****

Batch Name: 106709

Batch Creator: SWORD 1

Batch Creation Date: 2/8/2007

Batch Creation Time: 13:21:31

Number of Pages: 8 [All]

Printed by: SWORD 1

Print Date: 2/8/2007

Print Time: 13:24:3

****

by sigerson.sword.org (8.13.4/8.13.4/Debian-3) with ESMTP id l17Kub3P029471
by spamfirewall.muohio.edu (Spam Firewall) with SMTP id AAB7F3E69D3
(iPlanet Messaging Server 5.2 HotFix 2.09 (built Nov 18 2005))
id <0JD400C011RAN0@sms1.wright.edu>
(original mail from fill@www.libraries.wright.edu)
for requests@sword.org; Wed, 07 Feb 2007 15:52:25 -0500 (EST)
by sms1.wright.edu (iPlanet Messaging Server 5.2 HotFix 2.09 (built Nov 18
2005)) with ESMTP id <0JD400LT31ZDU5@sms1.wright.edu> for requests@sword.org;
Wed, 07 Feb 2007 15:52:25 -0500 (EST)
106709
Date: Wed, 07 Feb 2007 20:52:25 +0000 (GMT)
From: Fordham Interlibrary Loan <fill@www.libraries.wright.edu>
Subject: Please fill request
To: requests@sword.org
Content-transfer-encoding: 7BIT

Rule breakdown below

pts	rule name	description
0.00	UNPARSEABLE_RELAY	Informational: message has unparseable relay lines

This request has been forwarded from ILL by barb.

Please fill this request for FORDHAM HEALTH SCIENCES LIBRARY

106709

Call Number: 81386100508

Journal Title: Obstet Gynecol
Journal Vol: 50
Journal Issue:
Journal Year: 1977
Article Title: Clinical and endocrine studies in menopausal womoen after estradiol pellet implantation
Article Author: Nagamani, M
Article Pages: 541-

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

7pgs scanned 2/8/07

Clinical and Endocrine Studies in Menopausal Women After Estradiol Pellet Implantation

M. NAGAMANI, MD, T. J. LIN, MD, FACOG, P. G. McDONOUGH, MD, FACOG, H. WATATANI, MD, J. C. McPHERSON III, PhD, and V. B. MAHESH, PhD, D Phil

Eight patients who required prolonged estrogen replacement therapy were implanted with two 25-mg pellets of estradiol-17β and were followed with serial measurements of serum estradiol, estrone, follicle stimulating hormone, luteinizing hormone, and maturation index of the vaginal smears. There was a significant increase in estrogen levels within 24 hours after pellet implantation, and this level was maintained in physiologic premenopausal range during the rest of the period of followup. Gonadotropins were suppressed to a greater degree in gonadal dysgenesis patients as compared to postmenopausal patients. There was rapid relief of vasomotor symptoms within 4–10 days even though the gonadotropin levels were high. Implantation of 50 mg of estradiol pellets and periodic withdrawal bleeding with a progestational agent seems to be an effective method of long-term replacement therapy.

IMPLANTATION OF PELLETS for estrogen replacement therapy was first used by Bishop in 1938,[1] and it has been used by numerous investigators since then.[2–7] When hard pellets of pure crystalline steroids are implanted in the subcutaneous tissue, slow absorption of the hormone from the site of implantation results, and there is a 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 effectiveness will depend on the weight of the pellets.[2,3] In most of the earlier reports, followup of these patients with pellets had been mostly subjective in terms of improvement in symptoms and by changes in the vaginal smear. The availability of radioimmunoassays of steroids and gonadotropins has now made it possible for us to study these patients more extensively. Measurements of blood levels of estrone (E_1), estradiol (E_2), follicle stimulating hormone (FSH), and luteinizing hormone (LH) were carried out before and after pellet implantation. Maturation index of the vaginal smears was also used to follow these patients.

From the Departments of Endocrinology and Obstetrics and Gynecology at Medical College of Georgia, Augusta, Georgia.

