# CONTRACEPTION WITH LONG ACTING SUBDERMAL IMPLANTS: II. MEASURED AND PERCEIVED EFFECTS IN INTERNATIONAL CLINICAL TRIALS

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ABSTRACT

Hemoglobin levels, blood pressure, body weight and the subjects' impressions of changes in various conditions have been recorded during a multicentered study of levonorgestrel and norgestrienone subdermal implants. Data from a group of women using the Copper T 200 IUD at the same clinics and admitted under the same criteria are presented for comparative purposes.

A major reason for termination of use of the levonorgestrel implants was disturbance of menstrual patterns. When all subjects reported their experience with the two steroid regimens, substantially larger proportions of subjects using levonorgestrel implants noted changes in menstrual flow, duration of menses and intermenstrual bleeding and spotting than was the case of women contracepting with norgestrienone implants. Relative to the experience with implants, more users of the Copper T 200 in a control study reported increased dysmenorrhea, and an increase in the amount and duration of menstrual flow.

Despite the reported increases in menstrual flow and duration of bleeding, women using subdermal implants of either contraceptive steroid, levonorgestrel and norgestrienone, showed an increase in blood hemoglobin values during the course of one year of use. In the control group using the TCu 200 IUD, no change in mean hemoglobin levels was found. Neither mean systolic nor diastolic blood pressure of the women using steroids was affected. There was a small net increase in weight among the users of steroids, but none in the Copper T controls.

An increase in acne and other skin conditions was perceived by the same percentages of women using Copper IUDs as women using the steroids. A greater proportion of IUD acceptors noted increased nervousness and depression than was felt by the women contracepting with the steroid implants.

INTRODUCTION

On the basis of results from probing studies (1, 2) a double blind study of two progestin-only implants was undertaken in six countries. A report concerning the effectiveness and continuation rates with these two steroids, levonorgestrel (Ng) and norgestrienone (R2010), has been made elsewhere (3). This report showed the levonorgestrel implants to be highly effective (gross 12-month pregnancy rate = 0.6 per 100) and indicated both types of implants had continuation of the order of 75 to 80 per 100 per year. The present report focuses on the results of physical measurements and of questioning of subjects in the double blind study with regard to selected potential side effects of the regimens. Singled out for study were perceptions of menstrual changes, changes in hemoglobin levels, weight and blood pressure.

## MATERIALS AND METHODS

Participating investigators in Brazil, Chile, the Dominican Republic, Jamaica and Scandinavia enrolled 990 women in a study of subdermal implants, with one-fifth of the subjects in each area. Numbered packages containing sets of 6 capsules were sent to the investigators who placed the capsules subdermally. The identity of the steroid in individual sets was not known by the investigator or by the subject. 492 subjects received levonorgestrel (Ng) and 498 received norgestrienone (R2010) implants.

Participants were of generally good health, aged 18-35, and had no medical contra-indications to the use of steroids. A full description of the admission criteria is found elsewhere (3).

Visits to the participating clinics were scheduled at the end of months 1, 3, 6, 9 and 12. General physical and gynecological examinations were performed at these visits and weight and blood pressure measured. Hemoglobin was measured at the admission and the 6- and 12-month visits.

At the end of the year or at termination of use, if earlier, subjects were asked to report on whether selected menstrual events and other conditions had increased, remained the same or decreased since admission to the study.

During the course of the investigation, for comparative purposes, a group of 100 acceptors of the Copper T 200 IUD (TCu) were enrolled at each center except Jamaica. Criteria for enrollment were the same as those used in the implant study, and the schedule of visits, examinations and measurements were identical.

The cut off date for measurements and analysis in this study was January 31, 1978. Because the copper T investigation began somewhat later than the implant investigation, there are relatively fewer measurements at the end of the year for the IUD.

Classical 't' and 'F' tests for independent and correlated data have been used to test for statistical significance.

