Changes in Blood Coagulation Markers Associated with Uterine Artery Embolization for Leiomyomata

Boris Nikolic, MD, Craig M. Kessler, MD, Helena M. Jacobs, BS, Suhny Abbara, MD, Albert M. Ammann, MD, Ziv Neeman, MD, Michael F. McCullough, MD, Hilario Martinez, MD, and James B. Spies, MD

PURPOSE: To determine whether a transient hypercoagulable state is induced by the uterine artery embolization (UAE) procedure.

MATERIALS AND METHODS: Serial periprocedure blood samples were obtained from 27 patients undergoing the UAE procedure. Five blood samples were obtained from each patient at set time intervals: before the procedure (for baseline determination), immediately before and after embolization of the uterine arteries, 90 minutes after conclusion of the procedure, and between 18 and 24 hours later. Each blood sample was analyzed for the peripheral levels of the following parameters: thrombin-antithrombin complex (TAT), prothrombin fragment 1.2 (F1.2), platelet factor 4 (PF4), D-dimer, and plasmin–α_2-antiplasmin complex (PAP). For each parameter, the baseline values were statistically compared with the pre- and postembolization values for each individual to detect change over time. Overall and global occasion effects for continuous variables were assessed with the Friedman statistic and individual comparisons between occasions with the Wilcoxon signed-rank test.

RESULTS: No evidence was found for a difference in coagulability among the five occasions for D-dimer ($P = .7645$) or PF4 ($P = .09$). All three of the remaining measures were found to have statistically significant differences ($P < .0001$ for F1.2, $P = .0026$ for PAP, and $P = .0006$ for TAT). No evidence was found for a difference between preprocedure and preembolization levels for these three latter parameters ($P = .595$ for F1.2, $P = .128$ for PAP, $P = .9705$ for TAT). Hypercoagulability potential as measured by prothrombinase and F1.2 generation increased between preembolization samples and each of the successive postprocedure samples ($P < .0001$, $P < .0001$, $P = .0082$), whereas PAP increased at 90 minutes ($P = .0023$) and TAT increased immediately after embolization ($P < .0001$). No clinically apparent thrombotic complications occurred among any of the patients studied.

CONCLUSIONS: Surrogate markers of hypercoagulability increase as a result of UAE, suggesting that a prothrombotic state may result after the procedure.

J Vasc Interv Radiol 2003; 14:1147–1153

Abbreviations: F1.2 = prothrombin fragment 1.2, PAP = plasmin–α_2-antiplasmin complex, PF4 = platelet factor 4, TAT = thrombin-antithrombin complex, UAE = uterine artery embolization

UTERINE artery embolization (UAE) has been reported to be a safe and effective alternative to surgery for the treatment for leiomyomata (1). In a recent summary of complications after UAE, we reported three patients with thromboembolic disease, including pulmonary embolus, deep vein thrombosis, and arterial thrombosis (2). Although the three patients in our care were all on exogenous estrogen hormones (known to increase the risk of thromboembolic events), we were concerned that this procedure by itself might temporarily create a hypercoagulable state that may predispose to thromboembolic disease.

Although the exact trigger underlying the thromboembolic event is unknown, its occurrence in association with UAE suggests a temporary imbalance in the prothrombotic, anticoagulant, and fibrinolytic equilibrium (hemostasis) resulting in a transient hypercoagulable state. The embolization procedure causes sudden tissue injury, which in other contexts (surgery, major injury), is known to temporarily activate the extrinsic coagulation system by generating factor VIIa/tissue factor complexes (3–9). Embolic particle injection may additionally trigger platelet activation. A transient hypercoagulable state is characterized by temporary activation of blood coagulation followed by a limited reactive phase of secondary hyperfibrinolysis. Based on this coagulation acti-

From the Departments of Radiology (B.N., S.A., A.M.A., Z.N., M.F.M., H.M., J.B.S.) and Hematology-Oncology (C.M.K., H.M.J.), Georgetown University Hospital, Washington, DC. Manuscript received January 16, 2003; revision requested February 23; final revision received May 12; accepted May 15. **Address correspondence to** B.N., Department of Diagnostic Radiology, Emory University, 1365 Clifton Road, NE, Atlanta, GA, 30322; E-mail: bnikoli@emory.edu

This study was supported by a grant from the Cardiovascular and Interventional Radiology Research and Education Fund.

