Ovarian vein thrombosis: Incidence of recurrent venous thromboembolism and survival

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Summary

For patients with ovarian vein thrombosis (OVT), neither the rate of recurrence nor the expected survival are well established. Clarification of these natural history data would aid in defining the optimal management. We studied all female patients with OVT seen at the Mayo Clinic between 1990 and 2006. Survival, recurrent venous thrombosis rates, and prothrombotic factors were compared to a randomly selected group of 114 female patients with lower extremity venous thrombosis (DVT). Patients with OVT (n=35; mean age 44.8 ± 17.9 years) were significantly more likely to be under hormonal stimulation (48%), have an underlying malignancy (34%), experienced recent pelvic infection (23%) or undergone recent surgery (20%), compared to DVT patients. During a mean follow-up period of 34.6 ± 44.3 months, three patients suffered three recurrent venous thrombi (event rate: three per 100 patient years of follow-up). This recurrence rate was comparable to patients with lower extremity DVT (2.2 per 100 patient years). Recurrent thrombosis involved the contralateral ovarian vein, left renal vein, and inferior vena cava. The five-year mortality rate for OVT patients was 43% compared to 20% for DVT patients (p=0.08). All OVT deaths were cancer related. Survival was greater in OVT patients without cancer compared to those with active cancer (p<0.0001). In conclusion, venous thromboembolism recurrence rates are low and comparable to lower extremity DVT. Therefore general treatment guidelines for lower extremity DVT may be applicable. Poor survival rates in OVT are principally governed by the presence of malignancy.

Keywords

Ovarian vein, venous thrombosis, hormones

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Introduction

Ovarian vein thrombosis (OVT) was originally described as a rare yet often dramatic complication of the postpartum state (1–4). This suppurative pelvic thrombophlebitis has been found to involve the right ovarian vein in up to 90% of cases presumably due to its length, tortuosity, multiple incompetent valves and antegrade flow (1, 5). Complications of OVT, defined principally in case reports, are rare and include: pulmonary embolism (5–9), thrombus extension (3, 8, 9) or ureteral obstruction (5, 8, 10). OVT has historically been diagnosed clinically during the post partum period in the face of fever unresponsive to antibiotics or at laparotomy (1, 5, 8). With the advancement of cross-sectional imaging, the understanding of the incidence and clinical spectrum of OVT has evolved. Though rare, OVT is now felt to be more common than previously believed. It often is found as an asymptomatic complication of pelvic malignancy or pelvic surgeries (1, 11–15). Computed tomography (CT) is currently recognized as the diagnostic modality of choice whereas the sensitivity and specificity of magnetic resonance imaging (MRI) and ultrasonography remain less certain (11, 15–18). Although unsubstantiated by prospective randomized clinical trial data, the current clinical practice is to provide a brief (7–10 day) course of heparin and antibiotics for postpartum OVT. Recommendations regarding anticoagulation, however, vary greatly and therapeutic management for OVT in non-pregnant patients remains unclear.

To define the rate of recurrent venous thromboembolism and the expected survival of patients with OVT, we studied all patients seen with this diagnosis at the Mayo Clinic between 1990 and 2006. Observed survival and recurrent venous thrombosis rates were compared with a randomly selected group of female patients with lower extremity DVT.

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Methods

Study population

All patients with the diagnosis of OVT who underwent evaluation at the Mayo Clinic between January 1990 and January, 2006 were included in this study. The diagnosis of OVT was confirmed by computed tomography, magnetic resonance imaging, pelvic ultrasound, or by pathology report. The control group consisted of a randomly selected group of 114 female patients with lower extremity venous thrombosis seen at the Mayo Clinic from 1990 to 2000. The study was approved by the Mayo Clinic Institutional Review Board.

