

Practical Perspectives

Management of Hormone Replacement Therapy Side Effects

R. Don Gambrell, Jr.

Department of Physiology and Endocrinology, Medical College of Georgia, Augusta, Georgia, U.S.A.

Abstract: Side effects of hormone replacement therapy (HRT) may keep a significant number of women from continuation of therapy. These include breast tenderness; edema or bloating; premenstrual syndrome (PMS)-like symptoms such as headache, irritability, depression, and lethargy; and withdrawal bleeding. With the many different progestogens and regimens available, therapy should be individualized to meet the patient's need. Each has its advantages and disadvantages, but it is sometimes possible to eliminate withdrawal bleeding. The continuous combined method of HRT may not be fully endometrium protective because cases of endometrial cancer are beginning to surface. There is increasing evidence that added progestogen may even protect the bones and the breast. When adequate dosages of estrogen are given, there is no adverse effect of HRT on lipids and lipoproteins over the long term. Side effects from added progestogens may be severe in a small percentage of women. However, by adding a mild diuretic, changing the type, dosage, route of administration, or the regimen, usually a progestogen can be found for symptom-free hormone replacement. **Key Words:** Hormone replacement therapy—Estrogen—Progestogen.

Compliance is a major problem with hormone replacement therapy (HRT) because up to 50% of women prescribed treatment are not still using their hormones after 1 year. Side effects of estrogens, and particularly progestogens, are the major reason. Yet progestogens are essential in women with intact uteri to prevent endometrial cancer. This author is in the minority who believe that there are other benefits of added progestogen. There is considerable evidence of synergistic action of estrogen plus progestogen to increase bone mineral content, particularly in cortical bone (1-5). Even more controversial is the effect of added progestogen on

breast cancer risk. With the publication of the 22-year study of Nachtigall et al. in 1992 and Laitinen's 20-year study in 1993, the direct evidence is increasing that added progestogen significantly reduces the risk for breast cancer (6,7). However, two epidemiologic studies observed nonsignificant increased risk of breast cancer (8,9). The Danish 5-year study showed a relative risk (RR) of 1.36 (95% CI, 0.98-1.87) (8), and the Swedish study observed an RR of 4.4 (95% CI, 0.9-22.4) after 6 years of estrogen-progestogen use (9). However, by adding 4 additional years of study, the RR in the Swedish study decreased from 4.4 to 1.3 (95% CI, 1.1-1.6) (10). The indirect evidence as to why added progestogen should decrease the risk for breast cancer is becoming almost overwhelming (11-21). Because of this increased protection of the bones and the breast, it has been my practice for more than a

Received February 23, 1994; accepted May 23, 1994.

Address correspondence and reprint requests to Dr. R. Don Gambrell, Department of Physiology and Endocrinology, Medical College of Georgia, Augusta, GA 30912, U.S.A.

decade to add progestogens to the therapy of all patients using estrogen replacement therapy (ERT), including women who have had a hysterectomy. With 30 years of experience of prescribing progestogens to postmenopausal women and the many different progestogens available, I have found a symptomless progestogen for almost all patients.

SIDE EFFECTS OF PROGESTOGENS AND THEIR MANAGEMENT

With HRT, withdrawal bleeding occurs in as many as 97% until age 60, decreasing to 60% after age 65. Patient acceptance of resumption of menses has been good when the benefits and risks are explained. The menses often change for the better with lighter withdrawal flow and less painful and less abnormal bleeding. After menopause, withdrawal periods from hormone replacement are usually only 3–4 days in duration, free from dysmenorrhea, and without premenstrual syndrome (PMS).

