

dramatic upswing is necessary to prevent an actual decline in national contraceptive prevalence rates and to achieve the demographic objectives of Tunisia's 1982-1986 Social and Economic Development Plan. The new targets provide for 35 percent of married women of reproductive age using a modern method of contraception and a crude birthrate of 30 per 1,000 by the end of five years.¹¹

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Résumé

Trente-trois pour cent des 39.000 femmes mariées et en âge de procréer pratiquaient la contraception au moment de l'enquête sur la prédominance des méthodes contraceptives réalisée en 1979 dans le gouvernorat de Jendouba, en Tunisie. Dix-huit pour cent des femmes s'étaient fait stériliser, sept pour cent utilisaient la pilule, et la même proportion, le stérilet. L'utilisation d'une méthode de contraception se trouvait la plus répandue chez les femmes des zones urbaines, chez celles âgées de 35 à 44 ans, et chez les femmes qui avaient reçu au moins sept années d'instruction scolaire.

Soixante-huit pour cent des femmes qui

n'utilisaient pas de méthode ont exprimé un intérêt à la pratique future de la contraception, bien que 18 pour cent d'entre elles aient répondu qu'elles ne savaient pas où obtenir les services de planning familial. Chez les femmes qui habitaient les zones r-u-ales, 40 pour cent ont signalé qu'elles ignoraient où se procurer la pilule.

Un projet pilote du planning familial par le couple en milieu rural (PFPC), conçu dans le but de démontrer la possibilité de diffuser plus largement la distribution des contraceptifs à domicile, a été exécuté dans trois délégations du gouvernorat de Jendouba en 1977-1979. Les résultats du projet laissent voir une forte demande non satisfaite de services de planning familial. Après avoir été contactées par des animatrices et par d'autre personnel du projet PFPC, presque la moitié des femmes âgées de 15 à 44 ans et exposées au risque de grossesse ont accepté d'utiliser une méthode contraceptive. A la fin du projet, l'acceptation globale des méthodes contraceptives par les femmes est passée de 26 à 33 pour cent. L'accès difficile aux fournisseurs se dégage comme raison saillante des taux réduits de persévérance parmi les femmes rurales. Le cas de Jendouba fournit des leçons importantes pour le programme national de planning familial en Tunisie.

Special Report

Sterilization Without Surgery

By Michael Klitsch

For about two decades, investigators around the world have been trying to develop a safe, 95 percent effective method of nonsurgical female sterilization that could be performed under local anesthesia on an outpatient basis by nonphysicians, preferably after only a brief training period. Such a method has been called vital for meeting the worldwide demand for voluntary sterilization, since it is projected that around 180 million men and women will be seeking sterilizations over the next 10 years.¹ Researchers have experimented with various chemical sterilants--phenol-based compounds, quinacrine and methylcyanoacrylate--and with silicone rubber delivered by a variety of techniques. However, the goal remains elusive, in that either failure rates have exceeded five percent, the method's safety cannot be assured,

the procedure is too complex or the method requires too many administrations. This is the conclusion to be drawn from the International Workshop on Nonsurgical Methods for Female Tubal Occlusion, a three-day workshop held in Chicago in June 1982, by the Program for Applied Research in Fertility Regulation.

Phenol-Based Occluding Agents

The most intriguing and least known methods, developed in the People's Republic of China, were described by two physicians, Shueh-Ping Tien and Hui-Guo Zheng. Both techniques utilize a thick paste containing phenol. Phenol, or carbolic acid, is a highly caustic chemical that, when injected into the fallopian tubes, rapidly causes extensive damage to the epithelial tissue that lines the

interior of the tubes, or the lumen. After extended exposure to the phenol, the tubes eventually become completely filled with scar tissue.

