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FERTILITY REGULATION IN NURSING WOMEN. VI. Contraceptive Effectiveness of a Subdermal Progesterone Implant

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ABSTRACT

Six progesterone pellets implanted subdermally were tested as contraceptive method for lactating women. One pregnancy was diagnosed in 1614 woman-months of observation, a failure rate which was similar to that observed in a contemporary group of Copper T users. Nineteen pregnancies were diagnosed in the 677 woman-months observed in untreated lactating women. The progesterone implants were effective when administered either at 30, 60 or 240 days after delivery. The duration of the effective life was 5 months and fertility was quickly restored afterwards. There were no deleterious effects upon maternal or infant health or upon lactation and the rate of child growth. The main problem encountered was the occurrence of pellet expulsion at a variable rate which appeared related to the manufacturing procedure.

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INTRODUCTION

The inhibition of fertility associated with breastfeeding is highly variable among individuals and tends to decrease as time elapses following delivery. This fact determines the need for contraceptives that can be used during lactation without interfering with milk production or child health (1, 2, 3).

In previous publications (4, 5) we discussed the potential advantages of using the natural hormone, progesterone, as a contraceptive during breastfeeding and the preliminary results obtained with a subdermal implant of six progesterone pellets were reported. This paper gives an updated account of the contraceptive effectiveness of progesterone administered by this means and discusses the observed advantages of such a method.

MATERIAL AND METHODS

Population: Volunteers enrolled in the study were selected from among healthy postpartum women who met the following requirements: ages 18 to 35, parity 1 to 3, normal pregnancy and vaginal term delivery of a healthy infant with a birth weight adequate to the gestational age. They had to be regularly cohabiting, free from drug therapy and willing to nurse their infants as long as possible.

Selection was done at the maternity ward where instructions on the technique of breastfeeding on demand were given. Additional requirements at the time of initiating treatment were normal postpartum evolution, normal physical examination of mother and child, hemoglobin values higher than 10 g% and a normal nutritional state. All cases were required to be in exclusive breastfeeding with an adequate infant growth rate before admission.

Treatments: Progesterone was administered by subdermal insertion of six progesterone pellets. Contemporary control groups were formed by women treated with an IUD or a placebo injection. The allocation to an injectable method or an IUD was at patient choice.

- Progesterone pellets: Pellets were made by compressing 100 mg of the steroid into a cylinder of approximately 11.8 mm length by 3.2 mm diameter. Three different batches (I, II and III) were manufactured using different techniques. Compression was applied along the longitudinal axis in batches II and III and perpendicular to it in batch I. The progesterone used was powdered in batches I and II and precompressed in batch III. Each subject received 6 progesterone pellets that were inserted subdermally in the gluteal region through a No. 9 gauge trocar under local anesthesia. Insertion of pellets was done at day 30 or 60 after delivery. Pellets were expected to have an effective life of 5 or 6 months. Accordingly, women who were treated at day 60 were offered a second set of pellets at approximately day 240 postpartum provided they were still nursing their babies.

- Intrauterine device: The IUD used in this study was the Copper T 200 (supplied by the Asociación Chilena de Protección de la Familia). It was inserted at day 30 or 60 postpartum to match the contemporary groups using progesterone pellets.

- Placebo: The placebo consisted of an injection of 3 ml of distilled water, offered as a test treatment to sustain lactation and therefore to support the fertility inhibition associated with breastfeeding. Women enrolled in this group were offered non-hormonal contraceptives at the 6th postpartum month or earlier if supplementary bottle feeding was introduced. The placebo was administered at day 30 postpartum. This group was discontinued when it became evident that full nursing alone or partial nursing supplemented with barrier methods provided poor protection (6).

Follow-up: Follow-up was designed to determine the occurrence of pregnancy, breastfeeding performance, infant growth, side effects and bleeding pattern. Visits were scheduled at monthly intervals up to the sixth postpartum month and at two-month intervals thereafter. At each visit, the maternal and infant histories were recorded and both mother and child were examined. Breastfeeding performance and infant growth were carefully evaluated using the Boston curve for boys (7) as the reference standard. Special calendars were distributed to record all bleeding and spotting days and the number of breastfeeding episodes per day.