However, side effects from either unopposed estrogens or the added progestogen are real and may be severe in some patients. With cyclic sequential therapy, they are severe enough in 8% of patients to require some type of medical intervention. The various methods of hormone administration are given in Table 1. With continuous sequential therapy, they are severe in 14%, which is why the cyclic sequential therapy is preferred for new patients. These include breast tenderness, edema or bloating, and PMS-like symptoms such as headache, abdominal pressure, irritability, depression, and lethargy. Many of these are related to fluid retention, and 50% of patients with side effects will respond to a mild diuretic such as 25–50 mg of either spironolactone or hydrochlorothiazide. Paradoxically, breast tenderness may be either aggravated or relieved with added progestogen. Breast tenderness and sometimes slight breast enlargement may occur during the first 2–3 months of estrogen therapy. Mastodynia usually abates with time, so reassurance is often all that a patient needs. If breast tenderness persists, the estrogen dosage can be re-

duced if >0.625 mg conjugated estrogens was prescribed. However, this should be the lowest dosage, because 0.625 mg is needed to prevent osteoporosis.

Adding a progestogen to unopposed estrogen therapy reduces breast tenderness in time, although it may initially aggravate the discomfort. For this, 10 mg medroxyprogesterone acetate for 12–14 days is usually the most effective progestogen. In severe cases, a 1% progesterone cream can be applied directly to the breast or 50–100 mg danazol may be given for 3 months. Reassurance to the patient is often all that is needed. Adding androgens to estrogen therapy or to estrogen–progestogen therapy may also ameliorate breast tenderness. For this, usually 2.5–5 mg of either methyltestosterone or fluoxymesterone is used.

A mild diuretic will relieve symptoms caused by estrogen-related fluid retention, such as edema, abdominal pressure, bloating, breast tenderness, or PMS-like symptoms (headache, irritability). The diuretic is usually given 7–10 days before menses or during the days of added progestogen and will resolve at least 50% of the side effects from hormone replacement. A change to a different estrogen is sometimes necessary, or a change in the route of administration, such as transdermal estradiol, may help. Nausea is rare with the low dosages of estrogen usually required for replacement. If nausea persists for >2 months of therapy, a change of estrogens or the route of administration may help.

Headaches are usually relieved by estrogen replacement. Most headaches are transient and respond to analgesics or diuretics or both. Other headaches may occur only with cyclic therapy during the days at the end of the month when estrogens are not taken. Estrogens can be taken continuously as long as they are opposed with progestogens for 12–14 days each month. Migraine or migrainoid headaches during the reproductive years frequently cease at the time of menopause and may rarely recur with estrogen replacement. Sometimes headaches respond to a mild diuretic, but it may be necessary to add an androgen to the estrogen therapy. The best response is offered by combination products, such as esterified estrogens [methyltestosterone (orally)], estradiol cypionate [testosterone cypionate (injection)], or estradiol [testosterone (pellet implantation)].

Most of the side effects of added progestogen are PMS-like symptoms such as lethargy, depression and irritability, abdominal bloating, and cramping.

TABLE 1. *Methods of hormone administration*

Regimen	Estrogen	Progestogen
Cyclic sequential	1st–25th/month	13th–25th/month
Continuous sequential	Every day	1st–14th/month
Continuous combined	Every day	Every day
Cyclic combined	1st–25th/month	1st–25th/month

Mild PMS-like symptoms usually respond to a mild diuretic but in some women can be severe, requiring a change to another progestogen (Table 2). The lowest dosage of medroxyprogesterone acetate that will fully protect the endometrium is 10 mg when given cyclically for 12–14 days. For cyclic combined therapy, the 2.5 mg medroxyprogesterone acetate seems to be sufficient. Although 5 mg medroxyprogesterone acetate may protect the endometrium in some women using ERT, nearly every study that has compared the two dosages has found fewer favorable changes than with 10 mg (22–25). In a 1-year prospective study, Gelfand and Ferenczy (22) observed a 10% endometrial hyperplasia rate with 5 mg medroxyprogesterone acetate for 11 days combined with 25 days of conjugated estrogens, 1.25 mg. Although they had no endometrial hyperplasia in patients using 0.625 mg conjugated estrogens and 5 mg medroxyprogesterone acetate, this was only a 12-month study, and the cases of endometrial cancer did not start appearing until 2–4 years of low-dosage continuous combined estrogen–progestogen use. In their dose-ranging studies, Whitehead and Fraser (23) not only observed endometrial hyperplasia with 5 mg medroxyprogesterone acetate but also had proliferative and nonsecretory endometrium with only 64.7% showing full secretory transformation. Gibbons et al. (24) studied estrogen receptors and histologic patterns with dosages of medroxyprogesterone acetate of 2.5, 5, and 10 mg. Those receiving the 10-mg dosage had a better secretory transformation, and the parameters measured, including gland epithelial height, gland diameter, percentage of glands showing secretion, the quality of the secretion, the pseudodecidual stroma, and the percentage of subnuclear vacuoles, were significantly better in the group receiving the higher dosage.

