Women's Health

Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient

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BACKGROUND: The systematic analysis of morbidity and mortality for the Food and Drug Administration (FDA)–approved medical abortion regimen using mifepristone is possible using data from the FDA's Adverse Event Reporting System.

OBJECTIVE: To assess mifepristone's mortality, morbidity, sentinel events, and quality of postmarketing surveillance using mifepristone adverse event reports (AERs).

METHODS: Six hundred seven unique mifepristone AERs submitted to the FDA over a 4 year span were coded using the National Cancer Institute's Common Terminology Criteria for Adverse Events. Coding was based only on data in AERs and may underestimate severity and treatment rendered. Two board-certified obstetrician/gynecologists, the authors, made individual evaluations, compared them, and agreed upon final coding.

RESULTS: 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%.

CONCLUSIONS: Hemorrhage and infection are the leading causes of mifepristone-related morbidity and mortality. AERs relied upon by the FDA to monitor mifepristone's postmarketing safety are grossly deficient due to extremely poor quality.

KEY WORDS: adverse event reporting system (AERS), medical abortion, Mifeprex, mifepristone, mifepristone adverse events, mifepristone-induced septic shock (MISS), RU486.

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Since the Food and Drug Administration (FDA) approved mifepristone in September 2000, safety concerns have mounted; the FDA's July 2005 press release[1] announcing 2 additional deaths underscored these worries. To date, the FDA has not publicly described mifepristone's non-fatal sequelae as discovered through adverse event reports (AERs). This study systematically analyzes mifepristone AERs submitted between September 2000 and September 2004, using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAEv3; Table 1).[2] CTCAE coding allows for data analysis by providing uniform numerical grading of event severity across different diagnoses.

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Methods

The FDA released 637 mifepristone AERs documenting 607 unique events pursuant to a Freedom of Information Act request. All identifiers for patient, practitioner, or facility were removed from the AERs. Mifepristone's distributor submitted 592 of the 637 AERs; the rest were filed from various sources including foreign health authorities, Pharmacia, and others.

The vast majority of mifepristone AERs submitted to the FDA by the drug sponsor lacked critical information needed for complete case assessment.[3-10] Analysis and coding were based only on the contents of the AER. Even if the facts presented in the AER strongly suggested a stan-

dard course of treatment (eg, transfusion), that treatment was deemed not to have taken place unless there was explicit documentation. Consequently, poor AER documentation almost certainly resulted in the underestimation of the severity of some adverse events.

An absolute rate of mifepristone abortion complications in the US cannot be determined from the FDA's AERs because these voluntary and sporadically submitted reports provide neither an accurate numerator (number of adverse US events) nor an accurate denominator (number of US mifepristone abortions). However, the data allow some estimation of the types, severity, and percent frequency of reported events. Sentinel events requiring further investigation were also recognizable.

Results

The most frequent serious (CTCAE 3) and life-threatening (CTCAE 4) adverse events were hemorrhage (210 pts.), infection (46 pts.), and missed diagnosis of ectopic pregnancy (17 pts.). Table 2 contains the number of AERs by age and CTCAE grade. Five deaths (CTCAE 5) were reported,[11-15] including one 16-year-old,[11] along with 64 life-threatening events (CTCAE 4) and 224 serious events (CTCAE 3). The distribution of cases per CTCAE grade by age was roughly proportional except for deaths. The single death occurring in the 13–17 year age category represented 20% of the deaths, whereas this age group presented only 2% of all AERs (13 of 607).

Table 3 classifies AERs by CTCAE grade and diagnosis, including information on the group aged 13–17 years. Because the pediatric age encompasses a time of physical maturation, much of which is hormonally mediated, special scrutiny of this population is warranted. Both the US and French trial data specifically excluded women under 18 years of age; thus, the adverse events analyzed here present uncommon public information available on mifepristone's clinical use in the 13–17 year age range.

The 607 AERs included 5 deaths: 2 Californians, from sepsis[13,14]; a Tennessee woman with a ruptured ectopic pregnancy[12]; a Swedish teen, from massive hemorrhage[11]; and a British female, from "unknown etiology."[15] This last patient presented to the emergency department in shock and was found on autopsy to have 1 liter of blood in her stomach and 2 gastric ulcers. Sepsis is a known risk factor for stress-related gastrointestinal bleeding[16]; thus, sepsis is a plausible etiology for shock in this patient. Three deaths were not documented in these AERs: a participant in Canadian trials, from sepsis; an Asian Californian, from sepsis (December 2003); and a white Californian, from sepsis (June 2005). The FDA recently announced findings from the Centers for Disease Control and Prevention that all 5 of the sepsis deaths (4 Americans, 1 Canadian) have been linked to *Clostridium sordellii*.[17] Thus, there has been a total of 8 known deaths to date, including 5 Americans.

