

Evaluation of uterine perfusion in postmenopausal women receiving hormone replacement therapy

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Summary

Objectives: The authors evaluated uterine perfusion in postmenopausal women receiving hormone replacement therapy (HRT) by using transvaginal Doppler ultrasonography. **Materials and methods:** A total of 60 postmenopausal women receiving HRT were included in this prospective case control study. The patients were divided into two groups. The study group received HRT for at least one year. Uterine perfusion was evaluated by transvaginal Doppler ultrasonography and pulsatility index (PI) and resistance index (RI) of uterine arteries were also recorded with a 5-7.5 MHz transvaginal probe. All patients gave informed consent to the study. Statistical analyses were carried out by using the statistical packages for SPSS 15.0 for Windows. **Results:** Demographic characteristics of the cases showed no statistically significant difference between the groups. There was a statistically significant difference between PI and RI of uterine arteries. In the study group PI and RI were lower than in the control group. As the duration of HRT use was prolonged, a decline in PI and RI increased ($p < 0.05$). **Conclusion:** The current study showed that HRT has positive effects on uterine blood flow in postmenopausal women and may be evaluated by transvaginal Doppler ultrasonography.

Key words: Menopause; Hormone replacement therapy; Transvaginal; Doppler ultrasonography.

Introduction

Menopause is a time period in a woman's life that is defined as the permanent cessation of menses due to termination of ovarian function, including increased secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [1]. Climacterium indicates the period of time when a woman passes from reproductive stage of life through the perimenopausal transition and the menopause to the post menopausal years, menstrual cycle length increases, beginning at two to eight years before menopause [2]. The age at menopause varies among women and mean age reported is 54 years in Europe and 51.4 years in USA [3, 4]. Menopause is associated with some negative symptoms such as: hot flushes, vulvovaginal atrophy, vasomotor instability, osteoporosis, increased incidence of thrombo-embolic and ischemic heart disease, and psychological symptoms of anxiety, depression, and memory loss [5, 6].

Doppler ultrasound is a technique that is currently used to evaluate blood flow in artery vessels. In the recent years it has an increasing popularity in gynecological experience because it also enables an in-vivo assessment of uterine and endometrial vascularization [7]. Doppler ultrasound examination has a wide range of application in obstetrics and gynecology practice such as: high risk pregnancies [8], ovarian masses [9], precocious puberty [10], and hypoestrogenic amenorrhoea [11]. Previous studies focused on vascular responses of postmenopausal

women receiving hormone replacement therapy (HRT). Wender *et al.* [12] studied internal carotid artery, Guvenal *et al.* [13] cerebral blood flow, and Huang *et al.* [14] internal carotid and uterine arteries.

In current study, the authors evaluated uterine perfusion in postmenopausal women receiving HRT by using transvaginal Doppler ultrasonography.

Materials and Methods

This prospective case control study was conducted at Hacettepe University, School of Medicine, Department of Obstetrics and Gynecology. This is a tertiary referral and research hospital in the capital of Turkey. A total of 60 postmenopausal women were included in the study. The patients were divided into two groups as HRT receiving (study group) and not (control group). The duration of HRT use was one to five years. The patients received four different types of HRT: 0.625 mg conjugated estrogens + 2.5 mg medroxyprogesterone acetate, two mg estradiol valerate + one mg cyproterone acetate, two mg estradiol + one mg norethisterone and 2.5 mg tibolone. All women were amenorrheic for at least one year and all of the patients were naturally menopausal. Of the patients with surgical menopause, having menstrual irregularities in reproductive period, having systemic diseases, and with uterine and adnexal pathologies were excluded from the study. Transvaginal Doppler ultrasound and gynecological examination of the patients was managed by the same clinician. During ultrasound examination with empty bladder of patients, a vaginal probe 5.0–7.5 MHz was utilized.

Mean age, duration of menopause, endometrial thickness, serum FSH, LH, and estradiol (E_2) levels and uterine artery (UA) pulsatility (PI) and resistance index (RI) of both UAs in three cardiac cycles were evaluated, and mean PI and RI values were also recorded.

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Table 1. — The demographic and clinical characteristics of the patients.

	Study group (n = 20)	Control group (n = 40)	Statistics and <i>p</i> values
Age [years], mean ± SD	49.3 ± 3.0	57.4 ± 7.2	<i>p</i> = 0.605
E ₂ (pg/ml)	61.6 ± 25.3	24.7 ± 20.9	<i>p</i> < 0.05
ET (mm)	3.3 ± 1.0	2.18 ± 1.2	<i>p</i> < 0.05

E₂: estradiol; ET: endometrial thickness

Table 2. — The mean PI and RI values in study and control groups.

