

90674

From fill@www.libraries.wright.edu Thu May 18 12:14:26 2006  
 Return-Path: <fill@www.libraries.wright.edu>  
 Received: from mulnx11.mcs.muohio.edu (mulnx11.mcs.muohio.edu [134.53.6.66])  
 by sigerson.sword.org (8.13.4/8.13.4/Debian-3) with ESMTTP id k4IGEQxB0052  
 24  
 for <requests@sword.org>; Thu, 18 May 2006 12:14:26 -0400  
 Received: from mulnx24.mcs.muohio.edu (mulnx24.mcs.muohio.edu [134.53.6.11])  
 by mulnx11.mcs.muohio.edu (Switch-3.1.8/Switch-3.1.7) with ESMTTP id k4IGD  
 igh017652  
 for <requests@sword.org>; Thu, 18 May 2006 12:13:44 -0400  
 Received: from sms1.wright.edu (sms1.wright.edu [130.108.66.31])  
 by mulnx24.mcs.muohio.edu (Switch-3.1.8/Switch-3.1.6) with SMTP id k4IGDh  
 3F008963  
 for <requests@sword.org>; Thu, 18 May 2006 12:13:44 -0400  
 Received: from conversion-daemon.sms1.wright.edu by sms1.wright.edu  
 (iPlanet Messaging Server 5.2 HotFix 2.09 (built Nov 18 2005))  
 id <0IZG00D01YE11R@sms1.wright.edu>  
 (original mail from fill@www.libraries.wright.edu)  
 for requests@sword.org; Thu, 18 May 2006 12:13:43 -0400 (EDT)  
 Received: from CHANGE-ME ([130.108.169.150])  
 by sms1.wright.edu (iPlanet Messaging Server 5.2 HotFix 2.09 (built Nov 18  
 2005)) with ESMTTP id <0IZG00AKIYEV9D@sms1.wright.edu> for requests@sword.org;  
 Thu, 18 May 2006 12:13:43 -0400 (EDT)  
 Date: Thu, 18 May 2006 16:13:42 +0000 (GMT)  
 From: Fordham Interlibrary Loan <fill@www.libraries.wright.edu>  
 Subject: Please fill request  
 To: requests@sword.org  
 Message-id: <246078601.14395669122843441101@www.libraries.wright.edu>  
 Content-transfer-encoding: 7BIT  
 X-Real-ConnectIP: 130.108.66.31  
 X-Scanned-By: MIMEDefang 2.45  
 X-Scanned-By: MIMEDefang 2.52 on 134.53.6.11

This request has been forwarded from ILL by barb.

Please fill this request for FORDHAM HEALTH SCIENCES LIBRARY

90674

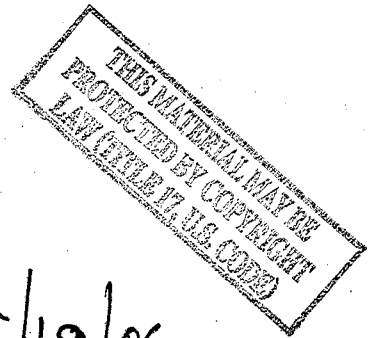
Call Number: 81384100418 OR 9

Journal Title: Am J Obstet Gynaecol  
 Journal Vol: 127  
 Journal Issue:  
 Journal Year: 1977  
 Article Title: Implantation of pure crystalline pellets of oestradiol for contrac  
 eption control  
 Article Author: Greenblatt  
 Article Pages: ~~420-4~~

520-524

Customer Information:

Name: Glaser, Rebecca  
 Status: Faculty  
 Address: SOUTHVIEW (via Kettering Hosp),  
 Site:  
 E-Mail Address: rglaser@woh.rr.com  
 Phone: 937-885-4555  
 Department: School of Medicine



5 pp scanned 5/18/06

# Implantation of pure crystalline pellets of estradiol for conception control

ROBERT B. GREENBLATT, M.D.

