9

Hemostasis in postmenopausal women

Currently, coagulation and fibrinolysis factors represent key points in the cardiovascular risk (Scarabin, 1996). To identify the influence of menopause on hemostasis parameters, an analysis of the available literature is presented here (table 9.I). Ten reports are directly devoted to this aspect. In most cases, they consist of large prospective studies analysing the cardiovascular risk. Only one study affords longitudinal information, which is the most convincing. This lack of data can be explained by the multiplicity and weak clinical relevance of the tests currently available to detect biological hypercoagulability. It can be also explained by the great difficulty of measuring the parameters of coagulation and fibrinolysis at a large population scale.

Longitudinal study

This British study, the Northwick Park Heart Study, performed by Meade, represents the first analysis of the relationships between hemostasis parameters and menopause (Meade et al., 1983) and the only study comprising a longitudinal analysis of data (Meade et al., 1990). The first results concerned 833 women (18 to 69 years old), belonging to different professional groups and recruited in the seventies, within a six-year period. A small number of these women (362) were followed biologically for six years, allowing a longitudinal analysis of coagulation factor VII, antithrombin III and fibrinogen. Significant increases in factor VII (14.9 %, $p < 0.0001$), antithrombin III (5.1 %, $p < 0.005$) and fibrinogen (0.41g/l, $p < 0.0001$) were shown to be associated with natural menopause. The same trends were observed in the case of artificial menopause, but the results could not be statistically significant because of the small number of women (only 28). All these results have been age-adjusted. Transversal results, published in 1983, were similar for the most part, showing that menopause onset is associated with a significant increase in coagulation factor VII and in fibrinogen. In addition, they demonstrated that menopause does not correlate with modifications in coagulation factors V and VIII.

Table 9.I : Menopausal status and hemostasis : characteristics of the studies

Authors	Study	Country	Design	Sample size	Age	Population	Recruitment Period
Meade et al. (1983)	Northwick Park	U.K.	Cross-sectional	833	18-69	Occupational groups	1972-1978
Meade et al. (1990)	Heart		Longitudinal	362	25-69		
Balleisen et al. (1985)	PROCAM	Germany	Cross sectional	1 306	17-69	Industrial Companies	1975
Scarabin et al. (1990a)	Paris	France	Cross sectional	259	45-54	Health Check-up center	1989
Folsom et al. (1991, 1994)	ARIC	USA	Cross sectional	6 737	45-64	Communities	1986-1989
Shahar et al. (1996)			Nested case-control	288			
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
Brunner et al. (1993)	Whiteall II	U.K.	Cross sectional	1 190	45-55	Civil Servant	1985-1988
Gebara et al. (1995)	Framingham	USA	Cross sectional	749		Framingham	1991-1992
Salomaa et al. (1995)	Finrisk Haemostasis	Finland	Cross sectional	851	45-64	Random sample	1992
Scarabin (1996)	Thrombocheck	France	Cross sectional	235	25-64	Health Check-up center	1995

Cross sectional studies

The German cohort study, the Procam study published in 1985, considered 1 306 women (17 to 69 years old) working in factories (Balleisen et al., 1985). Coagulating factors VII and VIII and fibrinogen were followed. The two first parameters were shown to increase at menopause, while, after age adjustment, no significant modifications in fibrinogen were observed.

Two French transversal studies, the Paris and Thrombocheck studies, have been published. In a 1990 report, 259 women, (45 to 54 years old) recruited in a check-up center, were included. After age adjustment, it was observed that menopause, especially when artificial, was associated with significant increases in coagulating factor VII, coagulation antigen VII and in the coagulating factor VII versus antigen VII ratio, which is a marker of factor VII activation. Fibrinogen levels were not significantly modified.

In a report published in 1996 (Scarabin et al.), 235 women (25 to 64 years old) were enrolled in the same center, to study the influence of their menopausal status on coagulation factor VII. Both this factor and antigen VII increased significantly after age adjustment. Moreover, at the onset of menopause, a significant rise in activated factor VII was observed, when its activation was directly evaluated using a coagulation-based method.

The American Aric study is the largest so far published (Conlan et al., 1994 ; Folsom et al., 1991) : 6 737 women (45 to 64 years old) were recruited in different communities during the eighties. 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, has been published. The case-control study concerned 142 women presenting a thickening of their carotid and 146 normal controls (Shahar et al., 1996). In both reports menopause was associated with significant increases in coagulation factor VII, fibrinogen and C protein. In contrast antithrombin III, PAI-1 antigen, tPA antigen and D-Dimers were not modified. In the two studies results were age-adjusted.