	Study group (n = 20)	Control group (n = 40)	Statistics and <i>p</i> values
Mean UA PI	2.0 ± 0.7	3.4 ± 1.5	<i>p</i> < 0.05
Mean UA RI	0.7 ± 0.1	0.8 ± 0.1	<i>p</i> < 0.05

Table 3. — Correlation between PI and RI values and age, menopause duration, HRT duration, blood E₂ levels and endometrial thickness in study group.

	UA PI	UA RI
Age (years)	-0.02	-0.23
Menopause duration	-0.25	-0.11
HRT duration	-7.74 ^a	-0.65 ^a
Blood E ₂ level	0.10	-0.01
Endometrial thickness	-0.37	-0.53 ^a

^a: *p* < 0.05

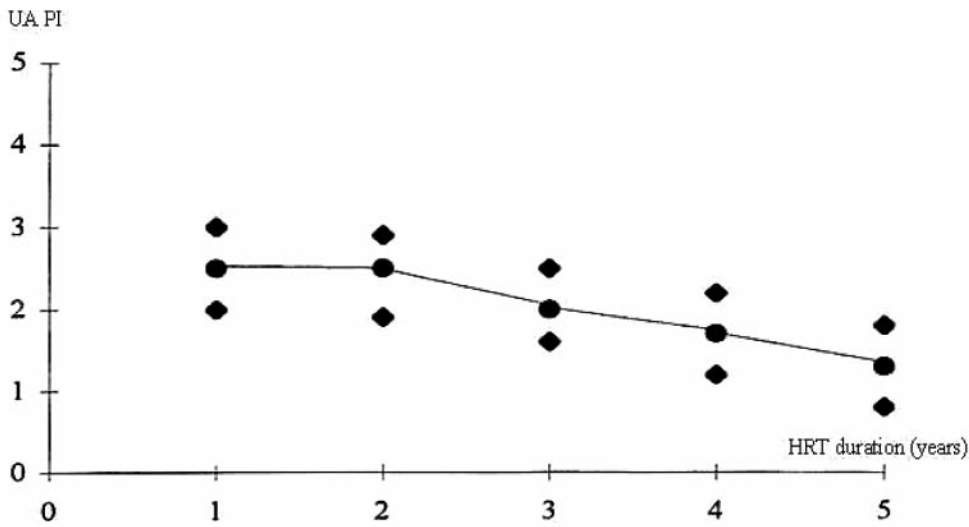


Figure 1. — The effect of HRT duration on uterine artery pulsatility index.

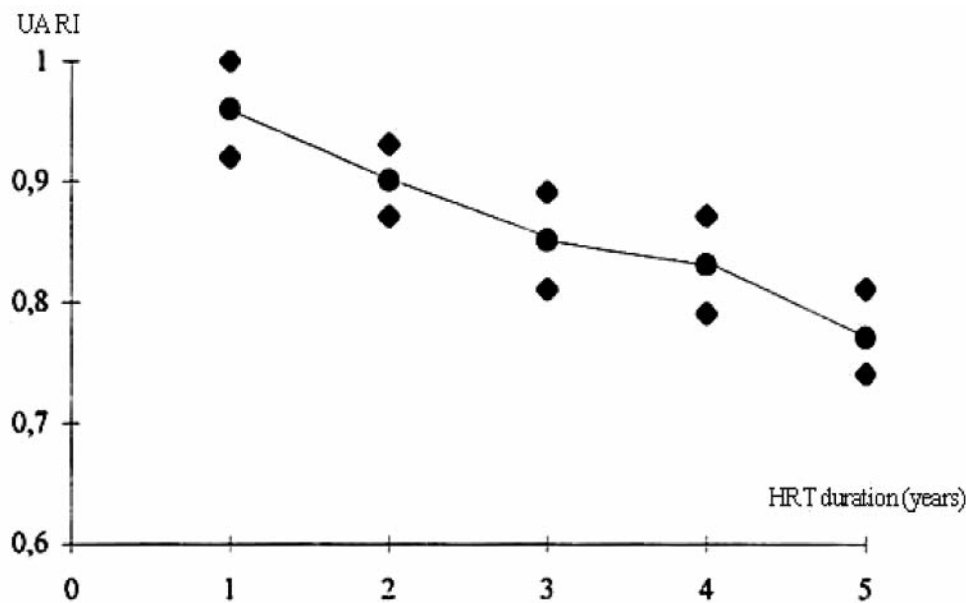


Figure 2. — The effect of HRT duration on uterine artery resistance index.