The severity of hemorrhage was coded based on the patient's pretransfusion hemoglobin level, the number of units transfused, the location and nature of surgical intervention, and the clinical description of the event according to the guidelines for CTCAE coding of hemorrhagic adverse events. However, in the majority of the AERs reporting hemorrhage, critical information (eg, baseline blood counts, vital signs, number of units transfused, posttransfusion hemoglobin or hematocrit level) was absent. 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.

Serious or life-threatening infections were reported for at least 46 women, of whom 2 were aged 13–17 years.[18-20] Four women who had life-threatening infections but survived were in septic shock at the time of presentation to the emergency department.[18,19,21,22] One patient (aged 15 y) pre-

Table 1. Common Terminology for Coding Adverse Events[2]

Grade	Severity of Adverse Event(s)
1	mild
2	moderate
3	severe
4	life threatening or disabling
5	death related to adverse event(s)

Table 2. CTCAE Grade and Patient Age of Mifepristone Adverse Events[a]

Age (y)	Grade 5 (N = 5) Pts., n (%)	Grade 4 (N = 64) Pts., n (%)	Grade 3 (N = 224) Pts., n (%)	Grade 2 (N = 344) Pts., n (%)	Grade 1 (N = 4) Pts., n (%)	Uncodable (N = 11) Pts., n (%)
13–17	1 (20)	3 (4.7)	4 (1.8)	8 (2.3)	0	0
18–35	2 (40)	46 (71.8)	172 (76.8)	281 (81.7)	2 (50)	9 (82)
36–46	1 (20)	12 (18.8)	42 (18.7)	36 (10.5)	2 (50)	0
Undocumented	1 (20)	3 (4.7)	6 (2.7)	19 (5.5)	0	2 (18)
TOTAL	5 (100)	64 (100)	224 (100)	344 (100)	4 (100)	11 (100)

CTCAE = Common Terminology Criteria for Adverse Events.
[a]Adverse events reported are greater than number of enrolled patients since some patients experienced more than one adverse event.

sented with adult respiratory distress syndrome (ARDS) from sepsis.[18] A second patient presented with ARDS from *Escherichia coli* sepsis.[21] A third presented with toxic shock syndrome.[22] A fourth (aged 16 y) presented with group B Streptococcus septicemia.[19] In addition to these 4 patients with documented infectious etiology, a fifth patient presented with disseminated intravascular coagulopathy (DIC) with hepatic and renal failure.[23] Her AER exhibited poor documentation, including only information on outpatient treatment for bacterial vaginosis. Because there was no documentation of infection, she was not included in the CTCAE 4 category for infection, although it is probable that the DIC was infectious in origin. Forty-three additional women required parenteral antibiotics for severe pelvic infection, and an additional 14 were treated for pelvic infections as outpatients. Overall, 11% of AERs reported an infectious complication.

The third most common class of severe adverse events was undiagnosed ectopic pregnancy. Seventeen patients had ectopic pregnancies that were undetected at the time of mifepristone administration. Eleven of these were ruptured at the time of diagnosis[12,24-33] (CTCAE genitourinary grade 4), including one death (CTCAE 5).[12] Three of the 17 were cornual pregnancies,[31,33,34] and one was a cervical pregnancy that resulted in a hysterectomy in a 29-year-old patient.[35] Overall, 2.8% of AERs reported unrecognized ectopic pregnancy.

Seven additional diagnoses of possible sentinel events were (1) myocardial infarction in a previously healthy 21-year-old woman,[36] (2) prolongation of QT interval on electrocardiogram in another woman,[37] (3) pulmonary embolism,[38] (4) exacerbation of Crohn's disease,[39] (5) precipitation of a sickle cell crisis,[40] (6) acute pancreatitis,[41] and (7) drug interaction resulting in liver failure in an HIV-positive patient.[42]

One unexpected finding was a number of allergic reactions ranging from hives to severe generalized urticaria. One patient was hospitalized for 4 days and treated with intravenous diphenhydramine and oral prednisone.[43] Eight patients were treated as outpatients, and 4 required no treatment.

