11

Hemostasis and protocols of postmenopausal HRT administration

A lower risk of cardiovascular disease, especially of myocardial infarction, has been reported in women treated with hormone replacement therapy (HRT). In contrast, recent papers have suggested that this treatment is also associated with an increased risk of venous thrombosis and pulmonary embolism (Daly et al., 1996 ; Grodstein et al., 1996 ; Jick et al., 1996). Hemostasis is ensured by several mechanisms involving platelets, the coagulation cascade and the fibrinolytic system. An imbalance between the regulatory mechanisms of hemostasis can lead to thrombosis (table 11.I). In population-based studies, a significant decrease in fibrinogen (Fgen), plasminogen activator inhibitor (PAI) and tissue plasminogen activator (t-PA) antigen, an increase in plasminogen (Plg) and a decrease in antithrombin (AT) have been reported (table 11.II). These changes may induce a profibrinolytic effect on one hand and a procoagulant effect on the other hand.

The effect of HRT on hemostasis has also been investigated in clinical studies involving different therapeutic schedules with oral or transdermal estrogens, combined or not with a progestogen. Only five studies included either a placebo or an untreated group : Caine et al., 1992 ; PEPI, 1995 ; Conard et al., 1995 ; Crosignani et al., 1996 ; Scarabin (published as an abstract in 1997). These papers will be reviewed together with non randomized studies.

Table 11.I : Changes linked to hypercoagulation and hypofibrinolysis

Hypercoagulation	Hypofibrinolysis
• Increased number or activity of platelets (ex. ↗ TXB2)	• Decreased fibrinolytic activity prolonged lysis time
• Increased coagulation factors : Fibrinogen, factor VII, VIII...	• Decreased plasminogen or t-PA activity
• Decreased coagulation inhibitors : AT, PC, PS	• Increased Pai (or t-PA antigen)
• Resistance to activated PC	• Increased D-dimers (marker of the effect of plasmin on fibrin)
• Increased coagulation activation : FPA, F1+2, thromin-AT complexes	
• Increased D-dimers (indirect marker of thrombin formation)	

NB : Venous thrombosis is classically associated with hypercoagulation (deficiencies in AT, PC, PS, resistance to activated PC) - Arterial thrombosis is classically associated with increased fibrinogen levels or hypofibrinolysis related to high levels of PAi.

Table 11.II : Effects of hormone replacement therapy on hemostasis. Cross-sectional population-based studies.

Authors	N	Type of study	Age	Treatment	Percentage change from the baseline				
					Fibrinogen	PAI	t-PA ag	F VII	Others
Scarabin et al. (1993) IPC	21/99	cross-section	45-54	E2+P/no	–8	–18		–14 activ	
Nabulsi et al. (1993) ARIC	853/3 119	cross-section	45-64	CE/no	–6			+9 activ	AT –5
Gebara et al. (1995) Framingham	82/374	cross-section		yes/no		–35 ag	–24		
Salomaa et al. (1995) FINRISK	351/851	cross-section	45-64	yes/no	–6			0 activ - +4 ag	Plasminogen +5
Shahar et al. (1996) ARIC	59/229	case-control	45-64	CE/no		–23 ag	–16		
Meilahn et al. (1996)	136/137	cross-section	65-82	E2/no	–6	–17 ag			

Oral conjugated equine estrogens (CE)

Table 11.III summarizes studies with oral conjugated equine estrogens (CE). In one randomized cross-over study (Caine et al., 1992), 29 women received CE at 0.625 mg and 1.25 mg per day and placebo for 3-month periods. The parameters studied were coagulation inhibitors : AT, total PS and PC, fibrinopeptide A (FPA), a marker of thrombin action on fibrinogen, and fragment 1+2 (F1+2), a marker of factor Xa action on prothrombin. They were measured by immunoassays. A decrease in AT and PS and an increase in FPA and F1+2 were observed in the CE groups.

