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Female Sterilization Using Pharmacologically Active Agents

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Attempts to utilize pharmacologically active agents to close the fallopian tubes date back at least to 1849 when Frierip reported passing a cannula transcervically to the uterine tubal ostia and cauterizing the tubal lumen with a nitric acid-coated probe.¹⁴ Salgado reported in 1941 that Brazilian midwives lavaged the uterine cavity with a mixture of tincture of iodine and carbolic acid as a contraceptive measure.³⁹ The procedure was designed to be temporary but in fact produced severe endometrial scarring and tubal closure that resulted in permanent sterility. The publication of Salgado's paper prompted the midwives to abandon this technique.⁴⁰ Dieckmann and Harrod reported in 1954 that they had used sodium morrhuate as an adjunct to tubal ligation in over 200 patients in the preceding eight years.⁹ They reported no failures. Pitkin, however, reported a 4% failure rate using a similar procedure in which sodium morrhuate was introduced into an isolated tubal segment to produce tubal sclerosis.²⁷

Aside from these sporadic reports there was no systematic effort to develop chemically-induced tubal blockage until the 1960s. At that time, a number of groups began to explore a variety of methods for producing tubal closure, including electrocoagulation, cryotherapy, intratubal devices, and the instillation of a variety of active chemical agents. These efforts have been considered extensively in a series of monographs and individual review articles.^{10,13,18,25,35,36,41,42} The active agents which have been studied for their tube-closing properties contain representatives from most major classes of toxic chemical compounds; the list includes silver nitrate, zinc chloride, formaldehyde, formalin-ethanol, paraformaldehyde, ethanol, copper sulfate, sodium lauryl sulfate, phenol, cadmium, iodoacetate, thio-TEPA, talc suspensions, podophyllin, colchicine, granuloma-producing agents, quinacrine, gelatin-resorcinol-formalin (GRF), and cyanoacrylates. Silicone rubber has also been used as a tube-occluding agent and, although its properties are principally mechanical rather than sclerotic, it will be included in this review because the delivery problems are similar to those associated with the delivery of toxic chemicals.

It became clear from the initial experiments in a variety of laboratory animals that, with the possible exception of quinacrine, prolonged tubal exposure to the chemical was necessary to produce a high rate of tubal occlusion. Although strong oxidizing or reducing agents could produce extensive necrosis

of the tubal epithelium, tubal blockage seldom followed an acute time-limited insult due to the efficiency of epithelial regeneration and repair. The problem of the low rate of tubal occlusion was compounded by the fact that extensive tubal damage was commonly produced, and by the concern that tubal damage without tubal occlusion would lead to a potentially high rate of ectopic pregnancy. In order to prolong the contact time between the chemical and the tubal epithelium, a variety of carriers were explored with which the toxic agents could be compounded and then slowly released following tubal instillation. The carriers included alginate, gelatin, carboxymethyl cellulose, and agar. Unfortunately, even these carriers failed to produce an adequately high rate of tubal occlusion in the early studies, and most were difficult to work with because the compounding had to be done at the time of the procedure, and the flow characteristics were difficult to control.

It was also recognized that acutely cytotoxic agents which produce immediate and extensive necrosis of the tubal epithelium would produce similar effects in the peritoneal cavity, and that any system which delivered these materials to the fallopian tube must also exclude their delivery from the peritoneal cavity. This imposed severe constraints upon the design of a delivery system, since it would require a highly controlled volume of material to be delivered bilaterally to the fallopian tubes in an organ which varied cyclically in a number of important anatomic and physiologic features.

The major attraction of a chemical tube-blocking agent was the assumption that it could be delivered transcervically on an out-patient basis. This feature imposed additional constraints on the system, however, in that the agents had to be delivered blindly and still reach the tubes so as to close them bilaterally in a high proportion of cases.

Only silver nitrate, quinacrine, silicone rubber, phenol, and methylcyanoacrylate have reached the stage of significant clinical trials, and the remainder of the discussion will be confined to these five agents. Although other chemicals have also been tested in limited numbers of experimental subjects, they are not presently being used, and experience with them has been reviewed previously.³⁵

Silver nitrate was used clinically by our group in a study in which it was compounded 10% by weight with hydrophilic ointment.³⁴ The ointment was then injected retrograde through the tubal fimbria at the time of culdoscopy. Although the tubal closure rate was 100% in the 14 patients who were treated, the patients experienced significant pelvic pain, fever, and leukocytosis, owing to leakage of the compound into the peritoneal cavity. Ringrose subsequently reported using 10% and 15% silver nitrate in a derma-base carrier in 160 women, and on an out-patient basis, applying from 0.15 to 1.5 ml to each fallopian tube, using a specially designed cannula.³⁸ He applied a 20% silver nitrate compound to an additional 60 patients. There were significant complications among those women in whom the 20% silver nitrate was used, but he reported that "tolerance remains satisfactory" in those patients in which 15% silver nitrate or less was used. Although a full report of complications and pregnancies is not included in the paper, six pregnancies are alluded to, 7% of the women had a transient vasovagal reaction, and one experienced generalized convulsions. As additional side-effects not reported in the original article apparently occurred,¹⁶ this type of blind delivery using a manually placed

cannula to deliver a highly toxic agent with uncertain volume control cannot be recommended.

