INTRODUCTION

My remarks today focus on a theory to explain how mifepristone may have contributed to the deaths of the four healthy women in California who had medical abortions. These four deaths were the result of septic shock due to a *Clostridium sordellii* infection following a medical abortion with mifepristone. These women were all less than two months pregnant, were given a single dose of 200 mg of mifepristone orally, and self-administered 800 ug of misoprostol vaginally 24 to 48 hours later. They died within the next 5 to 7 days with clinical signs of shock, absence of fever, leukocytosis and hemoconcentration.

How do we explain that a single dose of mifepristone could result, 7 to 10 days later, in a fulminating, lethal case of septic shock? Most drugs are eliminated from the body in a matter of a few hours. However, pharmacokinetic studies of mifepristone have shown that this drug generally has a long half-life life of 20 to 30 hours. With a half-life in this range, it takes 4 to 5 days to remove 95% of mifepristone from the body. However, it has been reported that some humans have an unusually long half-life that can be as long as 90 hours.\(^1\) In these individuals, 18 days would be required to remove 95% of mifepristone.

Mifepristone is removed from the body principally by metabolism. Mifepristone is metabolized by the cytochrome enzymes located in the liver microsomes. Six different metabolites of mifepristone have been identified.\(^2\) Some of these metabolites retain biological activity as progesterone antagonists. However, I am not aware of any studies that have looked at these metabolites of mifepristone to see if they retained or had increased anti-glucocorticoid properties. Study of these six metabolites for their effect on the Innate Immune System is grounds for future research.
In vitro studies with liver microsomal enzymes have shown that the CYP450 3A4 is the enzyme primarily responsible for metabolizing mifepristone. Furthermore, there is some evidence that the enzyme itself can be inactivated during the metabolism of mifepristone. This probable accounts for the relatively long biological half-lives seen in humans. The same enzyme, is also responsible for the O-demethylation of codeine to morphine. In mifepristone abortions, women are frequently prescribed codeine for pain. Thus codeine would compete for the enzyme that metabolizes mifepristone and prolong the biological half-life of mifepristone.

Mifepristone binds with high affinity to both progesterone and glucocorticosteroid receptors as evidenced by a dissociation constant in the pico-molar to nano-molar range. Mifepristone blocks cortisol receptors both in peripheral tissues and in the central nervous system. Blockade of negative feedback receptors in the hypothalamus results in increased serum levels of ACTH and cortisol. It appears that the initial effect of mifepristone is blockade of peripheral glucocorticoid receptors as cortisol levels begin to rise. Thus in some experimental animal protocols, mifepristone is referred to as producing a temporary drug-induced adrenalectomy.

Mifepristone, known as RU486, was initially called RU38486. Mifepristone was originally developed as an anti-glucocorticoid for the treatment of Cushing’s Disease. During the development of this anti-glucocorticoid drug, it was discovered to possess anti-progesterone activity and acted as an abortifacent. Mifepristone’s anti-progesterone activity results in four pharmacologic actions on the pregnant uterus, i.e. cervical ripening, ischemia of the decidua, necrosis of the products of conception, and sensitization of the myometrium to contraction by prostaglandins. The first three of these pharmacological actions enable the establishment of a favorable nidus in the ischemic decidua for an infection with the anaerobic bacteria C. sordellii. Different species of clostridium, including C. sordellii, have been found in the normal vaginal flora in 8 to 18% of women.

Macrophages, monocytes, neutrophiles and endothelial cells are the host’s first line of defense to counter bacterial invasion of the interstitial space of uterine tissue. I propose that
mifepristone’s anti-glucocorticoid action initially impaired the proper functioning of these cells of the Innate Immune System within the pregnant uterus and ultimately led to a uterine infection with *C. sordellii*. Specific molecular components, such as Lipoteichoic Acid and peptidoglycan, are unique to the cell walls of anaerobic bacteria and are known as Pathogen Associated Molecular Pattern molecules. These unique biochemical entities bind to and activate Toll-Like Receptors on tissue macrophages. Toll-Like Receptors, when activated, function as the principle sensors of infection in mammals. Activated Toll-like Receptors of the Innate Immune System cause an out pouring of pro-inflammatory cytokines at the site of bacterial invasion.