Submitted for publication April 7, 1977.

MATERIALS AND METHODS

In this study, implantation of estradiol pellets was done in 8 patients who needed prolonged estrogen replacement therapy. The patients included in the study consisted of 3 patients with proven gonadal dysgenesis, 1 patient with premature menopause, 2 postmenopausal patients, and 2 patients with hypopituitarism (1 after hypophysectomy and 1 with Sheehans syndrome). All patients before treatment had castrate vaginal smears with no superficial cells. All had elevated gonadotropins except the 2 patients with hypopituitarism. The FSH level in Case 6 was well above the normal range but below that found in menopausal women. This lower level was found only in the initial sample. All subsequent samples showed levels clearly in the menopausal range. All subjects were free from any kind of medication for at least 2 months prior to inclusion in the study. Ages of the patients ranged from 17 to 57 years, the gonadal dysgenesis patients being in the younger age group. Before the pellets were implanted, at least one sample of blood was drawn for FSH, LH, estrone, and estradiol to obtain the basal levels of these hormones and the vaginal smear taken for maturation index. These basal values are shown in Table 1. All patients were implanted with two 25-mg pellets of estradiol.*

Technique of Implantation

All implantations were done in the right lower quadrant of the abdomen using Kearn's pellet implantor under strict aseptic conditions. After local infiltration with 2–3 ml of Xylocaine, an incision about 2 mm in size was made with a No. 11 blade knife. Through this incision, the pellet implantor was thrust into the subcutaneous tissue so that the tip of the needle was just superficial to the rectus sheath. The stylet of the in-

* Progynon (Schering)

TABLE 1. CLINICAL DATA BEFORE PELLET IMPLANTATION

Patient	Age	Diagnosis	Vaginal cytology (maturation index)	FSH (mIU/ml)	LH (mIU/ml)
1	28	Gonadal dysgenesis	60/40/0	>100	26.6
2	29	Gonadal dysgenesis	90/10/0	>100	21.8
3	17	Gonadal dysgenesis	0/100/0	>100	13.6
4	29	Premature menopause	10/90/0	110	26.6
5	57	Menopause	95/5/0	>100	27.4
6	50	Menopause	5/95/0	33.1	12.7
7	24	Hypophysectomy	10/90/0	2.3	<0.9
8	45	Sheehans	95/5/0	2.9	<0.9

strument was withdrawn and the pellets were introduced into the groove of the hollow needle. The blunt plunger was then pushed through the needle so as to push the pellets deep into the subcutaneous tissue. The entire instrument was then withdrawn, and the skin edges at the site of implantation were closed with two sterile steri strips. The entire procedure took less than 5 minutes, and all patients were able to resume full activity immediately without any discomfort.

The study design we used in the followup of these patients is shown in Table 2. Vaginal smear for maturation index and blood samples for gonadotropins, estrone, and estradiol were obtained every day for the next 5 days after pellet implantation, every week for the next 3 weeks, and every month during the rest of the followup. The longest followup was for 13 months. At the end of 3 months, a progestational agent (Provera*) was given, 10 mg daily for 5 days, to produce withdrawal bleeding, and this was repeated on the last 5 days of each month during the rest of the followup. For the purpose of studying the feedback effects of estradiol on the gonadotropin levels, we waited for 3 months to give the progestational agent, but in clinical practice, it should be given every month from the time of pellet implantation.

Hormone Assays

Serum was separated from the clotted blood sample and stored at −20 C until assayed. A double antibody radioimmunoassay was employed for the estimation of FSH and LH. The material for the radioimmunoassay of FSH and LH was obtained through National Institute of Arithritis, Metabolic and Digestive Diseases Hormone Distribution Program. The assay method used in our laboratory has been described earlier.[8] Serum estrone and estradiol were measured by multiple steroid radioimmunoassay by the method of Parker et al.[9] The antiserum used was raised in our laboratory, and its specificity has been described previously.[9] Vaginal smears were stained by modified Papanicolaou technique,[10] and reported as number of parabasal, intermediate, and superficial cells. Paired comparison Student *t* test was used for statistical analysis.[11]

* Provera—medroxy progesterone acetate (The Upjohn Co., Kalamazoo, Michigan).

