

Prescription of hormone replacement therapy in postmenopausal women with renal failure

CATHERINE O. STEHMAN-BREEN, DANIEL GILLEN, and DEBBIE GIPSON

Division of Nephrology and Department of Biostatistics, University of Washington, Seattle, Washington, and Department of Nephrology, University of North Carolina, Chapel Hill, North Carolina, USA

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Background. Although patients with end-stage renal disease (ESRD) are at increased risk for early menopause, osteoporosis, cognitive dysfunction, and cardiovascular disease, few postmenopausal women are prescribed hormone replacement therapy (HRT). The reasons for the low prescription rate are not known. This study uses data from the United States Renal Data System (USRDS) to assess the prevalence and predictors of HRT use in postmenopausal women with ESRD.

Methods. Data were obtained from the USRDS Dialysis Morbidity and Mortality Study Wave 2. All women who were at least 45 years of age were considered postmenopausal and were selected for our analysis. Demographics, behavior and medical characteristics were abstracted from the database. Logistic regression was used to estimate the independent contribution of population characteristics in predicting the use of HRT. Linear regression models were used to estimate the relationship between HRT use and both triglycerides and total cholesterol.

Results. The overall prevalence of HRT prescription was 10.8%. Important predictors of HRT use included age (aOR = 0.74, 95% CI 0.13 to 0.88, $P < 0.001$), black ethnicity (aOR = 0.50, 95% CI, 0.31 to 0.78, $P < 0.002$), college education (aOR = 3.00, 95% CI, 1.70 to 5.24, $P < 0.001$), and the ability to ambulate (aOR = 1.99, 95% CI, 1.01 to 3.91, $P = 0.05$). Serum triglyceride and total cholesterol levels were higher among women treated with HRT than among those not treated with HRT (264 ± 155 vs. 217 ± 159 mg/dl, $P = 0.001$ and 220 ± 62 vs. 209 ± 55 mg/dl, $P = 0.02$, respectively).

Conclusions. HRT is prescribed less frequently in postmenopausal ESRD patients than in the general population. Younger age, higher education levels, white race, and the ability to ambulate were important predictors of HRT use. Targeting populations of patients who are likely to benefit from but less likely to be prescribed HRT may increase the prescription of HRT.

Key words: ESRD, women, hormone prescription, menopause, cardiovascular disease.

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In the general population, the benefits of hormone replacement therapy (HRT) have been confirmed in many clinical trials and include the relief of menopausal symptoms, the maintenance of bone mass, reduction in the risk for osteoporosis, improvement in cognitive function, and improvement of the lipid profile [1–5]. In addition, results of observational and cross-sectional studies of HRT have suggested that HRT may reduce the risk for cardiovascular disease by as much as 35 to 42% and may prevent the development of dementia [4, 6, 7].

As a result of these studies, the use of HRT in the general population has been increasing over the past 20 years [8]. Between 1982 and 1992, the number of HRT prescriptions dispensed increased from 13.2 to 36 million [8]. In the United States, 34% of postmenopausal women are prescribed HRT, but the prevalence varies considerably by a variety of factors, including patient and physician attitude, geographic location, and ethnicity [9].

Although patients with end-stage renal disease (ESRD) are at increased risk for early menopause, cardiovascular disease, osteoporosis, and cognitive dysfunction [10–13], only 10% of postmenopausal women are prescribed HRT [14]. The reasons for the low prescription rate among ESRD patients are not known. Recognition of factors important in predicting the prescription of HRT may help physicians target populations of patients who are prescribed HRT less frequently but who may benefit from HRT. This study uses data from the United States Renal Data System (USRDS) to assess the prevalence and predictors of HRT use in postmenopausal women with ESRD.

METHODS

Patient population

We performed a secondary analysis of data from the USRDS Dialysis Morbidity and Mortality Study (DMMS) Wave 2. Details of the design of the DMMS Wave 2 study are described in more detail elsewhere [15]. Briefly, the USRDS collects demographic and clinical data on patients who have survived more than 90 days on dialysis

and who qualify for Medicare. DMMS Wave 2 was a prospective study that included a random sample of incident dialysis patients in 1996 who were sampled from among 25% of the dialysis units listed in the December 1993 Master List in addition to all new dialysis units opening after January 1, 1994. The USRDS excluded patients from DMMS Wave 2 if they were younger than 18 years or were home dialysis patients or if they had been previously transplanted. Modality assignment was determined on day 60 of ESRD. All women who were at least 45 years of age were considered postmenopausal and were selected for our analysis.

