Effect on endometrium of combined oestrogen-progestogen replacement therapy of 1 mg 17β-estradiol and 0.5 mg norethisterone acetate

G. Iatrakis[1], C. Tsionis[2], S. Antoniadis[1], G. Kourounis[3]

[1]Technological Educational Institution of Athens; [2]Department of Obstetrics and Gynecology, "Agia Olga" General Hospital, Athens; [3]Department of Obstetrics and Gynecology, University of Patra (Greece)

Summary

The purpose of the study was to determine the effects of low-dose hormone replacement therapy (HRT) on ultrasound thickness of the endometrium and on endometrial histology in postmenopausal women. Two hundred and fifty-four postmenopausal women were included in the study; 124 completed three years of treatment with continuous HRT containing 1 mg oestradiol and 0.5 mg norethisterone acetate daily, and 130 women did not take HRT during the same time (control group). Ultrasound scan showed that the mean thickness of the endometrium was similar between the groups under investigation at the end of the study. Ninety-one percent of the women in the HRT group and 78% in the control group had an atrophic or unassessable endometrium and no cases of endometrial hyperplasia or malignancy were detected in either group at endometrial biopsy at the end of the study. It seems that low-dose continuous HRT of moderate duration is not associated with either endometrial hyperplasia or malignancy.

Key words: Menopause; Hormone replacement therapy; Endometrium.

Introduction

Although the sequential oestrogen-progestogen hormone replacement therapy (HRT) increases the risk of complex endometrial hyperplasia and endometrial carcinoma, short-term continuous combined (oestrogen and progestogen are given together) HRT is considered safe. Although continuous combined HRT has rarely been associated with endometrial carcinoma, this could be attributed to other coexisting risk factors such as a family history of endometrial carcinoma, history of unopposed oestrogen use and sequential use of HRT with just a few days of progestogen treatment [1-3]. The purpose of the study was to determine the effects of low-dose continuous HRT of moderate duration on ultrasound thickness of the endometrium and on endometrial histology in postmenopausal women.

Materials and Methods

Two hundred and fifty-four postmenopausal women with an intact uterus, who gave informed consent to participate, were included in the study. One hundred and twenty-four of the women completed three years of treatment with a low-dose oral HRT regimen containing 1 mg 17β-estradiol and 0.5 mg norethisterone acetate and 130 women did not take hormone replacement therapy during the same time (control group). The characteristics of the women included in both groups are shown in Table 1. Groups were similar in age at menopause and on weight and height at the inclusion in the study.

Endometrial aspiration histology at the initiation of the study in both groups is shown in Table 2. The percentages of unassessable and atrophic endometrium did not differ significantly between groups.

Vaginal ultrasound investigation was performed at the start of the study and after 9-11, 18-20, 27-29 and 36-38 months. Endometrial aspiration specimens were taken at the start of the study and after 18-20 months and 36-38 months. The histological samples were assessed and classified by two independent pathologists who were blind to any details of the protocol. Results were included in the analysis only for patients having the same diagnosis from both reports. Summary statistics were used to summarize data for both ultrasonography and histology findings. The t-test was used for comparisons between groups in ultrasound endometrial thickness and chi-square for endometrial biopsy comparisons.

Results

Ultrasound scanning: The mean thickness of the endometrium was similar between the groups under investigation at almost all intervals and at the end of the study. The difference observed after 27-29 months of observation was not confirmed nine months later and probably should not be taken into account. Intermediate and final results are given in Table 3.

Endometrial sampling: 18-20 months after the start of the study data on endometrial specimens were available for 120 (97%) women in the HRT group and for 105 (81%) women the control group. Data on endometrial speci-mens were finally available for 117 (94%) women in the HRT group and for 99 (76%) women in the control group at the end of the study. The rest of the women were lost on follow-up or refused further investigation. In three cases (one in the HRT group and two in the control group) pathology reports differed between pathologists and data were not included in the analysis. Three years after inclusion in the study, 60% of the HRT group and

Revised manuscript accepted for publication September 1, 2003

Table 1. — *Characteristics of the women included in the study.*

	HRT group (124 women) Mean (SD; range)	Control group (130 women)	s*
Age at menopause	48.1 years (4.2; 38-55)	47.2 years (5.2; 34-55)	ns**
Age at start of treatment	53.3 years (6.2; 41-67)	–	
Weight	69.8 kg (9.7; 44.2-99)	71.3 kg (11.1; 52-112)	ns
Height	155.6 cm (6.5; 142-179)	154.1 cm (5.9; 147-178)	ns

*significance; **non-significant.