J.B.S. is a consultant for Boston Scientific and Biosphere.

© SIR, 2003

DOI: 10.1097/01.RVI.0000086540.44800.FE

vation, transient hypercoagulability may occur and predispose the patient to the development of thrombosis.

Although the ultimate clinical manifestation of a transient hypercoagulable state is the occurrence of a thromboembolic event, the biochemical manifestations that precede and follow the events include significant but temporary changes of some procoagulant and fibrinolytic markers. We therefore obtained pre-, intra-, and postprocedure serial longitudinal measurements of coagulation markers in patients undergoing UAE to detect blood level changes of key coagulation and fibrinolytic parameters. By measuring these parameters in the periprocedure period, we hope to determine whether a transient hypercoagulable state is induced by the UAE procedure.

METHODS

Patient Population

Serial blood samples were obtained from 27 patients who underwent UAE procedures for the treatment of uterine leiomyomata between March and July 2001. The age range of the patient population was 33–56 years; the mean age was 47.4 years. The study was performed following a protocol approved by the Institutional Review Board, and informed consent was obtained from each patient. All participants were of childbearing age with symptomatic uterine leiomyomata and had completed a questionnaire to ascertain individual potential risk factors for the development of thromboembolic disease. These included details on estrogen-based contraceptive use (current or discontinued within the past 2 months), cigarette smoking, family history of a hypercoagulable disorder, or airplane travel within the past 24 hours. Those with a priori risk factors for a thromboembolic event were two patients who smoked cigarettes, three patients who used oral contraceptives, and four patients who had discontinued contraceptive use within the past 2 months. None of the patients had multiple risk factors, and there was no reported history of airplane travel.

Procedure

On the day of the procedure, a 4-F mid-line length intravenous catheter was inserted in each patient shortly before the beginning of the UAE procedure. The line was placed with a standard technique in each patient and was solely used to obtain the sequential blood samples. One dose of prophylactic antibiotics (gentamicin and clindamycin) was administered before the procedure began. Standard interventional radiology techniques were used for the embolization procedure. We used bilateral femoral access and selectively catheterized each uterine artery with a crossover technique with a 4- or 5-F catheter. On occasion, a microcatheter was also used. Embolization of both uterine arteries was performed with Tris-acryl gelatin microspheres (Embospheres; Biosphere Medical, Rockland, MA) until uterine arterial flow had substantially slowed but slight antegrade flow was still present in the uterine arteries. After the UAE procedure, the patients were admitted to a nursing unit, observed overnight, and discharged the day after the procedure (ie, 18–24 hours post-UAE). The mid-line catheter was removed after the fifth blood sample had been obtained. Each patient was evaluated for clinical evidence (symptoms and physical findings) of thromboembolic complications at the time of discharge from the hospital, by telephone 24 hours after discharge, at an office visit 1 week after discharge, and at 3 months after treatment.

Sample Collection

Venous blood samples for analysis of the study laboratory parameters were collected from the mid-line in each patient after 5–10 mL had been discarded. Each sample was analyzed quantitatively for thrombin-antithrombin complex (TAT), Prothrombin fragment 1 and 2 (F1.2), platelet factor 4 (PF4), and plasmin–α_2-antiplasmin complex (PAP) levels as well as qualitatively for the presence of D-dimer. The ranges of normal for each parameter in plasma in our laboratory are as follows: D-dimer is normal when negative, F1.2 = 0.6–1.1 nmol/L, TAT = 1–24.3 μg/L, PAP = 0–250 ng/mL, PF4 = 64–90 IU/mL.

