The Effects of Continuous Combined Oral Estradiol and Norethisterone on Pulsatility Index in Internal Carotid and Uterine Arteries in Early Postmenopausal Taiwanese women—A Preliminary Study

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SUMMARY

Objective: This study analyzed whether continuous combined oral estradiol and norethisterone had any effect on the pulsatility index (PI) of the internal carotid and uterine arteries in Taiwanese early postmenopausal women.

Materials and Methods: A group of 40 healthy postmenopausal women with no history of hormone therapy (HT) participated in this study and were randomly subdivided into two groups: HT treatment group ($n = 20$) and placebo group ($n = 20$). PI was evaluated with color Doppler ultrasound at the beginning of the study and after 4 months of HT (2 mg 17β-estradiol + 1 mg norethisterone acetate) or placebo.

Results: There was no significant change in the PI of the internal carotid and the uterine arteries after 4 months of HT.

Conclusion: This HT regimen showed no significant negative impact on vascular resistance in Taiwanese early postmenopausal women. Results are compatible with the updated recommendations on HT stating that there is little cardiovascular risk when HT is initiated within a few years of the menopause. [*Taiwan J Obstet Gynecol* 2009;48(1):60–64]

Key Words: estradiol, estrogen/progesterone therapy, hormone therapy, menopause, norethisterone, postmenopause, pulsatility index

Introduction

After the menopause, cardiovascular disease increases and is the leading cause of death among postmenopausal women [1,2]. Over the last decade, many observational studies have shown that hormone therapy (HT) appears to reduce the risks of vascular disease [3–9]. In 1998, however, the findings of the Heart and Estrogen/Progestin Replacement Study, the first blinded, placebo-controlled, randomized clinical trial of HT for the secondary prevention of cardiac disease in postmenopausal women, found no overall reduction in risk of coronary heart disease events among postmenopausal women [10]. Results of the Women's Health Initiative regarding primary prevention of coronary heart disease showed similar results or even some harm during the first year using HT consisting of estrogen/progesterone therapy (EPT) [11]. However, the population in both clinical trials mainly included patients aged 60–80 years,

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Accepted: April 14, 2008

who were more than 10 years from the beginning of the menopause, as opposed to younger women receiving HT in Taiwan.

An increase in vascular resistance, as assessed by Doppler ultrasound, is related to a higher cardiovascular risk among postmenopausal women. The mechanism in which estrogen reduces the pulsatility index (PI), which is an expression of resistance to flow, was first observed in the uterine artery [12], then in the internal carotid artery [13–16]. The effect on peripheral vascular resistance might explain the cardiovascular protection attributed to estrogen. In women with an intact uterus, the concomitant use of progestogen has been suggested to protect the endometrium; women who receive continuous combined HT have a reduced risk of endometrial cancer [17]. Whether there is a difference in the coronary effects when the treatment includes adding progestogen rather than just estrogen alone has not been established. The effects, however, may be more favorable with the use of estrogen alone [18].

The aim of this study was to investigate whether EPT had beneficial or harmful effects on vascular resistance in the uterine and internal carotid arteries in early postmenopausal Taiwanese women.

Materials and Methods

This was a single centre, double-blind, placebo-controlled, randomized study.

Subjects

A group of 40 healthy postmenopausal women without any previous history of hormone use (aged 47–52 years; criteria of inclusion and exclusion shown in Table 1) participated in the study with informed consent. Menopause was diagnosed by natural amenorrhea of at least 6 months, follicle-stimulating hormone (FSH) level > 40 mIU/mL, and estradiol < 20 pg/mL.

Treatments and assessments

First, we evaluated the PI, defined as the ratio of the difference between maximal systolic velocity and final diastolic velocity to mean velocity, all obtained in the same cardiac cycle using color Doppler velocimetry of the internal carotid and uterine arteries, and obtained a baseline. Subsequently, the 40 women were randomized to either the experimental group ($n = 20$) or control group ($n = 20$). The former received 4 months of HT (2 mg 17β-estradiol + 1 mg norethisterone acetate), while the latter received matched placebo tablets. We re-evaluated the PI after 4 months of therapy.

