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Subcutaneous Implantation of Pure Crystalline Estradiol Pellets for Conception Control

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Key Words
Estradiol pellets · Conception control

Abstract

Objectives: Assessment of the contraceptive effectiveness of pure estradiol pellets implanted annually under the skin, thus avoiding the 'first passage phenomenon' through the liver, using a modification of Emperaire and Greenblatt's method. ***Study Design:*** 228 women wishing birth control for 1 year or more were included. 5 pellets of estradiol (25 mg each) were implanted initially. At each subsequent annual treatment, 4 pellets were implanted. Withdrawal bleeding was induced monthly with oral norethindrone acetate 5 mg taken for 7 days. Our experience encompassed 8,136 cycles, or 678 women years. The study obtained approval of the local Ethical Committee. ***Results:*** Annual continuation rates were 51 per 100 women in the second year, 65 in the third, 72 in the fourth and 84 ± 10.1 annually over the next 6 years. Through 12 years of our study, 2 accidental pregnancies occurred. The annual net cumulative pregnancy rates were 0.44 and 0.48 per 100 women at 1 and 2 years, and reduced to 0.29 at the end of 10 years. Return of fecundity after discontinuing treatment was 53% after 12 months, 81% after 24 months and 89% after 36 months. The mean estradiol levels were 1,413 ± 161 pmol/l one week following the pellet installation. The mean serum estradiol level of the 43 women who were assayed arbitrarily or a year following last insertion was 1,207 pmol/l (range 462–2,904 pmol/l); 22% had serum estradiol levels <1,000 pmol/l and 6.3% (3 women) had levels >1,750 pmol/l. A total of 28 endometrial biopsies were obtained –19 were proliferative, 6 showed slight simple hyperplasia, and three, benign cystic glandular hyperplasia. ***Conclusion:*** Subcutaneous implantation of pure estradiol pellets offers excellent birth control, has minimal untoward effects, is simple to insert and can serve as a possible alternative for conception control. It could be considered for 3 indications: for women who have completed family planning; for women in older age group (above 35 years) who are approaching the climacteric; and for women at any age, who need prolonged periods of contraception.

Introduction

Solid pellets of estrogenic hormones were first implanted in animals in 1937 [1]. In 1942, Corner [2] predicted that 'pellets will probably be used in human cases

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in which long continued action is required, not only because of the continuous absorption, but also because insertion of the pellet, which can be done through a hollow needle, avoids repeated hypodermic punctures'. In 1949, hormonal implants were first introduced by Greenblatt and Suran [3] as an alternative treatment for the climacteric syndrome.

Estradiol pellets were first shown to suppress ovulation by Emperaire and Greenblatt [4] in 1969. They also observed the contraceptive efficacy of a combination of implants and cyclical progestogen, the latter given 5 days monthly to induce regular withdrawal periods. Their method involved implanting pure estradiol pellets subcutaneously every 6 months in a step-down fashion: 4 pellets in the first insertion, 3 in the second, 2 in the third, and from the fourth implantation 1 pellet every 6 months.

So long as the pellets are implanted in the subcutaneous tissue, there is slow absorption of the hormone from the site of implantation, with continuous release of small quantities of the steroid. The amount of absorption is apparently a physical phenomenon depending on the surface area of the pellets exposed to the dissolving action of the tissue fluids. The rate of absorption will depend on the number of pellets that are implanted (surface area), and the duration of its effect will depend on the weight of the pellets [5, 6]. The fate of an estradiol molecule that is absorbed through the subcutaneous tissue or other parenteral routes differs considerably from that of one that is absorbed enterally. With oral administration of estrogen there is an important 'first passage phenomenon' with extensive metabolic change in the intestinal wall and the liver before the molecule reaches the general circulation; in some cases virtually no unaltered substance will reach the circulation. The parenteral route of administration avoids the enterohepatic circulation and is associated with a more 'physiologic' state of plasma hormone levels (e.g. estradiol and estrone) [7, 8].

Over the years, particularly in the late 1970s and early 1980s evidence accumulated indicating a link between the progestogen component of oral contraceptives and the risk of arterial vascular disease, particularly myocardial infarction. This may be related to the effect of several combined oral contraceptives on lipid metabolism [9, 10]. At that same time, studies proved a beneficial effect of subcutaneously implanted pure estradiol pellets on the lipid profile, with a reduction in VLDL, LDL and HDL-1 and an increase of HDL-2, HDL-3 and total HDL – a situation favorable for preventing atheromatosis [11–13]. Based on this information we became interested in the use of pure estradiol pellets for birth control.

Table 1. Distribution of annual implantation by age

Age	Number of implantations
20–25	142
26–30	168
31–35	192
36–45	176
Total	678

The aim of the present study was to assess the contraceptive effectiveness of pure estradiol pellets, using a modification of Emperaire and Greenblatt's method.

