Long Term Effects of Different Hormone Replacement Therapy Regimens on the Endometrium Thickness

FARKLI HORMON REPLASMAN TEDAVİ REJİMLERİNİN ENDOMETRIAL KALINLIK ÜZERİNE UZUN SÜRELİ ETKİSİ

Melike DOĞANAY*, Orhan S. AKSAKAL**,
Leyla MOLLAMAHMUTOĞLU***, Oya GÖKMEN****

* Uzm.Dr.Dr.Zekai Tahir Burak Kadın Hastanesi.
** Dr.Dr.Zekai Tahir Burak Kadın Hastanesi, Başasist,
*** Dr.Dr.Zekai Tahir Burak Kadın Hastanesi. Şef Muav.,
**** Doç.Dr.Dr.Zekai Tahir Burak Kadın Hastanesi, Başhek., ANKARA

Summary

Objective: To determine the effect of different hormone replacement therapy on the endometrial thickness in natural menopause.

Institution: The Department of Menopause of Dr. Zekai Tahir Buruk Hospital.

Materials and Methods: The research was undertaken between 1991 and 1996 on 2800 women, whose ages ranged between 45-65 and who were under natural menopause. These patients were divided into ten groups who received different treatments. The first group was given CEE + MPA (continous) ; the second group: CEE+ MPA (Cyclic): the third group: transdermal 17¡5 -oestradiol+MPA (continuous): the fourth group: transdermal 17ji -oestradiol+MPA (Cyclic): fifth group: CEE +Didrogesteron (Continous); the sixth group: CEE+Didrogesteron (Cyclic); the seventh group: transdermal 17/3 -oestrut/iol +Didrogesteron (Continous); the eighth group: transdermal 17¡3 -oestradiol + Didrogesteron (Cyclic); the ninth group: tibolon; the tenth group Estradiol va/erate+Ciproteron Ace/ate. Before the treatment, all groups were examined by vaginal ultrasonography and biopsy was laken if their endome/rial thickness was over 4 mm. During the 1 si, 2 nd, 3rd, 4 lh, and 5th years of their treatment, the patients' endometrial thickness was measured and endometrial biopsy was repeated if necessary. Variations in ten groups according to year by year carried out by ''One Way Variance Analysis "; the trends according to years in the ten groups was carried out by "Two Way Variance Analysis of Dependent Samples "; the variations in every group one by one was done by using the "Paired I Test and calculating the Kappa Coefficient figures ".

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Yazışma Adresi: Dr.Melike DOĞANAY
Uzayan Sk. 5/2, Aydmlıkevler, ANKARA

_ özet

Amaç: Nature! menopozda farklı hormon replasman tedavilerinin endometrial kalınlık üzerine etkilerini belirlemek.

Çalışmanın Yapıldığı Yer: Dr. Zekai Tahir Buruk Kailin Hastanesi Menopoz Bölümü.

Materyal ve Metod: Bu çalışma 1991-1996 yılları arasında yaşları 45-65 arasında değişen 2800 hasta üzerinde yapılmıştır. Hastalar 10 farklı gruba ayrılmıştır, tik gruba devamlı CEE+MPA. ikinci gruba siklik CEE+MPA, üçüncü gruba devamlı transdermal 17fi-estradiol+MPA, dördüncü gruba siklik transdermal 17pl-estradiol+MPA, beşinci gruba devamlı CEE+Didrogesterou, altıncı gruba siklik CEE+ Didrogesteron. yedinci gruba devamlı transdermal 17 fi-eslradiol+Didrogesteron, sekizinci gruba siklik transdermal 17f3-estradiol+Didrogesleron, dokuzuncu gruba Tibolon, onuncu gruba Estradiol Valerat+Siproteron Asetat verildi. Tedavi öncesi bütün gruplara vaginal ultrasonogram ile bakıldı. Endometrial kalınlık finin üzerinde olan/ardan biyopsi alındı. Tedavinin f.2.,3.,4. ve 5. yıllarında hastaların endometrial kalınlığı ölçüldü ve gereğinde biyopsileri tekrarlandı. On grup orasında yıldan yıla olan değişimler ''tek yönlü varyans ana/izi " ile, gruplar arasında yıllara göre değişimler örneklere bağlı ''iki yönlü vaıvuns analizi " ile ; her grup arasındaki değişimler ''Paired t Test ve Kappa Kat Sayısı " kullanılarak değerlendirildi.

