CLIMACTERIC 2006;9:224–233

Moderate dosage estrogen–androgen therapy improves continuation rates in postmenopausal women: impact of the WHI reports

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Key words: POSTMENOPAUSAL, MODERATE-DOSAGE HRT, CONTINUATION RATES

ABSTRACT

Objective The purpose of this report is not to provide descriptive data for practice recommendations but to point the way to more liberal thinking than the conservatism of today. The patients in this historical practice, where moderate dosages of estrogen are used, with androgens added when indicated, continue hormone replacement therapy (HRT) for many years. These women were audited to determine the reasons for continuance.

Design During the 3 years from 1996 to 1999, 814 women have been followed prospectively, the date of this first visit recorded, as well as the date last seen, the years of hormone use, and their current hormone replacement, so that continuation rates could be determined. The records of the patients were reviewed in January 2005 to determine the impact of the Women's Health Initiative (WHI).

Results Of the 814 patients, there were 573 surgically menopausal women with a mean age of 61.8 ± 3.25 years and 241 naturally menopausal women with a mean age of 58.6 ± 3.08 years. During the 3 years of observation, 692 women continued HRT while 122 discontinued their therapy. Of those continuing therapy, 606 were treated with the implantation of various combinations of estradiol and testosterone pellets, while 86 used injectables, patches or oral hormones. Continuation rates for pellet patients were 96.7% for 10 years, 88.8% for 20 years, and 21.9% for 40 or more years. Continuation rates for the other hormone users were 53.5% for 10 years and 20.9% for 20 years. Eighty-one percent of the patients were prescribed progestogens, and 18 different progestogens or dosages or regimens were used to individualize therapy and provide as side-effect-free a regimen as possible. Continuation rates in the 692 remaining patients declined to 66.7% during the next 5 years.

Conclusions Moderate dosages of estrogens, with androgens added when indicated, improve continuation rates. Therapy must be individualized so that not only are menopausal symptoms relieved but also side-effects are minimal and women continue to feel good. The implantation of estradiol and testosterone pellets is not necessary for even the majority of postmenopausal women. However, estrogen dosages must be adequate to provide a sense of well-being. After the WHI reports, continuation rates declined more rapidly.

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ORIGINAL ARTICLE

DOI: 10.1080/13697130600643437

Received 6-07-05
Revised 8-02-06
Accepted 13-02-06

INTRODUCTION

To achieve the maximum benefits of hormone replacement therapy (HRT), postmenopausal women should continue their hormones for many years. Unfortunately, continuation rates are quite low. In one study, only 19% of women using continuous combined HRT and 24% of women using cyclic sequential HRT were still using these regimens at 3 years[1]. In another study, at the end of the first year, the continuation rate was 68.9% in the continuous combined HRT users and only 54.4% in the sequential HRT users[2]. In a study of women between 46 and 63 years of age enrolled in a prescription plan, continuation rates were 80% at 6 months, 62% at 1 year, and only 41% at 2 years[3]. The reasons women give for discontinuing therapy include resumption of bleeding, perceived increased risk of breast cancer, unacceptable side-effects, and that treatment is no longer necessary[1–4]. It has been suggested that low dosages of estrogens are less likely to have unacceptable side-effects, such as irregular bleeding, heavy bleeding, or breast tenderness, and that long-term continuance may be improved[5]. However, it has also been suggested that the most common cause of poor continuation is that the treatment does not work because the women do not feel better[6].

One of the founders of the International Menopause Society, Dr Robert B. Greenblatt, suggested many years ago that many women need higher dosages, higher estradiol levels, rather than the lowest possible dosages of estrogen that will eliminate the minor symptoms of menopause. Although hot flushes, night sweats and vaginal dryness are relieved, there is little to any improvement in depression, loss of energy, loss of libido, headaches, irritability and a decrease in general well-being. Women with the most severe symptoms are those who have their ovaries removed during their reproductive years. Not only do they miss their ovarian estrogens, but they also miss their androgens.