We are currently working on an alginate system using silver acetate as a sclerosing agent.¹⁵ This system has the potential advantage of a more precise delivery and, as the alginate is a thixotropic material, its flow can be controlled and its excursion into the fallopian tube limited.

Rakshit reported that he could deliver silicone rubber to the fallopian tubes transcervically and that "if the procedure is carried out correctly, sterilization should always be achieved."^{29,30} Erb and his colleagues subsequently reported on a series of animal experiments and devised a mixing chamber and delivery device which they believed would enable them to deliver the rubber compound to the fallopian tubes using a hysteroscope.^{7,8,12,13} Reed and Erb recently reported that they had applied the procedure to 135 patients and were able to successfully complete the procedure bilaterally in 99 patients.^{31,32} Of the 11 patients in whom occlusion of one tube was impossible, the uterus was in fixed retroflexion in eight women, the ostia were too far lateral for proper alignment with the hysteroscope in five women, and in one woman location of the tubal ostium was impossible. One patient became pregnant. The investigators reported that patients with previously diseased tubes should not be considered candidates for this technique, and certain patterns of plug formation were identified which require immediate removal and replacement. The investigators believe that the procedure can be used as an office procedure in approximately 90% of the women requesting sterilization with this technique.

The largest series of women in whom a pharmacologically active agent has been used for tubal closure was reported by the Research Group of Tubal Occlusion by Drugs, Second Teaching Hospital, Zhangshan Medical College in the People's Republic of China.³³ In this study, 3940 women were treated with a number of formulations of liquid phenol and mucilage over a 7 year period. The bilateral occlusion rate was 77.6% in the first series and 93.5% in the fifth. The composition of the most successful compound is given as:

Liquid phenol	35 ml
Mucilage	5 g
Glycerine	20 ml
Add distilled water	up to 100 ml

The compound was administered by inserting a cannula transcervically up to the tubal ostia and passing a 1 mm plastic catheter through it into the tubal isthmus. One-tenth to 0.15 ml mucilagophenol was injected. The procedure was performed blindly on an out-patient basis. Of the 2487 women in which the procedure was judged to be successful by means of a hydrotubation test, 64 (2.58%) subsequently became pregnant, 55 within 2 years, and nine in from 2 to 7 years.

Thirty-five women experienced acute pelvic inflammatory disease following the procedure, and three uterine perforations occurred. Of the patients, 40% had transient lower abdominal and back pain, and the recanalization rate was 1.65%.

Quinacrine has also been extensively studied as a tube-blocking agent. Zipper devised a technique of uterine lavage and studied several different concen-

trations of quinacrine for its tube-blocking With a single application of quinacrine, he reported bilateral tubal obstruction in 66% of his subjects and a 92% bilateral obstruction after two instillations. Other investigators have also studied quinacrine suspensions using a variety of delivery techniques, including hysteroscopic cannulation of the tubal ostia.^{1,2,3,5,6,17,21,26,28} Closure rates have been highly variable, and it is difficult to generalize from these reports. Zipper reported that the addition of xylocaine potentiates the effect of quinacrine and reported a rate of 94% bilateral obstruction after two instillations in one subseries of women he studied.⁴⁵ In his reports in 1975, he indicated that 638 women had been treated with quinacrine alone or with various potentiating agents, and that they had been followed for 14,677 months in aggregate.⁴⁹ Thirty-seven pregnancies occurred in 279 patients who received one instillation, and 13 pregnancies were reported in 158 patients receiving two instillations. No ectopic pregnancies were noted.

Most recently, Bhatt and co-workers reported on the tubal closure rates of women in whom 250 mg quinacrine pellets were inserted into the uterine cavity through a cannula.³ In the most recent series, 23 women had pellets placed at the fundus 30 days prior to hysterectomy. Forty-six fallopian tubes were studied. In 16 tubes, no identifiable damage was noted; in six, subepithelial hyalinization and scarring were seen; and in 23 tubes, epithelial destruction and subepithelial hyalinization and scarring were discovered.

