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Quality of life and hypertension after hormone therapy withdrawal in New York City

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Abstract

Objective: Many women stopped hormone therapy (HT) or estrogen therapy (ET) after the Women's Health Initiative results were published in 2002. This study assessed the incidence of hypertension, weight gain, and dyslipidemia; conditions that predispose to chronic diseases; medication use; and quality of life in women who used HT/ET for at least 5 years and subsequently stopped its use compared with those who continued its use.

Methods: A retrospective study was conducted. All consenting eligible women (aged 56-73 y) in physicians' offices were interviewed, and measurements of weight, height, waist-to-hip ratio, and body fat were performed. Standardized quality-of-life and menopausal and medical questionnaires were administered. Three groups were compared: group 1, women who have remained on HT/ET; group 2, women who have resumed HT/ET after stopping for at least 6 months; and group 3, women who have stopped HT/ET and have not resumed.

Results: One hundred fifty-nine women were enrolled in group 1, 43 women were enrolled in group 2, and 108 women were enrolled in group 3. Women's characteristics were similar, except that group 3 was 1.5 (0.5) years older and had 4.4 (0.7) years less HT/ET use than groups 1 and 2. Utian Quality of Life scores were significantly lower in group 3 (83.4 [12.5]) than in groups 1 and 2 (87.6 [13.3], $P < 0.02$), particularly in the occupational satisfaction scale. About 16.6% and 16.3% of women in groups 1 and 2 were on antihypertensive medication, respectively, compared with 27.4% in group 3 ($P < 0.04$).

Conclusions: Discontinuation of HT/ET may predispose some women to the risk of hypertension and may affect their quality of life.

Key Words: Hormone therapy – Estrogen therapy – Quality of life – Hypertension.

Few studies have examined the effects of hormone withdrawal on women using hormones for menopausal symptoms. Since the results of the Women's Health Initiative (WHI) were published in July 2002, a large number of women have stopped hormone therapy (HT) because of their concerns about the risks of heart attacks and breast cancer. This discontinuation of HT is probably the largest sudden decline in the use of a medication in the history of American medicine. The initial drop in sales ranged between 32% and 38%,[1,2] with a continued annual decline of approximately 6%[3-6] and an eventual 45%[7] reduction in use that has stabilized without a further recent decline.[6,8] These women present a unique population, and these events represent an unparalleled opportunity to answer epidemiologic questions on risks and benefits in those women who initiated therapy at menopause and subsequently chose to stop HT. The hypoestrogenic menopausal state is associated with weight gain, changes in body composition, increased visceral fat, and increased secretion of inflammatory factors, and predisposes women to chronic diseases such as diabetes, heart disease, and metabolic syndrome.[9-11] The time elapsed since 2002 presents an optimal interval to observe the consequences of this experience, as risk surfaced after 5 years of therapy in the estrogen + progestin (E + P) arm of the WHI trial and after 8 years in the estrogen-alone trial.[12,13] Women who were aged 49 to 64 years and at fairly low risk for chronic diseases when the WHI results were announced are now aged 57 to73 years and therefore at greater risk for cardiovascular and other chronic diseases. Some data suggest that women are at high risk for chronic diseases after menopause and that HT may delay some of these effects.[14-16] This retrospective study aimed to compare the prevalence of conditions that predispose to chronic diseases (obesity, hypertension, hyperlipidemia, and diabetes, all components of metabolic syndrome) and medication use among women currently aged 56 to 73 years who used HT for at least 5 years and subsequently stopped, with comparable

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women who continued this therapy being drawn from the same practices. If HT had a preventive or delaying role, women stopping HT would be at greater risk for developing chronic diseases than the cohort continuing on hormones. We also assessed quality of life and medical morbidity.

