

AGENCY FOR INTERNATIONAL DEVELOPMENT
WASHINGTON, D. C. 20523
BIBLIOGRAPHIC INPUT SHEET

FOR AID USE ONLY

Batch 91

1. SUBJECT CLASSIFICATION	A. PRIMARY Serials	Y-PC00-0000-0000
	B. SECONDARY Population—Family planning	

2. TITLE AND SUBTITLE
Development of improved and new IUDs; progress report, Oct. 1977–March, 1978

3. AUTHOR(S)
(101) Int. Fertility Research Program, Research Triangle Park, N.C.

4. DOCUMENT DATE 1978	5. NUMBER OF PAGES 17p.	6. ARC NUMBER ARC
--------------------------	----------------------------	----------------------

7. REFERENCE ORGANIZATION NAME AND ADDRESS
IFRP

8. SUPPLEMENTARY NOTES (Sponsoring Organization, Publishers, Availability)
(Activity summary)

9. ABSTRACT

10. CONTROL NUMBER PN-AAG-044	11. PRICE OF DOCUMENT
12. DESCRIPTORS Contraceptives Intrauterine device	13. PROJECT NUMBER 932061800
	14. CONTRACT NUMBER AID/pha-C-1111
	15. TYPE OF DOCUMENT

**Six-Month Report
DEVELOPMENT OF IMPROVED AND NEW IUDS**



October 1, 1977 – March 31, 1978

**International Fertility Research Program
Research Triangle Park, North Carolina 27709
USA**

INTERNATIONAL FERTILITY RESEARCH PROGRAM

SIX-MONTH REPORT

DEVELOPMENT OF IMPROVED AND NEW IUDS

October 1, 1977 - March 31, 1978

Contract AID/pha-C-1111

TABLE OF CONTENTS

	Page
INTRODUCTION.....	1
I. POSTPARTUM IUDs AND INSERTERS.....	2
II. MEDICATED IUDs.....	4
III. PRESCRIPTIVE IUD INSERTION.....	6
IV. PUBLICATIONS.....	7
V. PLANS FOR NEXT PERIOD.....	8
VI. RECOMMENDATION ON CURRENT NEEDS.....	9
VII. ADMINISTRATIVE REPORT.....	10
APPENDIX 1 (Clinical Trials of the Lippes Loop D and the Cu-T with #2 Chromic Sutures).....	11
APPENDIX 2 (Person-Months; Actual and Projected Expenditures).....	13

INTERNATIONAL FERTILITY RESEARCH PROGRAM

SIX-MONTH REPORT DEVELOPMENT OF IMPROVED AND NEW IUDS October 1, 1977 - March 31, 1978

Contract AID/pha-C-1111

INTRODUCTION

The three main objectives of Contract AID/pha-C-1111 are the development of postpartum IUDs that have low expulsion rates when inserted immediately following removal of the placenta, medicated IUDs that will reduce IUD-related bleeding side effects, and a prescriptive approach to IUD insertion that will improve the quality of contraception by matching the IUD type to the woman's individual attributes.

Preliminary data on hand-inserted postpartum suture Loops and Cu-Ts show an expulsion rate at three months of 3.3 per 100 women. Biodegradable lateral extensions and nondegradable molded projections are also being evaluated. Inserters have been designed so that insertion by hand can be compared with insertion with an inserter. Four contributions to medicated IUD technology are being developed for clinical evaluation: 1) the AMCA-medicated Loop; 2) the Trasylo1-medicated Cu-T; 3) the Trasylo1-medicated Collagen Cu-T; and 4) the "Progestacoil" a progesterone-releasing U-Coil snaped device. A Photoreduced-Tapered Loop that can easily adapt to postpartum application has been developed. Techniques for prescribing IUDs are being developed that can reduce side effects and increase IUD acceptance by matching the device to acceptor attributes given at admission.

Progress has been made towards each objective and each can be achieved, but more time is required. Initially, it was anticipated that Battelle Memorial Institute with its considerable experience in IUD technology would be deeply involved as a subcontractor. For reasons beyond the control of IFRP their services have proven to be unavailable. Working with other subcontractors has proven to be impracticable, requiring that most of the work be done by IFRP. This has slowed the rate of progress.