RESULTS

The mean ± SE of the levels of estradiol and estrone before and after pellet implantation are shown in Figure 1. The mean increase in estradiol was 136.2 pg/ml, while the mean increase in estrone was 64.8 pg/ml. This increase in estrone indicates conversion of a portion of estradiol that is absorbed from the pellet into estrone. The increase in estrogen levels within 24 hours after pellet implantation was both substantial and significant. The estrogen level reached the premenopausal range of the follicular phase of the menstrual cycle, and this level was maintained during the rest of the period of followup. There was no statistically significant difference ($P > 0.1$) between the level of estradiol 24 hours after implantation and the mean of the levels during 1–76 days of the followup (Figure 2). The mean level of estrone during 1–76 days of followup was higher than the level at 24 hours after implantation, and the difference was statistically significant using the paired Student *t* test ($P < 0.05$) (Figure 3). This indicates that more estradiol is converted to estrone with increasing duration of implantation.

Figure 4 shows the levels of FSH with increasing duration of implantation. In postmenopausal patients, there was some reduction of gonadotropins, but they were not suppressed to premenopausal levels even though serum estrogen levels were maintained in the premenopausal range. The gonadotropin levels were found to be more suppressible in gonadal dysgenesis patients even though it took 3–6 weeks to reach the premenopausal range. The magnitude of suppression was more for LH than for FSH.

TABLE 2. STUDY DESIGN

Pellet implantation	Followup
Estradiol-17β 50 mg*	Vaginal cytology Estrone Estradiol FSH and LH
	Days 1–5 Weeks 1–3 Months 1, 2, 3, . . .

* Progynon (Schering)

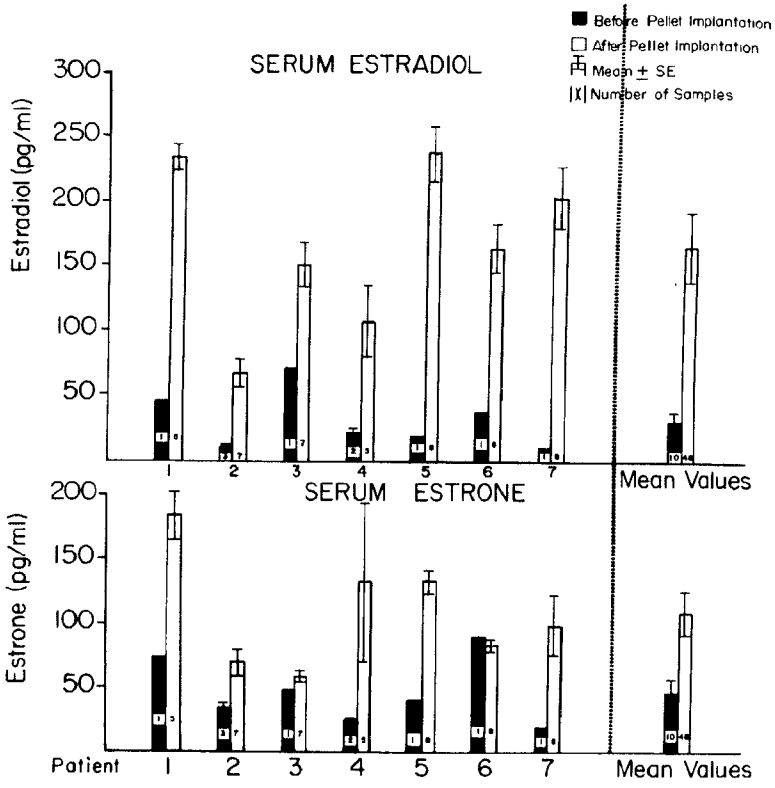

Fig 1. Levels of estradiol and estrone before and after pellet implantation in each patient and the mean values.

