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more complex, and there also began the study of various prostaglandin analogs. Of the several department members involved in patient and protocol management at UNC Memorial Hospital, Dr. William Brenner, Dr. James Dingfelder and nurse-midwife Linda Staurovsky played a substantial role in the execution of the project. Despite the early hopes that prostaglandins would provide an "easy" solution to the termination of unwanted pregnancy, the realities began to catch up with the hopes. Although the vast majority of cases were terminated by the use of prostaglandins, there were some cases in which the abortion did not occur completely. Thus, after the study of hundreds of patients, it finally became clear that, while prostaglandins would indeed initiate the abortion process in a large percentage of cases, no single-dose technique alone had been demonstrated to be a practical and effective agent which could be relied upon to replace all other methods then available. Much useful background data, however, had been obtained, which could advance the goals of the project utilizing other pharmacologic preparations. A number of features of prostaglandin-stimulated uterine contractility had also been demonstrated, which could aid in the understanding of prostaglandins for such uses as the induction of labor at term, for cervical ripening, and for use in combination with other modalities in term inductions. Observations had also been collected on such phenomena as "inter alia," the cardiovascular and respiratory response to infusion of prostaglandin F2a in the pregnant human female, and bronchospasm, complicating intravenous prostaglandin F2a.

History of the Spring Clip Development

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In 1967, I came to the department and to the newly-formed Carolina Population Center of the University of North Carolina at Chapel Hill convinced that preventing unwanted pregnancies and their complications could be a major contribution to our field. In laboratories of the Department of Obstetrics and Gynecology, I started with the hysteroscopic approach, since the cervix is accessible through the speculum in an office. Burning, freezing, plugging, gluing, and instilling silver nitrate in rabbit and pig models all temporarily plugged the utero-tubal junction. However, the inexorable process of wound healing in this area of constant fluid flow and peristalsis led to fistulas and resulted in unacceptable failure rates.

The experience of others with the alternative approach of the culpotomy for sterilization in developing countries had already been demonstrated to be associated with unacceptably high infection rates.

Seeking a safer and more effective route, I reluctantly turned to trials with the

new European instrument, the laparoscope. This approach had already been demonstrated to be feasible for sterilization by diathermy, but a major drawback to this method as used at that time was that it required general anesthesia and an operating room. In 1969, I visited Bob Neuwirth and other American clinical scientists who were using this new approach, and I began cautiously accumulating experience with laparoscopy at the University of North Carolina Memorial Hospital. Initially, laparoscopy replaced laparotomy and culdotomy in the expanding field of infertility. Diathermy for sterilization was cautiously used. To determine the degree of usefulness of this approach and to see if it was possible to improve the technique, we were looking toward the ultimate use of the method as a tool for population control.

The accumulated experiences to that time had indicated the rather sharp limitations of the use of laparoscopy combined with electrocautery. The laparoscope was expensive. The use of its technologically advanced methodology (to that point) was unfamiliar to surgeons, who were experiencing burns to their own fingers and eyebrows as well as burning their patients' skin and bowels, leading to a number of deaths. The first priority was safety, and the USAID and Rockefeller Foundation funded the Population Center for studies directed toward simpler and safer sterilization. The method of that day, unipolar current, where the live electrode on the tube discharges current flowing back through the patient to a base plate, needed to be replaced by a safer electric system or replaced completely by a non-electric mechanical one. Both avenues were explored with the development of a "contained cautery" prototype (similar to bipolar cautery), which was effective in the pig model but appeared needlessly hazardous to me after bleeding had occurred in the only human subject, who happened to be the wife of one of our faculty members.

Having discarded the electrocautery method, it appeared that the best remaining possibility would be mechanical occlusion of the tube. But there seemed to be limitations to the use of that method up to that point. All existing tantalum, silver, and stainless-steel clips were tried in the pig. All these proved to allow fistula formation through the crushed tissue area over time. The clip surfaces were never squeezed completely shut, but they always remained a few micrometers apart, leading to fistulas which allowed passage of sperm and egg. At this time, the Population Council in New York had just abandoned its interest in the "M device," an intrauterine device made of a two-millimeter-wide spring. These intrauterine devices retained their spring strength in the uterus, and due to the constant pressure, gradually eroded through the uterine wall. There was one thought: why not turn this biologic disaster into a solution to the problem of fistula formation inside clips? A "clothespin" spring arrangement to maintain pressure on a clip across a tube should gradually squeeze the space shut.

"M devices" were sent to my lab and 100 were used as the spring in the early animal clip prototypes. The Population Council also put me in touch with George

Clemens in Chicago, a mechanical engineer who wished to contribute to the population effort by helping to design a clip for occluding tubes.

Early clips were pushed off the tube by the tube's persistent peristalsis, which we eventually prevented by making strong teeth inside the jaws. Bleeding risk was minimized by avoiding any "latch" which could go through a large mesosalpingial vein. Enough space was left in the distal end of the clip for the mesosalpinx to go through. The problem of opening and closing the clip in the abdomen through a laparoscopic instrument was ingeniously solved by Clemens, by having the clip held open by the spring placed behind a hinge and closing the clip and the spring with two separate controls. The spring force was arbitrarily set at double the mean systolic pressure to prevent recanalization of arterioles inside the clip. The material selected for the jaws of the clip was Lexan, a hard, unyielding plastic approved for food containers by the FDA because of its biologic inertness. The spring was made of a rare surgical-grade (implantable) stainless-steel spring, gold-plated to maximize inertness in this implant. The allowable space between the upper and lower jaws was eventually reduced to zero tolerance by the Wolf Company engineers.

The Testing Phase

Now came the time to test the new device. Prototypes were applied by hand into pigs at the North Carolina State Reproductive Physiology Laboratories in Raleigh and modified until there was consistent prevention of pregnancy, as shown by no pregnancy in thirty-five operations. The clip applicator was next tested in a primate colony in Puerto Rico, sterilizing about twenty monkeys by laparoscopy. The first application of a clip in a human was performed at North Carolina Memorial Hospital in November 1972, in a young woman with severe sickle-cell disease. After twenty patients had been successfully sterilized, ten more clip applicators were made and distributed, together with 2,000 pairs of clips, to research centers throughout the world. The aim was to have a variety of physicians working in different cultures and to have data collection carried out through the International Fertility Research Program (IFRP), an international research arm of the Carolina Population Center of the University of North Carolina. IFRP later became independent of the University and is now Family Health International (FHI) of the Research Triangle Park.

In 1973 and 1974, over 1,000 women underwent clip sterilization, and over ninety percent were followed for one year, forming the basis for a full report of the clinical study in 1975. At this point, the clip was no longer considered experimental and was turned over by the university (which was the assignee of the patent) to the Richard Wolf Company for manufacture. A few early pregnancies using prototype clips had resulted from minor deficiencies (weak springs and gaps between the jaws). These deficiencies were eliminated by the Wolf Company. The clip was the biggest source of patent royalties to the University of North Carolina in the 1980s and is now used in one out of nine sterilizations in the United States.