PD-AAM-908

FINAL REPORT

UTERINE SYNECHIA PRODUCED BY CRYOSURGERY

AID-PHA-C-1176

TO

AGENCY FOR INTERNATIONAL DEVELOPMENT

May 10th, 1983

University of North Carolina
School of Medicine
Chapel Hill, North Carolina 27514

RESEARCH PERFORMED: University of Arizona, Health Sciences Center, Tucson, Arizona 85724

TABLE OF CONTENTS

COVER 1

TABLE OF CONTENTS 2

REPORT SUMMARY 3

RESEARCH REPORT

I. Narrative Summary of Accomplishments and Utilization 4

II. Substantive Research Report 7

A. Statement of Project Objectives 7

B. Overview of the Human Research 7

C. Summary of a Cryosurgical Procedure 7

D. Results from Nitrous Oxide Studies 8

E. Results from Liquid Nitrogen Studies 9

F. Accomplishments to Date 10

III. Dissemination and Utilization of Research Results 12

IV. Statement of Expenditures and Obligations 13

REPORT SUMMARY

1. Project Title and Contract Number:

   Uterine Synechia Produced By Cryosurgery - AID-PHA-C-1176

2. Principal Investigator, Contractor, and Mailing Address:

   William Droegemueller, M. D., University of North Carolina, School of Medicine, Chapel Hill, North Carolina 27514

3. Contract Period:

   August 29th, 1977 to April 15th, 1982

4. Period Covered by the Contract:

   August 29th, 1977 to April 15th, 1982

5. Total A.I.D. Funding of Contract to Date: $165,000.00

6. Total Expenditures and Obligations: $134,591.47

I. NARRATIVE SUMMARY OF ACCOMPLISHMENTS AND UTILIZATION

A. Significant accomplishments in research program to develop a new method of outpatient sterilization for females.

1. The operation can be performed without difficulty under paracervical block anesthesia.
2. There are no difficulties in consistantly placing the probe at the uterine cornu. The maximum diameter of the probe tip is 8 millimeters. The approximate diameter of the cornu is 2-3 millimeters. Serial histological sections of the uterine cornua demonstrated that the maximum necrotic isotherm always involves the target area.
3. None of the women who have undergone cryosurgical freezing of the endometrium have developed serious postoperative complications. There have been no cases of acute or chronic bleeding. Postoperative pain continues to be minimal.

B. During the past four and one half years the investigators have studied cryonecrosis of the cornua in 120 women.

During the first two and one half years of this investigation, 62 women had cryocoagulation of the cornu using nitrous oxide as the cryogen. The cornua of the uterus were studied by serial histological slides with hysterectomy being performed four to ten

weeks following the cryosurgical procedure. Obstruction of the cornu was observed in some cases, but the maximum necrotic isotherm was not sufficient to produce adequate necrosis. No matter how the repetitive freeze-thaw cycles were varied, cornual obstruction was only observed in approximately 40% of cases.

Therefore, during the last years of the project, the equipment was redesigned to use liquid nitrogen as the cryogen. During the past two years 58 women underwent cryocoagulation of the uterine cornua and subsequent hysterectomy. Using liquid nitrogen as the cryogen, coagulation necrosis was consistantly produced in the target area.

Cornual obstruction was produced using a single freeze-thaw cycle of 122 to 180 seconds. However, in some cases there was abrupt sloughing of the necrotic tissue, similar to the injury produced by a laser. Therefore, the investigators changed the protocol to reduce the area of coagulation necrosis by using repetitive free-thaw cycles from 30 to 60 seconds times three. That is the uterus is frozen for 30 seconds, thawed for 30 seconds, and then the probe was switched to the other cornu and frozen for 30 seconds and thawed for 30 seconds. This activity was repeated for a total of three cycles. With the multiple freeze-thaw cycles the necrotic slough is not abrupt and granualtion tissue

grows across the cornu before tubal epithelium has an opportunity to recanalize the area. This last protocol produced more consistant obstruction of the cornua. The coagulation necrosis had a depth of 5 millimeters and obstruction was seen over 2 to 3 millimeters of the uterine cornu. With the shorter cycles, obstruction was noted histologically in the cornu in eight out of thirteen patients. Granulation tissue was observed in all cases. However, a peculiar phenomenon was observed under the microscope in which a sleeve of tubal epithelium and specialized muscle grew downward from the interstitial portion of the tube through the granulation tissue. The hope for the future is to retard the growth of this specialized sleeve of epithelium and connective tissue until the granulation tissue forms a dense scar.

II. SUBSTANTIVE RESEARCH REPORT

A. Statement of Project Objectives

The objective of this research program was to develop a means of outpatient sterilization for women that has minimal morbidity and a short convalescence.

B. Overview of the Human Research

Recruitment of patients and the procedure were similar regardless of whether the cryogen used was nitrous oxide or liquid nitrogen. Women in the reproductive age group who were scheduled for abdominal or vaginal hysterectomy for benign disease were recruited for this investigation. After lengthy and detailed informed consent, the cryosurgical procedure was performed either during a diagnostic D&C or as an outpatient under local anesthesia.