Table 1. Criteria of inclusion and exclusion

Inclusion criteria—women who fulfilled all the criteria below:

1. Spontaneous menopause within 3 years and intact uterus
2. Follicle-stimulating hormone > 40 mIU/mL
3. Estradiol < 20 pg/mL
4. Menopausal symptoms

Exclusion criteria—women with any one of the below:

1. Hormone-related neoplasm, such as breast cancer or endometrial cancer
2. Hepatic disease with irreversible liver function impairment or cancer of liver
3. Thromboembolism or cerebral vessel disease
4. Abnormal uterine bleeding of unknown etiology
5. Uncontrolled hypertension or diabetes mellitus
6. History of prior hormone therapy within 3 months
7. Steroid-taking

Color Doppler ultrasound was performed by a well-trained technologist and supervised by an ultrasound specialist.

Statistical analysis

The statistical methods used included descriptive statistics, paired *t* test and two-sample *t* test. Treatment effect comparison between the two study groups employed the ratio T_4/T_0 (where T_4 = PI at 4 months and T_0 = PI at baseline), thus individual bias was deleted from the numerator and the denominator of the ratio.

Results

Of the 40 women enrolled, 37 completed the clinical trial, 20 of which were in the HT group and 17 in the placebo group. There was no significant difference between the groups in terms of age, time of menopause, height, and weight (Table 2). The menopause had occurred within 2.5 years (mean, 1.5 years). Baseline PI values for the internal carotid and uterine arteries were similar between the HT group and the placebo group ($p = 0.32$ and $p = 0.17$ for the internal carotid artery and uterine artery, respectively), in comparison of the mean values (Table 3). Although the results were insignificant in both groups, there was a slight increase in the PI value of the internal carotid artery and a slight decrease in the PI value of the uterine artery from baseline to 4 months in both the HT and the placebo groups (Figure 1 and Table 3). Table 4 and Figure 2 show T_4/T_0, where the geometric mean of

Table 2. Summary of patient demographics

Characteristics	Hormone therapy ($n=20$)	Placebo ($n=17$)	p
Age (yr)	51.5 ± 3.70	50.5 ± 2.79	0.359
Time since menopause (mo)	17.73 ± 8.38	19.58 ± 7.71	0.769
Body weight (kg)	54.29 ± 5.91	55.88 ± 6.73	0.449
Body height (cm)	151.5 ± 23.45	155 ± 5.40	0.514

Table 3. Internal carotid artery pulsatility index (PI) and uterine artery PI in different treatment groups and time points

PI	Placebo ($n=17$)			Hormone therapy ($n=20$)		
	Baseline (T_0^-)	4 months (T_4^-)	Paired difference ($T_0^- - T_4^-$)*	Baseline (T_0^+)	4 months (T_4^+)	Paired difference ($T_0^+ - T_4^+$)†
Internal carotid artery‡						
Mean	1.02	1.13	–0.10	0.96	1.13	–0.16
SD	0.15	0.19	0.15	0.15	0.35	0.36
Uterine artery§						
Mean	2.52	2.08	0.44	3.16	2.58	0.57
SD	1.04	1.30	1.39	1.61	1.17	1.85

**Paired t test for $H_1: \mu_D > 0$, where μ_D = mean of $(T_0^- - T_4^-)$, $p = 0.99$ (internal carotid artery) and 0.10 (uterine artery); †paired t test for $H_1: \mu_D > 0$, where μ_D = mean of $(T_0^+ - T_4^+)$, $p = 0.97$ (internal carotid artery) and 0.09 (uterine artery); ‡$p = 0.32$, comparing the mean values of placebo and hormone treatment groups at baseline; §$p = 0.17$, comparing the mean values of placebo and hormone treatment groups at baseline. SD = standard deviation.*