In addition to the pelletization of quinacrine, the International Fertility Research Program (IFRP) has undertaken initial trials with a T-shaped plastic device which has an 80% mixture of quinacrine and polyethylene oxide molded over it. In a limited number of pre-hysterectomy volunteers, they have reported good results.²⁰

Our own group has studied methyl-2-cyanoacrylate as a tube-closing agent and has developed a delivery system which is effective for a variety of liquids, polymers, and thixotropic materials of low viscosity.³⁷ Stevenson and Taylor first used MCA for tubal occlusion in humans and reported a 70% rate of bilateral closure on one injection using a balloon catheter delivery system.⁴⁴ Stevenson has reported that no pregnancies occurred in the 2 years subsequent to the hysterosalpingographic demonstration of bilateral tubal closure.⁴³ In the most recent series using the FEMCEPT delivery system and MCA, Neuwirth and associates reported that the bilateral closure rate in 23 women was 78% after one injection.²⁴ The series has since been extended to more than 100 women, and the bilateral closure rate is 80%. In the approximately 200 women who have been treated with MCA thus far, using a blind delivery system, no significant side-effects have been reported. Two pregnancies have occurred, one 12 months after hysterosalpingographic demonstration of bilateral closure, and one 24 months after apparent closure.

DISCUSSION

One hundred and thirty years after the first attempt to occlude the fallopian tubes using pharmacologically active agents and more than 15 years after the recent surge of interest in this area of investigation, a number of systems

presently offer promise of providing female sterilization as an office procedure. Each appears to have advantages and disadvantages.

The silicone rubber technique is not properly a chemical technique, because the applied agent is inert, yet it differs from the conventional intratubal devices because of its delivery system and polymerizing properties and because it affects the entire fallopian tube. It has the advantage of inertness and of an apparently negligible complication rate. The disadvantages are that the materials must be mixed at the time the procedure is performed and that they must be delivered by means of a hysteroscope. The material must also fully distend the fallopian tube and have close apposition without breaks in the plug. The degree of distention is apparently skill-dependent. Even in the hands of skilled hysteroscopists, consistent tubal cannulation requires a high degree of training and considerable experience to be performed consistently well. It seems unlikely that a hysteroscopic delivery approach will be amenable to large-scale use, not only because it is so highly skill-dependent but because it utilizes expensive instrumentation which is difficult to maintain and repair. If it were possible to deliver the silicone material using a simpler technique, its range of application might be improved considerably. This would be particularly true if a blind delivery system could be devised which could be utilized by paramedical personnel rather than a highly trained endoscopist.

The latest innovations in the delivery of quinacrine using pellets or a T-shaped intrauterine device show promise of being effective in producing tubal closure. The delivery systems are the essence of simplicity: they can be produced at low cost, they are potentially usable by paramedical personnel, and they may be amenable to widespread application. The presently available data would suggest, however, that multiple applications are still required—a significant drawback, particularly in developing nations. In addition, Zipper has reported that in some patients to whom quinacrine is administered, central nervous system excitation and convulsions occur, and the drug intercalates with DNA and produces chromosomal breaks. Also, gastrointestinal dilation and death have been reported in experimental animals.¹⁹ Further toxicologic studies are required before determining whether quinacrine will be acceptable for widespread use.

The MCA/FEMCEPT system utilizes a drug which has not been approved for commercial distribution for this application. In addition, the system currently requires multiple applications to produce a high degree of bilateral tubal closure. The delivery system is simple, can readily be applied by relatively unskilled personnel, and is potentially applicable to widespread use. Its fabrication may be more expensive than the simplest delivery system currently being evaluated, which uses quinacrine or phenol.

Although the phenol-mucilage system has been tested in a large number of women, the delivery system appears to be highly dependent upon fine tactile discrimination. Only one group has reported their experience with the technique, and further assessment must await the availability of additional data. Certain features are reminiscent of the devices described by Moulding and co-workers, which proved extremely difficult to use clinically.^{22,23} In addition, the high incidence of pelvic pain suggests that the compound may enter the peritoneal cavity in a high proportion of cases and produce a local pelvic peritonitis.

CONCLUSION

In the 1960s, the major problem in developing a simple technique for outpatient female sterilization was thought to be a delivery system. A number of effective alternate systems for the delivery of pharmacologically active agents to the fallopian tube, either blindly or under direct vision, have been developed. The present need is to integrate the delivery system with a safe, effective agent which will be delivered consistently to the fallopian tubes and, once delivered, will consistently produce tubal closure. Although the closure rates being reported by all the investigators studying a chemical approach to female sterilization are higher than those previously reported, no one system is clearly superior to any other at the present time. Further work is needed to increase the closure rates to even higher levels, to simplify the delivery systems, and to determine which agents will be acceptable for clinical use.

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