxin.[4]

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[1] Citizen petition re: Request for Stay and Repeal of the Approval of Mifeprex (mifepristone) for the Medical Termination of Intrauterine Pregnancy through 49 Day's Gestation Final. Before the Department of Health and Human Services: Food and Drug Administration. AAPLOG. 2002. 7-10. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/Documents/2002%20Aug%2020%20Citizen%20Petition_Mifeprex.pdf

[2] Center for Drug Evaluation and Research. Approval Letter for Mifeprex NDA 20-687. February 18, 2000. Food and Drug Administration. p 5. Accessed November 16, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20687approvable00.pdf

[3] US Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff. November 2019. p 7-8. Accessed Jan 16 2021. https://www.fda.gov/media/130216/download p7-8

[4] Emerging Clostridial Disease Workshop: May 11, 2006, Atlanta, GA. Department of Health and Human Services, Centers for Disease Control and Prevention, Food and Drug Administration, National Institutes of Health. 2006. p. 109,110. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/2006%20CDC%20FDA%20Clostridial%20Disease%20Transcript.pdf

There is evidence that both mifepristone[5,6,7] and misoprostol[8] can suppress immune response to *C. sordellii* in animal models.

In response to the septic deaths, Planned Parenthood changed their off-label protocol from vaginal administration of misoprostol to buccal in 2006.[9,10] Yet, as we found in our analysis, sepsis deaths from *C. sordellii* and other bacteria continued to occur after 2007. All sepsis deaths occurred with either vaginal or buccal misoprostol, which were both off label routes of administration until the buccal route was authorized in 2016.[11]

In 2011, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for Mifepristone incorporating the original restrictions.[12] In May 2015, Mifepristone's sponsor submitted a supplemental new drug application to the FDA to obtain approval to revise the drug's labeling, which the FDA approved in 2016.[13,14] The 2016 changes in the Regimen and Prescriber Agreement extended the original gestational age limit from 49 days to 70 days, changed the mifepristone dose from 600 mg to 200 mg orally, changed the misoprostol dose from 400 mcg orally on Day 3 to 800 mcg buccally on Day 2 or 3, allowed non-physicians to become prescribers, reduced the number of required office visits from 3 to just one initial office visit, and allowed a repeat dose of misoprostol if complete expulsion did not occur.[15] The prescriber agreement was changed so

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[5] Emerging Clostridial Disease Workshop: May 11, 2006, Atlanta, GA. Department of Health and Human Services, Centers for Disease Control and Prevention, Food and Drug Administration, National Institutes of Health. 2006. p. 109, 110 Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/2006%20CDC%20FDA%20Clostridial%20Disease%20Transcript.pdf

[6] Webster JI, Sternberg EM. Role of the hypothalamic-pituitary-adrenal axis, glucocorticoids and glucocorticoid receptors in toxic sequelae of exposure to bacterial and viral products. J Endocrinol. 2004;181(2):212, 213, 216, 217. doi.org/10.1677/joe.0.1810207

[7] Hawes AS, Rock CS, Keogh CV, Lowry SF, Calvano SE. In vivo effects of the antiglucocorticoid RU 486 on glucocorticoid and cytokine responses to Escherichia coli endotoxin. Infect Immun. 1992;60(7):2645, 2646. doi:10.1128/IAI.60.7.2641-2647.1992

[8] Aronoff DM, Hao Y, Chung J, et al. Misoprostol impairs female reproductive tract innate immunity against Clostridium sordellii. J Immunol. 2008;180(12):8227-8229. https://doi.org/10.4049/jimmunol.180.12.8222

[9] Trussell, J, Nucatola, D, Fjerstad, M, Lichtenberg, ES. Reduction in infection-related mortality since modifications in the regimen of medical abortion. Contraception, 2014;89(3):193-196. https://doi.org/10.1016/j.contraception.2013.11.020

[10] Fjerstad M, Trussell, J, Sivin, I, Lichtenberg, ES, Rates of Serious Infection after Changes in Regimens for Medical Abortion. N Engl J Med. 2009 July 9;361(2):148-149. July 9, 2009 N Engl J Med 2009; 361:145-151. doi:10.1056/NEJMoa0809146

[11] GAO-18-292 Revised Mifeprex Labeling: Food and Drug Administration Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts. Report to Congressional Requesters. Food and Drug Administration. 2018. p. 7. Published March 2018. Accessed November 13, 2020. https://www.gao.gov/assets/700/690914.pdf

[12] NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg: Risk Evaluation and Mitigation Strategy (REMS). Food and Drug Administration. 2011. 1-11. Reference ID: 2957855. Published June 8, 2011. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2011-06-08_Full.pdf

[13] GAO-18-292 Revised Mifeprex Labeling: Food and Drug Administration Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts. Report to Congressional Requesters. Food and Drug Administration. 2018. p. 1. Published March 2018. Accessed November 13, 2020. https://www.gao.gov/assets/700/690914.pdf

[14] NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg: Risk Evaluation and Mitigation Strategy (REMS). Food and Drug Administration. 2016. 1-8. Reference ID: 3909592. Published March 29, 2016. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf

[15] GAO-18-292 Revised Mifeprex Labeling: Food and Drug Administration Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts. Report to Congressional Requesters. Food and Drug Administration. 2018. p.7. Published March 2018. Accessed November 13, 2020. https://www.gao.gov/assets/700/690914.pdf

that instead of being required to "report any hospitalization, transfusion or other serious event to Danco Laboratories,"[16] providers were only required to report deaths.[17] The requirement to report ongoing pregnancies that are not terminated was also eliminated. "The FDA approved GenBioPro, Inc.'s abbreviated new drug application (ANDA) for generic Mifeprex on April 11, 2019" and "established a single, shared system REMS for mifepristone products" without substantially changing the REMS.[18]

During the COVID-19 pandemic the Maryland District Court issued a preliminary injunction prohibiting the FDA from enforcing the in-person dispensing and signature requirements contained in the mifepristone REMS.[19] This decision eliminated the need for an initial office visit for dispensing the medication and opened the door for dispensing of the drug via telehealth with no actual clinician contact. On January 12, 2021, the Supreme Court enabled the FDA to enforce the mifepristone REMS.[20] These requirements are essential for the safety of women and must be kept in place.