Pregnancies were diagnosed by clinical examination and urinary

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immunological tests for HCG. Pregnancy tests were performed when menses were delayed for 20 days or more, when amenorrheic women reached the 6th postpartum month and before the insertion of a second set of progesterone pellets at day 240 after delivery.

Progesterone blood levels: Blood samples were drawn at 10- or 15-day intervals from a subsample of users of the 3 different batches of progesterone pellets during the first segment of use and from control subjects. Progesterone levels were determined by RIA as previously described (8) using the procedures and reagents provided by the Programme for the Provision of Matched Assay Reagents for the RIA of Hormones in Reproductive Physiology of the World Health Organization.

Data analysis: The month of conception was estimated by adding 14 days to the first day of the last bleeding run observed. It was confirmed or adjusted when possible by reference to the estimated gestational age of the neonate. The Pearl Index was used to estimate the probability of pregnancy at various intervals during treatment.

Lactation was classified up to the 6th month of age as full nursing or exclusive breastfeeding if the breast was the only source of nutrients for the baby. After the 6th month, non-dairy food was prescribed routinely and lactation was still classified as full nursing if the breast was the only source of milk. The proportion of cases remaining in the full nursing condition was used to assess the effect of treatment upon lactation. Supplement was prescribed by the pediatrician when the rate of infant growth indicated inadequate milk supply. In several cases, the supplement was self-prescribed by the mother based upon her subjective evaluation of milk production and child satisfaction.

The occurrence of severe intercurrent disease, prolonged or repeated separation of mother and child, discontinuation of treatment or lost-to-follow-up determined exclusion of the case from analysis of lactation and infant growth following the last visit prior to the event.

In order to assess the effect of treatment upon infant growth, the average absolute weight at each month of life and the average weight increase

at monthly and daily intervals were calculated for each group. Only cases in exclusive breastfeeding were included. Calculations were done up to the 8th month of age.

The occurrence of uncomfortable or prolonged bleeding was analyzed through the proportion of women who experienced more than 6 days of bleeding plus spotting per 30-day interval after treatment.

Contingency table analysis and student's "t" test were used to assess the statistical significance of differences in distribution and mean values, respectively. Only p values <0.05 were considered significant.

RESULTS

The number of subjects enrolled in each treatment group is shown in Table I. Ninety-two out of 112 women (82.1%) accepted the reinsertion of progesterone pellets that was offered at day 240 postpartum.

The plasma progesterone levels achieved with the 3 different batches of pellets are shown in Figure 1. They reached their maximum within ten days of insertion and declined gradually thereafter remaining elevated at least for 5 months in comparison to the control group. Levels obtained with the 3 batches were of similar magnitude.

The local tolerance to progesterone pellets was poor. Expulsion occurred in 2.4% of subjects from batch I, in 31.7% of subjects from batch II and in 9.9% of subjects from batch III. The time elapsed between insertion and expulsion varied from several days to five months.

Table II shows the occurrence of pregnancy in women treated with progesterone pellets according to the breastfeeding status and the time of treatment. This table includes only the first 5 months after each progesterone implant insertion. For this reason, the 8th postpartum month is not included. No pregnancies were observed in the first 5 months of treatment in full nursing women when treatment was given at day 30, 60 or 240 postpartum. Only one pregnancy was diagnosed in partially nursing women and it occurred in the 4th month after insertion. The overall incidence of pregnancy was 1 in 1614 months. This figure is comparable to the fertility inhibition obtained with the Copper T in the same postpartum intervals. Both treatment groups showed a significantly lower incidence of pregnancy as

TABLE I

Distribution of Subjects According to Treatment and Day of Administration

Initiation of Treatment Postpartum Day	No. of Subjects
Progesterone Pellets	
Day 30: Batch I	84
Day 60: Batch II	41
Batch III	152
Day 240: Batch III	92
Copper T	
Day 30	125
Day 60	121
Placebo	
Day 30	130

