

FHI's Role in Search for Nonsurgical Sterilization

For two decades, scientists at Family Health International (FHI) and elsewhere have conducted research directed toward finding a safe, effective method of nonsurgical female sterilization. One of the most promising methods extensively studied by FHI is a drug called quinacrine.

The availability of a nonsurgical sterilization method would help meet a growing need for an alternative permanent family planning method. Surgical sterilization, the only permanent method currently available, is the most popular modern contraceptive method in both industrialized and developing nations. Worldwide, approximately 16 percent of women of reproductive age have undergone a sterilization procedure. An estimated 170 million men and women rely on sterilization for family planning, and the number is expected to reach 270 million by the year 2000.

The demand for sterilization, however, far outpaces health workers' ability to provide surgical services. Nonsurgical sterilization could increase access to family planning,

especially in rural areas where physicians, medical facilities and equipment often are in short supply.

"A nonsurgical sterilization method that is safe, highly effective, inexpensive and easy to administer would make voluntary sterilization accessible to millions of women who desire permanent contraception but currently lack access to surgical methods," says Dr. Theodore M. King, FHI president and chief operating officer.

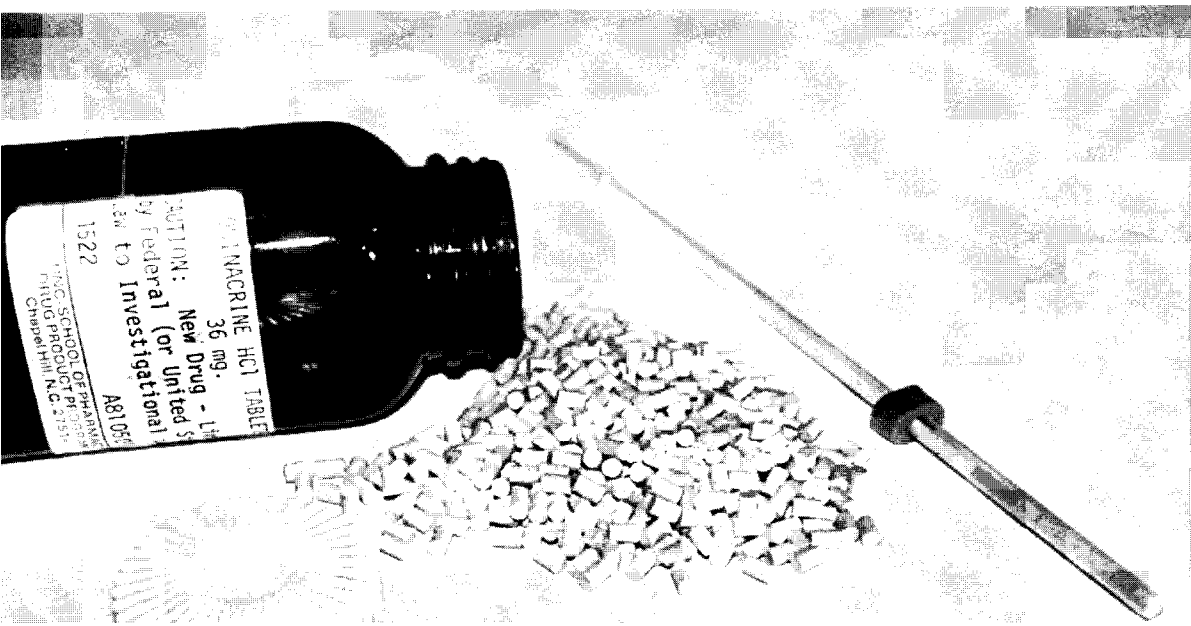
"Extensive data exist showing that quinacrine has great promise as a nonsurgical method; however, questions about the drug's toxicity, potential carcinogenicity and teratogenicity remain unanswered," Dr. King says. "Also, concerns have been raised that this method, like other contraceptives that are not completely controlled by the user, could be administered without the clients' full knowledge or consent.