All whole blood samples were collected in 3.2% sodium-citrate tubes (Becton Dickinson, Franklin Lakes, NJ) at a 9:1 blood-to-sodium citrate ratio. To prepare cell free plasma, the blood was centrifuged in an IEC Centra CL3R centrifuge (International Equipment, Needham Heights, MA) at 1,000*g* for 15 minutes. The plasma was separated into six aliquot tubes, 1.5 mL each, and frozen at −70°C until assayed.

Quantitative levels of TAT, F1.2, and PF4 were evaluated by an enzyme immunoassay (Enzygnost TAT micro ELISA, Dade Behring, Marburg, Germany; Enzygnost F1.2 micro, Dade Behring; Asserachrom PF4, Diagnostica Stago, Asnier-Sur-Seine, France). Quantitative PAP level determination was performed with an enzyme-linked sandwich immunoassay (Imuclone PAP ELISA kit, American Diagnostica, Greenwich, CT). D-dimer presence was determined by a latex agglutination test (Dimertest II latex kit, American Diagnostica). All laboratory tests were performed in the coagulation research laboratory in the Department of Hematology-Oncology at our hospital.

The first sample was drawn immediately after the mid-line insertion to determine the baseline levels of each coagulation factor in each patient. After bilateral uterine artery catheterization (but before the embolization began), the second blood sample was drawn. Immediately after the embolization of both uterine arteries, the third blood sample was obtained. The fourth blood sample was drawn 90 minutes after the conclusion of the embolization of both uterine arteries, and the fifth blood sample was obtained 18–24 hours after the UAE and shortly before discharge.

Data Analysis

Power calculations had preliminarily been performed to ensure a high probability of detecting clinically important increases from baseline in these measures (within the range of a 25%–50% increase). Because these clinically important differences have been identified in terms of the percentage of increase, all power calculations had been performed on the percentage of change scale for a two-sided Bonferroni *t* test with four comparisons and with a family-wise type I error rate of $\alpha = 0.05$.

A review of the published data suggested that, on average, most of the coagulation markers will change val-

ues by 100% or more during other surgical procedures (3–9). Exact threshold numbers for these parameters that would define clinical significance are unknown. However, these surrogate markers have been validated to accurately reflect a disruption of hemostasis as well as to prove the occurrence of biochemical changes in the perioperative/periprocedure setting, thus explaining thromboembolic events on biochemical and molecular grounds (3–9). It was the objective of this study to prove the presence of a transient hypercoagulable state caused by UAE based on these parameters that would explain the occurrence of thromboembolic events associated with the procedure.

To be conservative, for study size calculations, we assumed that a 25%–50% increase in any of these measurements from baseline might be of clinical significance.

All data were collected and entered into a Microsoft Excel data base. Several individual samples had to be excluded from analysis because of blood sample clotting, hemolysis, or delayed submission for further processing. These samples were excluded to avoid any potential inaccuracies in their evaluations. In addition, the PAP results of patient 20 were excluded from analysis because the exceptionally high results led us to believe that a processing error had occurred.

Statistical Analysis

On study completion, the data were transferred to a SAS (version 8.0, SAS Institute, Cary, NC) data set for statistical analysis. The measurements were recorded for each of five different clotting factors on five occasions: baseline, immediately before embolization, immediately after embolization, 90 minutes after embolization, and 24 hours after the procedure.

Four preplanned comparisons were evaluated to address the research hypotheses. Preembolization minus preprocedure scores estimated the immediate effect of artery catheterization, whereas the difference between preembolization scores and the scores from each of the three postembolization occasions provided estimates of the effects due to embolization, assuming there was no lingering catheterization effect. The analyses were conducted in three stages to control the overall type I error rate at $\alpha = 0.05$. First, an overall occasion effect across all continuous measures was performed that tested the null hypothesis of no difference among the different time points (or occasions). When the null hypothesis had to be rejected, then a global occasion effect was tested for each measure separately, with a Bonferroni adjustment for making four comparisons. The preplanned contrasts were evaluated for statistical significance only within those measures that had been identified as having a global occasion effect. A Bonferroni adjustment was again made to account for the four comparisons.