Statistical analysis

Mean values and standard deviations (SD) were calculated for continuous variables. Independent sample *t*-test, Mann-Whitney U test. (Wilcoxon rank sum test.), correlation analysis, and correlation analysis were performed. Two-sided *p* values were considered statistically significant at *p* < 0.05. Statistical analyses were carried out using SPSS for Windows.

Results

The demographic and clinical characteristics of the patients are shown in Table 1. There were no statistically significant differences among the groups in terms of age, FSH, and LH levels (*p* > 0.05). Endometrial thickness and E₂ levels were significantly higher in the study groups compared with controls (*p* < 0.05). UA PI and RI values were evaluated and their correlation between HRT duration, age, menopause duration, endometrial thickness, and type of HRT recorded. Table 2 shows the mean PI and RI values that were statistically significantly different between the groups and were higher in control group (*p* < 0.05).

In study group correlation between PI and RI values and age, menopause duration, HRT duration, blood E₂ levels and endometrial thickness are depicted in Table 3. There was a negative correlation between HRT duration and PI and RI values (*p* < 0.05). As the HRT duration was longer, PI and RI values were decreasing. Age and menopause duration showed no correlation (*p* > 0.05). Figures 1 and 2 show the correlation between menopause duration and UA PI and RI levels.

When the authors evaluated the correlation between endometrial thickness and other parameters, they noted that as HRT duration was longer, endometrial thickness was increasing. There was no correlation between HRT type and UA PI values between endometrial thickness. However, there was a negative correlation between UA RI and endometrial thickness (*p* < 0.05).

Discussion

The authors conducted an analysis of uterine perfusion in postmenopausal women receiving different types of HRTs. Uterine artery PI and RI values were lower in HRT receiving postmenopausal group. As the duration of HRT use became longer, the reduction of UA PI and RI increased. No association between HRT type and Doppler values were found. Previous studies evaluated the effects of HRT on blood vessels and cardiovascular risk factors in HRT receiving postmenopausal women [15-17]. Some authors have also described that receiving HRT reduces morbidity and mortality from coronary artery disease [18, 19]. The present authors also found a decrease in PI and RI values of uterine artery and these results were similar to the literature and related to the cardio-protective effect of HRT.

Jurkovic *et al.* [20] reported their experience on Doppler studies in HRT receiving postmenopausal women and they also found vasodilatation in the UA after HRT treatment. In this study, the authors also found that HRT has a circadian rhythm on arterial blood flow. Achiron *et al.* [21] studied in their study the prolonged effect of HRT in postmenopausal women and reported that endometrial blood flow impedance was higher in non-HRT receiving group. Dören *et al.* [22] also designed a study including two groups receiving HRT and not as controls. Their findings included increased blood flow in uterine vessels as in the present study. They also evaluated the endometrial thickness and found that duration of HRT has no effect on endometrial thickness. In contrast to this study, the present authors found an increase in ET in HRT group but not much than eight mm and pathology results were benign.

In conclusion, the authors believe that receiving HRT has a protective effect on vessels and cardiovascular system. These effects may be evaluated by non-invasive transvaginal Doppler ultrasonography. Clinicians may advise postmenopausal symptomatic women receiving HRT under regular visits.