"As with any contraceptive method, rigorous studies are needed to ensure safety and efficacy of quinacrine," Dr. King says. "FHI supports a stringent review process by appropriate regulatory bodies, such as the

U.S. Food and Drug Administration (FDA), to address these concerns. Follow-up studies can help confirm the results of FHI's initial retrospective study in Chile, concerning quinacrine's possible association with increased risks of cancer."

Dr. King notes that improved training and supervision for providers, education about quality of care issues, and appropriate informed

QUINACRINE PELLETS ARE INSERTED INTO THE UTERUS, SEVEN PELLETS AT A TIME, USING A MODIFIED IUD INSERTER.



choice procedures can help ensure that women who choose to undergo nonsurgical sterilization fully understand the risks and benefits, as well as the irreversibility of the method. Furthermore, research is needed to address the potential for contraceptive abuse by identifying circumstances that promote abusive practices within service systems and understanding their impact on the user.

FHI'S EXPERIENCE

In the 1960s, several groups of researchers began to investigate nonsurgical sterilization techniques, including the use of chemical agents to block the fallopian tubes. In Chile, Dr. Jaime Zipper and his colleagues explored the use of quinacrine hydrochloride, a drug long used to prevent and treat malaria and other parasitic diseases. Dr. Zipper conducted studies on quinacrine's contraceptive effects in rats and rabbits.

In the early 1970s, Dr. Zipper began administering quinacrine in a slurry solution to women in Chile. The technique was abandoned due to a tendency toward spillage of the slurry into the peritoneal cavity, which resulted in concerns about toxicity. Pregnancy rates also were unacceptable.

FHI became involved in quinacrine research in 1976, when its researchers transcribed and analyzed clinical trial data from Chile. At that time, FHI scientists began working with Dr. Zipper to develop a new method of administration. Quinacrine delivered in the form of pellets, which do not spill or leak into the peritoneal cavity, was the result of these collaborative efforts.

In 1977, in conformity with U.S. FDA guidelines at that time, scientists at FHI (then called the International Fertility Research Program) worked with local investigators to conduct clinical trials on quinacrine pellet insertions in Chile. Investigators found that pellet insertions eliminated the risk of transient psychoses previously reported in 2 percent of the women who received the slurry solution. Other side effects observed in the earlier work with slurry, including abdominal pain and amenorrhea, were less frequent with pellets at least in part because spillage was eliminated.²

Initially, three insertions were required of quinacrine pellets that would dissolve in about 10 minutes. In the 1980s, researchers from FHI and the University of North Carolina refined the process so that two insertions of 100-minute pellets were sufficient to close the proximal portion of the fallopian

1976

At the request of Chilean scientist Dr. Jaime Zipper, FHI begins transcribing and analyzing data from a clinical trial of quinacrine administered in a slurry solution to 200 Chilean women. High pregnancy rates (9.9 per 100 women after 12 months) and toxicity prompt FHI research on a new method of administration.

1977

FHI researchers develop 10-minute releasing quinacrine pellets.

1977

FHI works with Dr. Zipper to initiate clinical trials of 10-minute releasing pellets administered with thiopental sodium to 165 Chilean women. The 12-month pregnancy rate after three insertions is 4.3 per 100 women.

1979

FHI initiates clinical trials of 10-minute releasing quinacrine pellets without thiopental sodium among 81 women in Baroda, India; 151 women in Valdivia, Chile; and 143 women in Santiago Chile. Twelve-month pregnancy rates after three insertions are 0.0 per 100 women in Baroda; 0.7 in Valdivia; and 3.3 in Santiago.

1981

Following FHI-sponsored animal studies in the United States on mutagenicity and teratogenicity FHI receives an exemption for an Investigational New Drug (IND) application from the U.S. Food and Drug Administration.

1981

FHI develops 100-minute releasing pellets.

1984

FHI initiates clinical trial of 100-minute releasing pellets on 112 women in Santiago, Chile. Twelve and 24-month pregnancy rates are 2.0 per 100 women.

1984

FHI begins a Phase I clinical trial of quinacrine in the United States, investigating the effects of 10-minute releasing quinacrine pellets on 10 women 24 hours prior to hysterectomy.