Vaginal Cytology

All subjects responded with about 30% superficial cell count within 14 days after pellet implantation, and this was maintained approximately at this level during the rest of the period of followup. There were individual variations in the response of the vaginal epithelium to the serum estrogen levels. Some patients responded quickly within 48 hours, but some took 14 days to reach the 30% level, even though serum estrogen levels increased within 24 hours after implantation.

Figure 5 shows the followup for 76 days in 1 of our patients with serial vaginal smears and blood levels of gonadotropins and steroids.

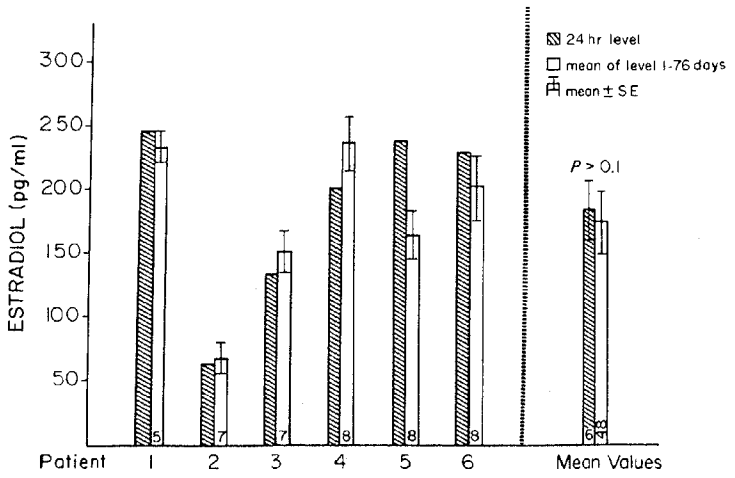

Fig 2. Serum estradiol levels in women 24 hours and 1-76 days after estradiol pellet implantation.

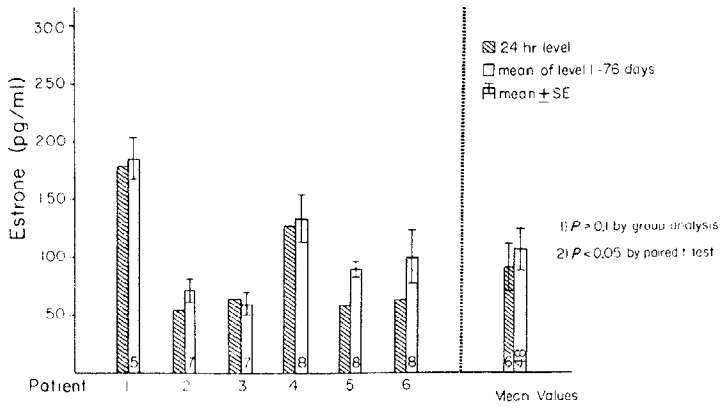

Fig 3. Serum estrone levels in women 24 hours and 1-76 days after estradiol pellet implantation.

DISCUSSION

Since estradiol is the major steroid involved in the regulation of gonadotropin secretion by its negative and positive feedback effects,[12] this study, in addition to assessing the clinical effectiveness of pellets, has also helped us to study the gonadotropin dynamics of patients with high levels of gonadotropins due to an unrestrained hypothalamic pituitary axis. In postmenopausal patients, the gonadotropins were not suppressed to premenopausal levels even though the estrogen levels were maintained throughout the study in the physiologic premenopausal range. In patients with gonadal dysgenesis, in whom the hypothalamic pituitary system had never been exposed to the cyclic feedback effects of endogenous estrogens, the gonadotropin levels were suppressed to a greater degree as compared to the postmenopausal patients. Nevertheless, it took as long as 3-6 weeks from the day of implantation to reach the premenopausal levels. Thus, the sensitive nature of the negative feedback mechanism in these patients seems to become modified by elimination or absence of the suppressing agent (endogenous estrogens) and permits castrate levels of gonadotropins to occur. Several investigators have studied the effects of acute infusions of different doses of estradiol on the gonadotropin levels in postmenopausal women.[13-15] At a low dose of estrogen, there was some lowering of the elevated FSH levels, but it was not suppressed to premenopausal levels. Uniform suppression was noted only with very high doses.[14] LH was suppressed more readily than FSH.[15] Oral estrogens in the form of 17β estradiol or ethinyl estradiol also resulted in significant suppression of gonadotropins only with large doses.[16-18] All these previous studies were done with administration of estradiol for a short period of time. In this study, we have maintained the blood estrogen levels in a physiologic premenopausal range for a period of several months. In the postmenopausal women, the gonadotropin levels were not suppressed to premenopausal levels even after this prolonged exposure to estrogens. The reason for this interesting change in the sensitivity of the negative feed-

