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Subcutaneous hormone replacement therapy

V.A. Tzingounis, A.G. Perdikaris, G. Lioutas and D. Dimopoulos

Department of Obstetrics and Gynecology, University of Patras, Rio Patras, 26500 Patras, Greece

Summary

It is estimated that 75% of women are in an acute estrogen deficiency state within a few years after the onset of the menopause. Every woman inevitably reaches this phase except for a fortunate few who have some source of endogenous estrogens available to them. We believe it would be prudent to offer hormone replacement therapy to every woman with symptoms of the menopause, and to those in whom symptoms are not patently manifest, if an estrogen deficit is present as indicated by vaginal cytology. Certainly even in the absence of symptoms, the presence of osteoporosis is sufficient reason to initiate small doses of estrogens (along with increased calcium and protein uptake, and exercise) for the remainder of the woman's lifetime. Crystaline pellets of 17β-estradiol offer excellent relief of symptoms for those postmenopausal women who fare poorly on oral estrogens or intramuscular injections. Although somewhat more expensive than other modes of therapy, pellet use is convenient, highly effective and associated with few side effects.

Estradiol; Pellets; Implantation; Menopause; Lipoproteins

Introduction

From what has been estimated, 75% of women are in an acute estrogen deficiency state within a few years after the onset of the menopause. Every woman inevitably reaches this phase except for a fortunate few who have some source of endogenous estrogens available to them.

In the past the opinion was that only those with hot flashes and atrophic vaginitis should receive estrogen therapy. The American College of Obstetricians and Gynaecologists had suggested therapy thought in the case of '...severe vasomotor instability and atrophic urethriris and vaginitis,... therapy should be designed to maintain the patient's health with the smallest effective dose'. Osteoporosis, emotional stability and decreased tissue tone were suggested as possible indications for therapy [1].

Furthermore, we believe that the very presence of a castrate smear, even in the absence of symptoms, is reason for hormone replacement therapy. However, all complaints arising in the climacteric should not be labelled 'menopausal', and therapy should be instituted after careful evaluation to eliminate other serious disorders. No more than 15–20% of women will undergo a symptom-free menopause [2].

Few will deny that sex steroids are of value in relieving menopausal symptoms. Oral and injectable modalities have long earned their place in therapy. For a small percentage, perhaps as high as 10–15% of estrogen-deficient women, oral medication is not completely satisfactory for a variety of reasons: unreliability in taking the drug, poor absorption and untoward effects such as nausea, headache or incomplete relief. Intramuscular therapy at 2–4-week intervals, may be inconvenient [3,4].

For such patients, crystaline pellets of 17β-

estradiol, for the past 55 years have been used [5–7]. Excellent patient acceptance and remarkable relief of symptoms have been the rule. Bishop [8] first described the use of estrogen pellets in treatment. Pellets have since been used by numerous other investigators [9,10].

Materials, Methods and Results

The local preparation of the skin for pellet replacement consist of the cleaning of the place of insertion with betadine and 95% ethyl alcohol. A 0.5 ml 2% xylocaine is injected intradermally, creating a wheal. A Kearn's implanter is inserted through the wheal subcutaneously approximately 4–5 cm above and parallel to Poupart' s ligament.

A variety of regimens is employed; from 1–4 E_2 pellets (25 mg) may be implanted at 6-month intervals. The dosage may be increased or decreased according to response. In those with an intact uterus, a progestogen (medroxyprogesterone acetate 10 mg or norethisterone acetate 5 mg p.o. per day for 7–10 days each month) must be given to induce withdrawal bleeding and avoid abnormal bleeding episodes as well as atypical endometrial hyperplasia.

We studied the effect of estrogens on serum lipids by the following procedure. Serum lipids levels were assessed in 24 menopausal women before and after hormonal-replacement therapy. The length of treatment was 12 months. Prior to treatment the average lipid levels were as indicated in Table I.

TABLE I

Serum lipids levels in menopausal women before and after hormonal replacement therapy

Parameter (mmol/l)	Prior therapy ($n = 24$)	After 6 months therapy ($n = 24$)
Total cholesterol	6.5	5.6
HDL cholesterol	1.6	1.8
LDL cholesterol	4.8	3.9
Triglycerides	1.1	0.9

*$P < 0.01$.

Levels of all lipids changed statistically significantly ($P < 0.001$) compared with the pretreatment levels, while there were no indications of vaginal bleeding or any adverse estrogen induced effects.

Discussion

Cytologic evaluation has liminations [11,12]. Individual sensitivity to various levels of estrogens causes differences in vaginal maturation [13]. Hormone profile — elevated serum FSH and LH and low estradiol — are far more accurate methods of assessing the menopause state.

The amount and rate of absorption of crystalline pellets of estradiol will vary depending on the implantation site and the number of pellets implanted (surface area) [9,10]. The serum estradiol levels will depend on the number of pellets implanted. Promenopausal levels were attained within 24 h [14]. When four pellets of estradiol were implanted and decreased by one every 6 months, the estradiol levels were maintained [15].

Estrogen favorably alters lipid metabolism and should therefore offer protection to the cardiovascular system in estrogen uses with the increase in cardiac output, in arterial blood flow velocity and a decrease in vascular resistance and blood pressure [16]. Estrogen therapy probably should not be used in patients with a history of phlebitis or thromboembolic episodes, undiagnosed vaginal bleeding, history of breast (unless therapeutic) or endometrial carcinoma [17] and, possibly, hypertension. Hypertension and liver disease rarely are sequelae of natural estradiol, estrone or estriol administration but may follow synthetic estrogens and estrogen-like substances. Weight gain can be controlled by diet, mild edema may be managed by limitation of salt and, if necessary, by a mild diuretic [18]. Breakthrough bleeding or menorrhagia occasionally occurs in those patients for whom the progestogen dosage is inadequate or after the patient's failure to take the progestogen as directed. If this happens, bleeding may be arrested readily (after obtaining an endometrial biopsy) by the administration of two 5-mg tablets of norethindrone acetate or two 10-mg tablets of medroxyprogesterone acetate every 2–4 h until

bleeding stops, then b.i.d. for 10 days an orderly withdrawal period usually takes place 2–3 days after completion of a course of progestogen therapy [19].

Another untoward reaction is the occurance of an occasional hematoma. Persistent oozing or bleeding from the site of implantation may be arrested by continuous pressure. A foreign body reaction, with suppuration and expulsion of the pellet, may be an unexpected but occasional complication [10].

Conclusion

The effect of estrogen on serum lipids is often cited as a possible mechanism of action, ERT use has been associated with a decrease in total serum cholesterol and low-density lipoprotein cholesterol and with an increase in high-density lipoprotein cholesterol [20,21]. The resulting lipid profile is favorable for the prevention of atherosclerosis [22] and also promotes the protection of cardiovascular system by vascular assessment and regulation.

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