5

Plasma lipids, lipoproteins and protocols of postmenopausal HRT administration

Variations in the circulating lipid fractions of women on HRT have been extensively studied. HRT can have different effects depending upon the type of estrogen, its dosage, its route and duration of administration. It may also involve a combined progestogen which can vary in its structure, its dosage and also length of combined treatment.

Most of the studies analyzed here (about 70 published since 1990) are randomized protocols and some are double – or single-blind prospective studies. Studies were selected using several criteria : number of patients included, duration of treatment, type of progestogen used. Some studies were analysed because they raised a specific question or used a special or recent methodology (such as Lp(a) analysis or LDL oxidation).

Concerning the progestogens, most of the studies have used normethyltestosterone derivatives or MPA and very few pregnane derivatives or natural progesterone. The analysis was thus restricted to all the studies using the two latter types of product. The procedures and aims of the studies retained for analysis are described in table 5.I

Effects of HRT on lipid fractions

In studies published between 1989 and 1996, the effects of estrogen treatments (conjugated estrogens, oral estradiol, percutaneous HRT and TTS) on circulating lipids and lipoprotein levels were investigated (see tables 5.II - 5.V).

Equine estrogens have a stronger action than oral 17β-estradiol and 17β-estradiol valerate on lipid fractions, but modifications tend to go in the same direction : significant rise in HDL (+ 10/16 % ; especially HDL2 : + 20/60 %) and triglycerides (+ 30 %) and reduction in LDL (– 10/20 %), total cholesterol (– 4/8 %) and apoB (– 4/10 %). This action is dose-dependent, reflecting the inhibition of hepatic lipase by estrogens given orally.

Studies of non oral estrogen administration have demonstrated that triglyceride levels are not increased, but rather tend to fall (as far as – 20 %). Most of these studies have indicated a drop in LDL cholesterol (as far as – 12 %).

Table 5.I : Procedure and aims of the studies retained for analysis

Authors	Type of study	Special interest
Conjugated estrogens		
Sherwin and Gelfand (1989)	R/ placebo vs MPA	2 doses of CE vs placebo or MPA/1year
Siddle et al. (1990)	R cross-over	Dydrogestone but 1.2mg of CE
Weinstein et al. (1990)	R	MPA continuous 2.5 vs 5 mg
Moorjanil et al. (1991)	R	Progesterone ± 2 types of estrogens (CE or E2)
Miller et al. (1991)	R	3 kind of progestins
Walsh et al. (1991)	R DB cross-over placebo	Metabolic studies but short term (6 weeks)
Adami et al. (1993)	R control group	E2T and CE +control group
Bolaji et al. (1993)	prospective open	Progesterone 23 days per month for one year
Luciano et al. (1993)	DB	Comparison of sequential and continuous MPA
Lobo et al. (1994)	R DB large study	CE alone and compared with MPA sequential and continuous. Study on carbohydrates metabolism
PEPI (1995)	R DB placebo	Very large and well conducted study includes progesterone. Study on carbohydrates metabolism
Anonymous (1996)	R DB large study	Number of patients - Comparison of CE± NG for one year
Wilcox et al. (1997)	R cross-over	Subfractions of CE. Study on insulin resistance and LDL oxidation
Estradiol per os		
Basdevant et al. (1991)	R	Comparison of E2P,E2M but short term (6 weeks) and estrogens alone
De Lignières et al. (1983)	open	Comparison of E2P, E2M and E2V
Christiansen and Riis (1990)	prosp open control	Long term study
Cano et al. (1991)	open	+ MPA continuous
Colvin et al. (1991)	R dose response	Increasing doses of E2 but short term
Wolfe and Huff (1995)	open	E2 alone, NG alone and combined. Lp(a). metabolic studies
Taskinen et al. (1996)	R	E2 vs E2T on Lp(a). but not the same progestin in the two groups (oral E2+NETA- E2T+MPA)
Ottosson et al. (1985)	R for prog	3 months of E2 ± progestins : either NG or MPA or P
Transdermal estradiol		
Crook et al. (1992)	control group	CE+NG compared with E2T+NETA
Lemay et al. (1995)	R control group	CE compared with E2T both combined with MPA. Long term. Lipidic fractions evaluated at the end of the estrog, P and interperiods
Castelo-Branco et al. (1993)	R control group	Comparison of CE, E2T, MPA seq or continuous
Habiba et al. (1996)	open	E2T 53 women. Lp(a)
Percutaneous estradiol		
Jensen et al. (1987)	R DB control placebo	E2P 1 year and + P 1 year
Fahraeus et al. (1982)	R	Comparison E2P / E2 oral
Fahraeus et al. (1983)	open	Comparison two progestins: P and NG

