Original Research

Ovarian Vein Thrombosis

Incidence of Recurrent Venous Thromboembolism and Survival

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OBJECTIVE: To identify the risk of venous thromboembolism recurrence, major bleeding, and mortality in patients with ovarian vein thrombosis so as to better define optimal treatment strategies.

METHODS: Patients with ovarian vein thrombosis (1990–2015) and age- and gender-matched patients with contemporary leg deep vein thrombosis (DVT) were assessed for differences in etiology, venous thromboembolism recurrence, and survival in a case–control study.

RESULTS: Over the timeframe of this study, only 219 ovarian vein thrombosis cases were identified compared with 13,417 leg DVTs. Median duration of follow-up was 1.23 years (interquartile range 0.25–4.14). Pulmonary embolism was identified at presentation in 6% of patients with ovarian vein thrombosis and 16% of those with DVT (P=.001). Frequent causes of ovarian vein thrombosis included cancer, hormonal stimulation, surgery, and hospitalization. Cancer was twofold more frequent in patients with ovarian vein thrombosis (44% compared with 21%; P<.01). Despite being less frequently treated with anticoagulation (ovarian vein thrombosis 54% compared with DVT 98%, P<.001), venous thromboembolism recurrence rates were similar between groups (ovarian vein thrombosis 2.3 compared with DVT 1.8 per 100 patient-years, P=.49). A personal history of venous thromboembolism and preceding surgery was found to be an independent risk factor for venous thromboembolism recurrence among those treated with anticoagulation (hazard ratio 6.7, P=.04 and hazard ratio 13.6, P=.03, respectively). There was no significant difference in overall survival.

CONCLUSION: Ovarian vein thrombosis is a rare thrombotic condition with an incidence 60-fold lower compared with leg DVT in our institution. The striking association with cancer adversely affects overall survival rates in patients with ovarian vein thrombosis. Venous thromboembolism recurrence rates argue for anticoagulation with a direct oral anticoagulant or vitamin K antagonist, particularly in those with a history of venous thromboembolism.

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Ovarian vein thrombosis is an uncommon event historically attributed to either pelvic inflammatory disease or the postpartum period. In recent years, gynecologic surgery and pelvic malignancy have emerged as important causative associations.[1–4] Ovarian vein thrombosis is estimated to complicate 1 per 600 to 1 per 2,000 pregnancies, typically in the postpartum period. The incidence has been reported to be as high as 0.18% of the general population,[5,6] yet the natural history of ovarian vein thrombosis is not well described including risk factors and recurrence rates. Knowledge of these variables would be useful for the development of optimal treatment strategies. In the absence of such data, there is little to guide clinicians in the management of these patients.

Anatomically, the ovarian vein represents a portion of the deep venous system with a direct connection to the inferior vena cava on the right and the renal vein on the left.[7] Treatment with anticoagulation has been suggested, but societal guidelines on the issue have not been published.[2,8–12] Despite this, the risk of thrombus propagation, pulmonary embolism, and venous thromboembolism recurrence remains poorly defined. Recent evidence suggests that the risk of recurrent

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venous thromboembolism depends strongly on risk factors present at the time of the initial thrombotic event.[2–4,8]

Given the relative rarity of ovarian vein thrombosis, it is unlikely that a randomized controlled trial will be forthcoming. The objective of this study is to identify the risk of venous thromboembolism recurrence, major bleeding, and mortality in patients with ovarian vein thrombosis so as to better define optimal treatment strategies. Outcomes were compared with a randomly selected group of female patients with contemporary leg deep vein thrombosis (DVT).

MATERIALS AND METHODS

A case–control study was conducted in which consecutive patients with the diagnosis of ovarian vein thrombosis evaluated at the Mayo Clinic between January 1, 1990, and October 22, 2015, were identified using an electronic database search for "ovarian vein thrombosis," "gonadal vein thrombosis," or a similar variant in the text of an electronic note. Patients were confirmed by radiology report or by clear documentation in the electronic medical record of the diagnosis including specific location. The control group consisted of randomly selected female patients diagnosed with leg DVT matched by age and diagnosis date. Patients with ovarian vein thrombosis were grouped by age (18–30, 30–40, 40–50, 50–60, 60–70, or older than 70 years) and diagnosis date (1990–1994, 1995–1999, 2000–2004, 2005–2009, or 2010–2015). All female patients with a diagnosis of DVT within each diagnosis date group and age group were identified from an electronic database of patients seen at the Mayo Clinic. A random number generator was then used to select a corresponding patient with DVT for each patient with ovarian vein thrombosis from among all patients with DVT identified in their corresponding age and diagnosis date group. Data were collected from a centralized electronic medical record that contains every inpatient hospitalization, outpatient visit, radiology examination, laboratory results, pathology results (including autopsy reports), death certificates, and relevant correspondence for all patients. The study was approved by the Mayo Clinic institutional review board.

