TABLE OF APPENDIX

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

TO: FILE

FROM: (b) (6) (b) (6) Digitally signed by (b) (6) Date: 2022.12.23 13:11:43 -05'00'

DATE: December 23, 2022

SUBJECT: Review of Supplemental Drug Applications Proposing Modifications to the Mifepristone REMS Program

FDA is currently reviewing a supplemental new drug application from Danco Laboratories, LLC (Danco) and a supplemental abbreviated new drug application from GenBioPro, Inc. (GBP) that propose to modify the Mifepristone Risk Evaluation and Mitigation Strategy (REMS) Program as approved under Danco's new drug application for Mifeprex (mifepristone) (NDA 020867) and GBP's abbreviated new drug application for Mifepristone Tablets 200 mg (ANDA 091178). Citing the Comstock Act, 18 U.S.C. §§ 1461, 1462, Plaintiffs in *Alliance for Hippocratic Medicine v. U.S. Food and Drug Administration*, No. 2:22-cv-00223-Z (N.D. Tex.), have alleged that FDA's actions regarding mifepristone do not comply with "federal laws that expressly prohibit the mailing or delivery by any letter carrier, express company, or other common carrier of any substance or drug intended for producing abortion" and also that FDA "failed to acknowledge and address" those laws. Complaint ¶¶ 22, 392 (Nov. 18, 2022). This memorandum notes that the Office of Legal Counsel of the United States Department of Justice, which provides controlling advice to Executive Branch officials on questions of law, has concluded that the Comstock Act provisions cited by Plaintiffs "[do] not prohibit the mailing of mifepristone or misoprostol where the sender lacks the intent that the recipient will use them unlawfully. And in light of the many lawful uses of mifepristone and misoprostol, the fact that these drugs are being mailed to a jurisdiction that significantly restricts abortion is not a sufficient basis for concluding that the mailing violates [these provisions]." Memorandum for Thomas J. Marshall, General Counsel, United States Postal Service, from Christopher H. Schroeder, Assistant Attorney General, Office of Legal Counsel, *Re: Application of the Comstock Act to the Mailing of Prescription Drugs That Can Be Used for Abortions*, at 15 (December 23, 2022).[1] Thus, even if the Comstock Act provisions bear on FDA's analysis of the pending supplemental drug applications, in light of the conclusions set forth by the Office of Legal Counsel, they pose no issue for FDA's approval of the applications.

[1] The Office of Legal Counsel's analysis applies to 18 U.S.C. § 1461 and § 1462. *See id.* at 1 n.3.

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

ALLIANCE FOR HIPPOCRATIC MEDICINE, on behalf of itself, its member organizations, their members, and these members' patients, et al., Plaintiffs, v. **U.S. FOOD AND DRUG ADMINISTRATION**, et al., Defendants.	**Case No. 2:22-cv-00223-Z**

DECLARATION OF DR. DONNA HARRISON

I, Donna Harrison, a citizen of the United States of America and a resident of Berrien Center, Michigan, declare under penalty of perjury under 28 U.S.C. § 1746 that the following is true and correct to the best of my knowledge.

1. I am over eighteen years old and make this declaration on personal knowledge.
2. I am a board-certified obstetrician and gynecologist.
3. I received my medical degree from the University of Michigan and completed my residency at a University of Michigan affiliate hospital, St. Joseph Mercy Hospital.
4. I am a diplomate of the American Board of Obstetrics and Gynecology.
5. I serve as the Chief Executive Officer of Plaintiff American Association of Pro-Life Obstetricians and Gynecologists (AAPLOG).

6. I also serve as the Chair of the Board of Plaintiff Alliance for Hippocratic Medicine (AHM).

7. I am familiar with AAPLOG, its members, their fields of practice, and AAPLOG's policies and positions, including as set forth in the complaint, which I have reviewed.

8. AAPLOG is the largest organization of pro-life obstetricians and gynecologists ("OB/Gyns") in the world and is headquartered in Fort Wayne, Indiana. AAPLOG membership includes more than 6,000 medical professionals nationwide and more than 300 members in Texas. AAPLOG members practice in accordance with the Hippocratic oath, which forbids physician participation in killing their preborn patients in elective abortion. AAPLOG members are committed to the care and well-being of both of their patients including both pregnant women and the human beings in their womb. AAPLOG members are concerned about the serious adverse impacts of chemical abortion on both of their patients as well as on the practice of medicine.

9. I am also familiar with AHM, its members, their members' fields of practice, and AHM's policies and positions, including as set forth in the complaint, which I have reviewed.

10. AHM is a nonprofit organization that upholds and promotes the fundamental principles of Hippocratic medicine, which includes a prohibition on physician

involvement in killing their patients. AHM is incorporated in the State of Texas and has its registered agent in Amarillo, Texas.

11. AHM's members include the American Association of Pro-Life Obstetricians and Gynecologists, American College of Pediatricians, Catholic Medical Association, Christian Medical and Dental Associations, and Coptic Medical Association of North America. In opposing chemical abortion, AHM's members are concerned about the safety and well-being of pregnant women and girls, their preborn children, and chemical abortion's adverse impacts on the practice of medicine.

12. Through my work at AAPLOG and now AHM, I reviewed the studies on which the FDA has relied to make its 2016 Major Changes. The FDA identified these studies in its Summary Review document. App. 624–52.

13. The 2016 Summary Review "serves as the Division's decisional memorandum." *Id.* 628. The FDA noted that "[a]s these major changes are interrelated, in some cases data from a given study were relied on to provide evidence to support multiple changes." *Id.* 630.

14. As stated in Plaintiffs Complaint, App. 055–56, and Brief in Support of the Motion for Preliminary Injunction, p. 19, *none* of the studies on which the FDA relied were designed to evaluate the safety and effectiveness of chemical abortion drugs for use under the conditions prescribed, recommended, or suggested in the proposed labeling.

15. Not only did the FDA rely on studies that evaluated a drug regimen that did not match the labeling in the 2016 Major Changes, but the agency also took a piecemeal approach to evaluating the safety and effectiveness of its removal of necessary safeguards. App. 055–56. Safety must be evaluated under the totality of the proposed conditions of use, not each change in isolation of the other conditions. None of the cited studies actually mirrored the totality of changes in conditions of use allowed by the FDA 2016 Major Changes. Thus, none of the cited studies provides meaningful safety data to support the sweeping changes FDA made in 2016.

16. In Column A of the chart below, I have identified the studies that the FDA cited in its Summary Review. Column B identifies the major changes in the 2016 regimen for which FDA cited that study as support. Column C shows the conditions of use in the study that significantly differ from the conditions of use allowed in the approved 2016 label. Thus, Column C demonstrates why the particular cited study fails to show the safety of chemical abortion drugs for use under the conditions prescribed, recommended, or suggested in the proposed labeling of the 2016 Major Changes.

Study	FDA cited the study in support of the following Major Change(s)	Aspects of the study which significantly deviate from the conditions of use allowed by the 2016 Major Changes, rendering the citation invalid for showing safety under the 2016 label changes
Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectiveness and acceptability of medical abortion provided through telemedicine. Obstet Gynecol 2011;118:296-303.	• Decrease mifepristone dose from 600 to 200 mg, followed by misoprostol at a dose increased from 400 mcg to 800 mcg, administered buccally instead of orally • Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex • Follow-up, although still needed, not restricted to in clinic at 14 days after Mifeprex	• All patients had their gestational age confirmed by an ultrasound, which ruled out ectopic pregnancy and determined the exact gestational age. • All patients had witnessed ingestion of mifepristone but unknown time interval between mifepristone ingestion and misoprostol ingestion. • All patients had an in-person follow-up visit at 2 weeks after taking mifepristone, and an ultrasound was performed to ensure completion of the abortion. • The study was limited to 63 days' gestation or less.

Goldstone P, Michelson J, Williamson E. Early medical abortion using low-dose mifepristone followed by buccal misoprostol: A large Australian observational study. Med J Austral 2012; 197: 282-6.	• Decrease mifepristone dose from 600 to 200 mg, followed by misoprostol at a dose increased from 400 mcg to 800 mcg, administered buccally instead of orally	• Retrospective chart review study conducted in Australia. • All patients had gestational age and pregnancy location confirmed by ultrasound. • All patients had witnessed ingestion of mifepristone but unknown time interval between mifepristone ingestion and misoprostol ingestion. • 85% of patients who completed the study had in-person follow-up exam with ultrasound to confirm completion of abortion. • The study was limited to 63 days' gestation or less. • All women who were Rh negative received Rhogam. • Women at high risk of infection received prophylactic antibiotics.
Upadhyay UD, Desai S, Lidar V, Waits TA, Grossman D, Anderson P, Taylor D. Incidence of emergency department visits and complications after abortion. Obstet Gynecol 2015;125(1):175-183. 21	• Decrease mifepristone dose from 600 to 200 mg, followed by misoprostol at a dose increased from 400 mcg to 800 mcg, administered buccally instead of orally	• Retrospective study reviewed Medicaid diagnosis codes for complications treated in the ER after abortion, but study failed to provide the conditions to determine applicability to proposed labeling. • The study was limited 63 days' gestation or less.

Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. Obstet Gynecol 2008;112(6):1303-1310.	• Decrease mifepristone dose from 600 to 200 mg, followed by misoprostol at a dose increased from 400 mcg to 800 mcg, administered buccally instead of orally • Addition that a repeat 800 mcg buccal dose of misoprostol may be used if needed • Increase the maximum gestational age from 49 days to 70 days	• Women required to be at least 18 years old. • Ultrasound performed to confirm gestational age of 57-70 days. • All patients had access to emergency transportation and a telephone. • Some patients were given antibiotics while others were not. • All patients had in person follow-up exam at the facility 7-14 days after mifepristone and had ultrasound to check for retained tissue.
Middleton T, et al. Randomized trial of mifepristone and buccal or vaginal misoprostol for abortion through 56 days of last menstrual period. Contraception 2005; 72: 328-32	• Decrease mifepristone dose from 600 to 200 mg, followed by misoprostol at a dose increased from 400 mcg to 800 mcg, administered buccally instead of orally	• All women had ultrasound to determine gestational age. • The study was limited to 56 days' gestation or less. • Women required to be at least 18 years old, or at least 16 years old with one parent's consent. • All women had observed ingestion of mifepristone in person. • All women who were Rh negative received Rhogam. • All women returned for an in-person follow-up exam before 15 days, which included an ultrasound to evaluation retained tissue.

Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273	• Decrease mifepristone dose from 600 to 200 mg, followed by misoprostol at a dose increased from 400 mcg to 800 mcg, administered buccally instead of orally • Removal of the instruction that administration of misoprostol must be done in clinic, to allow for administration at home or other location convenient for the woman • Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex • Increase in the maximum gestational age from 49 days to 70 days	• All patients had an ultrasound to determine gestational age. • All patients ingested mifepristone in the clinic. • All patients returned for in-person follow up visit at 10-14 days after taking mifepristone. • All patients received prophylactic antibiotics.
Raymond EG & Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. Obstet Gynecol 2012; 119: 215-9	• Removal of the instruction that administration of misoprostol must be done in clinic, to allow for administration at home or other location convenient for the woman	• This study has nothing whatsoever to do with misoprostol administration.

Raymond EG, et. al. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. Contraception 2013; 87(1): 26-37.	• Removal of the instruction that administration of misoprostol must be done in clinic, to allow for administration at home or other location convenient for the woman • Follow-up, although still needed, not restricted to in clinic at 14 days after Mifeprex • Increase in the maximum gestational age from 49 days to 70 days	• This is not a clinical trial but rather a re-analysis of different studies under different non-comparable conditions at multiple locations around the world. • Of the 87 trials reviewed, only 19 were performed in the United States. • Of those 19 trials, 11 studied vaginal misoprostol exclusively. Of the remaining trials, only four studies analyzed buccal misoprostol. In one study the buccal misoprostol was administered simultaneously with mifepristone. • Gestational age determined by ultrasound or clinical examination. • Half of trial groups required ultrasound to assess failure. • The study limited to 63 days' gestation or less.
Ireland LD, Gatter M, Chen AY. Medical compared with surgical abortion for effective pregnancy termination in the first trimester. Obstet Gynecol 2015;126:22-8.	• Removal of the instruction that administration of misoprostol must be done in clinic, to allow for administration at home or other location convenient for the woman • Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex	• All patients had an ultrasound to determine gestational age. • Patients given mifepristone in the clinic at time of visit. • All patients had one week follow-up exam with ultrasonography. • The study limited to 63 days' gestation or less.

Wedisinghe L and Elsandabesee D. Flexible mifepristone and misoprostol administration interval for first-trimester medical termination. Contraception 2010; 81(4): 269-74. doi: 10.1016/ j.contraception.2009.09. 007. Epub Oct 29, 2009.	• Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex	• This is not a clinical trial but rather a review of other studies. Five studies were reviewed. None of the 5 studies looked at buccal misoprostol. • Studies included in-person follow-up office visit with ultrasound after taking drugs.
Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. MOD Study Trial Group: A randomized comparison of misoprostol 6-8 hours versus 24 hours after mifepristone for abortion. Obstet Gynecol 2004; 103: 851-859	• Administration of misoprostol at 24-48 hours instead of 48 hours after mifepristone • Addition that an 800 mcg buccal dose of misoprostol may be used if needed.	• This study examined vaginal administration of misoprostol, not buccal administration. • All women had an ultrasound to determine gestational age. • All women had in-person evaluations to rule out contraindications including labs for anemia and Rh type. • All women who were Rh negative received Rhogam. • Patients returned for two in-person follow-up visits (7 days and 14 days) where an ultrasound was performed at each visit.

Shaw KA, Topp NJ, Shaw JG, Blumenthal PB. Mifepristone-misoprostol dosing interval and effect on induction abortion times. Obstet Gynecol 2013;121(6):1335-1347	• Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex	• This is not a clinical trial but rather a review of other studies. • All of the studies reviewed used mifepristone and misoprostol for gestational ages between 12 and 20 weeks. • Most studies in this review were not conducted in United States. • Studies included buccal, vaginal, and oral routes of administration.
Phelps RH, et al. Mifepristone abortion in minors. Contraception 2001;64:339-343.	• Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex	• Pilot study included only 28 girls (ages 14-17 years old). • Study examined vaginal, not buccal, administration of misoprostol. • All girls had an in-person examination including ultrasound to determine gestational age. • The study was limited to 56 days or less gestation. • All were checked for anemia and Rh type. • If Rh- then patient received Rhogam. • Almost 1/3 of the girls had in-person administration of vaginal misoprostol with a 4-hour observation period after. • Girls needed to live within 1 hour of research site.

Niinimaki M, et. al. Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study. BJM 2011; 342: d2111.	• Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex	• Data from Finnish national database for abortions in Finland.
Ngoc NTN, et al. Acceptability and feasibility of phone follow-up after early medical abortion in Vietnam: A randomized controlled trial. Obstet Gynecol 2014;123:88-95.	• Follow-up, although still needed, not restricted to in clinic at 14 days after Mifeprex	• Study conducted in Vietnam. • Patients screened at in-person first visit. • The study was limited to 63 days' gestation or less. • Standard care compared with phone follow up only. Standard care entailed 2-week follow up in person with exam and ultrasound. Women with phone follow-up had to complete a semiquantitative urine pregnancy test and if the urine hCG dropped by one interval, the abortion was considered "a success."
Cameron ST, Glasier A, Johnstone A, Dewart H, Campbell A. Can women determine the success of early medical termination of pregnancy themselves? Contraception 2015;91:6-11.	• Follow-up, although still needed, not restricted to in clinic at 14 days after Mifeprex	• Gestational age determined by ultrasound • Data collected from Scotland. • The regimen used vaginal, not buccal, administration.

Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. Obstet Gynecol 2012; 120: 1070-6	• Increase in the maximum gestational age from 49 days to 70 days • Addition that a repeat 800 mcg buccal dose of misoprostol may be used if needed	• Gestational age confirmed by ultrasound. • Women were at least 18 years old. • Study required in-person follow-up visit with ultrasound. • Providers intervened surgically if necessary or at woman's request.
Boersma AA, Meyboom-de Jong B, Kleiverda G. Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of amenorrhoea in a general practice in Curacao. Eur J Contracept Reprod Health Care 2011; 16: 61-6	• Increase in the maximum gestational age from 49 days to 70 days • Addition that a repeat 800 mcg buccal dose of misoprostol may be used if needed	• Gestational age confirmed by ultrasound. • Study conducted in Curacao.
Sanhueza Smith P, Pena M, Dzuba IG, et al. Safety, efficacy and acceptability of outpatient mifepristone-misoprostol medical abortion through 70 days since last menstrual period in public sector facilities in Mexico City. Reprod Health Matters 2015; 22: 75-82	• Increase in the maximum gestational age from 49 days to 70 days	• Study performed in Mexico. • Women had initial in person visit where they swallowed mifepristone in the clinic.

Olavarrieta CD, Ganatra B, Sorhaindo A, Karver TS, Seuc A, Villalobos A, Garcia SG, Pérez M, Bousieguez M, Sanhueza P. Nurse versus physician-provision of early medical abortion in Mexico: a randomized controlled non-inferiority trial. Bull World Health Organ 2015; 93: 249-258	• Increase in the maximum gestational age from 49 days to 70 days	• Study performed in Mexico. • All participants received in-person examination and ultrasound at first visit to determine gestational age and rule out ectopic pregnancy and other contraindications. • All participants had an in-person follow-up visit at 7-14 days with ultrasound to confirm complete passage of tissue.
Chen MJ, Creinin MD. Mifepristone with Buccal Misoprostol for Medical Abortion Obstet Gynecol: a Systematic Review. Obstet Gynecol 2015; 126(1): 12-21	• Increase in the maximum gestational age from 49 days to 70 days	• This is not a clinical trial but rather a review of published studies, including many of which are independently reviewed in this spreadsheet. • The study was limited to 63 days' gestation or less.

Louie KS, Tsereteli T, Chong E, Ailyeva F, Rzayeva G, Winikoff B. Acceptability and feasibility of mifepristone medical abortion in the early first trimester in Azerbaijan. Eur J Contracept Reprod Health Care 2014; 19(6): 457-464	• Addition that a repeat 800 mcg buccal dose of misoprostol may be used if needed	• The study was performed in Azerbaijan. • The study included only women 63 days' gestation or less. • Participants had gestational age evaluated by history, exam, or ultrasound, but no data was included on what percent had these determinations. • Study included women ages 18 or older. • Women swallowed mifepristone in person in the clinic and then either took misoprostol buccally immediately in the clinic, or took later at home. Later study changed to sending women home with mifepristone and misoprostol. • Two-week in-person follow-up exam at which time some women were evaluated with ultrasound (unknown %).

Chong E, Tsereteli T, Nguyen NN, Winikoff B. A randomized controlled trial of different buccal misoprostol doses in mifepristone medical abortion. Contraception 2012; 86: 251-256	• Addition that a repeat 800 mcg buccal dose of misoprostol may be used if needed	• The study was conducted in the Republic of Georgia and in Vietnam. • The study included only women 63 days' gestation or less. • Ultrasound was required at in-person visit. • Contraindications excluded from study. • Women swallowed the mifepristone at the clinic. Then randomized to 400 buccal misoprostol or 800 buccal misoprostol to be taken at home. • Women had in-person follow-up visit at two weeks.
Coyaji K, Krishna U, Ambardekar S, Bracken H, Raote V, Mandlekar A, Winikoff B. Are two doses of misoprostol after mifepristone for early abortion better than one? BJOG 2007;114:271-278.	• Addition that a repeat 800 mcg buccal dose of misoprostol may be used if needed	• The study was performed in India. • The study had an inclusion criteria "8 weeks of amenorrhea." • Gestational aged determined by clinical exam, LMP, and at times ultrasound (used as needed to determine age and ectopic pregnancy). • Misoprostol dose was not comparable to U.S. regimen: women were given 400 mcg of oral misoprostol, not buccal. Then the oral dose was repeated. • Women were observed up to 6 hours in the clinic. • Required in-person visit in 2 weeks with ultrasound for some.

Gallo MF, Cahill S, Castelman L, Mitchell EMH. A systematic review of more than one dose of misoprostol after mifepristone for abortion up to 10 weeks gestation. Contraception 2006;74:36-41.	• Addition that a repeat 800 mcg buccal dose of misoprostol may be used if needed	• This is not a clinical trial but rather a review of three studies, which investigated repeat misoprostol doses. • None of those studies looked at buccal administration of misoprostol.
Warriner IK, Wang D, Huong NTM, Thapa K, Tamang A, Shah I et al. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomized controlled equivalence trial in Nepal. Lancet 2011; 377: 1155-61	• Change of "physician" to "healthcare provider" in the label and Risk Evaluation and Mitigation Strategies (REMS) document	• The study was conducted in Nepal. • The study was limited to 63 days' gestation or less and age confirmed by pelvic exam and LMP. • In-person vaginal administration three days later of misoprostol by the assigned abortion provider. After misoprostol placement, the woman was observed in the hospital for 3 hours. • Women had an in-person return visit in 10-14 days.
Kopp Kallner H, Fiala C, Stephansson O, Gemzell-Danielsson K. Home self-administration of vaginal misoprostol for medical abortion at 50-63 days compared with gestation of below 50 days. Human Reprod 2010;25(5):1153-1157.	• Change of "physician" to "healthcare provider" in the label and Risk Evaluation and Mitigation Strategies (REMS) document	• The study was conducted in Sweden. • Gestational age confirmed by ultrasound and exam. • Mifepristone administered in the hospital under direct observation. • Women self-administered vaginal misoprostol at home. • Women had an in-person follow-up exam after 2 weeks. • The study was limited to gestational ages between 50-63 days.