Tien, who is chairman of the Department of Obstetrics and Gynecology of Xin-Hwa Hospital, at Shanghai's Second Medical College, presented the results of research involving nearly 2,000 women treated with phenol-atabrine paste between 1972 and 1976. The paste is composed of nearly equal amounts of phenol, atabrine and a radio-opaque substance that allows the extent of tubal occlusion to be checked by x-ray. Before the paste is administered, the woman's uterus is explored with a uterine sound to

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give the operator doing the procedure an idea of the orientation of the uterus and of the location of each tubal ostium, the entrance to the fallopian tube.

Such an approximation is necessary because the Chinese technique is essentially "blind": A flexible metal cannula is inserted into the uterus until it reaches the dome, or fundus, of the uterus; within the cannula is a plastic tube through which the caustic paste will be pumped. When the operator believes that the tip of the cannula has reached the tubal ostium, a small amount of saline is pumped through the plastic tube. If the saline does not immediately run back out through the cervix, it is assumed that the plastic tube is properly placed in the entrance to the fallopian tube. As a further test, a very small volume of saccharine is pumped through the plastic tube; if the tube is in the correct position, the saccharine runs through the fallopian tube and into the peritoneal cavity, where it causes a slight pain in the lower pelvis. Once the positioning of the plastic tube is confirmed, 0.42 ml of the phenol compound is pumped into it; only about 0.12 ml will actually enter the fallopian tube, as the rest remains in the plastic tube. After this procedure is carried out in both tubes, an x-ray is taken to confirm that both have been filled. The phenol component of the paste immediately causes extensive damage, while the atabrine creates additional long-term damage, inhibiting the tubal repair process and preventing recanalization.

Tien reported that 1,837 women were treated with this compound between 1972 and 1976; in about 93 percent of the cases, both fallopian tubes were successfully blocked. Follow-up of more than 1,600 women in a 4-7-year period showed that fewer than one percent had become pregnant. Of the 15 pregnancies reported so far, two were ectopic. In 1980, about 200 women underwent this procedure at Xin-Hwa Hospital. Again, both tubes were occluded in 93 percent of the women after one procedure; only one woman in this group has since become pregnant.

The technique described by Zheng is similar to that described by Tien, except that the occlusive material, phenol mucilage, contains, in addition to phenol, several compounds intended to increase the mixture's viscosity; in a recent series of studies, the material also contained a radio-opaque material. Zheng reported on the experience of more than 4,756 women treated with phenol mucilage between 1970 and 1981. Both tubes were occluded in 88 percent of the 4,300 women treated with a non-radio-opaque mixture and in 98 percent of the 450 women treated with radio-opaque phenol mucilage.

Overall, some 4,000 women have been followed up for 5-10 years. Only 1.6 percent have become pregnant; seven of the pregnancies have been ectopic.

Some side effects associated with both of these techniques were reported. Tien said that many women reported perspiring heavily and feeling dizzy either during or immediately after the procedure, and some were nauseated. Some women reported loss of appetite or vaginal discharge for up to 10 days after the procedure, and some said that they felt general abdominal discomfort for up to two weeks. Zheng reported that three women treated suffered a uterine perforation, and 33 contracted pelvic inflammatory disease.

The tubal ostium is tiny, only about 1-2 mm in diameter, and several physicians at the workshop expressed surprise at the level of technical skill that is achieved by the operators in placing the cannula into such a small opening without actually seeing it (as, for example, would be possible through a hysteroscope). Tien maintained, however, that the technique is not difficult to learn, and he noted that doctors, nurses and midwives are being trained to perform it. An experienced operator should be able to occlude both fallopian tubes in about 15 minutes, according to Tien, and the training period takes no longer than two weeks. He estimated that some 200 medical units in 28 Chinese provinces now have at least one person trained in the technique. Overall, about 30,000 women have been sterilized by this method. In addition, Dr. Yu-Hau Wu, one of the originators of the technique, has begun a visiting training program so that people in outlying provincial areas can learn to perform the procedure without traveling to a major city or health center. Tien added that in areas where this method is now available, few women choose to have the more conventional sterilization operations.