In one study, 200 patients were treated with the implantation of estradiol and testosterone pellets following hysterectomy[7]. The continuation rate at 2 years was 97.4% and the overall satisfaction was positive in 88.7% of patients. No progestogens were used by these women; this reduced the side-effects and, of course, there was no resumption of bleeding after the hysterectomy. However, progestogens can be added to estrogen replacement when side-effects are effectively managed and bleeding problems greatly reduced by individualizing therapy to each patient so that continuation rates are equally as good[8]. This report is from one practice, established 60 years ago, where estradiol and testosterone pellet implantation has been used in the majority of postmenopausal women.

The world of postmenopausal hormone users and prescribing physicians was turned upside down in the summer of 2002 with the media blitz over publication of the Women's Health Initiative (WHI) findings[9]. Women's concern about hormone use increased sharply following early termination of the estrogen–progestogen arm of the WHI. Many women discontinued therapy without even discussing it with their physician, and many clinicians, not understanding the methodology of the study, advised their patients to stop hormone therapy.

METHOLOGY AND SUBJECTS

The concepts outlined in this report are not representative of current recommendations. They stem from Dr Robert B. Greenblatt, one of the pioneers in hormone replacement, who initiated HRT in the majority of these patients 30–50 years ago. He also taught these concepts to the authors, 28 and 35 years ago, who continue to follow his original patients, adding many more throughout the years. The descriptive data may not prove anything, but may show how long women will continue HRT when they feel well, and may point the way to more liberal thinking than the conservatism of today. Not only is this of historical value, but could provide ideas for regimens that should be considered in future trials.

During the 3 years from 1996 to 1999, 814 women have been followed prospectively to determine continuation rates. They have been referred to our practice by other physicians and our patients primarily because they have side-effects using oral estrogens. A small book entitled *Estrogen Replacement Therapy User Guide*[10] is given to each new patient on their first visit. The number of estradiol and/or testosterone pellets is adjusted when necessary until menopausal symptoms are relieved, side-effects are minimized, and the patient continues to feel good. Oral progestogens are added to pellet implantation in all women with intact uteri and also in the majority of those who have had a hysterectomy. Side-effects are managed by adding a mild diuretic, or changing the type, dosage, or route of administration of the

progestogen until an effective, side-effect-free regimen is found[8,11]. Continuation rates decreased more rapidly following the publication of the WHI reports in July 2002. Records of 690 patients using HRT at the end of the 3-year prospective study in 1999 were reviewed in January 2005 to determine the impact of the WHI reports upon continuation rates that had previously been so good.

RESULTS

The 814 patients were divided into two groups: 573 who had a surgical menopause and 241 who underwent natural menopause. The naturally menopausal women were slightly younger, with a mean age of 58.6 ± 3.03 (SEM) years, while the surgically menopausal group had a mean age of 61.8 ± 3.25 years. A woman having a surgical menopause is defined as one who has had a hysterectomy and bilateral salpingo-oophorectomy. This group also contained those with hysterectomy with retention of one or both ovaries but whose ovaries had ceased to function. The mean age of the women was calculated from the attained age at the end of the 3-year prospective study in 1999. The ages ranged from 27 to 94 years and all the patients had used hormones for 1 to more than 50 years at this time. Figure 1 shows the 606 patients who continued pellet implantation during the 3 years of observation from 1996 to 1999. As indicated in Figure 1, 606 women used pellet implantation for at least 1 year, including 442 surgically menopausal women and 164 naturally menopausal women. At 10 years, 586 have continued pellet implantations, 542 for 20 years, 408 for 30 years, and 133 for 40 years. Two surgically menopausal women have used pellets for 50 years and one for 51 years. Continuation rates for pellet patients are 96.7% for 10 years, 88.8% for 20 years, 67.3% for 30 years and 21.9% for 40 or more years. Table 1 shows the mean duration of therapy for each combination of estradiol and testosterone pellet implantation and the other hormone therapies used in the 692 patients still continuing treatment in 1999. Injectables include estradiol cypionate (usually 5 mg every 4 weeks) and estradiol cypionate 4 mg/testosterone cypionate 50 mg, also usually given every 4 weeks. Oral estrogens include conjugated estrogens 0.625 mg, 0.9 mg or 1.25 mg, esterified estrogens 0.625 mg or 1.25 mg, and micronized estradiol 1 mg or 2 mg. Estrogen/androgen combinations include esterified estrogens 0.625 mg/methyltestosterone 1.25 mg or esterified estrogens 1.25 mg/methyltestosterone 2.5 mg. Transdermal estradiol

