

## Women's Health

## Pathophysiology of Mifepristone-Induced Septic Shock Due to *Clostridium sordellii*

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**OBJECTIVE:** To explain the role of mifepristone in medical abortions that results in fulminant and lethal septic shock due to *Clostridium sordellii*.

**DATA SOURCES:** MEDLINE, PubMed, and Google Scholar databases were searched (1984–March 2005). Key search terms were mifepristone, RU38486, RU486, Mifeprex, medical abortion, septic shock, innate immune system, cytokines, and *Clostridium sordellii*.

**STUDY SELECTION AND DATA EXTRACTION:** All articles identified from the data sources were evaluated and all information deemed relevant was included for the information related to the development of the understanding of the pathophysiology of mifepristone-induced septic shock due to *C. sordellii*.

**DATA SYNTHESIS:** The mechanisms of action of mifepristone were incorporated into the pathophysiology of septic shock due to *C. sordellii*. Mifepristone, by blocking both progesterone and glucocorticoid receptors, interferes with the controlled release and functioning of cortisol and cytokines. Failure of physiologically controlled cortisol and cytokine responses results in an impaired innate immune system that results in disintegration of the body's defense system necessary to prevent the endometrial spread of *C. sordellii* infection. The abnormal cortisol and cytokine responses due to mifepristone coupled to the release of potent exotoxins and an endotoxin from *C. sordellii* are the major contributors to the rapid development of lethal septic shock.

**CONCLUSIONS:** Theoretically, it appears that the mechanisms of mifepristone action favor the development of infection that leads to septic shock and intensifies the actions of multiple inflammatory cytokines, resulting in fulminant, lethal septic shock.

**KEY WORDS:** abortion, *Clostridium sordellii*, mifepristone, septic shock.

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In studies of analogs of steroid hormones for palliative treatment of diseases that involve excessive adrenal production of glucocorticoid hormones (eg, Cushing's syndrome), mifepristone was found to have potent antiglucocorticoid activity in vivo.<sup>1</sup> As early as 1992, it was suggested that mifepristone might predispose bacterial contamination of tissue toward infection that could progress to septic shock.<sup>1,2</sup> During the development of mifepristone as an antiglucocorticoid, the drug was found to have an additional side effect (ie, potent, long-acting antiprogestosterone action). This finding changed the research focus to the use of mifepristone's antiprogestosterone action as a potential medical abortifacient.

Prior to the Food and Drug Administration's (FDA's) approval of mifepristone for medical abortions, fulminant lethal cases due to *Clostridium sordellii* in women of childbearing age were rare and exclusively associated with postpartum infections.<sup>3-5</sup> Toxic shock syndrome due to *C. sordellii* has not been reported in surgical abortions. Since the FDA's approval of mifepristone, 4 US deaths and one Canadian death due to septic shock have been reported.<sup>6-8</sup> Two of the US cases<sup>7</sup> involved *C. sordellii* and resulted in mifepristone-induced septic shock. If the Canadian trial death<sup>8</sup> is counted in the totals, there have been 3 *C. sordellii*-related septic shock deaths and a total of 5 mifepristone-related septic shock deaths. The bacteria involved in the third and fourth US deaths have not been documented. An additional case was reported<sup>9</sup> but later retracted<sup>10</sup> after it was found to be a duplicate report of the earlier Canadi-

Author information provided at the end of the text.

an case.<sup>8</sup> *C. sordellii* is a gram-positive anaerobe. Clinical recognition of impending septic shock due to gram-positive bacteria in medical abortions can be delayed because this type of infection is usually accompanied by both an absence of fever and hemoconcentration due to third spacing that leads to a deceptive normal hemoglobin concentration, even in the presence of significant blood loss. Thus, the FDA has issued a Public Health Advisory on sepsis and medical abortion and revised the Black Box Warning on mifepristone's use in medical abortions.<sup>7</sup>

