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MENSTRUAL PATTERNS AND PROGESTERONE CIRCULATING LEVELS FOLLOWING
DIFFERENT PROCEDURES OF TUBAL OCCLUSION¹

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ABSTRACT

This study was undertaken to assess the effects of different tubal occlusion procedures on ovarian function. Three groups of subjects randomized to tubal occlusion by laparoscopy and Yoon ring (24 subjects), minilaparotomy and Yoon ring (19 subjects) and minilaparotomy and Pomeroy (22 subjects), and one separate control group of 26 healthy subjects not using any form of contraception were studied in a prospective design. The characteristics of the menstrual patterns were studied for one year after sterilization. Determination of the circulating progesterone levels were made on days 15, 20 and 25 of menstrual cycles initiated 1, 3, 6 and 12 months following the tubal ligation.

In the analysis of the bleeding pattern there was a statistically significant difference in the mean segment length and in the longest bleeding-free interval in the subjects who had been sterilized by minilaparotomy with Yoon ring, when compared to the other two study groups and to the control group. However, the magnitude of this difference in number of days was not considered clinically significant. There was no statistically significant difference in the percentage of ovulatory cycles within the study and the control groups, or when the results of the study groups were compared with each other or to the control group.

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INTRODUCTION

Tubal occlusion has become increasingly the most prevalent method of fertility regulation, this fact being particularly noticeable in several developing countries in the last decade. As a result there has been concern on the possible association of the tubal occlusion with changes in the ovarian function, resulting in alterations of the menstrual patterns or in the secretion of ovarian hormones.

A large number of studies addressing this subject have been undertaken; however, in developing countries, where the conditions in which tubal ligations are performed are unique and with particular social and biological characteristics, these types of studies have been limited. The main purpose of this work was to establish the effects of different procedures of tubal occlusion on the ovarian function, assessed by the analysis of the bleeding patterns in the first year after the occlusion, and by the determination of circulating progesterone levels during the luteal phase in menstrual cycles 1, 3, 6 and 12 following the procedure.

MATERIALS AND METHODS

Design of the Study

Three groups, each one with 25 subjects, were admitted to the randomized arms of the study. The participating subjects were women who voluntarily had requested interval sterilization for fertility regulation purposes, at the General Hospital of the Ministry of Health in Durango, Mexico. The fourth group, or control group, consisted of young women, mostly medical students of the local university, who were not using any type of systemic contraception. Prior to admission all the subjects of the study groups were informed of the purpose of the research, and then the women undergoing sterilization were randomly assigned to one of the procedures of tubal occlusion.

The surgical procedures used for sterilization were laparoscopy and Yoon ring, minilaparotomy and Yoon ring, and minilaparotomy with the Pomeroy technique of tubal occlusion. These procedures were performed following established techniques, in all cases by the same surgeon, and in the interval period. Epidural block was used for anesthesia in all cases. The procedure was usually performed between 8:00 and 10:00 in the morning and the patients left the hospital that same day in the afternoon. All the subjects returned to the hospital for evaluation by the same surgeon one week after the sterilization.

All the participating subjects were scheduled for a follow-up visit 1, 3, 6 and 12 months after the procedure, and were carefully instructed in the registering of the menstrual events, using a calendar designed for this purpose. The menstrual calendars were reviewed with the subject at each follow-up visit. To evaluate the ovarian function, the subjects were scheduled for progesterone determinations performed on days 15, 20 and 25 of menstrual cycles initiated on the first, third, sixth and twelfth month following the tubal ligation.

To implement this procedure, the subjects were visited periodically by a social worker in order to identify the beginning of the study menstrual cycles, and to establish the dates for the progesterone determinations. These visits were also used to insure the correct filling out of the menstrual calendars.

Fasting blood samples were obtained between 8:00 and 9:00 in the morning, in the majority of the cases in the home of the subjects by a trained nurse. The serum obtained was immediately frozen and kept at -20 degrees Celsius until analyzed.

