



## RU-486 (MIFEPRISTONE) SIDE-EFFECTS, 2000 – 2012

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On April 30, 2011 the United States Food and Drug Administration (FDA) staff completed a one-page assessment of the adverse event reports (AERs) it had collected on mifepristone (RU-486; Mifeprex<sup>®</sup>), the primary drug in the only medical abortion regimen approved in the United States.<sup>1</sup> Senator Orrin Hatch (R-Utah) requested a copy of the assessment and subsequently made it available to the Family Research Council (FRC) in the summer of 2011.<sup>2</sup> FRC has studied the RU-486 regimen's approval process and has tracked the drug's side-effects since mifepristone's FDA approval on September 28, 2000.<sup>3</sup> In the decade following the regimen's approval, FRC has continued to analyze the abortion regimen's side-effects as described in the RU-486 AERs and other public sources – both domestic and international. The FDA estimates that as of the end of April 2011, 1.52 million American women had taken RU-486 to induce an abortion.<sup>4</sup> While the loss of 1.52 million preborn children is inherently a moral tragedy, this paper focuses on the additional medical hazards that many women face when using RU-486 to induce an abortion.

### RU-486 Background

To have a well-grounded understanding of the FDA's RU-486 safety statistics, one first must have some basic knowledge about how RU-486 causes a medical abortion. Progesterone is one of the most important hormones affecting human pregnancy. It prepares the uterus for embryonic implantation and plays an essential role in maintaining an established pregnancy. RU-486 acts as a progesterone blocker or antagonist because it

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<sup>†</sup> A drug-induced abortion is typically referred to as a “medical” abortion. (On occasion, I will refer to such non-surgical abortions as a “chemical” abortion.) “Adverse Event Reports” are documents filed with the FDA, typically by the drug's U.S. distributor, reporting side-effects of the drug's use.

<sup>1</sup> Food and Drug Administration, “Mifepristone U.S. Postmarketing Adverse Events Summary through 04/30/2011,” (“April 2011 RU-486 Adverse Events Summary”) (<http://1.usa.gov/tZW1hf>). We believe these reports are compiled quarterly by the FDA staff to reflect new adverse event reports submitted to the agency.

<sup>2</sup> FDA has received AERs from the manufacturer of mifepristone, Danco Labs, since the drug's approval. Members of the public and the medical professions can submit AERs directly to FDA. Approximately 1,300 AERs for RU-486 have been obtained by Concerned Women for America and FRC through the Freedom of Information Act (FOIA). AERs obtained via the FOIA process have had any personal information redacted thereby preventing the identification of any patient who took mifepristone.

<sup>3</sup> The drug maker Roussel-Uclaf obtained French approval for RU-486 as an abortifacient on September 23, 1988.

<sup>4</sup> April 2011 RU-486 Adverse Events Summary.

prevents progesterone from binding to its receptors located in critical cells of the uterine lining (*i.e.*, endometrium).<sup>5</sup>

One can understand how mifepristone functions by using the following analogy. RU-486 is like a blank key that fits into a key hole but cannot turn the lock. A blank is the specific type of key for a lock but one that has not yet been cut by the locksmith to turn the lock. This useless blank key, RU-486, prevents a working key (progesterone) from entering the key hole and turning the lock's mechanism. RU-486's blockage of progesterone receptors leads to the deterioration of the uterine wall in which an embryo is implanted. As this deterioration worsens, the uterus is no longer able to sustain the pregnancy and the embryo dies.

Additionally, RU-486 is not sufficiently potent to reliably kill the developing embryo and expel the dead embryo or fetus. Accordingly, a second drug, misoprostol, is taken one to two days after RU-486 to trigger the uterine contractions needed to expel the remaining "products of conception" or viable embryo. FDA's approval mandated a mifepristone-misoprostol regimen to induce an abortion.<sup>6</sup> Misoprostol, marketed as Cytotec<sup>®</sup>, is a prostaglandin approved to prevent ulcers in certain patients who take NSAIDs.<sup>7</sup> However, powerful and often painful uterine contractions commence very soon after a pregnant woman ingests misoprostol. Obstetricians commonly use misoprostol now to induce labor in women reaching the end of their pregnancies.

We return to our lock and key model. The chemical-biological world contains many locks (chemical receptors) and the RU-486 blank key fits into two very important locks. As noted above, one is the lock – the receptor – for progesterone. The second is the lock for cortisol, a critical molecule in the functioning of the innate immune system, a biological defense mechanism that protects the body against bacterial infections. RU-486 fits into both locks because cortisol closely resembles progesterone in its molecular structure.

Dr. Ralph Miech, emeritus professor at Brown University's medical school, has published two peer-reviewed articles describing potentially undesirable effects related to RU-486 and

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<sup>5</sup> Technically speaking mifepristone is a "selective progesterone receptor modulator." On August 13, 2010, FDA approved a second generation drug of this type, ulipristal acetate (ella<sup>®</sup>), as an emergency contraceptive. Dovey and Sanfilippo note that mifepristone is an effective emergency contraceptive but observe that "mifepristone is also used to induce medical abortions, and thus, for various social and political reasons, has not been approved for use as an emergency contraceptive agent in many countries." Serena Dovey and Joseph Sanfilippo, "Emergency Contraception: Current Options, Challenges, and Future Directions," *Open Access Journal of Contraception* (2011): 107-117, 111-112.

<sup>6</sup> In this paper, when the use of RU-486 is discussed, unless indicated otherwise, it should be assumed that the mifepristone-abortion regimen is being discussed. The FDA-approved regimen calls for 600 mg of RU-486 to be taken within 49 days of the onset of the woman's last menstrual period. The FDA-approved regimen calls for taking 400 µg of misoprostol one to two days after the RU-486. In practice, there is considerable variation in dosages of both drugs in addition to the manner of administration. For example, a common regimen is 200 mg of RU-486 combined with 800 µg of misoprostol taken vaginally.

