

The Development of Mifepristone for Use in Medication Abortions

In the 1980s, researchers at the pharmaceutical company Roussel-Uclaf in Paris, France, helped develop a biological compound called mifepristone. When a woman takes it, mifepristone interferes with the function of hormones involved in pregnancy and it can therefore be used to terminate pregnancies. In 2000, the US Food and Drug Administration approved mifepristone, also called RU 486, as part of a treatment to induce abortions using drugs instead of surgery, a method called medication abortion. Women can receive medication abortions earlier in their pregnancies than surgical abortions, and medication abortions often result in less severe side-effects than their surgical counterparts. In that capacity, mifepristone has increased women's access to abortions throughout the world.

In April of 1980, Georges Teutsch, a researcher at Roussel-Uclaf pharmaceutical company, worked on a program to develop synthetic compounds called antagonists. Antagonists are molecules in the body that prevent certain chemical reactions from taking place. Receptors are molecules in the body that receive chemical signals. When chemical signals bind to receptors, a chemical reaction is initiated in the body. Antagonists bind to the receptors blocking any chemical signal from binding, thus preventing a chemical reaction from occurring. For example, physicians can prescribe certain antagonists called beta blockers to prevent the hormone adrenaline from binding to heart cell receptors. When the hormone adrenaline is unable to bind to receptors, the heart slows down, reducing the strain on the heart muscle. In 1980, Teutsch and other researchers synthesized an antagonist they named RU 38486, which the company later renamed RU 486, though it was also often called using its chemical name, mifepristone.

Mifepristone is an antagonist that prevents hormones, or the chemical messengers, of the body from binding to receptor cells. Hormones affect the body's tissues to produce changes, including readying a woman's body for pregnancy. Progesterone, one of the hormones that play a large role in pregnancy, thickens the lining of a woman's uterus and prepares it for the implantation of a fertilized egg, ensuring a successful pregnancy. Mifepristone binds to hormone receptor cells, preventing progesterone from binding to them and initiating progesterone's chemical changes. When that happens, the uterus does not receive the signal to begin preparing for the implantation of an egg, remaining inhospitable to an egg.

After seeing the effects of Mifepristone on progesterone, the researchers at Roussel-Uclaf began studying whether mifepristone could be used to prevent pregnancy. Researchers found that mifepristone bound to receptor cells in the lab better than progesterone did. That meant that even if progesterone was in a woman's body, the mifepristone would bind better to the receptor cells, negating the effects of progesterone. In non-pregnant female rabbits, mifepristone blocked progesterone from causing changes in rabbits' uterine lining. Since a thick uterine lining is necessary for sustaining a pregnancy, early research indicated that mifepristone could prevent a female from getting pregnant.

Researchers then asked whether mifepristone could terminate existing pregnancies, rather than just preventing them. Studies in female rats and female monkeys (*Macaca fascicularis*) showed that it could. In the first monkey studies, mifepristone caused non-pregnant monkeys to have a premature menstrual period forty-eight hours after they received the drug. Later studies with monkeys showed that the mifepristone performed the same way in pregnant monkeys, terminating their pregnancies. Other animal studies showed that mifepristone, even given in large doses, was not toxic, demonstrating that mifepristone was safe to use. The studies in monkeys, as well as other ani-

mals, demonstrated that mifepristone safely and effectively prevented and terminated pregnancies in animals. However, researchers still needed to show those same results in humans.

In October of 1981 Walter Hermann, a gynecologist at the University Hospital of Geneva, in Geneva, Switzerland, began clinical trials of mifepristone on pregnant women. Hermann wanted to show that mifepristone effectively terminated pregnancies in humans like it did in primates. In the clinical trial, researchers gave mifepristone to eleven pregnant women who had volunteered for the study. Mifepristone successfully terminated nine out of the eleven pregnancies by causing the women's bodies to expel the embryos from their uteri, up to five or six weeks into the pregnancies. After Hermann's trials, researcher Andre Ulmann led further clinical studies funded by Roussel-Uclaf. Other studies were run by the World Health Organization and the Population Council, a nonprofit based in New York City, New York. On the whole, the studies showed that mifepristone terminated the majority of pregnancies in human women and that it resulted in relatively few side effects.

In 1985, Ulmann directed a series of large-scale studies to determine which schedule for administering mifepristone terminated pregnancies most effectively. A drug schedule refers to how much of a drug the patient takes at what time. Each of the previous clinical trials had used differing amounts of the drug, taken at different times, and it was important to determine which schedule most successfully resulted in the termination of a pregnancy. Knowing the most effective schedule was required to enable physicians to administer the most effective doses to their patients. Ulmann deemed a schedule effective when the embryo and the uterine lining were expelled and the woman did not need surgery to complete the abortion process. After a series of studies, Ulmann concluded that one 600 milligram dose of the drug, taken at one time, terminated pregnancies most effectively. However, that dosage terminated pregnancies only eighty percent of the time and only if the woman received it within a week of missing the beginning of her expected menstruation. At that point, a woman was five or six weeks into the pregnancy.

