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Reproductive Medicine; *Endocrinology and Infertility*

Effect of Low-Dose Hormone Therapy on Metabolic Parameters and Bone Mineral Density

Ufuk ATLIHAN[1], Onur YAVUZ[2], Huseyin Aytug AVSAR[3], Can ATA[4], Tevfik Berk BILDACI[5], Selcuk ERKILINC[6]

İzmir, Türkiye

ABSTRACT

OBJECTIVE: Early menopause causes several health concerns that are related directly to the deficiency of ovarian hormones, especially estrogen insufficiency. The purpose of the research was to investigate the impact of low-dose hormone therapy on metabolic parameters and bone densitometry in patients with early menopause.

STUDY DESIGN: A total of 98 patients aged 38-42 years with an early-menopause and followed up were evaluated retrospectively in this cohort study. After the diagnosis of early menopause, combined oral contraceptive (COC) treatment including 3 mg Drospirenone + 0.02 mg Ethinylestradiol was recommended to the patients. After 1 year of COC treatment, metabolic, ultrasonographic, and bone densitometry measurements of patients who did and did not use COC regularly were compared.

RESULTS: At the 12th-month follow-up, endometrial thickness was significantly higher in the COC group (3.8±0.4 mm) compared with the non-COC group (3.5±0.4 mm) ($p<0.01$). At the 12th month follow-up, the estradiol value was significantly higher (16.1±1.5 pg/mL) in the COC group compared with the non-COC group (14.8±2.5 pg/mL) ($p<0.01$). At the 12th month follow-up, the total cholesterol value was found significantly lower in the COC group (197±24.2 mg/dL) compared with the non-COC group (211±28 mg/dL) ($p<0.01$). At the 12th month follow-up, the Z-score was found significantly higher in the COC group (0.02±0.3) compared with the non-COC group (0.2±0.3) ($p<0.01$).

CONCLUSION: Hormone replacement therapy is very important for women who enter early menopause, and adequate estrogen therapy must be taken to maintain bone density and reduce menopausal symptoms.

Keywords: Early menopause; Hormone replacement therapy; Premature ovarian failure

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[1] *Private Karatas Hospital Department of Gynecology and Obstetrics, İzmir, Türkiye*
[2] *Dokuz Eylul University, Institute of Health Sciences, Department of Gynecology and Obstetrics, İzmir, Türkiye*
[3] *Tinaztepe University Faculty of Medicine Private Galen Hospital Gynecology and Obstetrics, Izmir, Türkiye*
[4] *Buca Seyfi Demirsoy Training and Research Hospital Obstetrics and Gynaecology, İzmir, Türkiye*
[5] *Izmir Democracy University Faculty of Medicine Department of Gynecology and Obstetrics, İzmir, Türkiye*
[6] *Izmir Democracy University Faculty of Medicine Department of Obstetrics and Gynecology Gynecologic Oncology Surgery İzmir, Türkiye*

Address of Correspondence: *Ufuk Atlihan*
Private Karatas Hospital Department of Gynecology and Obstetrics Barbaros, 336. Sk. No:26, 35260 Konak İzmir. Türkiye
e-mail: cfl.ufuk@gmail.com

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ORCID IDs of the authors: *UA: 0000-0002-2109-1373*
OY: 0000-0003-3716-2145 *HAA: 0000-0003-0636-3104*
CA: 0000-0002-0841-0480 *TBB: 0000-0002-6432-6777*
SE: 0000-0002-6512-9070

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Introduction

One uncommon but significant factor contributing to female infertility and sex steroid insufficiency is early menopause, which is characterized by the presence of low menopausal follicle-stimulating hormone (FSH) levels and the absence or irregular menstrual cycle before the age of 45 years (1). Women who show these findings aged 40-45 years are said to have experienced early menopause because the average age of natural menopause is between 50 and 51 years (1). According to studies, 1% of women experience early menopause before the age of 40 years and 0.1% before the age of 30 years. Around 5% of women experience early menopause before the age of 45 years (2,3). A shortage of ovarian hormones, mostly estrogen, is directly linked to several health issues connected with early menopause. For that reason, the significance of physiologic hormone replacement therapy (HRT) is emphasized for women diagnosed as having early menopause (4,5). However, the data on adverse effects obtained in the Women's Health Initiative (WHI), which was research conducted on older postmenopausal women, discouraged many young women with early menopause from taking HRT (6). The World Health Organization reported many health risks linked with HRT, such as increased stroke risks, cardiovascular disease (CVD), and breast cancer (7). However, unlike women who