RICARDO H. ASCH, M.D.

VIRENDRA B. MAHESH, PH.D., D.PHIL.

JAMES R. BRYNER, M.D.

Augusta, Georgia

*Estradiol pellet implantation for contraception offers another alternative in conception control. The occurrence of only two pregnancies in 1,668 cycles (Pearl index: 1.42) reflects its efficacy. The advantages over oral contraceptives are: (1) absence of gastrointestinal symptoms, (2) minimal untoward effects, (3) no patient failure, and (4) convenience. Progressive stepdown in dose reduces the total amount of steroid used in long-term contraception. Contraceptive effect may not occur during the first month of implantation; adequate precaution should be taken. Because of the efficacy, minimal untoward side effects, and excellent patient acceptability, this regimen may be considered for contraception in developing countries and when other modalities are contraindicated. (AM. J. OBSTET. GYNECOL. 127: 520, 1977.)*

THE CONCEPT OF steroidal oral contraceptives was introduced two decades ago by Rock, Garcia, and Pinkus.<sup>1, 2</sup> Several untoward effects, such as increased risk of thromboembolic diseases and hypertension, are associated with the contraceptive's use. Mills and co-workers<sup>3, 4</sup> have demonstrated that steroids, such as mestranol and norethindrone, used in oral contraceptive medications disappear rapidly from the bloodstream; their metabolites, however, persist in the blood with a mean half-life varying from 37 to 83 hours. A "staircase effect" in the buildup of metabolites is observed with the daily ingestion of the pill.<sup>5</sup> Lebech and Borggaard<sup>6</sup> have reported that synthetic estrogen administration causes a rise in the triglyceride concentration and a fall in the antithrombin-III concentration in plasma. Such effects were not observed following natural estrogenic preparation. The search continues for

the contraceptive with minimal undesirable reactions and maximum efficacy.

Pure crystalline pellets of estradiol, implanted subcutaneously at 6 month intervals, have been employed for the management of various gynecologic disorders and menopause by one of us (R. B. G.) for 35 years.<sup>7</sup> Empeiraire and Greenblatt<sup>8</sup> reported that the implantation of four pellets of estradiol (25 mg. each) at 6 month intervals provided excellent conception control. A short course of potent oral progestogen was administered at monthly intervals to induce regular withdrawal bleeding. Pellet implants obviated patient-failure conceptions because of missed pills. The use of a pure natural estrogen is more biologic and appears to lessen many of the untoward effects. A step-down method for ovulation suppression using oral conjugated estrogens (U.S.P.) as reported by us in 1952 and 1954 prompted a similar step-down regimen with pure crystalline estradiol pellets.<sup>7, 9</sup> Thus a study was undertaken employing four, three, two, and one pellets at 6 month intervals. Such a plan greatly reduced the amount of estradiol needed for long-term conceptive control and proved most promising.

## Material and methods

A total of 123 sexually active women were studied in this series. Patients were followed for a total of 278

*From the Department of Endocrinology, Medical College of Georgia.*

*Received for publication August 12, 1976.*

*Revised October 5, 1976.*

*Accepted October 7, 1976.*

*Reprint requests: Robert B. Greenblatt, M.D., Dept. of Endocrinology, Medical College of Georgia, Augusta, Georgia 30902.*

trials, 1,668 cycles, or 128.3 woman years (Fig. 1). Informed consent was obtained from each subject. Ages ranged from 15 to 45 with a mean of 24 years. Previous ovulatory menstrual cycles were confirmed by basal body temperature (BBT), endometrial biopsies, and/or prior pregnancies. Body weight varied from 89 to 225.7 pounds with a mean of 131.3 pounds. Blood pressure values were within normal range. Nine patients complained of hypermenorrhea and 20 of premenstrual headaches prior to start of therapy. None of the patients presented a history of thrombophlebitis or diabetes. General disease and gynecologic disorders were ruled out with an exhaustive anamnesis and physical examination.