I. POSTPARTUM IUDS AND INSERTERS

The IFRP Protection of Human Subjects Committee (PHSC) has approved for clinical testing three types of postpartum IUDs developed under this contract:

1. Lippes Loop and "T" IUDs with biodegradable Chromic suture projections on the upper limb extending .5 cm in both the anterior and posterior directions;
2. Lippes Loop and "T" IUDs with biodegradable gelatin/polylactic acid or collagen lateral extensions on the upper limb that increase the width of the upper limb from 3 cm to 6 cm initially (the 3 cm width is restored as the material degrades); and
3. Lippes Loops with molded (nondegradable) projections on the upper limb extending .5 cm in both the anterior and posterior directions.

Postpartum devices are designed for the significant number of women in the developing world whose main access to medical care occurs at the time of delivery or abortion. Progress on the evaluation of Loops with gelatin/polylactic acid extensions and collagen extensions has been slow. This is due in part to the reluctance of women to participate in a study involving the insertion of a 6 cm long lateral IUD extension. In addition, these devices have not proven attractive to physicians. Only a few have been inserted thus far in pilot clinical evaluations.

A similar reasoning applies to the Lippes Loops with molded projections. The stiff, nondegradable projections, although only .5 cm long, have not proven attractive to physicians.

The absence of patient and physician acceptance of the devices numbered 2 and 3 above, as determined by pilot clinical evaluations, makes full clinical trials unlikely.

Of the postpartum devices developed under this Contract, the Loop and Cu-T with Chromic suture anterior-posterior projections have been tested in clinical trials. The expulsion rate for the Chromic suture Loop at 3 months for 238 cases pooled from 3 centers is 3.3 per 100 women users (see Appendix 1). For the Chromic suture Cu-T the expulsion rate at 3 months for 100 cases is 3.2 per 100 women users at a single center (see Appendix 1).

So far the PHSC has approved a total of 1200 cases of the Chromic suture Loop and 800 cases of the Chromic suture Cu-T. The completion of ongoing and scheduled studies of the biodegradable Chromic suture Loop and Cu-T should provide sufficient performance data to permit a more complete evaluation of their suitability for use in LDCs.

A Tapered-Photoreduced Loop with Chromic sutures is scheduled to be tested in a 200-case study in Bangladesh. This device was developed as part of a series of modifications to the Lippes Loop D which included the Tapered Loop and the Photoreduced Loop, both of which are currently engaged in the early stages of field testing.

The effort to develop and study retentive IUD modifications is being augmented by an investigation of the relative merits of hand versus inserter IUD insertion. The hand insertion technique was used in the postpartum studies reported in Appendix 1. To test the thesis that a specially-designed longer inserter can also improve IUD retention, the IFRP has added such instruments to proposed postpartum studies of the Loop and the Cu-T.

Summary: Postpartum IUDs and Inserters

The research and development work for IUD designs that improve IUD retention when inserted immediately postplacental is nearly complete. Clinical verification is ongoing under Contract 1172 and completion of preliminary trials is expected by April 1979.

II. MEDICATED IUDS

Four contributions to medicated IUD technology are being developed for clinical evaluation:

1. AMCA-medicated Lippes Loop;
2. Trasylol-medicated Cu-T;
3. Trasylol-medicated Collagen Cu-T; and
4. "Progestacoil," a progesterone-releasing U-Coil shaped device.

AMCA-Medicated Lippes Loop

In early February 1978, Southern Research Institute (SRI) delivered 80 AMCA-medicated Loops with a drug release system consisting of a reservoir of AMCA in a hydrophilic polymeric binder (a 50/50 copolymer of HEMA and MMA--hydroxyethyl methacrylate and methyl methacrylate). The reservoir is coated with a thin membrane of polyurethane, Estane 5716, which controls the release of drug from the device. The good physical characteristics and in vitro release rate analysis reports suggest that the SRI devices will perform well in clinical trials.

In this regard, the Protection of Human Subjects Committee (PHSC) has recommended that AMCA-medicated devices be inserted in five pre hysterectomy patients and remain in utero for one menstrual cycle in order to rule out the possibility of unacceptable swelling of the drug-loaded portion of the device. Although five devices (fabricated under the Becton-Dickinson subcontract) were delivered to Dr. Hefnawi in December 1977 the priorities of other IFRP projects have delayed initiation as of this date. Until these AMCA devices can be inserted in pre hysterectomy patients the clinical phase of the medicated IUD portion of the IUD project is in abeyance.

Trasylol-medicated Cu-T

Bend Research, Bend Oregon, has been awarded the work of developing a Trasylol-releasing system utilizing Hydron. Presently, Bend is fine-tuning the release rate parameters and swelling characteristics by means of cross-linking and additives. Although 100 packaged and sterilized devices are scheduled to be ready in mid-June, difficulties with the Hydron material encountered thus far may result in a delayed completion time. The present estimate places completion of the fabrication work at the end of July 1978.