<sup>7</sup> NSAIDs are non-steroidal anti-inflammatory drugs like naproxen.

its anti-glucocorticoid properties.<sup>8</sup> First, he believes that RU-486's blockade of cortisol receptors on bacteria-destroying white blood cells may impede the antibacterial defense mechanism of the innate immune system. Such interference, he hypothesizes, played a significant role in the deaths of at least five North Americans in which there was a post abortion, bacterial invasion of the uterus and subsequent septic shock.<sup>9</sup> Second, prompted by an article describing mifepristone-related adverse events with significant and unexpected levels of hemorrhage, Miech's second article argues that RU-486 appears to interfere with the body's ability to control uterine hemorrhage.<sup>10</sup> Such interference, if true, would be a dangerous feature of an abortion procedure that is designed to produce a simulated miscarriage. As will be noted below, the number of hemorrhage/transfusion and serious infection cases revealed by FDA support Miech's concern about RU-486 and hemorrhage.

### Immediate Complications of Medical and Surgical Abortion Compared

One significant study on medical abortion's safety and effectiveness was published by *Obstetrics & Gynecology* in October 2009.<sup>11</sup> It compared the immediate complications that occurred after medical and surgical abortions.<sup>12</sup> The study was conducted in Finland where there is a comprehensive network of medical registries that could be used to track abortion outcomes in that country's government-based medical system. From 2000-2006 all women (n=42,619) who had abortions up to 63 days gestational age were followed up until 42 days.<sup>13</sup>

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<sup>8</sup> Recently, Dr. Miech has published an article examining the immunopharmacological properties of ulipristal acetate (ella<sup>®</sup>), another progesterone antagonist. See Ralph P. Miech, "Immunopharmacology of Ulipristal as an Emergency Contraceptive," *International Journal of Women's Health* 3 (2011): 391-397.

<sup>9</sup> R.P. Miech, M.D., Ph.D., "Pathophysiology of Mifepristone-induced Septic Shock due to *Clostridium sordellii*," *Annals of Pharmacotherapy* 39 (Sep. 2005): 1483-8.

<sup>10</sup> R.P. Miech, M.D., Ph.D., "Pathopharmacology of Excessive Hemorrhage in Mifepristone Abortions," *Annals of Pharmacotherapy* 41 (Dec. 2007): 2002-7.

<sup>11</sup> *Obstetrics & Gynecology* is the official publication of the American College of Obstetricians and Gynecologists (ACOG). It is popularly known as "The Green Journal."

<sup>12</sup> Maarit Niinimäki, M.D., et. al., "Immediate Complications after Medical Compared with Surgical Termination of Pregnancy," 114 *Obstetrics & Gynecology* (Oct. 2009): 795-804. Studies making this medical-surgical comparison have not been conducted often. The authors note: "Only a few randomized controlled trials have been performed to compare success rates and complications between medical and surgical abortion." *Id.* at 796. Notable for its absence from the short list of studies that meet these criteria were the U.S. trials whose data was used to gain FDA approval for RU-486 as an abortifacient in the U.S. See Irving M. Spitz, M.D., C. Wayne Bardin, M.D., Lauri Benton, M.D., and Ann Robbins, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States," *New England Journal of Medicine* 338 (Apr. 30, 1998): 1241-47. Spitz wrote: "Among the 2015 women who returned for the third visit, the rates of pregnancy termination were 92 percent in the 49-days group, 83 percent in the 50-to-56-days group, and 77 percent in the 57-to-63-days group." Spitz et al., pp. 1242-1243 (incl. Table 1).

<sup>13</sup> The group cohorts numbered 22,368 women who had medical abortions and 20,251 who had surgical terminations. Niinimäki et al., p. 795. The study defined medical abortion as "the use of mifepristone alone or in combination with misoprostol or other prostaglandins." *Id.* at 796. The authors note that "[a] nationwide cohort with high-quality data derived from national health registries offers the possibility to estimate extensively the risk of adverse events associated with the two methods of early termination of pregnancy." *Id.* at 796.

Overall, medical abortion had roughly four times the rate of adverse events than surgical abortion did: 20.0% of women in the medical-abortion group and 5.6% of women in the surgical-abortion group had at least one type of adverse event.<sup>14</sup> Hemorrhage, as an adverse event, was experienced by 15.6% of medical abortion patients compared with 2.1% for surgical patients.<sup>15</sup> Incomplete abortions were experienced by 6.7% of medical abortion patients while only 1.6% of surgical patients had incomplete abortions.<sup>16</sup> The rate for surgical (re)evacuation of the uterus was 5.9% (medical) versus 1.8% (surgical) for all causes (hemorrhage, infection, incomplete abortion).<sup>17</sup> In summary, the Finnish registries revealed that first-trimester medical abortions with mifepristone and a prostaglandin – typically misoprostol – resulted in: 1) 20 out of every 100 women with a significant adverse event; 2) about 16 out of 100 women hemorrhaging excessively; 3) 7 out of every 100 women with tissue left inside; and, 4) approximately 6 out of every 100 women needing surgical re-evacuation of the uterus.

### Australian Safety and Effectiveness Reports

The complications associated with mifepristone use were also examined in an even more recent study from Australia, a country that introduced mifepristone-misoprostol abortions in 2009. The study examined the track record of the first 947 “early medical abortion cases” in South Australia.<sup>18</sup> (Apparently, these abortions and forty-nine second-trimester medical abortions did not include the first medical abortion death in Australia which was reported publicly on March 19, 2012.<sup>19</sup>)

A newspaper story by Jamie Walker in *The Australian* summed things up with the headline “Abortion Pill ‘Less Safe than Surgery.’”<sup>20</sup> The journalistic audit of approximately 6,800 surgical and chemical abortions produced important data comparing first-trimester RU-486 and surgical abortions:<sup>21</sup>

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<sup>14</sup> Niinimäki *et al.*, p. 797.

