Journal of
Controversies in Obstetrics & Gynecology and Pediatrics

Original Article

DOI: 10.51271/JCOGP-0008

# Evaluation of the effects of raloxifene treatment on uterus in asymptomatic postmenoposal patients by transvaginal Doppler ultrasonography

Asena Ayar Madenli

Department of Obstetrics and Gynecology, Liv Vadi İstanbul Hospital, İstinye University, İstanbul, Turkey

**Cite this article:** Ayar Madenli A. Evaluation of the effects of raloxifene treatment on uterus in asymptomatic postmenoposal patients by transvaginal Doppler ultrasonography. *J Controv Obstetr Gynecol Ped.* 2023;1(2):30-35.

**Corresponding Author:** Asena Ayar Madenli, asenaayar@yahoo.com.tr

**Received**: 06/03/2023 ◆ **Accepted**: 15/03/2023 ◆ **Published**: 28/04/2023

## ABSTRACT

**Aims**: To evaluate the effects of raloxifene treatment on uterus in asymptomatic postmenopausal patients by Doppler transvaginal ultrasonography (TvUS).

**Methods**: Randomized controlled prospective study, 57 healthy postmenopausal asymptomatic patients, aged 45-60, who applied Okmeydanı Training and Research Hospital Obstetrics and Gynecology Outpatient Clinic between 2003-2004. Four patients were excluded from the study because they did not apply the treatment regularly. All of the patients were in natural menopause. They had not received any hormone replacement therapy before. Their body mass index (BMI) was below 30 kg/m² and had no systemic diseases. The patients were divided into two groups as those who received raloxifene (n: 27) and those who did not (n: 26). Raloxifene was given 60 mg/day for 6 months. In all patients enrolled in the study, endometrial and uterine volume, pulsatility (PI) and resistance indices (RI) were evaluated by TvUS Doppler. Endometrial biopsies (EB) were obtained with pipelle at 0 and 6 months.

**Results**: There was no significant difference in terms of age, height, weight and BMI ($p<0.05$). Parity, menopause time and endometrial thickness were similar ($p<0.05$). EB results were similar ($p<0.05$). Uterine volumes at month 0 and 6 were similar ($p<0.05$). PI and RI were found to be similar in the right and left arteries at baseline ($p<0.05$). While PI and RI on the right side were similar at 6 months, left uterine artery PI was found to be significantly higher in the treated group. Left uterine artery RI was similar.

**Conclusion**: Raloxifene treatment neither did stimulate the endometrium, nor increased the uterine volume or uterine blood flow. It did not have any stimulating effect on the uterine tissue.

**Keywords**: Menopause, raloxifene, transvaginal Doppler ultrasonography, uterus

## INTRODUCTION

The World Health Organization (WHO) defines menopause as a permanent termination of menstruation as a result of loss of ovarian activity.[1] The menopause period is one of the stages of a woman's life and prolongation of the average life expectancy has extended it.[2]

The average age of onset of menopause in industrialized countries is in the 50s, although it is several years earlier in developing countries.[4,5] The mean age of menopause is reported as 52 in Western countries, 51 in the United States, and 47 in our country.[6,7]

The estimated life expectancy for women in Turkey is 81.2 years according to the 2022 data from the Turkish Statistical Institute (TUIK). In light of the provided data, if it is assumed that women will live approximately 81 years, one-third of their life which is approximately 27 years, will be spent in the postmenopausal period and may encounter health problems associated with this period.[5,8] This clearly demonstrates the importance of further studies on symptoms related to this period. Due to the increased risk of age-related diseases and cancer for women in this period, it seems essential to raise awareness about healthy living and preventive health services benefits. Many organs and systems undergo changes in the postmenopausal period. Early postmenopausal changes include; vasomotor symptoms (hot flashes on the face, neck, and chest, sweating, palpitations, insomnia) but later more serious changes such as bone mass loss, osteoporosis, increased risk of fracture, cardiovascular system changes and urogenital system atrophies are observed.[9]