Change in continuous measures was evaluated with nonparametric techniques based on medians. This reduced the influence of large outliers and avoided the assumption of normally distributed data. Overall and global occasion effects were assessed for the continuous measures with the Friedman statistic. Individual contrasts between occasions were assessed with the Wilcoxon signed-rank test. Simultaneous 95% confidence intervals were constructed for the contrasts within each measure. The D-dimer measure was evaluated to detect a change in the proportion of positive scores among the five occasions for the same group of subjects. The global occasion effect was evaluated with the Cochran Q statistic. Simultaneous 95% confidence intervals were presented for the difference in proportions from dependent samples.

RESULTS

A minority of our patients used oral contraceptives at the time of the UAE procedure (three patients) or had terminated use within 2 months preceding UAE (four patients). Among these patients, variable changes in parameters were found. Some dramatic increases were noted in some patients, whereas minimal changes were seen in others. This study was not large enough to statistically assess the potential additional influence of preexisting procoagulatory factors such as exogenous hormones and generalized conclusions concerning this or other risk factors cannot be determined without additional study. The values for the coagulation parameters were distributed in a nongaussian fashion due to substantial outliers, and nonparametric tests based on the median, therefore, had to be applied (**Table 1**).

F1.2, PAP, and TAT measures were seen to have a global occasion effect (**Table 2**). There was insufficient evidence to conclude that the median score changed among the five occasions for PF4 (**Table 2**) and D-dimer. F1.2 was seen to increase immediately after embolization, and the increase remained statistically significant at the two subsequent occasions. PAP elevation was statistically significant 90 minutes after embolization (**Table 2**). However, no statistically significant increase was observed immediately after embolization or after 18–24 hours (**Table 2**). TAT scores were higher immediately postembolization. An increase was also observed after 90 minutes and 18–24 hours; however, the large variability in scores at these later occasions prevented these increases from reaching statistical significance (**Table 2**).

We noted a maximal increase in mean TAT levels of approximately threefold (94.2/28.5 μg/L, comparison of measurement 5 with measurement 1) and 2.2-fold for mean F1.2 levels (4.1/1.9 nmol/L, comparison of measurements 5 and 1). The maximal mean increase for PAP was by a factor of 1.5 (448.2/302.2 ng/mL, comparison of measurements 4 and 1). The corresponding increases for the medians were 1.8 for TAT, 1.6 for F1.2, and 1.2 for PAP.

TAT increased between measurements 1 and 5 in approximately 71% (17 of 24 patients; three patients could not be evaluated for this comparison because of missing data), and TAT decreased in approximately 29% (seven of 24 patients) for the same comparison, although in four of these seven patients, TAT did actually increase, at least minimally, at some point postembolization compared with the baseline TAT measurement 1. The single most substantial increase between TAT measurements 1 and 5 in an individual patient was by a factor of 149 in patient 15 (618.1/4.1 μg/L), the single most substantial decrease for the same comparison by a factor of approximately 7 in patient 14 (102.1/14.8 μg/L).