Quinacrine

Quinacrine, which was used extensively during World War II to prevent or treat malaria, came under consideration as a tubal occlusive in the 1960s because of the extensive damage it causes to the tubal epithelium. However, after more than a decade of research, the mechanism by which quinacrine closes the fallopian tubes is not yet understood, and the method still has not completely met the criteria for the ideal chemical sterilant. Quinacrine may cause pain if it leaks through the tubes into the peritoneal cavity; it can also excite the central nervous system if it enters the bloodstream in large amounts, resulting in transient psychosis. Early experiments with liquid quinacrine

that was instilled into the fallopian tubes sometimes resulted in psychotic incidents and high pregnancy rates. Now, however, researchers led by Dr. Jaime Zipper, a Chilean physician who pioneered investigations of quinacrine, have developed a pellet that slowly releases quinacrine into the tubes,

Three types of pellets have been produced: One releases its entire dose of quinacrine in 10 minutes, another does so in 100 minutes, and the third, over about 16 hours. Zipper described the results of three studies involving about 500 women who received the pellets three times at intervals of one month or were given liquid quinacrine and were treated again one month later and six months later. Two hundred women were given three instillations of 1,500 mg of liquid quinacrine; 165 were given three treatments with the lo-minute pellet (seven pellets strung together, with a total dose of 250 mg of quinacrine), as well as a drug that would thicken the uterine fluid so as to keep the quinacrine in the area of the tubes for as long as possible; and 138 were given three treatments with quinacrine pellets alone. The pellets were placed in the uterus with the same type of cannula used to insert an IUD. The investigators explained that while quinacrine placed in the uterus causes some superficial damage to the endometrial tissue as well as to the tubal lining, the damaged tissue is sloughed off during the next menstrual cycle and the underlying tissue heals.

Ten percent of the women who received the liquid quinacrine became pregnant within one year of the last instillation, compared with three percent of those who were treated with pellets alone and four percent of those who were given the pellets and the additional medication. Several women who received instillations of liquid quinacrine suffered transient episodes of psychosis, apparently because some of the compound made its way into their circulatory systems; no woman who had the pellets placed in her uterus experienced psychotic episodes, Zipper noted, however, that while the pellets achieved a high rate of effectiveness, they still required three procedures, "thus falling short of the ultimate goal of an effective, blind, one-insertion technique." Dr. **René Guzmán-Serani**, an obstetrician-gynecologist at the University of Southern Chile, presented data on 150 women treated with the lo-minute quinacrine pellets; this group had a 24-month pregnancy rate of four percent.

In addition, Dr. Rohit Bhatt, head of the Department of Obstetrics and Gynecology at the Medical College of Baroda, India, reported that among 85 women treated with the pellets, there was a 24-month pregnancy rate of about five percent. One-fifth of these

women said that they had felt mild or moderate abdominal discomfort immediately after the treatment (discomfort similar to that following an IUD insertion), and one in seven said that their menses had become irregular after their treatment. (Most said their cycles became normal again after about four months.)

Several other experimental methods of delivering quinacrine were described. In one, particles of quinacrine are surrounded by a polymer sheath, and when the fiber is immersed in a liquid, it gradually releases the quinacrine. In this way, a timed-release quinacrine treatment could be developed in which the medication would be released over the course of days or weeks. Animal research is under way, but some skepticism was expressed over the usefulness of this method. Zipper pointed out that to deliver enough quinacrine to the tubal lining over a long period of time, it might be necessary to increase the dosage of quinacrine in the fibers to unacceptably high levels.

A second experimental method involves use of a quinacrine-bearing IUD; this was described by Leonard Laufe, a physician on the staff of the International Fertility Research Program. Quinacrine-bearing IUDs have been tried on 72 women, all of whom had been scheduled to have hysterectomies. The first results, in which a modified Cu-7 was the carrier, were inconsistent, according to Laufe; however, preliminary results have improved with the use of the No-Gravid, a nylon IUD shaped like the Greek letter Υ and having long arms that bring the quinacrine-covered tips of the IUD very close to the openings of the fallopian tubes. Such a device, covered with 200 mg of quinacrine, successfully blocked 20 of 22 tubes in nine of 11 women who used it.