The pellets are implanted subcutaneously in the abdominal wall, 1 to 2 inches above and parallel to Poupart's ligament. An intradermal wheal is raised with 0.5 ml. of 2 per cent procaine prior to insertion of a Kern's implant. Estradiol pellets are available from Schering Corporation, Bloomfield, New Jersey, as Progyon pellets. The implant and estradiol pellets are available from Bartor Pharmacals, Rye, New York or Bartor International, Box 1242, Palm Desert, California 92260. The procedure is simple and does not incapacitate the patient. The initial implant consists of four pellets of estradiol (25 mg. each), which is reduced by one on each subsequent visit at 6 month intervals. After the fourth implantation, the reduced dosage is continued as long as the patient desires. Some have been on this scheme for 8 to 10 years. Withdrawal bleeding is induced monthly with an oral progestogen, such as norethindrone acetate (5 mg.) or medroxyprogesterone acetate (10 mg.) for 5 to 7 days. Periodic evaluations were performed, with special attention to pelvic and breast examination. Pap smear, CBC, SMA 18 including triglycerides, T<sub>4</sub> determinations, and urinalysis were performed at each visit. Blood pressure and weight were recorded at regular intervals. In 11 selected patients, an oral glucose tolerance test was performed before and during treatment according to the standardized procedure of the American Diabetes Association as described by Klimt and associates.<sup>10</sup> Forty-nine endometrial biopsies were obtained at various time intervals during therapy and 186 basal body temperature records were available for analysis. Frequent measurement of serum FSH and LH were performed in several volunteers by radioimmunoassay. The material was obtained from the Hormone Distribution Program of NIAMD & D, of the National Institutes of Health, U. S. Public Health Service. Serum estradiol and progesterone were assayed by the multiple steroid radioimmunoassay technique of Parker, Jr., Ellegood, and Mahesh.<sup>11</sup>

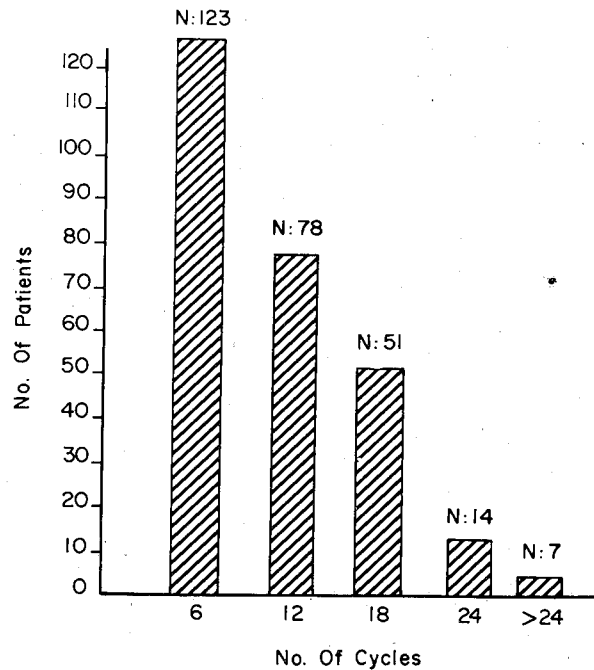


Fig. 1. Estrogen pellet implantation for contraception. Patients were on 100 mg. implants during cycles 1 to 6, 75 mg. during cycles 7 to 12, 50 mg. during 13 to 18, and 25 mg. for cycles 19 and above.