1985

FHI conducts a Phase I clinical trial in the United States, investigating the effects of 10- and 100-minute releasing quinacrine on 11 women 30 days prior to hysterectomy.

1989

FHI identifies eight cancer cases during long-term follow-up of women who received quinacrine pellet sterilizations in FHI-sponsored clinical trials in Chile.

1990

FHI chooses to withdraw the IND. FHI discontinues funding for prospective studies in Chile and initiates a retrospective cohort study on Chilean women who received quinacrine pellets.

1992

FHI receives a request for data from the Vietnamese government, which began an introductory program of quinacrine sterilization in 1989.

1993

Through the retrospective study in Chile, FHI documents 17 cancer cases among 1,492 quinacrine sterilizations performed from 1977 through 1989. FHI finds no evidence that quinacrine increases the risk of cancer above the normal risks for women in age-specific groups. FHI recommends continued surveillance of this cohort.

1994

At the request of the Vietnamese government, FHI begins a retrospective study of 3,178 quinacrine procedures carried out by the Ministry of Health in Vietnam. FHI begins analysis of sociodemographic data from all procedures, plus a survey of a sample of 1,800 quinacrine users in three provinces.

1994

FHI convenes a toxicology expert meeting on quinacrine. Experts conclude further research is needed on toxicity, teratogenicity, and potential carcinogenicity. FHI makes plans to apply for a new IND in order to conduct further testing on quinacrine safety.

tubes. The 10-minute and 100-minute release rates refer to the approximate time it takes pellets to dissolve in the uterus. The longer release rate resulted in higher rates of tubal occlusion. Pregnancy rates for women who received 10-minute releasing pellets were 3.3 per 100 women after a year, while rates for women who received 100-minute pellets were 2 per 100.³ The 10-year efficacy rate for older quinacrine regimens is about 93 percent. More recent regimens, using only two insertions, appear to have a similar failure rate, according to FHI data.

In the late 1970s, FHI sponsored preclinical studies on the mutagenicity and teratogenicity of quinacrine, which confirmed mutagenicity in a bacterial system. The studies did show that quinacrine, when given to rats and monkeys early in pregnancy, usually resulted in fetal deaths and resorption, but found no evidence of chromosomal damage or birth defects. Following completion of these studies, the U.S. FDA gave FHI permission to conduct Phase I clinical trials in the United States of quinacrine pellet insertion in women scheduled for hysterectomies. Two Phase I studies were conducted in the United States in the mid-1980s. These studies confirmed the findings of Dr. Zipper and others that immediate side effects were minor and self-limiting.

Meanwhile, FHI-supported research continued in Chile. In 1989, long-term follow-up studies detected eight cancer cases in six different anatomical sites among 572 Chilean women who received quinacrine pellets years earlier during clinical trials.⁴ Among the eight was one case of uterine leiomyosarcoma. Because of this, FHI discontinued prospective quinacrine research and initiated a retrospective study on the health of quinacrine recipients in Chile.

The retrospective study, which included 1,492 Chilean women who were voluntarily sterilized with quinacrine from 1977 through 1989, identified a total of 17 cancer cases. The pattern of cancer occurrence was evaluated using conventional cohort analysis, as well as sensitive space-time cluster methods. Because no cancer incidence data