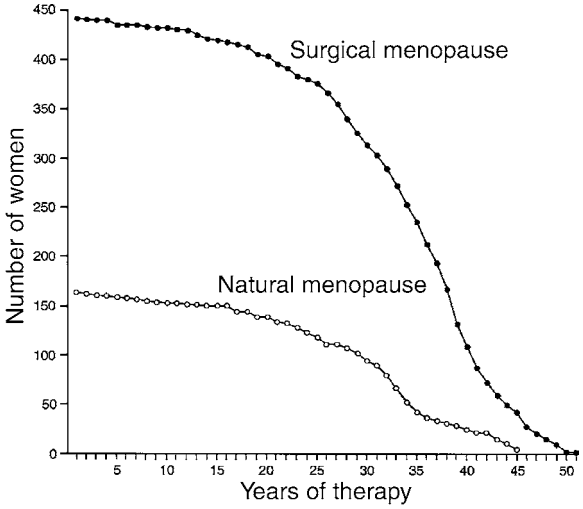

Figure 1 Number of patients who continued pellet implantation during the 3 years of observation and total years of use

was almost always prescribed with one of the 0.1 mg patches.

The continuation rates for the other than pellet hormone users were 72.1% for 5 or more years, 53.5% for 10 or more years, 37.2% for 15 or more years, 20.9% for 20 or more years and 10.5% for 25 or more years. Four patients used oral estrogens and/or estrogen/androgens for more than 30 years, including one patient who has used an estrogen/androgen combination for 42 years. This patient, as well as some others, was treated with pellets for several years before being changed to an oral preparation. Undoubtedly, the continuation rates are considerably higher in these non-pellet users. Many of the pellet patients come from great distances for reimplantation. Once a suitable oral regimen is achieved in the non-pellet users, some of these women return to their hometown physicians for continuation of the same or similar regimen.

Figure 2 illustrates the number of women who were using pellets in 1996 who discontinued therapy during the 3 years of observation from 1996 to 1999. It also shows the years of use before discontinuation. Of those who discontinued pellet use, 78 were treated for at least 1 year, 68 used pellets for 10 years, 56 for 20 years and 37 surgically menopausal women used pellets for 30 years, while 18 continued for 40 years before stopping. Table 2 lists the therapies and mean durations of use for all 122 women who discontinued treatment during 1996–1999. All women with an intact uterus were prescribed progestogens, while 358 of the 490 surgically

Table 1 Duration of therapy in patients continuing hormone replacement

	Surgical menopause		*Natural menopause*		
	Duration (years)		*Duration* (years)		
Therapy	*n*	*Mean ± SEM*	*n*	*Mean ± SEM*	*Total*
2T + 2E	157	17.6 ± 2.96	44	14.4 ± 2.59	201
2T + 1E	107	17.8 ± 3.08	64	15.7 ± 3.20	17
2E + 1T	75	21.7 ± 3.06	21	20.7 ± 3.46	96
3E + 2T	32	19.1 ± 2.72	10	14.7 ± 2.67	42
3E + 1T	31	17.8 ± 2.97	7	19.8 ± 3.25	38
1E + 1T	9	25.9 ± 3.95	6	21.5 ± 3.86	15
3E	12	20.9 ± 2.72	3	24.0 ± 3.40	15
2E	10	19.3 ± 3.41	5	23.6 ± 2.57	15
4E	2	15.0 ± 1.00	4	20.1 ± 2.18	6
3T + 2E	5	15.6 ± 2.06	0	–	5
4E + 1T	1	9	0	–	1
1E	1	31	0	–	1
Injectables	4	10.5 ± 2.70	0	–	4
Oral estrogen	19	10.4 ± 2.52	24	10.3 ± 3.13	43
Oral estrogen/androgen	19	13.3 ± 3.35	11	12.1 ± 2.50	30
Transdermal estrogen	6	5.0 ± 1.73	3	8.3 ± 1.94	9
Total	490	17.9 ± 2.97	202	15.7 ± 3.00	692