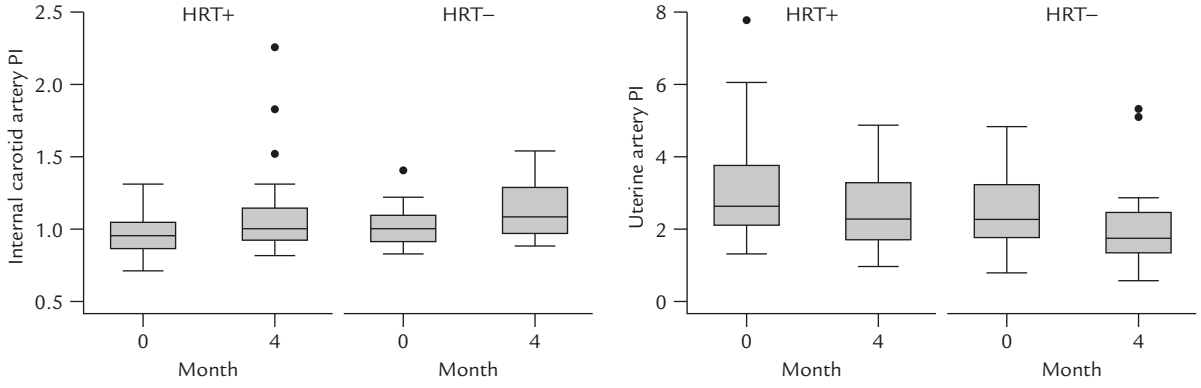

Figure 1. The box plots of pulsatility index from the internal carotid artery and uterine artery, with and without hormone therapy, and time points (baseline and 4 months). HRT+ = hormone therapy group; HRT– = placebo group.

Table 4. Comparing hormone therapy with placebo at T_4/T_0 for the internal carotid artery pulsatility index (PI) and uterine artery PI

T_4/T_0	Hormone therapy on internal carotid artery PI			Hormone therapy on uterine artery PI		
	+	–	p*	+	–	p*
Mean†	1.13	1.10	0.32	0.82	0.77	0.38
95% CI	(1.00, 1.29)	(1.03, 1.18)		(0.63, 1.07)	(0.55, 1.07)	

**t test $H_0: \mu_- < \mu_+$, in the log transform of the ratio, $\log(T_4/T_0)$, where the analyzed data will be more symmetric and closer to the normal distribution; †geometric mean, the anti-logarithm of the arithmetic mean of $\log(T_4/T_0)$. T_4 = PI at 4 months; T_0 = PI at baseline; + = with hormone therapy; – = without hormone therapy; CI = confidence interval.*

the internal carotid artery PI was 1.13 (HT group) and 1.10 (placebo group), and the geometric mean of the uterine artery PI was 0.82 (HT group) and 0.77 (placebo group). Note that the trends from baseline to 4 months are consistent with the above findings. In addition, from the t test, the mean of T_4/T_0 in the HT group was not significantly larger than in the placebo group in either the internal carotid artery PI ($p = 0.32$) or uterine artery