Furthermore, septic shock due to gram-positive pathogens has not been studied intensively compared with septic shock due to gram-negative pathogens.<sup>11</sup> Septic shock, acute respiratory distress syndrome, and multiple organ dysfunction are consequences of a poorly controlled inflammatory response to infection or injury.<sup>12</sup> There is a tight balance between proinflammatory and antiinflammatory cytokines that regulates the inflammatory process.<sup>13</sup>

Cytokines activate macrophages, monocytes, and neutrophils by favoring adhesion to endothelial cells and then extravasation from capillaries into the interstitial spaces of infected tissues. Cytokines are proteins that have paracrine, autocrine, and endocrine functions. They are secreted by tissue leukocytes when activated by lipoteichoic acid (LTA). Activation of the leukocytes in the innate immune system does not require presence or synthesis of specific antibodies. Excessive cytokines in the systemic circulation can be the forerunner of irreversible septic shock. This article examines the pathophysiology of septic shock associated with mifepristone/misoprostol medical abortions that resulted in endometritis due to *C. sordellii*.

### ***C. sordellii* in Post-Abortion Infections**

In addition to uncontrolled uterine bleeding, puerperal infection with *C. sordellii* leads to a distinctive and lethal toxic shock–like syndrome.<sup>3,14</sup> *C. sordellii* is part of the normal vaginal flora in about 10% of women. The clinical aspects of *C. sordellii* bacteremia have been reviewed.<sup>15</sup> Clinical infections of the vagina and/or uterus are usually prevented by the host's innate immune system.<sup>16</sup> LTA is a structural component and degradation product of the cell wall of all gram-positive bacteria. Receptors on leukocytes that recognize the components and degradation products of microorganisms are at the heart of the innate immune system.<sup>17</sup> LTA stimulates tissue macrophages and neutrophils to initiate phagocytosis of whole bacteria that manage to cross normal tissue barriers and invade interstitial tissue spaces. Thus, the innate immune system normally destroys bacteria that are able to penetrate mucosal barriers before they are able to multiply and secrete exotoxins as part of their lethal toxicity.

*C. sordellii* produces 2 potent exotoxins—lethal toxin and hemorrhagic toxin—in addition to the endotoxin LTA. Live bacteria actively secrete lethal and hemorrhagic toxin.<sup>5</sup> LTA is released into the surrounding interstitial fluid when bacterial cell walls disintegrate. Lethal toxin and LTA can be collectively or individually responsible for

septic shock in an infection caused by *C. sordellii*. Lethal toxin is a potent and specific inhibitor of G-proteins, which are critical for the transfer of external signals to the interior of mammalian cells.<sup>18</sup> Lethal toxin also causes disorganization or disruption of the cytoplasmic membrane and intracellular organelles, resulting in cell lysis.<sup>19</sup> LTA activates macrophages, monocytes, and neutrophils by binding to and stimulating toll-like receptors.<sup>16</sup> Activation of toll-like receptors, which are a functional component of the innate immune system, results in the synthesis and release of proinflammatory cytokines into the interstitial fluid.<sup>20,21</sup> Excessive absorption of interstitial proinflammatory cytokines into the systemic circulation contributes to the intensity of sepsis as indicated by the uncontrolled cascade of coagulation, fibrinolysis, and inflammation that, in turn, leads to septic shock, multiple organ dysfunction, and death.<sup>22</sup>

## **Mifepristone**

### **PHARMACODYNAMICS**

In the 1970s, steroid derivatives were investigated for their potential therapeutic use as glucocorticoid antagonists for palliative treatment of Cushing's syndrome.<sup>1</sup> In the course of toxicological studies in the 1980s, mifepristone was found to be an abortifacient.<sup>1</sup> Mifepristone is pharmacologically classified as both a progesterone antagonist and a glucocorticoid antagonist.<sup>23</sup> It binds to both progesterone receptors and glucocorticoid receptors without activating these receptors to any significant degree.

