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Estradiol implants for conception control

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Oral contraceptives are associated with serious untoward effects and have been proscribed for women over 35 years of age. It was thought that the use of a natural estrogen (pellets of 25 mg of 17β-estradiol) implanted in descending doses (four, three, two, one) at 6-month intervals might cause less disturbance in metabolic parameters and side effects. Our experience with this regimen encompasses 18,480 cycles or 1,540 woman years. The corrected Pearl Index was 0.273, which compares favorably with other modes of conception control. Pellet implants proved to be quite acceptable to those who could not tolerate oral contraceptives. (AM. J. OBSTET. GYNECOL. 138:1151, 1980.)

ORAL CONTRACEPTIVES remain the most effective tool yet devised for the control of conception. However, there are many women who do not tolerate oral contraceptives, are not candidates for and do not want an intrauterine contraceptive device, and prefer some method other than mechanical barriers. Then, again, several authoritative bodies believe that it is prudent to limit the use of oral contraceptives to women under 35 years of age because of the rise in mortality figures for oral contraceptive users over that age.[1]

Emperaire and Greenblatt[2] reported that four pellets of 17β-estradiol (25 mg each) implanted subcutaneously at 6-month intervals provided excellent control of conception.[2] Because of earlier experiences in which ovulation was successfully suppressed by the use of oral conjugated estrogens in a monthly step-down fashion, i.e., 5 mg, 3.75 mg, 2.5 mg, 1.25 mg,[3] we decided to try a similar scheme; the number of pellets were reduced every 6 months, i.e., four, three, two, one.[4] Of course, it is mandatory that an oral progestogen be employed for 7 to 10 days each month in order to induce orderly periods of uterine withdrawal bleeding.

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Material and methods

The pellets were implanted subcutaneously into the abdomen, one inch above and parallel to Poupart's ligament. A total of 490 sexually active women of reproductive age, 60% of whom were under 35 years of age, participated in this study; 410 returned for three pellets, 351 for two pellets, and 295 stayed on for the full course. Most of the women in this latter group continued at the one-pellet level every 6 months for a period ranging from 1 to 8 years. Table I shows that our experience encompassed 18,480 cycles or 1,540 woman years. The age distribution is given in Table II.

Physical examinations, including blood pressure and weight, were performed every 6 months. Blood for testing with the SMA-18 was drawn at the start and at yearly intervals. Biopsy specimens of endometrium were obtained at varying intervals to study histologic changes and also whenever abnormal bleeding occurred. Hormone assays were performed in selected patients.

Results

Endometrial studies. Because of a belief that continuous administration of estrogen is conducive to endometrial cancer, we obtained one or more biopsy specimens of endometrium in 148 women before and/or after a course of progestogen at varying intervals of