Materials and Methods

Women attending our gynecology outpatient clinic were included in this study. The study group consisted of 228 women – all sexually active and wanting birth control for 1 year or more. Data regarding their ages, parity and desire for children in the future were collected. Human experimentation has been approved by our institutional review board. Candidates were informed that the method was undergoing trials and had not yet been approved for general use. Informed consent was obtained from each subject. The women were screened for the standard contraindications to the use of steroid contraceptives. Candidates were rejected if tests for anemia or urinary glucose were positive or if they had a history of undiagnosed genital bleeding.

The pellets were implanted subcutaneously in the abdominal wall, 1 inch above and parallel to Poupart's ligament. An intradermal wheal was raised with 0.5 ml of 1% procaine prior to insertion of a Kearn's implanter. We modified the Emperaire and Greenblatt method described above: our initial implant consisted of 5 pellets of estradiol (25 mg each) and was intended for birth control of 1 year. At each subsequent annual implant 4 pellets were implanted. Withdrawal bleeding was induced monthly with oral norethindrone acetate 5 mg, taken for 7 days. The first implantation cycle in our study was performed during the period from December 1987 to November 1997. The follow-up period extended to January 2000. Our experience encompassed 8,136 cycles, or 678 woman-years. The number of implants performed in the different age groups is shown in table 1. Hormone studies were performed on 8 women weekly for the first 6 months following implantation. They included FSH and estradiol. Also serum estradiol levels of 43 women who had been treated by hormone implantation were studied. Blood tests were performed if the women returned complaining of symptoms, or for renewed implantation. Endometrial biopsies were obtained from 28 women at various time intervals during therapy: 10 of them volunteers and 18 because of excessive bleeding.

Results

Data regarding the women's ages, parity and wish for children in the future are presented in table 2. The median age of the women was 29 years. Median parity was 2.4. At the admission interview some 44% of the women expressed their desire to have at least 1 more child, and 45% wished to have no more children. The remaining participants had not made up their minds.

Acceptability and Continuation Rates

Annual continuation rates were about 51 per 100 women in the second year, 65 in the third, 72 in the fourth and 84 ± 10.1 annually over the next 6 years (tables 3, 4). The increased annual continuation rates after the third year reflect the early dropout of women most prone to discontinue use – those under age 25 and those who used implants as a birth spacing method. Those two groups of women had significantly lower continuation rates than did the other women in this study. The average annual continuation rates for women under 25 at acceptance were 40 in the second implant and 58 in the third. Similarly, for women who intended to have another child, the average annual continuation rate was 47 in the second implant and 61 in the third.

Table 2. Distribution of age, parity and future birth wish of the acceptors

Characteristics	n	%
Age, years		
20–25	62	27
26–30	84	37
31–35	46	20
36–45	36	16
Total	228	100
Median	29	
Parity		
0 or 1	58	26
2	92	40
3	55	24
>3	23	10
Total	228	100
Wish for future births (at first acceptance)		
Yes	101	44
No	103	45
Unsure	24	11
Total	228	100

Table 3. Annual net cumulative discontinuation and continuation rates and events (per 100 users)

Rate	Years									
	1	2	3	4	5	6	7	8	9	10
Pregnancy	0.44	0.58	0.47	0.40	0.38	0.35	0.33	0.31	0.30	0.29
Total discontinuation	0	49	67	76	79	82	84	85	90	92
Continuation	100	51	33	24	21	18	16	15	10	8
Cumulative events										
Pregnancy	1	2	2	2	2	2	2	2	2	2
Completed full year	228	116	75	54	49	42	37	35	23	19
Number of woman-years	228	344	419	473	522	564	601	636	659	678

Table 4. Annual gross cumulative discontinuation and continuation rates (per 100 users)

Rate	Years									
	1	2	3	4	5	6	7	8	9	10
Pregnancy	0.44	0.86	0	0	0	0	0	0	0	0
Total discontinuation	0	49	35	28	9	14	12	5	34	17
Continuation	100	51	65	72	91	86	88	95	66	83

Contraceptive Effectiveness

Through 12 years of our study, 2 accidental pregnancies occurred. The first occurred 4 months after the first implantation. The second occurred during the 21st month of the experiment – 9 months after the second implant. Two more pregnancies took place within 3 weeks of the first insertion and should not be considered as contraceptive failures. The annual net cumulative pregnancy rates were 0.44 and 0.48 per 100 women at 1 and 2 years, and reduced to 0.29 at the end of 10 years.