Data collection

Dialysis facility personnel abstracted data for patients from their dialysis record. A maximum of 15 medications prescribed to each study patient at the study start date (day 60) were recorded. From this list, the use of estrogen, progesterone, or combination preparations was determined. Patients were categorized as having been prescribed HRT if an estrogen, progesterone, or a combination preparation was found on their list of medications. Demographics and behavioral characteristics ascertained included age, race (white, black, other), gender, dialysis modality [hemodialysis (HD) or peritoneal dialysis (PD)], education (less than 12 years, high school graduate, some college, college graduate), employment status (employed, not employed), exercise (frequently, occasionally, never), the process of choosing the initial treatment for kidney failure (patient took the lead, medical team took the lead, medical team and patient jointly took the lead), marital status (married, not married), and tobacco use (active, former, never). The medical history ascertained included coronary artery disease (yes, no), peripheral vascular disease (yes, no), diabetes (yes, no), history of breast cancer (yes, no), history of uterine cancer (yes, no), total cholesterol, and triglycerides. The body mass index was calculated from height and weight, and obesity was defined as a body mass index ≥ 25 .

Statistical analysis

Logistic regression was used to estimate the independent contribution of demographic, behavioral and medical history variables in predicting the use of HRT in postmenopausal women with ESRD. The continuous variables of interest were analyzed separately in categorical form for ease of interpretation. In the final model, the odds ratios are interpretable as the adjusted odds of being prescribed HRT for each variable of interest, holding all other factors constant. The estimated standard error of the coefficient (B_1) from the logistic regression analysis was used to establish confidence intervals. Linear regression models were used to estimate the relationship between HRT use and both triglycerides and total cholesterol. Results were reported as the mean

Table 1. Selected characteristics of the patient population

	Hormone replacement therapy <i>N</i> = 162	No hormone replacement therapy <i>N</i> = 1337
	<i>N</i> (%)	
Age		
45 to 59 years	86 (53%)	417 (31%)
60 to 74 years	62 (38%)	690 (52%)
>75 years	14 (9%)	230 (17%)
Race		
White	123 (76%)	817 (62%)
Black	29 (18%)	400 (30%)
Other	10 (6%)	108 (8%)
Education		
Some high school	29 (20%)	493 (41%)
High school graduate	56 (39%)	421 (35%)
Some college	29 (20%)	152 (13%)
College graduate	30 (21%)	129 (11%)
Diabetes	74 (47%)	760 (58%)
Coronary artery disease	42 (28%)	464 (38%)
Uterine Cancer	3 (2%)	18 (1%)
Breast Cancer	3 (2%)	41 (3%)
Obesity	71 (46%)	674 (52%)
Exercise frequency		
Frequently	22 (22%)	168 (21%)
Occasionally	27 (27%)	198 (25%)
Never	52 (52%)	419 (53%)
Smoker		
Active	3 (3%)	21 (2%)
Former	22 (19%)	204 (19%)
Never	89 (78%)	846 (79%)
Treatment modality		
Peritoneal dialysis	100 (62%)	568 (43%)
Hemodialysis	62 (38%)	766 (57%)

difference in either triglycerides or total cholesterol between women who take HRT and those that do not, along with 95% confidence intervals. Data were analyzed with SPSS statistical software (SPSS, Chicago, IL, USA).

RESULTS

Prescription of HRT was assessed in 1499 women. The characteristics of the patient population are summarized in Table 1. Patients prescribed HRT tended to be younger, white, more educated, and treated with PD, and they were less likely to have diabetes or heart disease. Patients prescribed HRT were similar to patients not prescribed HRT with regard to history of uterine and breast cancer, frequency of obesity, exercise frequency, and use of tobacco.

The overall prevalence of HRT prescription among postmenopausal women with ESRD was 10.8% (162 out of 1499). The prevalence of prescription was 15% in the fourth decade of life, 18% in the fifth decade of life, 8% in the sixth decade of life, 8% in the seventh decade of life, and 7% in the eighth decade of life. Twenty women less than 45 years of age were also taking HRT but were not included in the analysis. Five percent ($N = 8$) of

Table 2. Odds of being prescribed hormone replacement therapy among postmenopausal women with end-stage renal disease