Mifepristone blocks glucocorticoid receptors throughout body tissues and even blocks cortisol's negative feedback receptors in the hypothalamus and anterior pituitary. Blockade of these receptors results in the activation of the hypothalamus–pituitary–adrenal (HPA) axis and results in an increased rate of synthesis and release of cortisol from the adrenal cortex. Blockade of glucocorticoid receptors in leukocytes inhibits the secretion of interleukin-10 (IL-10), a very potent antiinflammatory cytokine.<sup>24</sup> Without sufficient release of IL-10 at the appropriate time, inflammation ceases to be a host defense and becomes an uncontrolled and detrimental response to bacterial infection.

The complex relationship between proinflammatory cytokines and IL-10 has been demonstrated in an animal model of septic shock that employs cecal ligation and needle puncture, resulting in polymicrobial intraabdominal sepsis. In this animal model, systemic levels of both the proinflammatory cytokines and IL-10 were correlated directly with the severity of septic shock.<sup>25</sup> Production of IL-10 at the site of tissue infection was suggested as the best indicator of disease activity compared with measurement of systemic levels of IL-10. Furthermore, the precise timing of the expression of IL-10 was found to be critical in preventing mortality in the cecal ligation/needle puncture model. Blockade of glucocorticoid receptors by a single dose of mifepristone lowered survival of mice to 15% from the control level of 71%.<sup>26</sup>

## PHARMACOKINETICS

Pharmacokinetic studies have shown that mifepristone has a plasma half-life of 20–25 hours and is metabolized by the liver. Approximately 5 days are required for elimination. It is slowly demethylated by the microsome system and, in particular, by CYP3A4. The plasma half-life of mifepristone is markedly prolonged in patients who are also taking other drugs that are metabolized by CYP3A4, such as codeine. It is common practice to prescribe codeine for women who experience severe pain during mifepristone abortions, thus prolonging the effects of mifepristone.

## ANTI-PROGESTERONE AND THE ANTIGLUCOCORTICOID ACTIONS

Mifepristone is a potent progesterone antagonist that, in addition to its ability to block glucocorticoid receptors, blocks progesterone receptors.<sup>27</sup> Progesterone receptors have an affinity for mifepristone that is 5 times greater than its affinity for progesterone. Blockade of progesterone receptors in the decidua results in decidua ischemia which, in turn, results in rejection of the developing placenta and death of the embryo. Prolonged ischemia of the decidua and the embryonic placenta causes necrosis of these tissues. Mifepristone also blocks the progesterone receptors in the cells of the cervical canal, causing cervical dilation and liquefaction of the cervical mucus plug.<sup>27</sup>

The combined loss of a closed cervix and the protective cervical mucus plug permits contamination of the decidua and the intrauterine necrotic cells with aerobic and anaerobic bacteria from the normal vaginal flora. Necrotic anoxic tissue favors the growth of anaerobic bacteria and, as noted above, *C. sordellii* is a strict anaerobe. Furthermore, blockade of glucocorticoid receptors by mifepristone either at the level of the HPA axis or tissue macrophages, monocytes, and neutrophils can prevent the innate immune system from functioning properly to eradicate contaminating bacteria in the decidua.

## Mifepristone-Induced Septic Shock

Two different theoretical mechanisms could account for mifepristone causing the in utero growth of *C. sordellii* with resultant fatal septic shock. Future research may be able to distinguish whether one or both of these mechanisms are operative. Knowledge of the correct pathophysiology of this type of septic shock would allow for early diagnosis and initiation of effective therapy.

### FIRST THEORETICAL MECHANISM

In the absence of mifepristone, the innate immune system stimulates controlled production and timely release of glucocorticoids to prevent an overshoot of an ongoing localized inflammatory process.<sup>28</sup> In the treatment of septic shock not associated with mifepristone, low doses of glucocorticoids have therapeutic effects by correcting for adrenal cortex

exhaustion, exerting appropriate antiinflammatory properties, and enhancing endogenous catecholamine effects.<sup>29,30</sup>

Host survival in bacterial and viral infections is dependent upon the proper sequence and timely activation of the HPA axis for the production of cortisol.<sup>31</sup> Mifepristone disrupts the negative pituitary feedback of the morning cortisol rise,<sup>13</sup> thus altering the normal circadian rhythm for the production of cortisol. This blockade of the normal negative feedback receptors results, therefore, in a sustained and excessive synthesis and release of cortisol from the adrenal cortex. Poorly controlled and elevated levels of cortisol, in turn, produce excessive levels of IL-10 at the inflammatory site of the infection.

