Use of Oral or Subcutaneous (pellet) Estradiol 17B with Natural Progesterone in 200 Patients Followed for 10 years

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INTRODUCTION

Hormone replacement therapy in the peri- and post-menopausal patient has assumed a major role in office gynecology. The number of patients requiring initiation or adjustment of hormone regimens is rapidly increasing with many of these patients in the perimenopause. An even larger number of women will experience menopausal symptoms. In fact, by the year 2000, the number of women over the age of 65 will be double what it is now.[1] The gynecologist must be able to individualize treatment by altering routes of administration, type and dose of hormone to achieve the best result in a given patient.

The benefits of long term hormone replacement therapy are well established and include reduction of mortality due to cardiovascular disease[2-5] and hip fractures (osteoporosis).[6,7] Relief from perimenopausal symptoms including dysfunctional uterine bleeding, premenstrual syndrome, migraine headaches, mood and behavioral disorder can be attained when proper hormone balance is achieved. In the postmenopause patient, reversal of hot flashes, genital atrophy, bladder symptoms, loss of libido, depression, memory loss and insomnia will result from proper hormone replacement therapy. Despite the beneficial effects, 50% of women prescribed treatment will not be using their hormones after one year. This is due to unwanted bleeding that occurs with the sequential use of estrogen and progestin but can occur also with the combined use. The other reason for non-compliance is side effects of the progestin.

Estradiol (EB) and progesterone (4-pregnane-3, 20 dione) as they occur naturally in humans would appear to cause less bleeding problems than non-human estrogen. Non-human estrogen has a varied effect on the endometrium and a greater impact on the liver.[8] In addition, using micronized natural progesterone, one can achieve the uterine carcinogenic protective effect while minimizing the adverse effects of progestin on high density lipoprotein (HDL) cholesterol.[9,10] Additionally, natural progesterone is not associated with the side effects of progestin namely fluid retention, breast tenderness, depression and weight gain. Therefore, estradiol and progesterone appear preferable for long-term hormone replacement therapy.

The purpose of this study was to evaluate the use of oral or subcutaneous (pellet) estradiol[12,13] and oral micronized progesterone in peri- and post-menopausal patients followed for 10 years.

MATERIALS AND METHODS

Two hundred patients from a private practice of OB/GYN were started on hormonal replacement therapy for a variety of symptoms.

The patients presented with symptoms relating to ovarian hormone imbalance or hormone deficiency were all seen initially by the author. Many of the patients were seen in consultation for hormonal problems after having an evaluation elsewhere. The patients were seen at +1,3,6 month intervals and then annual visits thereafter. At each visit, the women were interviewed and questionnaires about symptoms or bleeding patterns were completed. They had a complete physical examination and initial blood work including FSH1 Blood Panel, Cholesterol, HDL and LDL. Mammograms were obtained according to ACOG recommendations. Endometrial biopsies, pelvic sonography, D&C, and hysteroscopy were accomplished as clinically indicated.

The patients were divided into two groups:

1. Perimenopause (PEM) defined by irregular or excessive menstruation or clinical symptoms and FSH> 15 IU/L.

2. Postmenopause (POM) defined by natural or surgical absence of menses. There were 73 (PEM) patients and 127 (POM) patients. Many of the (PEM) patients might also be defined as having premenstrual syndrome. The initial complaints of the (PEM) patients included dysfunctional uterine bleeding, cyclic vascular headaches, anxiety, depression, insomnia, diminished libido, breast tenderness, bloating and dysmenorrhea. The (POM) patient's symptoms included hot flashes, night sweats, vaginal dryness, dysuria, dysparuenia, diminished libido, depression,, memory loss and insomnia.

The patients in Group 1 (PEM) received sequential estradiol [E2] and progesterone [P] therapy, while Group 2 (POM) received combined E2 & P therapy. A subgroup of (POM) patients who did not respond to oral therapy satisfactorily were placed on subcutaneous (pellet) implants. Of these patients, those with an intact uterus received oral micronized progesterone daily, while those with surgical menopause and no uterus received only the estradiol implants. In some cases, estradiol and testosterone implants were utilized.