Sonuçlar: Gruplar karşılaştırıldığında her bir grup arasında istatistiksel olarak anlamlı bir fark gözlenmedi (p>0.05). Ortalama endometrial kalınlık 2.9 mm olarak belirlendi. Histopatolojik olarak % 53.4 atrojik, %32.8 proliferatif. %13.2 oranında disosiye glandlar lespıı edildi.

Results: *When we compare groups and with respect to treatment periods there was no statistical significance between each of them (p>0.05). The mean of endometrial thickness was found 2.9 mm. Atrophic changes were observed as a rale of 53.4%. The rate of proliferative changes was 32.8%, and the rale of dissosiative glands changes was found to he 13.2%,.*

Conclusion: *This study will provide a new outlook in choosing the best treatment for protecting the endometrium during hormone replacement therapy in natural menopause.*

Key Words: Menopause, Hormon replacement therapy, Endometrial thickness

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Tartışma: *Bu çalışma, naturel menopozda uygulanan hormon replasman tedavilerinin endometriyuınu en iyi koruyanının seçimine yeni bir bakış açısı kazandıracaktır.*

Anahtar Kelimeler: Menopoz, Hormon replasman tedavisi, Endometriumkalınlığı

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The Menopause is defined as the period that encompasses a variety of somatic and psychological changes due to estrogen deficiency and because of this, it alters life quality importently and even seriously.

In the postmenopausal women having no menses at least twelve months. Estrogen replacement therapy (ERT) has been started in order to prevent the risks they will have and relief the uncomfortable situations in which they've been in. In addition to this replacement therapy progesterone is added to control unwanted effect of estrogen on endometrial tissue.

History and risk factors, endometrial biopsy, transvaginal ultrasonography, if necessary D&C and/or histeroscopy, are present in endometrial examination. Obesity is one of the important risk factors for endometrium. Chronic anovulation, infertility, history of irregulcr bleeding, liver disease, diabetes mcllitus, usage of tamoxifen and alchol are other risk factors.

Endometrial biopsy must be done for patients with risk factors endometrium thickness of 5 mm. D&C and/or histeroscopy must be done in patients with endometrium thickness of 8 mm. Endometrial biopsy may be done by pipelle, Z-sampler and gynosampler nowdays. Sensivity of these techniques is 85-95% and can be easly and cheapy.

It is suggested that transvaginal ultrasonography is the first choice in endometrial moniterization. In this examination skin thickness can be measured in vertikal plane. Order of endometrial borders can be obtained. Fluid collection, if present is pointed out (it will be accepted a negative prognostic factors).

Endometrial thickness of < 5 mm is accepted as normal, 5-8mm as grizon and 8mm as a pathologic as a result of mechoanalysis sensivity is 95-100% and productivity is 87-94% according to these results.

Histeroscopy is performed usually in patients with endometrial hypertrophy and/or bleeding, endometrial thickness of 8 mm, suspection of endometrial polyp and if result of endometrial biopsy is pathologic.

Before the treatment systemic and gynecologic examinations of the patients has been done carefully and any conditions that could contraindícate this therapy has been searched and treated. In addition, during the treatment period patients were followed with regular intervals every 3 months for first year and 6 months for second years and up and examined if necessary.

In this study, difference between various hormonal regimens that had been used for patients in our clinic was searched with respect to the effect on endometrium. Before and after treatment endometrial tissue samples were taken and correlations among then was examined.