Table 5.II : Effects of conjugated estrogens on circulating lipoproteins

Authors	N	Duration (months)	E type (dose/duration)	Percentage change from baseline				
				C	HDL *(HDL2•HDL3)*	LDL *(apo-B)*	TG	Lp (a)
Sherwin and Gelfand (1989)	95	12	CE (0.625/days 1- 25) ± MPA (5mg)	+8/–2	+13.7/+4.3	–0.3/–3.4	+34/+39	
			CE (1.25/days 1- 25) ± MPA(5mg)	–5/–0.1	+19/+13.4	–17.6/–8.3	+19/+42	
Siddle et al. (1990)	14	9	CE (1.25/days 1- 25)	–4	+17 *(+20•0)*	–16 *(–17)*	+56	
			± DD (20/10mg)	idem	idem	idem	idem	
Weinstein et al. (1990)	92	12	CE (0.625)+ MPA continuous (2.5/5 mg)	–2.8	+4.5 *(+6.2•-5.1)*	–7.6 3 mth and after	+7.1	
Moorjani et al. (1991)	15	6	CE (0.625/days 1- 25)	–8	+ 7 *(+14•+2)*	–16 *(–4)*	+34	
	16	6	CE (0.625/days 1- 25) + P (day 12-day 25)	–6	+12 *(+17•+9)*	–13 *(–7)*	+13	
Miller et al. (1991)		3	CE (0.625/days 1-25)	–4 to 8	+9 to 13 *(HDL2 : 5 to 28)*	–12 to 19	+6 to 38	
	7/10/11	3+3	CE (0.625)+ MPA (10)/ NG/NETA (days 13-25)	–5 to 9	–9 to 17 *(0/27/13.6• –8.8/0/+4.8)*	–7/-8/+12	+26/0/+6.8	
Castelo-Branco et al. (1993 et 1996)	12	12	CE (0.625)+ MPA2.5 seq: 25 days+12 days	+3.4	+18.2	–2.5 *(–4.2)*	–3.4	
	15 20		CE (0.625) continuous + MPA 2.5 mgx12 days	+7.1	+27.4	–1.1 *(–0.1)*	–2.8	
	19		CE + MPA2.5 continuous	–0.6	+19.6	–6.6 *(–2.1)*	+5.8	
			control	+2.8	–6	8.2 *(1.2)*	+2.3	
Walsh et al. (1991)	31	3	CE 0.625mg	–4	+16 *(HDL2+50)*	–15	+24	
			CE 1.25 mg	–6	+18 *(HDL2+60)*	–19	+36	
Adami et al. (1993)	(81)29 C=35	12	CE (0.625/days 1-25) +MPA (10mg/ 12days)	–6.5	+8	–18	+8.8	
Bolaji et al. (1993)	40	12	CE (0.625/23 days) +P (100mg/23 days)	–6	+15	–16	+32	

Table 5.II : Effects of conjugated estrogens on circulating lipoproteins *(continued)*

Authors	N	Duration (months)	E type (dose/duration)	Percentage change from baseline				
				C	HDL *(HDL2•HDL3)*	LDL *(apo-B)*	TG	Lp (a)
Luciano et al. (1993)	29	12	CE (0.625/days 1-25) +MPA(5mg/ 12 days)	–3	+10	–12	+25	
			CE 0.625 mg continuous+MPA (2.5/ 5mg)	–7/–7	+2.5/+5	–25/–18	+10/+22	
Whitcroft et al. (1994)	61(30)	36	CE 0.625mg + NG 0.150 mg (12 days)	–12	–7.8	–14	–2.5	
Lobo et al. (1994)	525	13	CE 0.625	ns	+15 *(+70 • ns)*	–8	+40	
			+ MPA 2.5mg		ns *(+37 • ns)*	–10	+24	
			or 5 mg continuously		ns *(+40 • ns)*	–10	+17	
			or MPA 5mg /14 days		ns *(+30 • ns)*	–8	+22	
			or MPA 10 mg /14 days		ns *(+35 • ns)*	–10	+19	
Lemay et al. (1995)	15	24	0.625 + MPA 5 mg (days 14-25)	–12.7	ns	sign.decrease	+4 +11	
PEPI (1995)	875	36	EC 0.625	–4	+8.7	–12 to –14	+20 to + 25	
			+MPA 10 mgx 12 days	–6	+0.2			
			MPA 2.5 mg continuous	–6	+0.2			
			P 200 mg x 12 days	–4	+6.8			
Anonymous (1996)	55	12	CE 0.625mg	–7	+15	–7	+25	
	70 (321)		± NG 0.150mg (12 days)	–9	0	–8	0	
Kim et al. (1996)	140	12	EC 0.625	0	+16.5	–10.9	+8	–37.1
	97		+ MPA 5 mg	–4	+10.8	–14	+4	–28
	109		+ MPA 10 mg	–4	+11.8	–12	–12	–30
	134		E2V +0.5NG	–13	0	–17.6	–35	–31
	71		Control	0	0	0	0	+10
Wilcox et al. (1997)	21	3	17α-dihydroequilin (0.2mg)	–8	–2.6	–5.4		
			E1S (1.25mg)	+0.8	+92	–29.3		
			Combined	–12.5	+79	–21.6		

