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A COMPARATIVE STUDY OF INTRAUTERINE DEVICES,
TCu 380A VERSUS TCu 200
IN MEDELLIN, COLOMBIA

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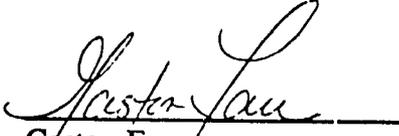
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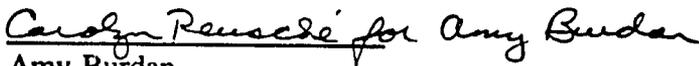
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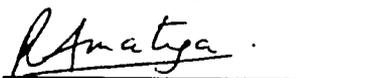
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I. INTRODUCTION

The intrauterine device (IUD) is a popular and highly tested method of contraception. About 85 million women worldwide use IUDs, with the highest concentration of users in China and Southeast Asia. The current generation of IUDs is safe for most women and about 99 percent effective over one year of use. However, not all women should use IUDs. The provider must carefully screen potential users, insert the IUD correctly and follow-up users to assess safety. This study was part of Family Health International's (FHI) Investigator Network Needs (INN) program to train doctors in conducting clinical trials. The study compared the clinical performance and contraceptive effectiveness of the TCu 380A and TCu 200 IUDs at the General Hospital of Medellín, Colombia.

II. MATERIALS AND METHODS

Study Objective

The major objective of this clinical trial was to evaluate the use of the TCu 380A IUD among women in particular geographic locations. The TCu 380A has been extensively tested in order to verify its efficacy and safety. The factors evaluated in this trial were complications and complaints, participant's status after twelve months of use, and gross cumulative life-table discontinuation rates over a twelve-month follow-up period.

Study Design

In this study, the TCu 380A IUD and the TCu 200 IUD were randomly assigned to the volunteer participants according to sealed random allocation envelopes preprinted at FHI. At the time of each woman's admission to the study, the envelope corresponding to her assigned patient order number (PON) was opened, indicating the IUD to be inserted. If a woman was inadvertently admitted and discovered to have an exclusion condition, she was discontinued from the study and the PON was not reused. The next available PON was assigned to the next woman using the appropriate random allocation envelope. The subjects agreed to use their assigned IUD as their sole method of contraception during the study.

The protocol, as well as the fact sheet and volunteer agreement form to be used in the study, were approved by the FHI Protection of Human Subjects Committee and by the Comité de Investigaciones of the Hospital General de Medellín before initiation.

Study Products

The TCU 380A is a T-shaped IUD made of polyethylene with barium sulfate for x-ray detectability. It has two 33 mm² solid copper sleeves on each transverse arm and 314 mm of copper wire wound tightly around the vertical stem. The increased copper surface area has been shown to improve the efficacy of the TCU 380A over the TCU 200 IUD. The device is 32 mm wide and 36 mm long with a plastic ball at the bottom of the vertical stem to guard against cervical penetration. A polyethylene filament is tied through the ball and provides two marker threads.

The TCU 200 is also a T-shaped IUD made of polyethylene with barium sulfate added for x-ray detectability. It is wound with copper wire on the stem providing a total surface area of 200 mm². The cross-arm is 32 mm in width and the vertical arm is 36 mm in length. The bottom of the vertical stem of the IUD is provided with two polyethylene marker threads.

Selection Criteria

Women 18 to 40 years old who were healthy, sexually active, parity of one or more, ≥ 42 days postpartum, could conveniently return for follow-up, willing to rely solely on the IUD for contraception, and agreed to participate in the study, were admitted into the trial. Women were to be excluded if there was evidence of pregnancy, a history of ectopic pregnancy, current sexually transmitted disease (STD) or pelvic inflammatory disease (PID). In addition, women were excluded if they had undiagnosed vaginal bleeding, allergy to copper, or a history or evidence of clinically significant gastrointestinal or renal disease. Candidates were also to be excluded if they had an abnormal Papanicolaou smear three months or less prior to admission into the study.

Admission Procedures

At the initial visit, women were screened for study eligibility using the predetermined screening criteria mentioned above. The screening process included taking a medical history and performing a pelvic examination. The risks and benefits of study participation were explained to each woman. All participants gave informed consent before admission and agreed to return to the clinic for follow-up visits. The TCU 380A IUD and the TCU 200 IUD were randomly assigned to the volunteer participants according to the procedure explained above, and the insertion procedure was carried out.

