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Quinacrine IUDs

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It is 15 years since Corfman reviewed transcervical oviduct occlusion and chronicled the history of the concept.² In 1849 a technique was developed to produce tubal occlusion with the application of silver nitrate to the cornua. Many other agents have since been evaluated for their tubal occlusive capabilities, such as zinc, phenol, chloride, sodium morrhuate, salicylic acid, a mixture of gelatin-resorcinol-formaldehyde, and cyanoacrylates.⁴ Richart and others at Columbia University have worked extensively with a variety of these drugs and methods, and currently, they are working exclusively with methyl cyanoacrylate.

Zipper, of Santiago, Chile, has worked extensively with quinacrine and his technique has finally evolved into the quinacrine pellet concept discussed in Chapters 9 and 10.

EVOLUTION OF IUD DELIVERY SYSTEMS

As our interest in the further development of the concept of chemical sterilization with quinacrine was pursued, we realized that we must determine the exact pathologic changes induced by quinacrine. In 1980, Bhatt and associates reported on the quinacrine-induced pathologic changes in fallopian tubes.⁷ This limited study was accomplished by inserting one application of 250 mg quinacrine pellets into the uterine cavity of 23 women awaiting hysterectomies; therefore, 46 tubes were studied. The changes induced by quinacrine were documented, and in about 50% of the cases an obstructive lesion commensurate with tubal closure was induced.

As a result of this study, a concept was developed to provide a better delivery system of quinacrine to attempt to ensure a more accurate application of the drug to the tubal ostia and to reduce the delivery system to a single event. At that time, studies were initiated using the IUD as a vector for delivering quinacrine. Requirements for these studies were that the par-

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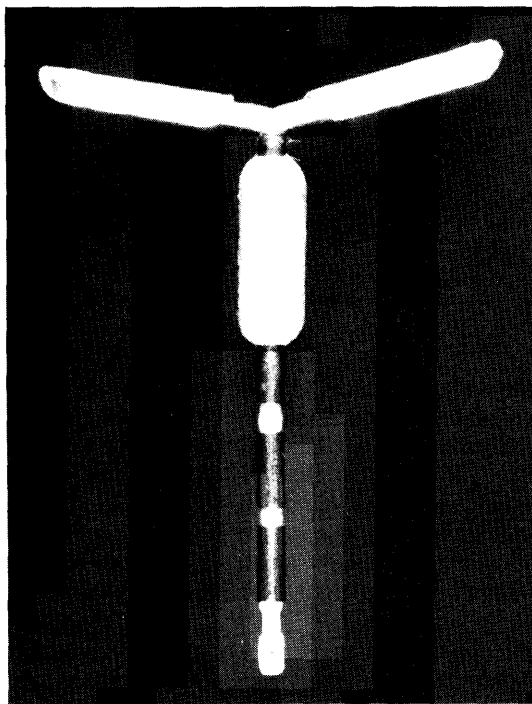


FIG. 12-1. Copper-T 220 with 300 mg quinacrine.

ticipants were awaiting an elective hysterectomy and had no distortion of the uterine body such as myomas and no severe endometrial disturbances. Most of the hysterectomies were in women with prolapse or a premalignant lesion of the cervix. To date, 72 women have been studied. No patient has had any adverse reaction.

In the first five procedures done in Santiago, Chile, a T-vector was inserted, carrying an ethylene vinylacetate (EVA) matrix containing quinacrine. The release rate of the quinacrine from this matrix proved to be extremely limited, and in only one woman could tubal occlusion be demonstrated by hysterosalpingography. Next, a mixture of 80% quinacrine and 20% polyethylene oxide (PEO) was used. PEO is a water-soluble, biocompatible plastic and acts as a binder to hold the quinacrine forms together. The powder mixture was mixed with water to form a very thick paste. The paste was allowed to dry almost completely and was then loaded into a split die and pressed into its final form. The quinacrine/PEO forms were then placed on the arms of the IUD.