experience menopause at the expected time, estrogen deficiency is a pathologic situation among young women who have early menopause (8,9). Although HRT is an important therapeutic option for women with early menopause, the prescribed hormones replace the normally existing hormones (8,9). Physiologic HRT addresses many healthcare concerns related to early menopause for women (8,9). Hormone replacement therapy should be continued until age 50 years, which is the usual age of natural menopause unless there is a particular contraindication (such as estrogen-dependent cancer) (10). The onset of premature menopause can stem from various causes, such as autoimmune conditions, genetic factors, or treatments like radiation therapy or chemotherapy, as well as spontaneous occurrences or surgical interventions (10). A specific underlying cause cannot be determined in 90% of patients with early menopause (10). Women who experience early menopause often state that they have problems with disruptive menopausal symptoms that can occur suddenly or gradually (11-14).

Women with early menopause have symptoms similar to those experienced by women undergoing natural menopause, which can include insomnia, night sweats, hot flashes, sexual dysfunction because of decreased libido, painful intercourse (dyspareunia), and vaginal dryness (11-14). Decreased estrogen production in the ovaries is responsible for these symptoms (15). It is crucial for women and their physicians to take menopausal symptoms seriously because they can significantly impact their quality of life and may indicate hormonal deficits that could worsen an illness (16). Several studies report that low bone mineral density (BMD) is associated with a markedly higher incidence of fractures in women who go through early menopause (before age 45 years) (17,18). Many studies also report reduced fracture rates in women with early menopause treated with HRT (17,18). However, it has been proven that HRT in early menopause creates changes in serum lipids, thyroid hormones, and glucose parameters (19-22). Primary health problems may occur in women with early menopause, especially if HRT use is not initiated immediately after the beginning of the process (23-26). The purpose of the present research was to investigate the impact of low-dose hormone therapy on metabolic parameters and bone mineral densitometry in patients with early menopause.

Material and Method

The present retrospective cohort study followed the Declaration of Helsinki Principles. For the current investigation, signed informed consent forms were obtained from the participants. This study was started after receiving ethics committee approval from our hospital (Date: 31/01/24, Number: 2024/226). The study included 98 patients, who experienced menopause naturally, were diagnosed as having early menopause, aged 38-42 years, and were monitored in our clinics for menopause. The early menopause diagnosis was made after 1 year of amenorrhea and laboratory test results being compatible with menopause. Exclusions from the research included patients with known estrogen-dependent malignancies, abnormal Pap-smear findings, uncontrolled diabetes mellitus, chronic kidney or liver illness, gallbladder sickness, thromboembolic sickness, and prior or current cerebrovascular and cardiovascular disease. The ages, body mass index (BMI), smoking status, and family history of early menopause in the patients were evaluated retrospectively. Combined oral contraceptive (COC) treatment, which included 3mg Drospirenone + 0.02 mg Ethinylestradiol, was recommended after the diagnosis of early menopause was made for all patients in the study, and regular follow-up was recommended. Patients who came for follow-ups after 1 year of COC treatment and used COCs regularly and patients who did not accept the treatment were compared retrospectively as two separate groups. Endometrial thickness values of the patients were evaluated using transvaginal ultrasound at the time of diagnosis and the follow-up visits 1 year after diagnosis. Blood samples were taken for serum biochemistry and hormonal analysis after an 8-hour overnight fasting for the patients in the study group at the time of diagnosis and during follow-up visits 1 year after the diagnosis. Fasting blood sugar, fasting insulin, total cholesterol, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), high-density lipoprotein (HDL), triglyceride, thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol levels were checked. The Homeostasis Model Assessment (HOMA) was employed to assess insulin sensitivity. In this formula, [fasting blood sugar mmol/mL) x fasting insulin (μmol/1)] / 22.5 analysis was taken as reference. The bone densitometry Z-scores of the patients were evaluated at diagnosis and 1 year after diagnosis.