Due to diminished ovarian function in postmenopausal women, bone turnover accelerates, bone mass decreases hence the risk of fracture increases. Hormone replacement therapy (HRT) may cause some undesirable effects as well as various beneficial effects. It prevents hip and spine fractures but some authors suggest it may pose increase therisk of coronary heart disease, venous thromboembolism, stroke, and breast cancer.[10] Selective estrogen receptor modulators (SERMs) have been developed as an alternative to HRT to increase bone mass. These molecules exert selective estrogen agonistic or antagonistic effects on the tissue. While an agonistic effect is observed on the skeletal system, serum lipid metabolism, and coagulation factors, an antagonistic effect is observed in breast and uterus tissue.[11]

Raloxifene, a tamoxifen analogue, belonging to the benzothiophene group of the SERM family, has a pronounced tissue-specific effect. It has been shown to prevent bone loss and reduce serum cholesterol levels without stimulating the endometrium.[12,13] Raloxifene, a non-steroidal benzothiophene, has been shown to inhibit estrogen receptor-dependent dimethyl benzantracene-induced mammary tumor growth in rats and reduce the occurrence of nitrosomethylurea-induced mammary tumors.[14] In the skeletal system it inhibits the osteoclastic differentiation process by binding to the Receptor activator of nuclear factor kappa-B ligand (RANKL), and stimulates the production of osteoprotegerin, which helps osteoclastic apoptosis by osteoblasts, resulting in an antiresorptive effect.[15] In addition, raloxifene has been reported to reduce the risk of spinal fractures in postmenopausal women.[16]

In the uterus and breast, raloxifene binds to the estrogen receptor and acts as an estrogen antagonist by competing with estrogen. The complex formed after the binding of raloxifene to the estrogen receptor does not induce transcriptional activity in these tissues. Thus, raloxifene effectively inhibits the induction of classical estrogen-response-element (ERE) containing genes, such as the progesterone receptor in the uterus, by competition for the estrogen receptor.[11]

Transvaginal Doppler ultrasound (TvUS) has been used for so many years for endometrial thickness measurement to assess risk for malignancy in the postmenopausal period. Interpretation of the uterine artery resistance index (RI) measurement together with endometrial thickness using color Doppler TVUS in the assessment of malignancy helps in the differentiation of malignant histopathology, especially at the first examination.

This study aimed to evaluate the effects of raloxifene treatment on the uterus with Doppler TVUS in asymptomatic postmenopausal patients.

## METHODS

This study is a product of the first author's specialization in gynecology and obstetrics thesis numbered 1175860 and titled "Evaluation of the effects of raloxifene treatment on the uterus in asymptomatic postmenopausal patients by transvaginal doppler ultrasonography."

Okmeydanı Training and Research Hospital granted ethical approval to this prospective randomized controlled study (Date: 2002/5 Decision No: 797388). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki

This study evaluated 57 healthy postmenopausal asymptomatic patients aged 45-60 years who applied to Okmeydanı Training and Research Hospital Gynecology and Obstetrics Outpatient Clinic between December 2003 and February 2004. 28 patients who did not want to receive treatment were included in the control group, 29 patients who agreed to receive treatment were included in the study group that received raloxifene 60 mg/day. Two patients in the control group started to receive hormone replacement therapy after their menopausal complaints predominated hence were excluded from the study. Two patients in the raloxifene group were excluded from the study because they delayed their follow-up. Finally, a total of 53 patients were included in the analysis, 26 patients in the control group and 27 patients in the raloxifene treatment group.

The inclusion criteria for the study sample were: 1) Being in natural menopause, 2) The last menstrual period is at least 1 year ago, 3) FSH > 30 IU/L and Estradiol <20pg/mL, 4) Absence of severe menopausal vasomotor complaints, 5) No HRT until at least 6 months before the start of the study, 6) Body mass index (BMI) below 30 kg/m², 7) No complaint of vaginal bleeding of unknown cause, 8) Absence of endometrial/adnexal pathology and fibroids larger than 3 cm, 9) Absence of systemic disease, 10) Absence of deep vein thrombosis and any other thromboembolic disease,11) Absence of alcohol and smoking. Healthy asymptomatic postmenopausal patients of whom met these criteria were enrolled in this prospective controlled study with a 6-month follow-up period.