While quinacrine in some form appears to be approaching 95 percent effectiveness--the minimum considered acceptable--research needs to continue in order to ensure quinacrine's safety, as well as to improve the methods of administering it; thus, quinacrine is not yet ready for general use.

Methylcyanoacrylate

Methylcyanoacrylate (MCA) is a material that polymerizes from a liquid to a solid upon contact with water. It was originally studied for use as a tissue adhesive for closing wounds or suturing blood vessels, but was found to be unsuitable for these purposes because the heat that it produces when it polymerizes damages the tissue to which it adheres. This very property brought it to the attention of investigators who were searching for a chemical sterilant. MCA destroys the tubal epithelium as it solidifies; then, as the MCA gradu-

ally biodegrades, it is replaced with scar tissue. MCA is nontoxic and shows no sign of being either carcinogenic or mutagenic. Research on MCA has continued for over a decade, as scientists have tried to design a system for instilling the substance into the tubes before it polymerizes.

The device developed for accomplishing this, called Femcept, consists of a plastic-bodied tube and pump mechanism which narrows into a four-mm semirigid cannula; the MCA is pumped through this cannula into the uterus. To propel the MCA into the tubes before it solidifies, a small balloon located at the tip of the cannula is inflated an instant after the MCA is released into the uterus; the pressure of the balloon's expansion (in about 1/25 second) drives the MCA into both tubes just as it polymerizes. The device delivers about 0.2 cc of MCA into each tube. Femcept was designed to be disposable.

The device has been tested in six centers around the world. Data from preliminary clinical trials show that MCA is probably no closer to general use than the other methods described at the workshop. Dr. Robert Neuwirth, director of Obstetrics and Gynecology at St. Luke's--Roosevelt Hospital in New York City, described the results of tests of three different types of treatment involving MCA. In one, 102 women received a single application of MCA and were checked by hysterosalpingogram four months afterward. Both tubes had been blocked in 78 percent of the women. In a second group of 102 women, two applications of MCA were delivered in consecutive months. This procedure produced bilateral occlusion in 87 percent of the women. A third protocol, calling for saline lavage followed by a single application of MCA, produced a closure rate of 68 percent among the 91 women who used it, and was subsequently abandoned. The addition of a radio-opaque substance that also increases MCA's spreadability produced bilateral closure in 54 of 62 women (87 percent) after one application; after retreatment of the women for whom the first application was unsuccessful, the closure rate exceeded 95 percent. Among nearly 300 women followed up for 1-21 months, there have been only two confirmed pregnancies.

Neuwirth reported that among more than 800 women who were treated with MCA in trials in Brazil, Canada, India, Norway, the Philippines and Venezuela, there have been 17 pregnancies; none of these pregnancies were ectopic, and most occurred prior to the hysterosalpingogram that was to be performed four months after the last treatment. Of 622 women who reported side effects, 22 percent said that they felt abdominal pain for

up to one month following the treatment, four percent reported pain up to three months later, and five percent had fevers for up to one month. One percent of the women involved in the trials required hospitalization for treatment of pelvic inflammatory disease. The proportion of women who had bilateral tubal closure in various trials in the six countries ranged from 65 percent in the Philippines to 88 percent in Brazil.

Tubal Occlusion with Plugs

Several methods for plugging the fallopian tubes were described at the workshop. One theoretical advantage of plugs is that they can be removed, which may make possible the reversal of sterilization; however, reversibility has not yet been demonstrated. A substantial disadvantage is that plugs must be introduced into the tubes by means of a hysteroscope, an expensive, delicate fiberoptic device that requires careful handling and maintenance.