Anticoagulation was defined as treatment of thrombosis with a direct oral anticoagulant or vitamin K antagonist. A recurrent venous thromboembolism event was defined as upper or lower extremity DVT, pulmonary embolism (PE), or atypical venous thrombosis. Atypical venous thrombosis included thrombi affecting the cerebral venous sinuses or splanchnic or renal veins. A recurrent thrombotic event within the same vascular territory was distinguished from the original thrombus by comparing serial imaging modalities.[13,14] 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.[13,14]

Hospitalizations, malignancy, hormonal stimulation, trauma, infections, surgeries, or active inflammatory disease were considered a positive risk factor if they occurred within the 3 months preceding the diagnosis of ovarian vein thrombosis. Hospitalizations included any overnight inpatient stay in a hospital. Malignancy included any active cancer or treatment for cancer. Infection included any diagnosis of a bacterial infection that required treatment. This infection could have occurred anywhere in the body and was further classified by organ system. Pelvic inflammatory disease, pelvic abscess, urinary tract infections, and endometritis were considered genitourinary infections. Trauma was considered a risk factor if an injury or trauma was severe enough as to require medical or surgical treatment. Hormonal stimulation was considered a risk if a patient was on hormone therapy, pregnant, or on oral contraceptive pills. Surgeries were considered a risk if performed at any location. Active inflammatory disease included any noninfectious inflammatory disease such as inflammatory bowel disease or an autoimmune condition. Thrombi were considered unprovoked if no risk factors could be identified during this interval.

Differences between Kaplan-Meier curves were determined using the two-sample log-rank test. Fisher exact test was used to determine significance of a difference in categorical variables. The Cox proportional hazards model was used to assess variables important in predicting survival and venous thromboembolism recurrence. Simultaneous CIs were used when constructing 95% CIs on survival curves. Thrombotic distribution differences (right compared with left, excluding bilateral) for patients with ovarian vein thrombosis and those with DVT was assessed using the χ^2 test. Analysis was performed using JMP 10.

RESULTS

Between January 1, 1990, and October 22, 2015, 219 patients with ovarian vein thrombosis were identified and compared with 220 patients with DVT. The number of patients identified per 5-year time window can be seen in Figure 1. The most frequent underlying associations with ovarian vein thrombosis included cancer, hormonal stimulation including estrogen

therapy and pregnancy, surgery, and hospitalization (Table 1). Cancer was more than twice as frequent in patients with ovarian vein thrombosis compared with those with leg DVT. The most common cancers included genitourinary and gastrointestinal malignancies implying a regional influence. Although infrequent (10% ovarian vein thrombosis compared with 3% DVT, $P<.01$), infection was more common in patients with ovarian vein thrombosis and also more often associated with proximate organ involvement (19 gastrointestinal or genitourinary infections in ovarian vein thrombosis compared with 0 leg infections in DVT, $P<.001$). Two patients had pelvic inflammatory disease and tested positive for *Neisseria gonorrhea*. A similar percentage of both groups had no identifiable provoking mechanism and would be considered "unprovoked" (16% ovarian vein thrombosis compared with 20% DVT, $P=.21$). Deep vein thrombosis was more commonly left-sided ($P<.001$), whereas ovarian vein thrombosis exhibited a trend toward more on the right ($P=.06$; Table 2).

Forty-two patients with ovarian vein thrombosis underwent thrombophilia testing. Patients with ovarian vein thrombosis who underwent thrombophilia testing were more likely than those who were not tested to have concomitant thrombosis in other locations (48% compared with 27%, $P<.01$), unprovoked thrombosis (26% compared with 13%, $P=.03$), preceding hormone exposure (29% compared with 15%, $P=.04$), pregnancy (26% compared with 8%, $P<.01$), noninfectious inflammatory disease (19% compared with 6%, $P<.01$), or a family history of venous thromboembolism (19% compared with 5%, $P<.01$). Those tested were less likely to have cancer (2% compared with 53%, $P<.01$). Of those tested, only six (14%) had a defined thrombophilia including lupus anticoagulant (n=3), heterozygous factor V Leiden (n=2), and one patient with antithrombin deficiency. This rate of positivity is much lower compared with those with leg DVT (24/79 [30%]; $P=.008$). Those patients with DVT who were tested for thrombophilia were more likely to have unprovoked thrombosis (30% compared with 15%, $P<.01$), preceding hormone therapy (27% compared with 10% $P<.01$), pregnancy (11% compared with 4%, $P=.04$), a family history of venous thromboembolism (16% compared with 4%, $P<.01$), and a personal history of venous thromboembolism (16% compared with 8%, $P=.05$). Those tested were less likely to have a preceding hospitalization (10% compared with 24%, $P=.01$), infection (5% compared with 0%, $P=.04$),