#### Results and comments

The weight changes in 66 patients 6 months after the first implantation, 45 patients after the second, and 22 patients after the third are shown in Tables I and II. The changes after the 25 mg. implant are not shown because of the small number of observations. The mean weight change was a gain of  $0.08 \pm .80$ ,  $0.18 \pm 0.93$ , and  $0.28 \pm 2.30$  pounds after 6, 12, and 18 months of treatment. A few patients did not show any weight change and the mean change for the entire group was even less. In spite of a very small and insignificant weight change by the entire group, some individual patients experienced a marked increase or decrease in weight and the maximum weight gained or lost is indicated in Table I. In addition, the percentage of patients with a change of more than 5 per cent of their initial weight is also shown (Table II). It is improbable that these changes are any different from normal variations in body weight of controls.

No patient was hypertensive before the start of treatment and none developed hypertension while on treatment. Table I shows the change in systolic and diastolic blood pressure in patients 6, 12, and 18 months after estrogen pellet implantation. The mean alteration in systolic pressure in patients showing a change was  $-4.7 \pm 1.9$ ,  $-1.7 \pm 1.6$ , and  $-1.4 \pm 2.8$  mm. Hg and in diastolic pressure,  $-1.8 \pm 1.2$ ,

**Table I.** Changes in body weight and systolic and diastolic blood pressure

	Courses of treatment*				
	No. 1 6 mo. after 100 mg.			No. 2 6 mo. after 75 mg.	
	Weight (lb.)	Systolic blood pressure (mm. Hg)	Diastolic blood pressure (mm. Hg)	Weight (lb.)	Systolic blood pressure (mm. Hg)
Total no. of patients	66	66	66	45	45
Patients showing change	54	36	35	40	26
Mean change $\pm$ S.E. those showing change	0.08 $\pm$ .80	-4.7 $\pm$ 1.9	-1.8 $\pm$ 1.2	0.18 $\pm$ .93	-1.7 $\pm$ 1.6
Mean change $\pm$ S.E. entire group	0.06 $\pm$ 1.1	-2.5 $\pm$ 1.1	-1.0 $\pm$ .6	0.16 $\pm$ .68	-1.0 $\pm$ .8
Maximum increase	11	20	20	9	30
Maximum decrease	18	50	30	21	20
Maximum blood pressure		138	80		140
Minimum blood pressure		80	50		88

\*Note that the second course of treatment was the result of 12 months of estradiol pellet exposure and the third course was after 18 months. All weight and blood pressure change comparisons are made with initial values at the start of pellet implantation.

**Table II.** Percentage of patients showing greater than 10 per cent change in systolic or diastolic pressure and 5 per cent or more weight gain or loss

Percentage of patients	Courses of treatment*		
	1 6 mo. after 100 mg.	2 6 mo. after 75 mg.	3 6 mo. after 50 mg.
10 per cent or greater increase in systolic or diastolic pressure	22.7	20	18.2
10 per cent or greater decrease in systolic or diastolic pressure	34.8	33.3	40.9
5 per cent or more weight gain	7.8	18.4	27.3
5 per cent or more weight loss	9.3	14.3	9.1

\*Note that the second course of treatment was the result of 12 months of estradiol pellet exposure and the third course was after 18 months. All blood pressure and weight comparisons are made with initial values at the start of pellet implantation.

-0.8  $\pm$  1.7, and -0.8  $\pm$  2.4 mm. Hg, respectively, after 6, 12, and 18 months of treatment. The mean change in the entire group was even smaller. In view of the ill-defined criteria of what constitutes a significant change in blood pressure, Table I provides values of maximum and minimum systolic and diastolic pressures in individual patients as well as the maximum change. Table II illustrates the percentage of patients that had a change greater than 10 per cent from the initial systolic and diastolic pressures while on estradiol pellets.

