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Hemostasis in postmenopausal women on HRT

Epidemiological observational studies have shown that menopause is associated with certain modifications in the parameters of hemostasis. It is thus reasonable to envisage whether HRT could influence these parameters (Gura, 1995). Different approaches can be followed to obtain an answer : the observational approach which consists of analysing the potential links between HRT and the variables of hemostasis, and the interventional approach (controlled randomized trial) which is the only way of assessing the distinct effect of HRT. In this chapter, studies of these two types will be reviewed and their results analysed and commented on.

Observational studies

The procedures and results of eight reports are summarized in tables 10.I and 10.II. Since most of these studies have been performed in the United States, HRT was administered orally and consisted of conjugated equine estrogen combined or not with a progestogen. In France (Derby et al., 1995), natural estrogen (17β-estradiol) is preferred ; it is administered transdermally and combined with a pregnane or a norpregnane, or with natural progesterone. It has to be pointed out that, in observational studies, the type of HRT is very rarely described in detail.

In the Healthy Women cohort study performed in the United States in the late eighties, 207 women (49 to 56 years old) were recruited using car insurance company listings (Meilhan et al., 1992). Thirty six per cent of the 163 postmenopausal women were on HRT. After age adjustment, the results indicated that HRT was associated with significant decreases in fibrinogen and antithrombin III and an increase in plasminogen. In contrast, factor VII was not modified.

The Scottish Heart Health study is a large cohort study. It considered 4 837 women, 25 to 69 years old, recruited by general practitioners during 1988 (Lee et al., 1993). Only 2 % of the 2 611 menopausal women were on HRT. A single hemostasis parameter, fibrinogen, was evaluated and shown to

Table 10.I : Hormone replacement therapy and hemostasis : characteristics of the studies.

Authors	Study	Country	Design	Sample size	Age	Population	Recruitment Period
Meilhan et al. (1992)	Healthy Women	USA	Cross-sectional	207	49-56	Car drivers	1988-1990
Lee et al. (1993)	Scottish Heart Health	Scotland	Cross-sectional	4 837	25-64	General population	1988
Scarabin et al. (1993)	Paris	France	Cross-sectional	259	45-54	health check-up	1989
Nabulsi et al. (1993)	ARIC	USA	Cross-sectional	4 958	45-64	Communities	1986-1989
Shahar et al. (1996)			Nested case-control	288			
Manolio et al. (1993)	Cardiovascular Health	USA	Cross-sectional	2 955	$\geq$ 65	Random sample from Communities	
Gebara et al. (1995)	Framingham	USA	Cross-sectional	749		Framingham	1991-1992
Salomaa et al. (1995)	Finrisk Haemostasis	Finland	Cross-sectional	1 202	45-64	Random sample	1992
Meilhan et al. (1996)	Osteoporotic Fractures	USA	Cross-sectional	273	65-82	Communities	1986-1988

Table 10.II : Hormone replacement therapy and hemostasis : main results

Authors	Study	F VIIc	Fibrinogen	ATIII	PAI-1	Others factors
Meilhan et al. (1992)	Healthy Women	→	↓	↓		Plasminogen ↗
Lee et al. (1993)	Scottish Heart Health		↓			
Scarabin et al. (1993)	Paris	↗	→		↓ act	
Nabulsi et al. (1993) Shahar et al. (1996)	ARIC	↗	↓	↓	→	VIII c → tPA ag ↓ D.dimers → Prot C ↗
Manolio et al. (1993)	Cardiovascular Health	↗	↓			
Gebara et al. (1995)	Framingham				↓ag	tPA ag ↓
Salomaa et al. (1995)	Finrisk Haemostasis	→	↓			VIIag ↗ Plasminogen ↗
Meilhan et al. (1996)	Osteoporotic Fractures		↓		↓ag	

be significantly decreased in HRT-treated women as compared with their untreated, age-matched, counterparts.

The Paris study, a transversal study, was published in 1993. Two hundred and fifty-nine women (45 to 54 years old), were recruited in a check-up center (Scarabin et al., 1993). Out of the 120 postmenopausal subjects, 17 % were on HRT (in most cases transdermal estrogen combined with a progestogen). After age adjustment, HRT was related to a significant decrease in coagulation factor VII and PAI-1 activity. Fibrinogen levels were not significantly modified.