In order to identify patients with OVT, the Mayo Clinic Diagnostic Index, a centralized electronic database of all patient diagnostic codes, was searched based on the following keywords: ovarian vein thrombosis, ovarian vein thrombophlebitis, septic pelvic thrombophlebitis, and pelvic vein thrombosis. Data were collected from a centralized system that contains complete records of all patients treated and followed at Mayo Medical Center. The Mayo Clinic medical record for each patient contains the details for every inpatient hospitalization, every outpatient visit regardless of the provider, every radiology examination and all laboratory and pathology results (including autopsy reports), death certificates and relevant correspondence. To ascertain potential causes of OVT, the medical record was specifically queried for laboratory analysis of acquired and congenital thrombophilia, recent trauma or surgery (within the previous three months of OVT diagnosis), active malignancy, rheumatologic or hematologic diseases. Pregnancy and puerperium, nephrotic syndrome, inflammatory bowel disease, the use of estrogen-containing drugs or chemotherapy were also regarded as potential causes of OVT. Patients who did not fulfill any of the above criteria and had negative thrombophilia testing were classified as idiopathic. Data on previous venous thromboembolism (VTE), history of miscarriage and family history of VTE were also collected.

Between 1990 and 2006 thrombophilia testing at the Mayo Clinic Special Coagulation and Special Coagulation DNA Diagnostic Laboratories has evolved considerably. Standard assays were performed to test for deficiencies of protein C, protein S, antithrombin III, dysfibrinogenemia, and disseminated intravascular coagulation (DIC/ICF). Heparin within the submitted blood sample was confirmed by prolongation of the thrombin time with normal reptilase time. Lupus anticoagulant assessment was based on aPTT, platelet neutralization procedure, and dilute Russell's Viper Venom time (dRVVT) assays to identify phospholipid dependence of prolonged and inhibited clot based assays. Antiphospholipid antibodies were measured by ELISA. When it became available, resistance to activated protein C was performed based on aPTT assay platforms. Genetic testing for factor V Leiden, prothrombin 20210, and MTHFR mutations became available in 1995, 1997 and 2000 respectively. At Mayo Clinic, thrombophilia testing is available as a panel of all of these assays. The ordering of single assays is actively discouraged.

The follow-up period began at the time of the initial diagnosis and ended at the time of the most recent medical evaluation or at the time of death. The use of warfarin anticoagulation and duration of therapy were recorded for all patients.

Major event definition and adjudication

For the purposes of this study, a major thrombotic event was defined as including venous thromboembolism, deep vein thrombosis, pulmonary embolism, or atypical venous thrombosis occurring within venous segments such as cerebral venous sinuses, mesenteric, renal, ovarian or retinal veins. Deep vein thrombosis (DVT) had to be confirmed by either compression duplex ultrasonography, venography, computed tomography (CT), magnetic resonance imaging (MRI), pathology examination of thrombus removed at surgery or autopsy, or impedance plethysmography performed in the Mayo Clinic Vascular Laboratory. Pulmonary embolism (PE) had to be confirmed by pulmonary angiography, contrast enhanced computed tomography (CT) scan, magnetic resonance imaging (MRI), pathology examination of thrombus removed at surgery or autopsy, or a ventilation-perfusion lung scan interpreted as high probability for pulmonary embolism. A recurrent thrombotic event within the same vascular territory was distinguished from the original thrombus by comparing serial imaging modalities. In order to be classified as a recurrent venous thrombosis, there had to be new filling defects evident on the second study not appreciated on the original images or an interval study clearly showing thrombus resolution. A major hemorrhage was defined as visible bleeding and a fall in hemoglobin of 2 g/dl, hemorrhage requiring transfusion of two units of blood, or intraocular, intracerebral, or retroperitoneal hemorrhage.

Statistical analysis

The Kaplan-Meier product limit estimator was used to calculate event rates and to compare event free survival between OVT and DVT patients. Differences between the curves were tested using the two-sample log-rank test. Multivariate analysis was performed to assess variables important in predicting both venous thrombosis recurrence as well as survival. The analyses were performed with JMP, Version 5.(SAS Institute Inc., Cary, NC, USA; 1989–2002 statistical software).