Trasylol-medicated Collagen Cu-T

Contract Office approval was sought in mid-March 1978 to support the development and fabrication of 105 Trasylol-medicated erodible collagen devices by Dr. Milos Chvapil of the University of Arizona. The progress of this work will be included in the next report.

Progestacoil

An IFRP-designed system for releasing progesterone from a coiled vector can be available for clinical testing in July 1978. The "Progestacoil" is designed to provide the same low pregnancy rate as the

U-Coil and the Spring Coil but without some of the problems that have characterized those devices: difficult insertion, poor device "memory" following insertion and increased menstrual blood loss. The device consists of an EVA rate-controlling membrane surrounding a progesterone-loaded matrix. The release rate is between 75 to 100 ug/day and can be set at other adjacent levels if necessary. The PHSC has approved three studies including a total of 250 devices. These studies can be initiated as soon as delivery is made on the necessary materials and a production run can be made.

Summary: Medicated IUDs

The research and development work on IUD designs that reduce IUD-related bleeding is nearly complete. In order to provide timely clinical verification, clinical trials under AID Contract 1172 must be initiated soon.

III. PRESCRIPTIVE IUD INSERTION

The IUD is an effective method of contraception that for many women is the only practical option. There is growing evidence showing that the quality of contraception provided by an IUD depends upon matching the IUD type with the woman's individual attributes. By selecting the most suitable device for a woman, side effects and failure rates may be reduced as compared to routine use of a standard IUD.

Although a large variety of IUDs are commercially available, clinical testing to date has not produced a rational procedure for selecting the device most suitable for each woman. In order to meet this need, the IFRP is using its data base on IUD acceptors to develop an IUD selection procedure. The practical application of this method consists of assigning each woman to a specific category based on her personal attributes. The physician would then refer to a table which lists the expected event rates for each category of women by IUD type. This would enable the physician to make a decision taking into account the relative risks of each event such as pregnancy, pain and bleeding. Accuracy of the predictions may be tested by retrospective application of the method to completed IUD studies. The effort expended to prescribe the appropriate IUD will be rewarded by improved continuation rates. Protocols for preliminary clinical evaluation of IUD prescription methods are presently being designed and are expected to be ready for trial by September 1978.

Further to the conviction that there is a link between IUD events and the dimensional disproportion of a device within the uterine cavity is the development of the Uterine Cavity Depth Sound II. This instrument indicates the distance from the inner os to the fundus. One hundred of these instruments will be delivered in July 1978 and will be available for incorporation into interval IUD studies.

IV. PUBLICATIONS

An article entitled "Development of a Postpartum IUD" by Laufe, Wheeler and Friel is being prepared for publication.

Robert Wheeler presented a paper entitled "Estimation of Menstrual Blood Loss" at the 34th Annual American Fertility Society Meeting in New Orleans on 31 March 1978.

V. PLANS FOR NEXT PERIOD

1. Central to the work of the IUD project is the requirement that new or improved devices be designed to meet the special fertility control needs of the developing world. To this end, the postpartum Chromic suture Loop and Cu-T are designed to be easily assembled using readily available materials in almost any setting. In addition, each subcontract for the development of medicated devices has stipulated the capability of local production among the principal specifications of the award. In order to realize this important goal, consideration has begun of establishing an IUD fabrication facility with a clinical affiliation in a developing country in the western hemisphere. Preliminary discussions are scheduled to take place in June with representatives of the family planning field in Mexico. For a relatively small sum of money it will be possible to set up and equip a small facility that will permit the fabrication of medicated and postpartum devices for local and regional use. Work on this facility is expected to be initiated in August 1978.

2. By the end of September 1978 the following should be achieved:

- a. Studies involving 2000 insertions by hand or inserter of the postpartum Chromic suture devices will be underway. Preliminary studies will have determined whether the molded projections and collagen or gelatin/polylactic acid extensions will be made available as alternatives to the suture devices.
- b. Devices sufficient for clinical studies to obtain the dose-response characteristics of IUDs that release Trasylol, AMCA or progesterone will be available.
- c. Protocols for clinical evaluation of IUD prescription methods will be ready for clinical tests. These studies will rely, in part, on improved uterine measurement methods developed by IFRP.

VI. RECOMMENDATION ON CURRENT NEEDS

Work to date does not indicate a need to modify project objectives as stated in the contract.