METHODS

Participants

Women were eligible for the study if they had been previously diagnosed as postmenopausal, were born between April 1, 1938 and March 31, 1953, and had used HT (including estrogen therapy [ET]) for at least 5 years. All participants were outpatients recruited by their physicians from two medical center practices (Columbia University Medical Center and St Luke's Roosevelt Hospital) and from the offices of practitioners identified as those treating menopause in New York City between 2009 and 2012. Participants who provided an informed consent form were interviewed and measured in a private area of their physician's office during a subsequent routine visit and, when necessary, followed up by telephone. Three groups were compared: group 1, women who have remained on HT/ET; group 2, women who have resumed HT/ET after stopping for at least 6 months; and group 3, women who have stopped HT/ET and have not resumed. No other criteria were used for inclusion or exclusion, although all women came from gynecologic or women's health practices with a focus on menopause.

Sample size was determined in the following manner: the study was designed to test whether discontinuance of HT would be associated with a higher incidence of hypertension and/or use of hypertensive medication and obesity. We assumed that hypertension had the lower incidence of the two primary aims and thus the largest sample size requirement, with an estimated change in incidence from 5% to 10% in women who discontinued HT. A two-tailed test with a type I error of 0.05 and 80% power would have required 95 women per study group. This was sufficient to determine one or both of the primary aims, provided there were no significant differences in other predisposing factors among the groups.

Measurements and study instruments

Women's weight, height, waist, and hip were measured using scales, heightometers, and tape measures available in the physicians' offices. Blood pressure was obtained from the chart at the time of the visit. Body fat percentage was measured by impedance.[17] Quality of life was measured by interviewers using previously validated instruments. The 23-item Utian Quality of Life scale was used to measure occupational, health, emotional, and sexual quality of life for perimenopausal and postmenopausal women.[18] The 21-item Greene Climacteric Scale was used to measure climacteric symptoms, including vasomotor, psychological, and somatic symptoms.[19] Interviews also assessed the reasons for hormone use, discontinuation, and resumption; sociodemographic status; and economic status using the WHI questionnaire.[20,21] Medical history, reproductive health information, personal history, physical activity, sleep habits, and use of health services were assessed using items from the Third National Health and Nutrition Examination Survey.[22] In addition, four new questions asked about urinary tract infections, and four questions asked about oral health.

The protocol was approved by the Institutional Review Boards at Columbia University Medical Center and St Luke's Roosevelt Hospital in New York. Recruitment was halted when statistically significant differences adjusted for study group differences were noted.

Determination of risk factors

In addition to measurements of blood pressure, body mass index (BMI), and waist, the questionnaires included information on risk factors for coronary heart disease, including hypertension or use of hypertensive medication, history of smoking, diabetes mellitus, hyperlipidemia, or use of lipid-lowering medication. In particular, we focused on two components of metabolic syndrome: central obesity and hypertension (or use of hypertensive medication); hypertriglyceridemia, low high-density lipoprotein cholesterol, and fasting hyperglycemia, which are also components of metabolic syndrome, are secondary aims. All components of metabolic syndrome are related to insulin resistance and predispose to diabetes mellitus and thus are considered risk factors for cardiovascular disease.[23]

Statistics

Data were analyzed using multiple *t* tests. All data are presented as mean (SD). We used independent *t* tests to measure differences between groups. Significance was set to $P < 0.05$ for all comparisons. Normally distributed data in the different treatment groups were compared by one-way analysis of variance (ANOVA). To analyze continuous variables among the three groups, we used ANOVA or analysis of covariance when controlling for age. If there were significant results, we performed multiple comparisons using the Bonferroni method. We also used two-way ANOVA to evaluate differences within and between groups of normally distributed data to compare medication use. Statin use was related to cholesterol as a dependent variable, and blood pressure medication was related to blood pressure. χ^2 tests were used to determine differences between groups of categorical variables. Logistic regression was performed to determine the predictors of blood pressure medication use, controlling for age, weight, BMI, and family history of hypertension. All statistical calculations were run on SPSS (SPSS, Chicago, IL).

RESULTS

The study enrolled 310 consenting eligible women, including 159 women who remained on HT/ET (group 1), 43 women who have resumed HT/ET (group 2), and 108 women who have not resumed HT/ET or replaced HT/ET with alternative therapies such as over-the-counter remedies for hot flashes

TABLE 1. *Reasons for discontinuation*

Adverse media	70.2
Physician's recommendation	24.5
Cancer	9.3
Other	6.6
Thromboembolism	<0.01
Heart condition	<0.01
Stroke	0
Myocardial infarction	0

Values are expressed as percentages.