Results

Demographic characteristics

A total of 45 patients with the diagnosis of OVT during the study period were identified. Ten patients were excluded due to insufficient objective data for diagnosis confirmation. Thus, 35 patients with confirmed OVT comprised this study group. The base-line characteristics of patients with OVT and controls with lower extremity deep venous thrombosis are summarized in Table 1. Patients with OVT were significantly younger (MN ± SD 45 ± 18 years) compared to those with lower extremity DVT (56 ± 23 years). Figure 1 depicts the age distribution of patients with OVT compared to those with lower extremity DVT. The age distribution of patients with OVT appears unimodal with a skew favoring younger age of onset.

OVT was confirmed by computed tomography (CT) in the majority of patients (92%). Three patients had other additional diagnostic modalities. In four patients diagnosis was confirmed during laparotomy. Contrary to previous reports, the right ovarian vein was involved in 46% (Fig. 2). The left ovarian vein was involved in 37% and both in 17% of cases. In five patients, the left ovarian vein thrombus extended into the left renal vein. In

Table 1: Base-line clinical characteristics of patients with ovarian vein thrombosis (OVT) and lower extremity venous thrombosis (DVT) controls.

Variable N (%)	OVT (n=35)	DVT (n=114)	p-value
Age (mean ± SD)	45 ± 18	56 ± 23	0.01
Idiopathic	1(3)	24 (21)	0.009
Cancer	12 (34)	15 (13)	0.01
Surgery Abdominal Orthopedic Cardiac	(20) 7 0 0	8(7) 4 3 1	0.05
Pelvic Infection	8 (23)	1(1)	<0.001
Trauma Abdominal Orthopedic Other	1 (3) 1 0 0	5 (4) 0 2 3	1.0
Estrogen – OCPs/HRT Pregnancy	 12 (34) 5 (14)	 10 (9) 4 (4)	 <0.001 0.03
Family History VTE	5 (14)	10 (9)	0.35
Personal History VTE	3 (9)	12 (11)	1.0
Inflammatory bowel disease	2 (6)	0	0.05

OCPs, oral contraceptives; HRT, hormonal replacement therapy; VTE, venous thromboembolism.

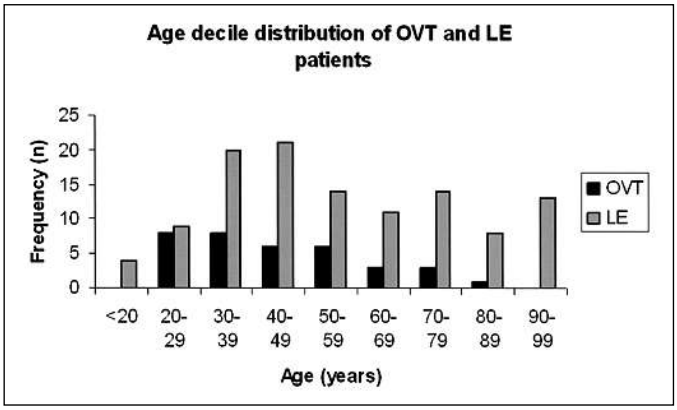

Figure 1: Age distribution by decade of patients with OVT (black bars) and lower extremity DVT (grey bars).