The first systematic analysis of these Adverse Event Reports (AERs) obtained by the Freedom of Information Act (FOIA), was published by Gary and Harrison in 2006.[21] This paper extends that analysis to AERs not previously published and augments the scant published literature on mifepristone safety.

Objectives

Primary: To analyze and codify the significant adverse events and their treatment after the use of mifepristone as an abortifacient, extending the previously published analysis by Gary in 2006.[22] Secondary: To examine maternal decisions in the case of ongoing pregnancy after attempted mifepristone termination, and to determine if failing to take misoprostol after mifepristone increased the risk of hemorrhage.

[16] NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg: Risk Evaluation and Mitigation Strategy (REMS). Food and Drug Administration. 2011. p. 7. Reference ID: 2957855. Published June 8, 2011. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2011-06-08_Full.pdf

[17] NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg: Risk Evaluation and Mitigation Strategy (REMS). Food and Drug Administration. 2016. p. 6. Reference ID: 3909592. Published March 29, 2016. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf

[18] Questions and Answers on Mifeprex. Food and Drug Administration. March 28, 2018. Updated 4-12-2019. Accessed November 13, 2020. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/questions-and-answers-mifeprex

[19] American College of Obstetricians and Gynecologists, et al., v. Food and Drug Administration, et al., No. 20-1320, 2020 WL 3960625 (D. Md. July 13, 2020). Accessed November 16th, 2020. https://www.courthousenews.com/wp-content/uploads/2020/07/093111166803.pdf

[20] FDA v ACOG. SCOTUS. 20a34_3f14. Accessed January 20, 2021. https://www.supremecourt.gov/opinions/20pdf/20a34_3f14.pdf

[21] Gary M, Harrison D. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. Ann Pharmacother. 2006 Feb 40(2):191-7. https://doi.org/10.1345/aph.1G481

[22] Gary M, Harrison D. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. Ann Pharmacother. 2006 Feb 40(2):191-7. https://doi.org/10.1345/aph.1G481

Materials and Methods

FDA AERs related to the use of mifepristone from September 2000 to February 2019 were obtained through the Freedom of Information Act (FOIA) from the FDA, and a comparison was made with FDA reports available online on the FDA Adverse Events Reporting System (FAERS) Dashboard.[23] Duplicate AERs were identified by comparing FDA case identification numbers, manufacturer identification numbers, dates of treatment, patient age, and descriptions of case scenarios to ensure that each case was included only once in this analysis. The authors excluded duplicates, cases originating outside of the United States, and cases previously published in the Gary analysis[24] (Figure 1).

One of the concerns in looking at AEs is the risk of falsely assigning causality. The FDA does not give guidance for determining causality for AEs in the AERs but does give guidance for selecting AEs for inclusion in the Adverse Reaction section of the Drug Label.[25] They recommend that, "Decisions on whether there is some basis to believe there is a causal relationship are a matter of judgment and are based on factors such as" the "frequency of reporting," "the extent to which the adverse event is consistent with the pharmacology of the drug," "the timing of the event relative to the time of drug exposure," and other factors. Although a causal relationship cannot be attributed with certainty to all reported AEs for a drug, a causal relationship seems probable for each of the categories of AEs we chose to analyze based on these factors, except for ectopic pregnancies and some of the deaths. Ectopic pregnancies were included in our analysis not because there is a causal relationship, but because ectopic pregnancy is a contraindication to the use of mifepristone and the diagnosis was missed, putting women's lives at risk. The deaths must be evaluated individually to determine causality.

Because reporting is often voluntary and sporadic, there is no denominator for how many mifepristone abortions are performed in the U.S. It was therefore impossible to calculate complication rates for mifepristone and misoprostol abortions based on AER data. For clarity, we specified the denominator used in each case. Coding for severity was done using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAEv3),[26] since this was

[23] FDA Adverse Events Reporting System (FAERS) Public Dashboard. Food and Drug Administration. Accessed November 13, 2020. https://fis.fda.gov/sense/app/d10be6bb-494e-4cd2-82e4-0135608ddc13/sheet/33a0f68e-845c-48e2-bc81-8141c6aaf772/state/analysis

[24] Gary M, Harrison D. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. Ann Pharmacother. 2006 Feb 40(2):191-7. https://doi.org/10.1345/aph.1G481

[25] Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER); January 2006. P. 8. Accessed January 8, 2021. https://www.fda.gov/media/72139/download

[26] Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Cancer Center Therapy Evaluation Program (CTEP); 2003. 1-77. Published December 12, 2003. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/CTCAEv3.pdf

the methodology used in the original analysis of the first 607 Adverse Events.[27] The five levels of coding are: Mild, Moderate, Severe, Life-threatening, and Death.

Overall severity (Figure 1) for each unique AER was determined independently by two board-certified physicians (Obstetrics and Gynecology or Family Medicine). Since within each AER, a patient may have experienced several Adverse Events (AEs), the overall severity of the AER was based on the highest severity of its AEs. For the diagnoses we analyzed (Table 1), each AE was coded in the same manner and stratified according to type, severity, and treatment. Disagreements were resolved by discussion or review by a third board-certified Obstetrician-Gynecologist who also reviewed coding for uniformity. Surgeries, transfusions, providers, and location of treatment were analyzed and tabulated.

Ruptured ectopic pregnancies were coded as Life-threatening and unruptured ectopic pregnancies as Severe.

Infections were coded as Life-threatening when evidence of sepsis was present, or ICU-level treatment was required. They were coded as Severe if parenteral/IV antibiotics were given and Moderate if oral antibiotics were prescribed.

Life-threatening hemorrhage was defined, as in the previous analysis, to be transfusion of two or more units of packed red blood cells (PRBCs), hemoglobin less than 7, or documented large volume, rapid blood loss with clinical symptomatology of acute blood loss anemia (e.g., syncope, tachycardia, hypotension). Severe hemorrhage was defined as requiring surgical intervention and/or less than 2 U PRBCs. Moderate hemorrhage was defined as management with fluids/medication alone.