Other cross-over studies did not include a placebo group. Kroon et al. (1994) studied 23 women who received, in the first step, either 0.625 mg of oral CE or transdermal estradiol for 6 weeks and in the second step, groups switched estrogens. The parameters studied were : factor VIII coagulant activity, the von Willebrand antigen, factor VII coagulant activity and antigen, fibrinogen, AT and PC activity, free fraction of PS antigen, PAI activity and F1+2. Koh et al. (1997) studied 30 women receiving 0.625 mg of CE : they were randomly assigned to begin either CE alone or CE and medroxyprogesterone acetate (MPA) 2.5 mg. After a one-month washout period, they were switched to the other treatment. The parameters studied were PAI antigen and D-Dimers. The study of the Medical Resarch Council (1996) included hysterectomized women, randomly allocated to CE alone or to CE and oral progestogen (norgestrel 150 µg) for the last 12 days of the cycle. In both groups, CE was administered for 28 days. Fibrinogen and factor VII coagulant activity were measured at 3, 6 and 12 months in 74 and 52 women who received CE either alone or plus progestogen.

Some patients were studied before and after treatment. Boschetti et al. (1991) studied 40 women who were randomly allocated to 0.625 mg CE (n=18) or transdermal estradiol (n=22). Estrogens were given for 3 weeks and 10 mg MPA per day was added the 3rd week. Fibrinogen, AT activity, factor VII and VIII and t-PA activity were measured before and after treatment (2, 4 months in all patients, 12 months in a subgroup). Chetkowski et al. (1986) and Alkjaersig et al. (1988) conducted a dose-response study in 23 women receiving 0.625 and 1.25 mg CE and different doses of transdermal estradiol, each being administered for 28 days. The tests performed were AT antigen and activity, fibrinogen, plasminogen, FPA and plasminogen antigen.

Modifications of the circadian pattern of PAI have been shown in 17 women receiving CE ± MPA (Katz 1996). At baseline, PAI showed the expected circadian variability with peak values in the early morning. During HRT, the PAI level was selectively lowered in the morning samples and there was a loss of circadian pattern. These results have been linked to the circadian pattern of atherothrombotic events, especially of myocardial infarction (peak incidence in the morning hours).

Table 11.III : Effects of conjugated equine estrogens (CE) on hemostasis.

Authors	N	Duration of treatment	Treatment	Percentage change from the baseline						
				Fgen	PAI	AT	Plg	F VII	Markers	PS
Chetkowski et al. (1986)	23	1 month	CE 1.25 mg vs placebo	–4		–5	+18		FPA : +28	
Alkjaersig et al. (1988)	9		CE 0.625 mg	–4		–6	+5		+21	
Boschetti et al. (1991)	23	12 months	CE 0.625 mg+MPA	–0.4		–13		+14		
Kroon et al. (1994)	158	6 weeks	CE 0.625 mg	–9	–48	–5		+21	F1+2 : +38	
MRC 1996	30	6 months	CE 0.625 mg	–9				+24		
Koh et al. (1997)	29	1 month	CE 0.625 mg						D-dimers : +25	
Caine et al. (1992)		3 months	CE 1.25 mg CE 0.625 mg vs placebo		–56	–13 –9			F1+2 : +98 +40	–19 –15

Table 11.III shows the changes reported during treatment with CE : a decrease in PAI (– 48 and – 56 %, Kroon et al., 1994 ; Koh et al., 1997), in AT (– 5 to – 13 % in five studies in which it was measured, the difference being statistically significant or not) and in PS (– 15 and – 9 % with 1.25 and 0.625 mg E2, respectively). A significant increase in plasminogen (+ 18 and + 5 % respectively with 1.25 mg but not with 0.625 mg E2, Alkjaersig et al., 1988) and in coagulation markers (+ 38 to + 98 % for F1+2, Caine et al., 1992 ; Kroon et al., 1994) and an increase in FPA (+ 37 to 71 %, Caine et al., 1992 ; Chetkowski et al., 1986) and in factor VII, which is difficult to interpret. Factor VII is classically considered as a cardiovascular risk factor. There was a negative relationship between the decrease in PAI and the increase in D-Dimers in one study (Koh et al., 1997).

Oral estradiol (E2)

Table 11.IV summarizes studies with oral estradiol (E2), two of which included a placebo or untreated group. Conard et al. (1995) in a double-blind randomized prospective study compared the effect of two cyclic oral estradiol-nomegestrol acetate combinations (1 mg-2.5 mg and 1.5 mg-3.75 mg) with a placebo over a 3-cycle period in three groups of 19 women. The parameters studied were : fibrinogen, AT and plasminogen activity, PC, total and free PS and F 1+2 (immunoassays). Scarabin et al. (1997) investigated hemostasis in 15 women treated with cyclic oral estradiol combined with micronized progesterone and in 15 untreated women. The variables studied before and after a 6-month period were : fibrinogen, PAI activity, t-PA antigen, global fibrinolytic activity, factor VII, von Willebrand factor, D-Dimers, F 1+2, plasminogen and AT.