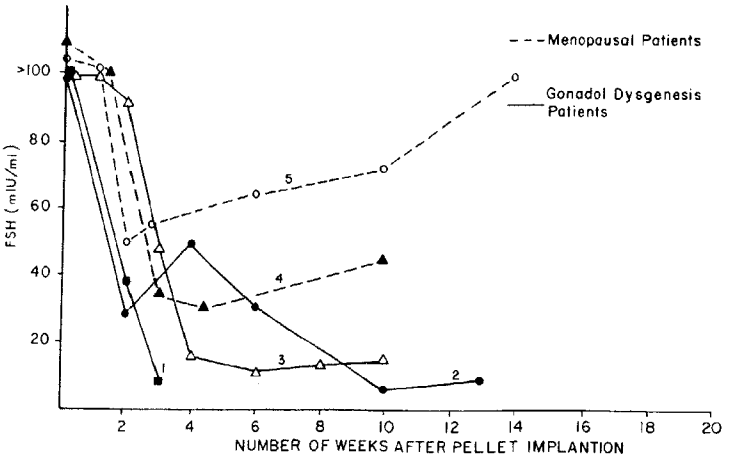

Fig 4. FSH levels with increasing duration of pellet implantation.

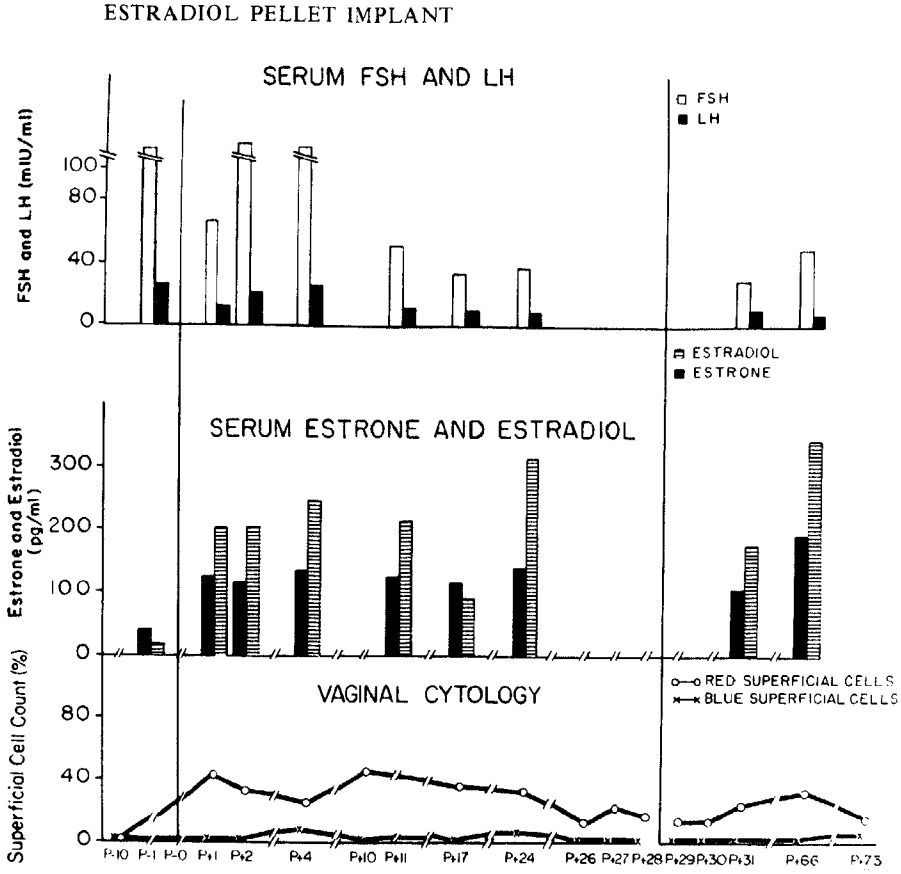

Fig 5. Followup for 76 days in Patient 4 with serum gonadotropins, estrone, estradiol, and vaginal cytology. P-O represents the day of pellet implantation, −1, −10, and +1, +2, etc, represent number of days before and after pellet implantation, respectively.

back mechanism in these patients is not well understood. Dilman[19] postulates that there is gradual decrease in the sensitivity of the hypothalamic pituitary axis with increasing age. The feedback suppression of the hypothalamus by estrogens becomes less and less effective with aging. Dilman further notes that during perimenopausal years there is progressive increase in both phenosteroids (classic and nonclassic estrogens) and gonadotropins, and this simultaneous increase in phenosteroids and gonadotropins is evidence of alteration in the sensitivity of feedback systems with the process of aging. Experimental evidence for change in sensitivity in the rat has been obtained in our laboratory. In the 26-day-old immature rat, a dose of 0.2 μg/kg bodyweight of estradiol was able to prevent the postcastration rise of gonadotropins, whereas in the adult rat, 1.6 μg/kg bodyweight dose of estradiol was necessary for a similar effect.[20] However, in 23-month-old anovulatory rats, a much larger dose of estradiol (12.8 μg/kg bodyweight) was necessary to prevent the postcastration rise of gonadotropins.[21] There are considerable species differences in the rat and the human, especially during the process of aging, which should always be kept in mind in extending the results of animal studies to the human.

There was rapid relief of symptoms such as hot flashes, sweating, nervousness, and dryness of the vagina in all patients within 4–10 days after implantation of the estradiol pellet, even though the gonadotropin levels were high. This confirms the belief that vasomotor symptoms are unrelated to gonadotropin levels.