To improve the effectiveness of mifepristone as an abortifacient, researcher Mark Bygdeman at the Karolinska Institute in Stockholm, Sweden, suggested administering another drug after mifepristone. The other drug Bygdeman proposed was a prostaglandin, a class of drugs that promote muscle contractions, including uterine contractions. Bygdeman hypothesized that additional uterine contractions would help expel the contents of the uterus more effectively after administration of mifepristone. To test Bygdeman's hypothesis, researchers around the world ran new clinical trials in France, Great Britain, Sweden, and China. In the new trials, women received 600 milligrams of mifepristone, as in previous trials. But between thirty-six and forty-eight hours later, after mifepristone had affected the uterine muscles, the women received a dose of prostaglandins.

The mifepristone-prostaglandin combination terminated women's pregnancies ninety-six percent of the time, which was the same success rate as found in women who underwent surgery to terminate their pregnancies. In addition, researchers found that the combination of drugs effectively terminated pregnancies up to three weeks past a woman's missed period, or seven to eight weeks into the pregnancy. That meant the combination treatment was effective two weeks longer than the mifepristone-only treatment. The drug was not as effective past seven weeks' gestation, or three weeks past a missed menstrual period. The addition of prostaglandins both increased the effectiveness of the treatment and extended the time during which the treatment could be used to terminate a pregnancy. As a result of the treatment, women experienced menstrual bleeding due to the shedding of uterine lining, and some experienced pain from the uterine contractions. Researchers considered those minor side effects, similar to those experienced after a surgical abortion.

After researchers demonstrated the safety and efficacy of mifepristone to induce abortions, the drugs still needed to be approved for use in countries around the world. On 23 September 1988, France became the first country to approve the use of RU 486 to terminate pregnancies, as long as it was used with a prostaglandin. Due to the results from previous clinical trials, the French health authorities stipulated that mifepristone could be used only up to the seventh week of pregnancy. Between 1988 and 1990, the mifepristone-prostaglandin combination was used to terminate over 40,000 pregnancies in France.

After France approved the drug in 1988, the US Food and Drug Administration, or FDA, placed mifepristone on an import alert list, which prevented individuals from importing the drug into the

US for personal use. At the time, the president George H. W. Bush took an anti-abortion stance and sought to prevent more abortions taking place in the US through the prescription of mifepristone. However, in 1993, after the election of Bill Clinton to the presidency, the FDA fast-tracked the approval of mifepristone using the regulatory pathway designed for drugs that treat life-threatening diseases. The FDA approved mifepristone in 2000. On the original label for the drug, with a brand name Mifeprex, the FDA required that pregnant women seeking an abortion take three 200 milligram tablets of Mifeprex at one time. The women then had to return to the physician forty-eight hours later to take two 200 microgram tablets of a prostaglandin. The specific prostaglandin recommended was called misoprostol. The FDA then required that the woman return to the physician a third time two weeks later to ensure that a full abortion had been induced. If a full abortion had not occurred, leaving the embryo alive in the uterus, the FDA recommended that a surgical abortion follow to prevent fetal malformation.

The FDA's label for mifepristone contained some inconsistencies and was subject to much disagreement. Though the FDA advised use of oral misoprostol in the label for mifepristone, the FDA had not approved any oral misoprostols for use in medication abortions. The FDA had approved vaginal misoprostol, but the label for mifepristone specifically noted oral misoprostol. That meant that for physicians to follow the mifepristone label, they had to use misoprostol off label. Off label use refers to situations where a physician prescribes a drug for a purpose other than the one the drug is approved for. Off label prescription is legal in the US. However, when physicians administer drugs without formal approval from the FDA, they rely on their own medical judgment as to the safety and efficacy of the drug, which can be risky. Physicians prescribing drugs off label rely on the most current scientific knowledge, but that knowledge may not be complete, leaving some risks.

As well as the inconsistency within the FDA label, the recommendations for use by the FDA were also inconsistent with scientific knowledge at the time. After Mifeprex's approval, researchers began conducting more studies that changed the recommended guidelines for administering medication abortions. Studies conducted in the early 2000s indicated that 200 milligrams of mifepristone, one third of the FDA's recommended dose, was just as effective as 600 milligrams and that the combination of mifepristone and misoprostol was effective up to nine weeks' gestation, two weeks longer than the FDA's original guidelines. Additionally, researchers showed that women could self-administer the second drug, misoprostol, at home without reducing the effectiveness or increasing their risk of injury. That eliminated the need for women to return to the physician's office a second time to receive medication. In March of 2016, the FDA changed its recommended regimen to match those evidence-based guidelines.

Sources

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