Follow-up Procedures

The subjects were requested to return for follow-up visits at 1, 3, 6, and 12 months after IUD insertion or at any time complications occurred. At the follow-up visits, pelvic examinations

were performed, and if any complications or infections were noted, appropriate treatment was provided. The data collected were documented on the case record form (CRF) by clinic staff.

Women were terminated from the study if pregnancy occurred, if their IUD was partially or totally expelled, or if their IUD was removed for any reason. Depending upon the physician's judgment, a woman's IUD could be left in place at the end of the study period for the then recommended IUD lifespan of the time of four years, and the woman was to be followed-up according to standard medical practices.

Data Analysis

Data were sent to FHI for processing and analysis. Differences in complications and complaints between the two groups returning for follow-up were examined using Fisher's exact test. Comparison of important study events were made on the basis of pregnancy, expulsion, bleeding and/or pain, and other specific removal rates. The following definition was used for classifying discontinuation cases when both conception and expulsion were reported for the same woman. Accidental pregnancy includes:

- all conceptions occurring after insertion of the IUD and prior to removal or an expulsion noticed by the wearer, or
- all conceptions associated with an expulsion not noticed by the wearer, or
- all conceptions associated with a perforation of the uterus.

This does not include conceptions prior to insertion or after a noticed expulsion, or after the IUD was removed for whatever reason. In these instances discontinuation was due to the event leading to IUD removal [1]. The estimated date of discontinuation for noticed and unnoticed, complete or partial expulsions is calculated as the midpoint between the date of last follow-up and the visit at which the expulsion was reported.

The life-table method was used to calculate all termination rates. Single decrement gross life-table rates were compared using the log rank statistic which permits the overall comparison of cumulative life table event rates. Statistical significance was set at $p \leq 0.05$ for comparing complications and complaints, and $p \leq 0.05$ for comparing discontinuation rates. For the purposes of this report, the power statement was calculated according to the center's results.

III. RESULTS

Subject Population

A total of 393 women were recruited, of which 16 were excluded from analysis due to difficulty in determining their interval status, whether the IUD was inserted postpartum, or post-abortion. Enrollment extended over a 13-month period beginning September 1, 1987. By random allocation, 187 received the TCu 380A IUD and 190 received the TCu 200 IUD. All subjects had the IUD inserted six weeks or more since their last pregnancy termination. One subject was over the maximum age, at 42 years. This was considered a minor protocol violation, and the subject was permitted to continue in the study.

Baseline Measures

The mean age [\pm standard deviation (SD)] of the women in the TCu 380A IUD group was 25.1 (\pm 4.7) years and 25.8 (\pm 5.1) years for the TCu 200 IUD group (Table I). The reproductive history for the women also is detailed in Table I. All the women had at least one live birth prior to study admission. The mean (\pm SD) for the total number of live births was 1.8 (\pm 0.9) for the TCu 380A IUD group and 1.8 (\pm 1.1) for the TCu 200 IUD group. Almost half of the women in both groups reported using no contraceptive method during the month prior to study enrollment. When a method was used, the most frequent choices were oral contraceptives, or IUDs (subjects were returning for IUD replacement).

Insertion Status

There were no complications or complaints reported at insertion (Table II), but a few pre-existing conditions were reported. In the TCu 380A IUD group, three subjects had dysmenorrhea. In the TCu 200 IUD group, three had dysmenorrhea, and one had intermenstrual spotting.

In addition, five TCu 380A IUD users reported having had a previous, unspecified STD and one TCu 200 IUD user had a single episode of previous PID. In each case the investigator determined that these women were no longer at risk. The greater number of subjects having a previous STD in the TCu 380A IUD group was statistically significant ($p=0.03$). (However, this finding did not have an effect on the IUD performance comparison. At follow-up, only one subject in the other IUD group, reported an unspecified STD.)

Follow-up Status

Six subjects from the TCu 380A IUD group were lost to follow-up, and four subjects of the TCu 200 IUD group were lost to follow-up. Three hundred and thirty-two out of the 377 subjects, or 88% completed the study through the 12-month follow-up visit.