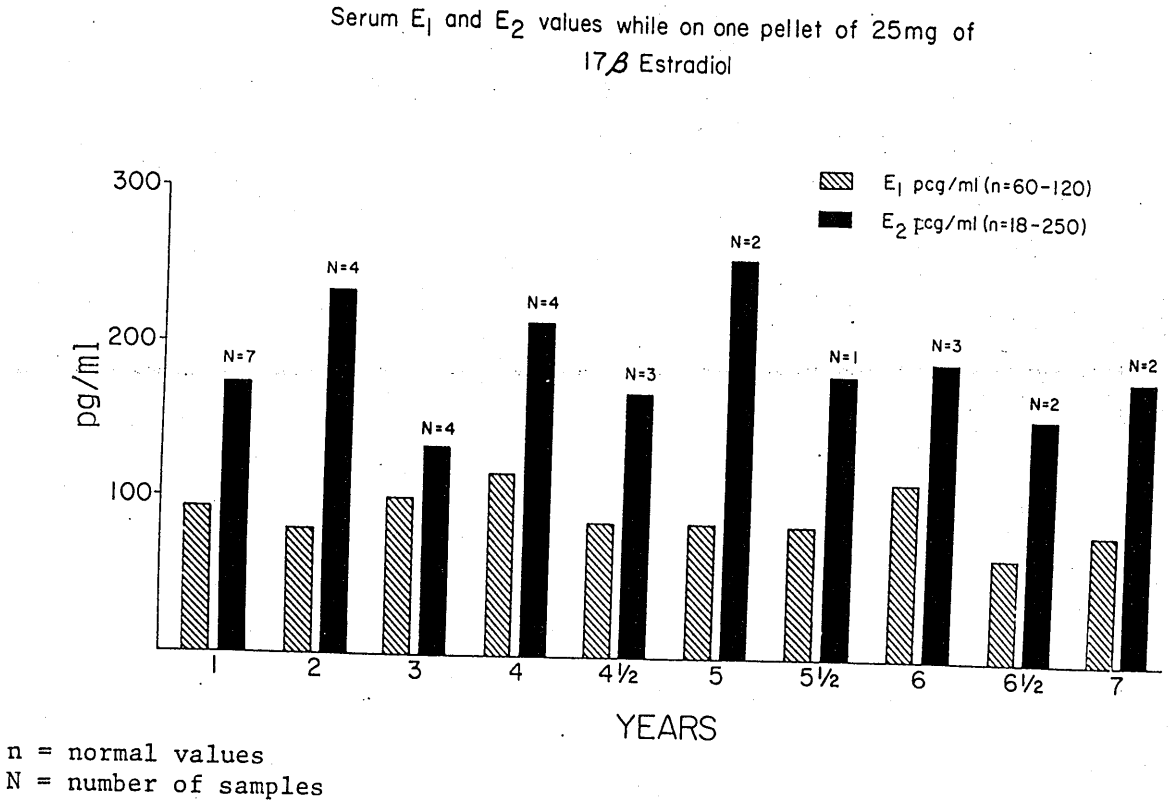

Fig. 1. Note that serum levels of estrone and estradiol are maintained within physiologic levels on one pellet of estradiol every 6 months.

Table I. Step-down course of estradiol pellet implants in 490 females

Pellets	*No. of patients*	*Cycles*	*Woman years*
4	490	2,940	245
3	410	2,460	205
2	351	2,106	175.5
1	295	10,974	914.5
Total		18,480	1,540.0

Table II. Incidence of abnormal uterine bleeding in 490 women on hormone therapy

Age (yr)	*Total No. of patients*	*Hypermenorrhea*	*Menorrhagia*
<20	24	—	—
20-24	82	1	0
25-29	95	1	2
30-34	94	1	1
35-39	134	2	3
40-44	61	5	1
Total	490	10	7

time over a 10-year period (mean, 3.4 ± 1.9 years) (Table III). In addition, we performed 20 biopsies in 17 women who experienced hypermenorrhea (excessive withdrawal periods) or menorrhagia (breakthrough bleeding). The mean length of time after beginning the implantation of the pellets was 3.0 ± 2.4 years (Table IV). Most of the patients were on a 5-day course of progestogen (either 5 mg of norethindrone or 10 mg of medroxyprogesterone acetate). Whenever we encountered any form of hyperplasia, the duration of administration of progestogen was increased to 7 to 10 days and sometimes 13 or 14 days. The frequency of hyperplasia declined rapidly and none was found by the fourth biopsy. Two hundred sixteen endometrial biopsy specimens, obtained by suction curettage, were available for study (Table V). Of the two women who had adenomatous hyperplasia, one responded to increased doses of the progestogen with a change to a secretory endometrium; the other opted for hysterectomy.

The histopathologic characteristics of endometria of uteri from 78 women in this series of 490 was studied. Only one case of adenomatous hyperplasia was found

Table III. Intervals and frequency of endometrial biopsies for routine histologic study

Endometrial biopsy	*No. of biopsies*	*<6 mo*	*6-12 mo*	*1-2 yr*	*2-3 yr*	*3-4 yr*	*4-5 yr*	*5-6 yr*	*6-7 yr*	*7-8 yr*	*>8 yr*
First	148	9	6	28	21	24	25	16	14	3	2
Second	34	—	11	6	1	2	4	3	4	1	2
Third	11	—	2	—	3	⅞	2	—	3	—	1
Fourth	3	—	—	1	—	1	1	—	—	—	—
Totals	196	9	19	35	25	27	32	19	21	4	5

Table IV. Endometrial biopsies in women experiencing abnormal bleeding

Endometrial biopsy	*No. of biopsies*	*<6 mo*	*6-12 mo*	*1-2 yr*	*2-3 yr*	*3-4 yr*	*4-5 yr*	*5-6 yr*	*6-7 yr*	*7-8 yr*	*>8 yr*
First	17	2	3	2	4	1	1	1	1	1	1
Second	3	—	1	1	1	—	—	—	—	—	—
Totals	20	2	4	3	5	1	1	1	1	1	1

Table V. Histologic findings in 216 endometrial biopsies after pellet implantation

Endometrial biopsy	*No. of biopsies*	*Proliferative*	*Secretory*	*Mild hyperplasia*	*Moderate hyperplasia*	*Adenomatous hyperplasia*
First	165	64	44	48	7	2*
Second	37	16	11	6	4	—
Third	11	3	5	2	1	—
Fourth	3	1	2	—	—	—
Totals	216	84	62	56	12	2

*One woman with adenomatous hyperplasia opted for hysterectomy. By increasing the length of time of progestogen administration from 5 to 10 days or longer, further occurrence of hyperplasia was prevented in those who had exhibited such.