There was an increase of F1.2 in 79% (19 of 24 patients; three patients

Table 1
Descriptive Statistics of 27 Patients Undergoing UAE

Variable	Numbers Missing	Frequency (%)*	Median (Mean)	Standard Deviation	Minimum	Maximum
D-dimer						
Preprocedure	0	2 (7.4)				
Preembolization	1	2 (7.7)				
Postembolization†	0	1 (3.7)				
90 min	2	3 (12.0)				
18–24 h	3	3 (12.5)				
F1.2						
Preprocedure	1		1.3 (1.9)	1.5	0.8	6.9
Preembolization	1		1.3 (1.7)	0.9	0.8	4.2
Postembolization†	0		2.1 (2.2)	1.0	1.1	5.3
90 min	2		2.1 (4.0)	5.6	1.1	26.5
18–24 h	3		2.1 (4.1)	5.7	0.5	25.1
PF4						
Preprocedure	1		92.0 (91.2)	9.4	69.4	109.1
Preembolization	1		88.1 (90.3)	11.2	68.1	121.8
Postembolization†	0		90.9 (87.1)	17.0	28.4	104.6
90 min	2		81.9 (78.3)	22.2	19.0	114.3
18–24 h	3		85.4 (84.4)	15.2	41.8	106.2
PAP						
Preprocedure	2		203.0 (302.2)	385.9	26	1,606
Preembolization	2		164.0 (312.2)	619.2	10	3,220
Postembolization†	2		166.0 (269.1)	312.4	31	1,623
90 min	4		236.0 (448.2)	551.9	53	2,341
18–24 h	5		248.0 (285.6)	220.8	32	821
TAT						
Preprocedure	1		17.2 (28.5)	36.5	2.1	128.1
Preembolization	1		16.8 (23.4)	21.9	3.3	92.8
Postembolization†	0		28.5 (34.8)	21.9	7.1	95.9
90 min	2		27.8 (57.4)	116.9	3.8	597.4
18–24 h	3		31.1 (94.2)	161.5	3.2	618.1

* Frequency refers to frequency of positive D-dimer test.
† Samples obtained immediately after embolization completion.

could not be evaluated because of missing data) when comparing measurements 1 and 5 and a decrease in 21% (five of 24 patients) for this comparison. The maximal increase for F1.2 between measurements 1 and 5 was by a factor of approximately 19 (patient 15, 25.1/1.297 nmol/L), the maximal decrease for the same comparison was by a factor of approximately 3 in patient 14 (3.802/1.259 nmol/L).

For PAP, an increase in measurement 4 compared with measurement 1 could be observed in 68% (17 of 25 patients, two patients could not be evaluated for this comparison due to missing data), and a decrease for the corresponding comparison in 28% (seven of 25 patients). In two of these seven patients, there was still an increase in the PAP number postembolization that occurred at measurements 5 and 3, respectively (patients 18 and 27). The maximal individual increase of PAP for measurements 1 and 4 comparisons was by a factor of 23 (patient 8, 2,341/102 ng/mL), the maximal individual decrease for the same comparison was sixfold (patient 17, 332/53 ng/mL).

To the best of our knowledge, none of the patients participating in this study sustained a thromboembolic event, either arterial or venous. Clinical studies to detect venous thromboembolism were not performed in any patient.

DISCUSSION

Women undergoing UAE procedures are usually young to middle-aged, healthy individuals with no significant medical history or complaints short of those caused by their leiomyomata. UAE is a minimally invasive procedure that usually requires only 6 hours of bed rest and an overnight hospital stay. The patient's brief immobilization alone can therefore not explain the reported thromboembolic events associated with UAE, and the reason for their occurrence has not been known. We theorize that hypercoagulability may be precipitated by embolization-induced tissue injury with subsequent generation of thrombin.

Surrogate markers indicating a prothrombotic tendency have been measured pre-, intra-, and postoperatively for other surgical procedures (3–12). The results of these measurements have been used for two purposes: to stratify preoperatively patients regarding their prospective risk for the development of a postoperative thrombotic event (12) and to demonstrate the transient effect of some types of surgeries on the coagulation system toward a state of temporary hypercoagulability (3–9). We chose to evaluate