Statistical analysis

The SPSS version 26.0 (IBM Inc., Chicago, IL, USA) was used for the analyses. The Kolmogorov-Smirnov test was used to determine the normalcy of the analysis. In addition to the statistical methods (mean ± standard deviation) for identification, the independent test was used to compare the pair groups in the study data evaluation, the matched test was used to ascertain the changes that occurred before and after the treatment, and the Chi-square test was used to compare qualitative data. A p-value of less than 0.05 was deemed statistically significant.

Results

No significant difference was found between the groups in terms of mean age and BMI measurements ($p=0.4$ and $p=0.8$, respectively). The rate of smoking in women using COCs was significantly lower than in women not using COCs ($p<0.001$). When evaluated in terms of family history and clinical symptoms, no significant difference was found between the groups ($p=0.7$ and $p=0.08$, respectively) (Table I).

Table I: *Demographic characteristics of the groups*

Variables	COC use (+) (n=49, 50%)	COC use (-) (n=49, 50%)	p
Age (years)	41 ±1.3	40.8 ±1.3	0.4*
BMI	23.4 ±1.8	23.4 ±1.7	0.8*
Smoking status	(8/49)-16.3%	(20/49)-40.8%	<0.001*
Family history	(5/49)-10.2%	(6/49)-12.2%	0.7*
Clinical symptoms			
Oligomenorrhea	32/49)-65.3%	(39/49)-79.6%	0.08*
Amenorrhea	((17/49)-34.7%	(10/49)-20.4%	

**Chi-square Test; BMI: Body mass index; COC: Combined Oral Contraceptive*

There was a significant increase in endometrial thickness in patients who used COCs in the 12th-month follow-up ($p<0.001$). At the 12th month follow-up, endometrial thickness was found as 3.8±0.4 mm in the COC group and 3.5±0.4 mm in the non-COC group and was found to be significantly higher in the COC group ($p<0.01$). When the groups were evaluated within themselves, a significant increase in FSH levels was detected in the 12th month follow-up in patients using and not using COCs ($p<0.001$ and $p<0.001$, respectively). When the groups were evaluated within themselves, a significant increase in LH levels was detected in the 12th month follow-up in patients using and not using COCs ($p<0.001$ and $p<0.001$, respectively). When the groups were evaluated within themselves, a significant decrease in estradiol levels was detected in the 12th month follow-up in patients using and not using COCs ($p<0.001$ and $p<0.001$, respectively). At the 12th month follow-up, the estradiol value was significantly higher (16.1±1.5 pg/mL) in the COC group compared with the non-COC group (14.8±2.5 pg/mL) ($p<0.01$). At the 12th-month follow-up, the total cholesterol value was significantly lower in the COC group (197±24.2mg/dL) compared with the non-COC group (211±28 mg/dL) ($p<0.01$). At the 12th-month follow-up, the LDL value was significantly lower in the COC group (97.8±23.8mg/dL) compared with the non-COC group (109.2±20.8 mg/dL) ($p<0.01$). When the groups were evaluated within themselves, a significant decrease in HDL scores was detected in the 12th-month follow-up in patients using and not using COCs ($p<0.01$ and $p<0.001$, respectively). ($p<0.01$). At the 12th month follow-up, the mean Z-scores were 0.02±0.3 in the COC group and -0.2±0.3 in the non-COC group; the mean score was significantly higher in the COC group ($p<0.01$) (Table II).