Table 2. — *Endometrial histology at the start of the study.*

	HRT group n	%	Control group n	%
Unassessable	58	47	55	42
Atrophic	53	43	64	49
Proliferative	6	5	4	3
Secretory	3	2	4	3
Other benign	4	3	3	2
Complex hyperplasia	0	0	0	0
Atypical hyperplasia	0	0	0	0
Total	124		130	

Table 3. — *Mean thickness of the endometrium on vaginal ultrasound in both groups.*

	Mean endometrial thickness (SD) on vaginal ultrasound (mm) HRT group	n	Control group	n	s*
Start of the study	6.1 (0.8)	124	6.0 (1.1)	130	ns**
After 09-11 months	5.9 (1)	124	5.9 (0.8)	118	ns
After 18-20 months	5.5 (0.8)	120	5.7 (0.9)	105	ns
After 27-29 months	4.1 (1.1)	119	4.4 (1)	102	$p < 0.05$
After 36-38 months	3.4 (0.8)	117	3.6 (0.7)	99	ns

*significance; **non-significant.

Table 4. — *Histological diagnosis of endometrial specimens in 18-20 months and in 36-38 months after the start of the study..*

	After 18-20 months HRT n	%	Control n	%	After 36-38 months HRT n	%	Control n	%
Unassessable	26	22	27	26	37	32	23	23
Atrophic	62	52	46	44	70	60	56	56
Proliferative	16	19	18	17	2	2	12	12
Secretory	14	17	10	10	7	6	2	2
Other benign	2	2	4	4	1	1	6	6
Complex hyperplasia	0	0	2	2	0	0	0	0
Atypical hyperplasia	0	0	0	0	0	0	0	0
Total	120		105		117		99	

56% of the control group had an atrophic endometrium (glands lined by single layer of flattened, inactive epithelial cells). During the same time, 32% of the HRT group and 23% of the control group had insufficient tissue for diagnosis (or no tissue or no endometrium identified). Benign endometrial or endocervical polyps, proliferative endometrium, endometritis or other benign conditions were detected in the rest of the women. No cases of endometrial hyperplasia or malignancy were detected in the HRT group at the 18-month interval and at the end of the study. Two cases with complex endometrial hyperplasia (crowded and irregular branched glands) were detected at 24-26 months in the control group and these cases withdrew from the study for further investigation (D+C) and treatment. The second patient (51 years old) underwent a total hysterectomy for persistent "spotting" despite pharmaceutical (progesterone) therapy. Intermediate (18-20 months) and final (36-38 months) histology results are reported in Table 4. The percentages of unassessable and atrophic endometrium, compared separately, did not differ significantly between groups at the end of the study. If unassessable and atrophic endometrium were taken as a sole group, the HRT group had the advantage of a statistically higher percentage of these endometrial specimens ($p = 0.01$).

Discussion

Complex endometrial hyperplasia was detected in two cases of untreated patients after 18 months of follow-up. On the other hand, no cases of endometrial hyperplasia or malignancy were detected in the HRT group after 18 months of HRT or at the end of the study. These findings give reassurance about the safety of low-dose HRT (given for up to three years) regarding the endometrium. After 1.5 years and after three years of HRT one of five cases and one of three cases, respectively, had an unassessable endometrium, which can be regarded as endometrial atrophy [4]. It seems that continuous combined hormone replacement therapy with 1 mg oestradiol and 0.5 mg norethisterone acetate daily is not associated with endometrial hyperplasia or malignancy and can be safely prescribed in menopausal women for (at least) up to three years. Taking into account that complex endometrial hyperplasia was detected only in untreated cases, it seems that low-dose HRT may protect the endometrium from abnormal changes.

