Past and Present Preferred Prescribing Practices of Hormone Replacement Therapy among Los Angeles Gynecologists: Possible Implications for Public Health

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Abstract: Usual prescribing strategies of hormone replacement therapy for postmenopausal women by Los Angeles area gynecologists, both now and 10 years ago, were investigated by a mail survey. Of the 330 gynecologists who responded, estrogen therapy is currently used as a routine by nearly all (95 per cent), for women both with and without a uterus. Over three-fourths of these physicians favor use of 0.625 mg of conjugated equine estrogen. The estrogen is combined with cyclic progestin therapy, usually 10 mg of medroxyprogesterone acetate, by 86 per cent of gynecologists using estrogen for women with a uterus, and by 47 per cent for women without a uterus. Although conjugated equine estrogens were used widely for both groups of patients 10 years ago, a higher dose generally was preferred. Use of progestin therapy was uncommon (less than 20 per cent) for any postmenopausal patients at that time. Although the most common monthly therapeutic regimen for estrogen/progestin therapy is estrogen for days 1-25 and progestin for days 16–25, there is wide variation in prescribing strategies. We present these findings in the context of the probable effects of estrogen/progestin therapy on various chronic disease outcomes. (*Am J Public Health* 1988; 516–519.)

Introduction

In the 1970s, in response to the growing number of endometrial cancers in postmenopausal women on estrogen replacement therapy, prescriptions for "unopposed" estrogens declined[1] and an estrogen-progestin regimen became widely recommended and prescribed. While the benefit of such a regimen in reducing endometrial mitotic activity induced by an estrogen has been clearly established in clinical practice,[2] the effect of an added progestin on endometrial cancer risk and, especially, on other components of the risk-benefit equation of hormone replacement therapy is unclear.

Use of oral estrogen, exclusive of oral contraceptives, is rising. After falling from a peak of about 28 million in 1975 to a low of 14 million in 1980, the number of dispensed prescriptions of estrogens increased to 18 million in 1983.[1] Between 1984 and 1985 the conjugated equine estrogen (CEE) Premarin™ moved from 17th to 12th place in the list of the top 200 prescribed drugs in the US.[3] Prescriptions of progestins, exclusive of oral contraceptives, are similarly increasing. In 1983, 3.2 million prescriptions of progestins were dispensed, up from less than 2 million just two years earlier.[1] Nearly 90 per cent of prescribed progestins are medroxyprogesterone acetate (MPA). Provera,™ the most popular brand of MPA, was the 78th most frequently prescribed drug in 1985, up 28 places from 1984.[3]

Despite these dramatic changes in the prescription of hormone replacement therapy, little is known about secular trends or the usual doses and most popular regimens by specialty group. We recently surveyed members of the Los Angeles County Obstetrics and Gynecology Society to answer these questions and to determine how such factors as years of practice and demographic characteristics of patient populations are related to prescribing strategies.

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Methods

In November 1984, each of the current members of the Los Angeles County Obstetrics and Gynecology Society was mailed a short questionnaire concerning prescription practices of hormone replacement therapy. If no response had been received, this same questionnaire was sent again in March 1985. This survey requested information about the number of years of practice, overall and in the LA area; a description of the demographic make-up of the patient population; and usual prescribing practices of hormone replacement therapy for women with and without uteri separately, now and 10 years ago (1975), including estrogen and/or progestin dose, brand and monthly regimen.

Results

After the two mailings, we received responses from 330 of the 516 gynecologists (64 per cent) who, as far as we could determine, were still active and practicing in Los Angeles (193 from mailing one, and 137 from mailing two). These 330 physicians had been practicing, on average, 21 years (19 years in the Los Angeles area); 25 per cent had been practicing for 30 years or longer; 268 (81 per cent) were practicing 10 years ago.

The median number of postmenopausal patients estimated by these physicians to be in their practices was 200. Twenty-five per cent had 400 or more postmenopausal patients. The estimated average racial distribution of these patients was 69 per cent non-Hispanic White, 13 per cent Hispanic, 10 per cent Black, 6 per cent Asian, and 2 per cent "other".

Three hundred twenty of the 330 respondent physicians (97 per cent) reported that they used hormone replacement therapy for at least some of their postmenopausal patients.

Women with Intact Uteri

Three hundred ten of the respondents (94 per cent) reported that they routinely use estrogens for postmenopausal patients with intact uteri. Ninety-seven per cent of these prefer CEE. Eighty per cent of those using CEE prefer a dose of 0.625 mg (Table 1).

Two hundred eighty-three of the respondents (86 per cent) also routinely use a progestin in the hormone replacement regimen of postmenopausal patients with intact uteri. Ninety-five per cent of these favor MPA, with 10 mg per day being the preferred dose of 73 per cent and 5 mg of 20 per cent.