E, 25 mg estradiol pellet; T, 75 mg testosterone pellet

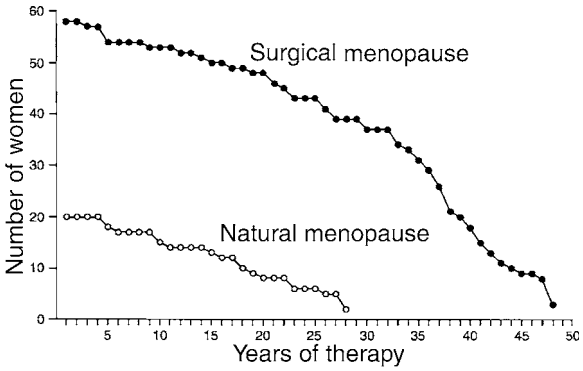

Figure 2 Number of patients who discontinued pellet implantation during the 3 years of observation and the total years of use before discontinuation

menopausal women (73.1%) were also treated with progestogens. Progestogen therapy was individualized to provide as side-effect-free a regimen as possible. Table 3 lists the different progestogens used including the type, dosage, and duration for the 660 women treated with complete HRT.

Table 4 shows the levels of estradiol and testosterone in a subgroup of 50 patients treated with estradiol and testosterone pellets for 6 months to 29 years. These were measured immediately before the next pellet implantation; the dose and frequency were determined from patient response and not based on levels of estradiol or testosterone. The only time estradiol levels are measured is when patients ask for either an increased number of pellets or for pellets at more frequent intervals. This is done to show them that symptoms may occur with minor decreases in hormone levels. By doing this with full explanation, tachyphylaxis is rare, every 2 years or less. If levels get too high, non-hormonal alternatives are given while allowing estradiol levels to decrease. The levels vary according to the number of pellets implanted and the interval between reimplantations. The majority of women have reimplantation every 4½–6 months but a few require reimplantation every 3–4 months. These levels of estradiol and testosterone are representative of the levels obtained with various combinations of estradiol and testosterone pellets implanted over many years. Figure 3 shows the estradiol levels in 20 surgically menopausal women implanted with two pellets of estradiol (50 mg) every 6 months and followed prospectively for up to 4 years during the 1980s.

There were 16 cases of breast cancer and one metastasis in an estrogen user with previous breast cancer diagnosed during the 3 years of observation after 9–50 years of hormone replacement. The mean duration of therapy at time of diagnosis was 22.4 ± 3.18 years. Ten of these women have continued their hormones after appropriate

Table 2 Years of therapy before discontinuing hormone replacement

	Surgical menopause		*Natural menopause*		
	Duration (years)		*Duration* (years)		
Therapy	*n*	*Mean ± SEM*	*n*	*Mean ± SEM*	*Total*
2T + 2E	23	18.0 ± 3.66	1	13	24
2T + 1E	15	9.5 ± 2.88	11	11.7 ± 3.14	26
2E + 1T	8	22.6 ± 2.91	4	15.0 ± 2.64	12
3E + 2T	2	19.5 ± 3.67	3	7.7 ± 2. 01	5
3E + 1T	4	22.3 ± 3.64	0	19.8 ± 3.25	4
1E + 1T	1	41	2	13.0 ± 3.16	3
3E	0	–	1	19	1
2E	10	19.3 ± 3.41	5	23.6 ± 2.57	15
4E	1	12	0	–	1
3T + 2E	2	15.6 ± 2.06	0	–	2
Injectables	3	19.3 ± 3.83	1	10	4
Oral estrogen	15	7.5 ± 2.36	7	10.6 ± 3.46	22
Oral estrogen/androgen	3	20.7 ± 3.34	7	11.3 ± 3.84	10
Transdermal estrogen	4	2.8 ± 1.34	2	2.5 ± 0.71	6
Total	83	15.5 ± 3.07	39	11.2 ± 2.94	122