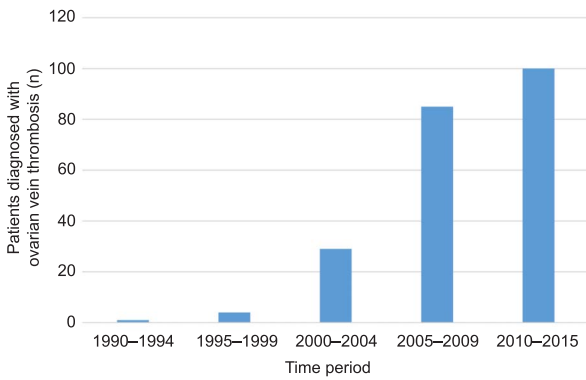

Fig. 1. Number of patients diagnosed with ovarian vein thrombosis by time period.

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Table 1. Baseline Clinical Characteristics of Patients With Ovarian Vein Thrombosis and Those With Lower Extremity Venous Thrombosis

Variable	OVT (n=219)	DVT (n=220)	*P*
Age (y)	50.8±18.0	51.7±18.1	.61*
Involved side			.003†
Left	90 (41)	125 (57)	
Right	110 (50)	77 (35)	
Both	19 (9)	17 (8)	
Idiopathic	34 (16)	45 (20)	.21†
Cancer	96 (44)	46 (21)	<.01†
Genitourinary	48	17	
Gastrointestinal	28	2	
Hematologic	7	7	
Breast	6	6	
Lung	5	5	
Thymic	1	0	
Unknown primary	1	0	
Brain	0	4	
Bone	0	4	
Thyroid	0	1	
OCP or HT	39 (18)	35 (16)	.60†
Pregnancy	26 (12)	15 (7)	.07†
Recently hospitalized	51 (23)	42 (19)	.28†
Surgery	57 (26)	53 (24)	.64†
Infection	22 (10)	7 (3)	<.01†
Genitourinary	13	1	
Gastrointestinal	6	0	
Other infections	3	6	
Trauma	4 (2)	25 (11)	<.01†
Inflammatory disease	18 (8)	21 (10)	.63†
Family history of VTE	17 (8)	19 (9)	.74†
Personal history of VTE	14 (6)	24 (11)	.09†

OVT, ovarian vein thrombosis; DVT, deep vein thrombosis; OCP, oral contraceptive pills; HT, hormone therapy; VTE, venous thromboembolism.

Data are mean±SD, n (%), or n unless otherwise specified.

* Two-tailed *t* test.

† Pearson χ^2 test.

Table 2. Venous Thrombosis Location by Group*

	Left	Right	Bilateral	*P*
OVT	90 (41)	110 (50)	18 (9)	.06
Leg DVT	125 (57)	77 (35)	17 (8)	<.001

OVT, ovarian vein thrombosis; DVT, deep vein thrombosis.
Data are n (%) unless otherwise specified.
* Thrombotic distribution differences (right compared with left, excluding bilateral) for patients with OVT and those with DVT was assessed using the χ^2 test.

preceding surgery (16% compared with 28%, $P<.05$), or cancer (9% compared with 28%, $P<.01$). All six patients with ovarian vein thrombosis with positive thrombophilia testing had thrombosis at more than one location, but none of these patients had recurrent venous thromboembolism during the time of the study. Five of these six patients were treated with anticoagulation for their ovarian vein thrombosis and other thrombosis. Demographic variables for patients with ovarian vein thrombosis with and without recurrent venous thromboembolism are provided in Table 3.

Computed tomography was used to identify ovarian vein thrombosis in 206 (94%) patients, magnetic resonance imaging in 10 (5%) patients, ultrasonography in two (1%), patients, and one case was diagnosed during surgical laparoscopy. For patients with ovarian vein thrombosis, thrombotic involvement of other venous territories included renal veins (n=25), lower extremity deep veins (n=15), inferior vena cava (n=13), and the portal system (n=8). Pulmonary embolism was found at presentation in 14 (6%) patients with ovarian vein thrombosis and in 36 (16%) patients with DVT ($P=.001$). In eight patients with ovarian vein thrombosis with PE, no other venous thrombosis was identified implying that this may have been the source of embolism. For patients with DVT, extension into contiguous leg veins was common (n=113). Contralateral lower extremity DVT (n=16) was less frequent. Inferior vena cava thrombosis was present in only one patient with DVT.