There were relatively few complications and complaints reported during the study; these are listed in Table II. Menstrual problems were the most frequently reported problem. Eight (4.4%) women in the TCu 380A IUD group and 8 (4.3%) women in the TCu 200 IUD group reported intermenstrual bleeding. Intermenstrual spotting was reported by 8 (4.4%) women in the TCu 380A IUD group and 3 (1.6%) women in the TCu 200 IUD group. Intermenstrual pelvic pain was reported by 5 (2.8%) women in the TCu 380A IUD group and 7 (3.8%) women in the TCu 200 IUD group. Dysmenorrhea was reported by 7 (3.9%) women in the TCu 380A IUD group and by 6 (3.2%) women in the TCu 200 IUD group. (Of these thirteen women, one woman from each IUD group had entered the IUD study with dysmenorrhea and reported the condition at the first follow-up visit, but no complaints of dysmenorrhea were made in subsequent follow-up visits.) Six (3.3%) of subjects in the TCu 380A IUD group and 2 (1.1%) women in the TCu 200 IUD group reported menorrhagia. The differences between the study groups were not statistically significant for any of these complaints.

Table II also lists the occurrence of PID, inflammations or infections, and other problems that occurred during follow-up. Four (2.1%) women in the TCu 200 IUD group had PID, and one (0.6%) subject in the TCu 380A IUD group had PID. Two TCu 200 women had their IUDs removed as part of their treatment. The remaining three PID cases were treated successfully; two continued in the trial and one TCu 380A user discontinued IUD use for another reason (bleeding). Only 1 (0.5%) subject in the TCu 200 IUD group was reported to have an unspecified STD. These differences were also not statistically significant.

There were a small number of other conditions reported; In the TCu 380A IUD group, 4 (2.2%) women had leukorrhea, and 1 (0.6%) developed an intraepithelial cervical carcinoma. In the TCu 200 IUD group 2 (1.1%) women had leukorrhea. Again, these small differences were statistically insignificant.

Two cases of perforation were reported during the follow-up phase of the trial, one in each IUD group. In both instances the IUD perforated the uterine wall. Upon diagnosis, these were successfully removed by laparoscopy and the women chose other contraceptive methods.

Subject Discontinuation

Table III summarizes the women's status at the end of twelve months of use and Table IV presents the 12-month gross cumulative life-table rates for these termination events. Evaluations of efficacy were made on the basis of various termination rates and continuation rates, with a focus on the accidental pregnancy and expulsion rates. Non-pertinent

termination reasons included planning a pregnancy and removals for other personal reasons. The differences in life-table rates between the two groups for the discontinuation reasons listed were not statistically significant ($p > .05$).

There were two accidental pregnancies (1.1%) in the TCU 380A IUD group yielding a 12-month life-table rate of 1.6 per 100 women. One subject was found to be pregnant approximately 10 weeks after insertion, with the IUD absent, presumably an unnoticed expulsion. At an approximate gestational age of seven weeks there was a spontaneous abortion, and curettage was performed. The subject subsequently chose to use oral contraceptives. The other subject in the TCU 380A IUD group was found to be pregnant approximately 9 months after insertion, with the IUD absent, also an unnoticed expulsion. The pregnancy was at seven weeks' gestation when found, but the pregnancy outcome was not reported. No pregnancies were reported in the TCU 200 group. With the final sample size, the power to detect a statistically significant difference between the two groups with pregnancy rates of 1.6% and 0.0% is about 30% ($\alpha = .05$).

There were a total of 11 IUD expulsions or displacements in the study: 5 (2.7%) in the TCU 380A IUD group and 6 (3.2%) in the TCU 200 IUD group. The 12-month gross life-table rates were 4.1 per 100 women for the TCU 380A IUD group and 3.5 per 100 women for the TCU 200 IUD group. This does not include the two pregnancy cases in the TCU 380A IUD group in which expulsion was also noted, as these women were discontinued due to their pregnancies.

Removals for bleeding and/or pain included eight women (4.3%) in the TCU 380A IUD group and four women (2.1%) in the TCU 200 IUD group. The life-table removal rates for these TCU 380A and TCU 200 IUD users were 5.7 per 100 women and 3.2 per 100 women, respectively.

Two women (1.1%) in the TCU 380A IUD group and three women (1.6%) in the TCU 200 IUD group were terminated from the study for a medical reason. In two subjects (one from each IUD group), the IUD had perforated the uterine wall and was removed by laparoscopy. One subject in the TCU 380A group had her IUD removed due to intraepithelial cervical carcinoma. Two subjects in the TCU 200 IUD group had their IUDs removed due to PID. The 12-month gross cumulative life-table rates for medical-related removals were 1.2 per 100 women for the TCU 380A IUD group and 1.8 for the TCU 200 IUD group.

There were a small number of women who requested IUD removal in order to plan a pregnancy. Two women in the TCU 200 IUD group requested removal for this reason, with a 12-month gross cumulative life-table rate of 0.9 per 100 women. No women in the TCU 380A IUD group discontinued early for this reason.