All patients' information were recorded and physical examinations were performed before inclusion in the study. Patients whose bone densitometry values showed osteoporosis were included in the raloxifene study group. Those found with abnormalities in other examinations were excluded from the study.

Endometrial and uterine volume were evaluated using Doppler TVUS and endometrial biopsies were performed at 0 and 6 months on all patients included in the study. PI and RI indices were measured with Doppler TvUS.

Evaluation of currents in Doppler was made with qualitative, quantitative, and semi-quantitative measurements. Qualitative measurements were evaluated by the presence of a current, the direction of the flow and the characteristics of the current. Quantitative measurements included flow rate and volume. The flow volume ($cm^3$/sn) was formulated by multiplying the mean velocity (cm/sn) and the cross-sectional area of the vessel ($cm^2$). Semi-quantitative measurements included peak systolic/diastolic ratio (SD), pulsatility index, also defined as impedance index, and RI.[17-19]

$$\text{Pulsatility Index (PI)} = \frac{\text{Peak systolic velocity} - \text{End diastolic velocity}}{\text{Average velocity}}$$

$$\text{Resistance Index (RI)} = \frac{\text{Peak systolic velocity} - \text{End diastolic velocity}}{\text{Peak systolic velocity}}$$

Endometrial biopsies were obtained with a Pipelle following ultrasonographical evaluation. All biopsy specimens were evaluated by the same specialist pathologist. Samples were classified according to Blaustein's morphological criteria. They were histologically divided into four categories: normal benign postmenopausal endometrium, benign stimulator postmenopausal endometrium, benign abnormal postmenopausal endometrium, and premalignant-malignant endometrial changes.

Endometrial double-layer thickness, uterus size, volume, and Doppler measurements were made by a specialist radiologist using a 2003 model ACUSON 128 XP 30 ART Color Doppler US system and a 5MHz endovaginal probe. Considering that prolonged manipulation of the uterus may activate the pelvic circulation and affect the results of the Doppler evaluation, Doppler analysis was performed first during the Doppler TvUS. The ascending branches of the uterine artery were detected at the level of the right and left uterine isthmus using equal pressure at an angle of approximately 0 degrees using a sample volume of 2 mm by means of color flow Doppler. Next, PI and RI were measured.

In the second part of the TvUS examination, uterine dimensions, endometrial thickness and echogenicity and adnexa were evaluated. All findings were recorded. Uterine volume was measured in the longitudinal (DI), anteroposterior (D2), and transverse (D3) planes of the uterus dimensions and was calculated by applying the DI *D2*D3*0.52 formula.

### Statistical Analysis

SPSS for windows 10.0 statistical package program was used to evaluate the data. Student's T test, Mann Whitney U test, Chi-Square test and Paired T tests were used for comparisons. $p<0.05$ was considered significant.

## RESULTS

The mean age at control group was 50.6±3,04 years and treatment group was 50±3,06 years. There was no statistically significant difference in terms of mean age ($p>0.05$). There was no statistically significant difference between the groups in terms of average height and weight ($p>0.05$).

There was no statistically significant difference between the groups in terms of mean body mass index (BMI), parity number, menopause time and endometrial thickness ($p>0.05$).

Endometrial biopsy results are presented in **Table 1**. There was no statistically significant difference in endometrial biopsy results between the groups ($p>0.05$).

**Table 1. Endometrial biopsy results**

| Endometrial biopsy | Control group | | Treatment group | | Chi-quare | p value |
|---|---|---|---|---|---|---|
| | n | % | n | % | | |
| Atrophic | 9 | 34.6 | 9 | 33.3 | 4,19 | 0,24 |
| Inactive | 9 | 34.6 | 4 | 14.8 | | |
| Superficial epithelium | 2 | 7.7 | 6 | 22.2 | | |
| Weak Proliferative | 6 | 23.1 | 8 | 29.6 | | |

In **Table 2**, comparisons of uterus volumes between the groups at 0 and 6 months are presented. There was no statistically significant difference between the groups in the mean of baseline and 6th month uterus volume ($p>0.05$).