The progesterone determinations were performed with matched assay reagents provided by the Human Reproduction Programme of the World Health Organization. All the samples of one subject were assayed in the same radioimmunoassay. The inter- and intraassay coefficient of variation for the progesterone determination in our laboratory is 4.3 and 3.0%, respectively.

Statistical Procedures

The menstrual patterns were analyzed at the end of the study period using the procedure of Rodriguez et al. (1) with terminology adapted to the WHO guidelines (2). The following characteristics of the menstrual patterns of each woman were included in the analysis:

1. Number of bleeding episodes in the reference period. The reference period was initiated on the first day of the menstrual cycle in which the tubal ligation was performed, and terminated the day before the beginning of the last recorded menstrual cycle.
2. Mean segment length, defined as the sum of the mean length of the bleeding episodes and the mean length of the bleeding-free intervals.
3. Total number of bleeding days in the reference period.
4. Total number of spotting days in the reference period.
5. Longest bleeding episode in the reference period.
6. Longest bleeding-free interval.
7. Mean length of the bleeding episodes.

Since the seven menstrual characteristics have skewed distributions, the summary measures reported for each group were the medians and the first and the third quartiles of each. To give additional detail on participants with unusual results and to permit a graphical comparison of the results, a modification of the box-whiskers plot proposed by Tukey (3) is presented for some of the more important characteristics. This modification follows the patterns utilized in SAS (4).

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In order to produce meaningful statistical tests of the difference between the menstrual patterns of the four groups, three of the menstrual characteristics were designated as primary analysis objectives to be tested.

They were: 1) mean segment length; 2) mean length of the bleeding episodes; and 3) longest bleeding-free interval. To maintain the experiment error rate close to 0.05, the type I error rate was fixed at 0.025 for each of these characteristics (Bonferroni correction). The nonparametric test of Kruskal-Wallis was used for each comparison. If this global comparison was statistically significant, then comparisons between the individual study groups were performed using Wilcoxon's.

The statistical analysis of the progesterone levels at the three distinct time points (days 15, 20 and 25) in the cycles that occurred during months 1, 3, 6 and 12 after entering the study was accomplished through reporting the medians and first and third quartiles. These are presented both in tables and figures.

In addition, using a cutpoint of 3 ng/ml of progesterone, the percentage of women "ovulating" in each of the above mentioned cycles was determined as those women whose progesterone levels exceeded the cutpoint. Comparison of these percentages among the four groups at each of the cycles was performed using the chi-square test statistic.

RESULTS

Admission Characteristics

Some subjects in each group did not complete the study because they were lost to follow-up, the main reason being a change in residence. However, there were no medical reasons in any case for discontinuing subjects from the study.

The characteristics of the women in the four groups, that completed the study, were as follows:

Group 1. Twenty-four women who had been submitted to tubal occlusion by means of laparoscopy and placement of the Yoon ring, with a mean age of 30.5 years (SD 4.4), and an average number of living children of 2.6.

Group 2. Nineteen women who had been submitted to tubal occlusion by means of minilaparotomy and placement of the Yoon ring, with a mean age of 30.3 years (SD 4.2), and an average number of living children of 5.9.

Group 3. Twenty-two women who had been submitted to tubal occlusion by means of minilaparotomy and the Pomeroy technique, with a mean age of 29.5 years (SD 4.4), and an average number of living children of 4.5.

Group 4. The control group with 26 healthy women, not using any contraceptive method, with no history of or current gynecologic or endocrine pathology, with previous normal menstrual cycles, a mean age of 22.1 years (SD 2.1), and without any living children.

There were no cases with any important trans- or post-operating complication, and all of the women left the hospital the same day the sterilization was performed.

Bleeding Patterns

The descriptive statistics of the most representative events of the bleeding patterns throughout the reference period are presented in Table I and Figure 1.