The extent of treatment required to manage the adverse events is presented in Table 4. Sixty-eight women received transfusions. Nineteen (28%) of these required 3 or more units of PRBCs. In 15% of cases with transfusion, the number of units was not documented in the AER. At least 513 surgical procedures were performed in the 607 patients with adverse events. When a patient had more than one surgery performed, only the most extensive surgery was included in the tabulation. (For example, if a patient had a dilatation and curettage and then a subsequent laparotomy, only the laparotomy was included. For patients with more than one dilatation and curettage, only one was included in the tabulation.) There were 235 emergency surgeries performed. Of these, 17 (7%) were emergency laparotomies: 16 were for ectopic pregnancies (1 ectopic pregnancy was managed laparoscopically) and one laparotomy was for sepsis. Two of the 5 deaths were intraoperative. The remaining 93% of emergency surgeries were emergency dilatation and curettage procedures performed to arrest hemorrhage. At least 40% of the patients were hospitalized for treatment, including 12 admissions to the intensive care unit. Fifty-seven percent were managed as outpatients and, in 3%, the site of treatment was not documented.

Because mifepristone abortions result in exposure of the fetus to known teratogens, the AERs were analyzed for information on fetal outcome after exposure, where documented (Table 5). Of the 278 pregnancies terminated after mifepristone failure without other diagnoses, 58 (21%) had documented fetal viability by ultrasound on return visit,

Table 3. CTCAE Grade and Diagnosis

	Hemorrhage		Infection		Genitourinary		Other		Total	
CTCAE Grade	All Pts. (n)	Adolescents (n)	All Pts. (n)	Adolescents (n)	All Pts. (n)	Adolescents (n)	All Pts. (n)	Adolescents (n)	All Pts. (n)	Adolescents (n)
5	1	1	3[a]	0	1	0	0	0	5	1
4	42	1	4	2	10	0	9	0	64	3
3	168	3	43	1[b]	7	0	5	0	224	4
2	19	0	14	1	301	6	10	1	344	8
1	0	0	0	0	0	0	4	0	4	0
Uncodable	7[c]	0	2	0	0	0	2[d]	0	11	0
TOTAL	237	5	66	4	319	6	30	1	652	16
% of diagnoses	36		10		49		5			

AERs = adverse event reports; CTCAE = Common Terminology Criteria for Adverse Events.

[a]This includes death of the British woman with clinical picture consistent with sepsis.

[b]Poor documentation precluded accurate coding. Actual event probably a 4 but pertinent lab data not documented on AER.

[c]This includes 2 patients with hemorrhage and infection, 2 patients with some indication of severe hemorrhage (Hb <7.5), and 3 patients with heavy bleeding. All patients in this category lacked critical information, which made coding impossible.

[d]Both are cardiac events that lacked adequate documentation to code.

and 36 (13%) had documented fetal demise or retained products of conception without a fetus. However, 184 (66%) had no documentation of fetal status. Of the 22 fetuses documented to be viable in the second trimester, 9 were lost to follow-up and 13 had a documented outcome to the pregnancy. Of those 13, 9 had a termination of pregnancy with no documentation of fetal morphology, 1 was enrolled in a fetal registry,[44] and 3 had documentation of fetal anomalies: (1) Mobius syndrome,[45] (2) neural tube defect,[46] and (3) oligodactylia, monodactylia, facial dysmorphia, and meningo-encephalocele.[47] (One additional AER[48] referred to a separate fetal report implying malformation. However, that fetal report was not included in the information released and thus not counted in our calculation of malformation rate.) Assuming normal fetal morphology in all 9 pregnancies that were terminated without documenting information about the presence or absence of malformations and assuming normal fetal morphology for the patient enrolled in the fetal registry, the rate of fetal malformations would still be at least 3 (23%) of 13.

Discussion

The pathophysiology of the rapid onset of sepsis following pregnancy terminations with mifepristone and the unusual afebrile and hemoconcentration presentation is still unclear. An interesting theory was recently published linking the rapid onset of sepsis with mifepristone's blockade of glucocorticoid receptors (mifepristone-induced septic shock).[49] Studies investigating the pathophysiology of septic shock have shown a noncompetitive, dose-dependent repression of the glucocorticoid receptor by both *Bacillus anthracis* lethal toxin[50] and the *Clostridium sordellii* lethal toxin.[51] Blockade of glucocorticoid receptors at the endometrial level may allow for ascending infection into a fertile medium of dead fetal tissue surrounded by an endometrium that lacks normal innate immune mechanisms. Further research into glucocorticoid receptor blockade by mifepristone resulting in the loss of the antibacterial role of the innate immune system at the endometrial level should be pursued.