Table 2
Periprocedure Analysis of Coagulation Parameters

Variable Time Comparison	Effective Sample Size of Comparison	Median of Differences	Joint 95% Confidence Intervals for Median Difference*	*P* Value†
Overall global time effect	504			<.0001 (.0004)
F1.2				
Global time effect	128			<.0001 (.0004)
Preproc.‡ vs. Preembo.§	26	−0.02	(−0.67, 0.28)	.595 (2.38)
Preembo.§ vs. Postembo.‖	26	0.70	(0.30, 0.97)	<.0001 (.0004)
Preembo.§ vs. 90 min	24	0.97	(0.34, 1.39)	<.0001 (.0004)
Preembo.§ vs. 18–24 h	23	0.86	(−0.11, 1.84)	.0082 (.0328)
PF4				
Global time effect	128			.09 (.36)
PAP				
Global time effect	120			.0026 (.0104)
Preproc.‡ vs. Preembo.§	25	−41	(−99.0, 46.0)	.1289 (.5156)
Preembo.§ vs. Postembo.‖	25	21	(−29.0, 74.0)	.2848 (1.1392)
Preembo.§ vs. 90 min	23	94	(44.0, 192.0)	.0023 (.0092)
Preembo.§ vs. 18–24 h	22	73.5	(−27.0, 131.0)	.1021 (.4084)
TAT				
Global time effect	128			.0006 (.0024)
Preproc.‡ vs. Preembo.§	26	2.26	(−15.57, 9.37)	.9705 (3.882)
Preembo.§ vs. Postembo.‖	26	10.00	(3.17, 18.26)	<.0001 (.0004)
Preembo.§ vs. 90 min	24	7.88	(−7.37, 30.07)	.2050 (.82)
Preembo.§ vs. 18–24 h	23	13.72	(−13.06, 73.83)	.0227 (.0908)

* Confidence intervals are distribution free estimates and provide joint coverage of at least 95% within a given coagulability measure.
† *P* values for global time effects were derived in the context of the Friedman test based on ranks. *P* values for specific time period comparisons were derived from the Wilcoxon signed-rank test. *P* values are unadjusted. Adjusted *P* values are computed by multiplication with factor of 4 and are given in parentheses.
‡ Preproc. refers to baseline number obtained before UAE procedure.
§ Preembo. procedure number refers to number obtained immediately before embolization.
‖ Postembo. refers to number obtained immediately after embolization.
Note.—Preproc. = preprocedure; Preembo. = preembolization; Postembo. = postembolization.

the procoagulant markers TAT, as the product of inactivation of thrombin by antithrombin; F1.2, as a reflection of prothrombin conversion to thrombin by prothrombinase; and PF4, as a platelet-specific α granule constituent released with platelet activation. Formation of the fibrin clot is usually followed by a secondary hyperfibrinolytic reaction, which manifests itself biochemically by increased levels of D-dimer and PAP levels. D-dimer is the result of fibrinolysis of crosslinked fibrin; PAP is a complex of plasmin with its specific protein α_2-antiplasmin.

We based the selection of our measurement points and intervals on those reported from prior studies examining these parameters during various surgeries. To prove our hypothesis that UAE is associated with a hypercoagulable state caused by the embolization itself, parameter measurement in the immediate periprocedure time frame as well as immediately pre- and postembolization seemed most reasonable. However, timing of the measurement points and intervals varies slightly in the available literature, and ideal measurement timing may depend on the type of procedure or surgery performed. Most thromboembolic events associated with UAE have been described during or 24 hours post-procedure. However, the occurrence of more delayed thromboembolic events associated with UAE may be possible. As more data may become available, patient risk assessment, risk stratification, and more accurate measurement timing than in the current early investigational stage of this complication will likely be feasible.

The use of these surrogate markers to detect transient states of hypercoagulability during surgery has been validated in numerous clinical scenarios, including cardiovascular surgery (5,6), partial gastric or hepatic resection (7), neurosurgical procedures (8), and lower extremity arthroplasties (10).

Boisclair et al (5) measured a significant progressive increase in the mean F1 and 2 levels of eight patients during open heart surgery. This research group attributes the transient hypercoagulable state to the surgical cutting of blood vessels. An increase in F1 and 2 of almost 12-fold was observed in this study between the preprocedure number and the intraprocedure peak value. Similar results from cardiac surgery have been obtained by Slaughter et al (6), who observed an increase in TAT and F1 and 2 levels by factors of 77 and 9, respectively. However, the increase of these factors was aggravated by the administration of Protamin in this study. Kambayashi et al (7) reported significant intraoperative elevation of TAT in two groups of patients who either underwent partial gastric or hepatic resection. Increases were threefold for TAT and minimal for PAP for gastric, and 7.5-fold for