Treatment with anticoagulation was significantly less common for ovarian vein thrombosis (54%) compared with patients with DVT (98%; $P<.01$). Despite being less frequently treated with anticoagulation (ovarian vein thrombosis 54% compared with DVT 98%, $P<.001$), venous thromboembolism recurrence rates were similar between groups (ovarian vein thrombosis 2.3 compared with DVT 1.8 per 100 patient-years, $P=.49$). Anticoagulant treatment for patients with ovarian vein thrombosis included warfarin (38%), low-molecular-weight heparin (11%), or direct factor Xa inhibitors (5%). Within the DVT group, anticoagulant treatment included warfarin (75%), low-molecular-weight heparin (15%), direct factor Xa inhibitors (6%), or unfractionated heparin (1%). Six patients (3%) were not treated. Treatment duration was nearly twice as long for patients with leg DVT compared with those with ovarian vein thrombosis (median 5.7 months [interquartile range 3.0–9.2] compared with 3.0 months [interquartile range 3.0–6.0], $P=.02$). One patient with ovarian vein thrombosis and 11 with DVT had an inferior vena cava filter placed. Fibrinolytic therapy was used in four patients with leg DVT and none of the patients with ovarian vein thrombosis.

Median duration of follow-up was 1.23 years (interquartile range 0.25–4.14) for patients with ovarian vein thrombosis for a total of 610 patient-years of follow-up. Median duration of follow-up for patients with DVT was 3.31 years (interquartile range 1.00–7.48) for a total of 978 patient-years of follow-up.

Table 3. Baseline Clinical Characteristics of Patients With Ovarian Vein Thrombosis and Recurrent Venous Thromboembolism as Compared With Those Without Recurrent Venous Thromboembolism

Variable	OVT With Recurrence (n=16)	OVT Without Recurrence (n=203)	*P*
Age (y)	49.4±20.0	51.0±17.8	.77*
Involved side			.66†
Left	5 (31)	85 (42)	
Right	9 (56)	101 (50)	
Both	2 (13)	17 (8)	
Idiopathic	33 (16)	1 (6)	.29†
Cancer	9 (56)	87 (43)	<.30†
Genitourinary	4	44	
Gastrointestinal	1	27	
Hematologic	2	5	
Breast	0	6	
Lung	0	5	
Thymic	1	0	
Unknown primary	1	0	
OCP or HT	4 (25)	35 (17)	.43†
Pregnancy	1 (6)	25 (12)	.47†
Recent hospitalization	4 (25)	47 (23)	.87†
Surgery	7 (44)	50 (25)	.09†
Infection	0 (10)	22 (11)	.17†
Trauma	0 (0)	4 (2)	.57†
Inflammatory disease	2 (13)	16 (8)	.52†
Family history of VTE	0 (0)	17 (8)	.74†
Personal history of VTE	3 (19)	11 (5)	.04†

OVT, ovarian vein thrombosis; OCP, oral contraceptive pills; HT, hormone therapy; VTE, venous thromboembolism.
Data are mean±SD, n (%), or n unless otherwise specified.
* Two-tailed *t* test.
† Pearson χ^2 test.

During the follow-up period, there were 17 recurrent venous thromboembolism events in 16 unique patients with ovarian vein thrombosis. These events included six leg DVTs, four PEs, one inferior vena cava thrombus, one renal vein thrombosis, one portal vein thrombosis, and four contralateral ovarian vein thromboses. There were 18 total recurrent events in the DVT group (11 DVT, three inferior vena cava IVC thrombus, and four PE). Kaplan-Meier analysis revealed no significant difference in survival free from venous thromboembolism recurrence between patients with ovarian vein thrombosis and those with DVT (Fig. 2A; P=.56). For patients with ovarian vein thrombosis, the recurrence rates at 1 year were 6.1% (95% CI 2.2–15.7%) and at 5 years 14.3% (95% CI 8.4–23.4%). There was no increased risk for recurrent venous thromboembolism in patients with cancer (Fig. 2B; P=.31). Patients with cancer-associated ovarian vein thrombosis were less often treated with anticoagulation compared with those without cancer (41% compared with 64%, respectively, P<.01).