Retained Products of Conception (RPOC) was coded as Severe if a dilatation and curettage/evacuation (D&C) was performed. Ongoing viable intrauterine pregnancy was considered equivalent in severity to RPOC requiring curettage and thus Severe. When the ultimate outcome was unknown, the pregnancy was considered ongoing if "ongoing pregnancy" was noted or ultrasound showed cardiac motion or significant growth.

AEs which did not contain sufficient information to assign an accurate severity code were deemed "Uncodable." AERs lacking any codable information were deemed overall Uncodable.

The percent of women with significant hemorrhage after mifepristone alone was compared to those who took both mifepristone and misoprostol, to investigate the validity of the assertion that lack of subsequent misoprostol administration was a causative factor in hemorrhage after mifepristone use.[28]

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[27] Gary M, Harrison D. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. Ann Pharmacother. 2006 Feb 40(2):191-7. https://doi.org/10.1345/aph.1G481

[28] Creinin MD, Hou MY, Dalton L, Steward R, Chen MJ. Mifepristone Antagonization With Progester-one to Prevent Medical Abortion: A Randomized Controlled Trial. Obstet Gynecol. 2020;135(1):158-165. doi:10.1097/AOG.0000000000003620

Results

Adverse Event Report Overall Severity

Figure 1 summarizes the handling of the AERs provided by the FDA and their severity coding. The FDA provided 6158 pages of AERs. Of these, any duplicates, non-US, or AERs previously published in the Gary paper were excluded from the analysis. There were 3197 unique, US-only AERs of which 537 had insufficient information to determine clinical severity, leaving 2660 Codable US-only AERs. Of these, 20 were Deaths, 529 were Life-threatening, 1957 were Severe, 151 were Moderate, and 3 were Mild.

Deaths (Table 1)

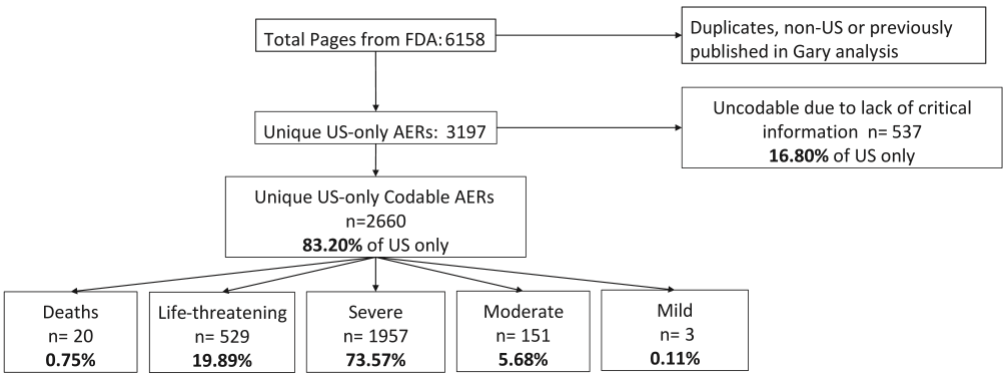
Our analysis identified 23 of the 24 deaths reported by the FDA as of 2018.[29] Three of those deaths were previously published in the Gary paper[30] leaving 20 deaths (Table 1). Our analysis yielded a total of 7 sepsis deaths. These included five cases of *C. sordellii* and one case of *Clostridium perfringens*, all consistent with those reported by the FDA. There was an additional death which we categorized as a sepsis death whereas the FDA labeled this case as "delayed onset toxic shock-like syndrome" but did not include it as a sepsis death. The patient had an exploratory laparotomy revealing green pus, which was culture positive for *prevotella* and *peptostreptococcus,* and she died intraoperatively.[31]

[29] RCM # 2007-525 NDA 20-687 Mifepristone U.S. Post-Marketing Adverse Events Summary through 12/31/2018. FDA. 1-2. Reference ID: 4401215. Accessed November 13, 2020. https://www.fda.gov/media/112118/download

[30] Gary M, Harrison D. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. Ann Pharmacother. 2006 Feb 40(2):191-7. https://doi.org/10.1345/aph.1G481

[31] Individual Case Safety Report number 4734082-4-00-01. Danco Laboratories, LLC. Office of Post-marketing Drug Risk Assessment, Food and Drug Administration. Received August 4, 2005. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/Peptostreptococcus%20death%209.10277-8.pdf

Figure 1. AER Distribution



Note: From 2000 to 2016 FDA only required the manufacturer to report AEs which were severe, life-threatening or had fatal outcomes. Since 2016, FDA only requires the manufacturer to report fatal outcomes.

We categorized two deaths as suspicious for infectious death. One case was labeled by the FDA as "undetermined natural causes," however, the AER reported the cause of death as "acute visceral and pulmonary (1420 grams) congestion and edema," [32] which is consistent with the clinical findings for sepsis/Acute Respiratory Distress Syndrome (ARDS). This patient had autopsy-proven retained products of conception and blood cultures which grew *Strep viridans* isolated at less than 24 hours incubation. One additional case which the FDA labeled "methadone overdose"[33,34] we considered suspicious for sepsis. Prior to her death, this patient had fever and chills and was treated by an outside physician with cephalexin, which would have been ineffective against infections from *C. sordellii* or anaerobic gram-negative bacilli. There was no autopsy report or toxicology report in the AER.

Non-infectious deaths include one death that the FDA listed as "natural," caused by "pulmonary emphysema."[35] This patient was a 40-year-old chronic smoker who died within hours of misoprostol ingestion and had a contusion on her head consistent with a fall, a scenario possibly related to a cardiac event or acute respiratory reaction to misoprostol. She had an intact fetus at the time of

[32] Individual Case Safety Report number 9587011-03-00-01. Danco Laboratories, LLC. Office of Post-marketing Drug Risk Assessment, Food and Drug Administration. Received May 21, 2014. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/death%20Visc%20pul%20cong.pdf

[33] Individual Case Safety Report number 4970303-0-00-01. Danco Laboratories, LLC. Office of Post-marketing Drug Risk Assessment, Food and Drug Administration. Received April 21, 2014. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/death%2023%20yo%20meth%20overdose%20fever%20and%20chills.pdf

[34] Individual Case Safety Report number 5063156-8-00-01. Danco Laboratories, LLC. Office of Post-marketing Drug Risk Assessment, Food and Drug Administration. Received July 27, 2006. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/methadone%20AER%20(1).pdf

[35] Individual Case Safety Report number 11283049-02-00-01. Danco Laboratories, LLC. Office of Post-marketing Drug Risk Assessment, Food and Drug Administration. Received December 8, 2015. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/emphysema.pdf

autopsy. Other non-infectious deaths included one death from a ruptured ectopic pregnancy, one from hemorrhage, 3 possible homicides, one suicide, and 4 deaths from drug toxicity/overdose. It is unknown whether the 8 women who died by homicide, suicide, or drug toxicity/overdose were screened for domestic violence, drug addiction, or depression prior to the abortion.