[22] There were no side effects except for transient mild breast tenderness noted in 2 of our patients. In all the earlier reports on patients with intact uteri being treated with pellets,[23–25] there was a high incidence of irregular breakthrough bleeding, which might be due to the fact that none of these patients was treated with progestational agents. One of our patients (Patient 8 in Table 1) who failed to take the progestational agent until the end of 4 months after pellet implantation experienced breakthrough bleeding, which was controlled once she was started on a cyclic regimen of a progestational agent. The rest of the patients who had regular followup and who were treated with Provera did not have any breakthrough bleeding. Periodic use of progestational agents in these patients not only produces predictable withdrawal bleeding, but also prevents unopposed estrogenic stimulation of the endometrium and other target organs, as in breasts. Incomplete shed-

ding of the endometrium, due to failure to take the progestational agent or inadequate dosage, may lead to development of varying degrees of hyperplasia of the endometrium. Whenever spotting or irregular bleeding are noted, an endometrial biopsy should be obtained. If hyperplasia or mild atypical changes are present, the monthly doses of oral progestogen are doubled and given for an extended period of 7–10 days, and a repeat biopsy is obtained. Progesterone in adequate doses had been shown to convert all degrees of cystic and adenomatous hyperplasia to secretory endometriums.[26] Greenblatt et al[27] administered 40 mg of norethindrone acetate (Norlutate) daily for 5 days when severe atypia was encountered. There is considerable controversy in the literature regarding the role of estrogens in the development of endometrial carcinoma. No clear-cut evidence on the cause and effect is yet available. Nevertheless, in view of the controversy, it is imperative that careful followup and evaluation of every patient on estrogen treatment be done and that no signs of endometrial abnormality be neglected.