None of the women in the TCU 380A IUD group, and a total of three women in the TCU 200 IUD group had their IUD removed because of personal reasons. One subject expressed

personal dissatisfaction, and the two other subjects did not specify their reasons. The 12-month gross cumulative life-table rates were 2.0 per 100 women for the TCu 200 IUD group.

IV. SUMMARY

From September 1, 1987 to September 29, 1988, IUDs were inserted in 377 women in a 12-month comparative clinical trial conducted at the Department of Gynecology and Obstetrics at the General Hospital of Medellín, Colombia. This study was designed to assess the contraceptive safety and efficacy with two comparative IUDs and to provide the investigator experience in conducting a clinical trial. By random allocation, 187 women received the TCu 380A IUD and 190 received the TCu 200 IUD. Participants in the two groups were similar with respect to socio-demographic characteristics and reproductive history. Although the greater incidence of previous STDs at admission in the TCu 380A IUD group were found to be statistically significant, none of these women developed PID or reported STDs at follow-up, making the overall baseline difference between the two IUDS groups clinically insignificant.

The most frequently reported menstrual complaints for both groups were intermenstrual bleeding, spotting, and dysmenorrhea. However, the incidence of these reports was low and generally did not lead to early removal of the IUD. The incidence of PID and other inflammations or infections was found to be only slightly, but nonsignificantly, higher in the TCu 380A group.

For this population of women, the TCu 200 IUD group had a zero accidental pregnancy rate while there were two discontinuations attributed to accidental pregnancy in the TCu 380A IUD group. Of the women enrolled in the study, 87.7% in TCu 380A IUD group and 88.4% in the TCu 200 IUD decided to continue with the IUD in place after the study had ended at 12 months. It should also be noted that both of the pregnancy cases reported the IUD had been expelled. As such, it was difficult to determine if the expulsions may have occurred prior to conception but these cases were arbitrarily classified in the accidental pregnancy category.

The descriptive data reported in this comparative trial suggest that the two T-shaped devices are generally similar in respect to reports of inflammations/infections, and discontinuation events. At the time of this study the approved lifespan of the TCu 380A was four years, with a published four-year life-table pregnancy rate of 2.8 per 100 women based on 1,927 women-years of use [2]. However, subsequent studies conducted by the Population Council have demonstrated an extended lifespan of eight years. An extended lifespan would allow for longer contraceptive protection. Another study completed in 1991 in Brazil has demonstrated that the effectiveness of the TCu 380A IUD did not decrease significantly after the eighth year of use and could be considered a reversible but potentially permanent method [3].

V. DATA QUALITY STATEMENT

The clinic staff was very dedicated to the study and meticulous in their work. Monitors commented that this disciplined, well-organized clinic facilitated the implementation of the study. Informed consent and random allocation procedures were conscientiously followed. Recruitment was steady, and completed in 13 months. There was one age requirement protocol deviation, which was considered minor. Follow up was good, and the staff created a wall chart to keep track of subjects. The forms were conscientiously completed and great attention was paid to answering queries and correcting data problems.

Note: This statement is provided to the investigator to help him set the study's results in the proper context. The quality of the data collected may affect the validity of the stated results.

VI. ACKNOWLEDGEMENT

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Table I
Subject Characteristics at Admission

Characteristics	TCu 380A (N=187)		TCu 200 (N=190)	
	No.	% ¹	No.	% ¹
<u>Age in Years Completed</u>				
Less than 20	20	10.7	18	9.5
20-24	67	35.8	68	35.8
25-29	65	34.8	58	30.5
30-34	29	15.5	34	17.9
35-39	5	2.7	10	5.3
40+	1	0.5	2	1.1
Mean (S.D.)	25.1	(4.7)	25.8	(5.1)
<u>Total Number of Live Births</u>				
1	86	46.0	100	52.6
2	72	38.5	55	28.9
3	20	10.7	24	12.6
4	6	3.2	5	2.6
5	2	1.1	4	2.1
6	1	0.5	1	0.5
7+	0	0.0	1	0.5
Mean (S.D.)	1.8	(0.9)	1.8	(1.1)
<u>Contraceptive Used in the Past Month</u>				
None	89	47.6	91	47.9
Orals	48	25.7	65	34.2
IUD	34	18.2	24	12.6
Other Barrier Method	6	3.2	3	1.6
Injectables	5	2.7	1	0.5
Condoms	4	2.1	1	0.5
Withdrawal/Rhythm	1	0.5	5	2.6

¹Percentages may not total 100 due to rounding.