## RESULTS

The two implant regimens and the TCu device had similar continuation rates at the end of 12 months, 74.6 per 100 for levonorgestrel, 79.4 for R2010, and 81.1 for the TCu 200.

Approximately half of the terminations from the levonorgestrel regimen were attributed to menstrual disturbances. No major single reason for termination of norgestrienone (R2010) implants emerged, but a 3.5 per 100 net (multiple decrement) one year pregnancy rate was significantly above the rates observed for the other two regimens. "Other medical" reasons were the principal reason for termination among women using the Copper T IUD, and abdominal pain was the chief component of "other medical terminations".

Decisions to terminate use in the first year because of disturbed menstrual patterns were primarily made by the subjects, not by the physicians (Table I). The table further indicates that for users of implants about half of the decisions concerning removals for "other medical reasons" were also made by the women themselves; removals of implants because of problems at the site of the implant were primarily the physician's decision. For the IUD, decisions to terminate for other medical reasons were primarily those of the women, not of the physician.

TABLE I

Percentage and Number of Terminations for Method Related Reasons Made by Physicians and by Subjects

| Reason for Termination & Regimen | Decision by Physician (Percentage) | Decision by Subject (Percentage) | No. of Terminations |
|---|---|---|---|
| Menstrual Problem | | | |
| Levonorgestrel | 12 | 88 | 60 |
| R2010 | 14 | 86 | 21 |
| TCu 200 | 14 | 86 | 14 |
| Infection & Other Medical | | | |
| Levonorgestrel | 50 | 50 | 20 |
| R2010 | 55 | 45 | 31 |
| TCu 200 | 21 | 79 | 29 |
| Other Method Related | | | |
| Levonorgestrel | 0 | 100 | 3 |
| R2010 | 0 | 100 | 6 |
| TCu 200 | 0 | 100 | 5 |

While terminations for method related reasons are the salient indicators of side effects, side effects in an experimental study may not be adequately measured by terminations in the first year. In this study, subjects were told at the outset that the planned duration of the study was one year. Accordingly cooperative or obliging subjects might postpone terminations for relatively minor reasons until released from the study at the end of the year. Be that as it may, terminations of use for specified medical reasons do not measure the pervasiveness of effects which are irritating or annoying or of potential importance, but which do not appear to be sufficiently serious to either subject or physician to warrant discontinuation. To assess the full extent of menstrual problems, headaches and other potential effects of the implant regimens, all subjects were asked to indicate at the end of the year or at termination whether selected events or conditions had increased, decreased or remained unaltered during the course of use.

Menstrual Changes

Forty percent or more of the users of norgestrel implants noted increased intermenstrual bleeding and spotting and an increase in the number of menstrual bleeding days (Table II). These percentages are significantly* greater than the 25-26 percent of women with R2010 implants reporting increases in these two categories.

Cycle length was perceived to have decreased for 26 percent of the norgestrel subjects and menstrual flow increased for the same percentage. Significantly smaller percentages of the women using R2010 implants reported these two phenomena.

The above indicators of increased menstrual bleeding appear to underlie the 12.3 per hundred one year termination rate among levonorgestrel acceptors attributable to menstrual problems (3) and the much lower 4.3 percent termination rate for menstrual problems among R2010 acceptors.

Decreased volume of menstrual flow was noted by about one-quarter of the implant users (Table II), and increased cycle length by 18-19 percent of users of either regimen. One-sixth or one-seventh of the acceptors, depending on the implant regimen, reported a decrease in the number of menstrual bleeding days. Decreased menstrual bleeding in users of both steroids has been reported by Faundes et al.(4) who noted that amenorrhea of 60 or more days was a common phenomenon in this study. Nevertheless only one percent of the acceptors of either implant terminated because of amenorrhea.

* In the text, a statement of statistical significance implies a probability of less than $<.05$.