The plug technique that is most highly advanced was described in detail by its developer, Dr. Robert Erb, a Fellow of the Franklin Research Center in Philadelphia. The method involves filling the fallopian tubes with liquid silicone rubber which, once it has solidified, forms a plug that occupies about two-thirds of the path through the tubes. Once the tubal opening has been located visually through the hysteroscope, a cannula and a preformed silicone obturator tip (so called because it serves to close off the tubal ostium) are inserted into the opening; liquid silicone rubber that is about the consistency of honey is then pumped through the cannula into the tube. When the silicone solidifies, forming a plug, the catheter is withdrawn, and the small tip snaps free of it and remains bonded to the silicone plug. By anchoring the plug solidly in the tubal ostium, the tip prevents the silicone rubber from sliding out of the tube past the fimbria into the peritoneal cavity; it also has a small loop hanging from it to aid in its removal, so that should a woman decide to try to have a child, removal of the tip would allow the rest of the silicone rubber plug to be flushed into the peritoneal cavity, leaving the tube open once again.

Dr. Theodore Reed, chief of gynecology at Philadelphia's Lankenau Hospital, described the combined results of research on silicone rubber plugs that has taken place in 10 centers in the United States, England and Belgium. The procedure has been attempted on 965 women; in 82 percent of the cases, both tubes have been successfully occluded. Thirteen pregnancies have occurred, including one ectopic pregnancy; however, all of these were associated with improperly formed

plugs and occurred early in the research. Women who had both tubes closed have had no pregnancies after more than 4,500 woman-months of use; 65 women have been sterilized for two or more years, with no pregnancies.

About **1,000** women have been treated with this method as part of a U.S. clinical trial, and the researchers have recently received approval from the U.S. Food and Drug Administration (FDA) to include additional women in the trial. Cumulative data will be submitted to the FDA in the near future in order to have the method approved for general use in the United States. However, the need for a hysteroscope, as well as the amount of training that is necessary and the time required for each procedure (ranging from 20 to 90 minutes, with an average of 30), will probably limit the use of this method to the developed world.

Future Directions

None of the methods discussed at the workshop has yet reached the ideal of a simple, safe, nonsurgical method of sterilization that is at least 95 percent successful and can be performed by a nonphysician in a single treatment. However, further investigations of these methods are contemplated. For example, it is believed that since estrogen promotes the repair of the lining of the fallopian tubes, progesterone therapy, used to offset that effect, may be one way to improve the effectiveness of either quinacrine or MCA.

Theodore King, director of the Department of Obstetrics and Gynecology at The Johns Hopkins University School of Medicine, emphasized that more research is needed on quinacrine in order to develop a timed-release system that will allow longer term exposure of the tubes to the drug; to determine whether there may be other substances related to quinacrine that have a similar effect but are less dangerous; and to understand more precisely the process by which quinacrine occludes the tubes.

Ralph Richart, professor of pathology at Columbia University's College of Physicians and Surgeons, and one of the major investigators of MCA, summarized the research agenda for this substance and for the Femcept system. He emphasized that in the opinion of investigators, "even at the present levels of bilateral closure, [MCA] has a place in the cafeteria of contraceptive methods." Further research should seek to enhance MCA's effectiveness at entering the tubes, perhaps by coupling its use with that of a medication that relaxes the muscles at the utero-tubal junction; to test other materials that modify MCA's polymerization rate; and to make the substance more radio-opaque so

that it is more clearly visible on x-ray plates.