Executed this February 24, 2023.

By: Donna Harrison MD

Donna Harrison, M.D.

The Danco Group

January 21, 2000

Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: **NDA 20-687, Mifepristone 200mg Oral Tablets**
- Amendment 039 - Mifeprex® – Distribution Plan

Dear

As previously agreed, we are submitting Danco Laboratories, Inc.'s Distribution Plan for Mifeprex®. This is a comprehensive distribution plan that emphasizes control of mifepristone at all points in the supply chain, from manufacturers through to individual patients. This plan has been prepared in light of the unique situation surrounding abortion provision in the United States and not out of any medical safety concerns. However, in preparation of this plan, we have taken into account advice from the FDA that it is considering approving the NDA under "Subpart H—Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses, Sec. 314.520--Approval with restrictions to assure safe use."

Our position is that we are willing to agree with the FDA on appropriate distribution controls for mifepristone but that the application of Sec. 314.520 under Subpart H seems unnecessary, in light of our voluntary acceptance of some appropriate distribution controls.

Specifically, Sec. 314.520(a) states that the FDA can apply post-marketing restrictions if it "concludes that a drug product shown to be effective can be safely used *only* if distribution or use is restricted" (emphasis added). Regardless of the distribution system for mifepristone, the medical safety of this drug is well documented in our IND application and in the label and, thus, we believe that Sec. 314.520 does not apply.

This document constitutes trade secret and confidential commercial information exempt from public disclosure under 21 C.F.R. 20.61. Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, Danco Laboratories, Inc. requests immediate notification and an opportunity for consultation in accordance with 21 C.F.R. 20.45. Contact telephone number is

On the contrary, scientific evidence demonstrates that mifepristone is an exceptionally safe drug. Mifepristone when taken by a woman whose pregnancy is ≤ 49 days LMP is associated with several relatively minor and predictable side effects. More serious adverse events are quite rare and are related to the entire treatment (not mifepristone *per se*), almost always following the use of the prostaglandin. There has never been a death related to the use of mifepristone in combination with misoprostol for medical termination of pregnancy. These details have been discussed and reported in our label and various submissions to the FDA.

In addition to concerns about patient safety, the possibility of teratogenic effects has previously triggered the application of section 314.520, as in the case of Thalomid (Thalidomide). These concerns relate to the inadvertent use of a known teratogen at the early stages of a pregnancy that was not scheduled for termination. In contrast, all women who will receive mifepristone will be known to be in early pregnancy and have elected to terminate that pregnancy. Of course, in the case of a successful application of mifepristone, concerns about teratogenicity are rendered moot as the woman will no longer be pregnant. Similarly, in the case of a failed medical abortion, women should have a surgical intervention to terminate the pregnancy and are counseled to do so before taking mifepristone and misoprostol. To date, there is no compelling evidence to suggest that either mifepristone or misoprostol produces teratogenic effects.

Based on the above reasons, we firmly believe that the NDA for mifepristone should not be approved under Sec. 314.520. In addition, applying Sec. 314.520 might draw increased and unwarranted attention to the product, the FDA, and to Danco and its manufacturers, in particular evoking queries about the product's safety. Nonetheless, given the contentious political climate surrounding *all* abortion provision in the United States, we feel that the distribution of mifepristone should be carefully monitored and controlled. Therefore, we have developed and are implementing a controlled distribution strategy and are submitting the details of this strategy in the enclosed Distribution Plan for your review and comment.

Sincerely,

/S/

President and Chief Executive Officer

/dns
Enclosure

cc:
Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council

MIFEPREX®

DISTRIBUTION PLAN

January 21, 2000

MIFEPREX®

DISTRIBUTION PLAN

CONTENTS

MIFEPREX®

DISTRIBUTION PLAN

CONTENTS

EXHIBITS

159

MIFEPREX®

DISTRIBUTION PLAN

EXECUTIVE SUMMARY

This Distribution Plan for Mifeprex® demonstrates Danco Laboratories Inc.'s ("Danco") commitment to distributing Mifeprex® safely and efficiently while, at the same time, providing needed services and information to providers and patients in a confidential manner. Danco has a keen awareness of and sensitivity to the regulatory requirements, as well as the market and political dynamics, surrounding introduction of Mifeprex® in the United States. Therefore, Danco has established a **controlled distribution strategy** to best meet the goals of safe, efficient and confidential distribution of Mifeprex®.

This strategy ensures that Danco exerts positive control over distribution of Mifeprex® through all phases of manufacturing, storage, shipment and administration from manufacturer to patient. Key control elements throughout the distribution process include the following:

- Secure manufacturing, receiving and holding areas for Mifeprex®
- Secure shipping procedures, including tamper-proof seals
- Controlled returns procedures
- Tracking system ability to trace individual packages to patient level, while maintaining patient confidentiality
- Use of only [redacted] authorized distributors and a logistics partner, all of whom have necessary expertise, capabilities and industry experience to handle distribution requirements for Mifeprex®
- Required Account Registration and Order Form signed by providers, prior to any Mifeprex® order being shipped
- Mifeprex® availability only to registered providers, not through retail pharmacies
- Documented patient acknowledgment (informed consent), signed by patient and provider

Alongside key control elements, Danco also recognizes the need to provide support and access to training, services and information throughout the supply chain. The support that is built into the distribution system is as follows:

Access to multi-media training materials and training programs with continuing medical education (CME) recognition and credits.

- Danco toll-free telephone information network for consumers and providers, with access to medical consultants for providers' medical questions
- Danco web site information network
- Trained service representatives for distributors' questions through the logistics partner

Danco has developed and assembled the infrastructure to ensure that Danco's goal of safe, efficient and confidential distribution of Mifeprex® is attained. The Distribution Plan for Mifeprex® details Danco's controlled distribution strategy, highlighting key control elements at each point in the supply chain.

161

MPI App. 914

MIF 000531

The Heritage Foundation

LEGAL MEMORANDUM

No. 324 | FEBRUARY 8, 2023

EDWIN MEESE III CENTER FOR LEGAL & JUDICIAL STUDIES

The Justice Department Is Wrong: Federal Law Does Prohibit Mailing Abortion Drugs

Thomas Jipping and Sarah Parshall Perry

KEY TAKEAWAYS

Federal law has prohibited mailing abortion drugs for more than 100 years.

The Justice Department bypassed the statutory interpretation rules to invent a version of the Comstock Act that would not hinder abortion access.

Congress has repeatedly chosen to maintain the Comstock Act's plain language, which clearly prohibits mailing abortion drugs.

First under English common law, then under American statutes, an "unbroken tradition of prohibiting abortion on pain of criminal punishment"[1] began more than seven centuries ago.[2] By 1868, "a supermajority of States (at least 26 of 37) had enacted statutes criminalizing abortion at all stages of pregnancy."[3]

Five years later, in 1873, in the middle of this national pro-life legislative movement, Congress enacted a statute with an ambitious title: *An Act for the Suppression of Trade in, and Circulation of, Obscene Literature and Articles of Immoral Use*.[4] It is often referred to as the Comstock Act after Anthony Comstock, the anti-vice crusader who championed its passage and spent more than 40 years enforcing it as a U.S. Postal Service special agent.[5] Section 2 of the Comstock Act appears today as 18 U.S.C. § 1461, prohibiting the Postal Service from delivering, and anyone from "knowingly" using the mail to send, any "article or thing designed, adapted, or intended for producing abortion."[6]

This provision could not, as a practical matter, be enforced while the Supreme Court's decisions in *Roe v. Wade*[7] and *Planned Parenthood v. Casey*,[8] which invented and subsequently affirmed a constitutional right to abortion, remained operative precedents. That blockade lifted on June 24, 2022, when the Supreme Court in *Dobbs v. Jackson Women's Health Organization* overruled *Roe* and *Casey*, holding that "the Constitution does not confer a right to abortion."[9]

One week later, the Postal Service's general counsel asked the Department of Justice's Office of Legal Counsel (OLC)[10] whether § 1461 "prohibits the mailing of mifepristone and misoprostol, two prescription drugs that are commonly used to produce abortions."[11] In a written opinion dated December 23, 2022, the OLC concluded that "section 1461 does not prohibit the mailing, or the delivery or receipt by mail, of mifepristone or misoprostol *where the sender lacks the intent that the recipient of the drugs will use them unlawfully*."[12]

The Postal Service should not see this as good news. The OLC did not explore the additional responsibilities that its interpretation of § 1461 would impose upon the Postal Service. On its face, however, that interpretation means that, to know whether it may handle a particular mailing of abortion drugs, the Postal Service must identify its "sender" and ascertain his or her specific intent regarding unlawful use by the "recipient." Neither the original Comstock Act, nor § 1461 today, however, mentions any "sender" or "recipient," and the OLC opinion makes no attempt to define these important new terms. The opinion nonetheless concedes that "those sending or delivering mifepristone and misoprostol typically will lack complete knowledge of how the recipients intend to use them and whether that use is unlawful under relevant law."[13]

The OLC has, therefore, effectively created a new statute, intentionally neutralizing the current one so that it poses no obstacle to the Biden Administration's agenda of maximizing abortion access. This exercise cannot be called "interpretation" of an existing statute enacted by Congress.[14] This *Legal Memorandum* does what the OLC chose not to do, following the established process of statutory interpretation to properly answer the Postal Service's question.

The Comstock Act

The OLC opinion's version of § 1461 is incompatible with both the context in which the Comstock Act was first enacted and its subsequent legislative development.

Context for the Comstock Act. Writing in 1958, Professor Glanville Williams, a widely acclaimed criminal law scholar law and an advocate of legalized abortion, acknowledged that American physicians led a 19th-century campaign against abortion "primarily because they believed unborn children must not be sacrificed unless the life of the mother was truly at stake."[15] Indeed, a century earlier at its May 1859 convention, the American Medical Association unanimously adopted a resolution condemning the "slaughter of countless children" and calling for laws prohibiting abortion, "at every period of gestation," except when necessary to save the mother's life.[16]

State legislatures and courts followed the physicians' lead, abandoning outdated concepts such as quickening, which recognized the unborn child as a living being only after its movement in the womb could be discerned.[17] As a result, during the 19th century, "the vast majority of the States enacted criminal statutes criminalizing abortion at all stages of pregnancy."[18] Congress enacted the Comstock Act (the Act) in this cultural and legal context.

In *Bours v. United States*, which reversed a Comstock Act conviction because of the indictment's wording, the U.S. Court of Appeals for the Seventh Circuit observed that including abortion in the original statute "indicates a national policy of discountenancing abortion as inimical to the national life."[19] In other words, the Comstock Act was Congress' contribution to the national movement toward prohibiting what the American Medical Association had called the "unwarrantable destruction of human life."[20]

This context, which the OLC completely ignored, is important because requiring proof, beyond a reasonable doubt no less, that the sender intends the recipient to use abortion drugs unlawfully virtually neutralizes the Comstock Act's application to abortion drugs. In other words, the OLC posits that Congress, at the urging of a well-known anti-vice crusader and in the middle of a national movement to prohibit abortion, enacted a statute that could not be enforced regarding abortion. That position is simply implausible on its face.

Legislative Development of the Comstock Act. Congress first prohibited the importation of obscene material in 1842 and, in the 1865 Post Office Act, prohibited using the "mails of the United States" to deliver an "obscene book, pamphlet, picture, print, or other publication of a vulgar and indecent character."[21] The Comstock Act soon followed. As first enacted, it prohibited only "materials relating to abortion and contraception from the mails; ordinary obscene publications slipped through the legislative net."[22] Congress quickly stepped in, expanding the statute's reach in 1876 to also include any written material "of an indecent character."[23]

As amended, § 1 of the Comstock Act directly prohibited such written materials and "any article whatever...for causing unlawful abortion" in any "place within the exclusive jurisdiction of the United States." Section 2 prohibited using the mail to deliver such materials elsewhere, and § 3 prohibited "all persons" from importing them into the United States.[24] After the Act's passage, Comstock was appointed a special agent of the U.S. Post Office with the express power to enforce the statute.[25] Two dozen states enacted their own version of the Comstock Act, some with provisions even harsher than the federal statute.[26]

In February 1878, groups led by the Liberal League presented a petition with some 70,000 signatures to Congress calling for the Act's repeal.[27] Later that year, however, the Supreme Court held that Congress' power to "establish post-offices and post-roads"[28] includes "the right to determine what shall be excluded"[29] from the mail. After a House committee hearing and recommendation, Congress left the Comstock Act unchanged.[30]

Each of Congress' subsequent amendments to the Comstock Act expanded its coverage and severity. In 1948, for example, Congress recodified the Act as 18 U.S.C. § 1461[31] and expanded it by adding "filthy" to "obscene, lewd, or lascivious" and three additional categories of written materials to which those descriptors applied. It also added "adapted" to "designed or intended" to describe the "article[s] or thing[s]" for producing abortion that could not be sent through the mail. Congress went further in 1955, adding the descriptor "vile" to the written materials that could not be sent through the mail[32] and, in 1958, doubled the fine for more than one violation of § 1461.[33]

The Comstock Act's context and overall legislative development point toward harsher penalties and broader application of its prohibitions on both written material and anything that can be used to produce abortion. In addition to the context in which the Act was passed, this legislative development makes the OLC's unusually narrow interpretation even more suspect. Turning to a more specific interpretive analysis of § 1461 further reveals the serious flaws in the OLC opinion.

Interpreting Section 1461

The OLC opinion appears so driven by the goal of eliminating § 1461 as an obstacle to the Biden Administration's abortion agenda that it simply bypassed the established process of statutory interpretation altogether. Instead, it immediately looked outside the statute for any basis for its pre-determined conclusion.

What the OLC Did Not Do. The OLC opinion did not even acknowledge, let alone follow, the well-established process of statutory interpretation, which is founded on the Constitution's grant of "All legislative Powers"[34] to Congress. Interpreting any written document involves "discovering...the meaning which the authors...designed it to convey to others."[35] Applied to one of Congress's statutes, interpretation requires "adhering to *Congress's* intended meaning."[36] The Supreme Court has identified principles, or canons, that help keep interpretation focused on that necessary objective.

Three of those interpretive canons are especially relevant here:

1. "In determining the meaning of a statutory provision, 'we look first to its language, giving the words used their ordinary meaning.'"[37]

2. "Absent any textual qualification, we presume the operative language means what it appears to mean."[38]

3. "[W]here...the words of the statute are unambiguous," the "judicial inquiry is complete."[39] In that case, a court "may not resort to extrinsic evidence to interpret them."[40]

If an argument existed that Congress intended the Comstock Act, either as originally enacted or as § 1461 today, to require proof of intended unlawful use, the OLC would surely have made it. If § 1461's text was even arguably ambiguous, justifying resort to extrinsic evidence of its meaning, the OLC would have made the case. The OLC opinion, however, did neither of these, failing to even mention either the obligation to determine what *Congress* intended § 1461 to mean or any of the principles necessary for meeting that obligation. In fact, the key terms at the heart of these interpretive principles—such as "plain," "ordinary," "ambiguous," or "ambiguity"—do not appear a single time in the entire OLC opinion. Instead, the OLC opinion simply bypassed the statutory interpretation process altogether.

What the OLC Should Have Done. In *Marbury v. Madison*, the Supreme Court held in 1803 that "[i]t is emphatically the province and duty of the judicial department to say what the law *is*."[41] A statute, the Court has repeatedly affirmed, "is" the meaning of its text at the time the legislature enacted it. Put simply, construing a statute requires determining what the legislature meant by what it enacted. The OLC opinion, therefore, should have begun by acknowledging its obligation to "adher[e] to Congress's intended meaning" for § 1461.

Keeping this necessary goal in mind, the OLC opinion should have then applied the interpretive canons noted above to determine whether, given its plain and ordinary meaning, the text of § 1461 remains sufficiently ambiguous to warrant reliance on extrinsic evidence for its meaning. "Absent any textual qualification," the Supreme Court has held, "we presume the operative language means what it appears to mean."[42] In fact, the Court has explained, "[i]n interpreting a statute a court should always turn first to one, cardinal canon before all others. We have stated time and again that courts must presume that a legislature says in a statute what it means and means in a statute what it says there.... *When the words of a statute are unambiguous, then, this first canon is also the last: 'judicial inquiry is complete.'*"[43]

Consistent with its original title, the text of § 1461 is focused squarely on "article[s] or thing[s]" that can be used for "immoral purposes" such as abortion. It says nothing about either senders and their subjective intent or recipients and their speculated use. It simply prohibits from the mail any "*article or thing* designed, adapted, or intended for producing abortion."

Similarly, neither the original Comstock Act nor § 1461 has ever been limited to articles or things that are designed, adapted, or intended *only* for abortion. Beginning with its title, the OLC opinion actually confirms this, addressing "prescription drugs that *can* be used for abortion."[44] The fact that mifepristone and misoprostol may have other uses, therefore, is irrelevant and does not make the text of § 1461 ambiguous.

Merriam-Webster defines *design* and *intend* to mean "have as a purpose" and *adapted* as "suited by...design to a particular use."[45] The plain and ordinary meaning of § 1461 is that if abortion is a purpose for which an article or thing is suited, it may not be conveyed or delivered through the mail. Since this unambiguous meaning of these terms is plain on its face, "a court may not resort to extrinsic evidence to interpret them."[46]

The Postal Service itself takes the same approach, prohibiting items because of how they can be used rather than speculating about senders and recipients. The U.S. Postal Inspection Service's website, for example, lists various "items and substances [that] should never enter the mail system."[47] These include anything that contains mercury, household products that contain aerosol, and even lithium batteries. How these items might be used by others, or whether that use is legal or illegal, has nothing to do with labeling them as "non-mailable," the same term that appears in § 1461. In fact, the term "unlawful" does not appear on this website at all. Designating an item as non-mailable is based solely on a judgment that the item, *in and of itself*, is potentially harmful. The same is true about any "article or thing designed, adapted, or intended for producing abortion."[48]

The obvious answer to the Postal Service's question, therefore, is that yes, § 1461 prohibits mailing abortion drugs.

The OLC's Opinion. The OLC opinion did not do any of that. It never acknowledged its duty to adhere to Congress' intended meaning or mentioned any of the necessary statutory interpretation principles. This includes even the canon that the Supreme Court has held takes precedence "before all others," the presumption that Congress "means in a statute what it enacts there." Rather than attempt to draw Congress's intended meaning *from* § 1461, or to satisfy the prerequisite of finding ambiguity for relying on extrinsic evidence, the OLC started by searching outside the statute for a preferred meaning to impose *upon* it.

The OLC found what it was looking for in a "*judicial* construction of the Comstock Act,"[49] a few U.S. Court of Appeals decisions that appeared to interpret the Comstock Act narrowly. Since the judiciary has no power to legislate, however, the OLC still needed to somehow connect this interpretation to Congress. The OLC's theory is that, because Congress did not "disapprov[e] of the [judicial] interpretation"[50] after it was "brought to Congress's attention,"[51] Congress necessarily "ratified"[52] or "accept[ed] that narrowing construction."[53] In other words, while Congress had to act for § 1461 to exist at all, the statute could be effectively, and significantly, amended by the judiciary while Congress did nothing.

One Note and One Statement. The interpretation that OLC prefers, it says, was "brought to Congress's attention" in two ways. First, a "Historical and Revision Note" found in a 1945 House committee report "'invited' the 'attention of Congress'" to appeals court decisions narrowly interpreting § 1461.[54] Such notes, the OLC explains, "were written by a staff of experts hired by Congress to revise the U.S. Code in the 1940s, including the editorial staffs of the West and Thompson publishing companies."[55] Second, a statement by the Postmaster General found in a 1970 committee report explained that the Postal Service had administratively "accepted the courts' narrowing construction of the [Comstock] Act."[56]

The OLC contends, in other words, that one note and one statement by non-legislative parties, appearing in committee reports 25 years apart, were so powerful that only Congress's explicit "disapprov[al] of that interpretation"[57] could prevent the resulting transformation of § 1461. This theory is inconsistent not only with the Constitution's grant of legislative power to Congress, but with the very authority the OLC cites for this approach: *Texas Dept. of Housing and Community Affairs v. The Inclusive Housing Project, Inc.*[58]

Texas Dept. of Housing. In that case, a nonprofit organization that assists low-income families in finding affordable housing sued the Texas housing agency under the federal Fair Housing Act (FHA). The group claimed that the agency's pattern of allocating housing tax credits had a disparate racial impact. The Supreme Court had to decide whether § 804 of the FHA, which prohibited housing discrimination based on "race, color, religion, or national origin,"[59] should be interpreted as allowing not only suits for disparate *treatment*, but also for disparate *impact*.