<sup>15</sup> Niinimäki *et al.*, p. 799 (Table 2).

<sup>16</sup> Niinimäki *et al.*, p. 799 (Table 2).

<sup>17</sup> Niinimäki *et al.*, p. 799 (Table 2).

<sup>18</sup> Ea Mulligan and Hayley Messenger, “Mifepristone in South Australia: The First 1343 Tablets,” *Australian Family Physician* (May 2011): 342-345.

<sup>19</sup> Samantha Donovan, “Death May Spark Backlash against Abortion Drug,” *The World Today* (ABC News) (Australia) (article) (March 19, 2012).

<sup>20</sup> Jamie Walker, “Abortion Pill ‘Less Safe than Surgery,’” *The Australian* (May 7, 2011).

<sup>21</sup> Mulligan and Messenger, Table 2 (“Common Complications of First Trimester Abortion”). There were 947 early medical abortions defined as: “Early Medical Abortion up to 63 Days Gestation. Mifepristone 200 mg oral followed by misoprostol 800 µg per vagina, sublingual or buccal after 0-72 hours. Further doses 200 µg per vagina, sublingual or buccal three times per day on subsequent 2 days if cramping or heavy bleeding persist.” *Id.* at Table 1.

- 3.3% of the women who used RU-486 in the first trimester of pregnancy reported to an emergency room compared with 2.2% who used a surgical method;<sup>22</sup>
- 5.7% (1 in 18 patients) of the women who used RU-486 had to be re-admitted to hospitals compared with 0.4% (1 in 250) of surgical abortion patients.

With respect to second-trimester RU-486 abortions:<sup>23</sup>

- A staggering 33% (16/49) required some form of surgical intervention;
- 4% had “significant haemorrhage;” one of the two patients in this category required a transfusion.

Walker also noted in *The Australian*, “Two of the 5823 surgical patients suffered severe haemorrhage, involving the loss of more than a litre of blood.” That approximated “a rate of one in 3000.” Walker observed as well “[f]our of the 947 women who had medical abortions had the same problem, lifting the rate to one in 200.” These statistics pertain to first-trimester abortions.<sup>24</sup>

In sum, the Australian study underscores the fact also seen in the Finnish data – RU-486 requires a substantial follow-up and support system to minimize dangers associated with its use. The back-up capacity should include ultrasound, transfusion ability, and emergent surgical capability to follow-up an incomplete abortion. These capabilities are not found readily in many less-developed countries where this drug regimen is touted as a cheap substitute for having a surgeon available who can be perform an abortion.

### **The April 2011 FDA Report on RU-486 Adverse Events**

FDA’s April 2011 RU-486 Adverse Events Summary states that “[t]he estimated number of women who have used mifepristone in the US through the end of April 2011 is approximately 1.52 million women.” As noted above, FDA calculated that by that date there had been 2,207 adverse event reports submitted to FDA.<sup>25</sup> Prior to a 2006 oversight hearing on RU-486 safety, FDA told Rep. Mark Souder (R-Ind.) that it had received 1,070 AERs.<sup>26</sup> Thus, in the second five years of mifepristone marketing in the United States, the

<sup>22</sup> It should concern us that 1 in 30 medical abortion patients needed to go to an emergency room.

<sup>23</sup> Mulligan and Messenger, Table 4 (“Complications of Second Trimester Medical Abortion”). Without ultrasound dating of the pregnancy second-trimester abortions might be administered in lesser developed countries.

<sup>24</sup> Mulligan and Messenger, Table 3 (“Serious Complications of First Trimester Abortion”).

<sup>25</sup> April 2011 RU-486 Adverse Events Summary. FDA eliminated duplicate submissions, “and in some cases, reclassified the adverse event terms for individual cases after reviewing the narrative details....” FRC’s experience with FOIA-produced AERs is that FDA in some instances has multiple reports for a case, but they are easily identified using information on the AER forms. FDA and FRC numbers for hemorrhage with transfusions were very close to each other.

<sup>26</sup> The Souder Hearing took place on May 17, 2006. See Staff Report, “The FDA and RU-486: Lowering the Standard for Women’s Health?” Hearing before the Subcommittee on Criminal Justice, Drug Policy and Human Resources,

FDA received an additional 1,137 AERs– a total which seems consistent with the first five years.

However, the only peer-reviewed article to analyze mifepristone AERs submitted to the FDA was published in December 2005 by Drs. Margaret Gary and Donna Harrison.<sup>27</sup> Gary and Harrison reviewed 607 AERs obtained pursuant to the Freedom of Information Act (FOIA).<sup>28</sup> Their analysis and other information related to mifepristone side-effects have been summarized in a 2007 FRC publication.<sup>29</sup> The data in the April 2011 FDA Report are consistent with the earlier findings of Gary and Harrison: the major categories of AERs have been hemorrhage, infection, and ectopic pregnancy.<sup>30</sup> Their article also noted that of the 278 D&Cs listed without other major indications, 184 were characterized as “continuing pregnancy with viability unknown.”<sup>31</sup> We can now look at some of the more specific adverse event categories.

### **Hospitalization, Excluding Deaths**

The April 2011 RU-486 Adverse Events Summary states that there were 612 reports of hospitalization received as of April 30, 2011. This is consistent with the figure of 232 total hospitalization reports received from FDA by Representative Souder in 2006.<sup>32</sup>

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Committee on Government Reform, House of Representatives, Representative Mark Souder, Chairman (October 2006) (Souder RU-486 Hearing Report), p. 25.

