blood advances

TO THE EDITOR:

Ovarian vein thrombus: to treat or not to treat?

Trisha Plastini,[1] David Henry,[2] and Katie Dunleavy[3]

[1]Department of Internal Medicine and [2]Department of Hematology and Oncology, [3]Pennsylvania Hospital, Penn Medicine, Philadelphia, PA

Prior studies have failed to draw a consensus regarding the best treatment of ovarian vein thrombus (OVT). The purpose of this study is to evaluate if patient outcomes change based on treatment, specifically anticoagulation. Patients who carried any diagnosis containing the words "clot" or "thrombus" from January 2010 to May 2015 in the Penn Medicine system were analyzed. If a patient was identified as having an OVT based on radiologic findings, data extraction was performed via retrospective chart review. Of the 1436 patients identified during the inclusion period, 50 with OVT were identified. Twelve subjects received no treatment, one was treated with aspirin, 3 were treated with anticoagulation and antibiotics, and 30 were given anticoagulation alone. Average length of follow-up was 23.7 months. Average length of anticoagulation was 13.2 weeks. Ten patients had imaging showing resolution of OVT after anticoagulation, whereas 2 who received no anticoagulation had radiographically confirmed resolution of OVT. Five patients treated with therapeutic anticoagulation exhibited persistent OVT following treatment, whereas 4 who did not receive anticoagulation had persistent OVT on follow-up imaging. Symptomatic recurrence or bleeding was not seen in any subjects. There was no statistically significant correlation found between treatment and no treatment in terms of overall outcomes for patients diagnosed with OVT. Based on our findings, unless an OVT is symptomatic, septic in nature, or associated with another deep venous thrombosis (DVT) requiring treatment, an incidentally detected OVT does not necessarily warrant anticoagulation therapy.

OVT is a rare condition that has been associated with the postpartum period, malignancy, abdominal and pelvic surgery, pelvic inflammatory disease, and inflammatory bowel disease.[1-3] It has been reported to occur in 0.05% to 0.16% of pregnancies, mainly in the postpartum period, and up to 2% of Caesarean sections.[4-6] Several theories have been proposed to explain the increased risk of OVT in the peripartum and postpartum periods, including venous stasis or damage, endometritis, and increased circulation of von Willebrand factor and clotting factors I, II, VII, VIII, IX, and X.[4,7-9] Ovarian vein diameter increases threefold in pregnancy, and after delivery blood flow in the veins decreases, leading to stasis.[5,6] OVT occurs in the right gonadal vein in up to 90% of cases, most likely because of its longer length, multiple incompetent valves, and the dextrorotation of the gravid uterus.[2,4,5]

The classic presentation of OVT is the triad of pelvic pain, fever, and a right-sided abdominal mass, but tachycardia, hypotension, tachypnea, lower quadrant or flank pain, nausea, vomiting, ileus, and pyuria have also been reported.[2,4,6,8,10] Blood cultures are positive in rare cases.[6,11] Symptoms generally occur in the first 4 weeks postpartum but most frequently occur in the first 10 days.[4-6,12] It has been suggested that up to 50% of patients who are found to have OVT have a prothrombotic predisposition, such as antiphospholipid syndrome, factor V Leiden mutation, or protein S deficiency.[1,6,13]

In the past, laparotomy was used as a diagnostic tool for OVT and is still considered the gold standard.[8,11] Prior studies have evaluated various imaging modalities to diagnose septic puerperal OVT, and a consensus has not been reached as to which type of imaging is the modality of choice. One study showed magnetic resonance angiography had 100% sensitivity and specificity, computed tomography (CT) scan with IV contrast had 78% sensitivity and 62% specificity, and color Doppler ultrasound had 56% sensitivity and 42% specificity.[14] Conversely, a different study showed CT had 100% sensitivity and 99% specificity, and magnetic resonance imaging had 92% sensitivity and 100% specificity.[15] Differences in reported sensitivities and specificities may be attributable to broad confidence intervals for sensitivity without actual statistical difference, given both studies used similar reference standards and imaging equipment; however, this is difficult to confirm given confidence intervals were not reported by both studies.