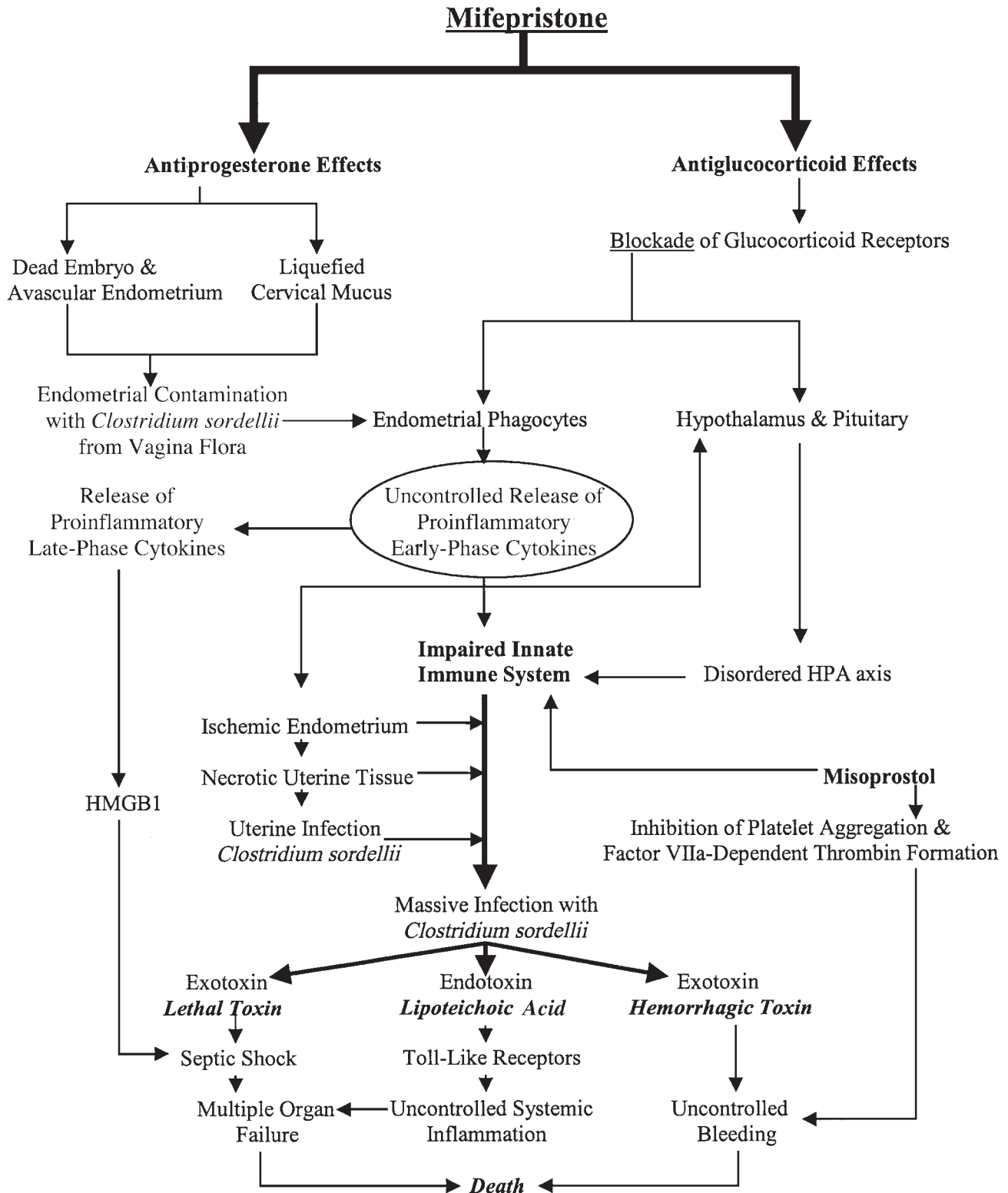
IL-10 inhibits the synthesis and release of early phase proinflammatory cytokines IL-1, IL-6, and tissue necrosis factor (TNF)- $\alpha$ .<sup>32,33</sup> Normally, these proinflammatory cytokines set in motion a protective but controlled chain of events used by the innate immune system to rid the tissue of invading bacteria.<sup>34,35</sup> Thus, according to this model of mifepristone-induced septic shock, sustained and excessive levels of IL-10 inhibit the production of these proinflammatory cytokines, favoring the growth of *C. sordellii*. As the infection progresses, the secretion of lethal toxin increases. As more bacteria die, decomposition of their cell walls leads to increasing levels of LTA that further increases the production of proinflammatory cytokines by macrophages. As infected tissue levels of lethal toxin and proinflammatory cytokines increase, they are absorbed into the systemic circulation, allowing the development of irreversible septic shock (Figure 1).