<sup>27</sup> Margaret M. Gary, M.D., and Donna J. Harrison, M.D., “Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient,” 40 *Annals of Pharmacotherapy* (Feb. 2006): 191-7 (published online Dec. 27, 2005). At p. 191, Gary and Harrison stated that they “systematically analyze[d] mifepristone AERs submitted between September 2000 and September 2004, using the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAEv3; Table 1).”

<sup>28</sup> A commonly stated rule of thumb in the food and drug law community is that FDA only receives AERs for 1-10% of actual side-effects or adverse events. This appears to be reasonable as many doctors who see severe reactions are emergency room physicians who are very busy. They are not the patient’s primary doctor. The rate of reporting also depends on the severity of the adverse reaction. In a wealthy nation like the United States with a sophisticated medical and law enforcement infrastructure, the reporting accuracy for fatalities is likely to be better especially with a highly-scrutinized drug like RU-486. However, with respect to hemorrhage and infection the reporting rate is probably far lower – probably approximating the 1-10% rate.

<sup>29</sup> Christopher M. Gacek, “Politicized Science: The Manipulated Approval of RU-486 and Its Dangers to Women’s Health” (Washington, D.C.: Family Research Council, 2007), pp. 16-21.

<sup>30</sup> Gary and Harrison (p. 191) summarized their findings as follows for 607 AERs:

The most frequent AERs were hemorrhage (n = 237) and infection (66). Hemorrhages included 1 fatal, 42 life threatening, and 168 serious cases; 68 required transfusions. Infections included 7 cases of septic shock (3 fatal, 4 life threatening) and 43 cases requiring parenteral antibiotics. Surgical interventions were required in 513 cases (235 emergent, 278 nonemergent). Emergent cases included 17 ectopic pregnancies (11 ruptured). Second trimester viability was documented in 22 cases (9 lost to follow-up, 13 documented fetal outcome). Of the 13 documented cases, 9 were terminated without comment on fetal morphology, 1 was enrolled in fetal registry, and 3 fetuses were diagnosed with serious malformations, suggesting a malformation rate of 23%.

<sup>31</sup> Gary and Harrison, Table 5 (184 of 607 amounts to 30% of all the AERs examined). A D&C, or dilatation and curettage, is a follow-up surgical procedure.

<sup>32</sup> Souder RU-486 Hearing Report, p. 25 (Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (May 2, 2006)(“Boyer May 2, 2006 Letter”).

## Hemorrhage

FDA's April 2011 RU-486 Adverse Events Summary indicates that 339 women "experienced blood loss requiring a transfusion" after taking the RU-486 abortion regimen. In May 2006, Rep. Souder was told there had been 116 transfusion cases reported.<sup>33</sup> Gary and Harrison noted 68 cases of bleeding requiring transfusions.<sup>34</sup> Going back to the rule of thumb that only 1-10% of cases are reported to FDA in AERs (see n.28) the potential that thousands of transfusion cases may have occurred is both plausible and alarming. This total brings important implications for the use of RU-486 in less developed nations. Many of these countries do not have Western-level emergency medical facilities that can perform surgery or offer transfusions to women who have had extensive bleeding during a medical abortion.

## Infections

According to FDA's April 2011 RU-486 Adverse Events Summary numerous patients reported cases of infection. FDA had two categories: infections and severe infections. There were 256 baseline infections cases defined as:

This category includes endometritis (involving the lining of the womb), pelvic inflammatory disease (involving the nearby reproductive organs such as the fallopian tubes or ovaries), and pelvic infections with sepsis (a serious systemic infection that has spread beyond the reproductive organs). Not included are women with reported sexually transmitted infections such as Chlamydia infections and gonorrhea, cystitis and women with toxic shock syndrome not associated with a pelvic infection.

There were also 48 reports of "severe infections" which were described as a subset of infections including:

.... cases that were determined to be severe based on medical review of the case details. Severe infections generally involve death or hospitalization for at least 2-3 days, intravenous antibiotics for at least 24 hours, total antibiotic

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<sup>33</sup> Souder RU-486 Hearing Report, p. 25.

<sup>34</sup> Gary and Harrison, p. 192. Using a coding framework they developed, Gary and Harrison broke down the hemorrhage cases as follows:

Forty-two women experienced a life-threatening hemorrhage, as defined by active hemorrhaging with hemoglobin less than 7 g/dL and the transfusion of 2 or more units of packed red blood cells (PRBCs). One hundred sixty-eight women had severe hemorrhage, defined by hemoglobin of 7 g/dL or above and transfusion. Overall, 39% of AERs reported hemorrhage.

There is no requirement that AERs reporting transfusions report hemoglobin levels, but sometimes that information is provided. AER reporting is far from perfect and needs to be adjusted to encourage the reporting of such critical information when available.

usage for at least 3 days, and any other physical or clinical findings, laboratory data or surgery that suggest a severe infection.

FDA states that eight of fourteen fatalities it had tracked were associated with sepsis and “7 cases tested positive for *Clostridium sordellii*, 1 case tested positive for *Clostridium perfringens*[].” We will discuss the fatalities in more detail below, but it is clear that infection is a major cause of life-threatening side-effects with RU-486.<sup>35</sup>

Gary and Harrison identified 66 infection cases in their review of mifepristone regimen AERs. At least 46 were serious or life-threatening – two of these infections occurred in girls age 13-17 years old. Four women who survived life-threatening infections were experiencing septic shock at the time of presentation to the emergency room.<sup>36</sup>

### Ectopic Pregnancies

By April 2011 FDA had received fifty-eight reports of ectopic pregnancy cases – with two resulting in death – in conjunction with mifepristone-misoprostol use.<sup>37</sup> Two percent of American pregnancies develop outside the uterus – usually in the fallopian tubes. They are referred to as “ectopic pregnancies.” When an ectopic pregnancy ruptures, the woman will rapidly bleed to death internally unless she undergoes immediate surgery. The signs and symptoms of ectopic pregnancy (*e.g.*, cramping and bleeding) resemble those experienced by women who are having an RU-486 abortion. Consequently, an RU-486 patient with an ectopic pregnancy might delay treatment thinking her symptoms were being caused by the RU-486 abortion – not an ectopic pregnancy. This could be a fatal error. It is one reason that pro-life doctors, prior to RU-486’s approval, urged FDA to require that all prospective RU-486 patients be screened for ectopic pregnancies with ultrasound. FDA has refused to adopt this reasonable safety precaution.