Given the nonspecific presentation of OVT, it is critical to maintain a high level of suspicion because a delay in diagnosis may lead to potentially life-threatening complications, including ovarian abscess, ovarian infarction, septic thrombophlebitis, extension into the inferior vena cava (IVC), pulmonary embolization (PE), uterine necrosis, and ureteral compression.[2,4,6,8,14,16] When symptomatic and incidental PE were included, PE incidence rates in patients with OVT have been reported in up to 13% to 25% of cases and have even been observed after laparotomy to treat OVT.[4,11,16]

There are currently no treatment guidelines defined for OVT, but prior treatment recommendations for symptomatic and asymptomatic OVT have included antibiotics, hysterectomy, thrombectomy, ovarian vein ligation, ovarian vein excision, IVC ligation, and IVC filter placement.[3,6,17,18] Given an OVT can resolve spontaneously, the need for treatment, particularly anticoagulation, has also been debated.[3] In many cases, treatment when thrombophlebitis is suspected currently consists of 7 to 10 days of anticoagulation with IV heparin bridged to warfarin plus broad-spectrum antibiotics.[12,19] Up to 3 months of warfarin has been recommended if thrombus extends into renal veins or the IVC.[9] If septic thrombophlebitis is suspected, antibiotic options include ampicillin-sulbactam, piperacillin-tazobactam, ticarcillin-clavulanate, or ceftriaxone plus metronidazole.[20] Antibiotic choice has been guided by cervical or endometrial cultures in the past when available.[12]

The appropriate length of anticoagulation in patients diagnosed with OVT is still under investigation. Wysokinska et al analyzed the recurrence of OVT when compared with lower extremity DVT to determine the appropriate length of anticoagulation. The study included 35 patients diagnosed with OVT and 114 patients diagnosed with DVT over a 16-year period. The average length of anticoagulation with warfarin was 5.3 months in the OVT group and 6.9 months in the DVT group. Recurrence was comparable between the OVT and DVT groups at 3 per 100 patient-years of follow-up when thrombus extension was included in recurrence rate. All events within the OVT group occurred within the first 2 months of the initial thrombus. Given the comparable recurrence rates between the OVT and DVT groups, the authors concluded that general treatment guidelines for DVT may be applicable to OVT. They recommended 3 months of anticoagulation if an underlying cause was identified, whereas a longer course might be considered if an OVT was idiopathic.[3]

One study examined CT scans from 50 women with gynecologic malignancies who were 3 to 20 months postoperative from total abdominal hysterectomy and bilateral salpingo-oophorectomy. They found that 80% of these patients were found to have incidental, occlusive, unilateral OVT. Twenty patients had repeat CT scans at 3 to 24 months that showed unchanged OVT. Anticoagulants were not given to these patients. These subjects had CT scans every 3 months over a 2-year period and no apparent complications from OVT were seen. The authors argued that patients who had no radiologic evidence of phlebitis and were without symptoms of PE did not require treatment.[7]

Another study looked at 6 patients with known malignancies who were incidentally noted to have OVT on CT scans that were obtained for surveillance after treatment of their malignancies. None of the subjects was given antibiotics, and only 1 patient was treated with a week of heparin, whereas the other 5 subjects received no anticoagulants. Only 1 subject was symptomatic, and no apparent complications, including PE, were seen in any of these patients. Two subjects were noted to have resolution of OVT based on follow-up CT scans without treatment with anticoagulation; however, length of time between diagnosis and follow-up was not clearly defined for all subjects.[1]

Brown et al conducted a prospective randomized trial analyzing treatment of OVT in the setting of pelvic infection. After 5 days of IV antibiotics, 15 subjects who were persistently febrile had CT scans showing OVT. Half continued antibiotics alone and the other half continued antibiotics and IV heparin. There was no statistical difference between groups for time to fever resolution or length of hospital stay; however, the study had adequate power to evaluate fever resolution alone. None of the subjects continued anticoagulation upon discharge, and there were no apparent complications at 3 months of follow-up. Hypercoagulability and thrombus extension were not discussed by the authors of this study.[21]

Prior studies have failed to draw a consensus regarding the best treatment of OVT. The purpose of this study is to evaluate if patient outcomes change based on treatment, specifically anticoagulation. We hypothesize that there will be no difference in outcomes between patients anticoagulated and those not treated for OVT.

A retrospective chart review of patients in the Penn Medicine system was conducted with institutional review board approval. A list of subjects identified in either the outpatient or inpatient setting with any International Classification of Diseases, 9th edition (ICD-9), code corresponding to any type of clot or thrombus was assembled through our data analytics center from January 2010 to May 2015. This time frame was selected to ensure adequate data could be extracted from patients' charts because most of the health system had converted to an electronic medical record by 2010. This method was used because OVT does not carry a specific ICD-9 or ICD-10 code. Only patients older than age 18 years were included. Radiologist readings of the subjects' pelvic imaging including ultrasound, magnetic resonance imaging, magnetic resonance angiography, and CT were reviewed and subjects were included if reports included ovarian or gonadal vein thrombus. Two individuals performed data extraction to ensure duplicate data were not analyzed. A total of 50 subjects were identified as having OVT of 875 subjects reviewed from the inpatient electronic medical record and 561 subjects reviewed from the outpatient electronic medical record. Once subjects were identified, the following data were extracted from their charts: race, age at diagnosis, date of diagnosis, family history of thrombus, hypercoagulable work up if applicable, laterality of OVT, if OVT was occlusive, if OVT extended into adjacent veins, prior thrombus, context of diagnosis, treatment used, length of treatment, complications, and date of last contact (Table 1).