(Table VI). In all, 294 endometria were evaluated and none revealed malignant change.

Indications for hysterectomy. Hysterectomy was performed in 78 women. The mean time that elapsed from onset of therapy ranged from 3.6 years in the age group 30 to 34 years to 5 years in the age group 40 to 44 years (Table VII). The indications for hysterectomy were abnormal uterine bleeding (nine); adenomatous hyperplasia (one); fibromyomas (eight); and a palpably enlarged ovary (two). Surgical procedures in the other 58 women were performed for varying reasons: repair of rectocele or cystocele (17); adenomyosis, (nine); uterine descensus (nine); chronic hypertrophic cervicitis (four); endometriosis (six); chronic pelvic congestion and pelvic pain (three); chronic pelvic inflammatory disease (three); and a desire for permanent control of conception and continuation of estrogens without the fear of developing uterine or cervical malignancy in the future (seven).

Influence of pellet implants on metabolic parameters. Reports have appeared which purport to show that oral contraceptives adversely influence weight, blood pressure, glucose, and lipid metabolism. Table VIII illustrates the average increase, decrease, and mean change in these parameters. The data show slight increases in all areas. Computerized statistical scattergrams for triglycerides, cholesterol, weight, glucose, and blood pressure revealed that there was no marked variation, and that overall mean change was slight. Our experience parallels that reported by Lobo and associates,[5] at the University of Southern California, on the effects of subdermal estradiol implants. They concluded that, "Unlike orally administered natural or ethinyl estrogens, parenteral estrogen replacement by E_2 pellets has minimal effects on hepatic proteins and serum lipids." Actually, their report indicates that high-density lipoproteins improved, and that overall

Table VI. Histopathologic findings in the endometria of 78 patients who underwent hysterectomy

Proliferative	*Secretory*	*Mild-to-moderate hyperplasia*	*Adenomatous hyperplasia*
59	14	4	1

Table VII. Age and indications for hysterectomy in 78 women

Age (yr)	*No. of hysterectomies*	*Mean yr on therapy (range of 6 mo to 10 yr)*	*Abnormal bleeding*	*Adenomatous hyperplasia*	*Fibromyoma*	*Benign ovarian cyst*	*Miscellaneous**
30-34	21	3.6	3	—	3	—	15
35-39	35	4	2	1	5	—	27
40-44	22	5	4	—	—	2	16
Total	78	4.2	9	1	8	2	58

*Cystocele/rectocele (17); adenomyosis (nine); uterine descensus (nine); chronic hypertrophic cervicitis (four); endometriosis (six); chronic pelvic congestion and pelvic pain (three); chronic pelvic inflammatory disease (three); requested hysterectomy to eliminate possible cancer in the future (seven).

Table VIII. Increase, decrease, and mean change in metabolic parameters in 490 patients while on pellets of 17β-estradiol

Data	*Average increase*	*Average decrease*	*Mean change*
Weight (lb)	10.0	8.9	+1.1
Triglycerides (mg/dl)	62.1	59.2	+2.9
Cholesterol (mg/dl)	28.1	26.7	+1.4
Glucose (mg/dl)	18.8	17.0	+1.8
Systolic blood pressure (mm Hg)	20.1	18.3	+1.8
Diastolic blood pressure (mm Hg)	12.6	11.1	+1.5

Table X. Interval between discontinuation of pellet therapy and pregnancy

Patients	*No. pregnant*	*<12 mo*	*1-2 yr*	*2-3 yr*	*3-4 yr*
30 Desiring pregnancy*	24	8	15	1	—
1 Not desiring pregnancy	1	—	—	—	1
Totals	25	8	15	1	1

*Six conceived after Clomid and two after Clomid with human chorionic gonadotropin. Four who have not conceived have been under observation for an average of 8 months; in two others the prospects are poor because of a very low sperm count.

Table IX. Pregnancy rate in 490 fertile women receiving estradiol pellet implants

No. of patients	*Cycle*	*Woman years*	*Pregnancies*	*Pearl index*
490	18,480	1,540	4*	0.273

*Two other pregnancies occurred during the first month of therapy: one patient, it appears, was pregnant prior to implantation of the pellet, and the other conceived a few days after implantation of the pellet.

cholesterol, triglycerides, and low-density lipoproteins were unchanged.