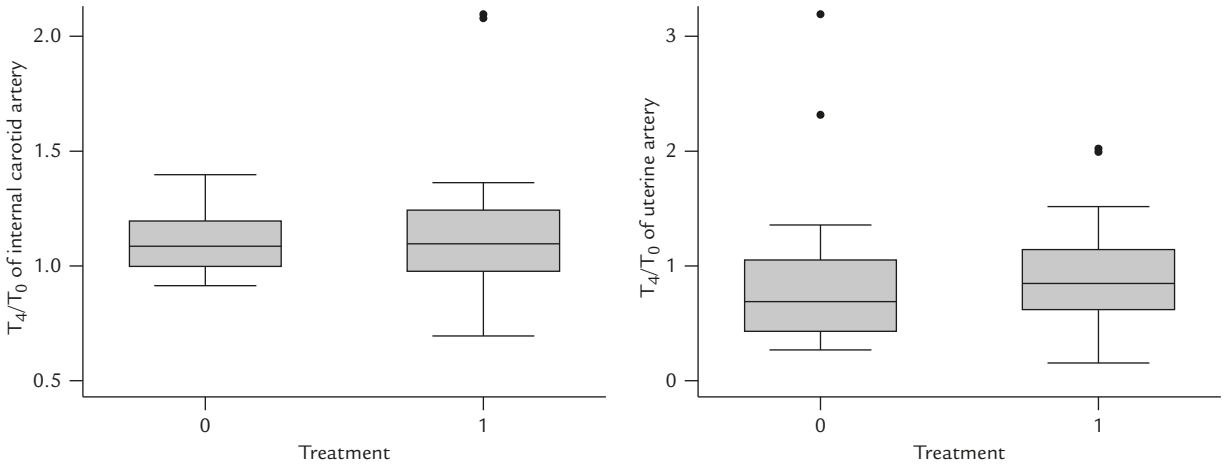

Figure 2. The box plots of pulsatility index (PI) ratio T_4/T_0, where T_4 = PI at 4 months and T_0 = PI at baseline, in the internal carotid and uterine arteries between hormone treatment (treatment 1) and placebo treatment (treatment 0).

PI ($p = 0.38$), i.e. the extent of increase in the internal carotid artery and the decrease in the uterine artery in the HT group was similar to that of the placebo group.

From this study, there is no significant evidence that HT increases PI in the internal carotid or uterine arteries.

Discussion

In this study, after 4 months of HT (2 mg 17β-estradiol + 1 mg norethisterone acetate), no significant changes were noted regarding the PI values of the uterine and internal carotid arteries. This implies that, at least for early postmenopausal Taiwanese women, this regimen of HT does not have a harmful impact on vascular resistance. This is compatible with the consensus that the cardiovascular risks are small when HT is initiated within a few years of menopause [18].

Estrogen benefits the vascular system, including improvement of the lipid profile [19], and production of prostacyclin and nitrogen oxide [20], the latter of which may cause the vasodilatory effects of estrogen (i.e. to reduce the PI). Nearly all studies involving the uterine arteries have demonstrated an important reduction in PI after estrogen administration [15,16,21]. However, the administration of a progestin to protect the endometrium may reduce the positive cardiovascular effects of estradiol. This reduction depends on the dose and the androgenicity of the progestin [22]. Nevertheless, no consensus has been reached regarding duration of use. In our present study, results after 4 months of HT showed no significant reduction in PI on the uterine artery and even a slight increase in the internal carotid artery. As we know, norethisterone is an estrane derivative which has relatively high androgenicity. In past studies, norethisterone partially antagonized the reduction in the carotid artery PI in postmenopausal women under estrogen replacement therapy [23]. Recent reviews demonstrated that the least antagonistic effect on lipid profile was seen with medrogestone, progesterone and cyproterone acetate. On the other hand, a marked antagonistic effect was observed with medroxyprogesterone acetate, norgestrel and norethindrone [24–30].

In conclusion, not all HT preparations (e.g. EPT) exert the same effects on the vasculature, and the choice of progestogen may influence vascular risk at different levels. In addition, it is possible that a lower dose of progestogen reduces the vascular benefit of estrogen to a lesser extent.

In the present study we observed that there is a tendency towards a reduction in the uterine artery PI value and an increase in that of the internal carotid artery. Similar results were also obtained in a short-term placebo-controlled trial carried out with 50 postmenopausal women [31]. The HT group also received 2 mg of estradiol plus 1 mg of norethisterone acetate and showed no significant decrease in the internal carotid artery PI. This might suggest that the increased flow obtained in the uterine bed cannot be extended to other organs. That is probably because, by comparison to other systems, the reproductive system is much more sensitive to the action of estrogens by having a larger amount of estrogen receptors. These results may explain why EPT had no effect in the prevention of coronary heart disease during the Women's Health Initiative clinical trial [11]. Further clinical trials are needed to clarify if other combinations, dosage, duration and routes of HT are involved in the complex and multiple mechanisms of cardiovascular action in Taiwanese postmenopausal women.

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