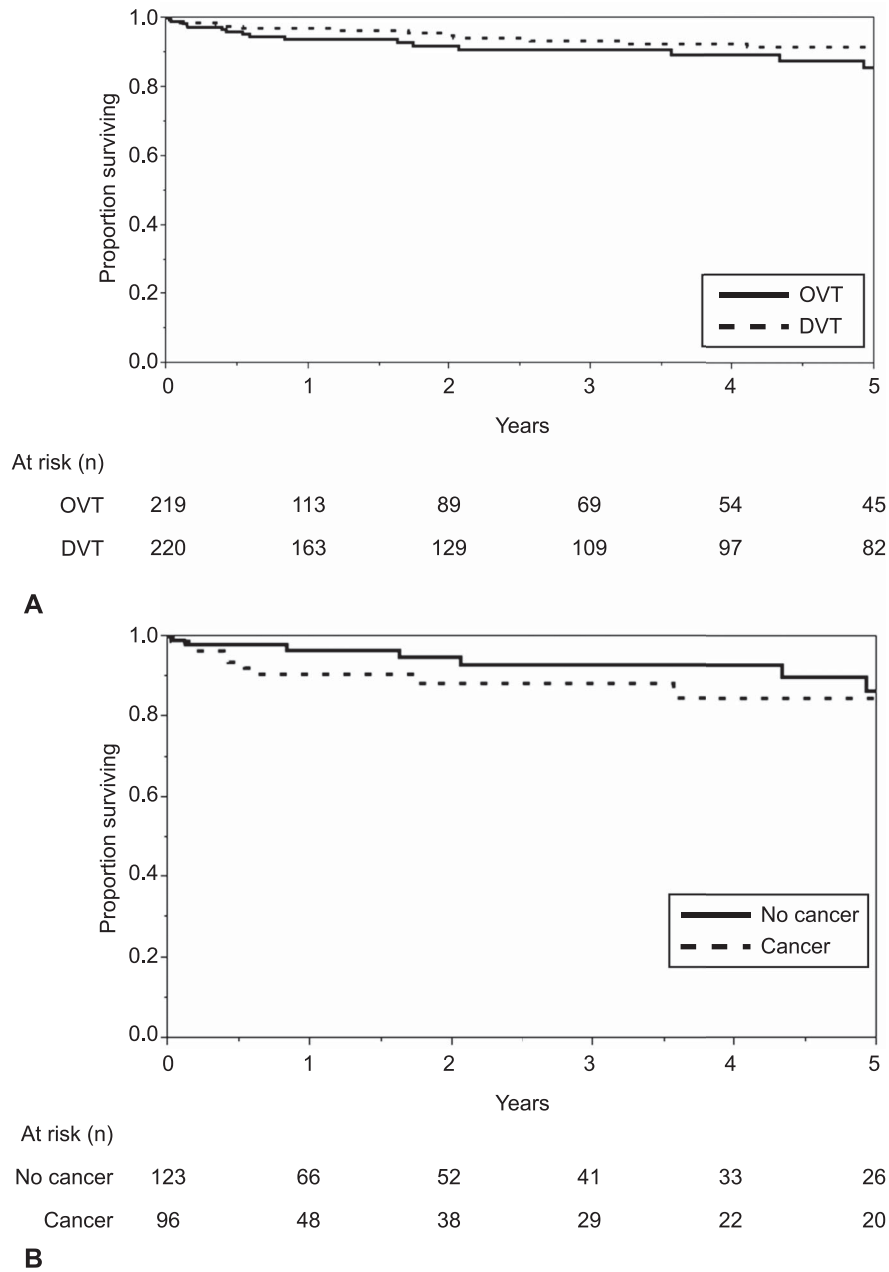

Fig. 2. Survival free of recurrent venous thromboembolism (VTE). Survival free of VTE recurrence (**A**) was similar for patients with ovarian vein thrombosis (OVT) and those with leg deep venous thrombosis (DVT) (P=.56) and did not differ by cancer status. Survival free of VTE recurrence (**B**) was similar for patients with OVT with and without cancer (P=.31).

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Multivariate analysis was performed using each of the variables in Table 3 (excluding location) to determine the effect on survival free of venous thromboembolism recurrence. A separate multivariate analysis was performed for those patients treated with anticoagulation and those not treated with anticoagulation. A personal history of prior venous thromboembolism and a preceding surgery were found to be independent risk factors for recurrent venous thromboembolism among those treated with anticoagulation (hazard ratio 6.7, 95% CI 1.12–36.94, *P*=.038 and hazard ratio 13.6, 95% CI 1.24–303.53, *P*=.033, respectively). Kaplan-Meier analysis revealed no overall difference in survival free from venous thromboembolism recurrence between those with ovarian vein thrombosis who were treated with anticoagulation and those with ovarian vein thrombosis who were not treated with anticoagulation (*P*=.44).