With mifepristone abortions, the rate of failure to cause complete termination of pregnancy increases dramatically, along with hemorrhagic events, as the gestational age and the size of the placenta increases. The US clinical trial demonstrated a failure rate of 8% at 49 days or less from the last menstrual period (LMP), increasing to 17% at 50–56 days from the LMP, and further increasing to a 23% failure at 57–63 days from the LMP, as established by sonographic criteria.[52] Based on the data from this trial, the FDA approved mifepristone for use as an abortifacient up to 49 days from the LMP, but failed to require sonographic data for the accurate determination of gestational age. Furthermore, clinics nationwide routinely advertise mifepristone's use up to 63 days from the LMP, and, thus, would incur a failure rate of 23% or higher in addition to the inaccuracies of the methods used to date the pregnancies.

One serious concern raised by this review of AERs is the suggested fetal malformation rate of at least 23% following mifepristone failures that resulted in continuation of a live pregnancy. Misoprostol is a known teratogen, but the extent of the teratogenicity of mifepristone has yet to

Table 4. Extent of Treatment Interventions

Treatment Interventions	Pts. (%)
Transfusions	68 (100)
≥4 units PRBCs	9 (13)
3 units PRBCs	10 (15)
2 units PRBCs	38 (56)
1 unit PRBCs	1 (1)
units not documented, n	10 (15)
transfusion implied but not documented[a]	1
Surgeries	513 (100)
emergent	235 (46)
emergency laparotomy	17
intraoperative death	2
hysterectomy	1
salpingectomy with or without oophorectomy	7
adnexal surgery unspecified	4
cornual surgery unspecified	3
emergency D&C for hemorrhage	218
nonemergent	
D&C for failures without other indications	278 (54)
Site of Treatment Intervention	607 (100)
hospitalizations	241 (40)
intensive care unit admissions	12
inpatient hospitalizations	130
emergency department outpatient	99
outpatient management	345 (57)
site of treatment not documented	21 (3)

D&C = dilatation and curettage; PRBCs = packed red blood cells.
[a]AER reported that patient said she was given blood.

Table 5. Fetal Outcome After Mifepristone Exposure

Outcome	Pts. (%)
Surgeries—Nonemergent	
D&C for failures without other indications	278 (100)
continuing viable pregnancy	58 (21)
continuing pregnancy with fetal demise	13 (5)
continuing pregnancy with viability unknown	184 (66)
retained products of conception	23 (8)
Fetal outcome after exposure	
second trimester with documented viability	22 (100)
lost to follow-up	9 (41)
known outcome	13 (59)
Known outcome of pregnancy	13 (100)
terminated without documentation of fetal status	9 (69)
documented fetal malformation	3 (23)
enrolled in fetal registry	1 (8)

D&C = dilatation and curettage.

be well documented. Fetal malformations were noted in 3 of the 13 women who had pregnancies with known outcome. Another 9 women continued pregnancies without any documentation in the AERs of the outcome of the fetus. It is clear that a mandatory fetal registry should be established to ascertain the true incidence of fetal malformation in pregnancies that are continued after exposure to mifepristone and misoprostol.

Another serious concern is the number of missed diagnoses of ectopic pregnancies that resulted in rupture. Ectopic pregnancy is an absolute contraindication to the use of mifepristone, and failure to rule out ectopic pregnancy resulted in one death, as well as unnecessary morbidity. Requiring ultrasound documentation of intrauterine location of the pregnancy by a qualified ultrasonographer prior to the administration of mifepristone would reduce this life-threatening complication to a minimum.

The incidence of allergic reactions to mifepristone requires closer examination. Assuming that all patients were exposed to mifepristone for the first time, they could not have mounted an immunoglobulin E–mediated mifepristone allergic response. Inflammatory reactions reported as allergic reaction in the AERs are due to the release of proinflammatory mediators, such as histamine, prostaglandins, leukotrienes, and interleukins, which result in urticaria, rhinitis, conjunctivitis, or asthma. Blockade of cortisol receptors by mifepristone can result in an uncontrolled production and release of an excess of these proinflammatory mediators. Mifepristone's ability to block cortisol receptors has been well documented.[53] These proinflammatory reactions reported as allergic reactions in AERs may be due to the action of mifepristone's blockade of cortisol receptors. This potentially serious adverse effect resulting from mifepristone-induced blockade of cortisol receptors deserves further investigation.