In another study (Sporrong et al., 1990), 60 women were randomly allocated to four groups who received 2 mg of estradiol-17§ combined with norethisterone acetate (NETA) (1 or 0.5 mg) or with megestrol acetate (5 or 2.5 mg) for one year. The following evaluations were performed : fibrinogen, activated partial thromboplastin time, factor VII antigen as well as coagulant and amidolytic activities, von Willebrand factor antigen, AT, plasminogen and PAI activity, PC antigen.

Gilabert et al. (1995) evaluated the effect of 2 mg estradiol valerate plus medroxyprogesterone acetate (MPA) 2.5 mg in 75 women before and after 3 to 4 and 12 months of treatment. The tests performed were : PAI antigen and activity, euglobulin lysis time, t-PA antigen and activity, t-PA-PAI complex, u-PA, plasminogen and AT activity, PC and total PS antigen.

The results of these studies are shown in table 11.IV and can be summarized as follows : no significant change in fibrinogen ; an increase in fibrinolysis (Scarabin et al., 1997), plasminogen (Conard et al., 1995) and F 1+2 —

Table 11.IV : Effects of oral estradiol on hemostasis

Authors	N	Duration of treatment	Treatment	Percentage change from the baseline				
				Fibrinogen	PAI	Plasminogen	F VII	AT
Sporrong et al. (1990)	15	12 mths	2 mg+NETA 1 mg		– 25	+ 4	– 34 ag	– 11
	15	"	2 mg+NETA 0.5 mg		– 8	+ 9	– 16 ag	– 9
	15	"	2 mg+MA 5 mg		0	– 1	– 10 ag	– 6
	15	"	2 mg+MA 2.5 mg		+ 8	+ 14	– 11 ag	– 9
Gilabertet al. (1995)	12	12 mths	2 mg		– 41	+ 4		+ 3
Conard et al. (1995)	15	3 mths	1 mg+NA 2.5 mg	– 3		+ 15		– 3
			1.5 mg + NA 3.7 mg	+ 3		+ 14		– 2
			placebo	0		+ 3		+ 3

Table 11.V : Effects of transdermal estradiol on hemostasis.

Authors	N	Duration of treatment	Treatment	Percentage change from the baseline				
				Fgen	PAI	Plg	F VII	AT
Boschetti et al. (1991)	12	4 months	E2 patch 50 µg+MPA	+10			–2	–3
Kroon et al. (1994)	23	6 weeks	E2 patch	–2	+9		+18	–4
Gilabert et al. (1995)	18	6 months	E2 patch 50 µg±MPA		+12	–6		0
Lindoff et al. (1996)	30	2 years	E2 patch 50 µg+MPA	–7	–16		–7	–1
Koh et al. (1997)	20	1 month	E2 patch 100 µg±MPA		+10			

(Scarabin et al., 1997) ; a decrease in PAI in women treated with E2 plus progesterone (Scarabin et al., 1997), which was not significant with E2 plus NETA, nomegestrol acetate or MPA, a decrease in AT, significant with E2 plus NETA 1 mg (Sporrong et al., 1990) or progesterone (Scarabin et al., 1995) and in factor VII with E2 plus NETA or megestrol acetate (Sporrong et al., 1990).

Transdermal E2 was administered mainly as a patch containing 50 µg, alone or in combination with MPA or progesterone (table 11.V).

In one study (Lindoff et al., 1996), a decrease in fibrinogen (–7 %), in PAI antigen (–16 %) and in factor VII (–7 %) were observed after a 2-year treatment ; a decrease in AT was reported in another study after one year (Boschetti et al., 1991). No modification was observed in other studies.

Influence of the progestogen

In five studies (table 11.VI), the addition of a progestogen (MPA, norgestrel or progesterone) to the estrogen has been studied or tested (Nabulsi et al., 1993 ; PEPI, 1995 ; MRC 1996 ; Koh et al., 1997 ; Gilabert et al., 1995). An increase in factor VII was observed with conjugated estrogens alone but not with this estrogen and MPA or norgestrel.