Table 5.III : Effects of oral estradiol on circulating lipoproteins

Authors	N	Duration (months)	E type (dose/duration)	Percentage change from baseline			
				C	HDL *(HDL2•HDL3)*	LDL *(apo-B)*	TG
Fahraeus et al. (1982)	R 16(38)	4+2	2 mg x 4 months	–10	+7	–16.6	+4
			4 mg x 2 months	id	+19	–19.5	+14
Basdevant et al. (1983)	R 20(40)	2	2 mg E2	–10	+6.7	–13.6	+25
	10		2 mg E2V	–5	+8.8	–18	+21
Ottosson et al. (1986)	R 58	3+3	2 mg E2V	–5.5	+8 *(+16•-3)*		
			+ P200 mg	ns	ns *(ns•ns)*		
			or NG 250 µg	–4	–18 *(–30•-5)*		
			or MPA 10 mg		–8 *(–17•-7)*		
De Lignières et al. (1983)	10	1 1/2	2 mg E2	–8	+14	–19	+14
			2 mg E2V				
Walsh et al. (1991)	31	1 1/2	2 mg		+15 *(+39•+4)*	–14 *(–10)*	+20
Christiansen and Riis (1990)	18	60	2 mg E2V + NETA 1mg	–20	ns	–20	
Cano et al. (1991)	21	8	2 mg E2V + MPA 2.5 mg	–9	+13	–12	ns
Colvin et al. (1991)	6 × 2	2	0.5, 1, 2 mg E2 (compared with NG 0.075 to 0.450 mg)		*(0 to +43•0)* *(–71•–11.6)*		
Basdevant et al. (1991)	10	1 1/2	2 mg E2	–8	+14 (–7)	–19	+14
Makkonen et al. (1991)	27	6	2 mg E2V+				
			7.5 mg MA	–6.2	0	–7.9	–6.3
			0.250 mg NG	–10.8	–18.5	–7	–26
Metka et al. (1992)	55R	6	E2V+CPA 21 days	–0.2	+2	–2.1 *(+7)*	–3.8
			E2V 2 mg	–5.6	+5.2	–8.7 *(–3.3)*	–2
Palacios et al. (1994)	23(70)	12	E2V 2 mg	-2	+11.6	–2.3 *(0.3)*	+2.2
Munk-Jensen et al. (1994)	113 R/ placebo	24	Kliogest	-15.7	–0.16 *(–12.3•–24)*	–14	ns
			Trisequens	-8.3	2.7 *(0•–10)*	–10.6	+19.5
Schram et al. (1995)	25(45)	12	E2V+CPA 21 days	-5	ns *(ns•ns)*	–13	+25
Wolfe and Huff (1995)	26	2 + 6	1 mg E2				
			± NG 75 µg	–5	ns	–12	–17
Taskinen et al. (1996)	60	12	2 mg + NETA 1mg	–14	–9	–17	ns