Materials and Methods

Between July 1991 and July 1996, 2800 postmenopausal woman were included in the study at Zekai Tahir Burak Women Hospital, Menopause clinic in Ankara. Patients were divided to 10 group according to the regimens used.

Group I (continous oral, combined) patients were given daily 0.625 mg conjugated estrogen and 0.5 mg progesterone orally (MPA), Group II (cyclic, oral combined) were given 0.625 mg conjugated estrogen from days 1-25 of each month and additionally 10 mg progesterone from days 16-26 of the month orally and then 1 week interval is given. Group III (continous transdermal combined) were given 50 mg estrogen transdermally twice a week and 5 mg daily progesterone orally. Group IV (cyclic transdermally combined) were given 50 mg estrogen transdermally twice a week and 10 mg progesterone (MPA) orally for 10 days of each month used. Group V (continous oral combined) were given daily 0.625 mg conjugated estrogen and 10 mg progesterone (didrogesterone). Group VI (cyclic oral combined) were given 0.625 mg conjugated estrogen and 10 mg progesterone (didrogesterone) from days 1-25 of each month and then one week interval is given. Group VII (continous transdermal combined) were given twice a week 50 mg estrogen transdermally with 10 mg progesterone (didrogesterone) orally. Group VIII (cyclic transdermal combined) were given twice a week 50 mg estrogen transdermally and progesterone (didrogesterone) orally 10 days of every month. Group IX were given daily tibolon (2.5 mg) . And group X were given Estradiol valerate (2 mg) plus ciproteron asetate (2.5 mg) for 21 days. For every woman, age, gravida, duration of menapause, BMI (body mass index) plasmal levels of estradial, FSH and LH, and endometrial thickness were examined before the treatment and 1, 2, 3, 4 and 5 years after the therapy.

Estradiol, FSH and LH measurements were made by double antibody RIA and magnetic seperation methods. Endometrial thickness was examined via transvaginal probe by B-mode real time kretz 320 combison Austria 5 mm Hz. Endometrial biopsy was taken as pipella puncture on the 23rd day of the treatment. Endometrial biopsy was performed in patients with risk factors, endometrial thickness of < 8 mm in HRT negative group and < 5 mm in HRT positive group.

For statistical analysis of the data following methods were used: one way variance analysis, two way varience analsis of independent samples, paired T test and calculating the kappa coefficent figures.

Results

Between groups age, gravida, BMI, duration of menopause, plasma levels of estradiol, FSH, LH and endometrial thickness before the treatment were analysed by one way variance analysis (univariate analysis) and were found not to be significant (Table 1). So, all the parameters between groups has been distributed homogenously.

The mean of endometrial thickness was found 2.8 mm in 300 patients with continous oral combined therapy; 2.4 mm in 280 patients with cyclic oral combined therapy; 3.6 ram in 310 patients with continious transdermal therapy; 2.4 mm in 250 patients with cyclic transdermal therapy; 3.8 mm in 290 patients with continious oral therapy; 3 mm in 320 patients with cyclic oral therapy; 2 mm in 295 patients with continious transdermal therapy; 3.2 mm in 215 patients with cyclic transdermal therapy; 1.5 mm in 262 patients with tibolon therapy; 3.2 mm in 278 patients with estrodiol valerate+ciproteron asetate therapy. Endometrial thickness was found to be most eugmented in continious oral therapy group. Endometrial thickness was increased to 20 mm from 7 mm in one patient with continious oral therapy in three years ; to 18 mm from 6 mm in one patient with continious transdermal therapy in four years; to 12 mm from 8 mm in one patient with continious oral combined therapy ; to 12 mm from 10 mm in one patient with cyclic transdermal therapy in 3 years; to 10 mm from 6 mm in one patient with estradiol valerate+ciproteron acetate therapy group in 2 years. Histopathology was changed from atropy to proliferation in these 5 patients.Histopatologic changes according to groups were shown in Table 3. Atrophic changes were observed as a rate of 53.4%. The rate of proliferative changes was 32.8:% and the rate of dissosiative glands changes was found to be 13.2%.