**Table 2. Comparisons of uterus volumes between groups at 0 and 6 months**

| Uterus volume | Control group | Treatment group | P value |
|---|---|---|---|
| | Mean±SD | Mean±SD | |
| Baseline | 48.96±10.44 | 52.07±17.64 | 0.44 |
| 6th months | 48.46±10.18 | 50.67±16.89 | 0.56 |

In **Table 3**, right and left uterine artery PI and RI indices were compared in both groups. There was no statistically significant difference between the groups in terms of baseline right PI and right RI values ($p>0.05$). There was no statistically significant difference between the groups in terms of baseline left PI and left RI values ($p>0.05$).

**Table 3. Initial right and left uterine artery PI and RI indices of both groups**

| Baseline | Control group | Treatment group | P |
|---|---|---|---|
| | Mean±SD | Mean±SD | |
| Right | | | |
| PI | 2.17±0.34 | 2.33±0.69 | 0.28 |
| RI | 0.83±0.04 | 0.84±0.05 | 0.66 |
| Left | | | |
| PI | 2.28±0.38 | 2.57±0.74 | 0.08 |
| RI | 0.85±0.05 | 0.85±0.05 | 0.94 |

Right PI value is given in **Figure 1**, left PI value in **Figure 2**, right RI value in **Figure 3**, left RI value in **Figure 4**.