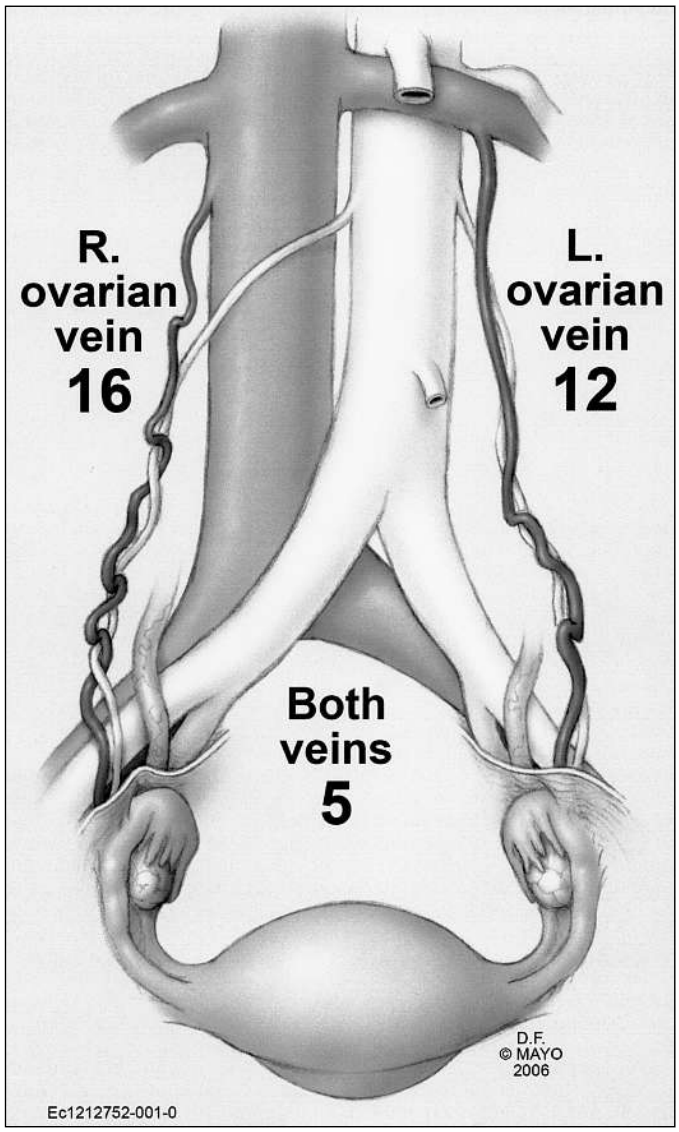

Figure 2: Thrombus location. The numbers represent the frequency of ovarian vein involvement with thrombosis.

one patient, the right ovarian vein thrombus extended into the inferior vena cava. In three patients, venous thrombosis was noted in the iliac veins. Of these, one patient had involvement of the femoral vein and one patient had a pulmonary embolism. One patient had concurrent portal and splenic vein thrombosis.

There were several etiologic variables distinguishing patients with ovarian vein from leg vein thrombosis (Table 1). Nearly half of patients with OVT were either taking hormonal therapy or were pregnant at the time of diagnosis compared to 13% of DVT patients. Furthermore, patients with OVT were more likely to have an underlying malignancy, to have undergone recent abdominal surgery, or to have experienced recent pelvic infection. Twelve patients (34%) had an active malignancy including: pancreatic (n=2), non-small cell lung cancer (n=1), endometrial carcinoma (n=2), ovarian cancer (n=2), peritoneal cancer (n=2), metastatic colon carcinoma (n=1), and lymphoma (n=2). Of the 12 patients with active malignancy, five received a combination of paclitaxel and carboplatin. Other chemotherapeutic agents included doxorubicin, streptozocin, gemcitabine and 5-FU. Three patients received no adjuvant chemotherapy. Twelve patients (34%) were receiving hormonal therapy including oral contraception (seven patients) and hormonal replacement therapy (five patients). In five (14%) patients, OVT occurred post partum. Seven patients (20%) had undergone a surgical procedure within the three months of the diagnosis: laparoscopic cholecystectomy (n=2), appendectomy (n=2), distal pancreatectomy with lymph node dissection (n=1), and laparotomy (n=2). Two of the surgeries were for cancer resection. One patient had experienced recent abdominal trauma. She was diagnosed with bilateral OVT before undergoing surgery. Active infection was present in eight patients (23%): endometritis (n=4), appendicitis (n=2), diverticulitis (n=1), pelvic inflammatory disease (n=1). Two patients (6%) had inflammatory bowel disease and one suffered from autoimmune hepatitis. Seventeen patients (49%) had more than

two underlying prothrombotic conditions. Only one patient with OVT had a history of miscarriage. For the control patients with DVT, the most common etiologies were cancer and surgery. A specific etiology could not be identified in only one patient with OVT compared to 21% of patients with leg vein thrombosis.