The Court held that Congress "ratified the unanimous holdings of the Courts of Appeals finding disparate-impact liability"[60] when it amended the FHA in 1988 but retained § 804's existing language. That much of *Texas Dept. of Housing* appears supportive of how the OLC today wants to treat § 1461. There is a reason, however, why the OLC only cited—but did not discuss—this precedent. If *Texas Dept. of Housing* is instructive, as the OLC apparently thinks it is, then it establishes a standard for congressional ratification of a judicial construction that the OLC cannot possibly meet with respect to § 1461.

1. The Supreme Court had previously interpreted language to allow disparate-impact suits in two civil rights statutes that are "equivalent in function and purpose" to § 804.[61]

2. By 1988, "all nine Courts of Appeals to have addressed the question had concluded the Fair Housing Act encompassed disparate-impact claims,"[62] six of them in the previous six years.

3. Congress affirmatively demonstrated its "aware[ness] of this unanimous precedent"[63] by the same actions, such as committee hearings and floor speeches, that it takes when enacting or amending legislation.

4. Congress rejected a proposed amendment that would have eliminated disparate-impact liability.[64]

These factors support the Supreme Court describing Congress as making a "considered judgment"[65] to retain the previous language of § 804 while accepting that it would be interpreted, going forward, as allowing disparate-impact suits. None of these factors, however, exist regarding § 1461. The Supreme Court has never interpreted § 1461[66] or any comparable or equivalent statute to require proof of intended unlawful use. Far from the unanimous, and recent, interpretation of § 804 of the FHA, the OLC opinion cites appeals court decisions in four circuits during nearly 30 years.

More importantly, while Congress' actions regarding § 804 demonstrated its actual awareness and considered acceptance of the statute's judicial construction, § 1461's legislative development described above points in the opposite direction.

First, § 1 of the original Comstock Act prohibited "any drug or medicine, or any article whatever...for causing *unlawful* abortion." In contrast, § 2, which would later become § 1461, prohibited "any article or thing designed or intended for the...procuring of abortion," without the "unlawful" qualifier that the OLC today wants to impose. This distinction makes a very real difference. The Supreme Court has held that "where Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion."[67] In other words, including "unlawful" in § 1 turns its absence from § 2 into an exclusion.

Second, this same principle applies between separate, but closely related, statutes.[68] The Tariff Act, for example, prohibits "importing into the United States from any foreign country...any drug or medicine or any article whatever for causing *unlawful* abortion."[69] The OLC opinion itself,[70] and appeals court decisions on which it relies,[71] note the difference in language between the Tariff and Comstock Acts but ignores the obvious implication that Congress, therefore, intended to exclude the "unlawful" qualifier from the latter.

Third, recodifying the federal criminal code in 1948[72] would have been the opportunity to add the "unlawful" qualifier to § 2 of the Comstock Act, which became § 1461. Instead, Congress repealed § 1, which contained the "unlawful" qualifier, and kept § 2, which did not.

Fourth, following the Supreme Court's decision in *Griswold v. Connecticut*,[73] which invented a constitutional right to use contraception, Congress in 1971 amended statutes such as § 1461 and the Tariff Act to remove their application to contraception.[74] Congress, however, did not do the same after the Supreme Court's decision in *Roe v. Wade*, retaining unchanged § 1461's application to "[e]very article or thing designed, adapted, or intended for producing abortion."

Fifth, on multiple occasions, Congress has considered, but has never adopted, amendments to § 1461 that would bring its text in line with the OLC's interpretation. Even suggesting such a change, of course, makes no sense if, as the OLC today claims, Congress had already ratified and accepted such a narrow interpretation. Congress' own actions show that it had not. For example:

- In 1978, when again recodifying the federal criminal code, Congress considered but did not adopt an amendment to § 1461 that would limit its application to "[e]very...drug, medicine, article, or thing *intended by the [sender]...to be used to produce illegal abortion*."[75] The House committee report confirmed that this would require "proof that the offender specifically intended that the mailed materials be used to produce an illegal abortion" under state law.[76]

- In 1996 and 1997, respectively, Representatives Patricia Schroeder (D–CO) and Barney Frank (D–MA) introduced legislation to drastically narrow the definition of "nonmailable matter" in § 1461, including eliminating any reference to abortion.[77] Neither bill, however, even had a Senate counterpart, and Congress took no action on either one.[78] As explained above, Congress including "unlawful" in § 1 of the Comstock Act and in similar statutes such as the Tariff Act created a presumption that Congress intended to exclude that element from § 2. Congress repeatedly passing up opportunities to insert a requirement of proving intended unlawful use means that nothing has rebutted that presumption.

Congress took none of the actions that, under *Texas Dept. of Housing*, would have evidenced its acceptance of the narrow judicial interpretation of § 1461 that the OLC favors. Quite the contrary. In at least these five different ways, Congress demonstrated the opposite, that it meant what it enacted in § 1461. Congress' "intended meaning" is what the statute's plain language has said from the beginning—that anything designed, adapted, or intended for producing abortion may not be sent through the mail.

Finally, the OLC opinion is problematic even on its own terms. Whether mailing abortion drugs is permissible under the OLC's preferred interpretation of § 1461 depends on whether their intended use is unlawful, which is determined by state law. The first appeals court decision cited in the OLC opinion, however, contradicts this position. In *Bours v. United States*,[79] the court held that in applying the Comstock Act "to an alleged offensive use of the mails...it is immaterial what the local statutory definition of abortion is, what acts of abortion are included, or what excluded. So the word 'abortion' in the national statute must be taken in its general medical sense."[80] The prohibition on using the mail to deliver abortion drugs, therefore, is not conditioned on the intent of the sender, the anticipated use by the recipient, or the legality of abortion in a particular state.

Conclusion

The U.S. Postal Service asked the Justice Department's Office of Legal Counsel whether 18 U.S.C. § 1461 prohibits mailing abortion drugs. Properly answering this question requires following the established process of statutory interpretation, including principles that help maintain the priority of "adhering to Congress's intended meaning."[81] Because this process inexorably provides an affirmative answer to the Postal Service's question, the OLC avoided it altogether. Instead, the OLC immediately looked outside the statute—and outside Congress altogether—to support the answer it wanted.

The Comstock Act's purpose was "to prevent the mails from being used to corrupt the public morals."[82] The context in which it was enacted and its legislative development both show that abortion was assuredly in this category. The evidence that the OLC completely ignored shows that Congress not only never limited § 1461's application to abortion, but actually intended that this application remain unchanged.

The plain, ordinary, and unambiguous meaning of § 1461 prohibits using the mail to send or deliver anything that is designed, adapted, or intended to produce abortion. The U.S. Food and Drug Administration has confirmed that mifepristone and misoprostol are in this category, approving their use for "termination of pregnancy through 10 weeks gestation."[83] The OLC opinion itself, in its opening paragraph, does the same by describing mifepristone and misoprostol as "drugs that are commonly used to produce abortions."[84] Planned Parenthood simply calls mifepristone the "abortion pill."[85] These drugs unquestionably fall within § 1461's prohibition.

Unfortunately, the Biden Administration's political priority of expanding abortion access compromised the OLC's duty to provide objective and unbiased legal analysis. As a result, the OLC wants Americans to believe that a law enacted as part of the national pro-life legislative movement and championed by an aggressive and uncompromising anti-vice crusader is today, with no change in its language, entirely unenforceable for its intended purpose. The OLC wants Americans to ignore what they can read for themselves, that the statute has clear and unqualified language, and that Congress repeatedly demonstrated its intention to keep it that way. The OLC wants Americans to believe that while enacting the Comstock Act required Congress to act, rendering it inert and unenforceable could be accomplished by Congress failing to act at all.

The Justice Department is wrong. Federal law prohibits mailing abortion drugs.

Thomas Jipping is Senior Legal Fellow in the Edwin Meese III Center for Legal and Judicial Studies at The Heritage Foundation. **Sarah Parshall Perry** is Senior Legal Fellow in the Meese Center.

Endnotes

1. Dobbs v. Jackson Women's Health Organization, 142 S.Ct. 2228, 2253 (2022).
2. *See id.* at 2249–54.
3. *Id.* at 2261.
4. 17 Stat. 598 (1873).
5. *See* Margaret A. Blanchard, *The American Urge to Censor: Freedom of Expression Versus the Desire to Sanitize Society—From Anthony Comstock to 2 Live Crew*, 33 William & Mary L. Rev. 741, 744–60 (1992). Comstock claimed that he successfully prosecuted more than 3,600 defendants and destroyed more than 160 tons of obscene literature in his role as a special agent with the U.S. Postal Service. *See* Comstock Law of (1873), JRank, https://law.jrank.org/pages/5508/Comstock-Law-1873.html#ixzz7qmkxsQb4.
6. 18 U.S.C. § 1461.
7. 410 U.S. 113 (1973).
8. 505 U.S. 833 (1992).
9. *Dobbs*, 142 S.Ct. at 2279.
10. The Office of Legal Counsel provides "written opinions and other advice in response to requests from the Counsel to the President, the various agencies of the Executive Branch, and other components of the Department of Justice." *Office of Legal Counsel*, U.S. Dep't of Just., https://www.justice.gov/olc.
11. Application of the Comstock Act to the Mailing of Prescription Drugs That Can Be Used for Abortion, O.L.C. Slip Op., at 1 (Dec. 23, 2022), https://www.justice.gov/olc/opinion/file/1560596/download.
12. *Id.* (emphasis added).
13. *Id.* at 17.
14. Instead, it does what Justice George Sutherland once warned against, amending § 1461 "under the guise of interpretation." West Coast Hotel Co. v. Parrish, 300 U.S. 379, 404 (1937) (Sutherland, J., dissenting).
15. Glanville Williams, The Sanctity of Life and the Criminal Law 141 (1958).
16. Frederick N. Dyer, The Physicians' Crusade Against Abortion 76 (1999).
17. *See*, *e.g.*, Lamb v. State, 10 A. 208 (Md. 1887).
18. *Dobbs*, 142 S.Ct. at 2252.
19. Bours v. United States, 229 F. 960, 964 (7th Cir., 1915).
20. See Dyer, *supra* note 16.
21. 13 Stat. 504, 507 (1865). See Blanchard, *supra* note 5, at 745–46.
22. Blanchard, *supra* note 5, at 749.
23. *Id.*
24. *Id.* at 746.
25. *Id.* at 748.
26. Comstock Law of (1873), *supra* note 5. *See also* Blanchard, *supra* note 5, at 751.
27. Blanchard, *supra* note 5, at 752.
28. U.S. Const., art. I, § 8, cl. 7.
29. Ex parte Jackson, 96 U.S. 727, 732 (1878).
30. Blanchard, *supra* note 5, at 754.
31. 62 Stat. 768 (1948), ch. 645.
32. Pub. L. 95–190, 69 Stat. 183 (1955).
33. Pub. L. 85–796, 62 Stat. 768 (1958).
34. U.S. Const., art I, § 1.
35. Black's Law Dictionary 824 (7th ed. 1999).
36. Valerie C. Brannon, Cong. Rsch. Srvc., R45153, Statutory Interpretation, Theories, Tools, and Trends 2 (2022) (emphasis added).

37. Lawson v. FMR LLC, 571 U.S. 429, 440 (2014), quoting Moskal v. United States, 498 U.S. 103, 108 (1990).
38. *Id.* at 441.
39. Desert Place, Inc. v. Costa, 539 U.S. 90, 99 (2003) (internal citations omitted). *See also* Babb v. Wilkie, 140 S.Ct. 1168, 1177 (2020); Lawson v. FMR LLC, 571 U.S. 429, 440 (2014), quoting *Moskal*.
40. Coast Fed. Bank, FSB v. United States, 323 F.3d 1035, 1040 (Fed. Cir. 2003) (en banc). *See also* Steimel v. Wernert, 823 F.3d 902, 912 (7th Cir. 2016).
41. Marbury v. Madison, 5 U.S. 137, 177 (1803) (emphasis added).
42. *Id.* at 441.
43. Connecticut Nat'l Bank v. Germain, 503 U.S. 249, 253–54 (1992) (emphasis added), quoting Rubin, 449 U.S. 424 (1981), at 430.
44. O.L.C. opinion, *supra* note 11, at 17–18.
45. *Design* and *Intend*, MerriamWebster (Online 2023), https://www.merriam-webster.com/dictionary.
46. *Coast Fed. Bank*, 323 F.3d at 1040.
47. U.S. Postal Inspection Serv., Prohibited, Restricted, and Non-Mailable Items (2022), https://bit.ly/3HCU4sY.
48. 18 U.S.C. § 1461.
49. O.L.C. opinion, *supra* note 11, at 2.
50. *Id.* at 14.
51. *Id.* at 14–15.
52. *Id.* at 12.
53. *Id.* at 15.
54. *Id.* at 12–13. This note also appears following the text of § 1461 in the U.S. Code. See *18 U.S. Code § 1461: Mailing Obscene or Crime-Inciting Matter*, Cornell L. Sch., https://www.law.cornell.edu/uscode/text/18/1461.
55. *Id.* at 12 n.14.
56. *Id.* at 11.
57. *Id.* at 14.
58. 576 U.S. 519 (2015).
59. *See* 42 U.S.C. § 3604.
60. *Id.* at 536.
61. *Id.* at 520.
62. *Id.* at 535.
63. *Id.* at 536.
64. *Id.*
65. *Id.*
66. With the exception of *Bours*, in fact, none of the appeals court decisions cited in the OLC opinion interpreted or applied the Comstock Act with regard to abortion.
67. Russello v. United States, 464 U.S. 16, 23 (1983), quoting United States v. Wong Kim Bo, 472 F.2d 720, 722 (5th Cir. 1972). *See also* Riegel v. Medtronic, Inc., 522 U.S. 312, 327 (2008) (When assessing two different clauses in the same statute to discern whether the Food, Drug, and Cosmetic Act's wording was intended to pre-empt state law for both drugs and medical devices, the court wrote: "It did not…but instead wrote a pre-emption clause that applies only to medical devices.")
68. *See* Sullivan v. Stroop, 496 U.S. 478 (1990).
69. 19 U.S.C. § 1905(a) (emphasis added).
70. O.L.C. opinion, *supra* note 11, at 8 n.9.
71. *See, e.g.*, U.S. v. One Package, 86 F.2d 737, 738 (2d Cir. 1936). The court's decision was based on a series of speculative phrases such as "seems hard to suppose," *id.* at 739, and "seems unreasonable." *Id.* at 740.
72. 62 Stat. 768.
73. 381 U.S. 479 (1965).
74. See Pub. L. 91–662, 62 Stat. 768 (1971).
75. Report of the Subcommittee on Criminal Justice on Recodification of Federal Criminal Law, 95th Cong., 39–42 (Comm. Print 1978) (emphasis added).

76. *Id.* at 39–42 (emphasis added).
77. H.R. 3057, 104th Cong. (1996).
78. In her remarks on the House floor, Schroeder focused on the Act's effect on abortion and criminalizing distribution of abortion information. She never said anything about "unlawful" or "illegal" abortion, but identified a violation of the statute as the strict liability offense it was. Schroeder said: "The problem is, this body just allowed the Comstock Act to be enforced on the Internet vis-à-vis anything doing with abortion. Previously, the Congress did away the Comstock Act dealing with family planning, thank goodness. But the Comstock Act has never been repealed; it is still on the books. And so, as a consequence, this has been thrown up on the Internet and could be used to bring people into a criminal conviction or arraignment if they decided to discuss anything about the big A word on the Internet.... The Telecommunications Act passed this year extended the Comstock Act's prohibitions to anyone who uses an interactive computer service. This Congress, therefore, revived Comstockery by making it a crime to use the Internet to provide or receive information which directly or indirectly tells where, how, of whom, or by what means an abortion may be obtained." Archives of Women's Political Communication, Iowa State University, posted March 21, 2017, https://awpc.cattcenter.iastate.edu/2017/03/21/comstock-act-still-on-the-books-sept-24-1996/.
79. Bours v. United States, 229 F. 960 (7th Cir., 1915).
80. *Id.* at 964.
81. *See supra* note 36.
82. *See* Comstock Law of (1873), *supra* note 5.
83. Information about Mifepristone for Medical Termination of Pregnancy Though Ten Weeks Gestation, U.S. Food and Drug. Admin. (2023), https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-about-mifepristone-medical-termination-pregnancy-through-ten-weeks-gestation. *See also Mifepristone (Oral Route)*, Mayo Clinic, https://www.mayoclinic.org/drugs-supplements/mifepristone-oral-route/proper-use/drg-20067123#:~:text=For%20oral%20dosage%20form%20(tablets,dose%20placed%20in%20the%20cheeks; *Uses*, WebMD, https://www.webmd.com/drugs/2/drug-20222-325/mifepristone-oral/mifepristone-oral/details ("Mifepristone (also known as RU 486) is used to cause an abortion during the early part of a pregnancy.").
84. O.L.C. opinion, *supra* note 11, at 1.
85. *How Do I Use the Abortion Pill?*, Planned Parenthood, https://www.plannedparenthood.org/learn/abortion/the-abortion-pill/how-do-i-use-abortion-pill.

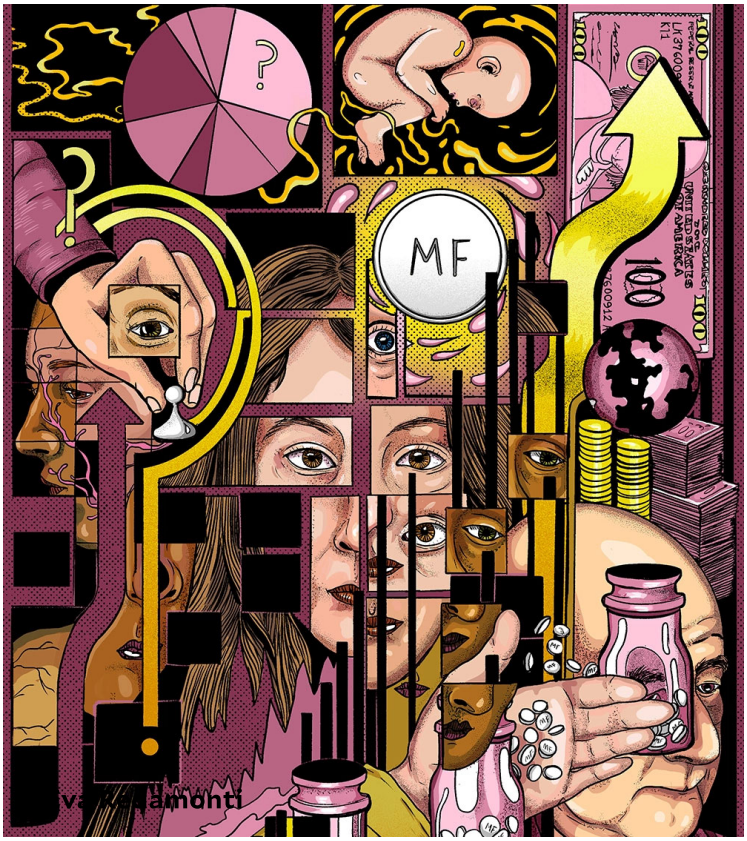
REPRODUCTIVE RIGHTS

The Abortion Pill's Secret Money Men

The untold story of the private equity investors behind Mifeprex—and their escalating legal battle to cash in post-Dobbs.

HANNAH LEVINTOVA

MARCH+APRIL 2023 ISSUE



Fight disinformation: Sign up for the free Mother Jones Daily *newsletter and follow the news that matters.*

In 1993, a group of activists rented a warehouse in suburban Westchester County, New York.

It was smaller than they'd hoped and had limited ventilation, but the two other locations they'd tried to rent belonged to universities and required jumping through too many bureaucratic hoops—the exact sort of paper trail this group was trying to avoid.

Led by renowned pro-choice activist Lawrence Lader, their goal was to replicate RU-486, the revolutionary abortion pill developed in the 1980s by French manufacturer Roussel-Uclaf—which was unwilling to navigate American abortion politics to bring the pill stateside. Lader's group, code-named ARM Research Council, set up shop just months after Dr. David Gunn was shot and killed outside his Florida clinic, the first US physician to be murdered by an anti-abortion activist. Perhaps unsurprisingly, no US manufacturer wanted to wade into the increasingly fraught abortion debate to bring the medication to American women, either. So with the help of lawyers and activists, Lader had smuggled RU-486 into the United States, and his group was going to try to reproduce it.

In their warehouse, they got to work building an underground drug laboratory, complete with a huge, customized ventilation hood, fire prevention devices, and specially designed sinks. The whole project "had the trappings of a CIA operation," Lader would later write. They figured out a system for replenishing their near-constant need for dry ice from a supplier 15 miles away, and crafted a strategy to avoid detection by anti-abortion groups, the garbage collector, and their landlord. If anyone asked what they were up to, the group—which included a doctor who lived 1,000 miles

away and asked to go by Dr. X, a Columbia University chemist working for free, and two assistants—agreed on a cover story: They were working on a new treatment for cancer.

Meanwhile, Roussel-Uclaf and its parent company were in a drawn-out negotiation with a Manhattan-based reproductive health nonprofit, called the Population Council, over the official patent for RU-486. The same month that the French company finally agreed to give the Council the patent, Lader's secret lab announced that it had successfully developed its own copy of the drug, whose scientific name is mifepristone. The two groups knew of each other's work, and Lader had even reached out to the Population Council about collaborating, but the Council had demurred.