The results of the standardized glucose tolerance test in 11 patients before and during pellet implantation

**Table III.** Serum FSH, LH, estradiol, and progesterone in two volunteers implanted with 100 mg. of estradiol

Date	FSH mI.U./ml.	LH mI.U./ml.	Estradiol ng./ml.	Progesterone ng./ml.
<i>Volunteer A*</i>				
Date of implant: 7/08/74				
Around early part of cycle				
7/10/74	7.2	<0.9	0.11	0.21
7/16/74	3.8	<0.9	0.26	0.28
7/19/74	5.5	<0.9	0.15	0.13
7/19/74	<3.0	<0.9	0.20	0.11
8/01/74	<3.0	<0.9	0.17	0.15
8/30/74	2.0	<0.9	0.20	0.17
<i>Volunteer B*</i>				
Date of implant: 8/15/74				
Around midcycle				
8/15/74	3.1	1.8	0.20	0.34
8/20/74	<1.5	<0.9	0.36	1.76
8/22/74	<1.5	<0.9	0.38	>3.0
8/26/74	<0.9	<0.9	0.33	>3.0
8/29/74	<1.5	<0.9	0.15	1.19
9/03/74	1.5	<0.9	0.09	<0.02

\*Volunteer A did not ovulate on the implant whereas Volunteer B ovulated with a normal duration corpus luteum function.

showed no abnormalities. No significant changes occurred in the blood profile or in the Pap smears. Five of the nine patients with a previous history of hypermenorrhea and 14 of 20 patients with premenstrual headaches improved during therapy. Untoward effects were headache in one, hypermenorrhea in nine, breast tenderness in seven, and mild fluid retention in 15 patients. The basal body temperature records appeared to be monophasic prior to the cycle ingestion of the progestogen and in a few the charts were equivocal. A total of 49 endometrial biopsies were obtained—24

No. 3 6 mo. after 50 mg.			
Diastolic blood pressure (mm. Hg)	Weight (lb.)	Systolic blood pressure (mm. Hg.)	Diastolic blood pressure (mm. Hg)
45	22	22	22
16	14	11	10
-0.8 ± 1.7	.28 ± 2.30	-1.4 ± 2.8	-0.8 ± 2.4
-0.3 ± .6	0.17 ± 1.44	-0.8 ± 1.7	-0.4 ± 1.1
20	11.3	10	20
20	23	20	12
80		120	80
50		90	50

were proliferative, four were secretory, 16 showed slight, simple hyperplasia, and five, benign cystic glandular hyperplasia. Of the biopsies taken from four patients in whom a secretory endometrium was found, two were obtained during the course of an oral progestogen; we cannot assume that ovulation escape did not occur in these two. In previous studies, we have shown that the hyperplasia and cystic glandular hyperplasia readily change to a secretory type of endometrium following a course of an oral progestogen.<sup>12, 13</sup> In the current study all subjects were receiving a progestogen on a monthly cyclic basis. If the biopsy is taken prior to day 18, it may show endometrial hyperplasia. However, if the endometrium is sampled on day 27, it will be secretory.

A volunteer of proved fertility has been on estrogen pellet implants for over 8 years for the purpose of contraception. During the last 5 years, she has received only one 25 mg. implant at 6 month intervals. Blood pressure and weight remained in the normal range.

It was of interest to examine the time period of pellet implantation. The results of pellet implantation in a volunteer in the early part of the menstrual cycle show prompt and sustained suppression of ovulation as judged by serum gonadotropins, estradiol, and pro-

gesterone (Table III). On the other hand, if the pellets were implanted near the midcycle, ovulation and corpus luteum function could take place (Table III). In this volunteer, the preovulatory rise of gonadotropins was not found, presumably because of lack of sampling between August 15 and 20. Nevertheless, ovulation was suggested by the BBT and serum progesterone levels. After the first induced period, there was a sustained suppression of ovulation.

In this series there were four pregnancies. Two of the four pregnancies occurred within the first month of the pellet implantation. In view of the inability of the pellet implant to suppress the first ovulation implanted at certain phases of the cycle as shown in Table III, it is important to emphasize that the first month after the initial implant is not a safe period for contraceptive efficacy. The other two pregnancies occurred several months after the 100 mg. pellet implantation and a Pearl index of 1.42 was estimated for the two cases of the method failure.