(group 3). Participation was high, with less than 1% declining in each of the groups. No between-group differences in reasons for discontinuation were noted. Of the women who discontinued HT/ET (groups 2 and 3), 70.2% discontinued because of adverse media about therapy, 24.5% discontinued because of a physician's recommendation, and 16% discontinued for other reasons. Some cited multiple reasons (Table 1). Women who continued or resumed HT/ET were significantly younger than those who discontinued HT/ET (groups 1 + 2 [64.8 (4.1) y] vs group 3 [66.3 (3.7) y], $P < 0.01$; Table 2). Group 1 was younger than group 2, which in turn was younger than group 3, but not significantly so. Women started HT/ET at 49.1 (5.4) years. The mean (SD) weight was 140.4 (24.9) lb, and the mean (SD) BMI was 24.0 (4.1) kg/m^2. Women remaining on HT/ET or restarting HT/ET were on HT for a significantly longer time (groups 1 + 2 [15.2 (6.4) y] vs group 3 [10.8 (5.4) y], $P < 0.01$). No between-group differences in weight, height, BMI, waist-to-hip ratio, and body fat were noted (Table 2). The mean (SD) time off HT for group 2 was 29.3 (28.9) months.

There were no between-group differences in socioeconomic status (SES), ethnicity, income, education, access to health care, types of health insurance, exercise, alcohol intake, or smoking. However, they differed in employment, with those who continued HT being more likely to be employed ($P < 0.03$) and to hold managerial positions ($P < 0.04$), particularly in a professional satisfaction subscale ($P < 0.04$), although the likelihood of holding a managerial position or professional satisfaction was no longer significant when age or ability to work (retired or disabled) was controlled for (Table 3). Ninety-five percent of the participants were white, and 84% had college education (Table 3). No woman discontinued HT/ET because of hypertension. There was no difference in the number of doctor visits or hospitalizations in the last 12 months between those women who stopped and those who did not.

Women on HT/ET scored higher on a quality-of-life scale (groups 1 + 2 > group 3; $P < 0.02$), particularly with respect to occupation ($P < 0.04$). However, women not on HT/ET scored higher on a vasomotor scale (group 3 > group 1 [$P < 0.05$, NS] vs group 2) and on vaginal dryness (group 3 > group 1; $P < 0.001$; Table 4). There was no difference in the depression scale of the Greene Climacteric Scale or in the use of antidepressive medication (Tables 4 and 5).

Triglycerides were slightly higher in the group remaining on HT/ET (Table 5). There was no between-group difference in

TABLE 2. *Anthropomorphic data*

	All women (N = 310)	(A) Group 1: continued HT/ET (n = 159)	(B) Group 2: resumed HT/ET (n = 43)	(C) Group 3: discontinued HT/ET (n = 108)
Age, mean (SD), y	65.3 (4.0)	64.6 (4.1)[a] 64.8 (4.1)[b]	65.7 (4.0)	66.3 (3.7)[a,b]
Age at diagnosis of hypertension, mean (SD), y	53.45 (1.44)	52.33 (2.37)	50.38 (3.88)	55.83 (1.92)
Age at start of HT/ET, mean (SD), y	49.1 (5.4)	49.4 (5.4)	48.0 (5.9)	49.1 (5.4)
Number of years on HT/ET, mean (SD)	13.4 (6.4)	14.7 (6.3)[c] 14.7 (6.4)[b]	14.6 (6.9)[c]	10.8 (5.4)[b,c]
Months off HT/ET, mean	—	—	29.3	—
Oral ET use, %[d]	41.6	30.4[c] 28.9[c]	23.3[c]	65.4[c]
Transdermal ET use, %[e]	35.1	43.0[c] 43.3[c]	44.2[c]	19.6[c]
Oral HT use, %[f]	20.1	10.1[c] 9.0[c]	4.7[c]	41.1[c]
Transdermal HT use, %[g]	5.5	5.1 4.0	0.0	8.4
Weight, mean (SD), lb	140.4 (24.9)	140.4 (24.9)	142.8 (30.9)	139.9 (24.7)
Height, mean (SD), in.	64.2 (2.5)	64.2 (2.5)	64.8 (2.6)	63.8 (2.4)
Waist, mean (SD), in.	32.1 (4.2)	32.1 (4.1)	32.2 (4.1)	32.2 (4.4)
Waist-to-hip ratio, mean (SD)	0.81 (0.06)	0.81 (0.06)	0.80 (0.07)	0.80 (0.06)
Body mass index, mean (SD), kg/m^2	24.0 (4.1)	23.9 (4.2)	23.9 (4.5)	24.2 (4.0)
Body fat, mean (SD), %	32.8 (6.8)	32.5 (7.0)	33.1 (6.7)	33.0 (6.4)