TAT and approximately 3.7-fold for PAP for hepatic surgery in this study. In neurosurgical procedures, Fujii et al (8) found TAT elevations by a factor of 4.5, PAP elevations by a factor of approximately 2.2, and a significant PF4 increase. Heesen et al (4) report a maximal TAT increase of 11.5-fold. The substantial difference in the magnitude of blood level changes of coagulation markers described in the literature likely relates to the type of surgery that was performed and perhaps the measurement intervals that were selected. In those patients who develop a deep venous thrombosis after undergoing hip and knee arthroplasty surgery, significantly increased postoperative blood levels of D-dimer have been detected (10). Patients with significantly lower PAP levels before abdominal surgery had a significantly increased incidence of a postoperative deep vein thrombosis when compared with those with higher PAP levels (11,12). The ability to incite a more active secondary hyperfibrinolytic response to the initial coagulation activation therefore seems to lower the risk of clot formation.

The incremental changes in our study are considerably lower than published results for major surgery. Our observed mean increases in TAT of approximately threefold and 2.2-fold for F1.2 with UAE certainly suggest a prothrombotic stimulus has been induced. Furthermore, the increased PAP of 1.5-fold indicates that an appropriate fibrinolytic response occurred. No significant rise of D-dimer levels was seen in our study. This is somewhat surprising but suggests that the downregulation of thrombin generation and inhibition of thrombin effects by antithrombin and other modulators not measured (eg, protein S and protein C) were very efficient for the relatively small prothrombotic effects of UAE. Platelet activation could not be measured at systemically significant levels, although it might be of significance locally at the uterine arterial occlusion sites.

In a small minority of our patients, a decrease of individual parameter measurements for hypercoagulability was noted during the study compared with baseline. For example, comparing measurements 1 and 5 for TAT and F1.2 and measurements 1 and 4 for PAP, the numbers actually increased substantially postembolization at least for one postembolization measurement when compared with the baseline value in four of seven patients for TAT (patients 1, 14, 23, and 27), in two of seven patients for PAP (patients 18 and 27), and in one patient for F1.2 (patient 1). We believe that the procoagulatory reaction and fibrinolytic response in these particular patients may have occurred more rapidly when compared with the majority of the patients in our study, and it seems indeed likely that the procoagulatory reaction and its fibrinolytic response do not occur on the same time scale in all patients. In effect, the parameter changes in these patients also do support our theory of the induction of a procoagulatory state from the procedure. This leaves three patients (patients 2, 6, and 22), five patients (patients 2, 3, 14, 17, and 22), and four patients (patients 2, 6, 14, and patient 22) for parameters TAT, PAP, and F1.2, respectively, for which subsequent numbers actually never increased above the baseline value. These patients had uniformly unusually high baseline numbers for both the procoagulatory and the fibrinolytic limb of the coagulation system, and the reason for these higher baseline levels is unknown. However, these patients still maintained hemostasis, albeit at a much higher level of biochemical activity when compared with the average patient. For unknown reasons, the numbers for these patients decreased for the second measurement but then also substantially increased postembolization, although not quite to the magnitude of their respective unusually high baseline levels.

No thrombotic events occurred in this current cohort compared with our prior anecdotal experience. However, none of the current participants used an estrogen medication, which could have lowered the effectiveness of protein S activity and exacerbated any prothrombotic tendencies of UAE. Although an association of increased levels of coagulation markers and postoperative thrombus formation has been shown, there is no defined rationale for their use in the clinical routine at the current time (13). At least as far as the preoperative use of coagulation markers is concerned, their association with a thrombotic event varies and is unpredictable for the individual patient. The same applies for UAE, where concurrent estrogen use may add to the morbidity of the procedure. The incidence of a thromboembolic event that may be associated with UAE is unknown. However, we estimate that it is much lower than those in the surgical studies. The parameter changes in our study were much less substantial than those seen during the reported surgical studies. Further, there have been very few reports of thrombotic events associated with UAE. Nevertheless, a causative relationship between UAE and a thrombotic event based on our data seems likely.