### Deaths from RU-486 Use

In the April 2011 RU-486 Adverse Events Summary FDA associated fourteen American deaths to the use of the mifepristone-misoprostol abortion regimen.<sup>38</sup> One or two deaths may not have been related to the mifepristone-induced abortions (*e.g.*, suspected homicide and a drug overdose). However, the two ectopic pregnancy fatalities clearly were. FDA also noted that it had received reports of five foreign deaths. One or two of these may not be attributable to the abortion regimen (*e.g.*, the thrombotic thrombocytopenic purpura

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<sup>35</sup> On May 11, 2006, the Centers for Disease Control (“CDC”) in Atlanta hosted a conference, “Emerging Clostridial Disease Workshop,” which focused, in part, on the *C.sordellii* deaths.

<sup>36</sup> Gary and Harrison, p. 2. Chairman Souder was told of 88 infection cases over a longer period of time. Boyer May 2, 2006 Letter, p. 8.

<sup>37</sup> April 2011 RU-486 Adverse Events Summary, n. 1 (indicating two ectopic pregnancy deaths). By 2004, Gary and Harrison found 17 AERs involving ectopic pregnancies including 11 ruptures and one death.

<sup>38</sup> April 2011 RU-486 Adverse Events Summary.



leading to intracranial hemorrhage; ruptured gastric ulcer). Footnote 1 of the April 2011 RU-486 Adverse Events Summary makes these observations:

Deaths were associated with sepsis in eight of the 14 reported fatalities (7 cases tested positive for *Clostridium sordellii*, 1 case tested positive for *Clostridium perfringens*). All but one fatal sepsis case reported vaginal misoprostol use; buccal misoprostol use was reported in one case. The six remaining U.S. deaths involved unique events; there was one case each of substance abuse/drug overdose, methadone overdose, suspected homicide, and a delayed onset of toxic shock-like syndrome (uterine cultures were positive for *Peptostreptococcus* and fibroid cultures were positive for *Prevotella*), and there were two cases of ruptured ectopic pregnancy. There were five additional deaths in women from foreign countries (non-US) who used mifepristone for termination of pregnancy. These included one death associated with septic shock (*Clostridium sordellii* identified in tissue samples) in a foreign clinical trial and four deaths identified from post-marketing data that were associated with a ruptured gastric ulcer, uterine hemorrhage, “multivisceral failure” and thrombotic thrombocytopenic purpura leading to intracranial hemorrhage, respectively.<sup>39</sup>

It does not appear that the FDA report covers the death of an Australian woman who died in 2010. According to a March 19, 2012 news report the patient died of sepsis associated with group *A streptococcus*. These facts do not resemble those of the international cases described in note 1 of the FDA report. The woman was a patient of Marie Stopes International.<sup>40</sup>

Clearly, these figures can pertain only to deaths for which there have been reports submitted to FDA. It would be impossible to approximate how many women have died who have taken the mifepristone regimen in countries like China or India where emergency medical care does not meet Western standards and where the adverse event reporting system is not well developed. Additionally, even in nations like the United States medical abortions typically take place under intense privacy and follow-up with sick patients may be difficult.<sup>41</sup>

It is fair to conclude that the FDA has received 15-20 reports from the United States and abroad in which fatalities can be attributed to the use of mifepristone and misoprostol as an abortifacient regimen. FRC’s tracking statistics from public sources and FDA documents acquired through the FOIA process indicate fourteen fatalities, but obviously

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<sup>39</sup> April 2011 RU-486 Adverse Events Summary, fn. 1.

<sup>40</sup> Samantha Donovan, *supra*, n. 19.

<sup>41</sup> For example, one American fatality who resided in California took the RU-486 and misoprostol tablets and then went to Las Vegas. After arriving in Nevada, she collapsed and died six days after taking mifepristone. Under such circumstances it is not clear that the proper governmental authorities would be informed of the mifepristone use.

FRC has access to much less information than does FDA. Thus, a total of 15-20 *reported* fatalities, both American and international, attributable to the mifepristone-misoprostol regimen is a reasonable estimate.<sup>42</sup>

### **Telemed Abortions**

A recent development with RU-486 is its use in “telemed” abortions. These are abortions in which the patient and physician communicate with each other via video connection from different locations. Often, the abortionist is in another state with the woman being in a satellite medical office. The doctor interviews the patient and by remote control releases a drawer in a table at which the patient is sitting. The drawer contains the mifepristone and misoprostol tablets. After the drawer is released, the patient then removes the tablets and takes the mifepristone either in the office or in another location. The misoprostol is taken later.

Telemed practice may provide satisfactory care in some instances in which the patient and physician have an established treatment relationship. Some follow-up visits may be handled adequately via telecommunications devices. However, with respect to diagnosing and treating new cases, a physical exam and face-to-face conversation would seem imperative with an abortion procedure with the high complication rate produced by the mifepristone-misoprostol regimen. Furthermore, if emergency care is needed the woman’s physician does not live in the vicinity and, therefore, is not available to meet the patient at an emergent care facility like a local hospital. Since telemed abortions were devised as a way to offset the scarcity of physicians in rural areas this is not a mere theoretical concern.