During the period of this analysis, thrombophilia testing evolved considerably with the identification of novel thrombotic risk variables. Fourteen patients underwent complete thrombophilia testing available at the time of diagnosis. Only one patient was found to have an abnormality. This included a protein S deficiency however the testing was performed during her pregnancy and was not repeated for clarification. Of the DVT control patients, 45 patients had thrombophilia testing performed. Of these, two patients had protein C deficiency, nine were heterozygous for Factor V Leiden and one was homozygous for this mutation. Six patients were heterozygous for prothrombin 20210 mutation and one was homozygous.

Anticoagulant therapy

Anticoagulant treatment and treatment duration varied considerably amongst the patients with OVT. Seventeen patients received both heparin and warfarin therapy whereas two patients received warfarin only. One patient was committed to lifelong anticoagulation after the diagnosis of OVT whereas she had previously experienced episodes of recurrent superficial thrombophlebitis. The average treatment duration with warfarin was 5.3 ± 3.2 months. Four patients were treated with aspirin, one of these was also treated with warfarin. No patients received fibrinolytic therapy. One patient had menometrorrhagia while on warfarin that fulfilled the criteria for major bleed and consequently underwent endometrial ablation. Of the DVT control patients, 25 (22%) were committed to lifelong anticoagulation. The average treatment duration for these control patients was 6.9 ± 6.8 months.

Recurrent venous thromboembolism

The mean duration of follow up was 34.6 (range 0–172 months) for a total of 100 patient-years of follow-up (Fig. 3). During the follow-up period, there were three venous thrombotic events occurring in three patients (event rate: three per 100 patient-years). All three events occurred within two months of the original thrombosis (11 days, 21 days and 53 days). One patient experienced contralateral ovarian vein thrombosis. This patient was initiated on anticoagulants only after the recurrence. One patient had extension of thrombus from left ovarian vein into the left renal vein and one patient had extension of thrombus from the right ovarian vein into the inferior vena cava. Two of these recurrences occurred in the setting of malignancy. This recurrence rate was nearly identical to patients with lower extremity DVT (event rate: 2.2 per 100 patient-years).

Multivariate analysis was performed using each of the variables in Table 1 to determine effects on recurrence rates. The final model was constructed using a stepwise selection process. The final model contained only personal history of venous thrombosis. After adjusting for this factor there was no significant difference in recurrent venous thromboembolism between the two groups (p=0.5).

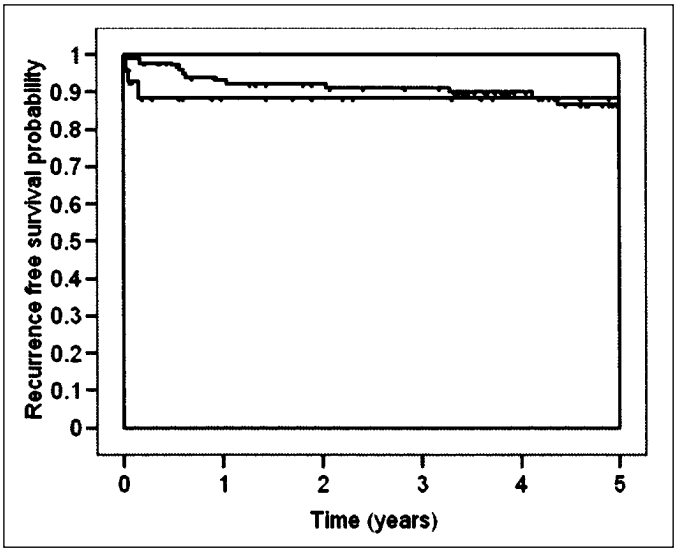

Figure 3: Recurrent venous thromboembolism. Venous thrombosis recurrence free survival at five years did not differ between patients with OVT (lower line) and lower extremity DVT (upper line).

Overall survival

Over the time period of this study, there were nine deaths in the OVT patients and 25 deaths in DVT patients (Fig. 4A). Survival differences between OVT and DVT patients did not reach statistical significance (p=0.08). Survival was significantly greater in OVT patients without cancer compared to those with active cancer (p<0.0001; Fig. 4B). The mean time to death in these patients was 1.8±1.6 years (median 1.0 year).