TNFα, IL-1 and IL-6 are the principle pro-inflammatory cytokines that are synthesized and secreted by activated phagocytes.\(^5,6\) Inflammation, when properly controlled, destroy invading bacteria without tissue damage. If the local actions of pro-inflammatory cytokines are not controlled, two things can occur. One, *C. sordellii* can successfully establish an infection with the secretion of Lethal Toxin, and two, excess pro-inflammatory cytokines gain access to the systemic circulation. Both of these events contribute to the etiology of septic shock and multiple organ dysfunction.

The proper timing and proper amount of cortisol are crucial to maintain control of the inflammatory response and prevent tissue damage. Cortisol binds to its intracellular glucocorticoid receptors in phagocytes to cause an increase in transcription of DNA resulting in the synthesis and secretion of the anti-inflammatory cytokine Interukin-10. This anti-inflammatory cytokine suppresses the generation of excessive pro-inflammatory cytokines, TNFα, IL-1 and IL-6 by the cells of the Innate Immune System.

The hypothesis that mifepristone could facilitate infection and lead to lethal septic shock is supported by animal experimentation\(^7,8\) As an example, a single dose of mifepristone given in an animal model of poly-microbial septic shock dramatically increased the mortality rate almost 3 fold in mifepristone treated mice.

It is my opinion that mifepristone impairs the Innate Immune System just long enough to delay the proper removal of contaminating *C. sordellii* from the decidua. This delay allows the
bacteria to secrete Lethal Toxin into uterine interstitial fluid. Lethal Toxin taken in by phagocytes, endothelial cells, and other cells in the uterus prevents them from properly participating in the defensive inflammatory responses of the Innate Immune System.

When Lethal Toxin is internalized by the uterine phagocytes and endothelial cells, it functions as an intracellular enzyme that catalyzes the glucosylation of G-Proteins.\(^9\) G-Proteins are the molecular switches that activate or inhibit a multitude of vital biochemical cascades and vital genetic transcription functions that are necessary for cells to function properly. Glucosylation of G-proteins in uterine phagocytes renders them useless in destroying bacteria.

In summary, mifepristone’s anti-progesterone effects prepare the aborting uterus as an ideal bacterial culture medium for *C. sordellii* by causing ischemic decidua that that leads to necrotic products of conception.

Mifepristone’s anti-glucocorticoid pharmacologic actions disrupt the hypothalamic-pituitary-adrenal axis and interfere with the functioning of the peripheral glucocorticoid receptors at a crucial time and results in the lack of control of the pro-inflammatory cytokine response.\(^{10}\) This allows for the establishment of a nidus of infection with *C. sordellii* and the localized secretion of Lethal Toxin. Phagocytes in the decidua are permanently inactivated by Lethal Toxin. This allows *C. sordellii* to multiply unchecked and secrete excess Lethal Toxin into the systemic circulation. In conclusion, the combination of both Lethal Toxin and excess inflammatory cytokines in the systemic circulation would work together synergistically to produce the clinical findings of rapid, fulminating, lethal septic shock that were the hallmark of the four cases that occurred in California.

Thank you for your time and attention. If you have any questions, I would be happy to try to answer them.
Title of Presentation: The Pathophysiology of Mifepristone – Induced Septic Shock Due to Clostridium sordellii

Ref. #1

Ref. #2

Ref. #3

Ref. #4

Ref. #5

Ref. #6
Ulevitch RJ: Therapeutics targeting the innate immune system, 2004; Nature Reviews (Immunology), 2004; 4:512-20

Ref. #7

Ref. #8

Ref. #9

Ref. #10