Discussion

Hormone therapy is employed on a global scale for relieving menopause symptoms. Endometrial thickness, carbohydrate, lipid metabolism, and bone mineral densitometry levels of patients who did and did not use COC including 3xmg Drospirenone + 0.02 mg Ethinylestradiol after the diagnosis of early menopause were measured and compared in this retrospective study. Smoking was observed to be significantly less in the patient group that used COC in the present study. At the 12th month follow-up, endometrial thickness was found to be significantly higher in the group that used COCs in comparison with the group that did not. A significant increase was detected in serum FSH and LH scores and a significant decrease was detected in estradiol levels at the end of the 12th month in both groups using and not using COC. In the 12th month follow-up, the group that used COC had considerably higher blood estradiol levels than the group that did not use COC. In the 12th month follow-up, LDL and serum total cholesterol scores were significantly lower in the COC group compared with the non-COC group. In this research, a significant decrease was observed in bone mineral densitometry Z-scores at the end of the 12th month in the non-COC group. Bone mineral densitometry Z-scores were observed to be significantly higher in the COC group in the 12th-month follow-up when compared with the non-COC group. The mean age of the participants was 40.9 years in the present study, which is significantly younger than the mean age of menopause (27). An increase was detected in endometrial thickness at the end of the 12th month in the COC group, but a decrease was detected in endometrial thickness in the non-COC group. In the 12th month follow-up, endometrial thickness was significantly higher in the COC group compared with the non-COC group. In their study, Song et al. reported an increase in endometrial thickness in the group receiving low-dose hormone therapy and ultra-low-dose hormone therapy, but no statistically significant difference was observed between the two groups (28). The fact that the control group in the present research did not receive hormone treatment was the reason for the discrepancy between the research described and the current study. At the end of the 12th month, a significant increase was observed in serum FSH and LH levels and a significant decrease in estradiol levels in the groups using and not using COC. Kawai et al. observed a decrease in FSH and LH levels and an increment in estradiol levels in the 12th month follow-up after HRT, unlike the present study (29). The difference between their study and the present study may be the difference between the administered hormone therapy doses. In the 12th month follow-up, serum total cholesterol and LDL values were signifi-

Table II. *The comparison of intergroup and intragroup laboratory and ultrasound results before and after treatment*

Variables		COC use (+) (n=49, 50%)	COC use (-) n=49, 50%)	p
Endometrial thickness (mm)	Baseline	3.7±0.4	3.6±0.4	0.7**
	12 months later	3.8±0.4	3.5±0.4	<0.01**
	p	<0.001***	<0.001***	
FSH (mIU/mL)	Baseline	35.8±5.4	35.7±5.4	0.8**
	12 months later	41.1±5.5	42.3±5.4	0.3**
	p	<0.001***	<0.001***	
LH (mIU/mL)	Baseline	35.1±5.3	35.6±5.5	0.8**
	12 months later	39.7±5.4	40.5±5.4	0.5**
	p	<0.001***	<0.001***	
Estradiol (pg/mL)	Baseline	17.1±1.5	16.9±2.8	0.7**
	12 months later	16.1±1.5	14.8±2.5	<0.01**
	p	<0.001***	<0.001***	
Glucose (mg/dL)	Baseline	87.4±9.7	87.6±9.9	1.0**
	12 months later	88.5±9.6	88±9	0.5**
	p	0.05***	0.6***	
Insulin (µU/mL)	Baseline	8.6±3.1	8.7±3.1	0.8**
	12xmonths later	8.5±2.8	8.6±2.9	0.9**
	p	0.09***	<0.01***	
HOMA-IR	Baseline	2.1±0.2	2.1±0.2	0.8**
	12 months later	2.1±0.2	2±0.2	0.2**
	p	0.3***	<0.001***	
Total Cholesterol (mg/dL)	Baseline	195.5±22.3	196±22.4	0.8**
	12 months later	197±24.2	211±28	<0.01**
	p	0.1***	<0.001***	
LDL (mg/dL)	Baseline	99.3±19.8	103.7±20.6	0.2**
	12 months later	97.8±23.8	109.2±20.8	<0.01**
	p	0.4***	<0.001***	
VLDL (mg/dL)	Baseline	23.5±6	23.5±5.8	0.9**
	12 months later	24±4.9	24.1±5.5	0.9**
	p	0.3***	0.2***	
HDL (mg/dL)	Baseline	54.3±6.3	57.3±4.3	0.02**
	12 months later	51.5±6.7	51.4±4.8	0.8**
	p	<0.01***	<0.001***	
Triglyceride (mg/dL)	Baseline	164.4±21	159±16.3	0.2**
	12 months later	158.3±27.5	157.5±14.2	0.4**
	p	0.1***	0.4***	
TSH (µU/mL)	Baseline	2.6±0.6	2.6±0.6	0.9**
	12 months later	2.6±0.6	2.6±0.6	0.9**
	p	0.7***	0.6***	
Z Score	Baseline	0.03±0.3	-0.03±0.2	0.2**
	12 months later	0.02±0.3	-0.2±0.3	<0.001**
	p	0.5***	<0.001***	