References

- [1] Nelson H.D.: "Menopause". *Lancet*. 2008, 371, 760.
- [2] Fritz M.A., Speroff L.: "Menopause and the perimenopausal transition". In: Seigafuse S. (ed). *Clinical gynecological endocrinology and infertility*, 8th ed., Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2011, 673.
- [3] Dratva J., Gómez Real F., Schindler C., Ackermann-Liebrich U., Gerbase M.W., Probst-Hensch N.M., *et al.*: "Is age at menopause increasing across Europe? Results on age at menopause and determinants from two population-based studies". *Menopause*, 2009, 16, 385.
- [4] Gold E.B., Bromberger J., Crawford S., Samuels S., Greendale G.A., Harlow S.D., Skurnick J.: "Factors associated with age at natural menopause in a multiethnic sample of midlife women". *Am. J. Epidemiol.*, 2001, 153, 865.
- [5] Chiu C.L., Lujic S., Thornton C., O'Loughlin A., Makris A., Hennessy A., Lind J.M.: "Menopausal hormone therapy is associated with having high blood pressure in postmenopausal women: observational cohort study". *PLoS One*, 2012, 7, e40260. Epub 2012 Jul 11.
- [6] Wnuk A., Korol D.L., Erickson K.I.: "Estrogens, hormone therapy, and hippocampal volume in postmenopausal women". *Maturitas*, 2012, 73, 186.
- [7] Chan F.Y., Chau M.T., Pun T.C., Lam C., Ngan H.Y., Leong L., Wong R.L.: "Limitations of transvaginal sonography and color Doppler imaging in the differentiation of endometrial carcinoma from benign lesions". *J. Ultrasound Med.*, 1994, 13, 623.
- [8] Hoffman C., Galan H.L.: "Assessing the 'at-risk' fetus: Doppler ultrasound". *Curr. Opin. Obstet. Gynecol.*, 2009, 21, 161.
- [9] Cohen L. Transvaginal ultrasound assessment of the premenopausal ovarian mass. *J Assist Reprod Genet.* 2007;24(11):507-12.
- [10] Battaglia C., Regnani G., Mancini F., Iughetti L., Venturoli S., Flamigni C.: "Pelvic sonography and uterine artery color Doppler analysis in the diagnosis of female precocious puberty". *Ultrasound Obstet. Gynecol.*, 2002, 19, 386.
- [11] Pellizzari P., Esposito C., Siliotti F., Marchiori S., Gangemi M.: "Colour Doppler analysis of ovarian and uterine arteries in women with hypoestrogenic amenorrhoea". *Hum. Reprod.*, 2002, 17, 3208.

- [12] Wender M.C., Vigo F., Oliveira P.P., Bittelbrun F., Furtado A.P., Schwartzman L., *et al.*: "Effect of conjugated estrogen versus conjugated estrogen associated with medroxyprogesterone acetate in postmenopausal women on internal carotid artery pulsatility index: a randomized pilot study". *J. Obstet. Gynaecol. Res.*, 2011, 37, 815.
- [13] Guvenal T., Durna A., Erden O., Guvenal F., Cetin M., Cetin A.: "Effects of different postmenopausal hormone therapy regimens on cerebral blood flow and cognitive functions". *Adv. Ther.*, 2009, 26, 805.
- [14] Huang C.Y., Fu C.Y., Tseng J.Y., Yang T.S., Chao K.C.: "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". *Taiwan J. Obstet. Gynecol.*, 2009, 48, 60.
- [15] Persico N., Mancini F., Artini P.G., Regnani G., Volpe A., de Aloysio D., Battaglia C.: "Transdermal hormone replacement therapy and Doppler findings in normal and overweight postmenopausal patients". *Gynecol. Endocrinol.*, 2004, 19, 274.
- [16] Mancini F., Persico N., Genazzani A.D., Volpe A., Battaglia C., De Aloysio D.: "Effects of hormone replacement therapy on plasma viscosity and Doppler variations in postmenopausal non-smokers and heavy smokers". *Gynecol. Endocrinol.*, 2005, 20, 221.
- [17] Bonilla-Musoles F., Martí M.C., Ballester M.J., Raga F., Osborne N.G.: "Normal uterine arterial blood flow in postmenopausal women assessed by transvaginal color Doppler sonography: the effect of hormone replacement therapy". *J. Ultrasound Med.*, 1995, 14, 497.
- [18] Fait T., Vrablik M.: "Coronary heart disease and hormone replacement therapy - from primary and secondary prevention to the window of opportunity". *Neuro. Endocrinol. Lett.*, 2012, 33, 17.
- [19] Harman S.M., Vittinghoff E., Brinton E.A., Budoff M.J., Cedars M.I., Lobo R.A., *et al.*: "Timing and duration of menopausal hormone treatment may affect cardiovascular outcomes". *Am. J. Med.*, 2011, 124, 199.
- [20] Jurkovic D., Ross D., Aslam N., Whitehead M.: "Diurnal variation in uterine artery blood flow in post-menopausal women on oestrogen hormone replacement therapy". *Hum. Reprod.*, 1999, 14, 2716.
- [21] Achiron R., Lipitz S., Frenkel Y., Mashiach S.: "Endometrial blood flow response to estrogen replacement therapy and tamoxifen in asymptomatic, postmenopausal women: a transvaginal Doppler study". *Ultrasound Obstet. Gynecol.*, 1995, 5, 411.
- [22] Dören M., Süselbeck B., Schneider H.P., Holzgreve W.: "Uterine perfusion and endometrial thickness in postmenopausal women on long-term continuous combined estrogen and progestogen replacement". *Ultrasound Obstet. Gynecol.*, 1997, 9, 113.

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