The next approach was to add a total dose of 300 mg of the drug to a T-vector, with 75 mg quinacrine at the ends of each of the lateral arms and a central bolus of 150 mg on the stem (Fig. 12-1). The results were erratic, and the central bolus appeared to contribute nothing to the sclerosing effect observed in the tubes. About 50% of the tubes contained a definitive lesion, as with the pellet studies. Results were highly variable. One tube in a given specimen could be totally occluded and the other untouched. The T-vector was next used with the arms upward, as with the original device, but without

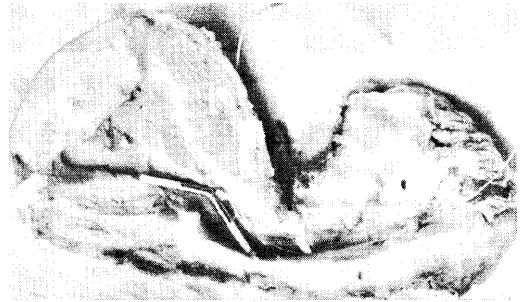


FIG. 12-2. Vaginal hysterectomy specimen with spring device.

the central bolus. In approximately 60% of the tubes, we were able to produce definitive sclerosis.

In the next group, instead of flexing the arms of the IUD upward, we bent them downward by redirecting the mold that applied the quinacrine. This improved the closure rate. In the women treated in this fashion, the tubal closure rate was 75%. Considerable emphasis was placed on proper IUD placement, so that the IUD was reaching the fundus and the arms were properly deployed.

Although the results were improved with the configuration in which a "T" with 75 mg quinacrine on each arm was flexed in a downward posture, examination of specimens with the IUD *in situ* showed that it was not properly deployed in all instances.

An attempt was made to design a vector containing a stainless steel spring in the middle to provide outward flexion of the arms.³ Devices with this design contained no quinacrine, and we asked contributing physicians to insert them in either fresh hysterectomy specimens or when the patient was on the operating table. These devices proved to be inappropriate, in that either the spring was too weak or it could not be inserted high enough in the fundus to obtain proper deployment of the arms to the tubal ostium (Fig. 12-2).

In the hope of finding a better vector, use of the copper-bearing No-Gravid device made in Verona, Italy, was examined (Fig. 12-3). This device, unlike most IUDs, is made of nylon and is relatively rigid; its arms deploy vigorously toward the tubal ostia. The manufacturer of the No-Gravid provided No-Gravid skeletons. Devices were prepared with 100 mg quinacrine per arm (Fig. 12-4). Twelve hysterectomy specimens have been examined.

During surgery, the devices were left *in situ*. Cornual blocks were taken of each specimen and examined prior to opening the uterus. A uterine fundus containing the device is shown in Figure 12-5. This group of specimens provided the most enlightenment. In all six specimens, the devices were properly deployed and each arm was aimed directly at the tubal ostia. In five uteri, there was bilateral tubal closure throughout the intramural portion of the tubes. In the sixth woman, there was absolutely no effect from the quinacrine,

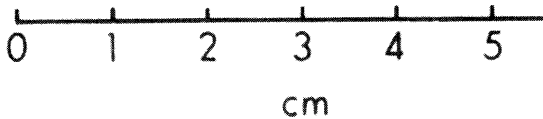
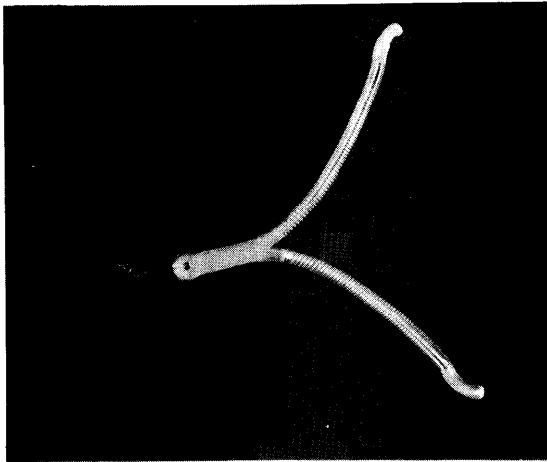