Table 5.IV : Effects of percutaneous estradiol on circulating lipoproteins

Authors	N	Duration (months)	E type (dose/duration)	Percentage change from baseline			
				C	HDL *(HDL2•HDL3)*	LDL *(apo-B)*	TG
Elkik et al. (1982)	(R)10 (19)	1	3 mg E2				–14
Fahraeus et al. (1982)	(R)16(38)	6	3 mg x 6 months	–3	+4	–10.6	0
Basdevant et al. (1983)	R 20	2	3 mg E2	0	+5	0	–11.5
Fahraeus et al. (1983)	26	6+6	3 mg E2 x 6 months	–11	–15		
			+ 120 µg NG or		–20*(-30•–14)*	+3.5	–8
			300 mg P (day 11-21)	0	–10 *(0•–1)*	–4.2	–20
			x 6 months				
De Lignières et al. (1983)	10 (23)	2	3 mg ?	0	+3	+3.7	–20
Jensen et al. (1987)	R-DB-	12+12	3 mg ? x 1 y	–4	+3	–6	+2
	29 (57)		+200 mg P x 1y	–7	+4	–12	0
Moorjani et al. (1991)	R 16	6	1.5 mg (day 1-25)	–4	+ 11 *(+13•+9)*	–6 *(-3)*	–1
	16	6	1.5 mg (day 1-25)+ P (day 12-25)	–3	–6 *(–9•–6)*	–3 *(0)*	+8
Basdevant et al. (1991)	R 10	1 1/2	3 mg	–1.9	+3.6	–1.8	–12
Palacios et al. (1994)	R 22	1 1/2	1.5 mg	+5.3	+8.8	+3.5 *(–3.62)*	+4.2

Table 5.V : Effects of the estradiol transdermal system on circulating lipoproteins

Authors	N	Duration months	E2 [dose (unit)]	Percentage change from baseline				
				C	HDL *(HDL2•HDL3)*	LDL *(apo-B)*	TG	Lp(a)
Chetkowski et al. (1986)	23	1	25/50/100/200 µg	ns	ns	ns	ns	
Crook et al. (1992)	31	6	50 µg+NETA 250 µg	–11.4	–10 *(0•–13.9)*	–11 *(–8)*	–18	
Castelo-Branco et al. (1993)	20		50 µg day 1-24+ MPA 2.5mg 12 days	–0.8	+14.3 *(ns at 6 months)*	+1.8 *(–0.9)*	–10.1	
Lindgren et al. (1992)	25	12	50 µg 28 days +NETA 0,25x14 days	–5.7	–18.75	–5.6*(0)*	0	
Adami et al. (1993)	24 (35)		50+MPA10 mg 12 days	–9.9	–8.4	–12	–11	
Mattson et al. (1993)	52R dB		50+MPA (5 mg 14 days) 100+MPA (5 mg 14 days)	–4.3 –5.8	–1.6 *(+3.6•–5.6)* +0.5 *(+8.9•–4.5)*	–5 –7	–8.2 –15.2	
Whitcroft et al. (1994)	61 R 29 C	36	50 µg 28 days +NETA 0,25 x14 days	–8.4	–10.7 *(id control: –7)*	6.6	–16.4	
Shram et al. (1995)	25(45)	12	50+20 mg DD	ns	ns *(ns•ns)*	ns	ns	+12
Castelo-Branco et al. (1996)	25	12 +24	50 µg +MPA 2.5 50 µg	ns ns	+19.8 id	–6.4 id	–19 –19	
Habiba et al. (1996)	42	6	50 µg	–7	0	+13.8	–7	ns
Palacios et al. (1994)	25	12	50	+2.8	+5.5	+6.2 *(–11.5)*	+12	
Taskinen et al. (1996)	60 (120)	12	50 µg 28 days + MPA 10 mg 12 days	–5.7	0 –4.7	–4 –4.8	ns –15.7	–16 +12

Tableau 5.VI : Effects of HRT on circulating lipoproteins in hypercholesterolemic patients

Authors	N	Duration (months)	E type (dose/duration)	Percentage change from baseline				
				C	HDL *(HDL2•HDL3)*	LDL *(apo-B)*	TG	Lp (a)
Tonstad et al. (1995)	76 - R placebo	12	Trisequens+diet LDL ≥ 4.2mmol/l	–14 –3	ns ns	–19(–18) ns	ns ns	–18
Tonstad (1996)	Follow-up of the above	18	6 Trisequens 35 Kliogest 21 controls All subgroups on HRT		0 –16 0	–22 –19 +5 If LDL ≥ 4.9 –22.6 *(–20.7)* If LDL < 4.9 –2.3 *(–10.6)*	+10 +16 0	mean :–15 If LDL≥4.9 –19.2 If LDL < 4.9 –15.2 smokers: –21 non smokers: –0.3
Wolfe and Huff (1995)	open	3 mth diet 24	E2 1mg+NG.075	–11	+8	–17	–31	
Perrone et al. (1996)	42 R	6	E2T 50+MPA 10 mg CE+MPA 10 mg 12 days	–11.5 –11.3	+13.9 +24.7	–21.6 –16.3	ns ns	ns ns

It should be noted that lipid modifications appear more rapidly when estrogen is administered *per os* than by other routes.