### Summary

Estradiol pellet implantation for conception control offers another alternative in the wide choice of methods available. The occurrence of only two pregnancies in 1,668 cycles (Pearl index: 1.42) reflects the efficacy of the scheme. The advantages over oral contraceptives are absence of gastrointestinal symptoms, minimal untoward effects, and no possibility of missing a pill at a critical time (patient failure). The progressive stepdown in dose reduces the total amount of steroid necessary for effective long-term contraception. Adverse reactions are infrequent.

Caution should be exercised during the month of the first implantation should it take place after seventh day of the cycle. Patients who could not tolerate oral contraceptives because of headaches, nausea, and other untoward responses found the pellet regimen satisfactory. A new approach to contraception is thus available for those in whom oral contraceptive agents and/or intrauterine devices are contraindicated. It is believed that by using natural estrogens, the incidence of thromboembolic disease may be greatly reduced.

### REFERENCES

1. Rock, J., Garcia, C. R., and Pincus, G.: Synthetic progestins in the normal human menstrual cycle, *Recent Prog. Horm. Res.* **13**: 323, 1957.
2. Rock, J., Garcia, C. R., and Pincus, G.: Effect of certain 19-norsteroids on the normal human menstrual cycle, *Science* **124**: 891, 1956.
3. Mills, T. M., Lin, T. J., Hernandez-Ayup, S., et al.: The metabolic clearance rate and urinary excretion of oral contraceptive drugs. I. Norethindrone, *AM. J. OBSTET. GYNECOL.* **120**:764, 1974.
4. Mills, T. M., Lin, T. J., Hernandez-Ayup, S., et al.: The metabolic clearance rate and urinary excretion of oral contraceptive drugs. II. Mestranol, *AM. J. OBSTET. GYNECOL.* **120**: 773-778, 1974.
5. Mills, T. M., Lin, T. J., Braselton, W. E., et al.: Metabolism of oral contraceptive drugs. The formation and disappearance of metabolites of norethindrone and mes-

- tranol after intravenous and oral administration, *AM. J. OBSTET. GYNECOL.* In press, 1976.
6. Lebech, P. E., and Borggaard, B.: Serum lipid and anti-thrombin. III. Changes effected by synthetic and natural estrogen therapy, *In* Greenblatt, R. B., Mahesh, V. B., and McDonough, P. G. editors: *The Menopausal Syndrome*, New York, 1974, Medcom press.
  7. Greenblatt, R. B.: *Office Endocrinology*, ed. 4, Springfield, Illinois, 1952, Charles C. Thomas, Publisher.
  8. Empeaire, J. C., and Greenblatt, R. B.: L'implantation de pellets d' oestradiol dans la contraception, *Gynecologie pratique* 5: 327, 1969.
  9. Greenblatt, R. B., Clark, G. L., and Hammond, D. O.: Membraneous dysmenorrhea: Studies in etiology and treatment, *AM. J. OBSTET. GYNECOL.* 68: 835, 1954.
  10. Klimt, C. R., Prout, T. E., Bradley, R. F., et al.: Standardization of the oral glucose tolerance test: Report of the Committee on statistics of the American Diabetes Association, *Diabetes* 18: 299, 1969.
  11. Parker, C. R., Jr., Ellegood, J. O., and Mahesh, V. B.: Methods for multiple steroid radioimmunoassay, *J. Ster. Biochem.* 6: 1, 1975.
  12. Dalla Pria, S., Audebert, A., and Greenblatt, R. B.: Current thoughts on the management of dysfunctional uterine bleeding, *AM. J. OBSTET. GYNECOL.* 105: 1185-1191, 1969.
  13. Gambrell, R. D., Jr.: Perimenopausal and post-menopausal bleeding: Mechanism, pathology, management with progestational agents, *In* Greenblatt, R. B., Mahesh, V. B., and McDonough, P. G., editors: *The Menopausal Syndrome* Ed., New York, 1974, Medcom Press.