C. Summary of a Cryosurgical Procedure

The patient was prepped and draped in a routine fashion. Pelvic examination was performed. The cervix was grasped with a single-tooth tenaculum and paracervical block anesthesia obtained.

The cervix was then dilated to and including a #31 Pratt dilator. The uterine cavity was sounded and measured both

in the midline and to each cornu. A dummy probe was then placed in the cornu to test the fit and the patient's reactivity to the probe. Subsequently, the active cryosurgical probe was placed in the cornu and frozen for 30 to 180 seconds depending on the protocol. The patient could not discern either the active freezing or warming process. The patient would have mild to moderate uterine cramps from fifteen minutes to two hours following the procedure. Total blood loss during the procedure averaged 5-10 ccs.

D. Results from Nitrous Oxide Studies

During the first two years of the study 62 women had cryocoagulation of the uterine cornua using nitrous oxide as the cryogen. None of the 62 women developed postoperative bleeding or infection, and postoperative pain was relieved by oral medication. There were no acute or chronic complications.

However, the difference in temperature developed by nitrous oxide and the tissue, that is the delta-T, was not sufficient enough to develop the necessary necrotic isotherm.
No matter how the investigators varied the repetitive freeze-thaw cycles, the necessary depth of necrosis did not develop with a thick endometrium and/or large uterus. Cornual

obstruction was obtained, but in a minority of cases; therefore, the equipment was redesigned to use liquid nitrogen.

E. Results of Liquid Nitrogen Studies

During the last two years of the study 58 patients underwent cryosurgical necrosis of the cornua using liquid nitrogen. During the first phase of the liquid nitrogen protocols 27 women were studied using the original equipment. The equipment was modified because of problems in the liquid nitrogen transfer lines, and 31 women were studied using this new equipment during the last year of the project. In the last year women had a single freeze-thaw cycle of between 120 seconds and 350 seconds. The average patient received between 120 and 150 seconds. The last 13 patients received multiple freeze-thaw cycles. These cycles ranged from 30 to 60 seconds. Average tip surface temperature on the outside surgical surface of the probe with liquid nitrogen was approximately -168°C.

None of these 58 patients had problems with bleeding. One patient had an acute activation of chronic pelvic inflammatory disease secondary to the procedure. This patient had been treated repetitively for pelvic inflammatory disease in the past. Forty-eight hours

following the procedure she had a low grade fever and pelvic pain. This responded to outpatient management with broad spectrum antibiotics. None of the patients had to be admitted to the hospital for complications of the procedure.

The majority of women had hysterectomies four to ten weeks following the cryosurgical procedure. The uterus was studied by Dr. John Davis who is a Professor of Pathology. He personally dissected the area of the cornu and made serial slides of this region. The average case had eight to ten slides made of each cornu. These slides were then studied by Dr. Davis and the principal investigator.

F. Accomplishments To Date

1. The operation can be performed as an outpatient under paracervical block anesthesia.
2. A large series of human patients demonstrated the absence of postoperative bleeding and significant pain or infection.
3. The use of the dummy probe allows the operator to gain the necessary skill to consistantly place the active probe in the uterine cornua.
4. By rigid criteria, that is observing dense scar tissue in serial histological slides, the cornu was

obstructed in selected cases following uterine cryosurgery.

Obviously, the challenge for the future is to produce scarring in the vast majority of cases, so that the procedure can be clinically applicable. The investigators propose that to accomplish this they will have to develop a single protocol in regards to repetitive freeze-thaw cycles for all women and most importantly, will have to inhibit the regeneration of the selective sleeve of tubal epithelium that grows down from the interstitial portion of the tube. It is hoped that this can be accomplished by using shorter freeze-thaw cycles and chemically or hormonally arresting the regenerating sleeve. Obviously, drugs such as Depo-Provera, Danazol and Quinacrine could be tried.

III. DISSEMINATION AND UTILIZATION OF RESEARCH RESULTS

A brief discussion of the progress of this research program was presented at the international meeting sponsored by Program for Applied Research on Fertility Regulation (PARFR) in June 1982. It is anticipated that a paper describing the liquid nitrogen data will be written in the next year.

Valley Laboratories of Boulder, Colorado, who sponsored the engineering portion of this research, was recently purchased by Pfizer. Pfizer Laboratories has made an administrative decision to limit Valley Laboratories' participation in cryosurgical research. However, Valley Laboratories is willing to relinquish the equipment trade secrets to another cryosurgical company. It is hoped that the principal investigator can interest another cryosurgical company into pursuing this research.

IV. STATEMENT OF EXPENDITURES AND OBLIGATIONS

Salary, Wages, and Fringes:	$82,851.89
Consultant Fee:	Ø
Equipment/Material:	6,341.16
Travel:	1,560.42
Sub-contract University of Illinois:	Ø
Study Proposals by F.D.A.:	Ø
Other Direct Costs Including Patient Stipend:	15,254.10
Indirect Costs:	28,583.90
	$134,591.47