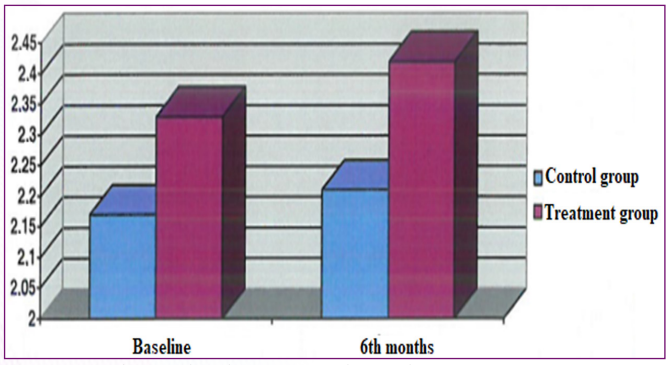


**Figure 1**. Right PI values by groups and periods

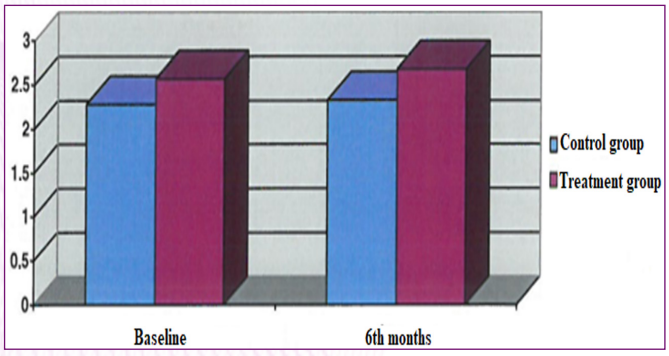


**Figure 2.** Left PI values by groups and periods

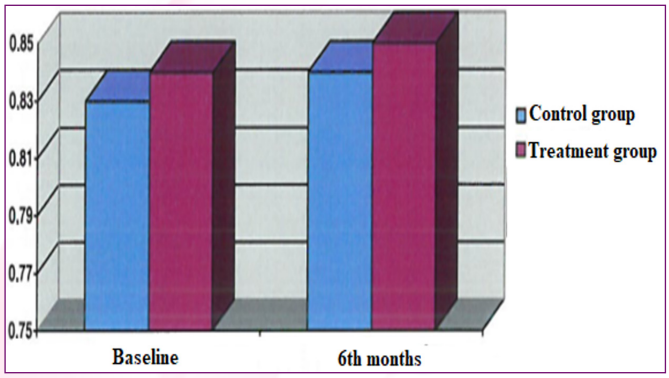


**Figure 3.** Right RI values by groups and periods

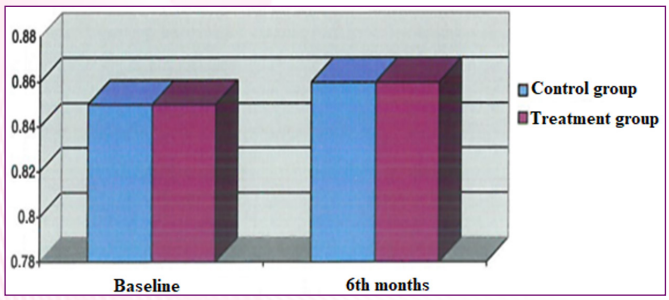


**Figure 4.** Left RI values by groups and periods

In **Table 4**, the PI and RI levels at 6 months of the right and left uterine arteries of both groups are presented. There was no statistically significant difference between the groups in terms of right PI and right RI values at 6 months (p>0.05). Left PI value at 6 months was significantly higher in the treatment group compared to the control group (p<0.05). There was no statistically significant difference between the groups in terms of RI values at 6 months (p>0.05).

**Table 4. Right and left uterine artery PI and RI indices at 6th months of both groups.**

| 6th months | Control group | Treatment group | p |
|---|---|---|---|
| | Mean±SD | Mean ±SD | |
| Right | | | |
| PI | 2.21±0.33 | 2.42±0.65 | 0.15 |
| RI | 0.84±0.04 | 0.85±0.04 | 0.41 |
| Left | | | |
| PI | 2.33±0.38 | 2.68±0.69 | 0.02 |
| RI | 0.86±0.05 | 0.86±0.04 | 0.61 |

**Table 5** shows the comparison of the baseline and 6th month uterine volume and Doppler results of the control group. There was no significant change in uterine volume in the control group (p>0.05). At 6 months, the right PI and RI values were significantly higher than at baseline (p<0.05 and p<0.001). At 6 months, left PI and RI values were significantly higher than at baseline (p<0.05 and p<0.001).

**Table 5. Comparison of the baseline and 6th month uterine volume and Doppler results of the control group**

| Control group | Baseline | 6th months | p |
|---|---|---|---|
| | Mean±SD | Mean±SD | |
| Uterus volumes | 48.96±10.44 | 48.46±10.1 | 0.178 |
| Right PI | 2.17±0.34 | 2.21±0.33 | <0.001 |
| Right RI | 0.83±0.04 | 0.84±0.04 | <0.033 |
| Left PI | 2.28±0.38 | 2.33±0.38 | <0.001 |
| Left RI | 0.85±0.05 | 0.86±0.04 | <0.033 |

**Table 6.** Comparison of the uterine volume and Doppler results of the treatment group at baseline and 6 months is presented. There was a significant decrease in uterine volume in the treatment group (p<0.001). At 6 months, the right PI and RI values were significantly higher than at baseline (p<0.05 and p<0.001). At 6 months, left PI and RI values were significantly higher than at baseline (p<0.05 and p<0.001).

**Table 6. Comparison of the baseline and 6th month uterine volume and Doppler results of the treatment group**

| Treatment group | Baseline | 6 months | p |
|---|---|---|---|
| | Mean±SD | Mean±SD | |
| Uterus volumes | 52.07±17.64 | 50.67±16.89 | 0,000 |
| Right PI | 2.33±0.69 | 2.42±0.65 | <0.008 |
| Right RI | 0.84±0.05 | 0.85±0.04 | 0.028 |
| Left PI | 2.57±0.74 | 2.68±0.69 | 0.000 |
| Left RI | 0.85±0.05 | 0.86±0.04 | 0.012 |

## DISCUSSION

In this 6-month prospective randomized controlled study, the effects of raloxifene on the uterus were evaluated by endometrial pipelle biopsy, TvUS, and Doppler TvUS. The results obtained after 6 months of treatment were not different from the control group. These results supported other studies claiming that raloxifene had no stimulatory effect on the uterus.[20]

Numerous studies have shown that raloxifene, a SERM, has no stimulatory effect on the breast. In our study, after 6 months of treatment, the uterine volume of the patients decreased, and PI and RI evels increased. At the end of 6 months, the right PI levels between the treatment group and the control group were clinically insignificant. As a result, Doppler indices in both groups showed changes suggesting atrophy.

In order to demonstrate the estrogen antagonistic effects of raloxifene in the uterus, healthy asymptomatic women who were by endometrial biopsy histologically diagnosed with benign postmenopausal endometrium at baseline, participated in the study. Thus, the stimulating effect of raloxifene on the endometrium could be easily detected.