Lower dosages of the C-19 progestogens may fully protect the endometrium, so many of the side effects can be eliminated by lowering the dosage to 2.5 mg of either norethindrone acetate or norethindrone. Alternatively, the low-dosage progestogen-only birth control pills can be used to decrease the dosage even further. Even 1 mg norethindrone or 0.150 mg norgestrel, when given for 12–14 days, may be endometrium protective (23,25). None of the 73 patients given 0.7 to 5 mg norethindrone had either hyperplasia or proliferative endometrium, although 13.7% did not show full secretory transformation. Some women cannot tolerate any of the oral synthetic progestogens because of side effects. These patients can be treated with progesterone suppositories 25 mg b.i.d. for 12 to 14 days. Oral micronized progesterone is becoming more readily available. To fully protect the endometrium, 300 mg daily in divided dosages must be given for 12–14 days. Because the major side effect of oral progesterone is sedation, it is usually given 100 mg in the a.m. and 200 mg at h.s., when sedation is desirable.

Side effects from added progestogens may be severe in a small percentage of women. However, by adding a mild diuretic, changing the type, dosage, or route of administration, usually a progestogen can be found for symptom-free hormone replacement.

METHODS OF HORMONE REPLACEMENT

Several methods of hormone replacement are suitable for treating menopausal symptoms, and each has its advantages and disadvantages. Therapy should be individualized to fit each woman's need. The method preferred for new patients with an intact uterus is the cyclic sequential regimen (Table

TABLE 2. Available progestogens

Brand name	Progestogen	mg Available	Minimum effective dosage
Provera	Medroxyprogesterone acetate	2.5, 5, 10	10 mg daily
Curretab	Medroxyprogesterone acetate	10	10 mg daily
Cycrin	Medroxyprogesterone acetate	10	10 mg daily
Amen	Medroxyprogesterone acetate	10	10 mg daily
Aygestin	Norethindrone acetate	5	2.5 mg daily
Norlutate	Norethindrone acetate	5	2.5 mg daily
Norlutin	Norethindrone	5	2.5 mg daily
Megace	Megestrol acetate	20, 40	40 mg daily
Ovrette	Norgestrel	0.075	0.150 mg daily
Micronor	Norethindrone	0.35	1.05 mg daily
Nor-Q.D.	Norethindrone	0.35	1.05 mg daily
	Progesterone vaginal suppositories	25, 50	25 mg b.i.d.
	Oral micronized progesterone	50, 100	300 mg in divided doses

1). This has the fewest side effects except for withdrawal bleeding: 97% of women will have resumption or continuation of menstrual periods until age 60. After 65, ~40% will cease having withdrawal bleeding; however, 60% of women will continue to menstruate with either the cyclic sequential or continuous sequential methods. These withdrawal periods are usually light with 3–5 days of flow that is usually painless. Because cyclic sequential therapy has fewer side effects than the continuous sequential therapy, it is preferred for new patients. However, if women on this regimen have menopausal symptoms such as hot flashes, night sweats, or insomnia during the days off estrogen at the end of each month, the estrogen can be given continuously and the progestogen added for the first 12–14 days each month (continuous sequential).