HT, hormone therapy; ET, estrogen therapy.
[a] $P < 0.01$, A versus C (one-way analysis of variance).
[b] $P < 0.01$, (A + B) versus C.
[c] $P < 0.01$, A or B versus C; (A + B) versus C.
[d] Oral ET includes Premarin, Cenestin, Enjuvia, Estrace, Femtrace, and Estratest.
[e] Transdermal ET includes Climara, Vivelle, Vivelle-Dot, Estrogel, Divigel, Femring, and Estraderm.
[f] Oral HT includes Premphase, Prempro, Femhrt, Activella, and Angeliq.
[g] Transdermal HT includes Combi-Patch and ClimaraPro.

TABLE 3. *Social and demographic data*

	(A) Group 1: continued HT	(B) Group 2: resumed HT	(C) Group 3: discontinued HT	*P*
White, %	94.3	95.3	87.9	NS
College degree, %	84.4	81.0	85.7	NS
Employed, %	**54.7**	36.8	39.8	**0.028**
Managerial position, %	75.0	**47.6**	74.5	**0.012**[a]
Retired, %	30.3	31.7	46.7	NS
Annual income ≥US$50,000, %	89.2	90.9	93.4	NS
Private health insurance, %	71.7	72.1	68.5	NS
Medicare/Medigap, %	45.3	62.8	62.0	NS
Other insurance coverage, %[b]	8.8	2.3	6.5	NS
Current cigarette use, %	11.6	0.0	5.8	NS
Alcoholic drinks per day, mean (SD)	0.93 (0.83)	0.91 (0.75)	0.96 (0.81)	NS

HT, hormone therapy; NS, nonsignificant. Boldface indicates group in which significance was found.
[a]NS when controlling for age.
[b]"Other insurance coverage" includes military health care, state-sponsored health care, other government programs, single-service plans, and unknown (type of coverage not known).

blood pressure or cholesterol even when controlling for the use of hypertension-lowering medications or statins, respectively. Women who discontinued HT/ET were on significantly more antihypertensive medications: 27.4% of group 3 (29 of 106) versus 16.6% of group 1 (26 of 157) versus 16.3% of group 2 (7 of 43; Table 5). Combining the groups on HT/ET, we found that 16.5% of women currently on HT/ET (33 of 200) were on antihypertensive medications compared with 27.4% of women not on HT/ET (29 of 106, $P < 0.04$; Table 5, Fig. 1). These results were significant when controlling for age and weight ($P < 0.005$; Table 4) and time off HT/ET in group 2.

The results were even more significant ($P < 0.003$) when hypertension in the family was controlled for. Thus, when controlling for other predictors of hypertension (age, weight, BMI, family history, and heart problems before starting HT), the odds of being on antihypertensive medication were 2.289 times greater for those who were not on HT than for those who were. Years on HT/ET was not significantly related to the use of hypertensive medication. There was no significant difference in the incidence of hypertension, number of women on hypertensive medications, cardiovascular events, cardiovascular disease, or diabetes at baseline or at the start of HT among groups 1, 2, and 3.