E, 25 mg estradiol pellet; T, 75 mg testosterone pellet

Table 3 Type, dosage and duration of progestogens

	Continuation		*Discontinuation*		
Progestogen	*Surgical menopause*	*Natural menopause*	*Surgical menopause*	*Natural menopause*	*Total*
MPA 10 mg × 10 days	166	–	40	2	208
MPA 10 mg × 13 days	–	76	–	13	89
MPA 2.5 mg × 25 days	–	8	–	2	10
NEA, 2.5 mg × 10 days	166	–	20	3	189
NEA, 2.5 mg × 13 days	–	2	–	5	7
NEA, 5 mg × 10 days	–	11	–	4	15
NEA, 5 mg × 13 days	2	77	–	8	87
NEA, 10 mg × 13 days		2	–	–	2
Oral MP 200 mg × 10 days	14	–	–	–	14
Oral MP 300 mg × 13 days	–	11	–	1	12
Progesterone VP 25 mg b.i.d. × 10 days	3	–	–	1	4
Progesterone VP 25 mg b.i.d. × 13 days	–	4	–	–	4
Vaginal MP gel 90 mg × 13 days	–	3	–	–	3
MGA 40 mg × 15 days	1	–	–	–	1
MGA 40 mg × 25 days	1	4	–	–	5
MGA 20 mg × 15 days	4	–	–	–	4
MGA 20 mg × 25 days		4	–	–	4
Norethindrone 1.05 mg × 10 days	1	–	1	–	2
Total	358	202	61	39	660

MPA, medroxyprogesterone acetate; NEA, norethindrone acetate; MP, micronized progesterone; VP, vaginal suppositories; MGA, megestrol acetate

treatment, usually radical mastectomy, while four have discontinued hormone replacement because of the recommendation of their surgeon and/or oncologist. Three have died, one from breast cancer, one from endometrial cancer, and one from lung cancer. Neither of the latter two patients had any evidence of residual breast disease at the time of death. There were two cases of ovarian cancer after 31 and 35 years of pellet implantation, both living and well, and one

Table 4 Mean estradiol and testosterone in 50 current patients

Therapy	*n*	*Estradiol mean ± SEM* (pg/ml)	*Testosterone mean ± SEM* (ng/ml)
1E + 1T	8	84.7 ± 6.46	80.3 ± 5.83
2E + 1T	18	266.5 ± 11.79	95.6 ± 7.06
2E + 2T	11	264.2 ± 11.15	171.5 ± 11.85
3E + 1T	10	432.5 ± 7.25	112.5 ± 7.38
3E + 2T	3	412.3 ± 11.05	262.3 ± 14.61

1E, 25 mg estradiol; 2E, 50 mg estradiol; 3E, 75 mg estradiol; 1T, 75 mg testosterone; 2T, 150 mg testosterone Pellets reimplanted q 3–6 months from 6 months to 29 years; mean interval between reimplantation, 4.43 ± 0.98 months; mean duration of therapy, 9.4 ± 2.83 years

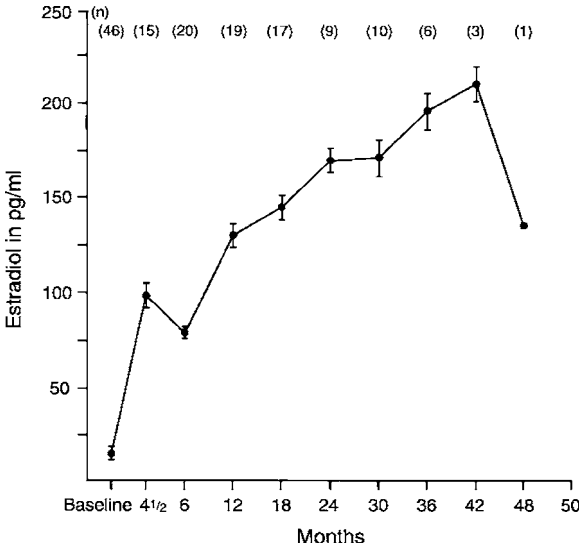

Figure 3 Serum estradiol levels at baseline and every 6 months in 20 surgically menopausal women followed prospectively. Two pellets of estradiol (50 mg) were implanted every 6 months for up to 4 years

case of endometrial cancer. After 14 years of HRT, this patient had a radical mastectomy at age 65. The estrogen was discontinued and testosterone pellets were reimplanted every 6 months plus norethindrone acetate 2.5 mg 13 days monthly for 5 years. In 1990, one estradiol pellet was added to the testosterone pellets and the norethindrone acetate was increased to 5 mg on cycle days 13–25. Withdrawal bleeding became irregular in early 1998 and changes to various progestogen dosages and regimens were not successful. Endometrial cancer was detected in late 1999 and the patient died from endometrial cancer at age 80 in 2000, after 10 years of resuming estrogen replacement.