TABLE II

Percentages Reporting Perceived Changes in Menstrual Events From Admission to Termination or to the End of One Year

| | | Perceived Change | | | | All |
|---|---|---|---|---|---|---|
| | | Increase | Decrease | None | Irregular | Perceptions |
| Dysmenorrhea | - Ng | 12 | 10 | 78 | - | 100 |
| | R2010 | 8 | 9 | 83 | - | 100 |
| | TCu | 30 | 8 | 62 | - | 100 |
| Menstrual Flow | - Ng | 26 | 23 | 51 | - | 100 |
| | R2010 | 15 | 25 | 60 | 1 | 100 |
| | TCu | 40 | 8 | 51 | - | 100 |
| Bleeding Days | - Ng | 44 | 14 | 42 | 1 | 100 |
| | R2010 | 25 | 17 | 57 | 1 | 100 |
| | TCu | 41 | 8 | 50 | 1 | 100 |
| Cycle Length | - Ng | 18 | 26 | 53 | 3 | 100 |
| | R2010 | 19 | 18 | 62 | 1 | 100 |
| | TCu | 7 | 24 | 65 | 5 | 100 |
| Intermenstrual Bleeding and Spotting | - Ng | 41 | 2 | 56 | - | 100 |
| | R2010 | 26 | 2 | 72 | - | 100 |
| | TCu | 23 | 1 | 76 | - | 100 |

Number of Subjects - Ng 480
R2010 480
TCu 286

Users of the Copper T IUD had notably different perceptions of changes in menstrual events. Forty percent of the women responded by saying that menstrual flow had increased. This was statistically a significantly greater proportion than found in users of implants (Table II). Moreover for both implant regimens, reports of decreased menstrual flow were equal to (for norgestrel) or greater in number than (R2010) reports of increased flow. This was not the case for users of the TCu 200 IUD. Only 8 percent of the women reported a decrease in flow while using the Copper T. Similar proportions of women contracepting with the Copper T 200 and norgestrel experienced a prolongation of menstrual bleeding days (41 and 44 percent, respectively). Cycle length was perceptibly shortened for about one-fourth of the IUD subjects, but unlike the experience with norgestrel or R2010 implants only 7 percent of the IUD subjects noted increased cycle length.

Four out of five users of the implants did not note any important effects of implants on dysmenorrhea; reports of symptomatic change were balanced between increases and decreases. On the other hand only 62 percent of the users of the IUD reported no change in the frequency or severity of symptoms of dysmenorrhea. About 30 percent stated dysmenorrhea increased and only 8 percent noted decreased dysmenorrhea. While only 1 acceptor of the Copper T terminated use because of 'dysmenorrhea (the physician's coding), the numerous terminations for abdominal pain (18 - a net rate 4.7 per 100 at one year) may be reflected in these reports of dysmenorrhea.

Hemoglobin

For both the norgestrel implant regimen and the TCu 200, the above reports of changes in bleeding events led to concern that increased bleeding may produce anemia. The evidence of hemoglobin readings taken during the course of the study indicates that, to the contrary, both steroids appear to be associated with an increase in hemoglobin levels among the users. Acceptors of the Copper T maintained the same levels of hemoglobin following use, a result previously reported in Sweden by Liedholm et al, (5). As shown in Table III women using norgestrel implants had an average hemoglobin level of 12.9 grams per 100 ml at admission to the study while women using the implants for a year had an average level of 13.5 gms per 100 ml. A somewhat larger increase is seen in Table III for users of R2010, where the indicated change is from a mean of 12.9 at admission to a mean of 13.7 gms per 100 ml at the end of the first year. With a standard deviation of 1.4 gms per ml, the changes observed during the course of the study are highly significant ($P < .001$), to the extent that they represent an unselected group. The question remained however as to whether the observed average increase was a result of early discontinuation by women with menstrual problems.