Women object to resumption or continuation of menstruation so the continuous combined and cyclic combined regimens have been devised to produce amenorrhea. With the continuous combined method, low dosages of estrogens such as 0.625 mg conjugated estrogens, or equivalent dosages of other natural estrogens, are given along with medroxyprogesterone acetate 2.5 mg of norethindrone acetate 2.5 mg every day for 365 days a year. For the first 4–6 months, there is a lot of spotting or breakthrough bleeding, but by 6 months, 60–65% of women using continuous combined therapy become amenorrheic. The other 35–40% will need to use one of the sequential methods.

After 2–3 years of amenorrhea with the continuous combined regimen, some women will start spotting or breakthrough bleeding again. Until December 1992, all endometrial biopsies performed by this author showed atrophic endometrium. These are difficult to manage, and increasing the dosage of progestogen to 5 mg, even 7.5 mg, rarely helps the breakthrough bleeding, so these patients usually must be given one of the sequential regimens. In December 1992, an 81-year-old patient of mine was found to have grade 3 poorly differentiated adenocarcinoma of the endometrium with >50% myometrial invasion. This was not the well-differentiated adenocarcinoma seen with unopposed estrogen therapy years ago. Leather et al. (26) had previously reported two cases of endometrial cancer after 2 and 4 years of amenorrhea in the 41 patients remaining on continuous combined estrogen-progestogen therapy after 8 years. Between July 1993 and April 1994, this author has learned of 12 other cases of endometrial cancer for a total of 15

with the continuous combined method. This may be only the tip of the iceberg after a decade of experience with this regimen. It may be very important to withdraw the progestogen for a few days each month to allow any build-up of endometrium to be shed.

A BETTER METHOD?

For the past 4 years, this author has been using the cyclic combined regimen to produce amenorrhea (27). Low-dosage estrogen and low-dosage progestogen are given by the calendar from the 1st through the 25th of each month (Table 1). In my experience, it is clinically superior to the continuous combined method in that after a comparable amount of spotting the first month of therapy, there is less breakthrough bleeding, usually 1 or 2 days of spotting on the 26th or the 27th or both. More women will become amenorrheic by 4 months (75%) compared to 60–65% with the continuous combined regimen. When bleeding does occur with the cyclic combined method, it is usually only 1 or 2 days of spotting on the 26th or 27th or both, which most patients can accept when a full explanation and reassurance are given. Whether the cyclic combined regimen will be more endometrial-protective than the continuous combined method remains to be proven, because we have only 4 years' experience. Theoretically it should be, because discontinuing the progestogen should allow for shedding any build-up of endometrium. Side effects are fewer with cyclic combined therapy, although they are also very infrequent with the continuous combined regimen.

WHY ADDED PROGESTOGEN SHOULD DECREASE BREAST CANCER RISK

Carcinoma of the breast is not primarily a hormonal disorder but is more related to family history, diet, smoking, and alcohol, and the greatest risk factor is age. Hormones or hormonal deficiency may serve as cofactors or predisposing factors or perhaps even promoting agents. The indirect evidence that added progestogen reduces the risk for breast cancer is increasing; several studies have shown an increased risk of breast cancer in women with long-term progesterone deficiency (11–13). Comparative trials between tamoxifen and either medroxyprogesterone acetate or megestrol acetate indicate that progestogens are just as effective in