The 3-year prospective study ended in 1999. After the devastating impact of the WHI report in 2002[9], up to 65% of the 15 000 000 HRT users in the US stopped their estrogen within the next few months. The records of the 690 original patients in our study were reviewed to determine drop-out rates, as well as continuation rates. Of the 690 original patients in 1999, 230 discontinued their HRT during the next 5 years, 2000–2004. Figure 4 shows 9.7% dropped out in 2000, 9.6% in 2001, 12.2% in 2002, 9.3% in 2003, but only 0.002% in 2004. Total patients also decreased during the 5 years, but there were a total of 122 new patients beginning HRT during those 5 years (shown by the numbers at the bottom of each total patient bar in Figure 5): 24 in 2000, 30 in 2001, 26 in 2002, 18 in 2003, and 24 in 2004.

Figure 4 also demonstrates the percentage decrease in hormone use each year in the 690 patients, as well as the percentage decrease in total number of HRT patients, and the cumulative percentage decrease for each group. Drop-outs increased each year, with the greatest increase in drop-out rates for both the original and total patients occurring between 2001 and 2002. The trend began to reverse in 2003 so that by the end of 2004, after publication of the estrogen-only arm of the WHI[12], there was only a 0.002% (a single patient) drop-out rate in the remainder of the 690 original patients and a 16.4% increase in total patients, compared to 2003. Figure 5 indicates the number of original patients and total patients continuing therapy each year. The numbers at the base of the bars indicate the number of new patients starting hormone replacement each year.

DISCUSSION

Our study indicates that, when moderate dosages of estrogen and androgen are used, continuation rates are vastly improved. Not all postmenopausal women need estradiol/testosterone pellet implantation, not even the majority; however, adequate

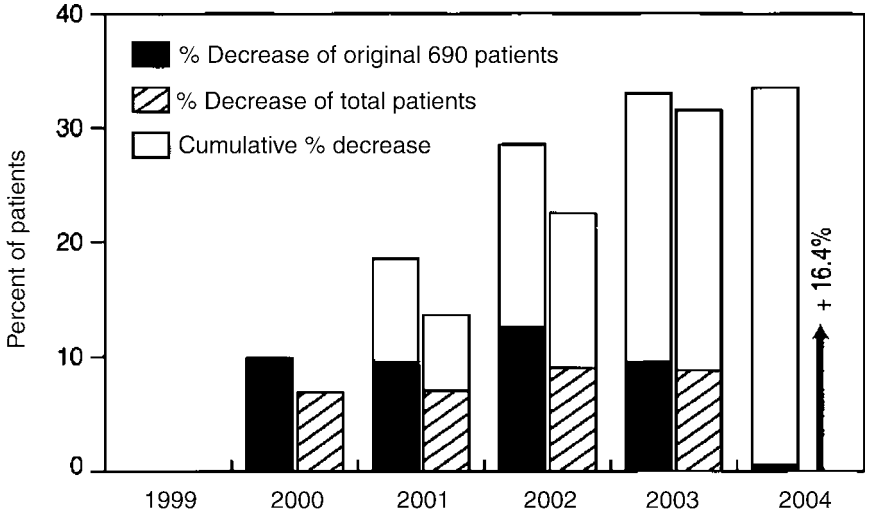

Figure 4 Patients discontinuing HRT during the 5 years of follow-up. Black bars indicate the percentage of original patients discontinuing therapy each year; hatched bars show the percentage of total patients discontinuing hormones, while the open bars show the cumulative percentage discontinuation