Table IV shows that early discontinuation among implant users was not associated with decreased hemoglobin levels. For both norgestrel and R2010 implant subjects, the number of women with increased readings effectively balanced the number with decrease in months 2-4. In months 5-8 as well as in months 9-13, increases in hemoglobin were more numerous than decreases. Over all the months after admission the total number of women with increases was significantly greater than the number with decreases for both regimens ($P < .001$). The generality of these findings is indicated in Table III where the end of year readings for both implants are higher than the admission readings in all countries with the exception of the norgestrel implants in Scandinavia.

For the women using the Copper T, neither Table III nor IV shows a consistent pattern of increases or decreases in hemoglobin values. As only 3.8 percent of the Copper T acceptors terminated use because of menstrual problems, the negligible net effect of the IUD on hemoglobin levels is not surprising. The fact that there was a concomitant rise in hemoglobin levels in the implant-using groups is therefore likely to be related to the experience of oligomenorrhea and amenorrhea by many of the implant subjects.

Blood Pressure Readings

Routine monitoring of systolic and diastolic blood pressure was performed at each scheduled visit. Tables V and VI, summarizing this information for systolic readings do not point to distinct trends in these measurements for either implant regimen. For both steroids the initial systolic readings averaged 114 mm of mercury and the one year values averaged 115 mm (Table V). Increases as well as decreases in the average systolic readings, were noted in different countries. The number of women with increased systolic readings (Table VI) was not significantly greater than the number with decreased readings for either steroid regimen.

Diastolic readings averaged 71 mm of mercury at the beginning and at the end of the year for acceptors of either type of implants (Tables VII & VIII). The number of decreases in diastolic readings somewhat, but not significantly, exceeded the number of women with increased readings.

During the course of the study one woman with levonorgestrel and two with R2010 capsules terminated use following marked and repeated elevations in blood pressure. Among Copper T acceptors the number with decreased readings significantly exceeded those with increased readings.

Weight Changes

Women using implants for one year experienced an average increase of 1.1 - 1.4 kilograms in weight. Copper T acceptors on the other hand did not experience a change in average weight (Tables IX & X). For both implant regimens the proportions of women experiencing increases in weight was similar, about 51-52 percent, and significantly greater than the percentage of women experiencing decrease (32-35 percent). Among IUD users there was a fine balance between measured increases and decreases in weight, 40 percent of acceptors put on weight and 41 percent lost weight.

Other Side Effects

At the end of the first year of use or at termination, if earlier, subjects in the study and in the control group of Copper T users were asked about selected symptoms that are associated with the use of steroid contraception. Results are displayed in Table XI.

Copper T acceptors reported increases in acne in the same proportion, 15-16 percent, as the implant users; and other skin problems were noted by similar proportions of users of implants and of the IUD.

Copper T acceptors also reported an increase in headaches in the same proportions (12-15 percent) as that noted by users of implants. However, reports of increased nervousness and depression were significantly greater among Copper T acceptors than for the implant acceptors.

TABLE III

Admission and One Year Mean Hemoglobin Values
by Regimen

(Grams per 100 ml)

| | Admission | | | Months 12-13 | | |
|---|---|---|---|---|---|---|
| | Ng | R2010 | TCu 200 | Ng | R2010 | TCu 200 |
| | Mean Values | | | | | |
| Total | 12.9 | 12.9 | 13.1 | 13.5 | 13.7 | 13.2 |
| Brazil | 12.5 | 12.9 | 13.1 | 13.6 | 13.8 | 13.4 |
| Chile | 13.2 | 13.2 | 13.3 | 13.4 | 13.6 | 13.3 |
| Dominican Republic | 12.6 | 12.6 | 12.4 | 13.4 | 13.8 | 12.8 |
| Jamaica | 12.3 | 12.2 | - | 13.4 | 13.4 | - |
| Scandinavia | 13.9 | 13.6 | 13.4 | 13.8 | 13.8 | 13.1 |
| N (Total) | 468 | 464 | 376 | 286 | 307 | 204 |
| | Standard Errors of Values | | | | | |
| Total | .07 | .06 | .06 | .07 | .07 | .10 |
| Brazil | .16 | .15 | .12 | .15 | .12 | .15 |
| Chile | .13 | .11 | .11 | .13 | .11 | .16 |
| Dominican Republic | .14 | .16 | .16 | .21 | .19 | .27 |
| Jamaica | .14 | .13 | - | .17 | .25 | - |
| Scandinavia | .10 | .09 | .11 | .15 | .13 | .14 |