Multivariate analysis was performed using each of the variables in Table 1 to determine effects on overall survival. The final model contained age and cancer . After adjusting for these factors there was no significant difference in survival between the two groups (p=0.44).

Discussion

The principal findings of this study include an important estimate of anticipated rates of recurrent OVT and venous thromboembolism at other locations. During 100 patient-years of follow-up, there was one episode of recurrent ovarian vein thrombosis and two cases of thrombus extension, one from the left ovarian vein into the left renal vein and the other from the right ovarian vein into the inferior vena cava. Furthermore, these recurrence rates were nearly identical to the control group with lower extremity DVT (Fig. 3). All three recurrent thrombi and thrombus extension occurred within the first two months diagnosis. Two of the three events occurred in patients with malignancy. Importantly, there was only one patient with symptomatic pulmonary embolism which occurred in the setting of the original thrombotic event. To our knowledge, this is the first study to determine the likelihood of recurrent venous thrombosis in patients suffering from OVT. In the largest published series, the prevalence of incidental OVT was assessed in patients who underwent hysterectomy, oophorectomy and lymph node dissection for ovarian, cervical, or endometrial cancer (15). Of 50 patients imaged by CT, 40 had ovarian vein thrombosis. None of the patients were treated with anticoagulants

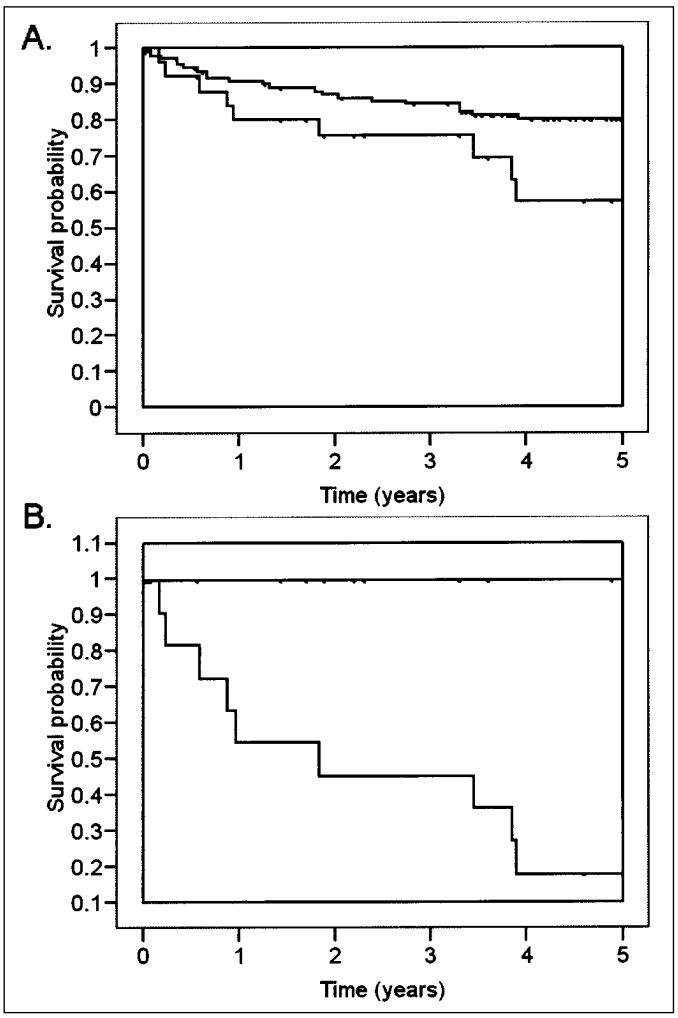

Figure 4: Overall survival in patients with OVT. The five-year survival in patients with ovarian vein thrombosis (lower line) compared to patients with lower extremity DVT (upper line) did not reach statistical significance (p=0.08; Fig. 4A). Survival was significantly greater in OVT patients without cancer (upper line, n=23) compared to those with cancer (lower line, n=12) at five years (p<0.001; Fig. 4B).

and none reported symptoms suggestive of pulmonary embolism. Although the authors concluded that no anticoagulant treatment was necessary, follow up was available on only half of the patients and neither survival nor venous thromboembolism recurrence rates were provided.