There were two major bleeds in the ovarian vein thrombosis group (alveolar hemorrhage in a patient on warfarin and subarachnoid hemorrhage in a patient not on anticoagulation) and seven in the DVT group all of whom were on anticoagulation (two intracranial bleeds, one retrosternal bleed, two gastrointestinal bleeds, and one retroperitoneal hemorrhage). Major bleeding rates were similar (*P*=.95) between patients with ovarian vein thrombosis (2.1 per 100 patient-years; 95% CI 0.2–7.4) and those with leg DVT (2.3 per 100 patient-years; 95% CI 0.9–4.7).

Survival rates were similar between groups (*P*=.41). There were 42 deaths in the patients with ovarian vein thrombosis and 51 deaths in the patients with DVT over

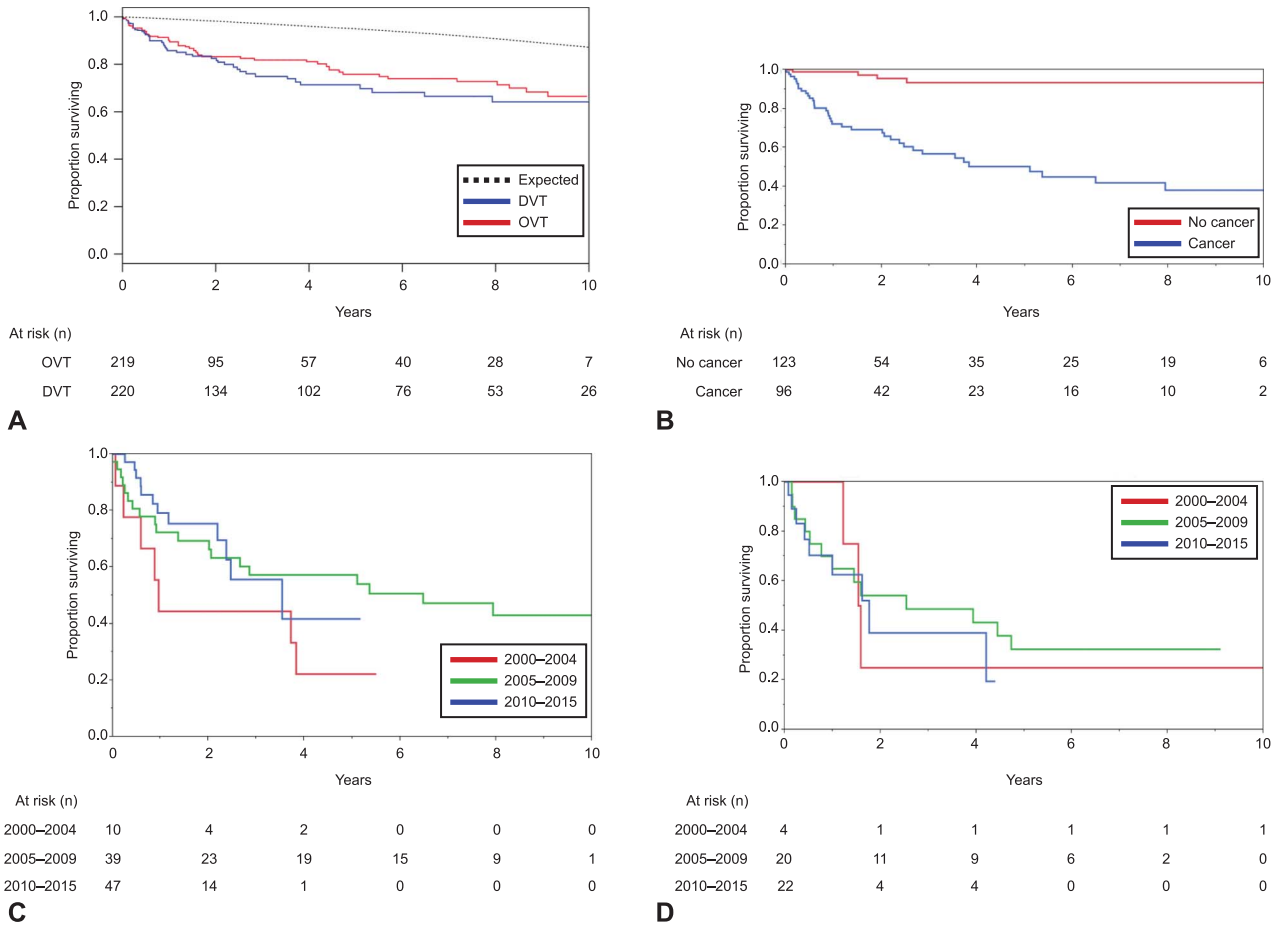

Fig. 3. Survival in patients with ovarian vein thrombosis (OVT) compared with expected survival and those with deep venous thrombosis (DVT). Overall survival (**A**) was significantly worse in OVT as compared with the age- and gender-matched Minnesota population (*P*<.01). Overall survival did not differ between patients with OVT and those with DVT (*P*=.41). Among patients with OVT, overall survival was significantly worse in patients with cancer (**B**) as compared with those without cancer (*P*<.01). Survival of patients with cancer with either OVT (**C**) or DVT (**D**) did not change over the time period of the study (*P*=.18 and *P*=.37, respectively).

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the course of the study. These deaths were not necessarily related to venous thromboembolism recurrence, but represent all-cause mortality. Survival in ovarian vein thrombosis was significantly worse than the expected general population of age- and gender-matched patients from published Minnesota death rates (Fig. 3A; $P<.01$). Active cancer was the only independent predictor of poor survival in patients with ovarian vein thrombosis in a multivariate model (hazard ratio 6.2, 95% CI 1.9–30.0, $P<.01$; Fig. 3B). Among those with cancer, there was no change in survival by diagnosis period in either the ovarian vein thrombosis or the DVT group ($P=.83$ and $P=.18$, respectively; Fig. 3C–D).

A subgroup analysis was performed excluding patients who had pregnancy-associated DVT or ovarian vein thrombosis and there was no significant difference in survival or survival free from venous thromboembolism recurrence in those with ovarian vein thrombosis compared with those with DVT on Kaplan-Meier analysis ($P=.19$ and $P=.28$). There were no deaths in those who had pregnancy-associated DVT or ovarian vein thrombosis. There was one recurrent PE in a patient with pregnancy-associated ovarian vein thrombosis and no other risk factors and one recurrent DVT in a pregnancy-associated DVT.

DISCUSSION