Table I shows that only two of the menstrual events analyzed showed statistically significant differences in one of the groups. These were the mean segment length ($p=0.02$) and the longest bleeding-free interval ($p=0.017$). In both instances, the women who had been sterilized by minilaparotomy with Yoon ring (Group 2) had greater median values of these two bleeding pattern characteristics than the other two study groups or the control group. For the mean segment length, this difference in medians was approximately 2 days. For the longest bleeding-free interval, this difference in medians between groups was approximately 10 days. No differences were found in any of the other bleeding patterns characteristics in or between the other groups.

Progesterone Levels

The median progesterone values obtained on days 15, 20 and 25 of the study cycles in the subjects of the four groups are presented in Figure 2. The progesterone determinations were conducted in prospectively established and fixed days of the menstrual cycle, therefore they represent different days of the luteal phase. No formal statistical test was used or considered appropriate to compare the summary statistics of progesterone levels from the groups. As expected the median progesterone values were higher on days 20 or 25 as compared to day 15 of the menstrual cycle.

Defining ovulation as one or more progesterone determinations over 3.0 ng/ml in any of the three samples obtained in each of the studied cycles, the frequency of ovulation was established for each group. If any of the progesterone data were missing for a woman in a particular cycle, then the data of the percentage of ovulatory cycles was calculated without the data of the woman in question (Table II). Using this criterion, the percentage of ovulatory cycles in the control group was close to 80% over the four cycles. It appears that there was some tendency in the three study groups to a higher frequency of ovulation in cycles 6 and 12, as compared to cycles 1 and 3 of the same groups. Also, it would seem that the frequency of ovulation in cycle 1 was higher in the control than in the study groups. However, these differences between the four groups were not statistically significant at any of the cycles ($p > 0.25$).

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Table I. Comparison of the menstrual patterns after different procedures of tubal occlusion and for a control group

<u>Characteristic</u>	<u>Group</u>	<u>Median</u>	<u>Interquartile range</u>	<u>Global P-value⁺</u>
Mean Segment Length (Days)	Laparoscopy-Yoon Ring	32.7	31.7 - 34.2	.022
	Minilaparotomy-Yoon Ring	35.0 ^(a)	33.9 - 35.6	
	Minilaparotomy-Pomeroy	33.4	31.6 - 35.9	
	Control Group	33.0	31.5 - 34.4	
Mean Length of Bleeding Episodes	Laparoscopy-Yoon Ring	3.3	3.2 - 3.9	.433
	Minilaparotomy-Yoon Ring	3.7	3.2 - 4.5	
	Minilaparotomy-Pomeroy	3.6	3.3 - 4.1	
	Control Group	3.6	3.3 - 4.4	
Longest Bleeding-Free Interval	Laparoscopy-Yoon Ring	37.0	31.5 - 42.0	.017
	Minilaparotomy-Yoon Ring	48.0 ^(a)	39.0 - 53.0	
	Minilaparotomy-Pomeroy	38.5	33.0 - 49.0	
	Control Group	35.0	32.0 - 46.0	
No. of Bleeding Episodes	Laparoscopy-Yoon Ring	14.0	12.0 - 14.0	
	Minilaparotomy-Yoon Ring	13.0	12.0 - 13.0	
	Minilaparotomy-Pomeroy	13.0	12.0 - 14.0	
	Control Group	13.0	13.0 - 14.0	
Total Days of Bleeding	Laparoscopy-Yoon Ring	45.5	40.0 - 52.0	
	Minilaparotomy-Yoon Ring	50.0	39.0 - 54.0	
	Minilaparotomy-Pomeroy	47.0	41.0 - 53.0	
	Control Group	48.0	43.0 - 53.0	
Total Days of Spotting	Laparoscopy-Yoon Ring	0	0 - 2.5	
	Minilaparotomy-Yoon Ring	0	0 - 3.0	
	Minilaparotomy-Pomeroy	0	0 - 3.0	
	Control Group	0	0 - 1.0	
Longest Bleeding Episode	Laparoscopy-Yoon Ring	5.0	4.0 - 6.0	
	Minilaparotomy-Yoon Ring	6.0	4.0 - 8.0	
	Minilaparotomy-Pomeroy	5.0	4.0 - 6.0	
	Control Group	5.0	4.0 - 6.0	

(a) Only this group showed a result statistically different from the other groups.