The tale of who funded this effort to legally bring mifepristone to women across the country, and what benefits those funders might reap, has been mostly kept quiet.

Lader's group knew American women could not wait the many years it would take for the Council to arrange an official manufacturing operation with full approval from the Food and Drug Administration. So, it got its own permission from the FDA to conduct limited testing, which would allow it to start distributing small batches of the drug to a network of 10 clinics. There, patients could get both mifepristone and misoprostol, a common ulcer drug, which, when taken in tandem, can cause a medication abortion. For the few who were able to try it, it was an emotional and physical relief: It meant they could have an abortion privately and without a vacuum aspiration machine, whose suction "feels like you're getting the life sucked out of you," as one early mifepristone recipient described it to the *Boston Globe*.

All the while, the Council was working to find a manufacturer willing to make the drug, win full FDA authorization, and sell it across America.

When the FDA finally approved mifepristone seven years later, the Council's distribution venture, which came to be called Danco Labs, was ready to go. Within two months, the drug was shipped out to doctors. At the clinics brave enough to be early adopters, women began showing up from farther and farther away; in some places the medicine was double the cost of a surgical abortion, but that hardly seemed to matter. By 2020, the pill had become the most popular way to get an abortion in the United States.

- Everything Everywhere All at Once: How Private Equity Rules Your World
- Biden and Trump Both Trashed Private Equity's Favorite Tax Dodge. Surprise! It's Still Here.
- These Are Congress' Biggest Private Equity Investors
- The Fight to Keep Their "Poor People's Paradise" out of Private Equity's Hands
- My Newspaper Was Gutted by Journalism's Biggest Bogeyman

Over the last two decades, mifepristone's dramatic origin story has made its way into books and the pages of the *New York Times*. But the tale of who funded this effort to legally bring it to women across the country, and what benefits the funders might reap from their investments, has been mostly kept quiet. This was in part because the 1990s were the apex of anti-abortion violence, so investors required secrecy. It was also because the funding sources seemed like a minor plot point in a project that had the potential to transform reproductive health care for millions.

"I don't think anybody thinks they're going to make a lot of money," Peg Yorkin, one of the activists crucial to the US mifepristone campaign, told the *Los Angeles Times* when the pill became available. "We're just happy that it's going to be happening."

But the small group of investors who backed the Population Council's drive to manufacture and distribute the drug since its earliest days have made a lot of money on the mifepristone business—tens of millions of dollars, according to court filings. Their windfall has come through a byzantine corporate structure set up in the 1990s by a private equity fund, now called MedApproach Holdings, to allow investors to pour money into Danco Labs—until 2019 the only US retailer of mifepristone—without disclosing their identities. As states have imposed ever-stricter limits on abortion access, their investments have generated hefty returns.

On the heels of the Supreme Court's ruling in *Dobbs v. Jackson Women's Health Organization* last June, undoing the federal right to abortion—and the FDA's announcement, in January, that retail pharmacies can now sell abortion pills—these investors are likely to earn even more, as medication abortion becomes the only option for millions of women living in the 26 states where abortion is now illegal or severely restricted. The potential is so promising that two of the primary investors have engaged in a bitter court battle to take control of the investment, and Danco itself.

Their story has a dizzying plot that involves Cayman Islands shell companies, LLCs named after racehorses, a shadowy priest, a disbarred attorney, and a finance whiz behind an infamous Wall Street hedge fund collapse. The legal battle, which has been fought in three states and cost millions in attorneys' fees, shows how investors have come to view the desperation of pregnant women as an important problem to solve—but also a golden ticket.

In 1986, a North Carolina lawyer named Joseph Pike purchased one of the earliest manufacturers of intrauterine devices for $1.1 million. The company, Finishing Enterprises Inc., was making IUDs for another business called GynoPharma. At the time, GynoPharma wasn't selling IUDs in the United States—American women shunned them after the Dalkon Shield, a different IUD, was found to cause severe injuries in the '80s. Its copper IUDs were primarily being purchased by governments and NGOs for distribution in developing nations, but Pike spent the next five years

helping to bring this IUD, the Paragard, to the United States. After it hit the market, he sold FEI for a reported $65 million—an astounding return of more than 5,800 percent. "It was a good play for me," he says.

A multimillionaire at just 41, Pike ditched his lawyer job and moved to La Jolla, one of San Diego's most exclusive neighborhoods, to "enjoy life." He took up golf and played as often as he felt like it. But soon Pike heard from the Population Council about a business proposition: It wanted to develop and market medication abortion in the United States. At that time, advocates were flying lobbyists to Europe and picketing outside the New Jersey office of the French pill's parent company to get them to sell the drug in America. As Pike saw it, it was another opportunity to make some real money—and do some good along the way.

Pike was the Council's go-to because they'd worked together on the copper IUD. The Council had developed it and then granted GynoPharma the license, and it collected royalties as Pike successfully built up the IUD business and sold it. Pike had proved himself to be a businessman who could breathe life, and dollars, into a controversial women's health product. The Council gave him the exclusive right to sell mifepristone in the US and tasked him with drumming up investors.

The controversy surrounding mifepristone meant that neither the government nor mainstream companies would go anywhere near it.

Typically, drugs in the United States are not funded by private individuals. Instead, the federal government finances initial research, while later stages of development are paid for by pharmaceutical companies. Venture capitalists and private equity investors usually only get involved in drugs developed to treat rare diseases—those that affect fewer than 200,000 people per year—because pharma companies are unlikely to invest in these typically less-profitable treatments. But mifepristone was far from a "rare disease" drug—in the 1990s, about 1.5 million American women were having abortions annually. (That number has since come down to just under a million, thanks to the growing availability of contraceptives.) Yet the controversy surrounding mifepristone meant that neither the government nor mainstream companies would go anywhere near it.

In 1994, Pike got to work, traveling the country with Susan Allen, a doctor and abortion provider he'd brought on to be the face of the abortion pill effort. Pike recalls that they spent their time pitching wealthy liberals, including Susan Buffett, Gloria Vanderbilt, a George Soros representative, and a handful of other celebrities. His fundraising overlapped with the O.J. Simpson murder trial, and Pike says he even met with one of Simpson's defense lawyers, Bob Shapiro. Pike won't say which, if any, of these people invested in the project, but he estimates that altogether there were about 50 pitch meetings.

One of the investors who did sign on was Greg Hawkins, a veteran of the major investment bank Salomon Brothers, who was then helping run the hedge fund Long-Term Capital Management. (Hawkins did not comment for this story.) Pike met Hawkins in New York City in 1995 and told him what he'd told everyone else: To protect investors' privacy, he would craft a corporate structure that would be based offshore and involve a slew of sub-entities—in essence, a Russian nesting doll of holding companies that would quietly fund the mifepristone effort. The project did not have FDA authorization yet, which meant there was no immediate way to bring in revenue. But eventually, they would pay back their investors, and then some. Hawkins decided he wanted in.

Pike set about creating a dizzying chain of intermediate companies registered around the world. First, he filed paperwork to create Danco Laboratories Inc. as a Cayman Islands company, also registered in Delaware. (Danco was named after Pike's son.) Then he listed an intermediate company in California, Danco LP. He also registered another intermediate company, ND Management, in the Cayman Islands.

Each entity controlled the next one: ND Management oversaw Danco LP, which owned Danco Labs, the company that would actually sell the abortion drug whose backers this tangle of entities was set up to obscure. The secrecy was paramount, given the threat of reputational or financial consequences—or worse—for anyone publicly tied to the project; anti-abortion violence was continuing to escalate. Extremists murdered abortion providers in Florida and Massachusetts, and anti-abortion groups threatened a boycott of more than 70 medications made by affiliates of RU-486's manufacturer, Roussel. Pike, who'd been identified in news stories, got death threats himself.

Pike had already found someone to help build this financial vehicle: an experienced health care financier from Nashville named Brad Daniel. Daniel had started two biotech hedge funds, as well as a private equity fund, called Bio-Pharm Investments, that specialized in providing seed money to pharmaceutical ventures. Like Pike, Daniel would later recall that his motivations were twofold: He believed in the social benefits of mifepristone, and in the enormous financial potential. (Daniel did not comment for this story.)

Daniel created a fund, MedApproach, where investors would plunk their money in Danco's mifepristone business. His private equity fund, Bio-Pharm, would oversee MedApproach, receiving a 1 percent management fee and 20 percent of all profit distributions that MedApproach's investors got from their stakes in Danco's business.

All this was happening when private equity investing was becoming in vogue. It began in the 1980s, when a generation of shrewd financiers popularized a type of business takeover, called a leveraged buyout, that secured private equity's status as a new place for wealthy investors to grow their money. They had also kicked off a broader philosophical shift —one where the main value of a business lies less in the benefit a product offered customers and other stakeholders, and more in the financial returns extracted for its shareholders.

By the 1990s, when the mifepristone venture was getting off the ground, this new attitude had propelled private equity investment into new sectors, like health care, technology, and pharmaceuticals. The pill presented an obvious financial opportunity: the rare sort of drug that they'd never have trouble selling, for a condition that would never cease to exist.

The pill presented an obvious financial opportunity: the rare sort of drug that they'd never have trouble selling, for a condition that would never cease to exist.

Within two years, Pike and Daniel found a handful of willing investors who together put more than $13 million into MedApproach. Hawkins was the largest investor funding the Russian nesting doll of financial entities, pitching in $1.5 million, so that, by 1996, he owned three-quarters of MedApproach. Over the next two years, he loaned the Danco project an additional $4 million, according to his declarations in court.

But then the project hit a roadblock. The Population Council discovered in 1997 that Pike had an unsavory history that they worried could tank the abortion pill project just as it was in the middle of clinical trials and its campaign for FDA approval. The prior year, as he'd been ramping up the mifepristone investments, Pike had pleaded guilty to a misdemeanor forgery charge in North Carolina, tied to a 1985 real estate deal. He'd gotten a suspended two-year sentence, 18 months of probation, and a fine. He had also been stripped of his law license.

(Pike explains that the charge came from a disgruntled former client he'd once helped buy land. When the client wanted to get rid of it years later, Pike couldn't help because he had retired from practicing law. The client claimed Pike had misrepresented facts; Pike says he pleaded guilty to make the case go away.)

The Population Council wanted the mifepristone project to be squeaky clean. If Pike stayed on, they felt that years of work, the $13.3 million in investments he'd secured, and FDA approval could all be in danger. Keeping him involved in the project, they said, would mean that "another weapon with which to attack [the abortion pill] will be furnished to its ideological opponents."

It took a lawsuit to get Pike off the project. As part of his exit, the Population Council insisted that the investors Pike had found have the chance to leave, since the Council could no longer guarantee the promises Pike had made to them. Spooked by the disarray and the fact that Danco still did not have government approval to sell its only product, many investors opted to pull their funds. But Hawkins stayed in and paid $3.5 million to buy out most of Pike's investment. Daniel also stayed involved, securing more control over the company and further compensation that would amount to hundreds of thousands annually. (Pike, meanwhile, fought to keep a 25 percent stake, $1.5 million in consulting fees, and a portion of the future profits on the shares he'd given up, capped at $21 million.) Hawkins also pledged up to $13.7 million to buy up shares ditched by other investors, potentially giving him a majority of the entire investment.

Three months later, in July 1998, Hawkins invited Daniel to visit him at his home in Saratoga, New York. Over lunch at the Saratoga Race Course's private club, he told Daniel that something was "terribly wrong." His hedge fund was having liquidity issues and would have little or no additional funds to invest in MedApproach—meaning he would not be able to cover the nearly $14 million commitment he'd made to buy out investors.

Hawkins asked to transfer his existing stake to his wife, Sharon—to protect himself, his family, and that investment from whatever might come next at his hedge fund. Daniel agreed. Later, Hawkins told Daniel that he would solicit other investors to cover the millions he'd committed to MedApproach but now could not come up with.

Over the next two months, Hawkins' hedge fund, Long-Term Capital Management, collapsed. Famed on Wall Street for sophisticated math that delivered huge returns, it lost billions in a matter of weeks, thanks to a mix of events that included Russia's default on a chunk of its Treasury debt, which LTCM had heavily invested in. At its peak, LTCM had controlled 5 percent of assets on the global market, so its downfall roiled the worldwide financial system. Soon, the Federal Reserve stepped in to organize a $3.5 billion bailout financed by the leading Wall Street banks.

Amid all that, Daniel and Hawkins began having weekly talks to figure out how to move forward with the mifepristone investment. The buyout of the original investors would wrap up in the summer of 1999, and Hawkins was scouting new funders.

According to Daniel, Hawkins said that he had heard from a Catholic priest who wanted to invest in medication abortion but required absolute anonymity.

In these calls, Hawkins told Daniel about an idea: He'd created five different LLCs, several named after his racehorses, where new investors could put money for the abortion pill project while staying unidentified. One LLC in particular, Shiroyama, he said, required extra care. According to Daniel, Hawkins said that he had heard from a Catholic priest who wanted to invest in medication abortion but required absolute anonymity. So sensitive was this investment that Hawkins needed to entice the priest with a $320,000 sweetener. He asked Daniel to move that sum from his wife's stake into the Shiroyama LLC—forfeiting some of the Hawkinses' own investment in the deal and passing it to the priest to entice the clergyman to invest further. By approving the transfer, Daniel said he was also losing out financially: Less of the money invested this way would end up in his pocket, because the LLC would not have to pay his private equity fund's 1 percent management fee (or 20 percent of any profits it accrued). But it seemed that both Daniel and Hawkins were giving something up to help the project get on its feet, in hopes of reaping the rewards later.

After the sweetener, the priest seemed to come through—according to Daniel, Shiroyama LLC invested just shy of $950,000 over the next year. Later on, Hawkins asked Daniel to move another $1.7 million of his wife's interest into three of the LLCs, as additional enticements for more investors he was drumming up. Yet another LLC plowed $700,000 into the project.

The LLC investments came just in time: On September 28, 2000, the FDA officially approved Mifeprex, the commercial name for Danco's mifepristone pill. These investors' financial bet was finally on track to pay dividends.

Within three years, the Danco project had earned enough on Mifeprex to start repaying investors. Several Supreme Court cases soon made it easier for states to enact abortion restrictions, an opportunity that conservative states took up with gusto—sending ever more women looking for the discreet pill they could take at home. By 2010, about a quarter of early abortions were done with mifepristone, and Danco had paid everyone back. Now that everyone had been made whole, it was time to finally start making a profit, which was great news for both investors and Daniel's

private equity fund, now named MedApproach Holdings, which would get somewhere between 10 and 20 percent of profits made by investors, as well as the management fees it had deferred while the project got off the ground.

Daniel contacted Hawkins to get clearer information on all of the investors so he could pay them their portions of the profits. He says he sent multiple emails, heard nothing for five months, and eventually mailed him a letter. That's when Hawkins called Daniel, who recalls Hawkins angrily reiterating that Shiroyama's investor was a priest who required absolute confidentiality. "You are never going to find out who he is," he said, "and it is none of your business!" In a second call, Daniel says Hawkins offered to pay him money instead of providing any documentation revealing the identities of the investors he'd brought in. (A source with knowledge of the proceedings says that Hawkins never made this offer.)

That started a snowball of suspicion, and within a matter of months, Daniel filed a lawsuit against Hawkins in federal court. The proceedings led to a stunning revelation: There never was a priest. The money that had passed through the Shiroyama LLC had been from the purportedly broke Hawkinses. (In federal court documents, Hawkins maintained that he never called the investor a priest; rather, he had merely said he was a religious friend. This friend had planned to invest but backed out due to his faith and fear of anti-abortion reprisals, forcing Hawkins to use his own money to cover the investment. The friend filed a declaration in court supporting much of Hawkins' account, though he contests that he'd ever committed to an investment in the first place.) The whole thing looked like a scheme by the Hawkinses to expand their investment in medication abortion and reap its returns—while paying less in management fees and sharing fewer profits. Daniel claimed that the demise of LTCM had been a hit on the Hawkinses' wealth, and the tale of the secret, abortion-supporting priest was a way to make some of it back. The Hawkinses disagreed, saying they'd never misled Daniel, and that their investment in the Shiroyama LLC was aboveboard and never intended as a profitable runaround. Eventually, Daniel and the Hawkinses opted to settle for an undisclosed amount.

Documents filed by Daniel as part of a lawsuit say that the Hawkinses' investment in MedApproach has made a return on investment of 228.79 percent.

Both parties have made a fortune on Mifeprex. Documents filed by Daniel as part of a different lawsuit say that the Hawkinses' investment in MedApproach has made a return on investment of 228.79 percent. The actual dollar amount has been fastidiously redacted in all the case's legal filings, but based on the Hawkinses' disclosures of their total investment in the mifepristone project—between $9 million and $11 million—their earnings would come to between $20.5 million and $25.1 million. (A source familiar with the suit disputes this return on investment, arguing it is far lower.)

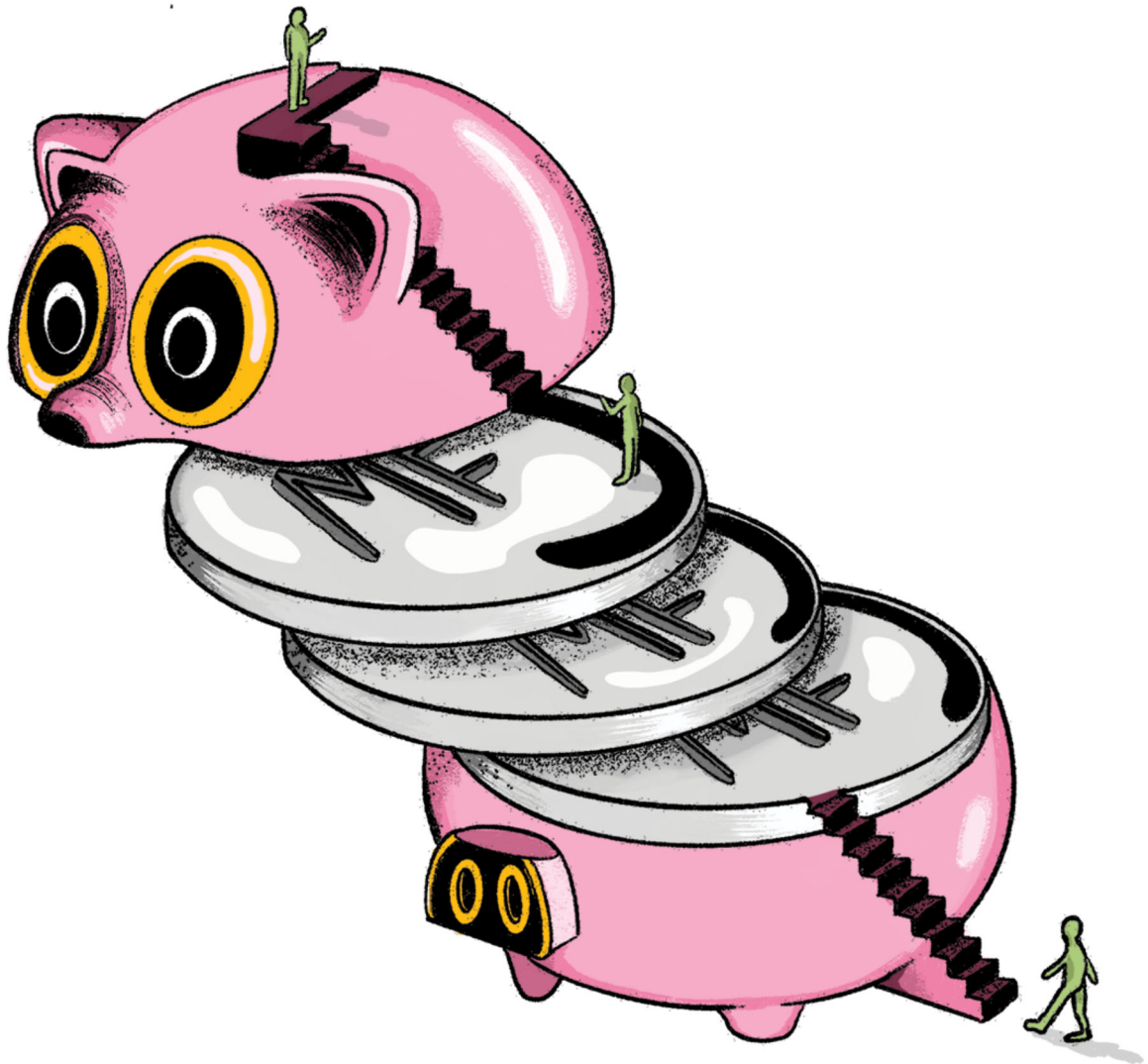
Those same filings say that the average return on investment for everyone who invested in Danco was about 452 percent over 23 years. Even in the high-flying world of private equity—where the average annual return over the last 20 years has been about 10.5 percent—that's nothing to sneeze at. In a 2022 deposition, the CFO of Danco confirmed that "the Project has ultimately become quite successful," and investments have "been extremely profitable."