The principal finding of this study is that thrombosis of the ovarian vein is a relatively uncommon occurrence with only 219 patients identified at this tertiary medical facility over a 20-year time period. By comparison, there were 13,417 leg DVTs in women diagnosed over that same time period. In other words, ovarian vein thrombosis is 60-fold less frequent compared with DVT (1.6%). However, ovarian vein thrombosis has been more commonly diagnosed over the past 10 years, and a better understanding of this clinical entity is necessary for optimal treatment strategies to be determined. The increased rate of diagnosis may be explained by several reasons. First, this increase may simply reflect a growth of our practice. Second, the frequency of imaging and technologic advances may increase the sensitivity of detection. Third, radiologists may be more accustomed to looking for this entity. Fourth, changing patient and disease demographics may also be contributing to this incidence evolution. Regardless of the factors responsible for this growth, health care providers must be equipped to manage the increasing number of these patients.

Cancer is the most common risk factor for ovarian vein thrombosis and twice as frequent compared with patients with leg DVT. It is well established that patients with unprovoked venous thromboembolism carry a fourfold increased risk of occult malignancy and that 10% of these patients will have a new diagnosis of cancer within the ensuing year after the venous thromboembolism diagnosis. The most common cancer was ovarian cancer followed by pancreatic and hepatic malignancies.[15,16] Although recent trials assessing extensive cancer screening including positron emission tomography–computed tomography compared with limited testing have failed to show a survival benefit in patients with unprovoked DVT, the striking association between ovarian vein thrombosis and cancer represents a different clinical scenario.[17] For example, in the present study, 44% of patients had an underlying cancer. In a study of 196 patients with cancer-related ovarian vein thrombosis, 10.8% developed recurrent thrombotic events over a median follow-up of 14.5 months.[18] In this cohort of 196 patients, active cancer was the only risk factor associated with recurrent thrombotic events. Given the strong association, it is therefore imperative to consider cross-sectional imaging (computed tomography or magnetic resonance imaging) to assess for underlying malignancy, particularly if the diagnosis was established by ultrasonography. The majority of patients with ovarian vein thrombosis in this study were identified by cross-sectional imaging and thus the appropriate assessment had already been completed. Identifying malignancy carries both survival and venous thromboembolism recurrence implications and greatly affects treatment decisions.

Ovarian vein thrombosis was originally described as a complication of either the postpartum period or pelvic inflammatory disease.[5,18–20] In the current study, hormone stimulation in the form of pregnancy, oral contraception, and hormone replacement remains an important causation and accounted for 30% of cases. Furthermore, an association between ovarian vein thrombosis and infection including genitourinary and gastrointestinal sources is also an important consideration. For this reason, screening for sexually transmitted diseases, urinary tract infections, and infectious colitis in patients with idiopathic ovarian vein thrombosis may be reasonable.