### SECOND THEORETICAL MECHANISM

Mifepristone could promote the inflammatory response to bacteria by virtue of its ability to block glucocorticoid receptors in phagocytes located at the site of invading bacteria. Mifepristone has been shown to bind to glucocorticoid receptors in lymphoid cells and block the receptor from dissociating into its subunits, thus preventing nuclear receptor translocation.<sup>36</sup> In experimental animals, blockade of glucocorticoid receptors by mifepristone was shown to increase the mortality of endotoxemic rats administered lipopolysaccharide, a pathogen-associated molecular pattern compound.<sup>16,37</sup> By blocking glucocorticoid receptors in macrophages, monocytes, and neutrophils, mifepristone would prevent the synthesis and release of IL-10. For example, rats pretreated with mifepristone had a markedly attenuated increase in plasma IL-10 level in response to tissue necrosis due to exposure to carbon tetrachloride.<sup>38</sup> In the absence of sufficient IL-10, the production and release of IL-1, IL-6, and TNF- $\alpha$  would progress in an uncontrolled manner, leading to an imbalance between the proinflammatory and antiinflammatory cytokines. Systemic absorption of excessive proinflammatory cytokines would contribute to the further development of septic shock by causing additional systemic vasodilation, thus resulting in a critical fall in blood pressure and the inability to maintain homeostasis.

Mifepristone's blockade of peripheral glucocorticoid receptors has been shown to increase production of endotoxin-induced TNF, which contributes to the pathogenesis of septic shock.<sup>39</sup> Glucocorticoids, at the proper time and in

proper amounts, normally down-regulate cytokine synthesis. Therefore, blockade of these receptors by mifepristone enhances the susceptibility to septic shock.<sup>40</sup> Furthermore, excessive levels of proinflammatory cytokines would con-



**Figure 1.** The interactions and complex relations of biologically active ligands in mifepristone-induced abortions. HPA = hypothalamus–pituitary–adrenal; HMGB1 = highly mobile group box 1.

tribute to the development of necrotic tissue in the uterus by their ability to cause coagulation of the microvasculature of the decidua as part of the inflammatory response. As the inflammatory response progresses, there is release of the late-phase cytokine HMGB1 from leukocytes.<sup>41</sup> HMGB1 functions as a paracrine, autocrine, and endocrine stimulus by stimulating the toll-like receptors on leukocytes.<sup>42,43</sup> The net result of the stimulation of toll-like receptors is the further increase in synthesis and release of early phase cytokines.<sup>44</sup> Thus, HMGB1 contributes to the intensification of widespread tissue necrosis and also intensifies the ongoing septic shock process (Figure 1).<sup>45</sup>