Since the Supreme Court gutted *Roe*, demand for medication abortion has skyrocketed. One study analyzed nearly 43,000 medication requests from 30 states and found the average number of daily requests nearly tripled, driven primarily by increases in the 12 states where lawmakers have banned abortion completely. Meanwhile, two of the main digital health startups offering medication abortion by mail—Hey Jane and Choix—reported enormous jumps in interest from potential customers. Choix raised $1 million in venture capital funding in the weeks following the leak of the Supreme Court decision. In October, Hey Jane raised $6.1 million from venture capital investors, after seeing a

ninefold increase in new telehealth patients per day. During the fundraising round, venture capitalists wanted to invest more in the company than Hey Jane had asked for.

All of that suggests that Danco's business is set to remain profitable, even as a cheaper generic version of mifepristone has cut into Mifeprex's business over the past few years. Just how profitable is anyone's guess—but valuable enough that Daniel and the Hawkinses have kept fighting about it. In May 2021, the Hawkinses filed a lawsuit in Delaware to wrest control of Danco from Daniel. Their goal was to put an end to what they see as Daniel's extractive, autocratic management of the company by installing a proper board to oversee him. The lawsuit also had the potential to secure more profits for the Hawkinses.

When the Danco project was restructured in the '90s and the Hawkinses' shares got moved around, a restriction was appended to their stake: Daniel, whose private equity fund controlled the investment, would hold votes attached to the shares. In other words, the Hawkinses' investment gave them the right to partake in Danco's profits, but they could not have a say in the operations of the company. That right stayed with Daniel, in the form of a proxy vote. The Hawkinses' lawsuit sought to win back their votes, ostensibly to sell their stake at a better price. (Shares that don't have votes attached are worth a lot less.)



For Daniel, the stakes are enormous. His proxy vote affords him control over company operations and, combined with his role as executive chair of Danco's board of directors—which gives him final approval of the company's budget—

earns him about $455,000 in annual fees and compensation. He earns an extra $75,000 each year for work related to particular entities that are part of Danco's complex financing structure, as well as tens of thousands more for other Danco-related business. All told, Daniel has earned about $10.3 million in fees alone.

This past January, the Delaware Supreme Court sided with the Hawkinses. The consequences of the decision are still unfolding. But now that the Hawkinses have regained their shares' voting power, they have additional authority to push for changes at Danco. "This has been an incredibly challenging ordeal for Mrs. Hawkins," her spokesperson said in a statement. "Her focus has always been on preserving women's right to safe, reproductive health care. The battle over corporate governance has threatened women's ability to receive the full benefit of this impactful medicine. We are deeply grateful that the courts in Delaware have cleared the way for that to happen."

For both sides, each of these lawsuits have been a fight to preserve the wealth they've built through the mifepristone project, and to pave the way for earning even more—while keeping the other party from wresting away money and control. A source close to the Hawkinses, for example, called Daniel a "control freak" who hoards money from Danco for himself. Meanwhile, one of Danco's other major investors accused the Hawkinses of trying to steal the business.

Pike told me something similar. "Greg, this is basically his only asset," he said. "His billion dollars he thought he had [through LTCM], he doesn't have, and he's obsessed with not being able to control his destiny."

That destiny could not be more promising. The end of *Roe v. Wade*, mixed with the FDA's new approval of retail sales for mifepristone, could unlock immense profit. Their product's mission may be a social good, but creating value for investors—themselves—seems to have become a driving motivation: one where women faced with impossible circumstances are reduced to the impersonal language of customer capture.

Systematic Review

SAGE Open Medicine

SAGE Open Medicine
Volume 5: 1–17

DOI: 10.1177/2050312117740490
journals.sagepub.com/home/smo
SAGE

Pregnancy associated death in record linkage studies relative to delivery, termination of pregnancy, and natural losses: A systematic review with a narrative synthesis and meta-analysis

David C Reardon[1] and John M Thorp[2]

Abstract

Objectives: Measures of pregnancy associated deaths provide important guidance for public health initiatives. Record linkage studies have significantly improved identification of deaths associated with childbirth but relatively few have also examined deaths associated with pregnancy loss even though higher rates of maternal death have been associated with the latter. Following PRISMA guidelines we undertook a systematic review of record linkage studies examining the relative mortality risks associated with pregnancy loss to develop a narrative synthesis, a meta-analysis, and to identify research opportunities.
Methods: MEDLINE and SCOPUS were searched in July 2015 using combinations of: mortality, maternal death, record linkage, linked records, pregnancy associated mortality, and pregnancy associated death to identify papers using linkage of death certificates to independent records identifying pregnancy outcomes. Additional studies were identified by examining all citations for relevant studies.
Results: Of 989 studies, 11 studies from three countries reported mortality rates associated with termination of pregnancy, miscarriage or failed pregnancy. Within a year of their pregnancy outcomes, women experiencing a pregnancy loss are over twice as likely to die compared to women giving birth. The heightened risk is apparent within 180 days and remains elevated for many years. There is a dose effect, with exposure to each pregnancy loss associated with increasing risk of death. Higher rates of death from suicide, accidents, homicide and some natural causes, such as circulatory diseases, may be from elevated stress and risk taking behaviors.
Conclusions: Both miscarriage and termination of pregnancy are markers for reduced life expectancy. This association should inform research and new public health initiatives including screening and interventions for patients exhibiting known risk factors.

Keywords

Maternal mortality, pregnancy associated death, longevity, pregnancy loss, termination of pregnancy, abortion, miscarriage, risk factors, pregnancy screening, health policy

Date received: 9 November 2016; accepted: 9 October 2017

Introduction

Maternal deaths associated with pregnancy are a major public health concern. Death rate calculations based on death certificates alone, however, consistently miss cases due to the fact that registrars often lack information about the deceased's woman's complete pregnancy history. This problem can be alleviated in part by linking death certificates to birth certificates, fetal death records, termination of pregnancy (TOP) registries, and medical treatment records.

Without such record linkage only 26% of deaths during pregnancy or after live birth or stillbirth would have been

[1]Elliot Institute, Springfield, IL, USA
[2]Department of Obstetrics and Gynecology, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Corresponding author:
David C Reardon, Elliot Institute, PO Box 7348, Springfield, IL 63376, USA.
Email: elliotinstitute@gmail.com

identified from the death registry or death certificates alone, according to a Finnish study.[1] Using death certificates alone, only 12% of deaths following miscarriage or ectopic pregnancy and just 1% of deaths following termination of pregnancy (TOP) could be identified without record linkage.[1] The importance of systematically using record linkage to identify deaths associated with pregnancy losses (TOP, miscarriage, and ectopic pregnancies) is further demonstrated by the same study's findings, which demonstrate that the mortality rate in the year following a pregnancy loss was two to four times higher than that of delivering women.

Record linkage studies are therefore clearly necessary to properly identify the effects of pregnancy on the health and longevity of women. This methodology is especially important to understanding mortality rates associated with TOP and natural pregnancy losses precisely because such deaths are (a) much more common than deaths during pregnancy or after delivery, and (b) less likely to be identified on death certificates alone.[1]

Compared to women who deliver, those who miscarry or have TOP face significantly elevated rates of psychiatric disorders,[2–10] substance use,[5,6,10–13] suicidal behaviors,[5,6,13–16] sleep disorders,[17] post-traumatic stress disorders,[7,18,19] a decline in general health,[20] and elevated rates of recourse to medical treatments in general,[21,22] most of which have been observed within the first through ten years following the pregnancy loss. Any and all of the aforementioned conditions may shorten longevity. It is therefore especially important from a public health and economic viewpoint to improve investigations regarding the mortality rates associated with pregnancy losses.

While the importance of research on maternal mortality is widely recognized, it has appeared increasingly evident to the authors that insufficient attention has been devoted to examining the subset of women's deaths following pregnancy losses. Greater insight into this subset of deaths may help to guide and prioritize the development of proactive health initiatives that can save women's lives and improve health.

Therefore, the authors identified the need for a systematic review which would provide (a) a description and synthesis of all the available qualifying literature, including proposals for research priorities and actionable interventions based on the best available evidence, and (b) a quantitative meta-analysis of the available evidence. To meet these goals, we determined that we should first seek to identify all record linkage studies examining mortality rates associated with pregnancy outcome regardless, without any limitation on time frame. This initial assessment would help us to identify any missed opportunities for examining pregnancy loss associated mortality. Second, we seek to identify all record linkage studies that have specifically examined death rates associated with pregnancy losses, including voluntary and therapeutic terminations. Using this subset of studies, we would then (a) develop a narrative synthesis of the common and specific findings of the relevant studies and (b) undertake a meta-analysis of any comparative mortality rates associated with different pregnancy outcomes which are appropriate to the methods of meta-analyses.

The importance of this investigation is underscored by numerous studies which have found that that parity and the exposure to various pregnancy outcomes has significant effects on life expectancy.[23–25] Record linkage studies examining pregnancy associated life expectancy are needed to help to identify how the number of pregnancies, number of deliveries, and types of pregnancy outcomes may affect the health and longevity of women. These findings, in turn, may then contribute to better screening to identify the subsets of women who may most benefit from interventions to ameliorate any harmful effects and/or to enhance any beneficial effects associated with pregnancy and pregnancy management.

Definitions

Pregnancy loss, as used herein, includes all pregnancy outcomes that do not end in a live birth.[2]

Natural loss is a subset that includes all pregnancy losses except TOP. While the vast majority of natural losses are miscarriages, it should be noted that some researchers have chosen to report only on miscarriages while others have included ectopic pregnancies, still births and other natural losses together. Still other investigators have grouped women who had stillbirths with women who had live births since these pregnancies continued to term or near term.[1]

Pregnancy associated death, has been defined by the American College of Obstetricians and Gynecologists (ACOG) and the United States' Centers for Disease Control (CDC) to include all deaths during pregnancy or within one year of a pregnancy outcome regardless of presumed cause of death.[26] The identification of pregnancy associated deaths has been recognized is an important precursor to efforts to identify maternal deaths, which are defined to include only those deaths for which there is a medical opinion that some aspect of the pregnancy or pregnancy management was a contributing cause of death.[26]

Pregnancy associated long-term mortality is defined to include all deaths following one or more pregnancy outcomes without an imposed time limit. While the time limits used in each study reporting pregnancy associated long-term mortality should always be noted, this definition avoids establishing any arbitrary time limits and prepares the way toward calculating pregnancy associated mortality and life expectancy rates relative to variables such as gravidity, parity, live births, and exposure to pregnancy losses.

Abortion related deaths are defined by the CDC as any "death from a direct complication of an [induced] abortion (legal or illegal), an indirect complication caused by a chain of events initiated by an abortion, or an aggravation of a pre-existing condition by the physiologic or psychologic effects

of abortion."[27] The deliberate choice to place no time limit on the definition of TOP related deaths reflects the fact that there is no clear temporal limit on physiological and psychological effects that may contribute to subsequent death.

TOP associated deaths (or abortion associated deaths) are herein defined as the subset of pregnancy associated deaths which are within one year of a TOP. The one year limit corresponds to that for "pregnancy associated deaths."

TOP *associated long-term mortality* is an extension of the CDC's "abortion related deaths" and include all deaths among women with a history of TOP without regard to time. Just as the systematic identification of early and late maternal deaths must be preceded by a systematic identification of pregnancy history, so the identification of *abortion related deaths* should be preceded by the systematic identification of TOP history without a predefined time limit.

Materials and methods

PRISMA guidelines were consulted and employed where appropriate in the development and writing of this review.

Eligibility criteria

The first level of predefined eligibility criteria were: (1) the study was available in English; (2) the study examined mortality rates of women relative to one or more pregnancy outcomes; and (3) the study included systematic linking of death certificates to independent records used to identify if the deceased had one or more pregnancy outcomes within a year of her death. The independent records might be one of the following: birth certificates, fetal death certificates, TOP registries, paid insurance claims, or comprehensive hospital or medical records documenting treatments related to pregnancy.

The second level of eligibility criteria was to identify all publications meeting the first level of inclusion criteria which reported on death rates associated with any form of pregnancy loss (miscarriage, legal TOP, ectopic pregnancy, still birth, or any other failed pregnancy) as identified through records independent of the death certificates. This step eliminated studies that examined only mortality rates associated with childbirth, or which failed to distinguish between deaths associated with childbirth and pregnancy loss. This step helped to both identify missed research opportunities and to identify the eligible studies which do have information regarding mortality rates associated with pregnancy loss but failed to report this data.

The third step was to identify studies eligible for inclusion in a meta-analysis. This subset was drawn from the list of studies meeting the second level of eligibility. This third level of eligible studies included only those that (a) report mortality rates within one year for all three pregnancy outcomes of interest (childbirth, natural losses, and TOP) and (b) provided the most recently relevant data, thereby excluding duplication of results when the same population of women were examined in more than one study.

Information sources and search terms

In July of 2015, a SCOPUS search was conducted using the search (((TITLE-ABS-KEY (maternal mortality) OR TITLE-ABS-KEY (maternal death))) AND ((TITLE-ABS-KEY (record linkage) OR TITLE-ABS-KEY (linked records)))) OR (((TITLE-ABS-KEY (pregnancy associated mortality) OR TITLE-ABS-KEY (pregnancy associated death))) AND ((TITLE-ABS-KEY (record linkage) OR TITLE-ABS-KEY (linked records)))). A total of 458 records of potential interest was returned.

A MEDLINE search was conducted using the search ((("pregnancy associated mortality" OR "pregnancy associated death") AND ("record linkage" OR "linked records")) OR (("record linkage" OR "linked records") AND ("maternal mortality" OR "maternal death")). This search returned 20 references.

Additional candidates were identified using the "snowball method," the review of all references cited by eligible papers plus citations from other maternal mortality reviews.

Study selection. After elimination of duplicates, all titles and abstracts were examined to identify publications with a prospect for meeting the predefined inclusion criteria. Those deemed candidates for inclusion were retrieved for full text review and studied to determine which articles met the predetermined inclusion criteria. Assessments of those studies qualifying for both levels of inclusion criteria were conducted by two reviewers, with disagreements resolved by discussion.

Risk of bias. Studies qualifying for both levels of inclusion were scored for bias using the Newcastle-Ottawa Quality Assessment Scale (NOQAS) for cohort studies.

Data collection for descriptive summary of literature. Each study meeting the second level of eligibility was entered into a table identifying the source, population size, time period examined, types of pregnancy outcomes examined, means of identifying deaths and pregnancy outcomes, any confounding variables that were examined in the study, NOQAS score, and a summary of major findings. The table was completed by two reviewers, with disagreements resolved by discussion.

Data collection for meta analysis. To calculate the age adjusted number of deaths in the first year for each subgroup's population for our meta-analysis we extracted data relative to the reported age adjusted risk of death during the first year following the pregnancy outcome from each country. To avoid duplication of cases, only the most recent study for each country

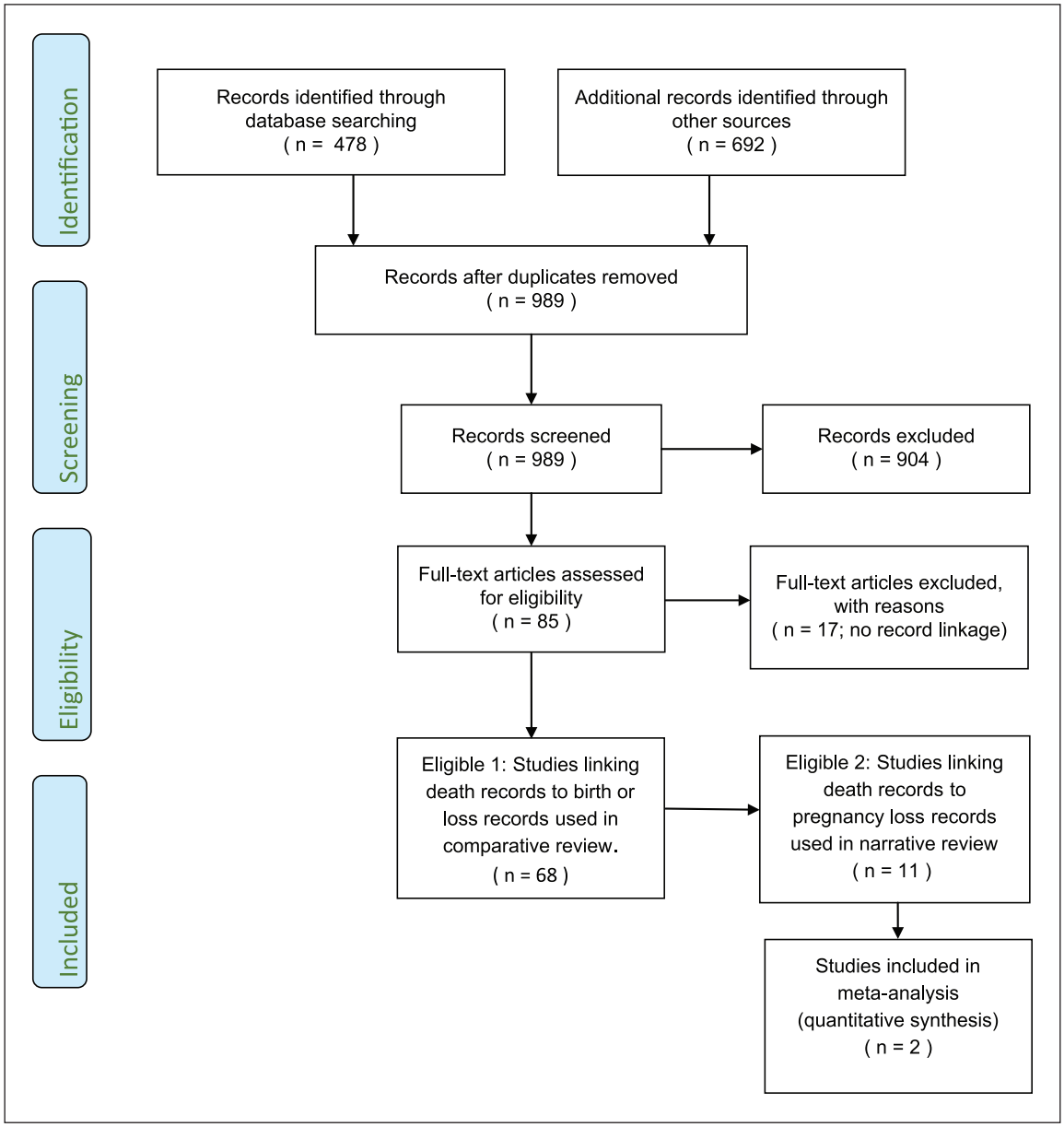


Figure 1. Flow chart of search results, reasons for exclusion, and three levels of inclusion.

was used in the meta-analysis. Using the age adjusted mortality rate of delivering women as the control in each case, odds ratios and confidence limits for each subgroup (TOP vs birth, and natural losses vs birth) and for each study were calculated using EpiInfo 7's StatCalc. These results were then entered into the Comprehensive Meta Analysis software package to produce results using the fixed effects model.

Results

After removal of duplicates, a total of 989 titles were identified by the combination of search terms and review of additional references (Figure 1). Review of abstracts eliminated 904 references. At the second level of review, 14 more were eliminated after full text review because they did not identify pregnancy history using record linkage. Three non-English studies were also identified, but their abstracts indicated that none included data on pregnancy loss associated mortality so English translations were not sought. Thus, a total of 17 studies were eliminated at this stage.

A total of 68 studies examining populations in 11 countries met the criteria for the first level of eligibility. All of the studies identified significantly more maternal deaths than would have been identified by reliance on death certificates alone.

Of the 68 studies identified, 57 included record linkage of only birth and death records. In other words, they lacked any data on deaths associated with pregnancy losses. The distribution by country of these studies was as follows: one in

Bangladesh,[28] one in Brazil,[29] two in Canada,[30,31] one in Denmark,[32] one in Italy,[33] three in Netherlands,[34–36] four in Sweden,[37–39] one in Taiwan,[40] six in the United Kingdom,[41–46] thirty-four in the United States including Puerto Rico,[47–79] and three reporting data from multiple countries for which at least one country's data used record linkage which met our criteria for inclusion.[80–82]

The remaining 11 studies met the criteria for the second level of eligibility: reporting results of linkage of death certificates to independent records of pregnancy loss. These included seven studies from Finland,[1,83–88] two from Denmark,[89,90] and two from the United States.[91,92] Two of these investigated only deaths in the year following TOP.[88,91] The remainder investigated pregnancy associated deaths and/or pregnancy associated long-term mortality relative to both birth and pregnancy loss.

Details of the eleven studies are summarized in Table 1. The column labelled "Confounding Variables Examined" identifies factors which were either (a) controlled for statistically, such as was commonly done in regard to age of the woman, or (b) controlled for by study design, such as restriction of the population to only the lowest economic class, or exclusion of women with prior psychiatric history, or (c) controlled for by showing segregated results for discrete groups, such as married and unmarried. The NOQAS assessment revealed that quality of these studies was very high, with low risk of bias. With a possible range from 0-9, (high corresponding to the highest quality) only the one very earliest study scored below 8.

Figure 2 shows the mortality rate per 100,000 person years for each outcome reported by the latest studies from each of Finland, Denmark, and the United States, showing cumulative mortality rates for both one year and two years. The graph illustrates that mortality rates remain elevated after pregnancy loss beyond one year. Notably, the mortality rate over two years, comparing results from Denmark and California, suggest that low income women are at higher risk but that socioeconomic effects do not fully explain the results. Alternatively, the difference may be due to only first pregnancies being examined in the Denmark study.