Table II
Complications and Complaints Reported During the Study

Complications/Complaint ¹	TCu 380A		TCu 200	
	No.	%	No.	%
Total Women at Insertion	187	100.0	190	100.0
<u>Admission</u>				
Single Episode of Prev. PID	0	0.0	1	0.5
Dysmenorrhea	3	1.6	3	1.6
Intermenstrual Spotting	0	0.0	1	0.5
Previous STD (unspecified)	5	2.7	0	0.0
Total Women ever Followed-up	181	96.8	186	97.9
<u>Menstrual Problems:</u>				
<u>Intermenstrual</u>				
Bleeding	8	4.4	8	4.3
Spotting	8	4.4	3	1.6
Pelvic Pain	5	2.8	7	3.8
Dysmenorrhea	7	3.9	6	3.2
Menorrhagia	6	3.3	2	1.1
<u>PID:</u>				
Confined to Adnexa	0	0.0	2	1.1
Confined to Uterus	1	0.6	1	0.5
Confined to Uterus & Adnexa	0	0.0	1	0.5
<u>Inflammations/Infections:</u>				
STD (Unspecified)	0	0.0	1	0.5
<u>Other Findings:</u>				
Leukorrhea	4	2.2	2	1.1
Perforation	1	0.6	1	0.5
Intraepithelial Cervical Carcinoma	1	0.6	0	0.0

¹More than one item can be diagnosed for each woman.

Table III
Subject Status at Twelve Months

Status	TCu 380A (N=187)		TCu 200 (N=190)	
	No.	% ¹	No.	%
Continuing	164	87.7	168	88.4
Accidental Pregnancy	2	1.1	0	0.0
Expulsion/ Displacement	5	2.7	6	3.2
<u>Removals for:</u>				
Bleeding/Pain	8	4.3	4	2.1
Other Medical Reasons	2	1.1	3	1.6
Other Personal Reasons	0	0.0	3	1.6
Planning Pregnancy	0	0.0	2	1.1
Lost to Follow-up	6	3.2	4	2.1

¹ Percentages may not total 100 due to rounding.

Table IV
Gross Cumulative Life-table Discontinuation Rates Per 100 Women

Discontinuation Type and Period	TCu 380A			TCu 200		
	At Risk (N)	Rate	(S.E.)	At Risk (N)	Rate	(S.E.)
Accidental Pregnancy						
3 months	167.5	0.0	(0.0)	166.0	0.0	(0.0)
6 months	143.5	0.6	(0.6)	138.5	0.0	(0.0)
12 months	80.5	1.6	(1.2)	89.5	0.0	(0.0)
Expulsion/Displacement						
3 months	167.5	0.6	(0.5)	166.5	2.2	(1.1)
6 months	144.0	1.2	(0.9)	138.5	3.5	(1.4)
12 months	80.5	4.1	(1.9)	89.5	3.5	(1.4)
Bleeding/Pain						
3 months	167.5	1.1	(0.8)	166.0	1.1	(0.8)
6 months	145.0	3.8	(1.5)	138.5	1.1	(0.8)
12 months	80.5	5.7	(2.0)	89.5	3.2	(1.7)
Other Medical Reasons						
3 months	167.5	0.6	(0.6)	166.5	1.1	(0.8)
6 months	143.5	1.2	(0.8)	138.5	1.8	(1.0)
12 months	80.5	1.2	(0.8)	89.5	1.8	(1.0)
Personal Reasons						
3 months	167.5	0.0	(0.0)	166.5	1.1	(0.8)
6 months	143.5	0.0	(0.0)	138.5	1.1	(0.8)
12 months	80.5	0.0	(0.0)	89.5	2.0	(1.1)
Planning Pregnancy						
3 months	167.5	0.0	(0.0)	166.0	0.0	(0.0)
6 months	143.5	0.0	(0.0)	138.5	0.0	(0.0)
12 months	80.5	0.0	(0.0)	89.5	0.9	(0.8)
Total Discontinuation Rate						
3 months	167.5	2.2	(1.1)	167.0	5.5	(1.7)
6 months	145.5	6.7	(2.0)	138.5	7.3	(2.0)
12 months	80.5	12.2	(2.9)	89.5	10.8	(2.6)
Continuation Rate						
3 months		97.8			94.5	
6 months		93.3			92.7	
12 months		87.8			89.2	