Previous studies showed that continuous treatment with natural oestrogens and progestagens is a method to avoid endometrial stimulation and that continuous combined HRT is not associated with increased risk of endometrial cancer [5, 6].

Although the progestogen dose of the HRT regimen given in our patients was low, it seems that the continuous administration of progestogen combined with a low dose of estrogen does not increase the risk of endometrial hyperplasia or cancer. Similarly, the type of progestogen may be an important factor in the safety of HRT and 19-nortestosterone derivatives are considered more safe in relation to the endometrium [7]. The oestrogen regimen and the route of its administration must also be taken into account [8, 9], although the short-term use of parenteral oestrogens with different kinds of progestogen seems safe [10].

Studies of longer duration are required for final conclusions regarding the long-term endometrial safety of low-dose HRT and the lowest effective dose will always be a demand [11].

Acknowledgments

We thank Asst. Consultant Ravazoula Panagiota and Asst. Professors Anthouli-Anagnostopoulou Fragiski & Stoikidou M. for part of patients contacts and advice related to interpretation of endometrial samples.

References

[1] Beresford S.A.A., Weiss N.S., Voigt L.F., McKnight B.: "Risk of endometrial cancer in relation to use of oestrogen combined with cyclic progestagen therapy in postmenopausal women". *Lancet,* 1997, *349,* 458.

[2] Comerci J.T., Fields A.L., Runowicz C.D., Goldberg G.L.: "Continuous low-dose combined hormone replacement therapy and the risk of endometrial cancer". *Gynecol. Oncol.,* 1997, *64,* 425.

[3] Pike M.C., Peters R.K., Cozen W., Probst-Hensch N.M., Felix J.C., Wan P.C. *et al.*: "Estrogen-progestin replacement therapy and endometrial cancer". *J. Natl. Cancer. Inst.*, 1997, *89*, 1110.

[4] Piegsa K., Calder A., Davis J.A., McKay Hart D., Wells M., Bryden F.: "Endometrial status in post-menopausal women on long-term continuous combined (Kliofem®): a comparative study of endometrial biopsy, outpatient hysteroscopy and transvaginal ultrasound". *Eur. J. Obstet. Gynecol. Reprod. Biol.,* 1997, *72,* 175.

[5] Staland B.: "Continuous treatment with natural oestrogens and progestagens. A method to avoid endometrial stimulation". *Maturitas,* 1981, *3*, 145.

[6] Hill D.A., Weiss N.S., Beresford S.A.A., Voigt L.F., Daling J.R., Stanford J.L. *et al.*: "Continuous combined hormone replacement therapy and risk of endometrial cancer". *Am. J. Obstet. Gynecol.,* 2000, *183*, 1456.

[7] Weiderpass E., Adami H.O., Baron J.A., Magnusson C., Bergstrom R., Lindgren A. *et al.*: "Risk of endometrial cancer following estrogen replacement with and without progestins". *J. Natl. Cancer. Inst.,* 1999, *91*, 1131.

[8] Lievertz R.: "Pharmacology and pharmacocinetics of estrogens". *Am. J. Obstet. Gynecol.*, 1987, *156*, 1289.

[9] Mattsson L.A., Christiansen C., Colau J.C., Palacios S., Kenemans P., Bergeron C. *et al.*: "Clinical equivalence of intranasal and oral 17β-estradiol for postmenopausal symptoms". *Am. J. Obstet. Gynecol.*, 2000, *182,* 545.

[10] Gompel A., Bergeron C., Jondet M., Dhont M., Van der Mooren M.J., Toth K.S. *et al.*: "Endometrial safety and tolerability of Aerodiol® (intranasal estradiol) for 1 year". *Maturitas*, 2000, *36,* 209.

[11] Pelissier C., De Kervasdone A., Chuong V.J., Mauges E., De Mourllac, Breil M.H. *et al.*: "Clinical evaluation, dose finding and acceptability of Aerodiol, the pulsed estrogen therapy for treatment of climacteric symptoms". *Maturitas,* 2001, *37*, 181.

Address reprint requests to:
G. IATRAKIS, M.D.
129 Menelaou street
17676 Athens (Greece)