Infection (Table 1)

Infection was the leading cause of mortality. There were 502 cases of infection, which included 9 Deaths, 39 had Life-threatening sepsis, 249 were Severe infections, 132 Moderate infections, and 73 infections which were Uncodable.

Ectopic Pregnancy (Table 1)

There were 75 ectopic pregnancies. Of these, 26 were ruptured, including 1 death. Twenty-four were unruptured, and there were 25 for which the rupture status was not given. Fifty-six ectopic pregnancies were treated surgically and 11 were treated with methotrexate. The management was not documented in 7 cases. The patient who died received no treatment as she died on the way to the hospital.

Retained Products of Conception (RPOC) (Tables 1 and 2)

RPOC was the leading cause of morbidity. There were 977 confirmed cases of RPOC, including 2 molar pregnancies, and 1506 likely cases of RPOC (documentation was inadequate for confirmation). Of the 2146 total D&Cs, most were for RPOC, including 897 for confirmed RPOC, 1058 for bleeding or presumed RPOC, but no pathology was provided, and 2 for molar pregnancy. A small percentage of RPOC had medical treatment or no treatment.

Hemorrhage/Bleeding (Table 1)

There were 1639 bleeding events including one death. These included 466 Life-threatening and 642 Severe events. There were also 106 events coded as Moderate, while 424 reports of bleeding were Uncodable given the information in the database.

Ongoing Pregnancy (Table 1)

There were 452 ongoing pregnancies. Of these 102 chose to keep their baby, 148 chose termination, 1 miscarried, and 201 had an unknown outcome. Of those with an unknown outcome, there were 44 patients referred or scheduled for termination, who did not follow through (39 no-showed, 3 canceled, 2 did not schedule).

Surgeries (Table 2)

There were 2243 surgeries including 2146 D&Cs, 76 laparoscopies/laparotomies without hysterectomy, 7 hysterectomies, and 14 other surgeries. Of the hysterectomies, 3 were performed for sepsis, 2 for hemorrhage, 1 for a cervical ectopic, and 1 for placenta accreta. There were 1291 surgeries performed in the hospital or ER and 952 in an outpatient setting. Of the 2146 D&Cs, 1194 were performed in the hospital or ER, and 952 in an outpatient setting. Of the 2146 D&Cs, 1194 were provided by the Hospital or ER, 853 by the abortion provider, and 99 by another outpatient provider.

Transfusions (Table 2)

Four hundred and eighty-one patients required blood transfusion following medical abortions. Of these, 365 received 1 to 10 units packed red blood cells (PRBCs) alone, 1 received fresh frozen plasma (FFP) alone, 8 received a combination of PRBCs and FFP, and 107 received an unknown amount of blood product.

Relationship of Misoprostol Use to Hemorrhage (Table 3)

The use of mifepristone with misoprostol was associated with a higher incidence of hemorrhage than the use of mifepristone alone. Of the 3056 women who took both mifepristone and misoprostol, 1572 (51.44%) hemorrhaged, whereas, among the 58 women who did not take misoprostol, only 13 (22.41%) hemorrhaged. It was unclear whether 84 patients took misoprostol or not. Fifty-four (64.29%) of them hemorrhaged. The hemorrhage rate was higher for the mifepristone with misoprostol group as compared to the mifepristone alone group even if all the unknowns were assigned to the mifepristone alone group or vice versa.

Table 1 - Diagnoses[a]

Deaths	Deaths (n)	Deaths (%)	Deaths: % of (3197) Unique US AERs (%)	Organism (%)
Sepsis	9	45.00%	0.28%	
Sepsis confirmed	7	35.00%	0.22%	100%
Clostridium sordellii	*5*	*25.00%*	*0.16%*	*71.43%*
Clostridium perfringens / Peptostreptococcus	*1*	*5.00%*	*0.03%*	*14.29%*
Peptostreptococcus	*1*	*5.00%*	*0.03%*	*14.29%*
Sepsis Likely, Unknown Organism	2	10.00%	0.06%	
Visceral and Pulmonary Congestion consistent with ARDS / sepsis	1	5.00%	0.03%	
Fever / chills treated with cephalexin, found dead[b]	1	5.00%	0.03%	
Ruptured Ectopic Pregnancy	1	5.00%	0.03%	
Hemorrhage	1	5.00%	0.03%	
Possible Homicide	3	15.00%	0.09%	
Suicide	1	5.00%	0.03%	
Drug Toxicity/Overdose	4	20.00%	0.13%	
Unknown[c]	1	5.00%	0.03%	
Total Deaths	**20**	**100%**	**0.63%**	
Infections, Level of Severity	**Infections (n)**	**Infections (%)**	**Infections: % of (3197) Unique US AERs (%)**	
Death	9	1.79%	0.28%	
Life threatening infection/sepsis	39	7.77%	1.22%	
Severe infection (IV anitbiotics)	249	49.60%	7.79%	
Moderate infection (oral antibiotics)	132	26.29%	4.13%	
Uncodable[d]	73	14.54%	2.28%	
Total Infections	**502**	**100%**	**15.70%**	

Table 1 – Diagnoses (Continued)

