ESTROGEN REPLACEMENT THERAPY (ERT) BY A SPECIAL REGIMEN IN THE YEARS FOLLOWING MENOPAUSE

M. BLUM (*) - D. ZACHAROVITCH (***) - J. PERY (**)
M. GILEROWITCH (***)
(*) Special Gynecological Outpatient Clinic
(**) Biochemical Laboratory
(***) Family Phisician Clinic
Mishmar Hayarden, Kupat-Holim, Givataim and Sackler School of Medicine
Tel Aviv University (Israel)

Summary: A group of 16 post-menopausal women, mean age 56.6 years, with typical and non typical climacteric symptoms, were treated by a combination of estrogen (Premarin® 0.625) followed by clomiphene citrate.

Beside an improvement in musculo-skeletal pain and a marked improvement of their sense of well-being there was an increase in Hdl cholesterol, the protecting factor against M.I., while weight and blood pressure remained stable.

The link between mood, sleep and libido improvement and catecholamine raise, is discussed, and so are the effects on blood pressure, in long lasting ERT.

There is consensus that estrogen replacement therapy (ERT) should be opposed by gestagens, in order to prevent endometrial proliferation and the risk of endometrial carcinoma. Therefore the ERT most widely accepted is a sequential treatment pattern of estrogen followed by gestagen, taking into account that most patients may present break-through bleeding ([1]).

In order to avoid vaginal bleeding a reason of concern in a lot of post menopausal women and endometrial hyperplasia, Kauppila *et al.* ([2]) suggested a conjugated estrogen followed by clomiphene citrate treatment.

It is the purpose of this study to report the preliminary results of ERT on the lipid metabolism, blood pressure and urinary catecholamine excretion in a small group of post menopausal women and the effect of ERT on their well being and mood.

PATIENTS AND METHODS

A group of 16 post-menopausal women aged 48-63 years (mean 56.6 years) was included in our study.

Their main complaints being skeletal pains and non-specific psychological symptoms characterized mainly by anxiety, depression, mood instability, loss of libido and insomnia. Urinary disturbances were another frequent symptom.

Before treatment each women underwent a careful physical and gynecological examination. Women with contraindication for ERT, were excluded by performing the following laboratory tests: Cholesterol by the method of Huang *et al.* ([3]), Triglycerides by Jiegels method ([4]), Hdl-cholesterol by an appropriate kit (Behringer F.R.G.). Free urinary catecholamines were determined by isolation of catecholamines on a specially prepared ion exchange resin column and the fluorometric detection by the classic trihydroxy-indole reaction using a kit from bio-rad. The method was described by Blum *et al.* in a previous paper ([5]). The normal range in our laboratory is 40-115 microgr./24 h. The same laboratory tests were performed after 4 months of ERT, so that each woman was her own control.

We mention that all the women were normotensive with slight overweight. The ERT regimen we used in our study was: Premarin® tablets (Ayerst U.K. - 48% estrone sulphate,

26® equiline sulphate, 15% 17-α-dihydroequilin sulphate and 11 conjugated estrogens) 0.625 mg daily for 20 days followed by 10 days of clomiphene citrate 50 mg daily.

RESULTS AND STATISTICAL ANALYSIS

The 16 patients completed their treatment showing a very good compliance, all of them reporting a marked increase in their sense of well being and na improvement in urethral symptoms, libido and muscolo-skeletal pain.

No change in blood pressure was recorded during the study period and weight remained stable (see table 1). As for the lipid profile, the mean total cholesterol, trigliceride and Hdl-cholesterol levels, at the begining and after 4 months of ERT are summarized in table 2. There was a significant increase in cholesterol, triglycerides and Hdl levels ($p<0.01$). We noted an increase in urinary excretion of free catecholamines, the increase being constant and significant ($p<0.01$) (see table 3).