Numerous studies have been conducted to determine the normal TvUS pattern of the endometrium in postmenopausal women. Although it is recommended to accept the cut-off value of the endometrium as 8 mm or above in postmenopausal asymptomatic women , it has been reported that the risk of endometrial disease is minimal when the endometrial thickness is less than 4 mm.[21,22]

In our study, the results of endometrial assessment with transvaginal ultrasonography after 6 months of raloxifene treatment did not differ from those before treatment. The Multiple Outcomes of Raloxifene Evaluation (MORE) study, which was a randomized double-blind placebo-controlled study, conducted at 180 centers in 25 countries between November 1994 and September 1999 supported the hypothesis that raloxifene did not increase the risk of endometrial hyperplasia or cancer.[23]

Post-treatment uterine volume did not differ significantly from baseline levels. These results were consistent with the results from previous studies by Azevedo et al.[24] and

Goldstein et al.[25] Goldstein et al., reported that the use of raloxifene did not affect the uterine volume, but there was a 22% increase in uterine volume in the estrogen-treated group.[25] Another study showed that when tamoxifen, a SERM drug with an estrogen agonistic effect on the uterus unlike raloxifene, was used, endometrial thickness and uterine volume increased.[26]

The cardiovascular effects of raloxifene are reported to be similar to those of estrogen.[27] The results of the MORE study showed that raloxifene did not have a cardiovascular risk, but significantly reduced the risk in the group at high risk of cardiovascular disease.[28] Another aim of our study was to show that besides its known cardioprotective effects, raloxifene does not increase blood flow in the uterine arteries and does not change Doppler indices, as it is a tissue-selective drug.

The onset of hypoestrogenism with menopause reduces the amount of blood going to the pelvic organs. This causes atrophy of the vaginal mucosa and lower urinary tract and a decrease in the volumes of the uterus and ovaries. High RI and PI levels detected in uterine artery Doppler analyses performed at this stage of women's life indicate high vascular resistance.[29] Although there is muchliterature on the vascular effects of estrogen, there is limited information on the vascular effects of raloxifene specifically, which is a second-generation SERM. Most information on SERMs is about the effects of tamoxifen on uterine perfusion.[30]

There are limited studies in which uterine perfusion was evaluated by Doppler ultrasonography during raloxifene treatment. A study by Post et al.[31] reported that postmenopausal women using 60 mg/d raloxifene did not show a significant difference in post-treatment PI values compared to the placebo group. In our study, there was no significant difference in Doppler indices after treatment compared to pretreatment. However, in the study by Post et al.[31], it was observed that PI values decreased significantly when 150 mg/d raloxifene was used. In the study conducted by Fugere et al.[32], it was shown that the use of raloxifene at a dose of 150 mg/d for at least 1 year did not affect uterine volume, endometrial thickness, and endometrial biopsy results. The conclusion reached in the study by Post et al.[31] was that high-dose raloxifene treatment reduces impedance in the uterine arteries and may therefore provide a cardioprotective effect at this dose. However, it is highly controversial whether uterine arteries can be a suitable model for investigating cardioprotectivity or not.

In our study, it was concluded that the 6-month raloxifene treatment administered at a dose of 60 mg/d did not stimulate the endometrium and did not increase the uterine volume and uterine blood flow. Our results supported the hypothesis that raloxifene has no estrogen agonistic effect on uterine endometrial tissue.

## CONCLUSION

In the postmenopausal period, the most important factor responsible for the decrease in compliance with HRT, which is widely used all over the world to reduce the systemic effects of aging, is the patient's fear of cancer. The effects of estrogen-progesterone-containing combined preparations on the breast and cardiovascular system are controversial. There are studies suggesting that the progesterone component overshadows the beneficial effects of estrogen in these systems. For these reasons, new therapies alternative to HRT, are being trialed. In light of this information, Raloxifene, although not capable of soothing the vasomotor symptoms, can still replace HRT for its reknown benefits on bone mineral density, in a selected group of patiens when conventional HRT is contrindicated.