The effects of estrogen on the lipid profile can be modulated by concomitant progestogen administration. The observed changes depend on the type of progestogen (pregnane or norsteroid) and the dose (e.g. the androgenic properties of high-dose medroxyprogesterone acetate). Norsteroid progestogens and MPA (10 mg/day) stimulate hepatic lipase, thereby countering the effect of estrogen on this parameter, with a drop in HDL and triglycerides, and a variable effect on LDL and total cholesterol. These progestogens also potentiate some effects of estrogen, through an action on regulatory mechanisms other than hepatic lipase. Pregnane progestogens other than MPA and progesterone have no apparent impact on lipid fractions.

While most studies suggest that non oral estrogen administration can reduce the level of LDL cholesterol, its action on HDL is more controversial. It seems to be less effective than oral estrogen in countering the hepatic effects of norsteroids. Thus, the combination of non oral estrogen and a norsteroid leads to a significant fall in HDL cholesterol and accentuates the fall in triglycerides.

Effects of HRT on subsets of patients with metabolic diseases

A few clinical studies have examined the effects of oral estrogen therapy in women with hypercholesterolemia. Tonstad et al. (1995) (table 5.VI) treated for 12 months 39 hypercholesterolemic (LDL>4.2mmol/l) women with Trisequens® (2mg E2+1 mg NETA) vs placebo in a randomized study. The decrease in LDL was 19 %, in Total Cholesterol 14 %, in Lp(a) 18 % and in apo B 18 %. No significant variation was seen in HDL Cholesterol.

In another paper, Tonstad (1996) studied 39 women on HRT and 29 women on a placebo for 18 months. Samples were obtained from 35 women taking Kliogest®, 6 Trisequens® and 21 on placebo. After 48 weeks, the reduction in LDL-cholesterol was 5-fold greater in the HRT group than in the placebo group. Lp(a) levels were reduced by 16.5 % in the HRT group vs a 4.2 % increase in the placebo group. Lp(a) levels were only reduced in non-smokers. The LDL reduction was greater in non-smokers, women with low to normal BMI and higher baseline levels of LDL. Other studies have found the same decrease in LDL cholesterol : –13 – 14 % (Munk-Jensen et al., 1994 ; Denke, 1996).

Wolfe et al. (1995) also studied the influence of HRT in hypercholesterolemic women, 13 of whom were treated with estradiol-17β (1 mg/day) and norgestrel (0.075 mg/day) for 2 years. Total cholesterol was decreased by

11 ± 3 %, LDL by 17 ± 3 %, triglycerides by 31 ± 6 % and VLDL triglycerides by 33 ± 9 %. HDL increased non significantly by 8 %.

Perrone et al. (1996) studied 42 postmenopausal women with hypercholesterolemia (TC > 240 mg/dL). These patients were treated for 6 months after a random assignment to 50 µg TTS + 10 mg MPA for 12 days or conjugated estrogens 0.625 + MPA 10 mg/day for 12 days. Total cholesterol decreased by 11 % in the two groups and the LDL decreased by 21 and 16 % respectively. The HDL increased by 14 and 25 % respectively whereas triglycerides and Lp(a) did not vary.

In case of hypertriglyceridemia, however, the increase in TG due to use of the oral route has to be taken into account. In contrast, a previous paper has reported that the percutaneous administration of E2 decreased TG in hypertriglyceridic women (Loeper et al., 1977).

Andersson et al. (1996) studied 24 post-menopausal women with non insulin-dependent diabetes mellitus (NIDDM) in a randomized, double-blind, cross-over study under HRT or placebo. The HRT consisted of 2 cycles of 2 mg estradiol-17b *per os* and 1 cycle of Trisequens®. The fasting glucose, HbA1c and C-peptide were significantly reduced with HRT. Total cholesterol decreased by 8.7 % and LDL by 23 %, and HDL increased by 20 % and TG by 11.7 %.

Mosnier-Pudar et al. (1991) randomized 14 NIDDM women with percutaneous estradiol-17β (1.5 mg × 21 days) + progesterone (200 mg/day × 14 days) for 6 months and a NIDDM control group (n=11). No significant difference between the two groups was seen in lipids or HbA1c.