Table 1. – *Blood pressure measurements and weight before and during ERT.*

Patient No.	Age	Weight B.	Weight D.	Blood pressure B.	Blood pressure D.
1	51	59	59	135/85	135/80
2	59	55	56	135/80	130/80
3	49	63	62	130/80	135/80
4	56	55	55	115/70	120/70
5	60	52	53	120/70	125/75
6	56	50	49	140/80	145/80
7	63	58	59	150/80	145/80
8	65	75	75	120/80	125/80
9	62	55	54	120/70	125/70
10	62	52	52.5	130/80	130/80
11	57	63	63	120/80	125/80
12	55	63	65	130/80	135/80
13	48	80	80	150/85	150/90
14	54	76	75	140/70	135/70
15	51	58	58	105/70	110/75
16	58	68	69	125/80	125/75
Mean	56.6	61.3	61.4	122.81/73.12	130.62/77.81

$P>0.05$ (non significant)

Table 2. – *Lipid metabolism before and during ERT.*

Patient No.	Cholesterol B.	Cholesterol D.	Triglycerides B.	Triglycerides D.	Hdl B.	Hdl D.
1	220	245	80	110	38	52
2	235	255	110	140	48	62
3	210	235	65	90	60	62
4	235	255	110	135	37	50
5	190	210	85	110	56	63
6	200	240	80	136	37	51
7	245	275	105	125	36	75
8	280	300	90	110	43	62
9	265	275	170	200	31	53
10	265	280	140	170	36	58
11	272	290	135	170	38	57
12	280	295	135	150	41	52
13	245	260	140	170	32	54
14	220	240	85	120	47	63
15	180	200	160	175	40	54
16	166	200	70	85	42	54
Mean	236.68	253.43	110	137.25	41.37	58.25
	$P<0.01$ (significant)		$P<0.01$ (significant)		$P<0.01$ (significant)	

Table 3. – *Free urinary catecholamines before and during ERT.*

Patient No.	Catecholamines B.	Catecholamines D.
1	45	72
2	46	80
3	39	54
4	31	60
5	45	57
6	42	70
7	54	68
8	28	40
9	58	73
10	54	80
11	46	62
12	50	69
13	42	64
14	48	67
15	78	100
16	68	90
Mean	47.12	69.12

$P<0.01$ (significant)

As stated previously, no increase in blood pressure was noticed and no correlation between changes in catecholamine excretion and blood pressure could be observed.

DISCUSSION

Post menopausal women usually show an increase in total cholesterol and Ldl cholesterol levels and a decrease in Hdl cholesterol levels, caused by the decrease in natural estrogenic activity ([6]).

From our study, we conclude that conjugated equine estrogens in small doses (Premarin® 0.625) cause an increase in Hdl cholesterol levels, resulting in a greater protection against atherosclerosis and heart attacks ([7, 8]).

There is a consensus that ERT should be opposed by gestagens in order to prevent endometrial hyperplasia and the risk of endometrial carcinoma taking in account that most patients will present breakthrough bleeding.

In order to avoid endometrial hyperplasia and bleeding, Kauppila *et al.* ([2]) suggested a conjugated estrogen followed by clomiphene citrate treatment which acts as an antiestrogen. It is known that progesterone also affects blood lipids. Most studies have shown an increase in total and Ldl cholesterol and a decrease in Hdl cholesterol levels by most preparations ([9]).

The effect could be avoided by using medroxyprogesterone acetate 5 mg as in the new combination Premarin® plus MP 0.625 from Ayerst UK.

On the other hand, little is known about the effect of clomiphene citrate on the blood lipids. In a study Kauppila *et al.* ([2]) found no changes in lipid profile during clomiphene treatment.

During the short period of ERT, the women showed a marked improvement in their sense of well-being.

Although plasma levels of catecholamines have been shown to rise after the age of 50 ([10]) the increase in our study might be explained by a decrease in high affinity nor-epinephrine uptake into synaptosomes ([11, 12]) and a decrease in catecholamines degradation ([13]). The rise in urinary catecholamine excretion in our study group, might explain the increased sense of well-being and mood improvement ([14]).

The hormonal regimen (Estrogen-clomiphene citrate) used in our study, had a very good influence on the clinical symptoms of menopausal syndrome, including musculo-skeletal pain but the chronic increase in catecholamine levels might predispose to a blood pressure increase, after a longer period of treatment. Further observation might clarify this question.

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