Covariate	OR (95% CI)	P value	aOR (95%CI) ^a	P value
Age (decades)	0.67 (0.57, 0.78)	<0.001	0.74 (0.13, 0.88)	<0.001
45–59 years	1		1	
60–74 years	0.44 (0.31, 0.62)	<0.001	0.49 (0.36, 0.72)	<0.001
>75 years	0.30 (0.16, 0.53)	<0.001	0.38 (0.20, 0.73)	0.003
Education				
Some high school	1		1	
High school graduate	2.26 (1.42, 3.60)	<0.001	1.83 (1.13, 2.95)	0.01
Some college	3.24 (1.88, 5.59)	<0.001	2.44 (1.39, 4.29)	0.002
College graduate	3.95 (2.29, 6.82)	<0.001	2.98 (1.70, 5.24)	<0.001
Race		0.002		0.009
White	1		1	
Black	0.48 (0.32, 0.73)	<0.001	0.50 (0.31, 0.78)	0.002
Other	0.61 (0.31, 1.21)	0.16	0.69 (0.33, 1.45)	0.33
Independent ambulation	2.86 (1.53, 5.37)	0.001	1.99 (1.01, 3.91)	0.05

Abbreviations are: OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio.

^a Adjusted for age, education, race, and independent ambulation

women were prescribed a combination preparation, whereas the remaining ($N = 154$) were prescribed estrogen and/or progesterone as separate prescriptions.

Important predictors of HRT prescription are summarized in Table 2. For every decade of life, patients were 26% less likely to be prescribed HRT after adjusting for education, race, and independent ambulation (aOR = 0.74, 95% CI, 0.13 to 0.88, $P < 0.001$). Patients who were more educated were more likely to be prescribed HRT after adjusting for age, race, and independent ambulation. Patients who were college graduates were threefold more likely to be prescribed HRT than those with less than a high school education (aOR = 2.98, 95% CI, 1.70 to 5.24, $P < 0.001$). Black patients were 50% less likely to be prescribed HRT than white patients (aOR = 0.50, 95% CI, 0.31 to 0.78, $P < 0.002$) after adjusting for age, education, and independent ambulation. Women who were able to ambulate were almost twofold more likely to be prescribed HRT than patients who were not able to ambulate after adjusting for age, education, and race (aOR = 1.99, 95% CI, 1.01 to 3.91, $P = 0.05$).

Diabetic women were less likely to be prescribed HRT than nondiabetic women (OR = 0.65, 95% CI, 0.47 to 0.91, $P = 0.01$). Women treated with PD were more than twofold more likely to be prescribed HRT than women treated with HD (OR = 2.17, 95% CI, 1.56 to 3.04, $P < 0.001$). Women who shared in choosing treatment options with their medical team were 1.78-fold more likely to be prescribed HRT than women who let the medical team make the decision (OR = 1.78, 95% CI, 1.11 to 2.84, $P < 0.01$). However, these associations were no longer statistically significant after adjusting for age, education, race, and independent ambulation and were not included in the final model. History of breast and uterine cancer, body mass index, exercise frequency, employment status, marital status, and tobacco use were not important in predicting HRT and therefore were not included in the final model.

Triglyceride levels in women prescribed HRT were 47.2 mg/dl (95% CI, 18.9 to 75.5) points higher on average than in women not prescribed HRT (264 ± 155 vs. 217 ± 159 mg/dl, $P = 0.001$). Cholesterol levels were 11.0 mg/dl (95% CI, 1.5 to 20.5) higher on average among women prescribed HRT compared with women not prescribed HRT (220 ± 62 vs. 209 ± 55 mg/dl, $P = 0.02$).

DISCUSSION

We estimated the prevalence of HRT use among women with ESRD to be 10.8%. Important predictors of HRT use among women with ESRD included younger age, higher education levels, white race, and the ability to ambulate. Serum triglyceride and cholesterol levels were higher among women with ESRD prescribed HRT than among those not prescribed HRT.

We found that HRT is used with less frequency in postmenopausal ESRD patients (10.8%) than in the general population. Investigators from The Commonwealth Fund 1998 Survey of Women's Health estimated the prevalence of HRT use in the United States among women ≥ 50 years of age to be 34%. They surveyed more than 2000 women over the age of 18 years, weighting results with census data by age, sex, race, education, insurance, and geographic region to produce results representative of women in the United States. The prevalence of HRT use has been reported to be as high as 47% among a cohort of women physicians in the United States [16] and as low as 9.3% among a population of middle-aged white women from Massachusetts [17]. Differences in the prescription of HRT have been explained by a variety of factors including physician attitude, secular trends, geographic location, and ethnicity [8, 17–19]. Variation in the demographic distribution between women with and without ESRD may account for much of the differences in prescription rate.