The hormones in Group 1 (PEM) patients were micronized estradiol 17B USP 0.5 mgm mixed with alpha lactose in gelatin capsules (Bajamar Labs, St. Louis, MO) taken 25 days a month with micronized USP progesterone 100 mgm in gelatin capsules (Bajamar Labs, St. Louis, MO) taken BID, 14 days per month.

The hormones in Group 2 (POM) patients were micronized estradiol 17B 0.35 mgm and micronized progesterone 100 mgm both in a single capsule taken daily. In some cases the dose was increased to one capsule BID. The implants were 25 mgm estradiol pellets, average 2 pellets and 75 mgm testosterone proprionate pellet. (College Pharmacy, Colorado Springs, CO.)

Table 1 Hormone Replacement Therapy: (PEM) Patients
E2 25 days/month P 14 days/month N=73

Symptom	Initial Visit	1mo.	6mo.	12mo.	Current
Dysfunctional Uterine Bleeding	58	35	12	3	10
Cyclic Vascular Headaches	15	15	8	2	2
Anxiety	43	40	22	18	15
Depression	26	9	12	11	6
Breast Tenderness	42	38	6	0	0
Bloating	19	18	3	0	0
Dysmenorrhea	32	21	11	10	9

Table 2 Hormone Replacement Therapy: (POM) Patients
E2 & P combined in One Capsule Daily* N=127

Symptom	Initial Visit	1mo.	6mo.	12mo.	Current

Hot Flashes	110	85	22	3	0
Vaginal Dryness	56	50	37	10	0
Dysuria	22	10	0	0	0
Diminished Libido	62	62	48	35	25
Depression	83	76	52	38	18
Memory Loss	96	90	73	45	38
Easy Crying	115	102	65	25	22
Insomnia	112	96	15	0	0
Uterine Bleeding or Spotting	35	32	0	0	0

RESULT

Thirty-two of the original two hundred patients are no longer being seen due to death, moving away from the area, or dissatisfaction with treatment. The remaining patients are continuing follow-up visits. The group 1 (PEM) patients who initially showed dysfunctional uterine bleeding patterns reverted to normal patterns in 75% of the cases. However, this is modified by the fact that some of the persistent cases subsequently underwent hysterectomy or endometrial ablation. Additionally, at an average age of 50, the (PEM) patients were successfully convened to (POM) patients by switching to a combined E2 & P regimen. It generally took 6 months after switching regimens for the amenorrheic pattern to occur.

In Table I the number of patients with residual symptoms at varying intervals of time are listed. Within one year, these patients showed regulation of their menstrual pattern and significant decrease in the symptoms associated with premenstrual syndrome. Those patient% continuing with significant hyper or polymenorrhea eventually came to hysterectomy or endometrial ablation. The menstrual flow pattern decreased the longer the patient was on sequential hormone therapy. When the patients were switched to a combined regimen, they eventually became amenorrheic. In some cases the decision to switch therapy was dictated by failure of withdrawal bleeding after 1 to 2 months of progesterone only therapy. This can be an indicator to convert a (PEM) patient to a (PONI) patient instead of an arbitrary age of 50.

In table 2, the (POM) patients showed excellent relief of hypoestrogenic symptoms on the combined regimen. In addition, compliance was aided by the necessity of taking only one capsule per day containing both E2 & P. The patients were especially satisfied by having no sporadic bleeding or spotting while obtaining benefits of estrogen therapy. Forty-two patients continued to complain of some hypoestrogenic symptoms and were given estradiol (and in some cases testosterone) pellets. This mode of treatment is very effective in this select group of patients. The use of hormone implants was initiated by Dr. Robert Greenblatt in the 1930's. It provides a constant hormone release and stable blood level for the patient who otherwise is unable to achieve relief of symptoms by the oral or transdermal (patch) route.