## ETHICAL DECLARATIONS

**Ethics Committee Approval**: The study was carried out with the permission of Okmeydanı Training and Research Education and Research Hospital granted ethical approval to this prospective cross-sectional study (Date: 2002/5, Decision No: 797388).

**Informed Consent:** All patients signed the free and informed consent form.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

## REFERENCES

1. Brambilla DJ, McKinlay SM. A prospective study of factors affecting age at menopause. *J Clin Epidemiol.* 1989;42(11):1031-1039. doi:10.1016/0895-4356(89)90044-9
2. Speroff L. Menopause and Postmenapausal Hormone therapy. In: Glass RH, Kasa NG, Speroff L (Eds). Clinical Gynecologic Endocrinology and Infertility. 5th ed. Baltimore;Williams and Wilkins, 1996:583-649.
3. Gokmen Karasu AF, Ates S, Gurbuz T, Sahin N, Takmaz T, Aydin S. "A clinico-pathological study of transvaginal endometrial thickness measurement in asymptomatic postmenopausal patients and patients with postmenopausal bleeding". *Gynecol Obstet Reprod Med.* 2019;25(2): 85-88. doi:10.21613/GORM.2018.851.
4. Gold EB. The timing of the age at which natural menopause occurs. *Obstet Gynecol Clin North Am.* 2011;38(3):425-440. doi:10.1016/j.ogc.2011.05.002
5. ACOG Practice Bulletin No. 141: management of menopausal symptoms. *Obstet Gynecol.* 2014;123(1):202-216. doi:10.1097/01.AOG.0000441353.20693.78
6. Vehid S, Aran SN, Köksal S, Işiloglu H, Senocak M. The prevalence and the age at the onset of menopause in Turkish women in rural area. *Saudi Med J.* 2006;27(9):1381-1386.
7. Ozdemir O, Cöl M. The age at menopause and associated factors at the health center area in Ankara, Turkey. *Maturitas.* 2004;49(3):211-219. doi:10.1016/j.maturitas.2004.01.013
8. Atasü T, Tekin Hİ. Menapozun semptomları. İçinde: Atasü T, Editörler. Menapoz Tedavisi ve Kanser. 1. Baskı. İstanbul: Nobel Tıp Kitapevi;2001:95-109.
9. Hassa H, Ünlü C, Yakın K, ve ark. Hormon replasman tedavisi, İçinde: Ertüngealp E, Seyisoğlu H. (ed) Menopoz ve osteoporoz. İstanbul;Menopoz ve Osteoporoz Derneği, 2000:142-300.
10. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288(3):321-333. doi:10.1001/jama.288.3.321.
11. Francucci CM, Romagni P, Boscaro M. Raloxifene: bone and cardiovascular effects. *J Endocrinol Invest.* 2005;28(10):85-89.
12. Wei GS, Jackson JL, Hatzigeorgiou C, Tofferi JK. Osteoporosis management in the new millennium. *Prim Care.* 2003;30(4):711-vii. doi:10.1016/s0095-4543(03)00090-3
13. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA.* 1999;282(7):637-645. doi:10.1001/jama.282.7.637