DISCUSSION

Some evidence suggests that HT improves quality of life,[24] especially for symptomatic women. In some observational and randomized studies, HT has been shown to exert protection against the development of chronic diseases such as osteoporosis, cardiovascular diseases, and diabetes,[15,25-28] although randomized trials have been conflicting, particularly with respect to cardiovascular disease.[12]

Our results suggest that discontinuation of HT affects quality of life, particularly occupational satisfaction, for this select group of women. Decisions to discontinue HT may be influenced by multiple confounders, but our sample was fairly uniform with respect to SES, education, access to health care, and other behavioral factors, including exercise, alcohol intake, and smoking. Some studies have shown that hormone

TABLE 4. *Questionnaires*

	(A) Group 1: continued HT	(B) Group 2: resumed HT	(C) Group 3: discontinued HT
Utian Quality of Life	87.7 (13.9)	87.5 (11.1)	83.4 (12.5)[a]
		87.6 (13.3)[a]	
Occupational satisfaction scale	26.8 (7.5)[b]	27.3 (5.8)[b]	24.6 (7.1)[b,c]
		26.9 (7.1)[c]	
Greene Climacteric Scale: vasomotor symptoms	0.7 (1.0)[d]	1.0 (1.4)	1.0 (1.3)[d,e]
		0.7 (1.1)[e]	
Greene Climacteric Scale: depression	2.5 (2.0)	2.6 (2.3)	2.6 (2.1)
		2.5 (2.1)	
Vaginal dryness	1.4 (0.7)[f]	1.6 (0.8)	1.9 (1.0)[f,g]
		1.4 (0.7)[g]	

Values are presented as mean (SD).
HT, hormone therapy.
[a]Based on the 100-point Utian Quality of Life scale: $P < 0.02$, (A + B) versus C.
[b]Based on the 35-point occupational satisfaction scale in the Utian Quality of Life scale: $P = 0.05$ overall, one-way analysis of variance controlling for age; $P < 0.04$, A versus C.
[c]Based on the 35-point occupational satisfaction scale in the Utian Quality of Life scale: $P < 0.01$, (A + B) versus C.
[d]Based on the 6-point vasomotor symptoms portion of the Greene Climacteric Scale: $P < 0.05$, A versus C.
[e]Based on the 6-point vasomotor symptoms portion of the Greene Climacteric Scale: $P < 0.04$, (A + B) versus C.
[f]$P < 0.001$, A versus C, one-way analysis of variance.
[g]$P < 0.001$, (A+B) versus C.

TABLE 5. *Medical data*

	(A) Group 1: continued HT		(B) Group 2: resumed HT	(C) Group 3: discontinued HT
Total cholesterol, mean (SD), mg/dL	200 (35)	203 (35)	214 (34)	203 (33)
High-density lipoprotein, mean (SD), mg/dL	73 (19)[a]	74 (19)	76 (18)	79 (21)[a]
Low-density lipoprotein, mean (SD), mg/dL	108 (30)	110 (31)	118 (33)	108 (30)
Triglycerides, mean (SD), mg/dL	100 (51)[b]	99 (49)[c]	98 (44)	88 (38)[b,c]
Systolic blood pressure, mean (SD), mm Hg	122.2 (15.8)	122.6 (15.9)	123.9 (10.7)	124.1 (14.3)
Diastolic blood pressure, mean (SD), mm Hg	76.9 (9.3)	77.1 (8.9)	77.6 (7.5)	74.8 (8.5)
Medication use, %				
Antihypertensives	16.6[d]	16.5[e]	16.3[d]	27.4[d,e]
Statins	26.8	27.0	27.9	30.2
Antidepressants	26.1	23.5	14.0	17.9
Aspirin	24.8	24.0	20.9	24.5
Anticoagulants	0.0	0.5	2.3	2.8