The thrombotic risk assessment may be compounded by additional individual risk factors (ie, oral contraceptive use, cigarette smoking, family history of thromboembolic disease, preexisting hypercoagulable state). The current study was too small to determine the impact of individual risk factors on the changes of the coagulation factors. In particular, the frequent use of oral contraceptives in this patient group is a concern, and further study of a potential additive effect of its use and the coagulation changes beyond those caused by the procedure itself seems warranted.

CONCLUSION

Our data provide evidence that the UAE procedure generally causes mild to moderate hypercoagulability when compared with the preembolization state, and clotting complications after UAE are unlikely to be coincidental. Based on the reported infrequency of clinical thromboembolic events after UAE and the much more dramatic procoagulable state associated with surgical procedures, the risk of thrombosis after UAE is likely to be low.

Additional study is necessary to determine the true incidence of thrombotic and thromboembolic events associated with UAE, to stratify patients with respect to their risk of development of such an event, and to assess the efficacy of short-term anticoagulation for those patients at greatest risk to prevent a potentially life-threatening thromboembolic complication. We believe that patients presumed to be at substantial risk of a thromboembolic event based on predisposing factors such as body habitus, oral contracep-

tive use, or personal or family history of thromboembolic disease may be treated with venous compression devices or even temporary anticoagulation. At this point, this decision should be left to the discretion of the individual physician until more specific recommendations based on results of future studies can be issued.

References

1. Goodwin SC, Bonilla SM, Sacks D, et al. Reporting standards for uterine artery embolization for the treatment of uterine leiomyomata. J Vasc Interv Radiol 2001; 12:1011–1020.
2. Spies JB, Spector A, Roth AR, Baker CM, Mauro L, Murphy-Skrynarz K. Complications after uterine artery embolization for leiomyomas. Obstet Gynecol 2002; 100:873–880.
3. Bohler K, Hinterhuber G, et al. Systemic activation of coagulation and fibrinolysis during varicose vein stripping. Dermatol Surg 1997; 23:46–50.
4. Heesen M, Kemkes-Matthes B, et al. Coagulation alterations in patients undergoing elective craniotomy. Surg Neurol 1997; 47:35–38.
5. Boisclair MD, Lane DA, et al. Mechanisms of thrombin generation during surgery and cardiopulmonary bypass. Blood 1993; 82:3350–3357.
6. Slaughter TF, LeBleu TH, Douglas JM, Leslie JB, Parker JK, Greenberg CS. Characterization of prothrombin activation during cardiac surgery by hemostatic molecular markers. Anesthesiology 1994; 80:520–526.
7. Kambayashi J, Sakon M, Yokota M, Shiba E, Kawasaki T, Mori T. Activation of coagulation and fibrinolysis during surgery, analyzed by molecular markers. Thromb Res 1990; 60:157–167.
8. Fujii Y, Tanaka R, Takeuchi S, Koike T, Minawaka T, Sasaki O. Serial changes in hemostasis after intracranial surgery. Neurosurgery 1994; 35:26–33.
9. Jorgensen LN, Lind B, et al. Thrombin-antithrombin III-complex & fibrin degradation products in plasma: surgery and postoperative thrombosis. Thromb Res 1990; 59:69–76.
10. Dunn ID, Hui AC, et al. Plasma D-dimer as a marker for postoperative deep venous thrombosis. A study after total hip or knee arthroplasty. Thromb Haemost 1994; 72:663–665.
11. Mellbring G, Dahlgren S. Prediction of deep vein thrombosis after extensive abdominal operations. Complex and fibrinogen concentration in plasma. Surg Gynecol Obstet 1985; 161:339–342.
12. Mellbring G, Dahlgren S, Wiman B, Sunnegardh O. Relationship between preoperative status of the fibrinolytic system and occurrence of deep vein thrombosis after major abdominal surgery. Thromb Res 1985; 39:157–163.
13. Lowe GDO. Prediction of postoperative venous thrombosis using hemostasis tests. Int J Clin Lab Res 1997; 27:153–157.