the treatment of metastatic breast cancer (14). One of the most effective therapies for stage IV metastatic carcinoma of the breast at the M. D. Anderson Cancer Center is a combination of estrogen and progestogen (15). Seven days of estrogen are given to enhance progesterone receptors in mammary cancer cells followed by 21 days of high-dosage medroxyprogesterone acetate for 21 days in repeated cycles. The objective remission response was 56.7% for up to 6 years. Not only do oral contraceptives significantly reduce the risk of benign breast disease, but either birth control pills or progestogens reverse both intraductal hyperplasia and atypia of the breast (16). Performing mastectomy during the luteal phase of the menstrual cycle improves overall survival and recurrence-free interval for breast cancer in premenopausal women (17,18). In a study from France, patients were treated with percutaneous application to the breast for 11–13 days before surgery of either a placebo gel, a gel containing progesterone, or a gel containing estradiol (19). The mitotic index was significantly lower in the progesterone gel group (0.04) than in either the placebo gel group (0.1) or the estradiol gel group (0.2). In a study of human breast cancer cells in tissue culture, growth factor was slightly stimulated (13–40%) with either estradiol or progesterone; however, estradiol plus progesterone significantly reduced growth factor in 85% (20). An Australian study of 90 patients with breast cancer treated with continuous combined low-dosage estrogen (conjugated estrogens, 0.625 mg), and moderate-dosage progestogen (medroxyprogesterone acetate, 50 mg), observed no deaths in the HRT users, whereas 9.86% of the control group died (21). A part of this study, matching 68 subjects with three controls in a case-control study, confirmed significantly fewer recurrences among the hormone users.

LIPIDS AND LIPOPROTEINS

Finally, concern has been expressed for more than a decade of potential adverse effects of progestogens on high-density lipoprotein (HDL) cholesterol, possibly decreasing the great benefit of estrogen therapy reducing the risk for coronary artery disease. The reduction of HDL cholesterol was observed only in short-term studies with no adverse effect from progestogens over the long term when adequate dosages of estrogen were given (28–32). In fact, there may even be a beneficial effect of the added progestogens on lipids. Most studies show

that oral estrogen therapy increases triglycerides, which may not be clinically important unless total cholesterol levels are also elevated. However, several studies have observed that the added progestogen at least partially blocks this increase in triglycerides (29–31).

REFERENCES

- Christiansen C, Christensen MS, Transbol I. Bone mass in postmenopausal women after withdrawal of oestrogen/progesterone replacement therapy. *Lancet* 1981;1:459.
- Jayo MJ, Weaver DS, Adams MR, et al. Effects on bone of surgical menopause and estrogen therapy with or without progesterone replacement in cynomolgus monkeys. *Am J Obstet Gynecol* 1990;193:614.
- Munk-Jensen N, Nielsen SP, Obel EB, et al. Reversal of postmenopausal vertebral bone loss of oestrogen and progestogen: a double blind placebo controlled study. *Br Med J* 1988;296:1150.
- Prior JC. Progesterone as a bone-trophic hormone. *Endocr Rev* 1990;11:386.
- Gallagher JC, Kable WT. Effect of progestin therapy on cortical and trabecular bone: comparison with estrogen. *Am J Med* 1991;90:171.
- Nachtigall MJ, Smilen SW, Nachtigall RD, et al. Incidence of breast cancer in a 22-year study of women receiving estrogen-progestin replacement therapy. *Obstet Gynecol* 1992;80:827.
- Lauritzen C. Östrogensubstitution in der postmenopause vor und nach behandeltem genital- und mammaakarzinom. *Menopause Hormonsubstitution Heute* 1993;6:76.
- Ewertz M. Influence of non-contraceptive exogenous and endogenous sex hormones on breast cancer risk in Denmark. *Int J Cancer* 1988;42:832.
- Bergkvist L, Adami H-O, Persson I, et al. The risk of breast cancer after estrogen and estrogen-progestin replacement. *N Engl J Med* 1989;321:293.
- Persson I, Yuen J, Bergkvist L, et al. Combined oestrogen-progesterone replacement and breast cancer risk [Letter]. *Lancet* 1992;340:1044.
- Coulan CB, Annegers JF. Chronic anovulation may increase breast cancer risk. *JAMA* 1983;249:445.
- Cowan LD, Gordis L, Tonascia JA, et al. Breast cancer incidence in women with a history of progesterone deficiency. *Am J Epidemiol* 1981;114:209.
- Ron E, Lunenfeld B, Menczer J, et al. Cancer incidence in a cohort of infertile women. *Am J Epidemiol* 1987;125:780.
- Buzdar AU. Progestins in cancer treatment. In: Stoll BA, ed. *Endocrine management of cancer*. Basel: Karger, 1988: 1–15.
- Hortobagyi GN, Hug V, Buzdar AU, et al. Sequential cyclic combined hormonal therapy for metastatic breast cancer. *Cancer* 1989;64:1002.
- Voherr H. Oral contraceptives and hormone replacement therapy: are progestogens and progestins breast mitogens? *Am J Obstet Gynecol* 1986;155:1140.
- Badwe RA, Gregory WM, Chaudary MN, et al. Timing of surgery during menstrual cycle and survival of premenopausal women with operable breast cancer. *Lancet* 1991; 337:1261.
- Senie RT, Rosen PP, Rhodes P, et al. Timing of breast cancer excision during the menstrual cycle influences duration of disease-free survival. *Ann Intern Med* 1991;115:337.
- Barrat J, de Lignières B, Marpeau L, et al. Effet *in vivo* de l'administration locale de progestérone sur l'activité mito-