HT, hormone therapy.
[a] $P < 0.02$, A versus C, two-way analysis of variance controlling for age.
[b] $P = 0.05$, A versus C.
[c] $P < 0.04$, (A + B) versus C, one-way analysis of variance controlling for age.
[d] $P < 0.04$, χ^2 test comparing three groups; $P < 0.003$, excluding those with preexisting heart conditions.
[e] $P < 0.04$, (A + B) versus C; $P < 0.005$, excluding those with preexisting heart conditions; $P < 0.005$, controlling for age and weight; $P < 0.003$, controlling for age, weight, and family history of hypertension.

users are healthier and wealthier than nonhormone users,[29,30] although the Nurses' Health Study found minor differences in risk factors and between users and nonusers, with increased cardiovascular risk in nonusers when adjusting for these.[31] Our study consisted mainly of women of high SES status; these findings may apply only to this group, as they represent a typical sample of hormone users. We do not have data on diet, but it is improbable that these women of similar ethnicity, SES status, educational background, and BMI, and from a small geographic area with access to health care differed significantly in their diet. Others have recently published findings that menopausal symptoms are negatively associated with work ability and increase the risk of sickness absence.[32] A negative effect on work outside the home was also

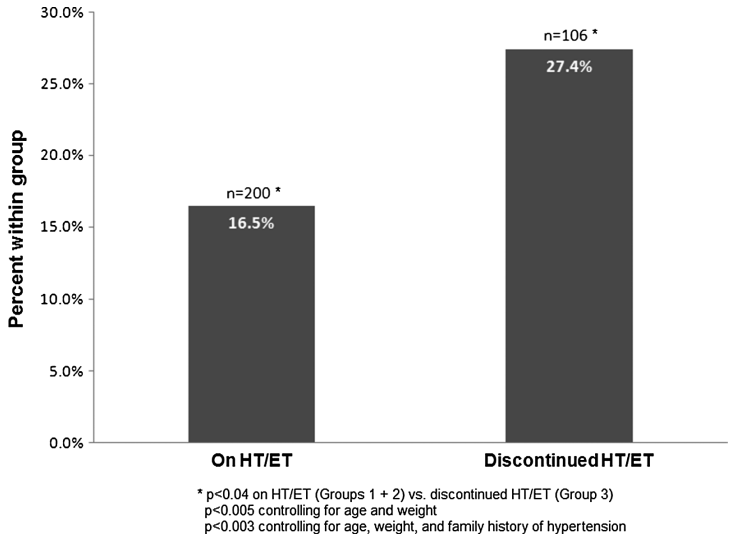

FIG. 1. Percentage of women on antihypertensive medications. HT, hormone therapy; ET, estrogen therapy.

documented in the Yale midlife study[33] and commented on by others.[34] It may not be coincidental that the most rapid decline in the rate of women's work ability occurs at 51 years, the peak time for menopausal symptoms.[35] The highest annual declining rate in work ability index was seen in this study among older women (aged 51 y), in comparison with men, during an 11-year period when a population working in the same occupation (age range, 44-51 y) was followed. The authors stated that "the role of physiological and mental changes associated with menopause among women should be studied." Our study found that women who continued hormones had better quality of life, reported more professional satisfaction, and held more managerial positions. However, these differences were not significant when controlling for age or ability to work. One explanation for greater hormone use among managerial women is that they could be more willing to assume risk for symptom relief.