### **RU-486 Use in Lesser Developed Nations**

As we have seen from the FDA statistics bleeding, infection, and ectopic pregnancies present serious dangers for the RU-486 user. The April 2011 RU-486 Adverse Events Summary notes that 2,207 distinct reports were filed with FDA. In a substantial number of cases, RU-486 produces an incomplete abortion or leaves an ongoing pregnancy, and surgical follow-up is needed.<sup>43</sup> FDA’s table did not track these latter two outcomes specifically, but they were included in the total number of reported cases with complications (2,207).

The Finnish and Australian studies, described above, make it clear that follow-up is critical for RU-486 patients. Approximately, six percent of the medical abortion patients had to

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<sup>42</sup> Other chemical abortion methods are excluded from this fatality total. For example, one fatality involving the use of misoprostol and laminaria is not included. See Adam L. Cohen, M.D., “Toxic Shock Associated with *Clostridium sordellii* and *Clostridium perfringens* after Medical and Spontaneous Abortion,” *Obstetrics & Gynecology* 110 (Nov. 2007): 1027-1033, 1028-9.

<sup>43</sup> Gary and Harrison, Table 5.

have a surgical proceeding to clear up various side-effects. That is about one in seventeen women in medically advanced countries like Finland and Australia. Therefore, one can imagine how the use of RU-486 would be even more dangerous in nations with a poor medical emergency infrastructure. There would probably be no ultrasound equipment to confirm the presence of an intrauterine pregnancy or retained tissue. Nor would there be rapid availability of blood for transfusions and antibiotics for infections. Furthermore, the undeniably necessary follow-up surgical procedures for medical abortions will not be readily available in vast regions of the less developed world. Sophisticated medical infrastructure and quality emergency care proved critical in the Finnish and Australian cases. One can infer that countries with less sophisticated health care systems would handle the deleterious effects of RU-486 use with a much lower success rate.

### **Misoprostol-Only Abortions**

Those who advocate the benefits of self-administered medical abortion for resource-poor nations strongly support using a misoprostol-only abortion regimen. One prominent example of advocacy for misoprostol abortions appeared in one of Nicholas Kristof's *New York Times* column in the summer of 2010.<sup>44</sup> Kristof's paean to misoprostol was entitled "Another Pill that Could Cause a Revolution."<sup>45</sup> Comparing the potential impact of misoprostol-only abortions to that of the birth control pill is bold, heady stuff.

Early in the article it becomes clear that Kristof's prime source is Dr. Beverley Winikoff, a medical abortion proponent and researcher who is the president of Gynuity Health Projects. Kristof states that "researchers are finding an alternative that is safe, cheap and very difficult for governments to restrict." That alternative is the self-induced medical abortion performed only with misoprostol which, as noted above, is used primarily to prevent stomach ulcers in those who take non-steroidal anti-inflammatory drugs. According to Kristof, Winikoff and her fellow researchers feel like those scientists must have felt "when they discovered the nuclear bomb." "This technology is world-shaking," she adds.

Kristof notes that RU-486 is not readily available in much of the world "because it is used only to induce abortions." However, misoprostol is found in nations where abortion is illegal because it can prevent ulcers and control postpartum hemorrhages. He then reveals that the researchers note that the misoprostol-only regimen's "effectiveness drops to 80 to 85 percent" when compared to a 95 percent rate for mifepristone-misoprostol abortions.<sup>46</sup> "That may sound low...." Kristof reports Dr. Winikoff's concession of low effectiveness, but, she adds "it's typically far better and safer than alternatives that women turn to...."

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<sup>44</sup> Nicholas Kristof, "Another Pill that Could Cause a Revolution," *New York Times* (Aug. 1, 2010).

<sup>45</sup> Kristof's article was not the first occasion on which the *New York Times* trumpeted the world-changing potential of self-administered misoprostol-only abortions. See John Leland, "Abortion Might Outgrow Its Need for *Roe v. Wade*," *New York Times* (Oct. 2, 2005). Leland approvingly observed that misoprostol "has been used in millions of self-administered abortions worldwide."

<sup>46</sup> The 95 percent completion rate Kristof cites exceeds that observed in the U.S. clinical trials, *supra* n. 12.

This is a shocking admission. Reasoning along those lines would justify the approval of any drug, no matter how ineffective and dangerous, merely because a worse therapy is used somewhere. Our standard for drug approval is far higher. Furthermore, the great fallacy in promoting medical abortions for poor, less-developed regions or nations is that *the back-up for an incomplete medical abortion is a surgical procedure*. Such surgical procedures are typically needed to stop bleeding or infection or to remove “retained products of conception.”<sup>47</sup> Thus, any location that does not have the facilities, equipment, and personnel to safely perform the requisite surgical follow-up is not a suitable location for medical abortions. In actuality, resource-deprived locations are least suitable location for the performance of safe medical abortions.

As described above, the use of the RU-486 abortion regimen is often a difficult, dangerous experience for patients even in wealthy Western nations. Since the misoprostol-only regimen fails even more frequently than the mifepristone-misoprostol combination, it will produce an even bleaker safety profile than RU-486 abortions. One American abortion supporter who had an RU-486-misoprostol abortion wrote an article (“I Was Betrayed by a Pill”) about the nine months of frightening, dangerous side-effects she experienced after taking the pills.<sup>48</sup>

These facts have no demonstrable effect on Kristof. He shows no awareness of the dangers that accompany medical abortion and fails to describe the drug’s side-effects and or mention any medical authorities with a different opinion about these drugs. He swallows the misoprostol-only story hook, line, and sinker. Kristof is practically giddy describing the fact that mifepristone + misoprostol blister packs are being purchased “for less than \$5 – and then shipped anywhere.” Better yet, “misoprostol on its own can be found all over the world, from Internet sites to over-the-counter pharmacies in Delhi.”<sup>49</sup>

Several months after Kristof’s piece appeared, *Contraception* published an article comparing the misoprostol-only and mifepristone-misoprostol abortion regimens. A team of Vietnamese and Americans that included Beverly Winikoff authored the study that was conducted in Ho Chi Minh City (Saigon). In their introductory paragraph, the research team made some important observations and startling admissions:<sup>50</sup>

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<sup>47</sup> “Retained products of conception (RPOC)” is a term, generally speaking, that indicates the presence in the uterus of placental and/or fetal tissue after a miscarriage or an abortion. The presence of retained products of conception indicates whether the miscarriage or abortion was complete. Daniela A Carusi, MD, MSc, “Retained Products of Conception,” (<<http://www.uptodate.com/contents/retained-products-of-conception> >).