Ectopic Pregnancies, Rupture Status	Ectopic Pregnancies (n)	Ectopic Pregnancies (%)	Ectopic Pregnancies: % of (3197) Unique US AERs (%)
Ruptured[e]	26	34.67%	0.81%
Unruptured[f]	24	32.00%	0.75%
Surgical Treatment	13	17.33%	0.41%
Methotrexate Treatment	11	14.67%	0.34%
Unknown Rupture Status[g]	25	33.33%	0.78%
Surgical Treatment	18	24.00%	0.56%
Unknown Treatment	7	9.33%	0.22%
Total Ectopic Pregnancies	**75**	**100%**	**2.35%**
Ectopic Pregnancies, Level of Severity	**Ectopic Pregnancies (n)**	**Ectopic Pregnancies (%)**	**Ectopic Pregnancies: % of (3197) Unique US AERs**
Death	1	1.33%	0.03%
Life Threatening (Ruptured, survived)	25	33.33%	0.78%
Severe (Not Ruptured)	24	32.00%	0.75%
Uncodable	25	33.33%	0.78%
Total Ectopic Pregnancies	**75**	**100%**	**2.35%**

Table 1 – Diagnoses (Continued)

Retained Products of Conception (RPOC)	RPOC (n)	RPOC (%)	RPOC: % of (3197) Unique US AERs (%)
RPOC confirmed	977	39.35%	30.56%
RPOC confirmed (by pathology or ultrasound); Had D&C	891	35.88%	27.87%
RPOC confirmed by U/S but D&C not documented	29	1.17%	0.91%
RPOC treated medically	27	1.09%	0.84%
Tissue at os (no D&C)[h]	27	1.09%	0.84%
Molar Pregnancy	2	0.08%	0.06%
No Treatment, RPOC on autopsy	1	0.04%	0.03%
RPOC Likely	1506	60.65%	47.11%
Had D&C, no pathology provided	1056	42.53%	33.03%
Unknown[i]	450	18.12%	14.08%
Total RPOCs	**2483**	**100%**	**77.67%**
Bleeding Events, Level of Severity	**Bleeding Events (n)**	**Bleeding Events (%)**	**Bleeding Events: % of (3197) Unique US AERs**
Death	1	0.06%	0.03%
Life threatening or Disabling: 2U or more transfusion or Hgb<7 or witnessed massive blood loss	466	28.43%	14.58%
Severe: surgical intervention and/or 1 U transfusion	642	39.17%	20.08%
Moderate: medical intervention	106	6.47%	3.32%
Uncodable[j]	424	25.87%	13.26%
Total Bleeding Events	**1639**	**100%**	**51.27%**

Table 1 – Diagnoses (Continued)

Ongoing Pregnancies, Outcome	Ongoing Pregnancies (n)	Ongoing Pregnancies	Ongoing Pregnancies: % of (3197) Unique US AERs (%)	Ongoing Pregnancies with Unknown Outcome (%)
Desired to Keep Pregnancy	102	22.57%	3.19%	
Kept Pregnancy	101	22.35%	3.16%	
Kept Pregnancy but baby died in-utero	1	0.22%	0.03%	
Terminated Pregnancy	148	32.74%	4.63%	
Surgical Termination[k]	139	30.75%	4.35%	
Medical Termination	9	1.99%	0.28%	
Unknown Intent, miscarried[l]	1	0.22%	0.03%	
Unknown Outcome	201	44.47%	6.29%	100%
Referred D&C but did not show	39	8.63%	1.22%	19.40%
Referred D&C but cancelled	3	0.66%	0.09%	1.49%
Told to schedule/referred D&C did not go	2	0.44%	0.06%	1.00%
Unknown outcome, no other information[m]	157	34.73%	4.91%	78.11%
Total	**452**	**100%**	**14.14%**	

[a] Because of rounding, percentages may not appear to add up exactly.
[b] FDA attributed to methadone overdose.
[c] 40 year old smoker died within hours of misoprostol ingestion. Per FDA, "natural causes due to severe pulmonary emphysema."
[d] Patients with documented infection but inadequate information to determine severity.
[e] One of the ruptured ectopics died on the way to the hospital. The other 25 were treated surgically.
[f] The unruptured ectopics include two cornual ectopics, one treated surgically and one treated medically.
[g] Includes two cervical ectopics, one treated with D&C/Hysterectomy/massive transfusion and one with unknown treatment.
[h] Either with path provided, or described as RPOC, placental fragments, fetus, or tissue.
[i] Suspected RPOC indicating D&C needed, but not documented as being done.
[j] Patients with documented bleeding but inadequate information to determine severity.
[k] Includes one hysterotomy for pregnancy in non-communicating horn.
[l] After no show for surgical termination.
[m] Includes 10 with known gestational age 20-29 weeks.

Table 2 – Treatment[a]

Type of Surgery	Type of surgery (n)	Type of surgery (%)	Surgery: % of (3197) Unique US AERs (%)
D&C[b]	**2146**	**95.68%**	**67.13%**
Hysterectomy	**7**	**0.31%**	**0.22%**
Sepsis (includes 2 deaths)	3	0.13%	0.09%
Hemorrhage after uterine perforation	2	0.09%	0.06%
Hemorrhage - Cervical Ectopic	1	0.04%	0.03%
Placenta accreta	1	0.04%	0.03%
Laparoscopy/Laparotomy without hysterectomy	**76**	**3.39%**	**2.38%**
Ectopic (Actual or Suspected)	66	2.94%	2.06%
Infection	7	0.31%	0.22%
Uterine Perforation	1	0.04%	0.03%
Salpingo oophorectomy for Torsion	1	0.04%	0.03%
Hysterotomy for pregnancy in non-communicating horn	1	0.04%	0.03%
Other Surgeries	**14**	**0.62%**	**0.44%**
Uterine Artery Embolization	1	0.04%	0.03%
Vaginal sutures (after 15 week surgical termination for ongoing pregnancy)	1	0.04%	0.03%
Paracenteses (multiple, same patient, death)	1	0.04%	0.03%
Necrotozing fasciitis debridement and below knee amputation	1	0.04%	0.03%
Upper and lower endoscopy for bright red bleeding	1	0.04%	0.03%
Unknown surgery for deep venous thrombosis	1	0.04%	0.03%
Angioplasty	1	0.04%	0.03%
Cholecystectomy	2	0.09%	0.06%
Appendectomy	1	0.04%	0.03%
Laceration repair (scalp, chin)	2	0.09%	0.06%
Unknown Surgery	2	0.09%	0.06%
Total	**2243**	**100%**	**70.16%**

Table 2 – Treatment (Continued)