- tique des galactophores humains. *J Gynecol Obstet Biol Reprod* 1990;19:269.
20. Jones B, Russo J. Influence of steroid hormones on the growth fraction of human breast carcinoma. *Am J Clin Pathol* 1987;88:132.
 21. Eden JA, Wren BG, Nand S. A study of the effect of hormone replacement therapy on all cause mortality and recurrence rate in women with breast carcinoma. Presented to the North American Menopause Society, San Diego, 2-4 September, 1993.
 22. Gelfand MM, Ferenczy A. A prospective 1-year study of estrogen and progestin in postmenopausal women: effects on the endometrium. *Obstet Gynecol* 1989;74:398.
 23. Whitehead MI, Fraser D. The effects of estrogens and progestins on the endometrium. *Obstet Gynecol Clin North Am* 1987;14:299.
 24. Gibbons WE, Moyer DL, Lobo RA, et al. Biochemical and histologic effects of sequential estrogen/progestin therapy on the endometrium of postmenopausal women. *Am J Obstet Gynecol* 1986;154:456.
 25. Whitehead MI, Townsend PT, Pryse-Davies J, et al. Effects of estrogen and progestins on the biochemistry and morphology of the postmenopausal endometrium. *N Engl J Med* 1981;304:1599.
 26. Leather AT, Savvas M, Studd JWW. Endometrial histology and bleeding patterns after 8 years of continuous combined estrogen and progestogen therapy in postmenopausal women. *Obstet Gynecol* 1991;78:1008.
 27. Darj E, Nilsson S, Axelsson O, et al. Clinical and endometrial effects of oestradiol and progesterone in postmenopausal women. *Maturitas* 1991;13:109.
 28. Jensen J, Nilas L, Christiansen C. Cyclic changes in serum cholesterol and lipoproteins following different doses of combined postmenopausal hormone replacement therapy. *Br J Obstet Gynecol* 1986;93:613.
 29. Barrett-Conner E, Wingand DL, Criqui MH. Postmenopausal estrogen use and heart disease risk factors in the 1980s. *JAMA* 1989;261:2095.
 30. Gambrell RD Jr, Teran A-Z. Changes in lipids and lipoproteins with long-term estrogen deficiency and hormone replacement therapy. *Am J Obstet Gynecol* 1991;165:307.
 31. Nabulsi AA, Folsom AR, White A, et al. Association of hormone-replacement therapy with various cardiovascular risk factors in postmenopausal women. *N Engl J Med* 1993;328:1069.
 32. Miller VT, Muesing RA, La Rosa JC, et al. Quantitative and qualitative changes in lipids, lipoproteins, apolipoprotein A-1, and sex hormone-binding globulin due to two dosages of conjugated equine estrogen with and without a progestin. *Obstet Gynecol* 1994;83:173.