Return to Fecundity after Discontinuation

During the test period, 32% (73) of the acceptors discontinued usage of the implant, stating that they wished to have another child. Seventy-three percent (53) of them conceived spontaneously, and in 27% (20) pregnancy was induced with clomiphene citrate, 500 mg. With that treatment, ovulation was readily induced.

Table 5. Life-table pregnancy rates after discontinuing estradiol pellets birth control for planned pregnancy (per 100 women)

Months	Cumulative pregnancy rate
3	11±4
6	38±7
12	53±7
24	81±8
36	89±6
48	97±3

The life-table pregnancy rates provide a summary of fecundity after implant removal (table 5). The 12-month pregnancy rate was 53 per 100 women, and the 24-month rate was 81. A cumulative pregnancy rate of 89% was achieved after 36 months.

Estradiol Levels

All 8 patients, in whom more extensive hormone studies were carried out, showed remarkable elevations of their plasma estradiol levels, starting 1 week following the implantation. The mean estradiol levels were 1,413 ± 161 pmol/l one week following the pellet installation. The high estradiol level remained steady throughout the study. Concomitantly, a decrease in follicle-stimulating hormone (FSH) levels was observed, from a mean of 8.7 to 5 IU after 8 weeks. This rate of decrease was somewhat slower than the change in estradiol. These results demonstrate the marked systemic effect of estradiol absorbed from the sustained release pellet – imitating the physiological situation. The mean serum estradiol level of the 43 women who were assayed arbitrarily or a year following last insertion was 1,207 pmol/l (range 462–2,904 pmol/l); 22% had serum estradiol levels <1,000 pmol/l and 6.3% (3 women) had levels >1,750 pmol/l.

Endometrial Biopsies

A total of 28 endometrial biopsies were obtained – 19 were proliferative, 6 showed slight simple hyperplasia, and 3, benign cystic glandular hyperplasia.

Clotting Factors

No cases of thrombophlebitis, blurred vision, cardiopathies or transient ischemic attacks were recorded during the whole study period.

Table 6. Reasons for method discontinuation of pellet implantation

	Years after first insertion									
	1	2	3	4	5	6	7	8	9	10
Continued method	228	116	75	54	49	42	37	35	23	19
Discontinued method	1	112	41	21	5	7	5	2	12	4
Reasons for discontinuing method										
Mild symptoms (headache, breast tenderness)	0	12	1	0	0	0	2	1	1	0
Uterine bleeding	0	7	5	2	1	1	1	1	0	0
Desire to conceive	0	47	15	7	4	4	1	0	1	0
No defined reason	0	45	20	12	0	2	1	0	10	4
Pregnancy	1	1	0	0	0	0	0	0	0	0

Reasons for Method Discontinuation throughout the Follow-Up Period

The reasons for discontinuation of pellet insertion appear in table 6.

Comment

Over the years evidence has accumulated indicating the link between the use of several oral contraceptives and the risk of atheromatosis, most probably due to their effect on lipid metabolism [9, 10]. In plasma, cholesterol and triglycerides are carried by lipoprotein fractions: chylomicrons, very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL). The synthetic progestogens used in oral contraceptives display androgenic and anti-estrogenic effects that can significantly alter lipoprotein metabolism. Several progestogens were found to decrease HDL cholesterol and increase LDL cholesterol [14]. Other effects include an increase in total plasma cholesterol, elevated triglyceride levels and increased levels of apolipoprotein B (Apo B – the main protein component of LDL), also associated with increased risk [15]. Conversely, a previous study of our group showed a beneficial effect of four subcutaneously implanted 25-mg pure estradiol pellets on the lipidogram [11–13]. In that study, high-density lipoprotein (HDL) cholesterol increased by 30%; there was a decrease in low-density lipoprotein (LDL) cholesterol levels of 25%; the percentage of HDL cholesterol of the total cholesterol increased by 50%. These changes are statistically significant. Triglycerides and VLDL levels showed no significant change. The subfraction of HDL also showed a positive change: as the total HDL increased, the subfractions HDL2 and HDL3 increased and HDL1 decreased. That shift is interesting as it mimics physiologic changes that occur to HDL subfractions close to ovulation time.

The estrogen concentrations attained in the liver sinusoids during the first passage are many times the maximum serum concentrations [8, 16]. That explains why oral administration can be associated with significant estrogen effects in the liver, such as stimulation of carrier proteins for hormones-including the sex hormone binding globulin (SHBG), proteins involved in the regulation of hemostasis, and the renin substance. The liver also affects lipid metabolism [17–19].

One of the most important effects of estrogen on the liver is its ability to increase procoagulant activity, primarily by inducing hepatic production of clotting factors [20]. This elevation in procoagulant activity can easily increase the risk for thrombotic events. We believe that the fact we had no thrombotic events of any kind during our 12-year series reflects the great advantage of this liver bypass method. We also assume that the usage of pure estradiol in itself lowered the likelihood of thrombotic events in this study, but this assumption has to be further investigated.