The duration of effectiveness of two 25-mg pellets of estradiol-17β from previous reports varies from 6–11 months,[28,29] and 100-mg pellets, 16–18 months.[30,31] In our present study, in 7 of our patients, the pellets have been effective for 11–12 months with maintenance of blood estrogen levels in the premenopausal range. In 1 patient who has been followed for only 9 months, the pellets are still active. We need to implant two 25-mg pellets of estradiol approximately once every year to maintain the estrogen levels in a physiologic range. Since the rate of absorption will be different in individual patients depending on the site of implantation, presence of scar tissue, etc., the exact time of reimplantation should be determined according to the development of symptoms and estrogen deficient vaginal smears. The obvious advantage of pellet implantation over other methods of replacement therapy is its prolonged duration of effectiveness. This eliminates the inconvenience of taking a pill every day except for the progestational agent taken on 5 days of the month. There is maintenance of steady levels of estrogens with pellet implantation compared to the wide fluctuations of blood levels seen during the day with oral or other routes of administration. This seems to give the patient a feeling of well-being, and we noticed a definite patient preference for pellets over other methods of administration. Additionally, there is the advantage of taking a natural hormone, since estradiol is the major steroid secreted by the premenopausal ovaries. Lebech and Boggaard have reported that synthetic estrogens cause a rise in triglyceride levels and a fall in antithrombin-III concentrations in the blood, and such effects were not observed with natural estrogens.[32] This may indicate less incidence of thromboembolic disorders with natural estrogens. Other side effects of synthetic steroids like glucose intolerence, hypertension, and weight gain have been reported to be significantly less with natural estrogens.[33]

REFERENCES

1. Bishop PMF: A clinical experiment in Estrin therapy. Br Med J 1:939–941, 1968
2. Greenblatt RB, Hair LQ: Testosterone propionate absorption in the female. J Clin Endocrinol 2:315–317, 1942
3. Greenblatt RB, Suran RR: Indications for hormonal pellets in the therapy of endocrine and gynecic disorders. Am J Obstet Gynecol 57:294–301, 1949
4. Perloff WH: Treatment of menopause. Am J Obstet Gynecol 58:684–694, 1949
5. Brown ML, Lucente ER, Alesbury JM, et al: Treatment of surgical menopause with estradiol pellets at the time of operation. Am J Obstet Gynecol 61:200–201, 1951
6. Kupperman MS, Delaplaine RW, Bottomy JR: Effective control of surgical menopause by estradiol pellet implantation at the time of oophorectomy and total hysterectomy. J Clin Endocrinol 11:788, 1951
7. Delaplaine RW, Bottomy JR, Blatt M, et al: Effective control of surgical menopause by estradiol pellet implantation at the time of surgery. Surg Gynecol Obstet 94:323–333, 1952
8. Greenblatt RB, Dmowski WP, Mahesh VB, et al: CLinical studies with an antigonadotropin—Danazol. Fertil Steril 22:102–112, 1971
9. Parker RC, Ellegood JO, Mahesh VB: Methods of multiple steroid radio immunoassay. J Steroid Biochem 6:1–8, 1975
10. Lin TJ, Doshi NS, John M, et al: Cyanophilic superficial cells during stilbestrol administration in patients with estrogen deficient vaginal cytogram, air dried smears and rapid modified Papanicolaou technique. Obstet Gynecol 35:676–684, 1970
11. Sokal RR, Rohlf FJ: Biometry. San Francisco, WH Freeman and Company, 1969, pp 331–333
12. Mahesh VB: The interrelationship between steroids and gonadotropin secretion during ovulatory cycle. Excerpta Medica International Congress Series No. 370. Recent Advances in Human Reproduction: Proceedings of the First International Congress on Human Reproduction. Rio de Janeiro, Brazil. Amsterdam, Excerpta Medica, 1974, pp 161–173
13. Yen SSC, Tsai CC, Vandenberg G, et al: Gonadotropin dynamics in patients with gonadal dysgenesis, a model for the study of gonadotropin regulation. J Clin Endocrinol Metab 35:897–904, 1972
14. Tsai CC, Yen SCC: Acute effects of intravenous infusion of 17β estradiol on gonadotropin release in pre- and post menopausal women. J Clin Endocrinol 32:766–771, 1971
15. Nillus SJ, Wide L: Effects of estrogen on serum levels of LH and FSH. Acta Endocrinol 65:583–594, 1970
16. Yen SSC, Martin PL, Burnier AM, et al: Circulating estradiol, estrone and gonadotropin levels following the administration of orally active 17β estradiol in post menopausal women. J Clin Endocrinol Metab 40:518–521, 1975
17. Wise AJ, Gross MA, Schlach DS: Quantitative relationships of the pituitary gonadal axis in post menopausal women. J Lab Clin Med 81:28–36, 1973
18. Odell WD, Swerdloff RS: Progestogen induced luteinizing and follicle stimulating hormone surge in post menopausal women: A simulated ovulatory peak. Proc Natl Acad Sci USA 61:529–536, 1968
19. Dilman VM: Age associated elevation of hypothalamic threshold to feed back control. Lancet 1:1211–1219, 1971
20. McPherson JC III, Elridge JC, Costoff A, et al: The pituitary