<sup>48</sup> Norine Dworkin-McDaniel, “I Was Betrayed by a Pill,” *Marie Claire* (June 27, 2007) (“The abortion pill was supposed to make termination safe, easy, and discreet. One pro-choice advocate found it anything but.”).

<sup>49</sup> While Kristof may be thrilled about abortifacients being available over-the-counter, the Indian version of the FDA is not. It is cracking down on pharmacists that sell RU-486 without a prescription from a gynecologist or a registered medical practitioner. Umesh Isalkar, “FDA Steps in to Stop Sale of “A” Pills without Prescription,” *Times of India* (July 21, 2011).

<sup>50</sup> Nguyen Thu Nhu Ngoc, Jennifer Blum, Sheila Raghavan, Nguyen Thi Bach Nga, Rasha Dabash, Ayisha Diop, Beverly Winikoff, “Comparing Two Early Medical Abortion Regimens: Mifepriston+Misoprostol vs. Misoprostol Alone,” 83 *Contraception* (May 2011): 410-7, 410-11. The article was published online Oct. 18, 2010.

Nonsurgical abortion methods using the drugs mifepristone and misoprostol have the potential to improve abortion care. Medical methods have several advantages over surgical evacuation, particularly for use in low-resource settings, including reducing the need for surgery, sterilization of instruments, specific clinic rooms and surgically trained personnel. In countries where demand for abortion has overwhelmed surgical abortion services or where access to surgical services may be restricted to higher level facilities, medical abortion could reduce the workload for providers and facilities currently providing surgical abortion care. Widespread adoption of mifepristone medical abortion has been limited due to lack of access to the drug and its perceived high cost in many low-resource countries. Misoprostol, on the other hand, is widely available and inexpensive, and has therefore been promoted as an alternative to the combined regimens. In recent years, a host of new mifepristone and misoprostol products have become available which has reduced the cost of both drugs and facilitated access to medical abortion methods. The mifepristone pill continues to cost considerably more than the misoprostol pill and alone represents the most significant portion of the cost of any medical abortion regimen.

Cheap access to abortion – not safety – is clearly their main concern. However, the data Ngoc *et al.* published regarding the poor effectiveness of a misoprostol-only regimen is staggering.

The data revealed that “[c]omplete abortion without recourse to surgical evacuation, determined by clinical exam and confirmed by ultrasound *in a large majority of women*, was recorded for 76.2% of misoprostol only users...”<sup>51</sup> The successful completion rate was probably even lower since ultrasound was only used “in a large majority of women,” and ultrasound is the most accurate way to determine if the abortion has been completed.

Thus, it is fair to say that misoprostol-only abortions were failing in one in four cases. It is hard to imagine that anyone bound by the Hippocratic Oath could advocate a medical procedure which produced this failure rate even with clinical oversight. Self-administration of misoprostol due to the accompanying potential for infection, hemorrhage, and ongoing pregnancy is even more dangerous. Additionally, misoprostol’s known ability to produce birth defects after fetal exposure is not a theoretical concern. When a misoprostol-only regimen fails 25% of the time, some cases of ongoing pregnancies are expected.

That said, the block quote from Winikoff’s study gives a window into the mindset of the abortion proponents. Their stated concern is that abortions take place even when adequate facilities are no longer available to perform the abortion safely. In poor nations, medical abortions like those using misoprostol-only have advantages over surgical

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<sup>51</sup> Ngoc *et al.*, p. 413 (emphasis added).

procedures “including reducing the need for surgery, sterilization of instruments, specific clinic rooms and surgically trained personnel.”<sup>52</sup> But how can misoprostol-only advocates profess authentic concern for maternal safety when the procedure fails one in four times and the back-up procedures for a botched chemical abortion require all the equipment, personnel, and training just listed?

## **RU-486 Can Be Used Secretively on Women**

There is one additional problematic use of abortifacient chemicals: that is, the criminal use of an abortifacient on an unsuspecting woman. Such actions are typically perpetrated by a spouse or boyfriend who intends to abort a baby without the mother’s permission. There have been cases of men using various drugs including misoprostol and veterinary drugs.<sup>53</sup> We also have one example from Appleton, Wisconsin, in which a man from India, Manishkumar M. Patel, surreptitiously used mifepristone on his pregnant girlfriend. He tried to slip the drug into her drink but she discovered what he was doing.<sup>54</sup> Since the

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<sup>52</sup> Ngoc *et al.*, p. 410-11.

<sup>53</sup> Attempts to use misoprostol to induce surreptitious abortions on pregnant women fail because the misoprostol quickly affects women by commencing uterine contractions. This alerts the women to the poisoning that has taken place. Frances Gibbs, “‘Loner’ Husband Tried to Abort Child by Hiding Pills in Wife’s Breakfast,” *The Times* (London) (March 1, 2008); Associated Press, “Man Put Abortion Pills in Lover’s Food: Swedish Woman Aborted Pregnancy over Tainted Food Fears” (Feb. 26, 2008) (further research by Swedish-speaker acquainted with the author of this paper discovered that the medicine given was misoprostol).