Coagulation studies were done on 11 patients at random, and no marked changes in antithrombin III were seen. In a battery of tests, levels of factor VIII were raised, but no increase in platelet adhesiveness was found. Prothrombin time, partial thromboplastin time, platelet count, fibrinogen, and factors II, VII, X were within the normal range for our laboratory.*

Untoward effects. Seven women experienced bouts of menorrhagia. The abnormal bleeding was readily arrested by the administration of two tablets of the oral progestogen every 2 hours until bleeding was staunched (usually within 48 hours), and then two tablets per day were administered for 10 more days—a normal withdrawal period usually followed. Ten women complained of hypermenorrhea, and when the progestogen dosage was increased from 5 or 7 days to 10 or more days, excessive withdrawal periods were corrected (Table II). It is our habit now to administer progestogen for 10 days in all but a few patients.

Retention of water was not an infrequent complaint; and in some instances a diuretic and potassium were prescribed. Tenderness and fullness in the breasts were occasionally distressful to patients; an analgesic plus diuretics usually sufficed for relief. Such complaints lessened with decreasing doses. A subcutaneous hematoma at the site of implant occasionally resulted; pressure and ice bags usually alleviated the situation.

Pregnancy rate. There were six pregnancies among the 490 women of this series. Two of the pregnancies should be discounted, since one apparently occurred before the pellets were implanted, and the other occurred a few days thereafter. Patients are now advised to use caution (other contraceptive methods) during the first month. As for the other four conceptions, two

*Courtesy of Dr. Charles Lutcher, Department of Hematology, Medical College of Georgia.

Table XI. Parity of patients who desired to become pregnant, and outcome of pregnancies after discontinuation of E_2 pellets

Age (yr)	*No. of patients desiring pregnancy*	*No. of pregnancies*	*Parity*		*Outcome of pregnancy*		
			Nulliparous	*Multiparous*	*Normal*	*Still pregnant*	*Spontaneous abortion*
20-24	9	7	4	3	6	1	—
25-29	14	12	9	3	10	1	1
30-34	6	5	—	5	4	—	1
35-39	1	1	—	1	1	—	—
Totals	30	25	13	12	21	2	2

occurred during the first 6 months, one occurred while the patient was on the second round of the one-pellet-only regimen, and the other occurred while the patient was on the fifth round. The corrected Pearl Index of four pregnancies during 1,540 woman years was 0.273, which compared favorably with other contraceptive methods (Table IX).

Future conception was not compromised. However, ovulation may not return for 6 to 12 months after discontinuation of pellet implants, and during that time the patients are advised to continue cyclic progestogen until ovulation occurs, as indicated by a Day 13 or 14 rise in basal body temperature, or is induced by the use of Clomid with or without the addition of human chorionic gonadotropin (hCG). Twenty-four of 30 women who were desirous of becoming pregnant did so within 3 years of discontinuation of therapy: eight during the first year, 15 during the second year, and one during the third year (Table X). Six required Clomid, and two required Clomid with hCG. One patient who did not wish to become pregnant conceived 46 months after discontinuing the regimen of estradiol pellets. The ages and parity of the patients and the outcome of the pregnancies are listed in Table XI.

Estradiol and estrone levels. In previous reports, we showed that estradiol and estrone were sustained at high physiologic levels on the descending-dose regimen.[4, 6] We studied the levels of estrone and estradiol in 32 women who were on the one-pellet-only regimen for 1 to 7 years. Fig. 1 indicates that the levels of estrone and estradiol remained within normal physiologic range.

Advantage of pellet implants. Women who experienced nausea, depression, sexual dysfunction, headaches, and/or acquired dysmenorrhea while on oral contraceptives usually found that such untoward reactions were rarely noticed after implantation of pellets. No instance of galactorrhea after implantation of pellets has been encountered thus far. We know of no case of pulmonary or cerebral embolus, although one patient had a questionable episode of cerebral ischemia. No endometrial cancers have resulted from this modality of conception control in an experience extending over a period of 10 years.

Comment

Pellet implants proved to be a worth-while alternative in those women who could not tolerate oral contraceptives, or who could not be relied upon to take their medication daily.

Ongoing investigations are in progress to learn more about the ratio of high-density to low-density lipoproteins and changes in coagulation factors with this form of medication. Of great interest also is the observation that, apparently, adequate cyclic oral progestogens are protective against the development of atypical hyperplasia of the endometrium and, thus, possibly prevent endometrial cancer in women who have been on continuous estrogen therapy for many years.

The pellet regimen was particularly welcome to the women over age 35, since many physicians refused to prescribe oral contraceptives for them.[6]

The favorable results noticed make us wonder whether the systemic absorption of estrogen, rather than through the gastrointestinal tract, and immediate clearance through the liver may be the explanation for decreased interference with clotting mechanisms, triglycerides, cholesterol metabolism, and glucose. Further studies are indicated to learn whether the use of a natural estrogen (E_2) induces less metabolic derangement than do the synthetic estrogens (ethinyl estradiol and mestranol).

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