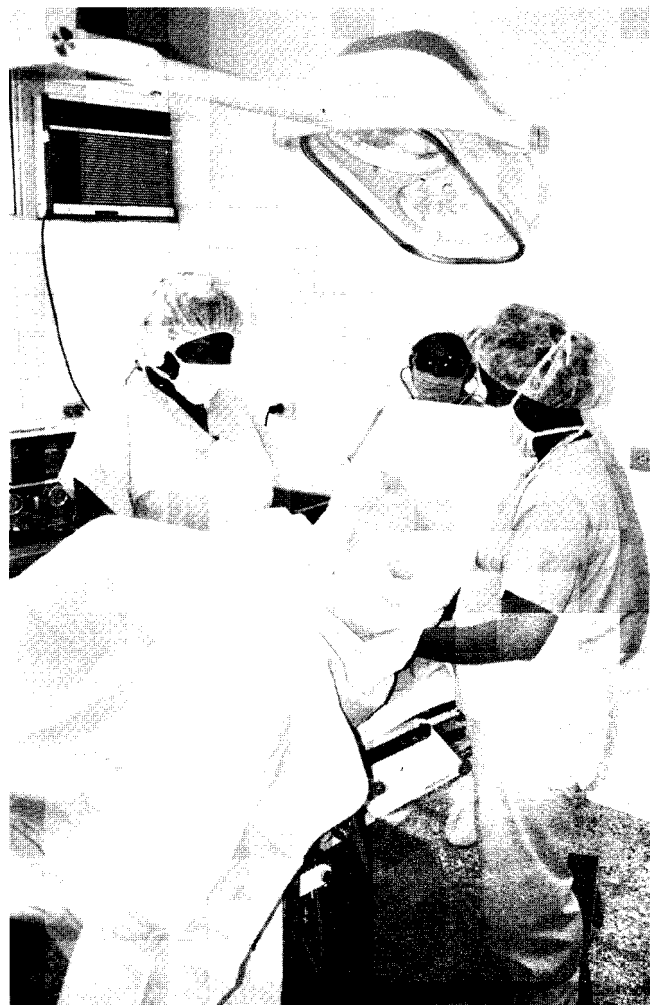
were available in Chile, data from a similar population in Colombia were used for comparison. Although the occurrence of an unusual cluster of cancers was confirmed, no evidence was found of excess cancer risk due to quinacrine.⁵ Because the study was too small to rule out the increased risk of an uncommon cancer, such as leiomyosarcoma, FHI will continue to monitor this group for another five years.

ADVANTAGES, DISADVANTAGES

Assuming that quinacrine pellets are shown to be non-carcinogenic, quinacrine's advantages as a contraceptive are its short-term safety, its potential to increase access to family planning, and its low cost. These factors may appeal to women who do not live near surgical facilities, who cannot afford the expense of surgery, or who do not want to spend time away from family.

More than 80,000 quinacrine pellet sterilizations have been performed worldwide, and no deaths have been attributed to quinacrine pellets. The comparable death rate for female surgical sterilization is from 2 to 20 per 100,000 procedures.⁶

Although no deaths have been documented in the scientific literature, three deaths have been reported among women who received quinacrine in a slurry solution. In one case that FHI is aware of, researchers have not determined if quinacrine was responsible or if xylocaine, contained in the slurry, was the cause.⁷ The slurry method is no longer used.



BECAUSE SURGICAL STERILIZATION REQUIRES EXPENSIVE EQUIPMENT AND HIGHLY-SKILLED STAFF, IT IS OFTEN UNAVAILABLE TO MANY WOMEN, ESPECIALLY THOSE IN RURAL AREAS. NURSES PREPARE FOR STERILIZATION SURGERY AT THE EVANGELINA RODRIGUEZ FAMILY PLANNING CLINIC IN SANTO DOMINGO, THE DOMINICAN REPUBLIC.

Quinacrine pellets are placed in the uterus, through the cervix, with a modified IUD inserter. The procedure does not require an abdominal incision or a lengthy recuperation. Insertion can be performed by trained non-physicians, and it can be performed in an outpatient setting. Because no anesthesia is required, some women whose health problems might make them unfavorable candidates for surgical sterilization could receive quinacrine.

Also, quinacrine is not expensive. Pellets and inserters typically cost less than U.S. \$1 for two insertions.

In addition to the remaining questions on long-term safety and the potential for abuse, a potential disadvantage of quinacrine use is the greater chance of contraceptive failure when compared to surgical sterilization. The efficacy rate for two insertions of quinacrine is approximately 9.5 to 98 percent after 12 months, according to various studies, while the rate for surgical methods is 99 percent or greater after 12 months.

Because quinacrine, like surgical sterilization, is considered a permanent, irreversible method, there is the potential for client regret.