In one study (Sporrong et al., 1990), different doses of NETA or megestrol acetate were combined with the same dose of estradiol. The highest dose of NETA was associated with a decrease in AT (–11 %) and factor VII (–34 %).

It cannot be excluded that some progestogens may induce changes in hemostasis that may counterbalance those observed with estrogens : for instance, during administration of nomegestrol acetate (Basdevant 1991), there is an increase in AT which could theoretically reverse the decrease in AT induced by oral estrogens.

Comparison between the oral and transdermal route of administration

The comparison conjugated equine estrogens vs transdermal estradiol was done in two cross-over studies (Chetkowski et al., 1986 ; Kroon et al., 1994) and two randomized studies (Boschetti et al., 1991 ; Koh et al., 1997) (table 11.VII). Changes in AT, PAI and factor VIII were observed with conjugated estrogens only.

In one study (Aune et al., 1995), oral estradiol was compared to transdermal estradiol but the progestogen was different (MPA 10 mg or NETA 1 mg) : a reduction in tissue factor activity in unstimulated and lipopolysaccharide-

Table 11.VI : Effects of the progestogens.

Authors	Type of study	N	Treatment	Duration of treatment	Commentaires
Nabulsi et al. (1993)	cross-section	853 173	CE CE + MPA		CE alone : F VII + 9%; CE + MPA : ns NS for Fg, AT, F VIII, PC
MRC (1996)	R	158 163	CE 0.625 mg CE + norgestrel	1 year	CE alone : F VII + 21%; CE + norgestrel : ns Decrease in fibrinogen in both groups
PEPI (1995)	placebo controlled	175 348 178	CE 0.625 mg CE + MPA CE + progesterone		ns for fibrinogen
Gilabert et al. (1995)	before/after	18 12	E2 50 µg E2 + MPA	4 months	ns for AT, PC, PS, Plgen, lysis, t-PA ag and activity, PAI ag and activity.
Koh et al. (1997)	cross-over 2 groups	30 20	CE 0.625 mg CE + MPA E2 100 µg E2 + MPA	1 month	No influence of MPA on results of PAI : decreased with CE, not modified with E2.
Sporrong et al. (1990)	R	15 15 15 15	E2 oral + NETA 1 mg E2 oral + NETA 0.5 E2 oral + MA 5 mg E2 oral + MA 2.5 mg	1 year	NETA 1 mg : decrease in AT and F VII no change in other groups

Table 11.VII : Comparison between the oral and transdermal routes of estrogen administration.

Authors	Type of study	N	Treatment	Duration of treatment	Commentaires
Chetkowski et al. (1986)	cross-over	23	CE 0.625 or 1.25 mg	1 month	CE 1.25 : Plg + 18%
Alkjaersig et al. (1988)			E2 25 to 200 µg		AT and Fg not modified
Kroon et al. (1994)	cross-over	23	CE 0.625 mg E2 50 µg	6 weeks	CE : AT - 5 %, PAI - 48 %, F VII + 21 %, F 1+2 + 38 %. Fibrinogen, PC, PS, F VIII not modified. E2 : F VII + 18 %, F 1+2 + 35 % Fibrinogen, PAI, AT, PC, PS, F VIII not modified
Koh et al. (1997)	R	30 20	CE 0.625 mg E2 100 µg	1 month	CE : PAI - 18 ng D-dimers : inverse correlation with PAI E2 : PAI not modified
Boschetti et al. (1991)	R	9 12	CE 0.625 mg+MPA E2 50µg+MPA	12 months	CE : AT - 12 %, F VIII : + 29 % E2 : AT - 6 %, F VIII : + 54 %
Aune et al. (1995)	R		E2 2 mg+NETA E2 50 µg+MPA	12 months	Reduction of tissue factor and TXB2 in both groups after 12 months.
Scarabin et al. (1995)	R vs placebo	15 15	E2 oral + progesterone E2 transderm + progest	6 months	E2 oral : decrease in AT, PAI, t-PA, increase in F1+2, lysis. No change with E2 transdermal.

stimulated monocytes and of plasma thromboxane B2 (TXB2) was observed in both groups at 12 months ; no significant change was found after 3 months. These effects suggest that a year of treatment reduces cellular activation of monocytes and platelets that may account for a reduction in the risk of cardiovascular disease.