The Aric study (an American study) is the largest so far published : 6 737 women, 45 to 64 years old, were recruited in different communities in the eighties (Conlan et al., 1994 ; Folsom et al., 1991 ; Nabulsi et al., 1993). An analysis of the first data collected in this cohort study and in a case-control study concerning 288 women selected out of the overall cohort have been published. The case-control study concerned 142 women presenting a thickening of their carotid and 146 normal controls (Shahar et al., 1996). After age-adjustment, the data showed that antithrombin III and tPA antigen were decreased in all treated women, as compared with untreated women. In subjects receiving only estrogens, coagulation factor VII and C protein were significantly increased, while in subjects receiving an estro-progestogen combination they were not modified. Fibrinogen, PAI-1 antigen, D-Dimers and coagulation factor VIII levels were not influenced by either treatment.

In the Cardiovascular health study (an American cohort study) 2 955 women were enrolled. They were older than 65 and lived in different communities (Manolio et al., 1993). HRT was or had been utilized by 39 % of them. Ongoing treatment was associated with a significant decrease in fibrinogen and a significant increase in coagulation factor VII, as compared with never-user age-matched subjects. Similar levels of coagulation factor VII were measured in never-users and in women who had discontinued HRT.

A transversal analysis has been performed using the Framingham cohort data (Gebara et al., 1995). PAI-1 and tPA antigen were analyzed in 749 subjects and a significant decrease in these two parameters was observed in treated menopausal women as compared with untreated women.

In the Finrisk hemostasis study, a randomized sample comprising Finnish women, (25 to 64 years old) was studied in relation to menopause and HRT, for coagulation factor VII, factor VII antigen, fibrinogen and plasminogen (Salomaa et al., 1995). Fibrinogen only was shown to be decreased in HRT users as compared with age-matched non-users. Factor VII was not significantly modified while factor VII antigen and plasminogen were significantly increased.

The osteoporotic fractures study (a cohort study) performed in the United States enrolled women 65 to 82 years old, living in communities. It was

essentially aimed at evaluating the fracture risk factors in aging women (Meilhan et al., 1996). Out of a total of 2 401 subjects, 273 were randomly chosen (139 HRT users and 138 age-matched non-users), and it was observed that fibrinogen and PAI-1 were significantly lower in treated subjects than in untreated subjects.

Interventional studies

In this approach, controlled and randomized trials are undertaken to appreciate the distinct effects of HRT. Table 10.III describes the five studies which are analyzed below.

Among these studies, four considered fibrinogen, which is a potent predictor of coronary disease in men and women (PEPI, 1995 ; Conard et al., 1995 ; Scarabin et al., 1997 ; Writing Group for the estradiol clotting factors study, 1996). The PEPI trial, which is the largest as it included 875 subjects, indicated that fibrinogen was significantly decreased in HRT-treated groups (combined or cyclic treatments) as compared with placebo (PEPI, 1995). Nevertheless the size of this fall was rather weak. These results have been confirmed by an Italian study (Estradiol clotting factors study group), showing that fibrinogen is lowered in women receiving continuous transdermal estrogen treatment combined with a sequential progestogen (medroxyprogesterone acetate) treatment (Writing Group for the estradiol clotting factors study, 1996). Two other trials including smaller groups did not confirm these data (Conard et al., 1995 ; Scarabin et al., 1997).

As far as factor VII is concerned, a significant decrease in HRT-treated women was observed only in an Italian trial. In this study a continuous transdermal estrogen combined with a sequential progestogen was compared with a placebo (Writing Group for the estradiol clotting factors study, 1996). This observation was not confirmed by Scarabin et al. (1997).

Antithrombin III and protein C are potent coagulation inhibitors. Caine et al. (1992) used two dosages of conjugated equine estrogens (1.25 mg and 0.625 mg) and found that a significant dose-dependent decrease in antithrombin III could be observed as well as a significant increase in protein C only in women receiving the high dose. In the Italian study, antithrombin III was shown to be decreased and protein C unchanged in women treated with continuous estrogen and sequential progestogen (Writing Group for the estradiol clotting factors study, 1996). Scarabin et al report that, following oral treament, antithrombin III was decreased while transdermal treatment did not modify this parameter (Scarabin et al., 1997). Finally no significant modifications in antithrombin III or protein C levels were reported by Conard et al. (1995).