TABLE 1—Usual Prescribing Practices for Postmenopausal Women with Intact Uteri by Los Angeles Gynecologists: Now and 10 Years Ago

Rx	Now (N = 330) N	Now (N = 330) %	10 Years Ago (N = 268) N	10 Years Ago (N = 268) %	Per Cent Difference	(95% CI)
Estrogen	310	94	213	79	15	(9–20)
Premarin	300	97*	202	95		
1.25 mg	48	16	99	49		
0.625 mg	240	80	87	43		
0.3 mg	4	1	5	2		
Other/unknown	8	3	11	5		
Progestin	283	86	46	17	69	(65–76)
Provera	270	95**	41	89**		
5 mg	53	20	9	22		
10 mg	197	73	30	73		
Other/unknown	20	7	2	5		

*% of Estrogen users
**% of Progestin users

Among the 283 physicians giving estrogen/progestin combination therapy to some of their postmenopausal patients, there was tremendous variation in regimens (84 different patterns of use). The most popular regimen by far was an estrogen on day 1 through day 25 of a monthly cycle with a progestin added from day 15 or 16 through day 25 (124 physicians) (Table 2).

Estrogen therapy for postmenopausal women with intact uteri was also a popular practice by Los Angeles County gynecologists a decade ago with 213 (79 per cent) of 268 physicians stating that they used such therapy routinely. CEE was the estrogen of choice among 95 per cent of these. Preferred dosage, however, was considerably higher 10 years ago than currently, with 49 per cent preferring 1.25 mg at that time versus 16 per cent now. Progestin therapy was much less popular for this group of patients 10 years ago, with only 46 (17 per cent) reporting routine use then versus 86 per cent now. As with current practice, 10 mg of MPA was the preferred brand and dosage (Table 1). Although there was much variation in usual regimens among those prescribing estrogen/progestin combinations, there was a tendency to use the progestin for shorter intervals during the monthly cycle a decade ago than currently.

Women without Uteri

Most gynecologists also treat women without uteri with estrogen. Ninety-seven per cent of respondents currently use estrogens for this category of patients (versus 85 per cent 10 years ago) and 97 per cent of these prefer CEE. As with non-hysterectomized patients, 0.625 mg is the preferred dose (76 per cent of physicians prescribing CEE). Progestin therapy is also a popular treatment for hysterectomized women, albeit considerably less so than for women with intact uteri, with 152 or 326 physicians (47 per cent) routinely prescribing it. Ten mg MPA is again the preference of dose and brand by a wide margin (Table 3). Only 11 per cent of gynecologists added a progestin routinely to estrogen 10 years ago, for those women without a uterus. The prescribing patterns for estrogen/progestin therapy for women without a uterus are similar to those for women with a uterus, again with considerable variation in preferred regimens (Table 4).

Other Factors

We looked at the effect of such factors as size and location of the practice, the percentage of minority patients in the practice, and number of years of practice on prescribing patterns of hormone replacement therapy. None had a major impact 10 years ago or now. Fewer years of practice and larger size of practice were associated with slightly higher rates of combined estrogen/progestin therapy and somewhat higher progestin doses, for women without a uterus.

TABLE 2—Preferred Regimens for Prescribing Estrogen/Progestin Therapy in Postmenopausal Women with Intact Uteri: Now and 10 Years Ago

Estrogen Day Start	Estrogen Day Stop	Progestin Day Start	Progestin Day Stop	N
Now (N = 283)				
1	25	10–12	25	7
		13	25	18
		14	25	8
		15	25	25
		16	25	99
		17–20	25	9
		Other		8
1	21	9–10	21	3
		11	21	12
		12	21	11
		14–17	21	9
		Other		15
1	5	1	5	5
Miscellaneous Estrogen/Progestin Combinations				46
Unknown				8
10 Years Ago (N = 46)				
1	25	13–15	25	4
		16	25	7
		17–21	25	8
		Other		1
1	21	15–17	21	6
		Other		5
Miscellaneous Estrogen/Progestin Combinations				7
Unknown				8

TABLE 3—Usual Prescribing Practices for Postmenopausal Women without Uteri by Los Angeles Gynecologists: Now and 10 Years Ago

Rx	Now (N = 326†) N	Now (N = 326†) %	10 Years Ago (N = 264†) N	10 Years Ago (N = 264†) %	Per Cent Difference	(95% CI)
Estrogen	316	97	224	85	12	(7–17)
Premarin	307	97††	210	94††		
1.25 mg	59	19	103	49		
0.625 mg	233	76	87	41		
0.3 mg	3	1	5	2		
Other/unknown	12	4	15	7		
Progestin	152	47	28	11	36	(29–37)
Provera	148	97†††	26	93†††		
5 mg	35	24	5	19		
10 mg	99	67	18	69		
Other/unknown	14	9	3	12		

†4 Unknowns
††% of Estrogen users
†††% of Progestin users

TABLE 4—Current Preferred Monthly Regimens for Prescribing Estrogen/Progestin Therapy to Postmenopausal Women without Uteri (N = 152)