In the Healthy Women cohort study, performed in the late eighties in the United States, 207 women (49 to 56 years old) were recruited using car insurance company listings (Meilhan et al., 1992). In contrast with factor VII and plasminogen, which remained constant, fibrinogen and antithrombin III significantly increased in relation to menopause, after age adjustment.

The large Scottish Heart Health cohort study considered 4 837 women (25 to 69 years old) recruited by general practitioners during 1988 (Lee et al., 1993). Only one hemostasis parameter, fibrinogen, was evaluated and increased significantly in postmenopausal women as compared with their premenopausal age-matched counterparts.

The Whitehall II study is a cohort study performed in Great Britain : 1 190 female civil servants, 45 to 55 years old, were enrolled. Significant

increases in fibrinogen and coagulation factor VII were reported with menopause.

A transversal analysis was 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 women as compared with untreated women.

In the Finrisk hemostasis study, a randomized sample comprising Finnish women, 25 to 64 years old was studied for coagulation factor VII, fibrinogen, factor VII antigen and plasminogen (Salomaa et al., 1995). Menopause was associated with a significant increase in factor VII and fibrinogen.

Critical analysis

It is important to discuss several methodological points. Most of the studies are transversal, they present mainly initial data, collected in large cohort studies specially designed to analyse the cardiovascular risk and using various clinical or biological markers. Their meaning is difficult to appreciate in terms of follow-up. Only longitudinal studies could answer the question. Only one such report is available so far, in which three parameters of hemostasis were evaluated (Meade et al., 1990). Thus, these results need to be confirmed.

A second important point is the definition of menopause. In most cases it is defined by clinical observations in absence of biological assays to ascertain the diagnosis. This can be confusing when women have undergone hysterectomy without bilateral oophorectomy. It is thus difficult to determine precisely their age at menopause. This lack of detail can be responsible for false classifications, hampering the statistical analysis and thus leading to false negative results.

As far as hemostasis variables are concerned, unfortunately, there are no analyses taking into account, as a whole, the main markers of coagulation and fibrinolysis. Only a small number of parameters have been considered in each of the ten studies reviewed here. Moreover these parameters have not always been proven to be linked to the cardiovascular risk. An increase in fibrinogen and most problably in PAI-1 and coagulating factor VII should be associated with this risk. It is also essential to discriminate between the markers of arterial risk (fibrinogen, factor VII, PAI-1) and those of the venous risk (antithrombin III, protein C or protein S). In addition, there are no data on the markers of coagulation activation (fragments 1+2).

Finally, it is difficult in some studies to appreciate the influence of age versus the influence of menopause. This uncertainty could be overcame only if limited age brackets (such as 45-55 years) were considered.

Table 9.II : Menopausal status and hemostasis : main results

Authors	Study	F VIIc	Fibrinogen	AT III	PAI-1	Others factors
Meade et al. (1983, 1990)	Northwick Park Heart	↗ ↗	↗ ↗	→ ↗		Vc, VIIIc →
Balleisen et al. (1985)	PROCAM	↗	→			VIIIc ↗
Scarabin et al. (1990b)	Paris	↗	→		act ↗	VIIag ↗ VIIc/VIIag ↗
Folsom et al. (1991) Shahar et al. (1996)	ARIC	↗	↗	→	ag →	Prot C ↗ tPA ag → D.dimers →
Meilhan et al. (1992)	Healthy Women	→	↗	↗		Plasminogen →
Lee et al. (1993)	Scottish Heart Health		↗			
Brunner et al. (1993)	Whiteall II	↗	↗			
Gebara et al. (1995)	Framingham				ag ↗	tPA ag ↗
Salomaa et al. (1995)	Finrisk Haemostasis	↗	↗			Plasminogen → VII ag →
Scarabin et al. (1996)	Thrombocheck	↗				F VIIag ↗ F VIIa ↗

Results are age-adjusted

To conclude, in most analysed studies, significant increases in coagulation factor VII, fibrinogen and PAI-1 are observed (table 9.II). These markers could reflect an imbalance between coagulation and fibrinolysis and thus indicate a procoagulating influence of menopause.

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10

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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