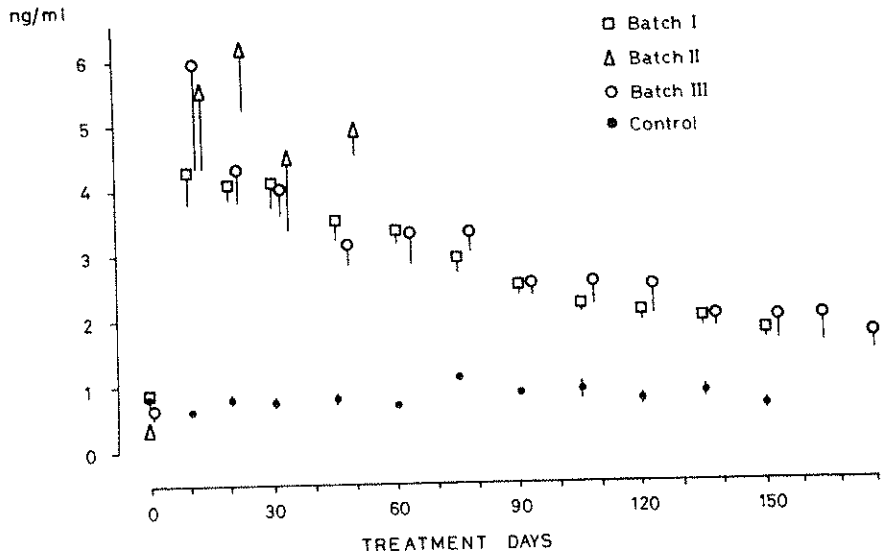

Fig. 1: Plasma progesterone levels (X ± S.E.) in lactating women treated with progesterone pellets from Batch I (□), Batch II (△) and Batch III (o) and in control cases (●).

TABLE II

Contraceptive Effectiveness of Progesterone Pellets versus Copper T and Placebo According to the Breastfeeding Status and the Observation Period

Treatment	Breastfeeding Status	No. Pregnancies / No. Woman-months Observation Period* (Postpartum Months)			
		2 - 6[a]	3 - 7[b]	9 - 13[c]	TOTAL
Progesterone Pellets	Exclusive	0/339	0/594	0/144	
	Supplemented	0/17	1/199	0/205	
	Weaned	0/10	0/37	0/69	
	All	0/366	1/830	0/418	1/1614
Copper T	Exclusive	1/471	0/420	1/252	
	Supplemented	0/43	0/164	0/268	
	Weaned	-	0/39	0/72	
	All	1/514	0/623	1/592	2/1729
Placebo[d]	Exclusive	9/502	-	1/49	
	Supplemented	4/49	-	5/77	
	Weaned	-	-	-	
	All	13/551	-	6/126	19/677

* Only the first five months postpartum following insertion were considered since this is the estimated effective life of progesterone implants (See Table III).

a Treatment initiated at day 30 postpartum.

b Treatment initiated at day 60 postpartum.

c Treatment initiated at day 240 postpartum in progesterone pellets group and at day 30 or 60 in the other two groups.

d Some women used spermicides after the sixth postpartum month.

compared to the placebo group in which 19 pregnancies were diagnosed in the 677 woman-months observed in comparable postpartum intervals.

Table III shows the overall contraceptive effectiveness of six progesterone pellets for different treatment lengths, regardless of the time of insertion. Treatment was highly effective during the first five months of use. The effectiveness decreased when the observation was extended to months 6 and 7 where 3 and 6 pregnancies were diagnosed in 239 and 72 woman-months of exposure, respectively.

The cumulative distribution of women according to their breastfeeding status at the 6th postpartum month is shown in Table IV. Treatment groups initiated at day 30 or 60 postpartum had breastfeeding evolutions similar to their contemporary control groups. Both series initiated at day 60 showed a higher proportion of supplemented cases at the 6th month when compared to the series started at day 30.

The growth of exclusively breastfed infants was similar in treated and control groups when analyzed through the average absolute body weight at each month of age and the average monthly and daily weight increase. Table V shows the average weight increase of exclusively breastfed infants from birth to the 6th month of age. Values for all groups were within the normal range according to the standard used for comparison.