VII. ADMINISTRATIVE REPORT

A report on actual and projected expenditures and personnel employed under the contract can be found in Appendix 2. There have been no new subcontracts implemented during the contract period. One substantial purchase order has been issued to Bend Research for the development of a Trasyol medicated device in accord with Bend response to IFRP bid request No. 128. Cost: \$24,000. ETC: July 1978.

Clinical Trials of the
Lippes Loop D with #2 Chromic Gut Sutures

Three studies are currently underway to evaluate the expulsion rate of the sutured Loop D inserted postpartum. With a total of 238 insertions, the gross cumulative expulsion rate for data pooled from all three centers is 3.3 per 100 users at 3 months and 5.0 at 6 months. A fourth study of the device was cancelled at the contributor's request. Due to difficulties with the hand insertion technique, his expulsion rate was unacceptably high (11.9 per 100 users at 1 month).

Gross Cumulative Event Rates

Center Location	Pregnancy	Expulsion	Bleeding/pain Removals	Cumulative Women Months of Use
Manila				
mo. = 1	0.0	4.3(2.1)*	0.0	90.0
3	0.0	4.3(2.1)	1.6(1.6)	230.0
N=100				
Santiago				
mo. = 1	0.0	2.8(2.8)	2.8(2.8)	35.0
N=40				
Cairo				
mo. = 1	0.0	0.0	0.0	93.5
3	0.0	0.0	0.0	240.0
N=98				
Pooled				
mo. = 1	0.0	2.3(1.0)	0.5(0.5)	218.5
3	0.0	3.3(1.2)	1.1(0.8)	559.0
6	1.0(1.0)	5.0(2.1)	2.1(1.2)	789.5
N= 238				
Bandung**				
mo. = 1	0.0	11.9(5.6)	0.0	31.5
N=36				

* Standard Error

**Not included in Pool.

Clinical Trials of the
Copper T-200 with #2 Chromic Gut Sutures

One hundred insertions have been performed via hand technique of the Copper T with sutures. Results are favorable to date with 1 and 3 month expulsion rates of 1.0 and 3.2 respectively.

Gross Cumulative Event Rates

Center Location	Pregnancy	Expulsion	Bleeding/pain Removals	Cumulative Women Months of Use
Manila				
mo. = 1	0.0	1.0(1.0)	0.0	95.5
3	0.0	3.2(1.8)	0.0	255.0
N=100				

Contract AID/pha-C-1111
Person-Months

Name	Cumulative Through 3/31/78	Estimated 4/1/78 Through 9/30/78	Estimated 10/1/78 Through 4/30/79	TOTAL
L. Laufe	10.25	3.0	3.5	16.75
R. Wheeler	30.50	6.0	7.0	43.50
P. Friel	29.15	6.0	7.0	42.15
M. Porter	17.29	-0-	-0-	17.29
R. Greenhill	7.20	6.0	7.0	20.20
A. Smith	3.23	-0-	-0-	3.23
E. Calamai	.45	-0-	-0-	.45
J. Elkington	2.24	-0-	-0-	2.24
D. Freer	0.84	-0-	-0-	0.84
E. Barnes	6.00	6.0	7.0	19.00
M. Jackson	0.20	-0-	-0-	0.20
Other	0.29	3.0	-0-	3.29
Adjustments	(1.29)	-0-		(1.29)
TOTAL	106.44	30.0	38.5	167.85

**AID/pha-C-1111 Actual and Projected Expenditures
7/1/75 through 4/30/79**

Item	Original Budget	Cumulative Through 3/31/78	Estimated 4/1/78 Through 9/30/78	Estimated 9/30/78 Through 4/30/79	Proposed Budget
Salaries	\$156,458	\$170,173	\$ 55,181	\$ 64,449	\$289,803
Merit Increase	5,881	(1)	(1)	(1)	-0-
Fringe Benefits	38,092	32,550	11,588	13,472	57,610
Consultants	25,530	14,438	7,500	9,750	31,688
Equipment	20,600	20,410	2,500	2,500	25,410
Expendable Supplies and Other Direct	112,107	60,133	28,000	31,600	119,733
Travel	20,000	12,309	3,300	6,000	21,609
Publications Costs	1,600	399	500	1,445	2,344
Subcontracts	341,018	91,490	5,000	7,500	103,990
Occupancy Expense	2,500	1,564	1,600	1,875	5,039
Overhead	136,686	107,524	43,355	52,367	203,246
Salary Support	3,528	3,528	-0-	-0-	3,528
TOTAL	<u>\$864,000</u>	<u>\$514,518</u>	<u>\$158,524</u>	<u>\$190,958</u>	<u>\$864,000</u>

(1) Merit increases included in salary expenditures.