<sup>54</sup> Appleton, Wisconsin, rated in 2004 by Farmers Insurance as one of the “Top 10 Most Secure Places to Live,” in 2007 became the center of a grisly case worthy of “Law and Order” as resident Manishkumar M. Patel was charged with attempted first-degree intentional homicide of an unborn child. The charges, filed in late November 2007, made national news because of the shocking method by which Patel was accused of committing the murder: he allegedly gave the abortion drug RU-486 (mifepristone) surreptitiously to his pregnant girlfriend in a smoothie, causing a miscarriage. (He did not give her misoprostol.)

An Indian immigrant, Patel was involved in an extramarital affair with the victim in this case and fathered a son by her in 2004. Prosecutors say he did not want another child and upon hearing the news in August 2007 that she was again pregnant Patel took criminal action. He allegedly became uncharacteristically attentive and even prepared meals for her on occasion. She became suspicious of his behavior after noticing powder on the rim of a cup containing a smoothie he had prepared for her at an ice cream store.

Patel’s girlfriend did not drink the smoothie, feigning ill health but saved a sample of the powder. Later, she experienced difficulties with her pregnancy and contacted a lab to obtain a test kit. Before it arrived, she miscarried. The lab subsequently identified the powder as RU-486. Even more distressing was the fact that she had also miscarried in September 2006. A search of Patel’s residence uncovered a cache of RU-486 pills, which he admitted had come from India. India classifies RU-486 as a prescription drug, but there is lax supervision of its distribution. Consequently, RU-486 can be purchased on something approaching an over-the-counter basis in India.

One important lesson can be gleaned from the Patel case: RU-486 or similar drugs (*i.e.*, progesterone antagonists) should never be sold through pharmacies or sold over-the-counter. Access must be secured tightly. A woman given RU-486 will not have the sharp symptoms of having been given misoprostol which would immediately start uterine contractions in a pregnant woman. In this case, had Patel’s girlfriend not seen the powder on the smoothie glass, he probably would have succeeded in getting away with this fetal murder. Patel and his wife fled Wisconsin and have not been seen for several years. Presumably, they returned to India.

drug can damage or destroy a pregnancy without immediately bringing on noticeable symptoms of miscarriage, RU-486 is well-suited for perpetrating fetal homicides.

Even though these cases do not appear to be common, they underscore the need for governments to tightly control access to pregnancy-terminating drugs. In the United States, mifepristone is not available through pharmacies. While misoprostol's use in such crimes should become known to the woman relatively quickly, the baby she is carrying will probably be killed. If not, misoprostol is known to produce birth defects in fetuses exposed to it. As the Patel case reveals, the surreptitious use of mifepristone is much more likely to go undetected.

## Conclusion

Since France approved RU-486 as an abortifacient in 1988 and the United States in 2000, medical experts have learned a great deal about the mifepristone-misoprostol regimen. In particular, the use of the FOIA process in the United States has allowed researchers to obtain redacted copies of adverse event reports submitted to the FDA. The Gary-Harrison article (2005), subsequent releases of information by FDA, and various research articles give a good picture of how the RU-486 abortion regimen affects women. Information from Australia has also been useful in this regard.

Medical abortions fail frequently, and they often produce serious hemorrhage and infection.<sup>55</sup> For example, according to the April 2011 RU-486 Adverse Events Summary there were reports to FDA that 339 American women had blood loss significant enough to require transfusions. There were 256 reported cases of infection reported in the United States. Approximately 15-20 known deaths have been associated with the regimen worldwide, but this number is almost certainly quite low since our data does not include developing countries like China and India where the regimen's use is heavy.<sup>56</sup>

The track record established by RU-486 makes it clear that the push for the widespread use of medical abortion in poor nations is inhumane and detrimental to the interests of the female patients who take these pills. First, unless ultrasound equipment is available, ectopic pregnancy cannot be ruled out. Second, access to clean blood for transfusions is a necessity. Third, a surgical procedure must be offered as the back-up for women who have had incomplete medical abortions. Therefore, all of the technologies, facilities, and skilled personnel needed to perform a surgical evacuation of the uterus must be in place

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<sup>55</sup> At the winter meeting of the American Association of Pro Life Obstetricians and Gynecologists (AAPLOG) (Matthew Bulfin Symposium), George Delgado, M.D., gave a paper on Feb. 25, 2012 entitled "Reversing Mifepristone: Case Reports." Dr. Delgado described six cases in which women *who had taken mifepristone but not misoprostol* attempted to save their babies. In six cases, physicians used repeated doses of 200 mg IM progesterone in oil. Publication of the article is pending. Physicians needing immediate information in this regard should contact AAPLOG.

<sup>56</sup> The difficulties of gaining accurate statistics are underscored by the news of an RU-486 death in Australia. That patient died in 2010, but her death did not become public until March 2012.

for medical abortion patients. Those pushing for medical abortions in developing nations do so arguing that the short supply of medical capabilities argues in favor of making medical abortions available to women in these areas. Good conscience and good medicine requires us to point out that the exact opposite is the case.

In closing, the Family Research Council believes that every abortion takes the life of a human being. Consequently, FRC opposes the use of these technologies to end the life of an embryo or fetus. Chemicals or surgical procedures are morally indistinguishable when used for such unacceptable purposes. That said, we feel a moral obligation to point out the additional dangers to women that are specifically posed by medical (chemical) abortions.

It is unfortunate that only those who oppose abortion are willing to present clear-eyed analysis of the dangers posed by these emerging abortion technologies. This paper has provided the reader with a thorough, documented examination of the dangers exhibited by medical abortion as of April 2012. FRC hopes that policymakers and medical experts will understand and address the poor safety record RU-486 has established in the years since FDA approved it in September 2000.

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