Discontinuation of HT may also place some women at risk for the development of hypertension, which may be an early indicator of metabolic syndrome, a significant risk factor for cardiovascular disease. When controlling for other predictors of hypertension (age, weight, family history, and heart problems before starting HT), the odds of being on blood pressure medication were 2.289 times greater for those who were not on HT. Estrogen withdrawal may also initiate remodeling leading to atherosclerotic cardiovascular diseases; the first symptom may be heralded by hypertension. The role of hormone replacement in blood pressure and arterial function has been debated for several decades. Women seem to be protected against cardiovascular disease–related death before menopause, with a progressive rise in cardiovascular disease–related deaths after menopause; higher blood pressure levels occur as well, becoming steeper after the age of 62 years.[36] Epidemiologic studies have been conflicting[37] with respect to the effects of menopause or hormone replacement on blood pressure, with some studies suggesting a role for HT in reducing blood pressure whereas others show no effect or even a small increase.[10,37] However, there have been no publications on blood pressure with HT withdrawal, except for the WHI. Results from the WHI E + P (HT) and estrogen-alone arms showed no difference in extension studies on withdrawal of treatment, but follow-up was conducted for 1.3 years only for the estrogen trial or reported only at baseline for E + P.[38-40] During active treatment of the WHI trial, blood pressure reports were carried out for 1 year only.[41,42] However, many of these women did not enroll and receive treatment close to the age of menopause, a time when vascular pathology is minimal and when they are significantly less likely to have complications such as cardiovascular disease or stroke (ie, complications reported in the WHI). In contrast to the WHI, the Nurses' Health Study followed 121,700 nurses prospectively to examine the role of hypertension in the development of cardiovascular events.[43] Careful examination of their data showed that women who used postmenopausal hormones were less likely to have hypertension.[43] A subsequent report showed a small decrease in hypertension and significantly fewer cardiovascular events with hormone use.[44] Women in the Nurses' Health Study started hormones at the normal age of menopause. Timing of intervention with ET to prevent atherosclerosis is crucial in primate studies, with significant protection seen only close to oophorectomy.[45,46]

Although epidemiologic studies are conflicting, physiological studies of HT for arterial stiffness and structure have been compelling and have been summarized.[37] Surrogate measures of arterial stiffness are reduced with HT. These include reduced pulse wave velocity,[47] improved systemic arterial compliance, and carotid distensiblity.[48] Multiple studies have also found a decrease in vascular intima-media thickness and an attenuation of its development, similar to findings when premenopausal women are compared with postmenopausal women.[37] Other nonendothelial factors may include improved lipid profile on menopausal therapy and enhanced secretion of nitrous oxide, a powerful vasodilator. Smooth muscle proliferation may also be inhibited.[49] Withdrawal of estrogen secretion or therapy, as suggested by these studies, probably causes progressive stiffening of the vasculature, thickening of large arteries, and impaired vascular reactivity and relaxation, which result in increased systolic blood pressure, pulse pressure, and future cardiovascular events, and may also lead to hypertension. Pulse pressure, a surrogate measure of arterial stiffness, is a predictor of future cardiovascular events.[50,51]

Our participants were also of normal weight. BMI is a strong indicator of endogenous estrogen, and women with higher BMI have higher levels of circulating estrogen. One very large cohort of 290,827 postmenopausal women found coronary protection only in women with lower BMI, where lower endogenous levels of estrogen would be expected.[52] The mean BMI in the E + P arm of the WHI was 28.5 kg/m^2, and that in the estrogen-alone arm was 30.1 kg/m^2,[12] whereas our participants averaged 24.0 (4.1) kg/m^2, similar to the Nurses' Health Study (24.3 kg/m^2), where coronary protection was observed.[53] However, a recent analysis of a large cross-sectional cohort of women suggests an increased risk of hypertension self-reported by women using HT. Women in this study were not hypertensive before menopause.[54] The baseline observational arm of the WHI also suggested an increased risk of hypertension in current hormone users.[55] Thus, women with higher BMI and more endogenous estrogen and risk factors may be at higher risk for developing hypertension on HT/ET, whereas healthier women with normal BMI may experience a protective effect.

Importantly, medication use was not reported in the WHI studies. Antihypertensive medication use is a meaningful proxy for hypertension diagnosis and is particularly sensitive when accompanied by a diagnosis,[56] which we obtained at interview. Medication history is an appropriate proxy because women who are being treated for hypertension will not have elevated blood pressure upon examination. We did not find differences in blood pressure between the groups of women. Treatment of hypertension is, however, considered an appropriate indicator of hypertension and has been used in recent clinical guidelines.[23] Results from retrospective and other