Figure 3 shows that the risk of death after pregnancy loss is most elevated in regard to deaths from external causes: suicide, homicide, and accidents compared to both delivering women and women who have not recently been pregnant.[87,92] The implication that psychological effects associated with pregnancy loss may contribute to deaths resulting from self-destructive or risk taking behavior is further supported by a finding of higher rates of death attributed to mental illness (RR = 3.21, 94% CI 1.11–9.27) following TOP, even after controlling for prior psychiatric history.[92]

As several the eleven studies undertook examined associations from a different perspective, a summary of their most important findings, including figures illustrating many of these findings, is provided below:

- Pregnancy loss associated mortality may be over twice that of birth associated mortality.[1] TOP associated mortality is higher than miscarriage associated mortality, which is higher than pregnancy and delivery associated mortality. (Figure 2)
- TOP associated mortality rates are higher than birth associated mortality during the first 180 days[89] and remains higher for six or more years.[89,90,92] (Figure 4)
- Differences in pregnancy associated life expectancy vary according to the type and number of exposures to various outcomes. Successful deliveries may mitigate some of the effects of pregnancy loss.[90,92] (Figure 5)
- There is a dose effect, whereby exposure to multiple pregnancy losses increases the negative effect on life expectancy whereas multiple births increases life expectancy.[90] (Figure 6)
- The risk of death associated with pregnancy loss remains elevated even after controlling for psychological differences and economic class.[92] (Figure 2)
- While the risk of death after pregnancy loss is most elevated in regard to deaths from violent causes,[87,92] there is also evidence that when risk of death after pregnancy loss is tracked beyond one year a significant higher risk is also associated with specific causes of natural death, such as circulatory disease (RR = 2.87, 95% CI 1.68–4.89)[92]

The meta-analysis used age adjusted mortality rates for each pregnancy outcome reported in most recent studies of the population of Finland[86] and Denmark.[89] While the eleven studies included data on women in three countries, neither American study reported age adjusted mortality rates for the first year after pregnancy outcome.

Figure 7 shows results of the meta-analysis using the fixed effects model. It illustrates the comparative risk of death in the first year after TOP compared to delivery and for the first year after natural losses compared to delivery. The risk of death during pregnancy and one year after a delivery the age adjusted pregnancy associated risk of death was 170 percent higher following a TOP (RR = 2.705; 2.243 < 95% CI < 3.263), and 84 percent higher following natural losses (RR = 1.843; 1.420 < 95% CI < 2.392). For all pregnancy losses compared to delivery, the risk was 137% higher (RR = 2.374; 2.038 < 95% < 2.764; Q-value = 8.220, P = .042). The I^2 statistic indicates that about 63% of the variation in the overall results is due to heterogeneity rather than chance.

Discussion

Our systematic review found 68 studies employing record linkage of death certificates to independent records of pregnancy and pregnancy outcomes. In nearly every case, the authors reported that record linkage significantly improved the identification of maternal deaths and pregnancy associated deaths compared to reliance on death certificates alone. We concur with the opinion that the direct and indirect effects of pregnancy on women's mortality rates cannot be accurately accessed without record linkage between death certificates and other medical records.[1]

Table 1. Record linkage studies examining deaths associated with one or more types of pregnancy loss with notes regarding key findings.

Study (year) Country	Population & Time Period (Births / TOP / Natural Losses / Deaths)	Records Examined and Linked	Confounding Variables Examined	Quality Score* Range 0–9	Summary of Major Findings
Shelton and Schoenbucher[91] (1978) United States	All fertile-aged Georgia women in 1975–Feb 1976 (NA / 19,877 / NA / 1,610)	death certificates TOP certificates	none	6	In this exploratory study Georgia death certificates were used to identify ten deaths preceded by an abortion, With an average observation period of 8 months, the one year abortion associated mortality rate was 75.5 per 100,000 cases. Deaths included 2 suicides (one four days after the TOP), 3 homicides (all within 4 months), 3 attributed to accidents, one sudden death from "coronary occlusion," and one death from ovarian cancer (the woman was receiving chemotherapy at time of TOP). Record linkage was incomplete due to limited information on the TOP certificates.
Gissler et al.[83] (1996) Finland	All fertile-aged women, 1987–1994. (513,472 / 93,807 / 71,701 / 9,192)	death certificates birth certificates TOP registry hospital discharge	age social class marital status	9	National suicide study. 1,347 suicides identified. No suicides while pregnant were found. Compared to women not pregnant in the year prior to suicide, women who aborted were three times more likely to commit suicide (3.08, 95%CI 1.57 to 6.03), pregnant and delivering women were half as likely (0.52; 95%CI 0.19 to 1.41), and women who miscarried were not significantly different. Suicide risk was highest in first two months following the pregnancy outcome.
Gissler et al.[84] (1997) Finland	All fertile-aged women, 1987–1994. (513,472 / 93,807 / 71,701 / 9,192)	death certificates birth certificates TOP registry hospital discharge	age	8	All death certificates were linked to medical and TOP registry to identify pregnancy within a year prior to death. Only 22% of pregnancies were identified on death certificates. Record linkage to TOP and hospital discharge records doubled number of deaths identified compared to linkage to birth certificates alone. Compared to women not pregnant, the age adjusted mortality ratio was half for delivering women (0.50, 95%CI 0.32 to 0.78) and significantly higher following TOP (1.76, 95%CI 1.27 to 2.42).
Gissler and Hemminki[85] (1999) Finland	All fertile-aged women, 1987–1994. (513,472 / 93,807 / 71,701 / 9,192)	death certificates birth certificates TOP registry hospital discharge	age	8	Compared to women who were not pregnant in the year before death, women who had TOPs had an 81% higher rate of death (1.81, 95%CI 1.31 to 2.50), women who gave birth had a 53% lower risk of death (0.47, 95%CI 0.30 to 0.74), and those who miscarried were not significantly different (0.85, 95%CI 0.58 to 1.24). 34% of deaths were from external causes. Women who had TOPs had significantly elevated risk of death from suicide, accidents, and homicides. Risk of death from natural causes was significantly lower for women giving birth (0.47, 95%CI 0.25 to 0.86) and for women who miscarried (0.39, 95%CI 0.20 to 0.75).

Table 1. (Continued)

Study (year) Country	Population & Time Period (Births / TOP / Natural Losses / Deaths)	Records Examined and Linked	Confounding Variables Examined	Quality Score* Range 0–9	Summary of Major Findings
Reardon et al.[92] (2002) United States	Medicaid eligible and fertile aged women in California with pregnancy outcome in 1989 (116,936 / 56,343/ NA / 1,294)	death certificates all paid medical claims	age economic class 12–18 months prior psychiatric history	9	Medical records for women with a Medicaid treated pregnancy in 1989 were linked to death certificates. After controlling for psychiatric history and age, women who had a TOP were at significantly higher risk of death. The relative risk was 2.03 (95%CI 1.33 to 3.10) in the first two years following pregnancy outcome, 1.98 (95%CI 1.25 to 3.15) in years three and four, and declined to an insignificant 1.35 (95%CI 0.89 to 2.05) in the fifth and sixth years, and 1.29 (95%CI 0.84 to 1.96) in the seventh and eighth years. Multiple pregnancy outcomes significantly affected mortality rates. During the eight years following pregnancy, women who aborted had a significantly higher age-adjusted relative risk of death compared to delivering women from all causes (1.61, 95%CI 1.30 to 1.99), suicide (3.12, 95%CI 1.25 to 7.78), and homicide (1.93, 95%CI 1.11 to 3.33), as well as from natural causes (1.44, 95%CI 1.08 to 1.91), circulatory diseases (2.00, 95%CI 1.00 to 3.99), and cerebrovascular disease (4.42, 95%CI 1.06 to 18.48).
Gissler et al.[1] (2004) Finland	All fertile-aged women, 1987–2000. (865,988 / 156,789 / 118,490 / 15,823)	death certificates birth certificates TOP registry hospital discharge	age	8	All death certificates were examined. A total of 419 deaths were among women pregnant in the year prior to death. Without record linkage, 73% of pregnancy associated deaths would have been missed. Following live or still birth, 27% of deaths within 42 days and 78% of deaths from 43–364 days would have been missed without record linkage. Following TOP 71% of deaths within 42 days and 97% of deaths between 43–364 days would have been missed without record linkage. Following miscarriage or ectopic pregnancy, 54% of deaths within 42 days of pregnancy outcome and 94% of deaths between 43–364 days would have been missed.
Gissler[86] (2004) Finland	All fertile-aged women, 1987–2000. (865,988 / 156,789 / 118,490 / 15,823)	death certificates birth certificates TOP registry hospital discharge	age	8	One-year age adjusted mortality rates were calculated for women not pregnant in the year prior to death and compared to age adjusted mortality rates of three groups of women who were pregnant at death or during the year prior to death. The death per 100,000 was 57.0 for not recently pregnant women, 28.2 for delivering or pregnant women (RR 0.49, 95% CI 0.43–0.56), 51.9 for women who miscarried (RR 0.91, 95% CI 0.71 to 1.17), and 83.1 for women who had TOPs (RR 1.45, 95% CI 1.22 to 1.73). Women aged 25–34 who had TOPs were significantly more likely to die of circulatory system disease compared to not recently pregnant women, delivering women, and those who miscarried (rates per 100,000, respectively: 8.7; 4.4; 3.3; 1.5).

(Continued)

Table 1. (Continued)

Study (year) Country	Population & Time Period (Births / TOP / Natural Losses / Deaths)	Records Examined and Linked	Confounding Variables Examined	Quality Score* Range 0–9	Summary of Major Findings
Gissler et al.[87] (2005) Finland	All fertile-aged women, 1987–2000. (865,988 / 156,789 / 118,490 / 15,823)	death certificates birth certificates TOP registry hospital discharge	age	8	This study examined only deaths from external causes. The death rate from external causes per 100,000 was 24.2 for women who had not been pregnant, 10.2 for those giving birth, 35.2 for those with natural losses, and 60.3 for those who had TOPs. The tables present segregated results show death rates from suicide, homicide, and those classified as accidental varied significantly by age and pregnancy outcome. The authors endorse recommendations for routine post-TOP checkup screening for depression and psychosis in the weeks following a TOP.
Reardon and Coleman[89] (2012) Denmark	All fertile-aged whose first pregnancy was in 1980–2004. (318,646 / 119,179 / 25,648 / 2,238)	death certificates birth certificates TOP registry hospital discharge	first pregnancy age at time of pregnancy; year of woman's birth	9	Age and maternal birth year adjusted mortality rates following first pregnancy outcomes were calculated over numerous time periods. Deaths rates for the first and second year are shown in Figure 1. Cumulative TOP associated mortality was significantly higher for every time period examined from 180 days to 10 years for both early and later TOP. The cumulative odds ratio for early TOP declined from a high at 180 days (2.03, 95% CI 1.11 to 3.71) to a low at ten years (1.39, 95% CI 1.22 to 1.60). Mortality rates associated with miscarriages were lower than for TOP and were significantly higher than for birth for periods over four years.
Coleman et al.[90] (2013) Denmark	All fertile-aged women, 1980–2004. (438,134 / 171,582 / 111,205 / 5,137)	death certificates birth certificates TOP registry hospital discharge	year of woman's birth age at last pregnancy number of births number of TOPs number natural losses	9	This study examined all causes of death using 25 years of data using numerous control variables, including exposure rate to various pregnancy outcomes. A dose effect was observed as shown in Figure 6. Exposure to various combinations of pregnancy outcomes was significant. The rate per 100,000 was 352 experiencing only births, 365 for those with both birth and natural losses, 541 for those with both births and TOP, 549 for those with no pregnancies, 550 for those with births, TOP and natural losses, 805 for those with only natural losses, and 1281 for those with only TOP. These findings suggest that TOP combined with natural loss compounds the risk of reduced longevity while a successful birth may reduce the risks associated with pregnancy loss.
Gissler et al.[88] (2014) Finland	All fertile-aged women, 1987–2012. (NA / 284,751 / NA / 3,798)	death certificates TOP registry	age	8	Based on prior research associating TOP with higher suicide rates, unofficial guidelines in Sweden recommended 2–3 week post-TOP assessments of psychological adjustment. These guidelines were made official in 2001. This study sought to examine if the guidelines adopted in 1996 may have reduced TOP associated suicide rates. The elevated risk of suicide after TOP declined from 2.84 (95% CI, 2.05 to 2.93) before 1997 to 2.44 (1.80 to 3.32) for 1997 thru 2012, but the drop was not statistically significant.

*Details of the Quality Score assessment can be viewed at: https://docs.google.com/spreadsheets/d/1T0GySPufF4MXnuTNwmiDgcqHf1yh66UIso1AotTP8IQ/edit?usp=sharing

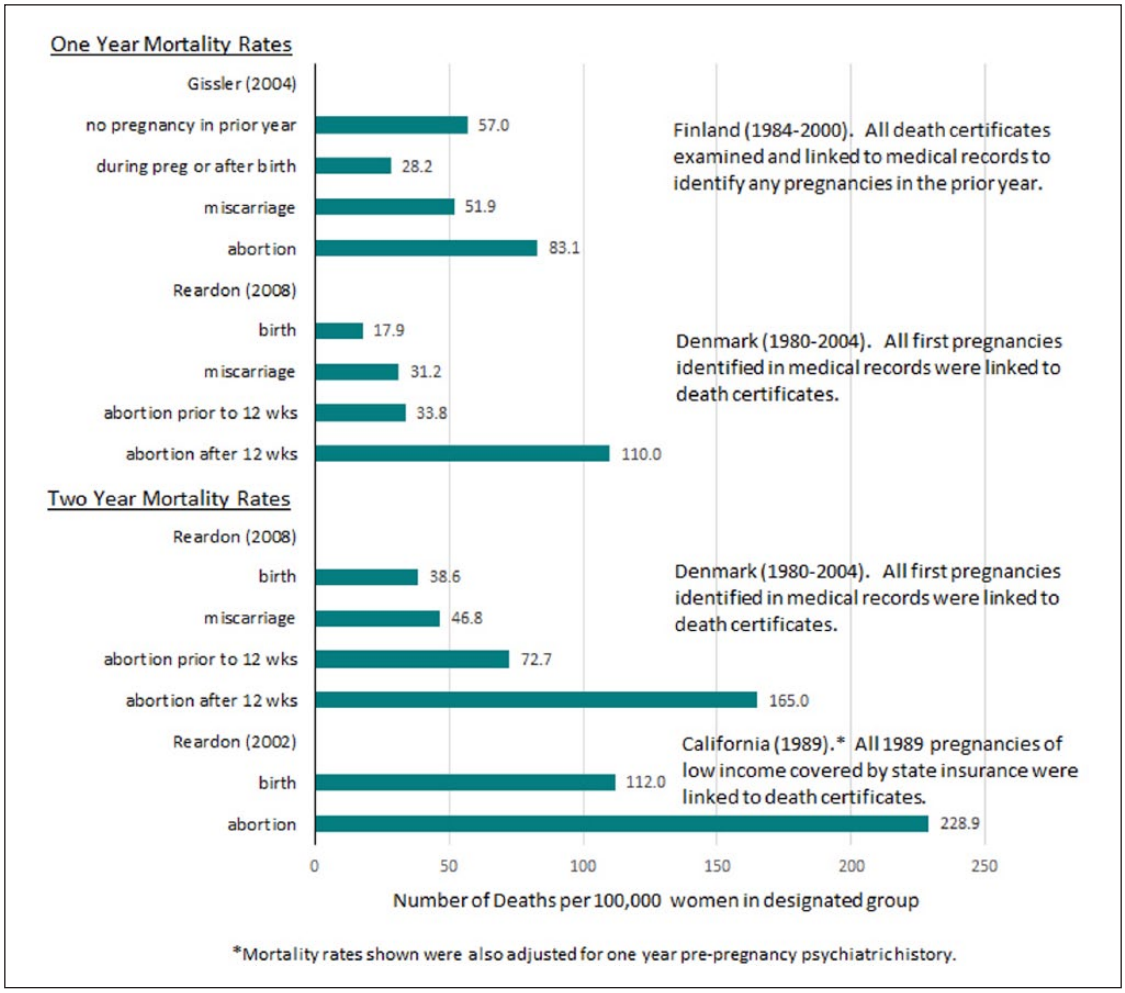


Figure 2. Cumulative Age Adjusted, All Cause Mortality Rates per 100,000 Women for One and Two Year Periods Following Pregnancy Outcome.

This systematic review also revealed that every record linkage study examining mortality rates relative to different pregnancy outcomes has revealed that pregnancy loss is associated with a higher risk of death than childbirth. These studies also show that this elevated mortality risk persists over many years, is multiplied by repeat exposure to pregnancy loss, and may be reduced by successful deliveries. The quality of these eleven studies is very high, with all but the one earliest attempt scoring 8 or above on the NCQAS (with a range 0–9).

Overall, the meta-analysis revealed that pregnancy loss associated mortality is more than double that of delivery associated mortality. Notably, the Danish data used in the meta-analysis included *only* first pregnancy outcomes while the Finnish data included all pregnancy outcomes. This may explain the higher pregnancy loss mortality rate observed in the Finnish data since a significant portion of the Finnish subjects would have been exposed to multiple pregnancy losses for which a dose effect of increased mortality risk has been observed.[90]

A disproportionate share of pregnancy loss associated deaths are due to suicides, accidents, or homicide.[83,86,87,92] In case study reports from mental health professionals and surveys of women struggling with pregnancy loss issues heightened risk taking and self-destructive behaviors are reported which may contribute to rates of accidents and homicide, in addition to suicide.[93] Risk of death from accidents and homicide may also be impacted by the elevated risk of substance abuse associated with TOP.[10–12] This hypothesis is supported by one U.K. study of pregnancy associated deaths that reported that[1] a major portion of accidental deaths were due to drug overdose, and[2] of eight women who died after being struck by cars as pedestrians, seven were drug users.[43] These findings underscore the importance of record linkage as a precursor to efforts to evaluate "abortion related deaths," as defined by the CDC.[27]

Strengths and weaknesses

A strength of the narrative portion of this review is that while only 11 of 68 record linkage studies of mortality rates associated with pregnancy included examination of deaths associated with pregnancy losses, these eleven examined a

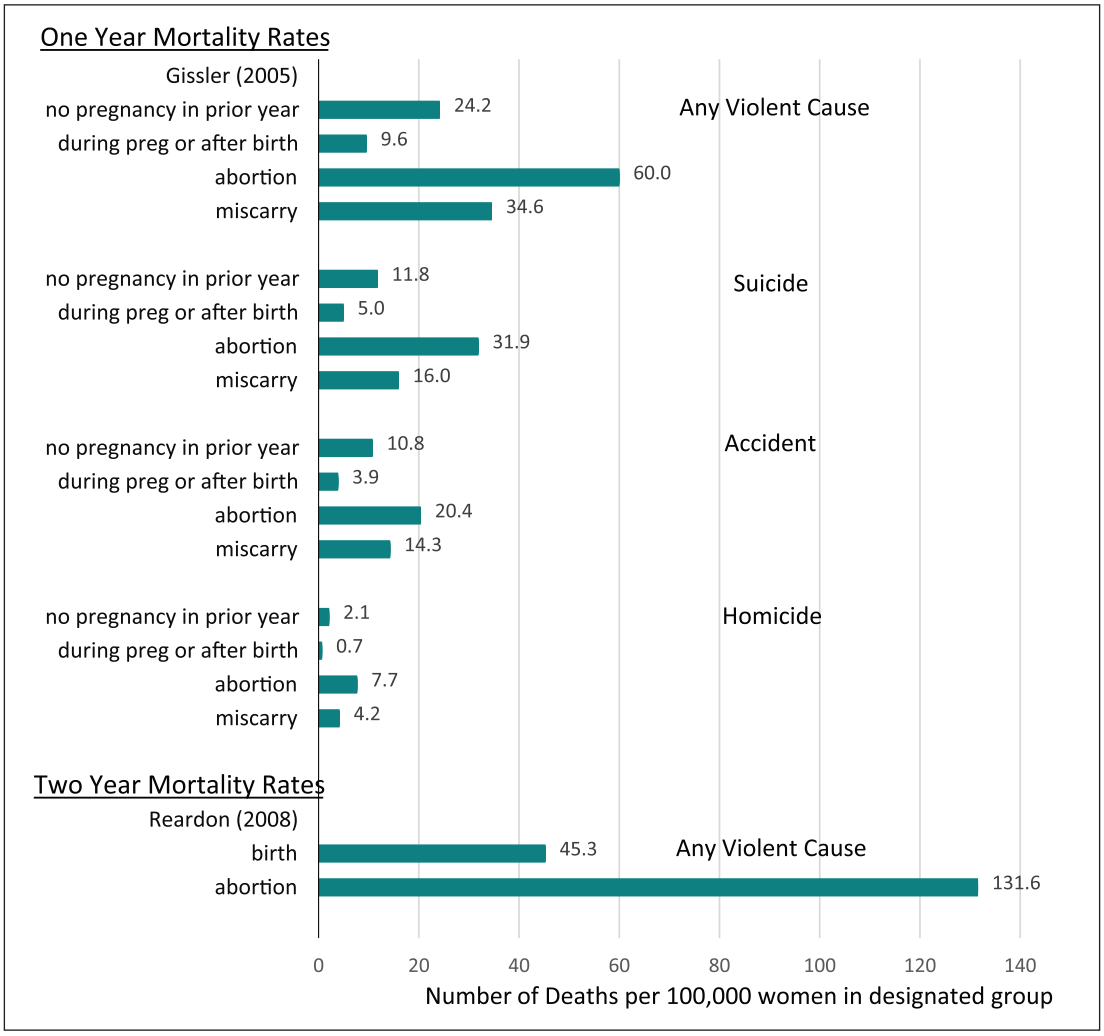


Figure 3. Cumulative Age Adjusted, Violent Cause Mortality Rates per 100,000 Women for One and Two Year Periods Following Pregnancy Outcome.
*Mortality rates shown were also adjusted for one year pre-pregnancy psychiatric history.

variety of different time frames and confounding variables, including economic class, marital status, age, number and types of prior pregnancy outcomes, and prior psychiatric history. At the same time, however, it is also a weakness that all of these confounding variable were not addressed in every study. The fact that all of these studies, despite variations, showed a consistent trend in findings indicates that the trend is a real one and is likely to replicated if applied to other populations.