Estrogen		Progestin		
Day Start	Day Stop	Day Start	Day Stop	N
1	25	10–12	25	6
		13	25	6
		14	25	4
		15	25	14
		16	25	46
		17–21	25	6
		Other		6
1	21	9–10	21	2
		11	21	3
		12	21	3
		14–17	21	6
		21	25	3
		Other		6
1	30	20	30	6
		Other		2
1	5	1	5	6
Miscellaneous Estrogen/Progestin Combinations				24
Unknown				2

Discussion

Our data demonstrate the widespread use of hormone replacement therapy as an elective mode of therapy for postmenopausal patients of Los Angeles area gynecologists. Our data on the current popularity of estrogen use for non-hysterectomized women compare favorably with results of a small survey of gynecologists recently conducted in San Diego.[4] A previous survey in upstate New York suggests that gynecologists are more likely to prescribe hormone replacement therapy than physicians in other specialties.[5] However, to the extent that gynecologists serve as a model for other physicians in the community in treating postmenopausal patients, use of combination estrogen/progestin therapy can be expected to increase further.

The increased popularity of combination estrogen/progestin therapy has substantial implications for the public health.

The exact level of risk of endometrial cancer in combination estrogen/progestin users relative to non-hormone users has yet to be demonstrated in epidemiologic studies. One might predict that risk would be substantially less than that of women using unopposed estrogen therapy, but still greater than that of women using no replacement therapy. This pattern of risk would occur if the endometrium is protected only during that part of the cycle when the progestin is actually used.

The effect of progestins on the breast are clearly different from those on the endometrium, but the long-term effect of estrogen therapy on breast cancer risk also is unknown. Although one study suggested a marked reduction in risk relative to non-users of any hormone replacement therapy,[6] certain aspects of the methodology of this study have been criticized. The possibility that estrogen/progestin therapy may actually enhance risk has also been raised. Mitotic activity in the breast reaches its peak in the luteal phase of the cycle,[7] although the significance of this observation to the role of progestogens in breast carcinogenesis remains unclear. There are highly disputed studies that progestins may cause breast cancer in dogs.[8] As oral contraceptive use during the perimenopausal period may enhance breast cancer risk,[9] a comparable effect from combination hormone replacement therapy might come as no surprise. Although data on the use of injectable progestin contraceptives suggest a slight decrease in risk of breast cancer,[10,11] firm conclusions cannot be drawn from the studies. If the decrease is real, it could be mediated via a reduction in estrogen due to anovulation, rather than a beneficial effect of progestins on breast tissue per se.

There is convincing evidence that certain progestins can increase bone formation slightly,[12] complementing the reduction in bone formation associated with unopposed estrogen therapy. However, as estrogen use alone begun during the perimenopausal period can virtually eliminate bone loss,[12] further marked reduction in fracture risk associated with estrogen/progestin therapy versus estrogen alone is unlikely.

The most important health consequence of prescribing progestins cyclically with estrogen may relate to ischemic heart disease (IHD). The majority of epidemiological data indicates a beneficial effect of estrogens on risk of IHD.[13] This effect is most likely mediated in large part through raised high density and reduced low density lipoprotein cholesterol.[14] Since there may be a residual reduction in risk of IHD associated with estrogen therapy after allowing for changes in lipid profiles,[15] other factors, such as increased cardiac output or altered regional blood flow, may also be important.[16] The best available data suggest that the addition of progestin will negate or even reverse the favorable effect of estrogen on lipid profiles,[17] and possibly negate or reverse the protection from IHD afforded women using unopposed estrogen therapy. The progestogenic effects on lipoprotein cholesterol are dose-dependent and, at equivalent minimal doses for control of endometrial proliferation (10 mg MPA, 1 mg norithisterone acetate, 0.15 mg d1-norgestrel), the adverse effects of progestins on lipid profiles are comparable.[17-19]

The shift to a lower preferred dose of estrogen over the past decade is likely to impact favorably on the risk-benefit equation of hormone replacement therapy, unless the beneficial effect on cardiovascular disease is dose-related. Current epidemiologic evidence suggests no strong dose effect,[20] but biochemical effects of estrogens on lipoprotein induction by the liver suggest otherwise.[21]

If the prediction of a reduction in the benefit on cardiovascular disease with estrogen/progestin therapy is correct, there would be no clear overall benefit to be derived and, therefore, little justification for the increasing use of estrogen/progestin therapy in women without a uterus. Although cyclic addition of a progestin to estrogen therapy offers an important benefit to non-hysterectomized women, even for this group of patients the adverse impact on cardiovascular disease risk may outweigh the benefit to the endometrium.

Any benefit to the endometrium from an added progestin is likely to be tied more closely to monthly duration of therapy than to dose. There is evidence that as little as 2.5 mg of MPA daily is sufficient to return to baseline (i.e., non-hormone therapy levels) the quantity of estrogen receptors in the endometrium.[22] However, these biochemical changes do not appear to correlate well with desired histological changes.[19] A recent study from Scandinavia suggesting that micronized progesterone causes no adverse lipid effects is encouraging.[22] If confirmed in doses sufficient to inhibit mitotic activity in the endometrium and if side effects do not preclude routine use, then this may emerge into a useful alternative to synthetic progestogen therapy.

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