## Discussion

The pathophysiology of septic shock in the presence of mifepristone and an infection with *C. sordellii* is multifaceted. Puerperal infection with *C. sordellii* is usually accompanied by excessive uterine bleeding but is characterized by the absence of the classic signs of ongoing severe infection (eg, fever) and a falling hemoglobin concentration. Figure 1 shows the complex relationships that are the result of blockade of both progesterone receptors and glucocorticoid receptors. Mifepristone's multireceptor blockade interferes with the protective function of the innate immune system. Malfunction of the innate immune system in combating the invasion of the decidua by *C. sordellii* leads to septic shock as a result of (1) the loss of physiologic control of both acute and late phase cytokines, (2) secretion of lethal toxin and liberation of LTA, (3) improper hormone secretion of cortisol, and (4) failure of appropriate formation and release of IL-10. An understanding of the intimate relationships of the innate immune system, cytokines, pathogen-associated molecular pattern compounds, glucocorticoids, and B-type natriuretic peptides may serve in the future as a clinically useful paradigm to alert physicians to the possibility of impending fulminating septic shock.<sup>46-49</sup>

## Summary

The FDA has reminded healthcare providers that serious bacterial infection and sepsis may occur without the usual signs of infection, such as fever and tenderness on examination. This article demonstrates the likely pathophysiologic basis for this reality; that is, mifepristone's capacity to increase a pregnant woman's susceptibility to an otherwise rare cause of sepsis. If physicians and patients are properly informed of the manner in which mifepristone can cause the rapid onset of septic shock, perhaps both groups will be more sensitive to any early warning signs, which would allow earlier treatment of this otherwise potentially lethal complication.

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EXTRACTO

**OBJETIVO:** Explicar el papel de mifepristona en abortos médicos y relacionar su potente actividad antigluco-corticoide en el desarrollo del choque séptico mortal fulminante debido a infecciones de *Clostridium sordellii*.

**FUENTES DE INFORMACIÓN:** MEDLINE, PubMed, y Google Scholar (de 1984 a marzo del 2005). Las palabras-clave usadas fueron mifepristone, RU38486, RU486, Mifeprex, medical abortion, septic shock, inborn immunity system, citokines, y *C. sordellii*.

**RESUMEN:** El mecanismo de acción de la mifepristona interfiere con la función protectora del sistema de inmunidad innata y constituye la base de la fisiopatología del choque séptico asociado con *C. sordellii*.

**CONCLUSIONES:** Teóricamente, parece que el mecanismo de acción de la mifepristona favorece el inicio de la infección que conduce al desarrollo del choque séptico e intensifica la acción de las múltiples citoquinas inflamatorias, lo que resulta en choque séptico mortal fulminante.

Carlos C da Camara

RÉSUMÉ

**OBJECTIF:** Expliquer le rôle de la mifepristone dans les avortements qui ont résulté en un choc septique fulminant et mortel due au *Clostridium sordellii*.

**PROVENANCE DES DONNÉES:** MEDLINE, PubMed, Google Scholar (1984–mars 2005). Les mots clés étaient mifepristone, RU38486, RU486, Mifeprex, avortement médical, choc septique, système immunitaire naturel, cytokines, et *Clostridium sordellii*.

**RÉSULTATS:** Deux mécanismes d'action de la mifepristone peuvent expliquer l'implication de celle-ci dans la pathophysiologie du choc septique due au *Clostridium sordellii*. L'un de ceux-ci est le blocage de la rétroaction de l'axe hypophyso-surrénalien, entraînant une synthèse et une libération excessive et soutenue de cortisol. Le second est le blocage des récepteurs glucocorticoïdes des phagocytes au site d'infection. Les 2 mécanismes affectent la cascade inflammatoire de cytokines, permettant une pullulation du *Clostridium sordellii* et de sa toxine létale.

**CONCLUSIONES:** En théorie, il apparaît que certains mécanismes d'action de la mifepristone favorisent l'initiation de l'infection qui résulte en un choc septique. L'action de multiples cytokines s'en trouve intensifiée, résultant ainsi en une réaction fulminante et le décès.

Suzanne Laplante