14. Anzano MA, Peer CW, Smith JM, et al. Chemoprevention of mammary carcinogenesis in the rat: combined use of raloxifene and 9-cis-retinoic acid. *J Natl Cancer Inst.* 1996;88(2):123-125. doi:10.1093/jnci/88.2.123
15. Messalli EM, Mainini G, Scaffa C, et al. Raloxifene therapy interacts with serum osteoprotegerin in postmenopausal women. *Maturitas.*2007;56(1):38-44. doi:10.1016/j.maturitas.2006.05.007
16. Reginster JY, Devogelaer JP. Raloxifene reduces fractures in postmenopausal women with osteoporosis. *Clin Orthop Relat Res.* 2006;443:48-54. doi:10.1097/01.blo.0000200234.99436.24
17. Stuart B, Drumm J, FitzGerald DE, Duignan NM. Fetal blood velocity waveforms in normal pregnancy. *Br J Obstet Gynaecol.* 1980;87(9):780-785. doi:10.1111/j.1471-0528.1980.tb04613.x
18. Gosling R, King D. Ultrasonic Angiography. In: Hascus AW, Adamson L, eds. Arteries and Veins, Edinburg: Churchill Livingstone;1975: 61-98
19. Pourcelot L. Applications cliniquesde l' examen Doppler transcutane. In: Pourcelot L, ed: Seminaire INSERM. Paris: editions INSERM;1974: 213-240
20. Delmas PD, Bjarnason NH, Mitlak BH, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *N Engl J Med.* 1997;337(23):1641-1647. doi:10.1056/NEJM199712043372301
21. Fleischer AC, Appelbaum MI, Parsons AK. Transvaginal sonography of the normal endometrium. In: Fleischer AC, Kurjak A, Granberg S, editors. Ultrasound and the endometrium. New York: Parthenon, 1997: 1-15.
22. Karlsson B, Granberg S, Wikland M, et al. Transvaginal ultrasonography of the endometrium in women with postmenopausal bleeding--a Nordic multicenter study. *Am J Obstet Gynecol.* 1995;172(5):1488-1494. doi:10.1016/0002-9378(95)90483-2
23. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. *JAMA.* 1999;281(23):2189-2197. doi:10.1001/jama.281.23.2189
24. de Azevedo GD, do Prado MF, Ferriani RA, et al. Raloxifene therapy does not affect uterine blood flow in postmenopausal women: a transvaginal Doppler study. *Maturitas.* 2004;47(3):195-200. doi:10.1016/S0378-5122(03)00280-9
25. Goldstein SR, Scheele WH, Rajagopalan SK, Wilkie JL, Walsh BW, Parsons AK. A 12-month comparative study of raloxifene, estrogen, and placebo on the postmenopausal endometrium. *Obstet Gynecol.* 2000;95(1):95-103. doi:10.1016/s0029-7844(99)00502-5
26. Kedar RP, Bourne TH, Powles TJ, et al. Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomised breast cancer prevention trial. *Lancet.* 1994;343(8909):1318-1321. doi:10.1016/s0140-6736(94)92466-x
27. Harris ST, Genant HK, Baylink DJ, et al. The effects of estrone (Ogen) on spinal bone density of postmenopausal women. *Arch Intern Med.* 1991;151(10):1980-1984.
28. Barrett-Connor E, Grady D, Sashegyi A, et al. Raloxifene and cardiovascular events in osteoporotic postmenopausal women: four-year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. *JAMA.* 2002;287(7):847-857. doi:10.1001/jama.287.7.847
29. Bourne T, Hillard TC, Whitehead MI, Crook D, Campbell S. Oestrogens, arterial status, and postmenopausal women. *Lancet.* 1990;335(8703):1470-1471. doi:10.1016/0140-6736(90)91505-5
30. 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(6):411-414. doi:10.1046/j.1469-0705.1995.05060411.x
31. Post MS, van der Mooren MJ, van Baal WM, Neele SJ, Netelenbos JC, Kenemans P. Raloxifene reduces impedance to flow within the uterine artery in early postmenopausal women: a 2-year randomized, placebo-controlled, comparative study. *Am J Obstet Gynecol.* 2001;185(3):557-562. doi:10.1067/mob.2001.117340
32. Fugère P, Scheele WH, Shah A, Strack TR, Glant MD, Jolly E. Uterine effects of raloxifene in comparison with continuous-combined hormone replacement therapy in postmenopausal women. *Am J Obstet Gynecol.* 2000;182(3):568-574. doi:10.1067/mob.2000.104768

## Asena Ayar Madenli

I was originally born in 1975 in İstanbul. After graduating from Uludağ University Faculty of Medicine, I successfully completed my obstetrics and gynecology specialization training in İstanbul SSK Okmeydanı Hospital in 2004. I continued mycareer in private hospitals providing tertiary health care services, and during this time. I had the opportunity to work and learn with experts who are appreciated in their field. I have attended trainings on Minimally Invasive Surgery abroad and in the country. I have attended more than 50 national and international congresses. Recently, I have published articles of which I am the author or contributed, and there are 4 book chapters of which 2 of them are in the process of publication. Finally, I have been working actively at Liv Hospital Vadiistanbul Hospital in affiliation with the University of İstinye with my experience of more than 15 years, while continuing my academic studies. My command in English is very good. I am married and have one daughter.