COMPARISON OF COMPLICATIONS

Side effects of quinacrine pellet insertion appear to be temporary and minor. An FHI study, involving 112 women in Chile, found approximately 15 percent experienced amenorrhea lasting one to three months following quinacrine insertions.⁸ Other side effects, reported in FHI studies and studies by other groups, include lower back pain, heavier menstrual bleeding, headaches, and vaginal itching. Symptoms lasted from a few hours to a few days.

Because quinacrine produces inflammatory changes, there is the potential for cervical stenosis, or narrowing, as a complication. Also, quinacrine can cause uterine adhesions, which can result in abdominal pain and bleeding. In rare cases, these problems can become severe and warrant a hysterectomy.

Stenosis and adhesions typically are not reported after surgical sterilization; however, problems may occur that are not present with quinacrine insertion. Surgical sterilization carries some risk of major complications, including infection, hemorrhage or anesthesia-related injuries. Also, there is a risk of bowel or bladder injuries and uterine perforation. While rates vary, major complications occur in less than 1 percent of the surgical cases. Minor complications after female surgical sterilization, such as wound infection or slight bleeding, occur in less than 5 percent of cases.⁹

Questions have also been raised about the risks of ectopic pregnancy in women with failed quinacrine sterilization. Ectopic pregnancy rates vary widely from one country to another, and recent research indicates that this is also true for ectopic pregnancy following surgical sterilization. Because the prevalence of surgical sterilization in Vietnam is too low to provide data for comparison, a recent study in that country compared the ectopic pregnancy rate following quinacrine sterilization with ectopic pregnancy among IUD users. The rates were similar.¹⁰

CURRENT, FUTURE WORK

At the request of the government of Vietnam, FHI this year began a retrospective study of quinacrine recipients in that country. From 1989 through 1992, the Ministry of Health in Vietnam performed 3,178 quinacrine pellet sterilizations in 24 provinces. With financial assistance from the U.S.-based Buffett Foundation, FHI is collecting data from a randomly selected sample of 1,800 quinacrine sterilization cases in three Vietnam provinces. Researchers are comparing the perceptions and experiences of quinacrine recipients with those of women who use IUDs, the only contraceptive that has been widely used in Vietnam.

In addition to obtaining data on health-related outcomes, such as complications, side effects and menstrual pattern changes, FHI researchers are asking women about factors that influenced their decisions to use either method and the impact of quinacrine sterilization on aspects of their lives other than health. Investigators plan to explore the relationships among client satisfaction, provider counseling and service delivery. Through this study, researchers also will measure the level of regret among quinacrine users. Information gained could be used to improve client services, to improve provider training and to develop educational materials. The retrospective study is expected to be completed this year.

Also, FHI is analyzing data from records of all quinacrine sterilizations performed in the Vietnam Ministry of Health field trial. Researchers hope to learn about the sociodemographic characteristics of women who underwent quinacrine sterilizations and to determine the impact of health care provider experience and timing of insertion on quinacrine efficacy.

Because of concerns raised by international donor agencies, quinacrine sterilizations have been suspended by the Vietnam Ministry of Health until the retrospective study and other evaluations can be completed.

In April 1994, FHI organized an expert panel, which met in Washington, to evaluate quinacrine research. Toxicology and drug development experts attended, as well as representatives from the World Health Organization, the FDA and several service delivery programs,

Because toxicity studies on quinacrine were conducted more than 10 years ago and FDA requirements for evaluating toxicity have been modified significantly, the panel recommended additional animal studies for quinacrine. These will include bacterial gene mutation, mammalian cell gene mutation, in vitro cytogenetics in CHO cells or human lymphocytes, and in vivo cytogenetics in mouse cells. In addition, the panel recommended a two-year carcinogenicity study on rats. FHI plans to repeat these pre-clinical studies, as well as to reapply for an exemption for an Investigational New Drug (IND) application from the FDA, which would allow FHI to repeat clinical trials in the United States following favorable results from completion of toxicology studies.

FOOTNOTES

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