Among postmenopausal ESRD patients, younger age,

higher education levels, white race, and the ability to ambulate were the most important predictors of HRT prescription. The results of this study are consistent with previous studies describing HRT use in women without ESRD [19–21]. It is possible that patients with higher education levels are more likely to consider the potential benefits of HRT and discuss its use with their physician. Ambulatory women with ESRD were more likely to be prescribed HRT. Patients who are bedridden may have more severe medical problems. Physicians may consider HRT not efficacious in this population of women who are at such high risk for death. It is not known whether this is a reasonable assumption. The declining use of HRT with advancing age has been noted among patients without ESRD and was observed in this study. Postulated reasons include fear of breast cancer with long-term use of HRT and side-effects of the medication [22, 23]. The lower prescription of HRT among black compared to white women has also been described [24]. Physicians may be less inclined to prescribe HRT to black women who are at lower risk for osteoporosis. Alternatively, race may be a marker for socioeconomic status, which has been shown to be predictive of HRT use.

In contrast to studies of women without ESRD, we did not find that body mass index, previous hysterectomy, or history of uterine or breast cancer were important predictors of HRT [16, 19, 25]. The lack of association between breast or uterine cancer and prescription of HRT may be the result of the relatively rare occurrence of these cancers in the study population. Alternatively, there may have been underreporting of previous neoplasms in the survey.

Although estrogen has many beneficial effects, it is also associated with an increase in serum triglycerides [5]. Our data demonstrated higher triglycerides among patients treated with HRT compared with those not treated. We also found that total cholesterol levels in women prescribed HRT were higher than in those not prescribed HRT. It may be that women with higher cholesterol and/or triglyceride levels are more likely to be prescribed HRT. If this were the case, despite HRT, total cholesterol may remain higher in those treated than in those not treated. Given the cross-sectional design of this study, a causal relationship between HRT and serum lipids can not be assessed.

There are many reasons why women with ESRD may receive particular benefit from HRT therapy. Among patients without ESRD, HRT is effective in improving the lipid profile, stabilizing bone mass, reducing fracture rate [1, 3], and improving cognitive function [4]. If the benefits are similar among ESRD patients to the general population, increasing the prescription of HRT could improve morbidity and mortality in women with ESRD. Further studies need to address the impact of HRT on

cardiovascular disease, bone disease, cognitive function and venous thrombosis in women with ESRD.

The analysis has certain limitations. Although we were able to determine the type of hormone preparation, we were unable to determine if women had previously been prescribed HRT, the duration of HRT use, or the reasons for discontinuation of HRT. It is possible that factors such as dysfunctional uterine bleeding associated with HRT in the setting of heparin use may be an important predictor of HRT use, which we were unable to quantify. In addition, because there were a limited number of spaces available to enter medications, HRT prescription may have been underestimated. Second, women who were home HD patients or who had been previously transplanted were excluded in the original data collection for DMMS Wave 2 by the USRDS. This may have resulted in the selection of a less healthy study population. If women who are healthier are more likely to be prescribed HRT, this may have underestimated the prevalence of HRT use among women with ESRD. However, the USRDS collected data for Wave 2 on incident (new) dialysis patients. A minority of patients are transplanted prior to the initiation of dialysis. In addition, home HD represents a very small number of patients (1.1%). Therefore, it is unlikely that many patients were ineligible secondary to previous transplant or home HD. Finally, although we defined menopause as an age of ≥ 45 years, there are very little data regarding the average age of menopause in women with ESRD. Menopause is thought to occur earlier among women with ESRD. A study by Holley et al reported that the median age of menopause was 47 years and ranged from 40 to 53 years [14]. Thus, ≥ 45 was chosen as a reasonable age to include most women who were postmenopausal. In addition, although we may have included some women in their 40s who were premenopausal, the overall prevalence of HRT use did not change significantly if ≥ 45 years or ≥ 50 years was used to define menopause (10.8 vs. 10.3%, respectively). Although there are number of acknowledged limitations, this study is the first to report the pattern of use of HRT in the dialysis population and the first to describe factors important in its prescription.

The prescription of HRT is lower in postmenopausal women with ESRD than in the general population. Among women with ESRD, younger age, higher education levels, white race, and the ability to ambulate were the most important predictors of prescription of HRT. Targeting these groups of women with ESRD who are likely to benefit from but less likely to be prescribed HRT may increase the prescription of HRT. Further studies need to identify factors that account for differences in prescription rate between women with and without renal disease and address the impact of HRT on cardiovascular disease, bone loss, cognitive function and venous thrombosis.

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Reprint requests to Catherine Stehman-Breen, M.D., Puget Sound Health Care System, 1660 South Columbian Way, Mailstop 111A, Seattle, Washington 98108, USA.
E-mail: cos@u.washington.edu

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