Effects of HRT on lipid subfractions

Some studies have shown that estrogen, regardless of the type, leads to a size reduction in LDL fractions and to changes in their composition. Too few studies have examined the action of estrogen (alone or combined with a progestogen) on Lp(a) to show any beneficial effect. The action of estrogen on LDL oxidation *in vivo* also has to be better documented, as current results are limited by technical assay problems.

Taskinen et al. (1996) reported a decrease in Lp(a) by 16 % following transdermal administration (50 µg) and by 31 % following oral E2 (2 mg) in 120 post-menopausal women. Androgens and progestins have also been reported to decrease Lp(a) but the mechanisms of action of these steroids are unknown.

Kim et al. (1996) studied 551 women distributed into five groups : 140 were treated with conjugated estrogens (CE) alone, 97 with CE+MPA (5mg), 109 received CE+ MPA (10 mg) and 134 received E2V+NG (0.5 mg). The

treated groups were compared with 71 controls for 12 months. In the CE alone group, Lp(a) fall by 37 %. In the progestogen group, the decrease reached respectively 27.7, 29.3 and 30.3 %.

In post-menopausal women, Walsh et al. (1994) observed that oral E2 accelerated the catabolism of LDL which exceeded the production rate. TTS treatment did not affect LDL metabolism.

Following treatment with estradiol 17β + norgestrel, Wolfe and Huff (1995) described a decrease in the production rate of LDL without a modification in their clearance and a lowering of their particle size. It has been reported that small particles have greater atherogenic properties than native particles. It is not known if the LDL particles generated on oral estradiol 17b are more or less atherogenic since their composition (in cholesterol and triglycerides) is also altered. In addition, the largest part of LDL is represented by the LDL2 fraction which is the least modified on estradiol 17β treatment.

Tilly-Kiesi et al. (1996) reported data in favor of the same hypothesis. They demonstrated that oral treatment (2 mg estradiol 17β + norethisterone acetate) decreased the LDL1 and LDL2 fractions and increased LDL3 after one year of treatment. In the TTS (50) + MPA (10 mg × 12 days) group, the changes were smaller with a decrease in LDL1 and increase in the denser particles (LDL3). The major differences were in an hepatic lipase activity which was decreased in the oral group and unchanged in the TTS group. The authors concluded that estrogens operate not only by inhibiting hepatic lipase activity but also by altering LDL fraction composition, which could be explained by their actions on the LDL receptor. Similar activity is reported with lovastatin, which preferentially removes the large cholesterol-rich LDL particles and reduces the cholesterol protein ratio in LDL.

Wakatsuki and Sagara (1996) reported a decrease in the post heparin activity of triglyceride hepatic lipase with CE ± 2.5 mg MPA but not with 5mg MPA. This activity was inhibited by oral estrogen and MPA exerted a dose-dependent stimulatory effect on it. Colvin et al. (1991) reported the same kind of effects. Previous studies by Basdevant reported the same effects with oral estradiol 17β and no effect with percutaneous estradiol 17β.

LDL oxidation has also been studied with different methods. It appears that E2 given orally as well as transdermally can inhibit the oxidation rate (Sack et al., 1994 ; Keaney et al., 1994). However, Van der Mooren et al. (1997) observed no clear effect of conjugated estrogens on LDL oxidation. This could depend upon the route of E2 administration, the type of progestogen and the duration of treatment (6 months in Van der Mooren vs 3 months and 16 weeks in previous studies). These points have to be clarified.

To conclude, most studies on CE are consistent. On CE alone, TC and LDL cholesterol decrease significantly after three months of treatment. HDL cholesterol and mainly the HDL2 fraction, increase significantly, as do TG. There is only one study concerning Lp(a), and a decrease was shown.

Combination with a progestogen can modify the lipid profile. MPA, less than norsteroid derivatives, can decrease HDL fractions and TG by acting at the hepatic lipase level, thus reversing partially or totally the action of oral estrogens. E2 administered orally has milder effects than CE on lipid fractions.

Concerning non oral administration of E2, the number of studies is smaller and they were shorter. The results reported indicate a mild increase in HDL, the most striking difference being the decrease in TG.

Concerning the progestogens other than normethyl-T and MPA, only the administration of natural progesterone has been studied properly. This progestogen does not alter the lipid profile.

Oral E2 administration to hypercholesterolemic women decreases TC and LDL fractions and seems thus interesting. However, the increase in TG does not mean that this route of administration can be used in hypertriglyceridemic women.

Concerning the effects of estrogens on lipid subfractions and LDL oxidation, more studies are needed to compare the two routes of administration.

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