When we compare groups with respect to treatment periods there was no statistical significance between each of them ($p>0.05$).

Proliferation was determined in 1/3 of the patients. During treatment period measurements of endometrial thickness made by ultrasound showed that this histopathologic change was not so important.

In this study no statistically significant difference was found between estradiol level and en-

Table 1. Characterictics of 2800 patients taking 10 various hormonal regimens.

	GI Continous oral combined CEE+MPA	Gil Cyclic oral combined CEE+MPA	GUI Continous transdermal ETTS+MPA	GIV Cyclic transdermal ETTS+MPA	GV Continous oral CEE+Didro
Patients No	300	280	310	250	290
Age	51.14±4.6	50.93+3.85	56.53+5.1	49.89+4.9	50.53+5.1
Gravida	4.38±3.58	5.74+3.63	4.64+2.25	5.21+1.6	4.27±2.77
Body Mass Index	28.69±2.56	30.07+7.67	26.6+7.15	29.65+4.71	27.69+9.10
FSH **(iu/L)**	65.84+19.3	58.35+16.4	54.99+18.3	55.43+14.4	56.18+19.4
LH (m/L)	56.18±24.95	50.4+21.18	49.34+25.05	52.55+19.55	51.86+21.6
E2 (pg/ol)	14.10+10.2	19.04+38.3	26.13+29.67	21.47+25.22	20.9+16.4

	GVI Cyclic oral CEE+Didro	GVII Continous transdermalETTS +Didro	G VIII Cyclic transdermal ETTS+Didro	GIX Tibolon	GX Estradiol valerat · Ciproteron Acetate
Patients No	320	295	215	262	278
Age	48.56+3.14	54.68+7.42	50.46+4.9	58.16+2.76	47.91+3.8
Gravida	3.47+29.18	3.84+3.82	5.34+9.9	5.47+2.23	4.72±3.42
Body Mass Index	27.92+7.44	29.32+18.60	30.12+6.82	28.16+3.42	31.27+6.3
FSH (iu/L)	53.26+18.7	57.64+23.5	61.81+20.3	63.42+28.4	59.76+3.4
LH (iu/L)	49.32±7.26	50.81+51.6	46.58+23.2	51.52+3.82	47.62+4.1
E2 (pg/61)	28.47+25.22	16.62+33.4	24.62+30.16	12.83+4.7	22.79+3.2

dometrial histopathology and between endometrial thickness and endometrial histopathology.

Discussion

This study was planned to disclose if the recently applied various hormonal regimens in the postmenopausal women have any different effect on plasma levels of estradiol, FSH ,LH,and endometrial thickness and histopathology.

Increase in estradiol during treatment period when considered with each treatment type has shown that it increased earlier in continous treatment type than cyclic therapy. However at the and of first year, plasma estradiol level reached optimum levels in every treatment regimen. This result suggests that during follow up dosage increase considering only plasma estradiol level up to the end of the first year, will not be suitable.

When we look at gonatotropines, in the continous regimens there was a stastically significant decrease in FSH in the first 3 months with respect toLH. LH decreased more than FSH both in continous and cyclic regimens. Some studies reported that decrease in FSH was more than LH in antrast to our findings. In the correlation analysis between estradiol and gonadotropines only in cyclic oral combined group a négatif correlation was detected. In conclusion during follow up of patients given replacement therapy plasma levels of gonadotropines should not be taken into consideration since they are affected by multiple factors.

Among each group endometrial thickness when compared with years, did not increase significantly in continous and cyclic oral combined groups. In the literature it is reported that endometrial thickness in the postmenopausal woman changed maximum between 9-10 mm.

Relation between plasma level of estradiol and endometrial thickness was searched both in continuous and cyclic treatment regimens. There was no difference between them. May and et al reported in their study including 112 women in 1992 that between groups given replacement therapy and control groups.