Location of Surgery	Location of Surgery (n)	Location of Surgery (%)
All Surgeries	**2243**	**100.00%**
Hospital or ER	1291	57.56%
Outpatient	952	42.44%
D&C	**2146**	**100.00%**
Hospital or ER	1194	55.64%
Outpatient	952	44.36%
Surgical Provider for D&C	**Surgical Provider (n)**	**Surgical Provider (%)**
Hospital/ER	1194	55.64%
Abortion Provider	853	39.75%
Other Provider	99	4.61%
Total	**2146**	**100%**
Indication for D&Cs	**Indication for D&C (n)**	**Indication for D&C (%)**
Confirmed D&C[c]	**2146**	**100%**
RPOC (confirmed by pathology or ultrasound)	897	41.80%
RPOC/Bleeding (no pathology provided)	1058	49.30%
Ongoing pregnancy, surgical termination by D&C	139	6.48%
RPOC ruled out	34	1.58%
Ectopic evaluation	12	0.56%
Molar pregnancy	2	0.09%
Not able to take misoprostol	4	0.19%
Possible D&C	**680**	
Possible RPOC, unknown treatment, possible D&C	450	
RPOC confirmed by U/S but D&C not documented	29	
Ongoing pregnancy Unknown outcome, possible D&C	201	
TOTAL (Confirmed and Possible)	**2826**	

Table 2 – Treatment (Continued)

Transfusions	Transfusions (n)	Transfusions (%)	Transfusion: % of (3197) Unique US AERs (%)
PRBC alone	**365**	**75.88%**	**11.42%**
1U	32	6.65%	1.00%
1-2U	1	0.21%	0.03%
2U	246	51.14%	7.69%
2.5U	1	0.21%	0.03%
3U	45	9.36%	1.41%
4U	27	5.61%	0.84%
5U	5	1.04%	0.16%
6U	5	1.04%	0.16%
7U	2	0.42%	0.06%
10U	1	0.21%	0.03%
Other Blood products	**9**	**1.87%**	**0.28%**
1 U FFP	1	0.21%	0.03%
2 U PRBC/1 U FFP	1	0.21%	0.03%
2 U PRBC/ 4 U FFP	1	0.21%	0.03%
3 U PRBC/ 1 U FFP	1	0.21%	0.03%
4 U PRBC/ 1 U FFP	1	0.21%	0.03%
4 U PRBC/ 2 U FFP	1	0.21%	0.03%
5 U PRBC/ 4 U FFP	1	0.21%	0.03%
6 U PRBC/ 2 U FFP	1	0.21%	0.03%
7 U PRBC/ FFP and Platelets unknown amount	1	0.21%	0.03%
Unknown amount (documented as given, units not recorded)	**107**	**22.25%**	**3.35%**
Total[d]	**481**	**100%**	**15.05%**

[a] Because of rounding, percentages may not appear to add up exactly.
[b] With or without suction, one with hysteroscopy.
[c] There were 8 patients who had 2 D&Cs and one who required uterine artery embolization. There were 4 perforations: two had resultant hysterectomies, one had a laparoscopy, and one received 2 U PRBCs but no documented surgery.
[d] Additionally there were 7 patients who likely received transfusion, but was not recorded, 3 patients who refused transfusion, and 1 patient for whom transfusion was considered but not given.

Table 3 – Relationship of Misoprostol to Hemorrhage[a]

	Mifepristone + Misoprostol		Mifepristone alone		Unknown		Mifepristone + Misoprostol + unknown [b]		Mifepristone alone + unknown [c]	
	n	%	n	%	n	%	n	%	n	%
No Hemorrhage	**1484**	**48.56%**	**45**	**77.59%**	**30**	**35.71%**	**1514**	**48.23%**	**75**	**52.82%**
Hemorrhage	**1572**	**51.44%**	**13**	**22.41%**	**54**	**64.29%**	**1625**	**51.77%**	**67**	**47.18%**
Death	1	0.03%	0	0.00%	0	0.00%	1	0.03%	0	0.00%
Life threatening	441	14.43%	5	8.62%	20	23.81%	461	14.69%	25	17.61%
Severe	633	20.71%	3	5.17%	6	7.14%	639	20.36%	9	6.34%
Moderate	101	3.30%	1	1.72%	4	4.76%	105	3.35%	5	3.52%
Uncodable	396	12.96%	4	6.90%	24	28.57%	420	13.38%	28	19.72%
Total US AERs	**3056**	**100%**	**58**	**100%**	**84**	**100%**	**3139**	**100%**	**142**	**100%**

[a] Because of rounding, percentages may not appear to add up exactly.
[b] Assumes all unknowns took both mifepristone and misoprostol.
[c] Assumes all unknowns took mifepristone, but not misoprostol.

Discussion

This article is critically important considering the paucity of published literature on mifepristone safety and the minimal analysis done on the AERs by the FDA.

Ectopic Pregnancies

Although reported as AEs, ectopic pregnancies are not a direct adverse event from the medication, but rather a contraindication to its administration. They were reported as adverse events because the ectopic pregnancies were missed.

The American College of Obstetricians and Gynecologists (ACOG) notes that "According to the Centers for Disease Control and Prevention, ectopic pregnancy accounts for approximately 2% of all reported pregnancies. However, the true current incidence of ectopic pregnancy is difficult to estimate because many patients are treated in an outpatient setting where events are not tracked, and national surveillance data on ectopic pregnancy have not been updated since 1992. Despite improvements in diagnosis and management, ruptured ectopic pregnancy continues to be a significant cause of pregnancy-related mortality and morbidity. In 2011–2013, ruptured ectopic pregnancy accounted for 2.7% of all pregnancy-related deaths and was the leading cause of hemorrhage-related mortality."[36]

[36] ACOG Practice Bulletin No. 193: Tubal Ectopic Pregnancy, Obstet Gynecol: March 2018; 131(3): e91-e103. doi:10.1097/AOG.0000000000002560