cantly lower in the group that used COC when compared with the non-COC group. Gregersen et al. reported a significant decrease in serum cholesterol and LDL scores in patients receiving HRT, similar to the present study (30). The authors assessed the correlation between lipid parameters and estradiol levels, which was not evaluated in the present research. No significant differences were found in HDL levels in the COC group in the 12th-month follow-up in the present study. In the literature, the effects of COC use on HDL levels are contradictory (31). No significant difference was detected in glu-

cose, insulin, and HOMA-IR levels in the group that used COC in the 12th-month follow-up in the present study. In the literature, the effects of HRT on glucose and insulin sensitivity are controversial. Studies are reporting that it had no effects and did not cause deterioration (32). No significant difference was detected in the present study in TSH levels in the COC group in the 12th-month follow-up. Xu et al. showed that HRT did not affect thyroid function, similar to the present study (33). Bone mineral densitometry Z scores were significantly higher in the COC group compared with the non-COC group at the 12th-month follow-up. In the literature, conflicting effects on bone densitometry are reported in patients who were diagnosed as having premenopausal, postmenopausal, and premature ovarian insufficiency and given HRT (34). The reason for this disparity might be the heterogeneity of the study populations and the wide range of drug treatment doses and spectra. In recent research conducted by Podfigurna et al., it was observed that HRT provided a significant improvement in Z scores, similar to the present study (35). This study has some limitations. The retrospective design and small sample size of our study may have led to difficulties in obtaining an optimal sample size, potentially affecting the representativeness of the participants. In addition, the lack of results on the effects of long-term treatment due to the comparison of only 1-year data after medical treatment can be considered as another limitation. The comparison of all hormonal and metabolic parameters as well as bone densitometry data, the presentation of comprehensive data on possible risks of the menopausal period, the extent to which these risks can be prevented, and the provision of a broad perspective can be shown as the strengths of the study.

Conclusion

HRT is very important for the quality of life and health of women who experience premature ovarian failure or early menopause. It should provide enough estrogen to limit the psychological consequences of estrogen insufficiency, prevent the early onset of dementia and cardiovascular disease, and lessen menopausal symptoms. It should closely mimic the production of normal ovarian steroid hormones. For women with early menopause, the progestin component of HRT must be cyclical to induce regular withdrawal bleeding and preserve the endometrium. The therapy must be continued up to the age of natural menopause. Based on the individual risks and needs, the dosage may be terminated at this age or decreased to postmenopausal levels. To avoid unnecessary health risks for women affected by this illness later in life, physicians should be skilled in the diagnosis and treatment of early menopause.

Declarations

Ethics approval and consent to participate: The study received ethical approval from the hospital's Ethics Committee (Approval number: 2024/226, Approval date: 31/01/24). Informed consent of all patients was documented and signed before participants were included in the study. The study was conducted in compliance with the guidelines outlined in the Declaration of Helsinki.

Availability of data and materials: The data supporting this study is available through the corresponding author upon reasonable request.

Conflict of interest: The authors declare that they have no competing interests.

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Authors' contributions: UA, OY, and HAA raised the presented idea. SE, TBB, HAA, and UA designed the study. OY conducted the analyses. UA, OY, CA, HAA, and TBB developed the first draft of the manuscript. UA, TBB, OY, and CA participated in data collection and result interpretation. UA, SE, HAA, CA, and OY assisted with data collection and analysis. SE and UA critically revised the manuscript. All authors contributed to the writing of the article and read and approved the final version of the article.

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