FIG. 12-3. No-Gravid IUD.

and the tubes appeared untouched. The patient had a clinical situation that was unusual. The woman was over 35 years of age and had suffered from extensive menorrhagia for the past year. Since a dilation and curettage performed 6 months prior to the IUD insertion revealed no malignancy, she had been treated extensively for 5 consecutive months with high doses of progestational compounds. With this information, we hypothesized that perhaps the extensive use of a progestational compound had made the epithelium resistant to the effect of quinacrine. Another possibility is that her persistent bleeding might have produced rapid dissolution of the quinacrine material and washed it from the uterus.

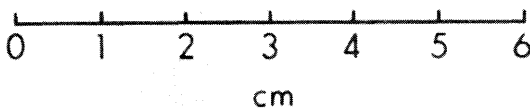
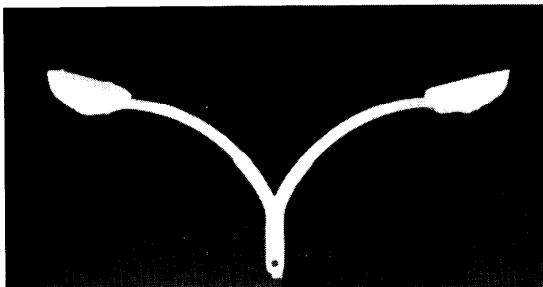


FIG. 12-4. No-Gravid skeleton with 100 mg quinacrine per arm.

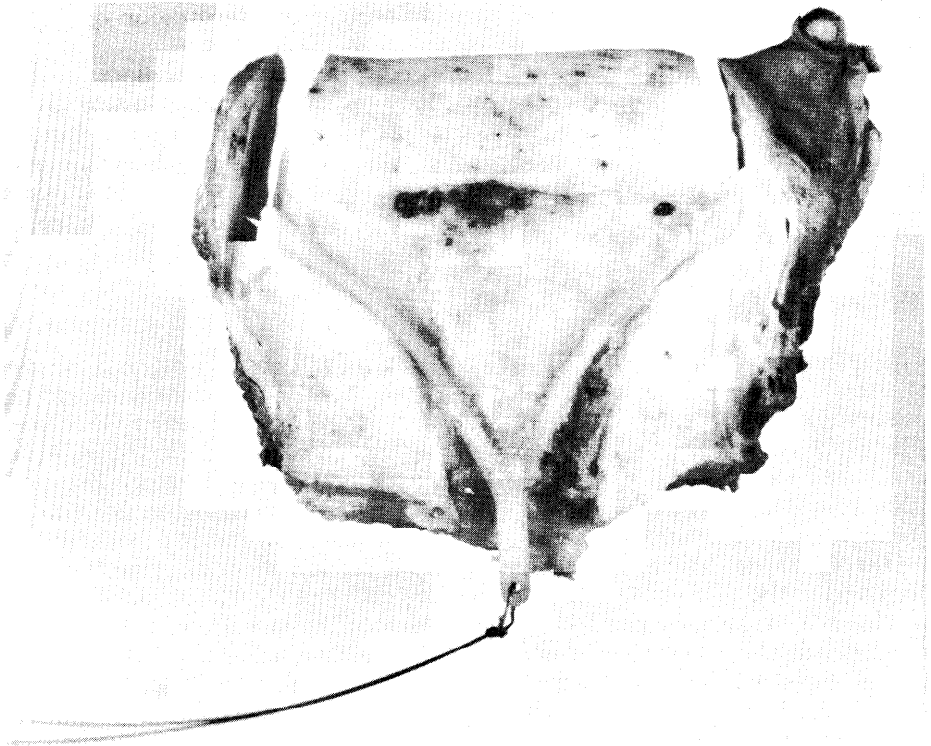


FIG. 12-5. No-Gravid IUD in fixed hysterectomy specimen.