Confirmed/suspected ectopic pregnancy and undiagnosed adnexal mass are contraindications to mifepristone use under current prescribing requirements. The label warnings state: "Ectopic pregnancy: exclude before treatment." [37] Unfortunately, it is difficult to rule out ectopic pregnancy by history alone because, "half of all women who receive a diagnosis of an ectopic pregnancy do not have any known risk factors."[38] According to ACOG Practice Bulletin No. 193, "The minimum diagnostic evaluation of a suspected ectopic pregnancy is a transvaginal ultrasound evaluation and confirmation of pregnancy." Of the 75 reported ectopic pregnancies in the FDA AERs we analyzed, over a third were known to be ruptured including one death. Clearly, an ultrasound should be required prior to the administration of mifepristone to document that the pregnancy is located within the uterus. Although not 100% effective, this will screen for ectopic pregnancy, confirm gestational age, which can be inaccurate based on menstrual history alone,[39] and screen for adnexal masses, another contraindication to mifepristone use.[40]

Ongoing pregnancies

Of the women with an ongoing pregnancy, less than a third were known to have proceeded with termination of the pregnancy, and almost a quarter were known to have kept their pregnancy; in almost half, the outcome was unknown. The significant percentage of women with ongoing pregnancy who changed their mind and chose to keep their pregnancy, after initially choosing termination, raises concerns regarding the pre-abortion counseling and informed consent they received. Women undergoing abortion should receive the same quality of informed consent and pre-procedural counseling that is standard of care prior to other medical treatment or surgery. It is imperative that women considering abortion be provided adequate and complete information and counseling on risks, advantages, disadvantages, and alternative options.

Additionally, the high percentage of women with ongoing pregnancies for whom there is no follow up or known outcome is concerning. As health care providers we are to continue to care for our patients and manage any complications, yet in the AERs we reviewed this was not typically the case for the abortion provider. Furthermore, a federal registry of known outcomes and birth defects is imperative. One of the initial FDA post-marketing requirements for

[37] MIFEPREX. Package insert. Danco; 2016. Approved March 2016. p. 1. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf

[38] ACOG Practice Bulletin No. 193: Tubal Ectopic Pregnancy, Obstet Gynecol: March 2018; 131(3): e91-e103. doi: 10.1097/AOG.0000000000002560

[39] Shipp, Thomas D. 2020. Overview of ultrasound examination in obstetrics and gynecology. Lit Rev current through Dec 2020. UpToDate. Edited by Barss A Vanessa. Wolters Kluwer. June 10, 2020. Accessed January 11, 2021. https://www.uptodate.com/contents/ectopic-pregnancy-clinical-manifestations-and-diagnosis/print?source=history_widget.

[40] MIFEPREX. Package insert. Danco; 2016. Approved March 2016. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf

Danco was a surveillance study of outcomes of ongoing pregnancies.[41] The FDA released them from this post-marketing commitment in January 2008 because Danco reported that only one or two ongoing pregnancies per year were followed for final outcomes in part because of consent requirements.[42] This is disturbing in light of the percentage of women in our analysis who kept their pregnancies, as well as those with ongoing pregnancy and unknown outcomes, all of whom could have been followed for final outcomes. The significant lack of follow-up of ongoing pregnancies (44.47% with unknown outcomes) and the very minimal information on those who chose to keep the pregnancy, highlights the need for a national registry especially considering the teratogenicity of misoprostol.[43]

Relationship of Misoprostol to Hemorrhage

The Creinin study of abortion pill reversal was stopped for safety concerns due to hemorrhage in 3 of the 12 study participants.[44] One of the conclusions of that study was that "Patients who use mifepristone for a medical abortion should be advised that not using misoprostol could result in severe hemorrhage, even with progesterone treatment."[45] The authors hypothesized that the absence of misoprostol caused these women to hemorrhage. The women who had documented use of misoprostol in our database hemorrhaged at a higher rate than those documented not to have taken misoprostol.

Reporting of Adverse Events

Although not the initial goal of this study, the analysis of the AERs revealed glaring deficiencies in the AE reporting system making it difficult to properly evaluate adverse events. When mifepristone was approved in 2000, FDA required that providers "must report any hospitalization, transfusion or other serious event to Danco Laboratories."[46] This created an inherent conflict of interest as it is not in the best interest of the entities or providers to report adverse events to those regulating them. Because only severe events were reportable, this requirement likely resulted in an underestimation of moderate and mild AEs. It

[41] Center for Drug Evaluation and Research. NDA 20-687. Approval Letter for MIFEPREX (mifepristone) Tablets, 200 mg to Population Council. Food and Drug Administration. Written September 28, 2000. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20687appltr.htm

[42] 2016 03 20 FDA resp to Cit Pet.pdf. Docket No. FDA-2002-P-0364. FDA. March 29, 2016. p. 31. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/2016%2003%2020%20%20FDA%20resp%20to%20Cit%20Pet.pdf

[43] Cytotec (misoprostol tablets). Package insert. G.D. Searle; Revised November 2012. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019268s047lbl.pdf

[44] Creinin MD, Hou MY, Dalton L, Steward R, Chen MJ. Mifepristone Antagonization With Progesterone to Prevent Medical Abortion: A Randomized Controlled Trial. Obstet Gynecol. 2020;135(1):158-165. doi:10.1097/AOG.0000000000003620

[45] Creinin MD, Hou MY, Dalton L, Steward R, Chen MJ. Mifepristone Antagonization With Progesterone to Prevent Medical Abortion: A Randomized Controlled Trial. Obstet Gynecol. 2020;135(1):5. doi:10.1097/AOG.0000000000003620

[46] M I F E P R E X™(Mifepristone) Tablets, 200 mg Prescriber's agreement. Food and Drug Administration. September 28, 2000, 1-2. Accessed November 16, 2020. http://wayback.archive-it.org/7993/20170113112742/http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111364.pdf

is also likely that some of the AEs that we coded as Mild or Moderate were actually Severe but there was not enough information in the AER for us to justify coding them as Severe. In March 2016, the FDA substantially reduced the prescribing requirements and changed the drug protocol [47] and yet at the same time eliminated reporting requirements except for deaths.[48] With the relaxation of reporting requirements, the ability to perform any relevant post-marketing evaluation of mifepristone was lost. It is imperative for the safety of women that the FDA restore and strengthen the 2011 REMS requirements.