Clearly, a priority of future research should examine a broader number of confounding variables across more populations to better understand the direct and indirect pathways and co-occurring risk factors that may guide future interventions. Future studies should seek to control for potential confounders including: income inequality, psychiatric history, access to medical care including birth control, intimate partner violence, intentionality of pregnancy, and level of maternal attachment to the pregnancy.

A major weakness of our meta-analysis is that data on mortality rates in the first year following pregnancy losses were only available from two countries, which highlights the failure of most researchers to address this issue. In addition, a minor weakness is that the Danish study included stillbirths in the natural loss grouping while in the Finnish study stillbirths were included in delivery category. Since the number of stillbirths were not reported, we could not adjust for this difference. But given the expected low number of stillbirths, this difference in categorization is very unlikely to have a major impact on the results. Another inconsistency is that all the studies from Finland included deaths during pregnancy in with deaths following a delivery (live or stillbirth), potentially adding nine months mortality risk to the one-year post-delivery mortality rate. This would tend to inflate deaths associated with delivery. Reporting deaths during pregnancy as a separate item would be preferable. These points highlight why more consistent classification standards would be helpful in future research.

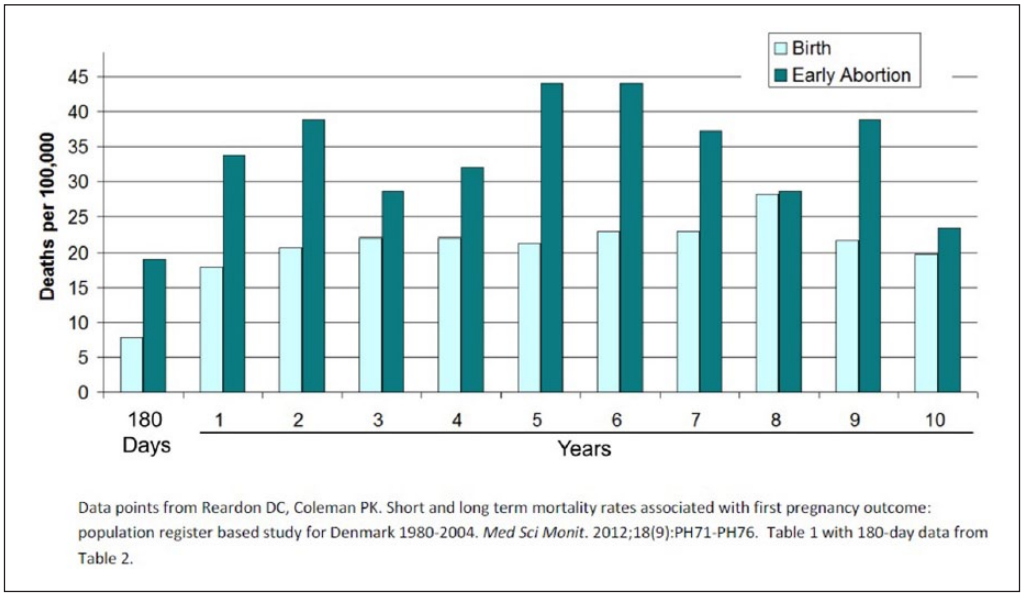


Figure 4. Death rates following first pregnancy outcome through 180 days and during each of the first through tenth years after pregnancy outcome.

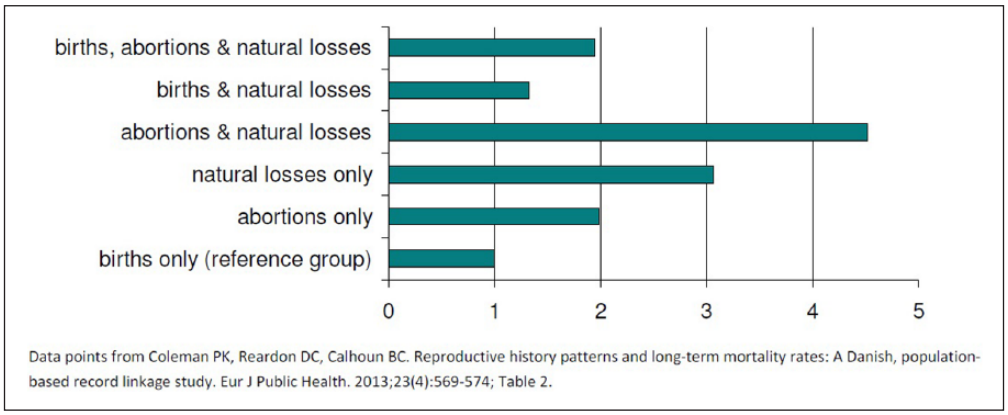


Figure 5. Adjusted odds ratios for pregnancy associated long-term mortality by exposure to types of pregnancy outcomes. Adjusting for age at last pregnancy and number of pregnancies.

In our opinion, any pregnancy that fails to produce a live birth should be treated as a pregnancy loss since there may be grief issues impacting future health. Rare cases of multiple gestations including both live birth and fetal loss are confounding and should be excluded from more general analyses or treated as a separate group.

Future research and missed opportunities

Unfortunately, many opportunities to investigate pregnancy associated mortality and long-term mortality have been missed, to date. Our literature review found that only 11 of 68 record linkage studies (and only 2 of 37 studies in the United States) explored mortality rates associated with pregnancy loss.

This oversight can and should be corrected. Even in countries without central TOP registries, such as exist in Finland and Denmark, exposure to TOP and miscarriage can be identified through medical records and insurance claims, as shown by researchers in the United Kingdom,[15] Canada,[22] and in the United States.[91,92] Unfortunately, except for these rare exceptions, most of the leading investigations into pregnancy associated deaths in Canada, the United Kingdom and the USA have failed to use these same techniques to investigate deaths associated with TOP or miscarriage.

Another missed opportunity appears to have occurred in a study of Italian women[33] in which researchers report that they did, in fact, link death certificates to records of terminations and miscarriages, but unfortunately their published analyses failed to provide any breakdown of death rates relative to each pregnancy outcome. Our request for a breakdown of deaths associated with each type of pregnancy outcome was rejected.

The failure of so many studies to report on pregnancy loss associated deaths indicates that there may be a risk of reporting bias. For example, social, political, or academic

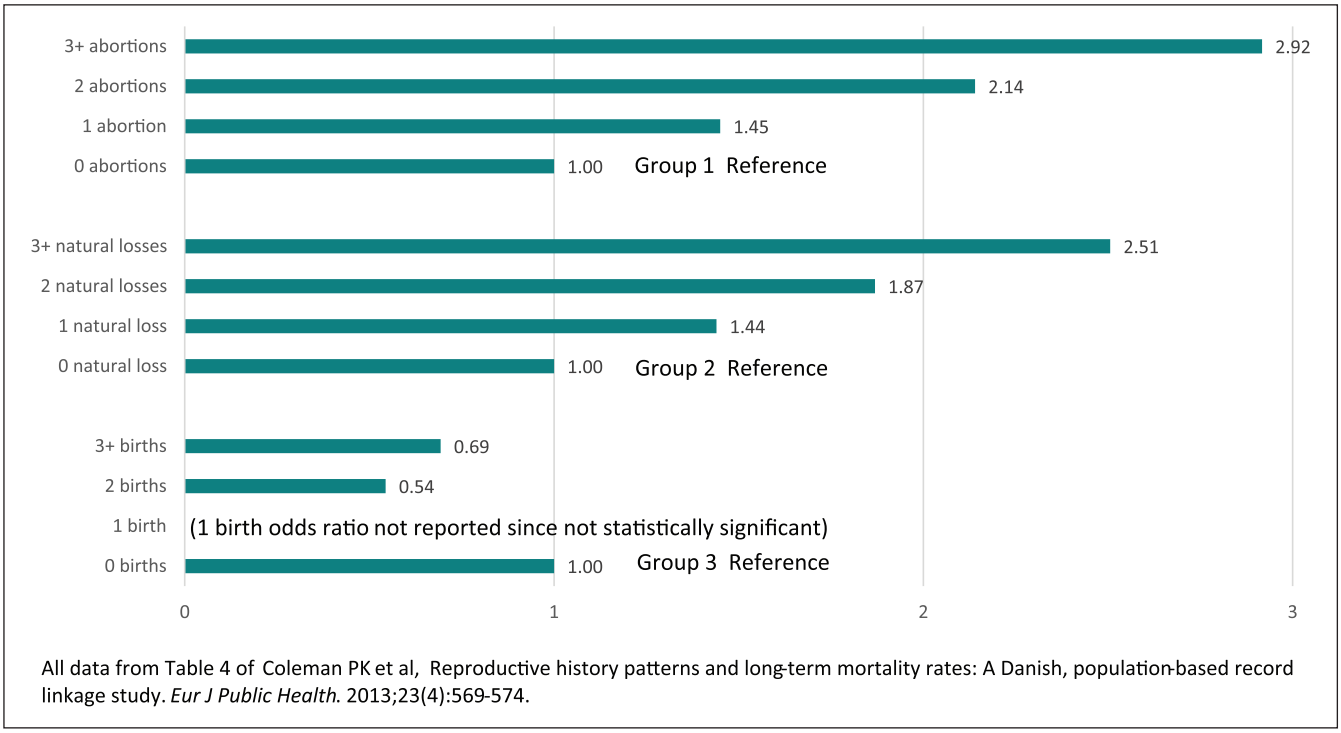


Figure 6. Adjusted Odds Ratios for Pregnancy Associated Long Term Mortality Rates by Frequency of Exposure to Each Pregnancy Outcome—Denmark 1980–2004.
Group 1. The odds ratios for exposure to abortion are adjusted for age at last pregnancy, number of births and number of natural losses.
Group 2. The odds ratios for exposure to natural loss are adjusted for age at last pregnancy, number of births and number of abortions.
Group 3. The odds ratios for exposure to birth are adjusted for age at last pregnancy, number of natural losses and number of abortions.
All data from Table 4 of Coleman PK et al.[90]

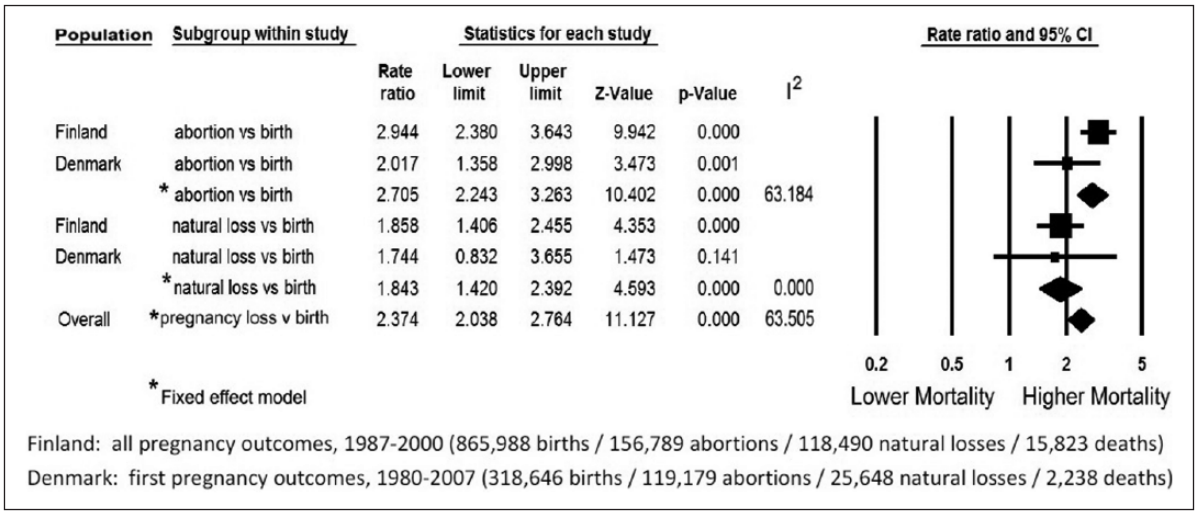


Figure 7. Meta-Analysis of Age Adjusted One Year Mortality Rates Associated with Comparative Pregnancy Outcomes.

sensitivities relative to efforts to promote legalization of safe abortion in developing countries may produce a bias against investigating and/or publishing findings that may show TOP is associated with an increase in mortality rates.[94,95] On the other hand, even though such findings have been reported since at least 1997,[83,84] there may also be lack of sufficient awareness among researchers regarding the elevated mortality rates associated with pregnancy loss. In either case, it is clear that in most countries where record linkage studies have been performed there *are no structural obstacles* to expanding record linkage studies to include pregnancy loss associated mortality. What is required is simply the academic and/or political will to undertake such investigations.

What is already sufficiently clear is that mortality rates and longevity are significantly affected by exposure to pregnancy losses, whether natural or induced. Therefore, in the interests of patients, future investigations into pregnancy associated mortality should *all* include efforts to identify and report on the comparative effects associated with prior exposure to TOP, miscarriage, and other natural losses. Such research is necessary to guide the development of better screening and treatment strategies for those subsets of women who may most benefit from targeted interventions.

Incidental or causal relationships?

As discussed above, termination of pregnancy remains a sensitive and politically charged issue, for both those who defend it as a fundamental woman's right and those who oppose it for moral reasons. In our experience, these passions often inspire a hypercritical level of suspicion regarding any epidemiological findings which run counter to preconceived expectations.

For readers to access their own biases regarding this subject matter, simply imagine if our results were all reversed and the risk of death in the year following a TOP was half that associated with childbirth. Would the reader consider such reversed results more comfortable or more disturbing? Would such results provoke more confidence in the value of record linkage studies or more suspicion?

In either event, it is important to interpret these findings in as balanced a perspective as possible. Correlation does not prove causation. There may be common risk factors for pregnancy loss which explain the elevated risks.[96] Indeed, given the fact that a disproportionate number of deaths associated with prior pregnancy loss are due to suicide and accidents, it would appear that causal contribution would most likely be indirect and chiefly mediated by psychological effects which are known to occur among women who experience a pregnancy loss.[2–10,17–19] Moreover, the finding that there pregnancy loss has a dose effect on increased risk of death[90] (Figure 6) strongly parallels the finding of pregnancy loss having a dose effect on increased risk of mental illness.[2,5,13]

But even if the elevated risks can be entirely explained by common risk factors, it is critically important to acknowledge that these findings are still clinically relevant and very useful. Why?

Because a history of pregnancy loss is at least a *useful marker* for identifying women who may need additional screening, counselling and care. Therefore, alert clinicians can and should screen for a history of pregnancy loss in order to use this actionable information as detailed in our clinical recommendations below. How this marker may be used to provide better screening and referrals will be discussed more fully in the next section.

Additional support for a causal interpretation is found in studies which have identified the first onset of psychological problems, such as sleep disorders[17] or substance abuse,[97] soon after a pregnancy loss among women who did *not* previously have these problems.[13] Another important study examined hospital admission rates for attempted suicide rates prior to pregnancy and after a TOP[15] and revealed a significant and dramatic shift from a "normal" rate of suicide attempts to an elevated rate after TOP, as seen in Figure 8. These findings led the researchers to conclude that "the increased risk of suicide after an induced abortion may therefore be a consequence of the procedure itself."

Another factor to consider regarding the question of causality is that negative effects may be substantially limited to small subgroups of women who are at greater risk. For example, experts on "both sides" of the legal abortion controversy are actually in agreement regarding the evidence that women who feel coerced or pressured into unwanted TOP are at greater risk of serious complications, including elevated self-destructive tendencies.[98] If we were to hypothesize, then, that all of the elevated risk of death associated with TOP reported in the studies we examined are limited to cases of coerced TOP, it would then follow that the findings reported herein may be an indirect measure of the frequency of coerced TOP. Such a conclusion would only further underscore the importance of the clinical recommendations offered in the next section.

Perhaps the most powerful evidence that pregnancy loss contributes directly to mental health problems is the frequency with which self-aware, introspective women specifically attribute the onset or worsening of substance use, depression, flashbacks, sexual dysfunction, self-destructive tendencies and other issues to their pregnancy loss experiences.[93,99,100] These self-assessments are further validated by therapists treating women for pregnancy loss related issues.[101,102] Additionally, evidence that post-abortion counselling programs reduce symptoms of psychological illness[103] also support the hypothesis that TOP can trigger or exacerbate psychological illness; after all, an effective treatment is evidence for an accurate diagnosis.

We are not asserting that pregnancy loss is the *sole* cause of the elevated risk of death identified in these studies, but rather that there is ample evidence to believe pregnancy loss can be a *contributing* cause. The discussion above is therefore intended to emphasize the importance of research designed to better understand the causal pathways and co-occurring risk factors which can then be used to better identify women who may benefit from appropriate interventions.

Clinical recommendations

Clinician's should be alert to the fact that a history of any pregnancy loss may impact many aspects of women's lives. Prior pregnancy losses, voluntary or involuntary, are also sensitive issues for many women which they may hesitate to dicuss. Therefore, it is highly recommended that as a standard intake question, or in periodic updating with patients, clinicians should make a gentle, non-judgmental query: "Have you had any pregnancy losses, like a miscarriage,

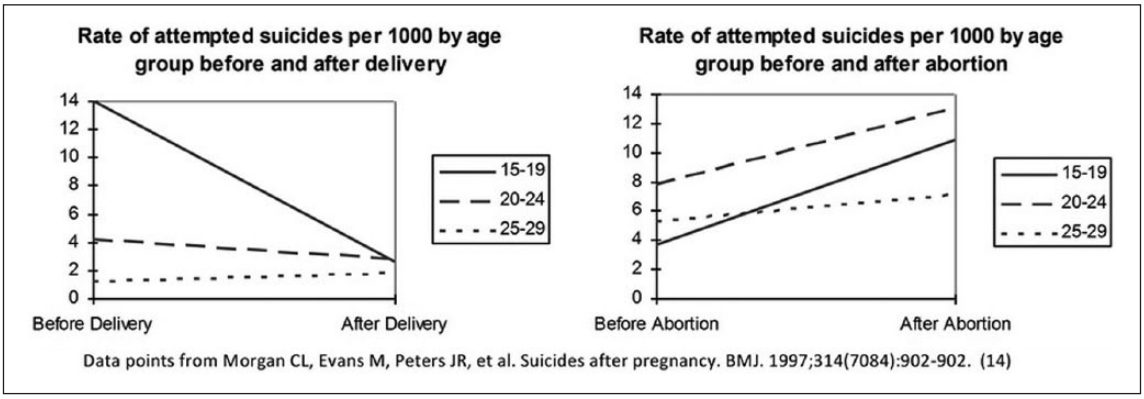


Figure 8. Rate of treatments for attempted suicide before and after delivery or TOP.

abortion, or still birth?" This query, which non-judgmentally names each type of pregnancy loss, gives women permission to discuss any sensitive feelings regarding past pregnancy losses and also opens up opportunities to discuss any lingering or intermittent concerns.

When women do report a prior pregnancy loss, or for women considering a termination of pregnancy, we recommend that clinicians should then investigate if additional risk factors are present. Especially useful in this regard, at least 15 risk factors for more severe reactions following TOP which have been identified by American Psychological Association Task Force on Mental Health and Abortion.[104] With slight modification, these risk factors can also be applied to miscarriage and other natural losses. They are:

- terminating a pregnancy that is wanted or meaningful
- perceived pressure from others to terminate a pregnancy
- perceived opposition to the abortion from partners, family, and/or friends
- lack of perceived social support from others
- various personality traits (e.g., low self-esteem, a pessimistic outlook, low-perceived control over life)
- a history of mental health problems prior to the pregnancy
- feelings of stigma; perceived need for secrecy
- exposure to antiabortion picketing
- use of avoidance and denial coping strategies
- feelings of commitment to the pregnancy
- ambivalence about the abortion decision
- low perceived ability to cope with the abortion
- history of prior abortion
- late term abortion.