+ Kruskal-Wallis test global X^2 statistic.

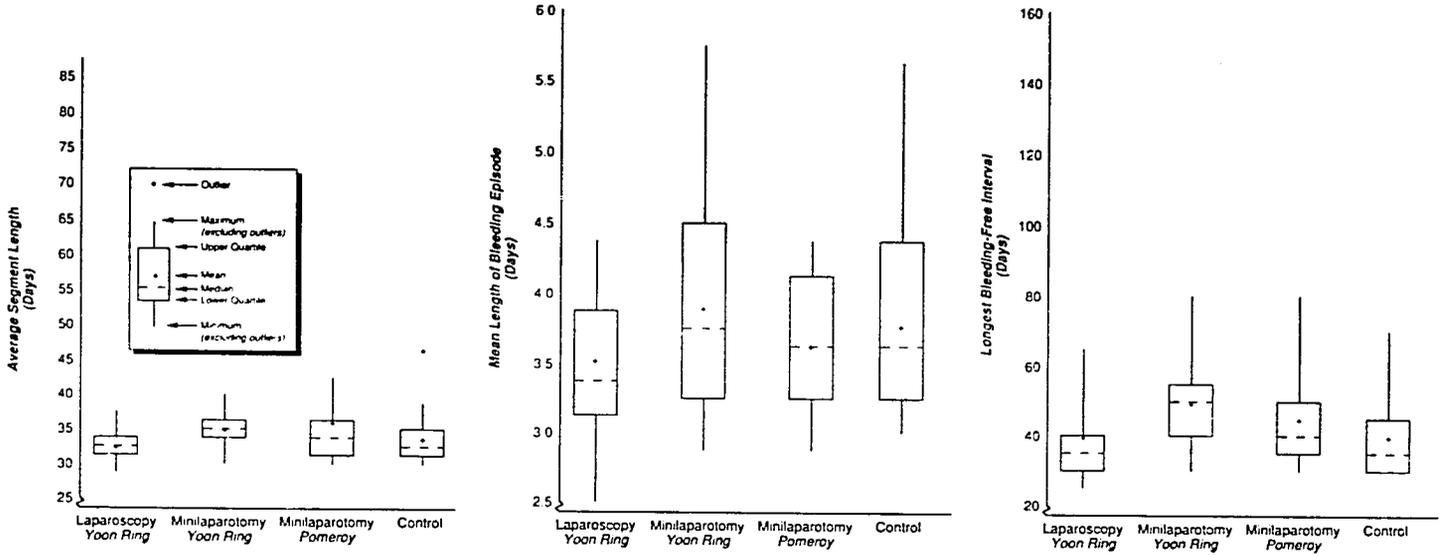


Figure 1. Average Segment Length, Mean Length of Bleeding Episode and Longest Bleeding-Free Interval in the Study and Control Groups.