TABLE IV

Number of Subjects with Changes in Hemoglobin Values from Initial Observation by Regimen and Time of Last Observation

| Changes from Initial Observation | Levonorgestrel Month of Last Observation | | | | R2010 Month of Last Observation | | | | TCu 200 Month of Last Observation | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2-4 | 5-8 | 9-13 | All | 2-4 | 5-8 | 9-13 | All | 2-4 | 5-8 | 9-13 | All |
| Increase | 4 | 28 | 160 | 192 | 3 | 30 | 167 | 200 | 3 | 33 | 77 | 113 |
| No Change | 10 | 20 | 91 | 121 | 3 | 24 | 90 | 117 | 1 | 26 | 76 | 103 |
| Decrease | 6 | 18 | 60 | 84 | 3 | 9 | 61 | 73 | 3 | 39 | 64 | 106 |
| Net No. of Changes | -2 | +10 | +100 | +108 | 0 | +21 | +106 | +127 | 0 | -6 | +13 | +7 |
| Ave. First Reading | 13.6 | 13.4 | 12.8 | 12.9 | 13.2 | 12.9 | 13.0 | 12.9 | 12.9 | 13.3 | 13.2 | 13.1 |
| Ave. Last Reading | 13.4 | 13.5 | 13.5 | 13.5 | 13.2 | 13.5 | 13.7 | 13.7 | 12.9 | 13.3 | 13.1 | 13.2 |
| | N = 397 | | | | N = 390 | | | | N = 322 | | | |
| Probability (Increase=Decrease) | P < .001 | | | | P < .001 | | | | P = .64 | | | |

Hemoglobin readings in gm/100 ml

TABLE V

Mean Systolic Blood Pressure (mm.Hg)
at Admission and One Year
by Regimen and Center
with Standard Errors

Mean Values

| | Admission | | | One Year | | |
|---|---|---|---|---|---|---|
| | Ng | R2010 | TCu 200 | Ng | R2010 | TCu 200 |
| All Centers | 114 | 114 | 116 | 115 | 115 | 115 |
| Brazil | 112 | 112 | 115 | 113 | 110 | 108 |
| Chile | 112 | 113 | 114 | 116 | 116 | 118 |
| Dominican Republic | 110 | 111 | 113 | 113 | 113 | 112 |
| Jamaica | 111 | 109 | - | 108 | 109 | - |
| Scandinavia | 123 | 124 | 125 | 122 | 122 | 122 |
| Percent $<$ 100 mm | 4.1 | 4.2 | 4.0 | 4.0 | 4.6 | 0.9 |
| Percent $\geq$ 130 mm | 12.6 | 14.1 | 15.4 | 8.7 | 12.4 | 9.9 |
| Number of Subjects | 492 | 497 | 402 | 322 | 348 | 232 |

Standard Errors

| | | | | | | |
|---|---|---|---|---|---|---|
| All Centers | 0.5 | 0.6 | 0.6 | 0.6 | 0.6 | 0.7 |
| Brazil | 1.1 | 1.1 | 1.2 | 1.3 | 1.7 | 1.9 |
| Chile | 1.0 | 0.9 | 1.0 | 0.9 | 0.8 | 0.6 |
| Dominican Republic | 1.3 | 1.4 | 1.3 | 1.6 | 1.4 | 1.3 |
| Jamaica | 1.0 | 1.0 | - | 1.7 | 1.7 | - |
| Scandinavia | 1.3 | 1.4 | 1.2 | 1.7 | 1.5 | 1.5 |