Thrombophilia testing is usually reserved for patients with idiopathic venous thromboembolism.[21] It is often considered in the evaluation of atypical venous thrombosis and yet it is unclear whether thrombophilia testing is clinically useful for patients with ovarian vein thrombosis. It has previously been suggested that thrombophilia may be relatively common in patients with ovarian vein thrombosis.[12] Despite similar rates of idiopathic thrombosis, thrombophilia testing, when performed, was less often positive compared with patients with leg DVT.

Anatomic differences between the right and left ovarian veins have been proposed as contributory to both the pathogenesis and location of ovarian vein thrombosis. Ovarian vein thrombosis has historically been found on the right with frequencies as high as 90% in some studies.[11,18] Venous tortuosity and length of the right ovarian vein, which enters directly into the inferior vena cava, have been thought to be contributing variables. We were not able to substantiate this finding either with the current or prior data sets.[3] These findings may relate to differences in case ascertainment. If investigators oversample pregnant women, trauma and stasis resulting from the gravid uterus might yield a predominance of right ovarian vein involvement. Where malignancy predominates, like in our series, equal thrombus distribution may be anticipated. In series with a high surgical rate, bilateral involvement might occur. Indeed, in our series, 10% of patients had bilateral involvement with 26% undergoing surgery. Whereby the left ovarian vein empties into the left renal vein, any pathology affecting the left kidney (eg, infection, nephropathy, cancer, trauma) will preferentially affect the left ovarian vein. This will not be mirrored for the right kidney.

Survival was lower than anticipated compared with an age- and gender-matched Minnesota population. However, survival did not differ between the study groups despite the more than twofold higher prevalence of malignancy in patients with ovarian vein thrombosis. Malignancy was the only independent risk factor for death identified in our cohort. Death was universally related to the underlying malignancy with no deaths documented secondary to recurrent venous thromboembolism or major bleeding. Survival in patients with nonmalignant ovarian vein thrombosis was much improved as compared with those with malignant ovarian vein thrombosis.

Venous thromboembolism recurrence was 6.1% at 1 year and 14.3% at 5 years for patients with ovarian vein thrombosis. These percentages did not differ compared with those with DVT. It is noteworthy that anticoagulation therapy was only given to approximately half of patients with ovarian vein thrombosis. By comparison, nearly all patients with DVT were treated with anticoagulation. It is possible that anticoagulation decision-making for patients with ovarian vein thrombosis was affected by en bloc surgical resection of the thrombus in patients with malignancy. Patients with a previous venous thromboembolism were at the highest risk for recurrent venous thromboembolism. It has been previously demonstrated that venous thromboembolism associated with malignancy has an increased risk for recurrent venous thromboembolism compared with those with venous thromboembolism not associated with malignant disease.[22,23] In our cohort, those patients with malignancy did not have any increased risk for recurrent venous thromboembolism compared with the nonmalignant cohort despite being treated with anticoagulation less often. Shortened survival for patients with cancer may have limited the time exposure for the possibility of having a venous thromboembolism recurrence.

Among those treated with anticoagulation, patients with a previous venous thromboembolism and those who underwent surgery were at the highest risk for recurrent venous thromboembolism, but the independence of these risk factors did not persist in the untreated group. This difference between the treatment groups also probably accounts for the lack of benefit seen with anticoagulation treatment. These inconsistencies in our cohort demonstrate the need for further research in this area. Nevertheless, it continues to be the recommendation of the Mayo Thrombophilia Clinic to at least consider anticoagulation with a direct oral anticoagulant or vitamin K antagonist in all patients with ovarian vein thrombosis.

In summary, this study provides natural history outcomes for patients with ovarian vein thrombosis secondary to both benign and malignant factors. These data extend our prior observations with a much larger cohort spanning two decades.[3] Decreased survival in these patients compared with the general population is largely influenced by underlying malignancy. Recurrent venous thromboembolism may be explained by several variables including a high prevalence of temporary risk factors (surgery, infection, hormonal stimulation) and malignancy with reduced survival for experiencing a venous thromboembolism recurrence. Given the relative rarity of ovarian vein thrombosis, randomized controlled trials of anticoagulation would be difficult and would require robust multicenter participation. Considering that the CI for our recurrence rate is relatively large and the association of ovarian vein thrombosis with PE on presentation, we recommend treatment according to venous thrombosis guidelines.[24]

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