In summarizing the imperatives for further research on methods of nonsurgical sterilization, James D. Shelton of the U.S. Agency for International Development observed that while millions of people around the world, including the developing world, have undergone voluntary sterilization, primarily because of its high level of effectiveness, surgical sterilization still has some disadvantages. Nonsurgical methods pose few of the risks of infection or injury to other organs associated with surgical methods, and they do not require the use of general anesthesia. (Minilaparotomy and laparoscopy are the only two sterilization procedures usually performed under local anesthesia, and laparoscopy is sometimes performed under general anesthesia.) In addition, surgical tubal sterilization is almost always performed by highly trained physicians in hospital operating rooms located, for the most part, in urban areas. Nonsurgical sterilizations are to be performed by nonphysicians or by less highly specialized physicians, and thus could help meet the demand for sterilization by rural couples in developing countries. Finally, according to Shelton, surveys have shown that many women in Third World countries fear surgery and are, therefore, hesitant about undergoing sterilization. Presumably, nonsurgical methods would have greater appeal for such women.

Reference

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Résumé

Bien que l'importance des méthodes chirurgicales de la stérilisation contraceptive ait grandi pendant la décennie qui vient de passer, la demande toujours croissante de la stérilisation féminine et les inconvénients associés avec les méthodes actuelles—l'anesthésie, la nécessité des praticiens d'une habileté supérieure et le besoin des instruments de haute complexité—ont stimulé les investigateurs scientifiques à développer des méthodes non chirurgicales de stérilisation. Celles-ci comprennent:

- **Les stérilisants à base de phénole, développés par des savants de la République populaire de Chine, s'agissent de l'injection d'un composé de phénole, un produit chimique très corrosif, dans les trompes. Le composé injure le revêtement intérieur des trompes et provoque une cicatrice qui les bloque. L'opération se fait "à l'aveuglette," c'est à dire, le technicien ne voit pas directement le débouché de la trompe, mais il apprend plutôt à**

tâtons où insérer le composé. Deux médecins chinois ont stérilisé à peu près de 7.000 femmes en utilisant cette méthode. Plus de 90 pour cent des cas ont les trompes bloquées avec succès, et les experts se proposent de diffuser la technologie plus largement.

- **La quinacrine est un autre produit chimique qui provoque la cicatrisation des trompes. Les chercheurs ont développé une méthode de poser la quinacrine dans l'utérus, où la matière se décharge lentement dans les trompes. Au bout de trois applications, les femmes stérilisées ont subi un taux de grossesse accidentelle de trois à cinq pour cent à la fin d'une année. D'autres technologies pour administrer la quinacrine aux trompes, à moyen des fibres ou des stérilets qui relâchent peu à peu le produit, sont décrites.**

- **L'acrylate de cyanométhyl est un produit chimique qui, en contact avec l'eau, provoque une chaleur extrême. Cette chaleur nuit au revêtement intérieur des trompes et provoque la cicatrisation, à mesure que l'acrylate de cyanométhyl se solidifie. Le produit s'introduit aux trompes avec un instrument qui est mi-pompe, mi-canule. Cet instrument met l'acrylate de cyanométhyl dans l'utérus et, quelques instants plus tard, on gonfle un tout petit ballon affixe autour de la pointe de la canule qui, en grandissant, pousse le stérilisant dans les trompes. Parmi plus de 800 femmes stérilisées par cette méthode, il y a eu 17 grossesses inattendues.**

- **Finalement, les tampons en caoutchouc et silicone, qui se forment à l'intérieur des trompes, accomplissent aussi la stérilisation. Le débouché de la trompe se voit par un hysteroscope, et l'on y insère une canule par laquelle un liquide, mélange de caoutchouc et de silicone, s'enfonce dans les trompes. Le liquide se solidifie au bout de quelques minutes et se forme en tampon, ou bouchon, qui remplit à peu près les deux-tiers de la trompe. Presque 80 pour cent des femmes stérilisées ainsi ont les trompes effectivement bloquées, et parmi les femmes dont les tampons se sont formés de façon correcte, aucune grossesse n'a eu lieu. On tire la conclusion que les méthodes non chirurgicales de stérilisation féminine ne sont toujours pas assez développées pour que leur utilisation se généralise, et l'on préconise encore des recherches scientifiques pour perfectionner de telles méthodes.**