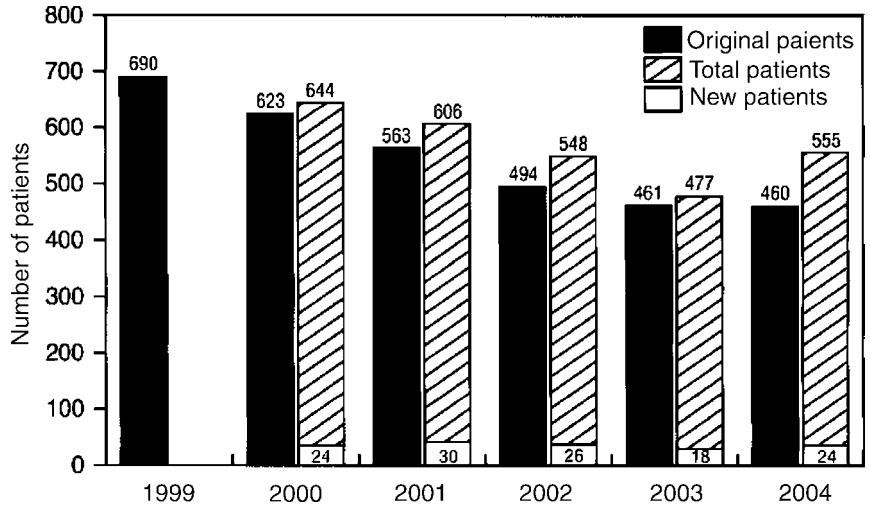

Figure 5 The black bars indicate the number of original patients continuing hormone use each year, while the hatched bars show the total patients continuing therapy. The number of new hormone users is shown at the base of each bar

dosages of estrogen with androgen added when indicated, in a symptom-relieving, side-effect-free regimen, where the patient continues to feel good, should be given. Androgenic side-effects such as hirsutism may be frequent but these can be managed by decreasing the dosage of testosterone, increasing dosage of estradiol, and/or adding spironolactone 100 mg daily, or the new elfornithine HCl facial cream. Patients are referred to us because they have side-effects and otherwise do not feel good using their oral HRT regimen. Therapy must be individualized if HRT is to be continued so that the regimen relieves symptoms and is as free as possible from side-effects. In fact, 128 of 814 patients (15.7%) were treated with other HRT regimens instead of pellet implantation. The continuation rates for the other than pellet hormone users, of 72.1% for 5 years and 53.5% for 10 years, are grossly underestimated. Where pellet patients will drive 100–500 or more miles for reimplantation, non-pellet patients do not have to drive these distances, many returning to their referring physician in their hometown for continuation of the same or similar HRT regimens. The addition of androgens to estrogen replacement, particularly for the young surgically

menopausal women, is important to provide a symptom-free regimen[7,8,13–15]. Young women undergoing hysterectomy and bilateral salpingo-oophorectomy for endometriosis or other disorders can have very severe symptoms. Not only do they suddenly lose 67% of their estrogen production but they may also lose 50% or more of their androgen production. Where estrogens prevent most menopausal symptoms, additional testosterone replacement is also effective for complete relief of symptoms such as fatigue, headache, loss of libido, depression, mood swings, mastalgia, loss of feeling of well-being, loss of muscle tone and dry skin. Vascular headaches may diminish at menopause, only to return with estrogen replacement. The addition of an androgen usually decreases these headaches again[7,13,15].