In the early pre-hysterectomy studies with quinacrine pellets, there was great concern about how the quinacrine acted and whether it operated on the lamina propria in those cases in which the epithelium was intact or had regenerated. One specimen from London, which contained the "T" device, was removed within 10 days of IUD insertion, and we were able to determine that although the epithelium had been damaged it was able to regenerate before sclerosis could occur.

Since the epithelial regeneration of the endometrium and the tubal epithelium is stimulated by estrogen and depressed by progesterone, the next six cases were provided high-dosage progestational therapy 5 days prior to and 5 days following IUD insertion. Megestrol acetate (Megace), 80 mg/day, was used. In these cases ten tubes were found to have definitive large lesions that could only lead to tubal closure. In one tube of one of the specimens, the epithelium was untouched; in one tube of another specimen, there was a mild degree of damage, but whether it would have healed or sclerosed could not be determined.

When these six No-Gravid insertions are added to the first six insertions, definitive tubal lesions are found in 20 of the 24 tubes. If we eliminate the patient with severe dysfunctional bleeding who did not fit the protocol and had received 5 months of intensive progestational therapy, 20 of 22 tubes

have definitive lesions that should provide permanent sterilization of the intramural portions of the tubes.

To construct a confidence interval for the proportion of the fallopian tubes closed, each tube is considered an independent experimental unit. If all 24 tubes are included, the 95% confidence interval for the proportion of closures is 0.66 to 0.98. If the one woman is disqualified on the basis of the arguments presented earlier, the 95% confidence interval for the proportion of closures is 0.79 to 1.00.

DISCUSSION

The results with the No-Gravid device appear most encouraging and the use of the IUD as a vector to deliver quinacrine to the tubal ostium should be pursued. Current plans call for variation on quinacrine delivery to the tube. The IUD vector will remain the same. Sustained-release pellets have been developed that leech the quinacrine out over a period of between 800 and 1200 minutes (13 to 20 hours). These have been fixed to the No-Gravid skeleton (Fig. 12-6) and are being studied in a limited number of volunteers.

One can speculate as to whether a rapid release of quinacrine, such as occurred in the earlier experiments, is more effective than a sustained release at a lower dosage. One can also hypothesize that the mixture of these release systems might be necessary for tubal closure. The sustained 7-day release system, developed by the Southern Research Institute with PARFR support, should also be applied to an IUD and may provide a better closure rate.

The original hypothesis of using an IUD as the vector for quinacrine in-

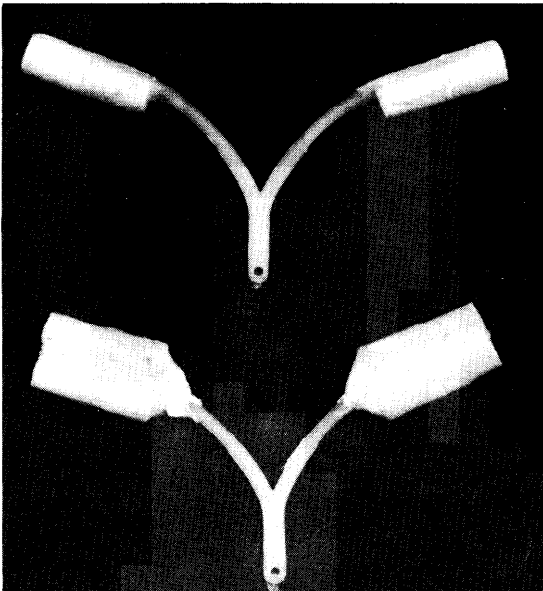


FIG. 12-6. No-Gravid IUD with sustained-release quinacrine pellets.

cluded the idea that the IUD remaining after dissolution of the quinacrine could act as a backup method of contraception. Certainly many variations on this theme are possible. For instance, subsequent to IUD insertion, if the patient wished to have the device removed, a dose of quinacrine pellets could be added at the time of the IUD removal. Patients having the IUD removed could also have a hysterosalpingogram and, if the tubes are patent, could be offered a standard method of surgical sterilization or another quinacrine IUD.

The possibilities are considerable, and we hope that the pursuit of this concept will continue successfully.

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