TABLE VI

Number of Subjects with Changes in Systolic Blood Pressure from Admission by Regimen and Time of Last Observation

| Type of Change & Average Value | Month of Final Observation 2-4 | 5-8 | 9-13 | All Months |
|---|---|---|---|---|
| **Norgestrel Capsules** | | | | |
| Increases | 14 | 17 | 143 | 174 |
| No Change | 22 | 12 | 124 | 158 |
| Decreases | 14 | 16 | 124 | 154 |
| Net Number of Changes | 0 | +1 | +19 | +20 |
| Average First Reading (mm Hg) | 115 | 114 | 113 | 114 |
| Average Final Reading (mm Hg) | 116 | 114 | 114 | 114 |
| Probability (Increase = Decrease) | | P = .27 | | |
| **R2010 Capsules** | | | | |
| Increases | 9 | 20 | 135 | 164 |
| No Change | 13 | 18 | 137 | 168 |
| Decreases | 10 | 9 | 132 | 151 |
| Net Number of Changes | -1 | +11 | +3 | +13 |
| Average First Reading (mm Hg) | 112 | 111 | 114 | 114 |
| Average Final Reading (mm Hg) | 112 | 117 | 114 | 114 |
| Probability (Increase = Decrease) | | P = .47 | | |
| **TCu 200 IUD** | | | | |
| Increases | 9 | 14 | 93 | 116 |
| No Change | 8 | 17 | 109 | 134 |
| Decreases | 15 | 16 | 105 | 136 |
| Net Number of Changes | -6 | -2 | -12 | -20 |
| Average First Reading (mm Hg) | 117 | 115 | 116 | 116 |
| Average Final Reading (mm Hg) | 113 | 114 | 115 | 114 |
| Probability (Increase = Decrease) | | P = .21 | | |

TABLE VII

Mean Diastolic Blood Pressure (mm.Hg)
at Admission and at One Year
by Regimen and Center

Mean Values

| | Admission | | | One Year | | |
|---|---|---|---|---|---|---|
| Center | Ng | R2010 | TCu 200 | Ng | R2010 | TCu 200 |
| All | 71 | 71 | 71 | 71 | 71 | 70 |
| Brazil | 71 | 72 | 73 | 71 | 70 | 71 |
| Chile | 69 | 70 | 71 | 71 | 72 | 72 |
| Dominican Republic | 65 | 65 | 65 | 63 | 61 | 60 |
| Jamaica | 71 | 70 | - | 69 | 71 | - |
| Scandinavia | 79 | 77 | 76 | 78 | 79 | 77 |
| Percent $<$60 mm | 2.8 | 3.6 | 6.5 | 4.0 | 4.9 | 4.7 |
| Percent $\geq$90 mm | 5.3 | 5.0 | 6.5 | 6.5 | 6.3 | 3.9 |
| N | 492 | 497 | 402 | 322 | 348 | 232 |

Standard Errors

| | | | | | | |
|---|---|---|---|---|---|---|
| All Centers | 0.4 | 0.4 | 0.5 | 0.5 | 0.5 | 0.6 |
| Brazil | 0.8 | 0.8 | 1.0 | 1.1 | 1.1 | 1.1 |
| Chile | 0.9 | 0.8 | 1.0 | 0.8 | 0.9 | 0.9 |
| Dominican Rep. | 1.0 | 1.0 | 1.1 | 1.3 | 1.0 | 0.8 |
| Jamaica | 0.8 | 0.8 | - | 1.3 | 1.4 | - |
| Scandinavia | 0.9 | 1.0 | 0.8 | 1.2 | 1.1 | 1.2 |