A second finding of this study is an important estimate of anticipated survival rate in patients with OVT. During 100 patient-years of follow up, there were nine deaths. All of the deaths occurred in the course of underlying malignancy. Survival comparison with the DVT control group (Fig. 4A) did not reach statistical significance (p=0.08) likely due to the small numbers of patients included in this study. For those patients without malignancy associated OVT, survival rates were excellent (Fig. 4B). The natural history of this disease is governed by the presence or absence of an underlying malignant neoplasm.

Several etiologic variables distinguish patients with OVT from those with leg vein thrombosis. The most common etiologies of OVT in this study were hormonal stimulation (exogenous therapy or pregnancy), malignancy, recent abdominal surgery or pelvic infection Of the nine patients receiving chemotherapy for active malignancy, five were treated with paclitaxel which is known to carry risk of thrombosis (12). These observations expand the prior understanding of etiologic variables. Of note, only five women had the classic post-partum presentation. We excluded six women with the clinical diagnosis of postpartum septic pelvic thrombophlebitis yet without confirmatory imaging studies. This broad spectrum of underlying clinical conditions is consistent with other recently published reports on OVT (13–15). In this series, the etiology of OVT could be attributed to a specific acquired thrombotic factor in all but one case (Table 1). Moreover, we were able to find only one case report of idiopathic ovarian vein thrombosis in the published literature (19). In contrast, 21% of the DVT controls in our study for example were idiopathic in etiology. These findings point to the uniqueness of thrombosis in this location relative to venous thrombosis in the lower extremities.

Thrombophilia testing is often reserved for patients with venous thrombotic events which are unexplained by acquired thrombotic risk factors. Whereas idiopathic OVT remains quite rare (19), the role of thrombophilia testing in these patients remains uncertain. One group of investigators found that an inherited thrombophilia was relatively common in patients suffering OVT in the postpartum setting (7). Of 22 patients assessed, four were heterozygous carriers of factor V Leiden mutation, four were homozygous for MTHFR C677T mutation, and two had protein S deficiency, one of which also was heterozygous for factor V Leiden mutation. Thrombophilia studies were performed in 40% of the patients in our study and only one abnormality was found. This patient was found to be protein S deficient, however the testing was performed during pregnancy and not repeated for confirmation. Thrombophilia testing performed during or shortly after pregnancy can be difficult to interpret due to hormonal related changes of coagulation factors. In particular, pregnancy is known to reduce protein S levels (20). If performed, thrombophilia testing should be postponed until the opportune time to enhance the sensitivity, specificity and accuracy of the assays. This includes resolution of the thrombotic event, delivery of the pregnancy, and discontinuation of anticoagulant medications all of which can affect assay results (21).

In general, a decision to initiate, continue or withhold anticoagulation therapy in patients with ovarian vein thrombosis depends on the anticipated risk of recurrent thrombosis and related morbidity and mortality weighed against the risk of hemorrhagic complications. The optimal dose and duration of anticoagulants for the treatment of OVT remain to be clarified by randomized trial data. Whereas our data indicate that OVT and DVT patients experience similar clinical outcomes, it would seem reasonable to follow the current treatment guidelines for lower extremity DVT and pulmonary embolism (22). If an underlying thrombotic etiology is transient or amenable to curative treatment, then three months of anticoagulation seems appropriate. If idiopathic in etiology or if the thrombotic risk is permanent, a more prolonged course of treatment is advisable. Due to the retrospective nature of this study, the limited number of patients meeting objective criteria for inclusion, and inconsistencies in anticoagulation

management, firm anticoagulation recommendations can not be offered based on this data-set.

This is the largest study to date documenting the clinical course of OVT. In the absence of malignancy, survival rates are quite favorable with a low rate of recurrent venous thrombosis. The recurrence rate is similar to patients with lower extremity DVT. Treatment guidelines for venous thrombosis may therefore be applicable until randomized trial data becomes available.

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