According to Greenblatt, pellets are implanted every 6 months in a step-down fashion: 4 pellets in the first insertion, 3 in the second, 2 in the third and from the fourth implantation 1 pellet every 6 months. With the aim of reducing the frequency of insertions, we modified Greenblatt's regimen: on the first implantation we inserted 5 pellets and continued with 4 pellets annually thereafter. Based on our modification, the first 2 years of conception control are achieved with 9 estradiol pellets, while Greenblatt's method uses 10. In order to achieve 3 years conception control, Greenblatt used 12 estradiol pellets, while we used 13.

Our data show that with the use of estradiol implants high serum estradiol levels only occur in only 6.3% of patients. A level of 1,750 pmol/l was chosen as the upper limit of the physiological range as this has been shown to be the highest level reached in the menstrual cycle of normal women at the time of the pre-ovulatory surge [22]. There is no evidence that estradiol values in excess of 1,750 pmol/l are associated with an increased incidence of deep venous thrombosis or carcinoma of the breast. Even the highest estradiol levels found are no greater than those recorded in the first month of pregnancy. However, further work is needed to determine the lowest dose of estradiol pellets necessary to achieve maximal contraceptive effect.

Greenblatt suggested induction of monthly withdrawal bleeding by oral norethindrone acetate, 5 mg, for 5 days. In order to reduce the incidence of dysfunctional uterine bleeding and endometrial hyperplasia, which occurred in some of Greenblatt's patients [6, 21], we extended the use of progestogen from 5 to 7 days monthly. In our series, bleeding occurred in only a few patients who did not follow orders for the proper monthly use of the progestogen. Greenblatt has shown that hyperplasia and cystic glandular hyperplasia readily change to a secretory type of endometrium following a course of an oral progestogen. In the current study, a total of 28 endometrial biopsies were obtained – 19 were proliferative, 6 showed slight simple hyperplasia, and three, benign cystic glandular hyperplasia. All endometrial histological changes were benign. However, as the progestational agent administered was for few (7) days only, further precaution, e.g. endometrial

biopsy, should be taken in all cases of dysfunctional uterine bleeding.

Following discontinuation of pellet implantation, resumption of fertility was somewhat slower compared to oral contraceptives; 73% of the women who wanted to conceive a child did so spontaneously, but 27% of them needed ovulation induction. In spite of the fact that we renewed the contraception annually it has to be emphasized that estradiol pellets, even if implanted just once, are able to prevent ovulation for a period of 3 years. We consider this one of the major disadvantages of this method. However, it should be stressed that ovulation can be induced at any stage during the contraception period (even immediately after pellet implantation) using clomiphene citrate. The reason of slow return of fertility lies in the fact that remnants of the inserted pellets remain and continue to secrete estradiol, albeit in decreasing doses, for up to 3 years.

In our study, 49% of those who discontinued did so after 1 year of pellet contraception, and a total of 67% did so after 2 years. Some investigators suggest that half or more of new users will stop using OCs within the first year [23, 24]. Among teenagers, 50% will discontinue use within the first 3 months [25]. Many of these women, most of whom still require contraception, will then either fail to immediately substitute another contraceptive method or will adopt a less reliable one [26]. The result is that pill discontinuation by women who remain at risk of pregnancy account for many unintended pregnancies. Our study shows a high continuation rate, in spite of the fact that the method is an investigational one.

Pure estradiol pellet implantation for conception control offers, in our opinion, an excellent alternative. The occurrence of only 2 pregnancies in 8,136 cycles reflects the efficacy of the method. Furthermore, this contraception method has several advantages over oral contraceptives, such as the absence of gastrointestinal symptoms, minimal untoward effects, and no possibility of patient failure through missing a pill. Patients who could not tolerate oral contraceptives because of headaches and nausea found the pellet regimen satisfactory.

In view of the efficacy, lack of untoward effects, the beneficial effect on the plasma lipid profile as discussed above, and the simplicity of insertion, we consider this contraception method a possible alternative for conception control. However, it remains to be investigated whether this promising method of contraception can be used whenever birth control pills and the IUD are contraindicated. In the meantime our recommendation is to consider this birth control modality for three indications: for women who have completed family planning; for women in older age groups (above 35 years) who are approaching the climacteric, since this treatment also provides estrogen replacement therapy, and for women at any age, who need prolonged periods of contraception.

Conclusion

Excellent contraception through subcutaneous implantation of estradiol pellets, thus avoiding the enterohepatic circulation, and good return of fecundity upon discontinuing treatment, was achieved.

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