No major side effects were detected. The bleeding pattern showed disruption during the first month of use of pellets comparable to that observed after insertion of a Copper T. Table VI shows the proportion of full nursing women who experienced 6 or more days of bleeding plus spotting per 30-day interval. Excessive bleeding was infrequent in all groups after the first month of treatment. After the insertion of the second set of implants at day 240 postpartum, the proportion of women who reported more than 6 days of bleeding per interval ranged from 6% (third month of treatment) to 16% (fifth month). In the same period, the proportion of Copper T users who experienced more than 6 days of bleeding ranged from 21% to 31%.

DISCUSSION

The results of this study show that the continuous administration of progesterone by means of an implant inhibits fertility in lactating women and

TABLE III

Duration of the Contraceptive Effectiveness of Six Progesterone Pellets

Months of Treatment	Pregnancies/ Woman-Months	Pearl Index
1 to 5	1/1614	0.74
6	3/239	15.1
7	6/72	100.0

TABLE IV

Cummulative Distribution of Women According to their Breastfeeding Condition at the 6th Postpartum Month

TREATMENT	Insertion (Postpartum day)	N	Exclusive Breastfeeding %	Use of Supplementary Feeding Medical Prescription %	Maternal Decision %
Progesterone Pellets	30	73	68	21	11
	60*	127	53	39	7
Copper T	30	106	60	29	11
	60	105	50	36	14
Placebo	30	105	71	26	3

N = Number of cases observed at day 180.

* Cases treated with pellets from Batch II were excluded because of the bias introduced by the high number of expulsions.

TABLE V

Average Weight Increase of Exclusively Breastfed Infants from Birth to the 6th Month of Age

Initiation of Treatment (Postpartum Days)	N	Weight Increase (g) X ± S.D.
Progesterone Pellets		
Day 30	46	4515 ± 621
Day 60	60	4730 ± 670
Copper T		
Day 30	64	4801 ± 817
Day 60	49	4798 ± 546
Placebo		
Day 30	68	4663 ± 529

TABLE VI

Percentage of Full Nursing Women who Experienced More than 6 Days of Bleeding or Spotting per 30-Day Interval

Interval (Postpartum days)	Progesterone Pellets 30*	Progesterone Pellets 60*	Copper T 30*	Copper T 60*	Placebo 30*
31 - 60	46	-	52	-	22
61 - 90	12	18	10	30	4
91 - 120	8	5	14	16	5
121 - 150	6	5	12	15	8
151 - 180	9	4	17	15	7

* Postpartum day of insertion.

that it can be used for contraceptive purposes. The pregnancy rate observed during the period of elevated plasma levels of the steroid is highly satisfactory and within the range of a Copper T IUD. The high incidence of pregnancies observed in the placebo group allows the conclusion that the low fertility of the treated groups was not determined exclusively by breastfeeding.

The duration of elevated plasma progesterone levels and of an acceptable contraceptive efficacy was limited to 5 months. After this period, fertility was quickly restored as can be inferred from the number of pregnancies observed at the 6th and 7th month after insertion. This led us to offer a second set of implants after the exhaustion of the first reservoir to women who were still lactating at that time. The low incidence of pregnancies observed in the second segment is reassuring of the contraceptive effectiveness of progesterone implants during lactation and shows that its efficacy applies also to long-term lactation.

The use of progesterone induced no adverse side effects on lactation as judged by the proportion of cases in exclusive breastfeeding and the growth rate of exclusively breastfed infants up to the 6th postpartum month. Treatment with progesterone pellets or a Copper T resulted in a higher proportion of subjects who experienced more than 6 days of bleeding as compared to the untreated women. Nevertheless, this was a transient problem, limited to the postinsertion period and did not represent a reason for discontinuation or a health risk for the subjects. No deleterious effects upon infant health were detected.

The percentage of women who were willing to use a second set of progesterone implants indicates that this is a well accepted alternative.

The main problem encountered during this experience was the high incidence of expulsion of the progesterone pellets which appears to be partially related to the manufacturing technique. The results reported justify new efforts to develop an improved system for the long-term delivery of progesterone.

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