Aside from specific safety issues related to mifepristone, studying these reports has been highly instructive for what they reveal about the FDA's Adverse Event Reporting System for all drugs. Michael F Mangano, principal deputy inspector general of the Department of Health and Human Services, stated in testimony before the US Senate[54]:

> Adverse Event Reporting systems typically detect only a small proportion of events that actually occur. They are passive systems that depend on someone linking an adverse event with the use of a product, then reporting the event…. Rather the system generates signals that FDA must assess to confirm if, in fact, a public health problem exists…. With limited information to draw upon to generate signals, it is not surprising that FDA rarely reaches the point of knowing whether a safety action is warranted to protect consumers.

If our survey of mifepristone AERs is representative of adverse event reporting for all drugs, the American public should be greatly alarmed. In this instance, a majority of the AERs analyzed do not provide enough information to accurately code the severity of the adverse event in question. The deficiencies were so egregious in some instances as to preclude analysis. It is clear that input quality control is necessary for Medwatch to function; this systemic deficiency clearly impairs the FDA's ability to fully assess mifepristone's safety profile because the necessary signals are not being generated.

Conclusions

The AERs discussed above relate to the use of mifepristone in otherwise healthy young women and document a significant risk of severe, life-threatening, or even lethal adverse events. The most common of these adverse events are hemorrhage, infection, and missed diagnosis of ectopic pregnancies. The most commonly fatal adverse event is sepsis, which may present without fever and progress rapidly to death.

Although neither the manufacturer nor the FDA recognizes a causal link between the use of mifepristone and the adverse events reported, it is undeniable that these women were healthy before the use of mifepristone and became very sick or died shortly after its use. Before any medication is used, a prudent practitioner weighs carefully the risks of the medication with the potential benefits. Medications, such as chemotherapy agents, with life-threatening or potentially lethal adverse effects are acceptable in treating conditions that are themselves debilitating or lethal such as cancer, HIV, sepsis, and others. In these cases, alternative treatments are limited and, without treatment, the disease is rapidly lethal. The use of mifepristone as an abortifacient, however, is radically different. Pregnancy in most instances is a benign, self-limited condition, with duration of approximately 8 months from diagnosis for most women. It generally occurs in otherwise healthy young women. The choice of mifepristone termination over surgical termination is based mainly on patient perceptions of safety, convenience, and privacy, but these perceptions do not accurately reflect the realities of the regimen.

Furthermore, complete, accurate data concerning the public health risk posed by the mifepristone/misoprostol regimen currently in use are not being gathered through the FDA's Adverse Event Reporting System. After reviewing over 600 AERs, we believe that the FDA must promptly conduct a thorough review of this aspect of its postmarketing surveillance system to determine whether the failures described above are peculiar to mifepristone reports or are systemic to all drug reports.

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Dr. Gary and Dr. Harrison are members of the Subcommittee on Mifeprex of the American Association of Prolife Obstetricians and Gynecologists (AAPLOG), the largest interest group of the American College of Obstetricians and Gynecologists. AAPLOG has filed a Citizen Petition with the Food and Drug Administration requesting withdrawal of approval for mifepristone based on safety considerations.

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EXTRACTO

TRASFONDO: Es posible analizar sistemáticamente la morbilidad y mortalidad del régimen de aborto terapéutico con mifepristona aprobado por la Administración de Alimentos y Drogas (FDA, por sus siglas en inglés) utilizando datos del Sistema de Reporte de Eventos Adversos (AERS, por sus siglas en inglés) de esa agencia.

OBJETIVO: Evaluar la mortalidad, morbilidad, eventos sentinelas, y calidad de la vigilancia posmercadeo utilizando los reportes de eventos adversos con mifepristona.

MÉTODOS: Seiscientos siete reportes de eventos adversos únicos con mifepristona sometidos a FDA durante un período de 4 años fueron codificados utilizando Criterios de Terminología Común para Eventos Adversos del Instituto Nacional del Cáncer (NCI's CTCAEv3, por sus siglas en inglés). La codificación se basó solamente en datos de los reportes de eventos adversos y puede subestimar la severidad y el tratamiento provisto. Los autores, 2 juntas de obstetras/ginecólogos, hicieron evaluaciones de CTCAE, las compararon, y acordaron la codificación final.