CONCLUSION

The perimenopausal patient with her associated symptoms of abnormal bleeding patterns, premenstrual syndrome, and vascular headaches can benefit from hormone balance therapy. The use of sequential estradiol 17B with oral micronized progesterone offers an excellent method of therapy. It does not appear advantageous to substitute progestogens which while effective can "muddy the water" by aggravating symptoms of breast tenderness, depression, bloating etc. - the very symptoms we are trying to relieve.

The postmenopausal patient benefits from combined estradiol and micronized progesterone therapy without the continued bleeding pattern associated with the use of medroxyprogesterone. The progesterone also does not alter the favorable changes in lipoproteins induced by estrogen. In addition, compliance is aided by the two hormones together in one capsule being ingested once per day.

It remains to be proven if the protection in the long term against osteoporosis and cardiovascular disease will remain the same with these agents. However, low dose micronized 17B estradiol has been shown to prevent bone loss in postmenopause women and micronized oral progesterone has been shown to be active in bone metabolism altering bone turnover and acting directly on the osteoblast to promote bone formation.

Finally, alternative routes of therapy must be utilized in individual patients for whom oral therapy is not successful. Subcutaneous (pellet) implants are an effective, simple method to be utilized when necessary.

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REFERENCES

1. World Health Communications Inc. News Letter: May, 1992.
2. Henderson, 13.E., Paganini-Hill, A., and Ross, R.K.: Estrogen replacement therapy and protection from acute myocardial infarction, Am. J. Obstet. Gynecol. 159:312-7, 1988
3. Henderson, B.E., et al.: Estrogen use and cardiovascular disease, Am. J. Obstet. Gynecol. 154:1181-6, 1988.
4. Barrett-Conner, E., Wingand, D.L., and Criqui, M.H.: Postmenopausal estrogen use and heart disease risk factor in the 1980's, JAMA 261:2095, 1989.
5. Nabulsi, A.A., and Folsom, A.R. et al.: Association of hormone replacement therapy with various cardiovascular risk factors in postmenopausal women, N. Engl.. J. Med. 328:1069, 1993.
6. Ettinger, B., Genant, H.K., and Cann, C.E.: Long term estrogen replacement therapy prevents bone loss and fracture, Ann. Intern. Med. 102:319-24, 1985
7. Horsman, A., et al.: The effects of estrogen dose on postmenopausal bone loss, N. Engl. J. Med. 309:1405-7,1983.
8. Mashchak. C.A., Lobo, R.A., Mishell, Jr. D.: Comparison of pharmaco dynamic properties of various estrogen formulations, AM. J. Obstet. Gynecol. 144:511, 1982
9. Jensen, j i'S, B.J,: Long term effects of percutaneous estrogen and oral progestetotic on serum lipoprotein in postmenopausal women, Am. J. ObstetOynecol. 156:66-71,1987.
10. Hargrove, J.T+, Maxson, W.S., Wentz, A.L., and Burnett, L.S.: Menopausal hormone replacement therapy with continuous daily oral micronized estradiol and progesterone, Obstet. Gynecol. 73:606-12, 1989.
11. Chakmakjian, L., et a!.: Bioavailability of progesterone with different modes of administration, J. of Reprod. Med. 32:443-447, 1987.
12. Brincat, M., Magos, A., Studd, J.W.W., et al.: Subcutaneous hormone implants for the control of climacteric symptoms, Lancet 1:16, 1989.
13. Schleyer-Saunders, E.: Hormone Implants, the menopause syndrome. Edited by Greenblatt, R.B., Mahest, V.B. New York, Medcom Press, 1974:88-94.
14. Ettinger, B., Genant, H.K., et al.: Low dosage micronized 17B estradiol prevents bone loss in postrnenopausal women, Am. J. Obstet. Gynecol. 166:479-88, 1992.
15. Prior, J.D.: Progesterone as a bone-trophic hormone, Endocr. Rev. 11:386, 1990.