Table **2.** Endometrial thickness of 2800 patients taking 10 various hormonal regimens according to pre-trcatmcnt and post-treatment years.

	G! Continents oral combined cnn+MPA	Gil Cyclic oral combined CEE+MPA	c m Continous transdermal ETTS+MPA	GIV Cyclic transdermal ' ETTS+MPA	GV Continous oral CEE+Didro
1	>	1	3	1	3
2	~>	2	3	2	3
3	3	3	4	2	4
4	3	3	**4**	**3**	4
5	4	3	4	4	5

	GVT Cyclic oral CEE+Didro	GVI1 Continous transdermal ETTS+Didro	GVIII Cyclic transdermal ETTS+Didro	GIX Tibolon	GX Estradiol valerat Ciproteron Acetate
1	1	-	2	_	2
2	3	2	3	1	3
3	3	·	3	2	3
4	I	3	4	2	4
5	4	3	4	2	4

The last parameter in our study was endometrial histopathology, In late 1960's it has been understood that the incidence of endometrial cancer in woman on estrogen replacement therapy increased and then progesterone due to it's antimitotic activity has been added to the therapy. Then the risk of endometrial cancer was found to be decrease as much as 96-98%.

When we examined the histopathogic findings; at the end of first year in the replacement therapy, atrophic endometrium was dominant character as in prc-trcatment period.

Different estrogen types must be examined with hormonal monitorization, vaginal ultrasonography due to mctobolic differences. E2 level must be observed as an important sign in complicnce monitorization.

There are two opposite opinions in endometrium examination before HRT. 1) Transvaginal ultrasonography and biopsy must be performed to all patients, because endometrial pathology can be seen in patients with no risk factors as a rate of 1 -2 / 1000. 2) Endometrial biopsy must be performed in patients with risk factors and endometrial thickness of 5 mm. **D&C** and histcrescopy must be done in patients with endometrial thickness of 8 mm. Transvaginal ultrasonography if needed biopsy can be done in cyclic therapy in patients with rcguler bleeding yearly. There are two opposite opinions in continous therapy. 1) Irreguler bleeding in first 6 months is accepted as normal. Endometrial biopsy and transvaginal ultrasonography may be performed in 12 th and 18 th months. 2) Endometrial biopsy must be repeated in first 6 months. In general opinion transvaginal ultrasonography and endometrial biopsy must be done in patients with bleeding more than 6 months and in patients with bleeding after amenoreic period.

Atrophic endometrium was observed as a rate of 85-90% in patients with endometrial thickness of < 5mm. Cut off value for determining the endometrial pathology was accepted as < 5 mm.

Scnsivity of pipelle biopsy in determining the endometrial pathology was found 93% and prcdictivity was found 85-95%. Scnsivity of endometrial thickness measurement was 95-100% and predictivity was 94-97%.

Table **3.** Endometrial histopathological changes of 2800 patients taking 10 various hormanal regiments according to post-treatment years.

	GI Confinons oral combined CEE+MPA	Gil Cyclic oral combined CEE+MPA	Gill Continous transdermal ETTS+MPA	G1V Cyclic transdermal ETTS+MPA	GV Continous oral CEE+Didro
Patients No	300	280	310	250	290
Atrophia	144	142	205	1 1 1	142
Proliferative	68	76	51	81	97
Dissosialive	36	15	18	14	28
Inadequate	52	47	26	34	17

	GVI Cyclic oral CEE+Didro	GVII Continous transdcrmalETTS+ Didro	GVI1I Cyclic transdermal ETTS+Didro	GIX Tibolon	GX Estradiol valeral + Ciproteron Acetate
Patients No	320	295	215	262	278
Atrophia	182	169	87	100	136
Proliferative	96	83	66	87	78
Dissosiative	24	12	33	21	13
Inadequate	18	31	29	54	41

In conclusion, various replacement therapies used in postmenapausal woman were not superior to each other with respect to endometrial thickness and histopathology. Because of this we recomend that any of them replacement treatment regimens can be given safely to the postmenopausal woman. Since at the end of 2 years in each treatment groups estradiol levels reach the same lcvel,we had better not change the dosage of estradiol until an important complication is seen.