gonadal axis before puberty. Effects of various estrogenic steroids in the ovariectomized rat. Steroids 24:41–55, 1974
21. McPherson JC III, Costoff A, Mahesh VB, Medical College of Georgia, Augusta, Georgia (Unpublished data)
22. Aitken JM, Davidson A, England P, et al: The relationship between menopausal vasomotor symptoms and gonadotropin excretion in urine after oophorectomy. J Obstet Gynaecol Br Commonw 85:150–154, 1974
23. Salmon VJ, Geist SH, Walter RI: Treatment of menopause, evaluation of estrogen implantation. JAMA 117:1843–1849, 1941
24. Perloff WB: Treatment of estrogen deficiency with estradiol pellets. J Clin Endocrinol Metab 10:447–454, 1950
25. Jarolim C, Bernard LI, Straus AH: Estrogen substitution therapy with pellet implantation. Am J Obstet Gynecol 94:170–177, 1966
26. Steiner GJ, Kistner RW, Graig JM: Histological effects of progestins on hyperplasia and carcinoma *in situ* of the endometrium: Further observations. Metabolism 14:356–386, 1965
27. Greenblatt RB, Bryner JR: Estradiol pellet implantation in management of the menopause. J Reprod Med 18:307–316, 1977
28. Okie V: Treatment of menopause by estradiol pellet implantation. NY State J Med 49:1175–1176, 1949
29. Soule DS, Burnstein R: Prophylaxis of post surgical menopause. Am J Obstet Gynecol 77:1254–1259, 1959
30. Hunter SJD, Akande EO, Carr P, et al: The clinical and endocrinological effect of estradiol implants at the time of hysterectomy and bilateral salphingo oophorectomy. J Obstet Gynaecol Br Emp 84:827–833, 1973
31. Hunter SJD: Oophorectomy and the surgical menopause, The Menopause. Edited by RJ Beard. Lancaster, England, MTP Press, 1976, pp 203–217
32. Lebech PE, Borggaard B: Serum lipid and antithrombin-III changes effected by synthetic and natural estrogen therapy. The Menopausal Syndrome. Edited by RB Greenblatt, VB Mahesh, PG McDonough. New York, Medcom Press, 1974, pp 68–74
33. Greenblatt RB, Asch RH, Mahesh VB: Implantation of pure crystalline pellets of estradiol for conception control. Am J Obstet Gynecol 127:520–524, 1977

Address reprint requests to
M. Nagamani, MD
Department of Endocrinology
Medical College of Georgia
Augusta, GA 30901

Accepted for publication June 6, 1977.