In one study (Scarabin et al., 1997), women allocated to E2 administered orally or transdermally and combined with progesterone were compared to untreated women. Oral estradiol induced coagulation activation and increased fibrinolytic potential, while the transdermal route had no substantial effect. A similar finding was observed with AT in a non randomized study published in 1983 comparing E2 gel and oral estradiol (Conard et al., 1983).

Duration of the treatment ; cyclic or continuous treatment

Hemostasis was usually studied after a one-month period (sometimes up to 6 months). In one study only (Boschetti et al., 1991), patients were investigated after different periods : there was no significant change at 2 or 4 months of treatment ; a decrease in AT and increase in factor VIII was observed after one year with conjugated estrogens as with transdermal estradiol. Modifications of cellular activation of blood monocytes and platelets were also significant after one year and not after 3 months of HRT (Aune et al., 1995). Significant modifications were also observed in the only study in which women were followed for 2 years (Lindoff et al., 1996).

Most results concern cyclic treatments. In one study, cyclic and continuous transdermal treatments were compared (Crosignani et al., 1996). Coagulation changes were observed in continuous treatments only (fibrinogen –0.20 g/L, AT –7 %, PS –7 %, factor VII –5 %) (table 11.VIII).

Critical analysis

Although interventional double-blind randomized studies are very few, hormone replacement therapy seems to be associated with modifications of hemostasis, namely activation of coagulation and a profibrinolytic effect. Different therapeutic schedules have been proposed : they differ by the nature and route of administration of the estrogen (conjugated equine estrogens or estradiol, oral or transdermal route) and their combination or not with a progestogen (natural progestogen, norsteroids, norpregnans, pregnans).

Oral conjugated equine estrogens are the most widely used estrogens. They induce a decrease in fibrinogen and PAI (considered as risk factors of cardiovascular disease) and may account for the decrease in myocardial risk

Table 11.VIII : Effects of the duration of treatment

Authors	N	Treatment	Duration of treatment	Commentaires
Boschetti et al. (1991)	12 9	E2 50 µg + MPA CE 0.625 + MPA	2 months 4 months 12 months	ns for AT, Fg, F VII, F VIII, t-PA idem E2 : AT - 6 %, F VIII +54 %, CE, AT - 12 %, F VIII : + 29 %
Crosignani et al. (1996)	167	E2 50 µg cyclic + MPA E2 50 continuous + MPA vs placebo	≥ 6 months	Changes in continuous E2 only : Fg - 0.20 g/l, AT - 7%, PS - 7%, F VII - 5% ns for PAI, PC, F VIII
Lindoff et al. (1996)	30	E2 50 µg + MPA	2 years	Fibrinogen - 0.21 g/l, F VII - 8%, PAI - 19 % ns for PAI, PC, F VIII

observed in epidemiological studies in treated women. In addition, these estrogens induce a decrease in antithrombin and in prothrombin fragment 1+2 (marker of coagulation) which may reflect a hypercoagulable state and may be involved in the increased venous risk recently associated with HRT (Daly et al., 1996 ; Grodstein et al., 1996 ; Jick et al., 1996). Concern over the risk of venous thrombosis during HRT has also been expressed in case reports (Knox et al., 1990 ; Strachan et al., 1995). This risk should probably be taken into account in women with a previous episode of venous thromboembolism or family history of venous thromboembolism (Conard, 1991 ; Vandenbroucke et al., 1996).

The natural estrogen, estradiol-17β, administered by the oral or transdermal route has been less widely studied. The modifications observed when given by the oral route are similar to those obtained with conjugated estrogens, although less marked. Transdermal estradiol does not seem to induce any change.

The results concerning progestogens combined with the estrogen indicate no increase in factor VII when MPA or norgestrel is combined with CE and no effect on the other parameters. The problem is that the progestogens administered by French gynecologists are different.

To conclude, oral administration of estrogen is associated with a decrease in an arterial risk factor, fibrinogen, which may be beneficial, but also with an activation of coagulation which may increase the risk of venous thromboembolism. It may require the detection of women in whom HRT would be a benefit and those at arterial or venous risk in whom HRT may be contra indicated or should be tailored. The administration of transdermal estradiol can be an advantage concerning the venous risk but, in return, the benefit to the arterial system may be questioned. Since coagulation and fibrinolysis test methodology has improved during the last years, it would be desirable to confirm the previous findings and to undertake the necessary randomized studies.

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