The information in the AERs is almost exclusively obtained from abortion providers, rather than the physician treating the complication, yet in this analysis, abortion providers managed only 39.75% of surgical complications (a number which is likely much lower since these are only the cases which are known to the abortion provider). Throughout the reports, there was also a lack of detail and many patients who were simply "lost to follow-up." This resulted in 16.80% of the AERs being Uncodable as to severity and likely under-coding of many AERs and AEs, as coding could only be assigned based on the scant information provided. Many of the AEs experienced by women were unknown to the abortion provider until the follow-up examination, which is troubling considering the poor follow-up rate and elimination of the requirement for an in-office follow up visit. Some of the patient deaths were not known to the abortion provider until they saw the death in an obituary or were contacted by an outside source. Because of this, in addition to abortion providers, hospitals, emergency departments, and private practitioners should be required to report AEs.

Complications occur in the best of hands in all areas of medicine, but as physicians, we are responsible to manage those complications and follow our patients through to resolution. The findings that: 1. the most common outcome of ongoing pregnancy was unknown outcome, 2. abortion providers performed less than half the D&Cs done for complications, and 3. a third of ectopic pregnancies (missed prior to administering the abortifacient) had unknown rupture status, leave us deeply concerned regarding the care these women received. A post-marketing requirement was that there be a "cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention."[49] The applicant was released from this requirement because they stated that because there were so few providers

[47] GAO-18-292 Revised Mifeprex Labeling: Food and Drug Administration Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts. Report to Congressional Requesters. Food and Drug Administration. 2018. p. 7. Published March 2018. Accessed November 13, 2020. https://www.gao.gov/assets/700/690914.pdf

[48] NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg: Risk Evaluation and Mitigation Strategy (REMS). Food and Drug Administration. 2016. p. 3, 6. Reference ID: 3909592. Published March 29, 2016. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf

[49] Center for Drug Evaluation and Research. NDA 20-687. Approval Letter for MIFEPREX (mifepristone) Tablets, 200 mg to Population Council. Food and Drug Administration. Written September 28, 2000. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20687appltr.htm

without surgical intervention skills, no meaningful study could be done.[50] Yet, that same year the FDA changed the provider agreement to allow non-physicians to become prescribers.[51] These findings highlight the importance of follow-up and management of complications by the abortion provider. Allowing any further relaxation of mifepristone prescribing requirements will put women at an even higher risk of adverse events

Limitations and Strengths

It was not possible to calculate complication rates for mifepristone and misoprostol abortions based on AER data because there is no denominator for how many mifepristone abortions are performed in the U.S. since reporting is often voluntary and sporadic. For clarity, we specified the denominators we used.

Our analysis was limited by the fact that the number of AEs for which we received reports is likely a gross underestimation of the actual number of AEs that occurred. In our analysis, the surgical management of over half the complications was performed by someone other than the abortion provider, yet treating physicians are not required to report complications. Few reports were generated by those in Emergency Departments and hospitals who treated the complications.

Our analysis was also limited by the lack of information in the AERs, including redaction of critical dates, a paucity of diagnosis and treatment information, and lack of follow up.

Our study has several strengths. Our data comes from information provided to the FDA and is the largest analysis of AERs for mifepristone abortions. This data is publicly available under the Freedom of Information Act so that anyone can verify the data for themselves. This analysis reviews all AERs not reported in the first study by Gary.[52] Although heavily redacted, there was sufficient information in over 80% of the AERs to evaluate severity. An objective standardized system, CTCAEv3, was used to code for severity, and each AER was coded by at least two board-certified obstetrician-gynecologists or family medicine physicians.

Conclusions and Relevance

This article is important because it augments the scant published literature on mifepristone safety.

Due to the lack of adequate reporting of adverse events, especially by those treating them, these unique AERs represent a fraction of the actual adverse events occurring in American women.

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[50] 2016 03 20 FDA resp to Cit Pet.pdf. Docket No. FDA-2002-P-0364. FDA. March 29, 2016. p. 31. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/2016%2003%2020%20%20FDA%20resp%20to%20Cit%20Pet.pdf

[51] GAO-18-292 Revised Mifeprex Labeling: Food and Drug Administration Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts. Report to Congressional Requesters. Food and Drug Administration. 2018. p. 7. Published March 2018. Accessed November 13, 2020. https://www.gao.gov/assets/700/690914.pdf

[52] Gary M, Harrison D. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. Ann Pharmacother. 2006 Feb 40(2):191-7. https://doi.org/10.1345/aph.1G481

Significant morbidity and mortality have occurred with the use of mifepristone as an abortifacient, including at least 24 US deaths reported by the FDA from September 2000 to December 2018. Because of this and the significant morbidity associated with this drug, the FDA should consider at a minimum reinstating the original 2011 REMS and strengthening the reporting requirements. The reporting of transfusions, hospitalizations, and other serious adverse events are essential.

Given the morbidity and mortality of undiagnosed ectopic pregnancy, a clear contraindication to the use of mifepristone, an ultrasound to confirm pregnancy location is essential before mifepristone is dispensed.

Considering the significant percentage of women with ongoing pregnancies who chose to continue their pregnancy, there must be reasonable waiting periods, parental involvement, and adequate pre-abortion counseling on all pregnancy options. It is also critical that a pregnancy registry be established.

In our analysis, the patients who used mifepristone alone had a lower rate of hemorrhage than those using mifepristone followed by misoprostol.

The FDA Adverse Event Reporting System is woefully inadequate to determine the post-marketing safety of mifepristone due to its inability to adequately assess the frequency or severity of adverse events. The reliance solely on interested parties to report, the large percentage of uncodable events, the redaction of critical clinical information unrelated to personally identifiable information, and the inadequacy of the reports highlight the need to overhaul the current AER System.

This analysis evaluated 3197 adverse events resulting from the use of mifepristone as an abortifacient and brought to light serious concerns about the safety requirements and care of women undergoing mifepristone abortion. Although complications may occur in the best of hands, and no medical procedure is without risks, safety measures must be employed to minimize these adverse outcomes. Women undergoing abortion should receive the same quality of informed consent and pre-procedural counseling that is standard of care prior to other medical treatment or surgery. It is imperative that women considering abortion be provided adequate and complete information and counseling on risks, advantages, disadvantages, and alternative options. Although there may be disagreements about the ethics of abortion, there must be total agreement that our patients—whether undergoing a medical abortion or otherwise—deserve the highest standard of medical care.

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