These risk factors can and should be used to identify women who may need more counselling and other services. Given the dose effects observed, screening for a history of pregnancy loss is especially important in preparing treatment plans for women in all subsequent pregnancies. Therefore, we recommend the APA identified screening criteria should be used on at least four occasions: (a) when women seeking mental health care report any history of pregnancy loss, (b) when women are seeking care in anticipation of becoming pregnant, (c) upon diagnosis of a pregnancy, and (d) before termination of a pregnancy.

Summary

Deaths associated with pregnancy, both within the first year and beyond, are significantly different relative to pregnancy outcome. Births have a positive effect on longevity while pregnancy losses have a negative effect, with negative effect of TOP being greater than that of natural losses. Multiple pregnancy losses are especially problematic. Pregnancy loss is at least a marker for adverse maternal outcomes, but is most likely a contributing risk factor driven by psychological stresses related to pregnancy loss.[2–22]

Many opportunities to investigate pregnancy loss associated long-term mortality rates have been missed. Future investigations into maternal mortality and pregnancy associated mortality should include systematic record linkage to medical and insurance records to identify pregnancy losses so that these patterns and risk factors can be better understood.

Screening for a history of pregnancy loss (induced or natural) is highly recommended as a means of identifying women who may benefit from additional counselling and interventions. Screening for risk factors associated with more psychological maladjustments following TOP, as identified by the APA,[104] is also highly recommended.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: No grants or outside funding were used. David Reardon's efforts were funded as part of his regular duties as Director of Research with the Elliot Institute. John Thorp's efforts were not funded.

Ethical approval

Ethical approval was not sought for the present study because it is a literature review and does involve any original research using human or animal subjects.

Informed consent

Informed consent was not sought for the present study because it is a literature review and does not involve any original research using human subjects.

Supplemental files submitted

- Prisma Checklist.
- Spreadsheet of Newcastle - Ottawa Quality Assessment Scale: Cohort Studies.

Trial registration

This was not a randomized clinical trial therefore it was not registered as such.

References

1. Gissler M, Berg C, Bouvier-Colle M-H, et al. Methods for identifying pregnancy-associated deaths: population-based data from Finland 1987–2000. *Paediatr Perinat Epidemiol* 2004; 18(6): 448–455.
2. Giannandrea SAM, Cerulli C, Anson E, et al. Increased risk for postpartum psychiatric disorders among women with past pregnancy loss. *J Womens Health* 2013; 22(9): 760–768.
3. Broen AN, Moum T, Bødtker AS, et al. The course of mental health after miscarriage and induced abortion: a longitudinal, five-year follow-up study. *BMC Med* 2005; 3: 18.
4. Munk-Olsen T, Bech BH, Vestergaard M, et al. Psychiatric disorders following fetal death: a population-based cohort study. *BMJ Open* 2014; 4: 1–6.
5. Fergusson DM, Horwood LJ and Boden JM. Does abortion reduce the mental health risks of unwanted or unintended pregnancy? A re-appraisal of the evidence. *Aust N Z J Psychiatry* 2013; 47(9): 819–827.
6. Coleman PK. Abortion and mental health: quantitative synthesis and analysis of research published 1995–2009. *Br J Psychiatry* 2011; 199: 180–186.
7. Van den Akker OB. The psychological and social consequences of miscarriage. *Expert Rev Obstet Gynecol* 2011; 6(3): 295–304.
8. Reardon DC, Cougle JR, Rue VM, et al. Psychiatric admissions of low-income women following abortion and childbirth. *CMAJ* 2003; 168(10): 1253–1256.
9. Coleman PK, Reardon DC, Rue VM, et al. State-funded abortions versus deliveries: a comparison of outpatient mental health claims over 4 years. *Am J Orthopsychiatry* 2002; 72(1): 141–152.
10. Fergusson DM, Horwood LJ and Boden JM. Abortion and mental health disorders: evidence from a 30-year longitudinal study. *Br J Psychiatry* 2008; 193(6): 444–451.
11. Coleman PK. Induced abortion and increased risk of substance abuse: a review of the evidence. *Curr Womens Health Rev* 2005; 1(1): 21–34.
12. Steinberg JR, McCulloch CE and Adler NE. Abortion and mental health: findings from the national comorbidity survey-replication. *Obstet Gynecol* 2014; 123(2 Pt 1): 263–270.
13. Sullins DP. Abortion, substance abuse and mental health in early adulthood: thirteen-year longitudinal evidence from the United States. *SAGE Open Med* 2016; 4: 2050312116665997.
14. Shadigian E and Bauer ST. Pregnancy-associated death: a qualitative systematic review of homicide and suicide. *Obstet Gynecol Surv* 2005; 60(3): 183–190.
15. Morgan CL, Evans M and Peters JR. Suicides after pregnancy. Mental health may deteriorate as a direct effect of induced abortion. *BMJ* 1997; 314(7084): 902.
16. Tishler CL. Adolescent suicide attempts following elective abortion: a special case of anniversary reaction. *Pediatrics* 1981; 68(5): 670–671.
17. Reardon DC and Coleman PK. Relative treatment rates for sleep disorders and sleep disturbances following abortion and childbirth: a prospective record-based study. *Sleep* 2006; 29(1): 105–106.
18. Daugirdaitė V, van den Akker O and Purewal S. Posttraumatic stress and posttraumatic stress disorder after termination of pregnancy and reproductive loss: a systematic review. *J Pregnancy* 2015; 2015: 646345.
19. Zulčić-Nakić V, Pajević I, Hasanović M, et al. Psychological problems sequalae in adolescents after artificial abortion. *J Pediatr Adolesc Gynecol* 2012; 25(4): 241–247.
20. Ney PG, Fung T, Wickett AR, et al. The effects of pregnancy loss on women's health. *Soc Sci Med* 1994; 38(9): 1193–1200.
21. Berkeley D, Humphreys PC and Davidson D. Demands made on general practice by women before and after an abortion. *J R Coll Gen Pract* 1984; 34(263): 310–315.
22. Østbye T, Wenghofer EF, Woodward CA, et al. Health services utilization after induced abortions in Ontario: a comparison between community clinics and hospitals. *Am J Med Qual* 2001; 16(3): 99–106.
23. Dior UP, Hochner H, Friedlander Y, et al. Association between number of children and mortality of mothers: results of a 37-year follow-up study. *Ann Epidemiol* 2013; 23(1): 13–18.
24. Sun F, Sebastiani P, Schupf N, et al. Extended maternal age at birth of last child and women's longevity in the long life family study. *Menopause* 2015; 22(1): 26–31.
25. McArdle PF, Pollin TI, O'Connell JR, et al. Does having children extend life span? A genealogical study of parity and longevity in the Amish. *J Gerontol A Biol Sci Med Sci* 2006; 61(2): 190–195.
26. Atrash HK, Rowley D and Hogue CJ. Maternal and perinatal mortality. *Curr Opin Obstet Gynecol* 1992; 4(1): 61–71.
27. Pazol K, Creanga AA, Burley KD, et al. Abortion surveillance – United States, 2010. *MMWR Surveill Summ* 2013; 62(8): 1–44.
28. Khlat M and Ronsmans C. Deaths attributable to childbearing in Matlab, Bangladesh: indirect causes of maternal mortality questioned. *Am J Epidemiol* 2000; 151(3): 300–306.
29. Sousa MH, Cecatti JG, Hardy EE, et al. Severe maternal morbidity (near miss) as a sentinel event of maternal death. An attempt to use routine data for surveillance. *Reprod Health* 2008; 5(1): 6.
30. Turner LA, Cyr M, Kinch RAH, et al. Under-reporting of maternal mortality in Canada: a question of definition. *Chronic Dis Can* 2002; 23(1): 22–30.
31. Turner LA, Kramer MS, Liu S, et al. Cause-specific mortality during and after pregnancy and the definition of maternal death. *Chronic Dis Can* 2002; 23(1): 31–36.

32. Andersen BR, Westergaard HB, Bødker B, et al. Maternal mortality in Denmark, 1985–1994. *Eur J Obstet Gynecol Reprod Biol* 2009; 142(2): 124–128.
33. Donati S, Senatore S and Ronconi A. Maternal mortality in Italy: a record-linkage study. *BJOG* 2011; 118(7): 872–879.
34. Schutte JM, Hink E, Heres MHB, et al. Maternal mortality due to psychiatric disorders in the Netherlands. *J Psychosom Obstet Gynecol* 2008; 29(3): 150–153.
35. Schutte JM, de Jonge L, Schuitemaker NWE, et al. Indirect maternal mortality increases in the Netherlands. *Acta Obstet Gynecol Scand* 2010; 89(6): 762–768.
36. Schutte JM, Steegers E, a P, et al. Rise in maternal mortality in the Netherlands. *BJOG* 2010; 117(4): 399–406.
37. Samuelsson E, Hellgren M and Högberg U. Pregnancy-related deaths due to pulmonary embolism in Sweden. *Acta Obstet Gynecol Scand* 2007; 86(4): 435–443.
38. Kvarnstrand L, Milsom I, Lekander T, et al. Maternal fatalities, fetal and neonatal deaths related to motor vehicle crashes during pregnancy: a national population-based study. *Acta Obstet Gynecol Scand* 2008; 87(9): 946–952.
39. Esscher A, Högberg U, Haglund B, et al. Maternal mortality in Sweden 1988-2007: more deaths than officially reported. *Acta Obstet Gynecol Scand* 2013; 92(1): 40–46.
40. Chang C-C, Chiu H-F and Yang C-Y. Parity, age at first birth, and risk of death from pancreatic cancer: evidence from a cohort in Taiwan. *Pancreas* 2010; 39(5): 567–571.
41. Lewis G and Drife J (eds). *Why mothers die 1997–1999: the confidential enquiries into maternal deaths in the United Kingdom*. London: RCOG press, 2001.
42. Oates M. Perinatal psychiatric disorders: a leading cause of maternal morbidity and mortality. *Br Med Bull* 2003; 67: 219–229.
43. Lewis G and Drife J (eds). *Why mothers die 2000–2002: confidential enquiry into maternal and child health*. London: RCOG press, 2004.
44. Lewis G (ed.). *Saving mothers' lives: reviewing maternal deaths to make motherhood safer 2003–2005*. London: CEMACH, 2007.
45. Cantwell R, Clutton-Brock T, Cooper G, et al. Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006–2008. The eighth report of the confidential enquiries into maternal deaths in the United Kingdom. *BJOG* 2011; 118(Suppl. 1): 1–203.
46. Hastie CE, Smith GCS, Mackay DF, et al. Maternal risk of ischaemic heart disease following elective and spontaneous pre-term delivery: retrospective cohort study of 750 350 singleton pregnancies. *Int J Epidemiol* 2011; 40(4): 914–919.
47. Rubin G, McCarthy B, Shelton J, et al. The risk of childbearing re-evaluated. *Am J Public Health* 1981; 71(7): 712–716.
48. Benedetti TJ, Starzyk P and Frost F. Maternal deaths in Washington state. *Obstet Gynecol* 1985; 66(1): 99–101.
49. Starzyk P, Frost F and Kobayashi J. Misclassification of maternal deaths – Washington state. *MMWR Morb Mortal Wkly Rep* 1986; 35(39): 621–623.
50. Comas A, Navarro A, Conde J, et al. Misreporting of maternal mortality in Puerto Rico. *Bol Asoc Med P R* 1990; 82(8): 343–346.
51. Allen MH, Chavkin W and Marinoff J. Ascertainment of maternal deaths in New York city. *Am J Public Health* 1991; 81(3): 380–382.
52. May W, Buescher P and Murray A. Enhanced maternal mortality surveillance – North Carolina, 1988 and 1989. *MMWR Morb Mortal Wkly Rep* 1991; 40(28): 469–471.
53. Dye TD, Gordon H, Held B, et al. Retrospective maternal mortality case ascertainment in West Virginia, 1985 to1989. *Am J Obstet Gynecol* 1992; 167(1): 72–76.
54. Floyd V, Hadley C, Lavoie M, et al. Pregnancy-related mortality – Georgia, 1990–1992. *MMWR Morb Mortal Wkly Rep* 1995; 44(5): 93–96.
55. Jocums S, Mitchel EF, Entman SS, et al. Monitoring maternal mortality using vital records linkage. *Am J Prev Med* 1995; 11(2): 75–78.
56. Harper M and Parsons L. Maternal deaths due to homicide and other injuries in North Carolina: 1992–1994. *Obstet Gynecol* 1997; 90(6): 920–923.
57. Dietz PM, Rochat RW, Thompson BL, et al. Differences in the risk of homicide and other fatal injuries between postpartum women and other women of childbearing age: implications for prevention. *Am J Public Health* 1998; 88(4): 641–643.
58. Jocums SB, Berg CJ, Entman SS, et al. Postdelivery mortality in Tennessee, 1989–1991. *Obstet Gynecol* 1998; 91(5 Pt 1): 766–770.
59. Fang J, Madhavan S and Alderman MH. Maternal mortality in New York city: excess mortality of black women. *J Urban Heal* 2000; 77(4): 735–744.
60. Horon IL and Cheng D. Enhanced surveillance for pregnancy-associated mortality - Maryland, 1993–1998. *J Am Med Assoc* 2001; 285(11): 1455–1459.
61. Lydon-Rochelle M, Holt VL, Easterling TR, et al. Cesarean delivery and postpartum mortality among primiparas in Washington State, 1987–1996. *Obstet Gynecol* 2001; 97(2): 169–174.
62. Buescher PA, Harper M and Meyer RE. Enhanced surveillance of maternal mortality in North Carolina. *N C Med J* 2002; 63(2): 76–79.
63. Nannini A, Weiss J, Goldstein R, et al. Pregnancy-associated mortality at the end of the twentieth century: Massachusetts, 1990–1999. *J Am Med Womens Assoc* 2002; 57(3): 140–143.
64. Chang J, Elam-Evans LD, Berg CJ, et al. Pregnancy-related mortality surveillance – United States, 1991–1999. *MMWR Morb Mortal Wkly Rep* 2003; 52(2): 1–8.
65. Baker N, Fogarty C, Stroud D, et al. Enhanced pregnancy-associated mortality surveillance: Minnesota, 1990–1999. *Minn Med* 2004; 87(1): 45–47.
66. Harper MA, Espeland MA, Dugan E, et al. Racial disparity in pregnancy-related mortality following a live birth outcome. *Ann Epidemiol* 2004; 14(4): 274–279.
67. Horon IL, Cheng D, Chang J, et al. Underreporting of maternal deaths on death certificates and the magnitude of the problem of maternal mortality. *Am J Public Health* 2005; 95(3): 478–482.
68. Wolfe EL, Davis T, Guydish J, et al. Mortality risk associated with perinatal drug and alcohol use in California. *J Perinatol* 2005; 25(2): 93–100.
69. Rosenberg D, Geller SE, Studee L, et al. Disparities in mortality among high risk pregnant women in Illinois: a population based study. *Ann Epidemiol* 2006; 16(1): 26–32.
70. Watson A, Thompson D, Burch D, et al. *Pregnancy-related mortality report, Florida 1999–2005*. Tallahassee, FL: Florida Department of Health, 2008.

71. Kavanaugh VM, Fierro MF, Suttle DE, et al. Psychosocial risk factors as contributors to pregnancy-associated death in Virginia, 1999–2001. *J Womens Health* 2009; 18(7): 1041–1048.
72. Horon IL and Cheng D. Effectiveness of pregnancy check boxes on death certificates in identifying pregnancy-associated mortality. *Public Health Rep* 2011; 126(2): 195–200.
73. Tran T, Roberson E, Borstell J, et al. Evaluation of pregnancy mortality in louisiana using enhanced linkage and different indicators defined by WHO and CDC/ACOG: challenging and practical issues. *Matern Child Health J* 2011; 15(7): 955–963.
74. Burch D, Noell D, Hill WC, et al. Pregnancy-associated mortality review: the Florida experience. *Semin Perinatol* 2012; 36(1): 31–36.
75. Burlingame J, Horiuchi B, Ohana P, et al. Sauvage LMM. The contribution of heart disease to pregnancy-related mortality according to the pregnancy mortality surveillance system. *J Perinatol* 2012; 32(3): 163–169.
76. Mitchell C, Lawton E, Morton C, et al. California pregnancy-associated mortality review: mixed methods approach for improved case identification, cause of death analyses and translation of findings. *Matern Child Health J* 2014; 18(3): 518–526.
77. Main EK, McCain CL, Morton CH, et al. Pregnancy-related mortality in California: causes, characteristics, and improvement opportunities. *Obstet Gynecol* 2015; 125(4): 938–947.
78. Hardt N, Wong TD, Burt MJ, et al. Prevalence of prescription and illicit drugs in pregnancy-associated non-natural deaths of florida mothers, 1999–2005. *J Forensic Sci* 2013; 58(6): 1536–1541.
79. Hardt NS, Eliazar J, Burt M, et al. Use of a prenatal risk screen to predict maternal traumatic pregnancy-associated death: program and policy implications. *Womens Health Issues*; 23(3): e187–e193.
80. Salanave B, Bouvier-Colle M-H, Varnoux N, Alexander S, et al. Classification differences and maternal mortality: a European study. *Int J Epidemiol* 1999; 28(1): 64–69.
81. Deneux-Tharaux C, Berg C, Bouvier-Colle MH, et al. Underreporting of pregnancy-related mortality in the United States and Europe. *Obstet Gynecol* 2005; 106(4): 684–692.
82. Gissler M, Deneux-Tharaux C, Alexander S, et al. Pregnancy-related deaths in four regions of Europe and the United States in 1999-2000: characterisation of unreported deaths. *Eur J Obstet Gynecol Reprod Biol* 2007; 133(2): 179–185.
83. Gissler M, Hemminki E, Lönnqvist J, et al. Suicides after pregnancy in Finland, 1987-94: register linkage study. *BMJ* 1996; 313(7070): 1431–1434.
84. Gissler M, Kauppila R, Meriläinen J, et al. Pregnancy-associated deaths in Finland 1987–1994 – definition problems and benefits of record linkage. *Acta Obstet Gynecol Scand* 1997; 76(7): 651–657.
85. Gissler M and Hemminki E. Pregnancy-related violent deaths. *Scand J Public Health* 1999; 27: 54–55.
86. Gissler M, Berg C, Bouvier-Colle M-H, et al. Pregnancy-associated mortality after birth, spontaneous abortion, or induced abortion in Finland, 1987–2000. *Am J Obstet Gynecol* 2004; 190(2): 422–427.
87. Gissler M, Berg C, Bouvier-Colle M-H, et al. Injury deaths, suicides and homicides associated with pregnancy, Finland 1987–2000. *Eur J Public Health* 2005; 15(5): 459–463.
88. Gissler M, Karalis E and Ulander V-M. Decreased suicide rate after induced abortion, after the Current Care Guidelines in Finland 1987–2012. *Scand J Public Health* 2014; 43(1): 99–101.
89. Reardon DC and Coleman PK. Short and long term mortality rates associated with first pregnancy outcome: population register based study for Denmark 1980–2004. *Med Sci Monit* 2012; 18(9): PH71–PH76.
90. Coleman PK, Reardon DC and Calhoun BC. Reproductive history patterns and long-term mortality rates: a Danish, population-based record linkage study. *Eur J Public Health* 2013; 23(4): 569–574.
91. Shelton JD and Schoenbucher AK. Deaths after legally induced abortion linkage. *Public Health Rep* 1978; 93(4): 375–378.
92. Reardon DC, Ney PG, Scheuren F, et al. Deaths associated with pregnancy outcome: a record linkage study of low income women. *South Med J* 2002; 95(8): 834–841.
93. Burke T and Reardon DC. *Forbidden grief: the unspoken pain of abortion*. Springfield IL: Acorn Books, 2007, p. 334.
94. Raymond EG and Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. *Obstet Gynecol* 2012; 119(2 Pt 1)215–219.
95. Grimes DA, Benson J, Singh S, et al. Unsafe abortion: the preventable pandemic. *Lancet* 2006; 368: 1908–1919.
96. Major B. Psychological implications of abortion – highly charged and rife with misleading research. *CMAJ* 2003; 168(10): 1257–1258.
97. Reardon DC and Ney PG. Abortion and subsequent substance abuse. *Am J Drug Alcohol Abuse* 2000; 26(1): 61–75.
98. Coyle CT. Coercion and/or pressure. In: Macnair RM (ed.) *Peace psychology perspectives on abortion*. Kansas City, MO: Feminism & Nonviolence Studies Association, 2016.
99. Stotland NL. Abortion: social context, psychodynamic implications. *Am J Psychiatry* 1998; 155(7): 964–967.
100. Rue VM, Coleman PK, Rue JJ, et al. Induced abortion and traumatic stress: a preliminary comparison of American and Russian women. *Med Sci Monit* 2004; 10(10): SR5–SR16.
101. De Puy C and Dovitch D. *The healing choice: your guide to emotional recovery after an abortion*. New York: Simon & Schuster, 1997.
102. Torre-Bueno A. *Peace after abortion*. San Diego, CA: Pimpernel Press, 1997.
103. Layer SD. Postabortion grief: evaluating the possible efficacy of a spiritual group intervention. *Res Soc Work Pract* 2004; 14(5): 344–350.
104. Major B, Appelbaum M, Beckman L, et al. *Report of the APA task force on mental health and abortion*. Washington, DC: American Psychological Association, 2008, p. 105.