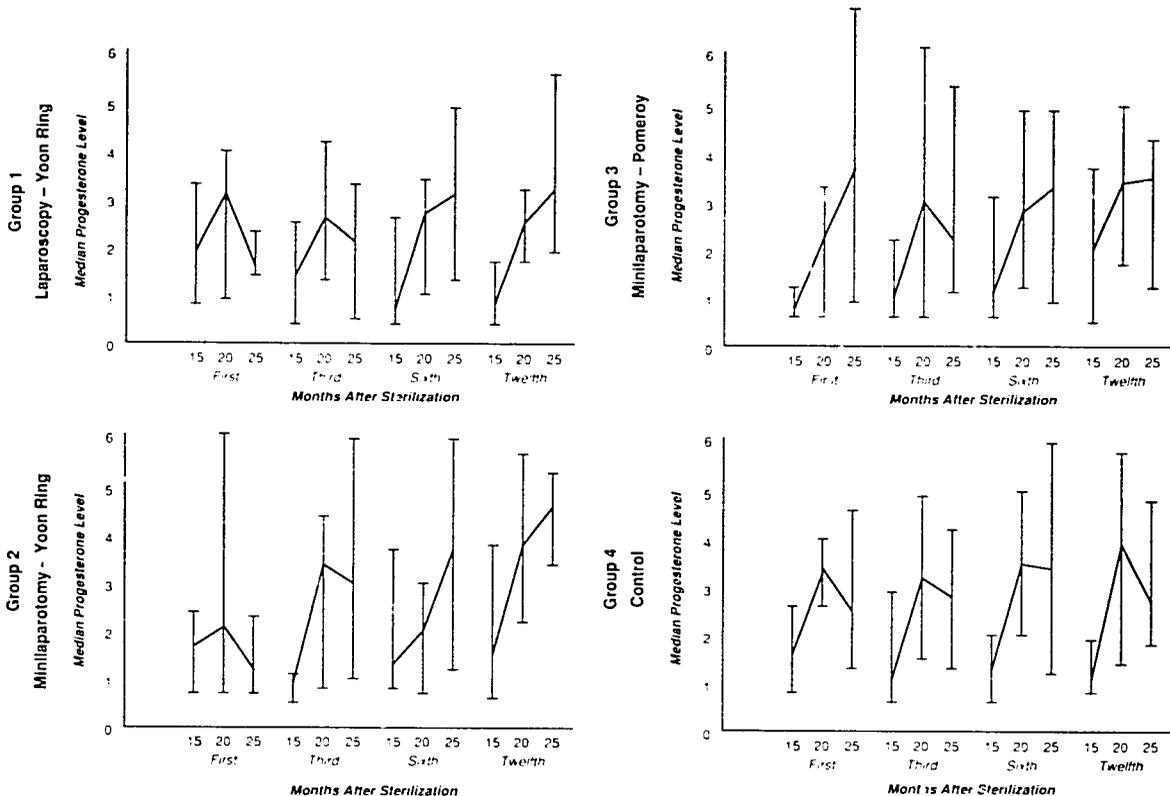


Figure 2. Serum progesterone levels (ng/ml, medians, first and third quartiles). Determinations conducted on days 15, 20 and 25 of the menstrual cycles initiated on the first, third, sixth and twelfth months after tubal ligation.

Table II: Percentage of ovulatory cycles in the three groups with tubal occlusion and the control group

<u>Group*</u>	<u>1</u>	<u>3</u>	<u>6</u>	<u>12</u>	<u>Total Average</u>
1	63%	63%	82%	71%	71%
2	57%	50%	71%	100%	70%
3	70%	56%	75%	86%	71%
4	78%	88%	76%	82%	81%

* Group 1 = Laparoscopy - Yoon Ring
 Group 2 = Minilaparotomy - Yoon Ring
 Group 3 = Minilaparotomy - Pomeroy
 Group 4 = Control Group

DISCUSSION

The occurrence of menstrual irregularities following sterilization by means of different procedures of tubal ligation has been reported. These irregularities may include shorter menstrual cycles, prolonged bleeding, increased or decreased menstrual blood loss and intermenstrual bleeding or spotting (5-9). It has been thought that effects on ovarian blood irrigation caused by the tubal ligation procedures may be the cause of the ovarian function problems. Also, it has been considered possible that some of the menstrual irregularities were already present and not observable due to use of oral contraceptives which was frequent before sterilization. The fact that, up to quite recently, most women were sterilized at relatively older ages, when ovarian problems associated with the approaching of the menopause might be expected, has also been considered as contributing to these findings (10, 11).

More recent studies that have controlled for these confounding factors have not found any significant changes in the menstrual patterns following sterilization (12-14). Another study with a prospective design of women serving as their own controls did not show any change in the menstrual characteristics one year after interval laparoscopic tubal sterilization with Silastic rings (15).