REFERENCES

1. Chetkowski R., Meldnim D ve ark. Biological effect of estradiol administered by a trasdermal therapeutic system (TTS) Paper presented at Soc. Gynecol. Investig. Annual Meeting Phoenix Arizona March 1985; 21-3.
2. Laufer L.R., De Fazio, J.L. ve ark: Estrogen replacement therapy by transdermal estradiol administration. Amer. J. Obstet. Gynecol 1983; 146,533.
3. Stcingold K A , Laufer I ve ark: Treatment ofhot Hushes witii transdermal estradiol administration J. Clin. Endoc 1985; 61, 627.
4. Due Pedcrson Oand, Kalund Jensen Ft. Longterm treatment with transeutenous estradiol and oral medroxyprogesteron acetate. Acta Obstet Gynecol Scand 1992; 71.
5. May C, Lin BA ve ark. Endometrial thickness after Menopause: Effect of Hormone Replacement R. adieeolog 1991; 180; 427-32.
6. Nasri M N , Coast GJ. Correlation of ultrasound findings and endometrial histopatology in postmenopausal women. Br J Obstet Gynecol 1989; 96; 1333-38.
7. Malpani A, Singer, J ve ark. Endometrial hyperplasia Value of endometrial thickness in ultrasonographic diagnosis and clinical signifiance. J C U 1990; 18; 173-7.
8. Speroff L. Clinical Gynelogie endocrinology and infertility. Forth Edition 1990; 148-9.
9. Clarke C L , Sutherland RL.Progestin regulation of celluler proliferation. Endocrin Rev 1990; 11:266.
10. Botsis D, Kassanos D, Pyrgiotis E et al. Vaginal sonography of the endometrium in postmenopausal women. Clin Exp Obstet Gynecol 1992; 19:189.
11. Wikland M, Granberg S, Karisson B. Asscsment of the endometrium in the postmenopausal woman by vaginal sonography. Ultrasound 1992; 10;15.
12. Pang SC, Greendale G A , Cedars MI, Gambaze SC, et all. Long term effects of transdermal estradiol with and without medroxyprogesterone acetate. Fertil Sterility 1993; 59:76.
13. Wanna TR. Effect of long term therapy with estrogen and progesterone on the endometrium of postmenopausal women. Acta Obstet Gynecol Scand 1985; 64:41.
14. Voigt L R . Weiss NS. Chu JR et al. Progesteron supplementation of exogenous oestrogens and risk of endometrial cancer. Lancet 1992; 338;274.

15.Jinekoloji ve Obstetrikde Yeni Görüş ve Gelişmeler. 1995; 5(3): 182-6.

16.8"' International Menopause Congress; 1996-Sydney, Absraet.

17.Berg G and Hammer M. The Modern Management of the Menopause-a perspective for the 21 st century. The proceedings of the VII International Congress on the Menopause, Stockholm, Sweden 1993.

1 S.Schneider PG, Birkhauser MH and Palacios S. Women's Healt after Menopause-fourth in a six part series. Menopause and Reproductive Cancers. International Journal of Fertility and Menopausal Studies, Vol 39, Supplement (2), 1994.

19. Cossery JM. Medikal-economic Aspects of Hormone Replacement Therapy. The International Congress, symposium and seminar series, Vol 6, 1993.

20. Rogerio A Lobo. Treatment of the Menopausal Woman. Basic and Clinical Aspects. New York, 1994.

21. Popkin DR and Peedle LJ. Women's Healt Today. 1994.

22. Kenemans P, Barentsen R, P van de Weijer. Practical HRT. 1995.