RESULTADOS: Reportes de eventos adversos más frecuentes: hemorragia (237) e infección (66). Las hemorragias incluyeron una fatal, 42 potencialmente fatales, y 168 casos serios; 68 requirieron transfusiones. Las infecciones incluyeron 7 casos de choque séptico con 3 casos fatales, 4 potencialmente fatales, y 43 que requirieron antibióticos parenterales. Las intervenciones quirúrgicas totalizaron 513 casos (235 urgencias, 278 no urgencias). Los casos de urgencias incluyeron 17 embarazos ectópicos (11 rupturas). La viabilidad de segundo trimestre fue documentada en 22 casos (9 sin seguimiento, 13 con resultado fetal documentado). De 13 casos documentados 9 terminaron sin comentario sobre morfología fetal, 1 inscrito en el registro fetal, y 3 fetos diagnosticados con defectos del tubo neural que sugieren una razón de malformación de 23% (3 de 13).

CONCLUSIONES: Las principales causas de morbilidad y mortalidad relacionadas con mifepristona son hemorragia e infección. Los reportes de eventos adversos en los que se fundamenta FDA para dar seguimiento a la seguridad posmercadeo de mifepristona son crasamente deficientes debido a su extremadamente pobre calidad.

Ana E Vélez

RÉSUMÉ

INTRODUCTION: Le système américain de pharmacovigilance (Medwatch) permet une analyse systématique de la morbidité et de la mortalité associées à l'utilisation de mifepristone pour induire un avortement.

OBJECTIF: Évaluer la mortalité, la morbidité, et l'incidence d'événements sentinelles associés à la mifepristone, de même que la qualité du système de pharmacovigilance américain en utilisant les cas de réactions indésirables rapportées à l'agence américaine des aliments et drogues.

DEVIS EXPÉRIMENTAL: Six cent sept réactions indésirables uniques associées à la mifepristone ont été rapportées à l'agence américaine sur une période de 4 ans. De celles-ci, 592 ont transité par le fabriquant. Chaque réaction a été codifiée en utilisant le dictionnaire terminologique de l'institut national du cancer (National Cancer Institute Common Terminology Criteria for Adverse Events).

RÉSULTATS: En général, les rapports de cas étaient de piètre qualité et beaucoup d'information nécessaire à une codification adéquate manquait. Dans d'autres cas, la codification n'utilisait que les données du rapport de cas et une évaluation par 2 gynécologues obstétriciens diplômés, les auteurs, a révélé une sous-estimation de la sévérité des réactions de même que du lien de causalité. Les réactions indésirables les plus fréquentes incluaient les hémorragies (237) et les infections (66). Parmi les hémorragies, on nota une réaction fatale, 42 ayant mis la vie en danger et 168 cas sérieux. De plus, 68 ont nécessité une ou plusieurs transfusions sanguines. Parmi les infections on a remarqué 7 cas de choc septique dont 3 ayant entraîné le décès et 4 ayant mis la vie de la patiente en danger. De plus, 43 cas ont nécessité l'administration intraveineuse d'antibiotiques. Un total de 513 cas a requis une intervention chirurgicale (235 urgentes, 278 non urgentes). Parmi les chirurgies urgentes on dénombra 17 grossesses ectopiques dont 11 avec rupture de la trompe. La viabilité du fétus jusqu'au second trimestre a été documentée dans 22 cas (9 sans suivi documenté, 13 avec documentation). Des 13 cas documentés, 9 grossesses ont été interrompues sans qu'aucune information sur la morphologie du fétus ne soit documentée, 1 grossesse a été incluse dans un registre médical de suivi de grossesse, et chez 3 fétus, une malformation du tube neural a été observé, suggérant un taux de malformation de 23% (3 sur 13).

CONCLUSIONS: Les hémorragies et les infections sont les causes les plus fréquentes de mortalité et de morbidité associées à l'utilisation de mifepristone pour induire un avortement. Les réactions indésirables rapportées au système de pharmacovigilance de l'agence américaine sont de piètre qualité rendant peu fiable l'évaluation du risque associé à l'utilisation d'un médicament par l'entremise de ce système.

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