Table 10.III : Characteristics and results of randomized controlled trials

Authors	Country	Sample size	Age	Follow-up (months)	Treatment (dose per day)	Results
Caine et al. (1992)	USA	29	43-69	3	1. CE 0.625 mg 2. CE 1.25 mg 3. placebo	F1+2 ↗ dose dependent Fp A ↗ HRT /placebo AT III, Prot S ↓dose dependent Prot C ↗ group 2/placebo
PEPI (1995)	USA	875	45-64	36	1. placebo 2. CE 0.625 mg 3. CE 0.625 mg + MPA 10 mg cyclic[2] 4. CE 0.625 mg + MPA 2.5 mg 5. CE 0.625 mg + MP 200 mg cyclic[2]	Only fibrinogen ↗ in placebo group / any active treatment No differences among any treatment
Conard et al. (1995)	France	47	52[1]	3	1. placebo 2. E2 1mg (25 days) + NA 2,5 mg cyclic[2] 3. E2 1.5mg (25 days) + NA 3.75 mg cyclic[2]	Plasminogen ↗ in treatment group/placebo No change AT III, Fibrinogen, F 1+2, Prot S, Prot C
Estradiol Clotting Factors Study Group (1996)	Italie	255	52[1]	6	1. TTS E2 50 mg (21 days)+ MPA 10 mg cyclic 2. TTS E2 50 mg + MPA 10 mg cyclic 3. placebo	Fibrinogen, FVII, AT III, Prot S, : ↓in group 2 / placebo No change FVIIIc, PAI-1 act, prot C. Same variations in group 1/placebo but not significant
Scarabin et al. (1997)	France	45	45-64	6	1. E2 valerate 2mg (25 days)+MP 200 mg cyclic 2. Gel E2 2.5 mg (25 days) + MP 200 mg cyclic 3. no hormonal treatment	F1+2 , GFC ↗ in group 1/3 AT III, t-PA ag, PAI-1 act ↓in group 1/3 F1+2 ↗ in group 1/ 2 Fibrinogen, FVII, vWF, Prot C, D-Dimer and plasminogen : no differences between the three groups.

[1] : mean ; [2] : 10 to 14 days / months

Markers of coagulation activation have been studied in two trials. Caine et al. (1992) observed that these markers (fragments 1+2) were significantly increased, this modification being dose-dependent. Scarabin et al. (1997) reported a similar effect when the treatment was administered orally.

Two trials have considered variables of the fibrinolytic system. No significant modifications of PAI-1 activity were observed in the Italian trial. In contrast, in the study reported by Scarabin et al. significant decreases in PAI-1 activity and in tPA antigen were found, but, once again, only in the oral treated group (Scarabin et al. 1997 ; Writing Group for the estradiol clotting factors study, 1996). Moreover, a significant increase in global fibrinolytic capacity was observed in this same group, while transdermal treatment did not modify these parameters (Scarabin et al., 1997).

Critical analysis

Results of observational studies suggest that an increase in fibrinolytic potential and a decrease in fibrinogen could be associated with HRT. Nevertheless, it is difficult to know what combination HRT was administered in terms of estrogens and progestogens.

In addition, observational studies are subject to biases, meaning that they cannot ascertain a cause-effect relation. Only randomized controlled trials can provide a scientific evaluation of treatment. So far, such trials are rare because they are difficult to undertake. The studies previously reported involved small samples and short periods (6 months). The PEPI trial is the only one to include a reasonable number of subjects (875) for three years, but fibrinogen was the sole coagulation parameter studied.

In the five case-control trials published, various HRT were used. Globally, oral estrogen treatments, alone or combined with progestogens, did not have a detrimental effect on fibrinogen and could even be beneficial.

Two studies considered markers of coagulation activation. Estrogen treatments administered *per os* are related to a significant dose-dependent increase in these markers.

As far as natural estrogens are concerned, the influence of their route of administration was studied in only one publication. It was shown that the oral route was related to an activation of the coagulation system and to a parallel increase in fibrinolytic potential, while the transdermal route did not modify hemostasis in the short term.

None of these randomized studies gives any information on the influence of the different progestogens used in France.

To conclude, results of observational studies suggest that an increase in fibrinolytic potential and a decrease in fibrinogen could be associated with HRT

but observational studies are subject to biases, meaning that they cannot ascertain a cause-effect relation. In the case-control trials published, globally, oral estrogen treatments, alone or combined with progestogens, did not have a detrimental effect on fibrinogen and could even be beneficial. When the markers of coagulation are tested, it appears that oral treatment is related with an activation of these markers. Long term randomized trials will be necessary for a better knowledge of the influence of the various available HRTs on hemostasis.

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