Side-effects of hormone replacement, particularly symptoms like those of the premenstrual syndrome that may occur with added progestogen, are a major reason for discontinuation of HRT. Where Studd and others have written against prescribing progestogens because of troublesome side-effects[1,6,7], one of the purposes of this report is to show that progestogens can be added to estrogen therapy with minimal untoward effects. However, diligence, persistence and determination must be used by the prescribing physician. With the Heart and Estrogen Replacement Study (HERS) and WHI studies indicating potential adverse effects, safe bleed-free regimens must be found for improved patient continuation[11,16,17]. Progestogenic side-effects include breast tenderness, edema or bloating, headache, irritability, depression and lethargy. At least 50% of these respond to a mild diuretic such as spironolactone or hydrochlorthiazide, 25–50 mg, given for 7–10 days before the expected bleeding or the last 5–7 days of the added progestogen[8]. Sometimes, it may be necessary to lower the dosage of the progestogen from norethindrone acetate 5 mg to 2.5 mg or change to another progestogen or change the regimen. However, the lowest effective dosage to protect the endometrium in sequential regimens is either medroxyprogesterone acetate 10 mg or norethindrone acetate 2.5 mg for 12–14 days[11]. To eliminate the side-effects or at least to reduce them to a level that could be tolerated, seven different progestogens with different dosages and/or regimens of each were used in our patients. The regimens included cyclic sequential, continuous sequential or cyclic combined[8,11]. Women will only continue HRT if a symptomless, side-effect regimen is achieved. Resumption of bleeding, withdrawal bleeding, or intermittent bleeding are other major reasons for discontinuation of HRT. To eliminate withdrawal bleeding, continuous combined HRT has been used for over a decade to produce amenorrhea. However, this regimen is not fully endometrium-protective since continuous progestogen causes down-regulation of progesterone receptors and over 100 cases of endometrial cancer have been reported[9,11]. Cyclic combined HRT is more endometrium-protective since the 5 or 6 days without progestogen at the end of each month are sufficient to allow up-regulation of progesterone receptors. A promising new regimen of continuous estrogen and interrupted progestogen will produce amenorrhea in 71–90% within 6–12 months[16,17]. The 3–4 days without progestogen each week seem to be sufficient to allow up-regulation of progesterone receptors[17].

There is no adverse effect upon lipids or lipoproteins in patients treated with estradiol and testosterone pellets, even with added progestogen, when adequate dosages of estrogen are used[11]. Mean high density lipoprotein (HDL) cholesterol levels were 72.8 ± 3.34 mg/dl in the unopposed estrogen users, 67.0 ± 3.94 mg/dl in the estrogen/androgen users, 64.5 ± 4.16 mg/dl in the estrogen/androgen/C-21 progestogen users, and 61.9 ± 3.84 mg/dl in the estrogen/androgen/C-19 progestogen users, all above the average risk range for HDL cholesterol in our laboratory (55–59 mg/dl). In addition, added progestogen may even have a beneficial effect on lipids since it helps to mediate the estrogen increase in triglycerides. Androgens also seem to block the estrogen-mediated increase in triglycerides[13]. Figure 3 shows the estradiol levels in 20 surgically menopausal women implanted with two pellets of estradiol (50 mg) every 6 months and followed prospectively for up to 4 years during the 1980s. These estradiol levels are not as high as the levels shown in Table 4 with two pellets of estradiol, since implantation was every 6 months in Figure 3, while some of our patients in Table 4 had reimplantation of pellets every 3–4½ months. When pellets are implanted more frequently, there is some accumulation in estradiol levels.

CONCLUSIONS

The WHI reports have impacted hormone replacement around the world, even affecting the excellent continuation rates in our long-term hormone users. The 96.7% 10-year continuation rate in our pellet patients declined more rapidly following publication of the HERS and WHI

studies, falling to 66.7% during the past 5 years. We concur with the 2004 Position Statement of the International Menopause Society (IMS) that, when hormones are prescribed in the menopause transition for symptoms, as was done in our study, outcomes are different than in the randomized controlled trials in older women[18]. We further agree with the Executive Committee of the IMS that presently accepted global practice be continued. Nor are there any new reasons for mandatory limitations in the length of treatment. Although there are risks of hormone use, such as deep venous thrombosis and pulmonary embolism, these risks are small compared to the great benefits of reduction in risk of colorectal cancer and bone loss. Estrogens can be given safely to women with early breast cancer[19]. If estrogens increased the risk of breast cancer, there should be a dose-related response, which there is not, in our patients who carry levels of 264–266 pg/ml estradiol for 20–40 years (Table 4), yet demonstrate no increased risk. The rationale for using progestogens in women who have had a hysterectomy is based on the authors' 28–35 years of experience, the low numbers of breast cancers in this study, and a review of many other supporting studies[20].

We certainly concur with the recommendations and findings of the IMS but emphasize that regimens should be modified to eliminate the symptoms of menopause, and to be free of side-effects so that women continue to feel good, because they are treated with adequate dosages of estrogen, with androgen replacement added when needed. The implantation of pellets is not necessary for even the majority of postmenopausal women since many feel quite well with oral and transdermal preparations. However, dosages must be adequate not only to relieve symptoms but also to provide a sense of well-being.

Conflict of interest Nil.

Source of funding Nil.

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