TABLE VIII

Number of Subjects with Changes in Diastolic Blood Pressure from Admission by Regimen and Time of Last Measurement

| Type of Change and Average Value | Month of Last Measurement 2-4 | 5-8 | 9-13 | All Months |
|---|---|---|---|---|
| | | Norgestrel Capsules | | |
| Increase | 13 | 14 | 123 | 150 |
| No Change | 22 | 17 | 126 | 165 |
| Decrease | 15 | 14 | 142 | 171 |
| Net No. of Changes | -2 | 0 | -19 | -21 |
| Average First Reading (mm Hg) | 73 | 71 | 71 | 71 |
| Average Last Reading (mm Hg) | 72 | 71 | 70 | 71 |
| Probability (Increase = Decrease) | | P = .24 | | |
| | | R2010 Capsules | | |
| Increase | 14 | 23 | 115 | 152 |
| No Change | 12 | 16 | 142 | 170 |
| Decrease | 6 | 8 | 147 | 161 |
| Net No. of Changes | +8 | +15 | -32 | -9 |
| Average First Reading (mm Hg) | 68 | 68 | 71 | 71 |
| Average Final Reading (mm Hg) | 69 | 73 | 70 | 71 |
| Probability (Increase=Decrease) | | P = .61 | | |
| | | TCu 200 IUD | | |
| Increase | 11 | 10 | 77 | 98 |
| No Change | 9 | 19 | 118 | 146 |
| Decrease | 12 | 18 | 112 | 142 |
| Net No. of Changes | -1 | -8 | -35 | -44 |
| Average First Reading (mm Hg) | 69 | 71 | 72 | 71 |
| Average Last Reading (mm Hg) | 68 | 69 | 70 | 70 |
| Probability (Increase = Decrease) | | P = .004 | | |

TABLE IX

Average Weight in Kilograms
at Admission & at One Year
by Regimen and Center

| | Admission | | | One Year | | |
|---|---|---|---|---|---|---|
| | Ng | R2010 | TCU 200 | Ng | R2010 | TCu 200 |
| All Centers | 56.8 | 56.2 | 54.9 | 58.2 | 57.3 | 55.3 |
| Brazil | 55.4 | 54.3 | 54.6 | 55.4 | 55.9 | 54.6 |
| Chile | 56.1 | 56.6 | 53.8 | 58.6 | 58.6 | 54.5 |
| Dominican Rep. | 51.0 | 51.9 | 51.5 | 51.8 | 53.9 | 51.9 |
| Jamaica | 60.8 | 59.4 | - | 63.6 | 59.6 | - |
| Scandinavia | 61.1 | 59.1 | 60.0 | 62.1 | 58.7 | 60.5 |
| No. of Subjects weighed | 485 | 491 | 401 | 331 | 350 | 232 |
| Standard Errors of Average Weights (kgs) | | | | | | |
| All Centers | 0.4 | 0.4 | 0.4 | 0.5 | 0.5 | 0.5 |
| Brazil | 0.9 | 0.9 | 0.9 | 1.1 | 1.2 | 1.2 |
| Chile | 0.8 | 0.9 | 0.8 | 1.1 | 1.1 | 0.9 |
| Dominican Rep. | 0.7 | 0.9 | 0.8 | 1.3 | 1.2 | 1.3 |
| Jamaica | 1.0 | 1.1 | - | 1.6 | 1.7 | - |
| Scandinavia | 0.9 | 0.8 | 0.8 | 1.1 | 0.9 | 1.0 |

TABLE X

Regimen Effects on Weight
Number of Changes in Weight by Duration of Use
by Regimen