The results obtained in this study indicate that three different procedures of tubal occlusion, laparoscopy or minilaparotomy with the Yoon ring, and minilaparotomy with Pomeroy, do not affect the ovarian function assessed by the registry of the menstrual patterns and progesterone levels in the first year after the procedures.

The clinical importance of the two statistically significant differences noted for the parameters of mean segment length and

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longest bleeding-free interval is small. This can be seen in the schematic plots which compare the four groups.

In Figure 1 it can be seen that the median of the average segment length as well as the first and third quartile tend to be greater in Group 2 (minilaparotomy-Yoon ring) than in the other study groups. However, the values for the women with the maximum value, who are the most likely to notice disruption of their normal menstrual cycles, are very similar to the maximum values of the other study groups. The case with the longest bleeding-free interval is similar, as can be seen in Figure 1.

In addition, Group 2, sterilized via minilaparotomy-Yoon ring, had no serious problems of amenorrhea, one case of which occurred in the minilaparotomy-Pomeroy Group 3 (with a bleeding-free interval of 150 days). Neither did Group 2 have a participant who had consistently long bleeding segments, a case of which occurred in the control group (a case with 46.2 days for mean segment length).

The progesterone levels obtained on selected days of the menstrual cycle, and the percentage of ovulatory cycles, were similar in the three study groups and in the control group. The inclusion in the study of a control group of healthy subjects with a previous history of regular menstrual cycles contributes to the validity of our findings, as does the fact that the control and the study groups were admitted simultaneously to the study and were subjected to a prospective follow-up for a 12-month period, even though the control group could not be randomized.

In our prospective study design, previous to the surgical procedure, the subjects were informed of the purpose of the study and carefully instructed on the collection of menstrual data, and on the need of timely blood sampling. The domiciliary permanent contact was an important factor for the accurate collection of the menstrual data and the blood samples for progesterone determination. Many of the studies to assess the effects of tubal ligation on the menstrual patterns have been retrospective, and based on the subject's recollection of past menstrual events, or have not included a control group, studied concurrently with the study groups.

An improved study design would have been using the subjects in the study groups as their own control. However, we were unable to enroll subjects willing to wait for two or three months of pre-operative evaluation. We also tried to have a control group composed of women whose husbands had had a vasectomy or who were using a natural family planning method. However, we did not have access to such a kind of population. The control group consisted of medical students of the same university where the study was conducted. A result was that the control subjects were nulliparous and younger than the women of the study groups. Nevertheless, the control group may be considered representative of healthy young women of the study area, and can be used as a reference to compare the menstrual patterns and the ovarian function of the study subjects.

Also, in our study, instead of using subjective or non-numeric observations of the menstrual events, we analyzed the menstrual patterns by means of more precise indicators, which are also more reliable for statistical analysis. Some of the subjects in the study groups had been using oral contraceptives until the cycle prior to the sterilization, which did not result in any significant change in the bleeding patterns. However, it might have played a role in the reduced frequency of ovulation in the first cycle after the ligation procedure though, as previously stated, this difference was not statistically significant.

Alterations in the function of the corpus luteum in subjects following tubal ligation have been reported (12, 16, 17). On the other hand, no changes in progesterone secretion patterns, comparing values before and after sterilization, have been reported (18-20).

In our study, three progesterone determinations were performed in the anticipated luteal phase of the study cycles; these dates were selected prospectively at the beginning of the cycle. When the progesterone values obtained at different cycles, after different procedures of tubal ligation and in the control group, were compared to each other, either within the same group or between the study and the control groups, no marked medically important differences were observed. There was tendency, though not a statistically significant one, to have a higher frequency of anovulatory cycles in the first three cycles after tubal occlusion, as compared to the controls. This effect is more likely to be due to hypothalamic functional alterations associated with the sterilization procedure than to a direct effect on the ovaries.

In general, our results did not show any medically or clinically important effects of tubal occlusion procedures by means of the Yoon ring after laparoscopy or minilaparotomy, or by minilaparotomy and Pomeroy on the menstrual patterns or on progesterone secretion, during the first year after these procedures.

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