TABLE 6. *Analysis of hypertension risk factors with use of hormone therapy*

Risk factors	Group 1: continued HT/ET (n = 159)		Group 2: resumed HT/ET (n = 43)		Group 3: discontinued HT/ET (n = 108)		Total participants (n = 310)
Hyperlipidemia, n (%)							
Yes	46 (34.3)	NS	12 (33.3)	NS	33 (36.7)	NS	91 (35)
No	88 (65.7)		24 (66.7)		57 (63.3)		169 (65)
Medical morbidity, mean (SD)[a]	1.9481 (0.91317)	NS	1.8810 (1.01699)	NS	1.8750 (0.74635)	NS	1.9133 (0.87275)
Obesity, n (%)							
Yes	13 (8.2)	NS	3 (7)	NS	10 (9.3)	NS	26 (8.4)
No	145 (91.8)		40 (93)		97 (90.7)		282 (91.6)
Diabetes mellitus, n (%)							
Yes	4 (2.6)	NS	0	NS	3 (2.9)	NS	7 (2.3)
No	148 (97.4)		42 (100)		101 (97.1)		291 (97.7)
Annual income ≥US$50,000, n (%)							
Yes	99 (89.2)	NS	30 (90.9)	NS	71 (93.4)	NS	200 (90.9)
No	12 (10.8)		3 (9.1)		5 (6.6)		20 (9.1)
College degree, n (%)							
Yes	130 (84.4)	NS	34 (81)	NS	90 (85.7)	NS	254 (84.4)
No	24 (15.6)		8 (19)		15 (14.3)		47 (15.6)

HT, hormone therapy; ET, estrogen therapy; NS, nonsignificant.
[a]Medical morbidity measured by a self-reported health scale (1, excellent; 5, poor).

observational studies have been inconsistent with respect to the effects of aging, menopause, and HT on blood pressure.[57,58] Any changes noted have been observed in the range of 1 to 2 mm Hg. Accuracy of measurements would be a large factor and suggests that these findings are not clinically relevant.

The use of a relatively small observational study to represent a sample selected from a healthy group of women who were highly educated and had normal BMI, as well as the nonapplication of the findings to other groups, was a limitation of this study. With respect to hypertension, a number of potential confounders were examined, but none showed significance in a multivariate-adjusted analysis examining HT status and use of hypertension medication—although our numbers were too small to include SES status, as many participants declined to answer questions concerning income. Obese participants composed only 8.3% of the sample, and women with diabetes only represented 2.3% (Table 6). However, these participants are typical of hormone users, and all of these women had been undergoing treatment with HT/ET for a significant length of time.[12,29] Gynecologic and women's health practices may also have attracted women without significant health problems. However, the observation that hypertensive medication use in the group deciding to remain off therapy is significantly different may have implications for the pathophysiology of atherosclerotic diseases, suggesting that HT/ET treatment may delay the onset of hypertension in some, particularly in this normal-weight sample. Also, many different preparations of ET and HT were used even in individual women, and no conclusions can be made on the effects of dose, delivery (oral vs transdermal), or role of estrogen or progestin. More women who continued or restarted treatment used transdermal hormones. This may be attributed to a shift in treatment after the WHI and perceptions that transdermal therapies may have vascular advantages. Another limitation of the study was the small sample, which prevented adjusting for multiple variables that influence the outcomes of interest, such as obesity, hyperlipidemia, diabetes, medical morbidity, and SES. However, the sample was relatively homogeneous, and the incidence of diabetes and obesity was very low such that multivariable adjustment was not possible for selected variables. Our findings are preliminary and should be examined in a much larger sample.

A strength of this study is uniformity in the sample and in the decision to discontinue therapy because of an external event at approximately the same time. Sampling from healthcare practices provided a uniform sample of women who had taken HT/ET under the care of a healthcare professional and did not favor employed women, despite our findings in this regard. However, application of these findings requires further study and may apply only to the typical healthy hormone user with access to health care.

CONCLUSIONS

We observe for the first time an effect of HT/ET withdrawal on the development of hypertension. We also find a higher quality of life among hormone users, particularly with respect to professional satisfaction. Our observations are important, as the effect of hormone/estrogen withdrawal on susceptible individuals may lead not only to functional symptoms but also to important health issues.

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