| Regimen | Weight Change | Month of Last Observation 2-4 | 5-8 | 9-13 | All |
|---|---|---|---|---|---|
| Levonorgestrel | Increase | 22 | 22 | 207 | 251 |
| | No Change | 12 | 3 | 45 | 60 |
| | Decrease | 16 | 18 | 133 | 167 |
| | Net No. of Changes | +6 | +4 | +74 | +84 |
| | Mean Wt. at Admission (kgs) | 56.5 | 56.8 | 56.8 | 56.8 |
| | Mean Wt. at Last Obs (kgs) | 58.0 | 56.7 | 57.9 | 57.8 |
| | Probability (Increase=Decrease) | | P | $< .01$ | |
| R2010 | Increase | 15 | 20 | 209 | 244 |
| | No Change | 10 | 11 | 59 | 80 |
| | Decrease | 7 | 13 | 134 | 154 |
| | Net No. of Changes | +8 | +7 | +75 | +90 |
| | Mean Weight at Admission (kgs) | 54.9 | 57.4 | 56.2 | 56.2 |
| | Mean Weight at Last Obs (kgs) | 55.2 | 58.1 | 57.1 | 57.1 |
| | Probability (Increase=Decrease) | | P | $< .01$ | |
| TCu 200 | Increase | 7 | 13 | 134 | 154 |
| | No Change | 12 | 11 | 51 | 74 |
| | Decrease | 13 | 24 | 121 | 158 |
| | Net No. of Changes | -6 | -11 | +13 | -4 |
| | Mean Weight at Admission (kgs) | 51.9 | 54.1 | 55.4 | 54.9 |
| | Mean Weight at Last Obs (kgs) | 51.2 | 53.5 | 55.5 | 55.2 |
| | Probability (Increase=Decrease) | | P = .82 | | |

TABLE XI

Percentage of Subjects Reporting Perceived Changes
in Selected Conditions
From Admission to Termination or to End of One Year

| Condition | | Increase | Decrease | No Change | |
|---|---|---|---|---|---|
| Headache | Ng | 15 | 10 | 75 | 100 |
| | R2010 | 13 | 9 | 78 | 100 |
| | TCu | 12 | 12 | 76 | 100 |
| Nervousness | Ng | 18 | 5 | 77 | 100 |
| | R2010 | 17 | 5 | 79 | 100 |
| | TCu | 27 | 6 | 67 | 100 |
| Depression | Ng | 12 | 3 | 85 | 100 |
| | R2010 | 9 | 2 | 89 | 100 |
| | TCu | 17 | 4 | 79 | 100 |
| Acne | Ng | 15 | 3 | 82 | 100 |
| | R2010 | 15 | 2 | 82 | 100 |
| | TCu | 16 | 5 | 79 | 100 |
| Other Skin Problems | Ng | 7 | 1 | 93 | 100 |
| | R2010 | 9 | 1 | 90 | 100 |
| | TCu | 5 | 1 | 94 | 100 |

Number of Subjects - Ng = 480
R2010 = 480
TCu = 286

DISCUSSION

The planning of the double-blind multi-centered implant study provided the opportunity for assessment of a number of direct- and side-effects of two progestins and an IUD in an unbiased, or at least equally biased, manner.

Since a major objective of the study was to assess the possible utility of an implant method of contraception in developing countries where poor nutrition and anemia may be expected, the fact that hemoglobin levels actually increased even with the levonorgestrel regimen is an important positive finding. The stability of the hemoglobin level among women using the Copper T 200 was previously noted in Sweden (5). The scope of this finding has been extended by the present study to developing countries.

In view of the reports that practically all women who take estrogen-containing oral contraceptives have a rise in blood pressure (6), it is reassuring that no significant changes were found in either systolic or diastolic blood pressure with use of either implant regimen.

The slight increase in weight during use of implants may also be considered a beneficial, albeit minor, effect.

Perceptions that the user has of a contraceptive method is obviously important to the acceptibility and continued use of that method.

It was of interest to find that the side effects commonly reported or warned about during use of contraceptive steroids were perceived by users of the IUD as having occurred with at least equal frequency as by users of the implants.

Increases in the incidence of headache and acne particularly have been thought to be associated with use of contraceptive steroids but in this study the same percentage of users of the IUD perceived increases in these events as did users of the implants.

Also, the IUD users reported increased nervousness at substantially higher rate than implant users. This appears to be in accord with findings from the Oxford group (7) which showed little variation between steroid (pill) and IUD users in the incidence of symptoms and ill defined conditions, and a difference of 2.4 per 1000 in the hospital referral rates for skin conditions.

We conclude that there are neither medical nor perceptual contra-indications for expanded trials of implant regimens.

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