Of the 50 subjects identified, average age at diagnosis was 43.4 years. Fifty-six percent of subjects were African American, 38% were Caucasian, and 6% were of another ethnicity. Eight percent of patients had signs or symptoms of OVT on presentation, whereas 18% OVTs were incidentally found. Sixty percent of OVT were within the right gonadal vein, 14% were bilateral, and 24% were in the left gonadal vein. Thirty-eight percent of OVT were occlusive. Eight percent extended into adjacent veins, and 7 subjects (14%) were diagnosed with thrombi into other locations at the time of OVT

Table 1. Demographic and characteristics of patients identified with OVT

Characteristics	No. of patients (%)
Age at diagnosis, y	Average, 43.4
	Range, 20-87
Race	Asian n = 1
	Black or African American, n = 28 (56%)
	Other, n = 2
	White, n = 19
Signs or symptoms of OVT	Incidental, n = 9
	Fever, n = 4
	Abdominal or pelvic pain, n = 36 (72%)
	Unclear/not documented, n = 1
Laterality	Bilateral, n = 7
	Left, n = 12
	Right, n = 30 (60%)
	Unknown, n = 1
Occlusive	No, n = 15
	Yes, n = 19 (38%)
	Unknown, n = 16
Hypercoagulable	Sickle cell trait, n = 1
	Anticardiolipin Ab positive, n = 1
Extension into adjacent veins or other thrombi identified simultaneously diagnosis	Extension in adjacent veins, n = 4 (into IVC, n = 3; renal veins, n = 1)
	Other pelvic thrombi identified simultaneously, n = 2
	PE identified simultaneously, n= 2
	Iliac vein thrombus identified simultaneously n = 2
	Symptomatic LE DVT identified simultaneously, n = 1
Context of diagnosis	Active malignancy, n = 11
	Peripartum or postpartum, n = 9
	Recent surgery (<3 mo), n = 11
	Remote surgery (>3 mo), n = 3
	Hypercoagulable by history or laboratory diagnosis, n = 2
	Active infection (appendicitis, pancreatitis, PID) n = 4
	No apparent risk factors/provocation: incidental finding, n = 8
	Unknown, n = 2
Treatment	Anticoagulation alone, n = 30 (warfarin or LMWH)
	Anticoagulation with antibiotics, n = 3
	Antiplatelet (aspirin,) n = 1
	IVC filter, n = 2
	None, n = 12
	Unknown, n = 2

LMWH, low-molecular-weight heparin; PID, pelvic inflammatory disease.

diagnosis. One subject had a diagnosis of sickle cell trait, whereas another had anticardiolipin antibody. Eleven subjects had an active malignancy, 9 were peri- or postpartum, 11 had surgery within 3 months of diagnosis, 3 patients had remote surgery, and 4 had an active infection at time of diagnosis.

Regarding treatment, 12 subjects had no treatment, 2 had IVC filters placed, 3 were treated with antibiotics and anticoagulation, 30 were given anticoagulation alone, and 1 was given aspirin alone. Average length of follow-up was 23.7 months. Average length of anticoagulation was 13.2 weeks. Twelve patients (24%) had follow-up imaging. Ten patients had imaging showing resolution of OVT after anticoagulation, whereas 2 who received no anticoagulation had radiographically confirmed resolution of OVT. Five patients treated with therapeutic anticoagulation exhibited persistent OVT following treatment, whereas 4 who did not receive anticoagulation had persistent OVT on follow-up imaging.

Similar to prior studies, we found that most patients had right-sided OVT, and most OVT were found in the context of malignancy, pregnancy, the postpartum period, or postoperatively. There was a preponderance for identifying this complication in African American patients, who made up 56% of identified subjects. Of those patients presenting with abdominal or pelvic pain, 21 had other potential sources of abdominal or pelvic pain identified, whereas 15 had no other explanation of their pain other than OVT. Four percent of subjects were identified as having a hypercoagulable state, although this was not screened for in most patients. Symptomatic recurrence or bleeding was not seen in any of the subjects. PEs were seen in 4% of the subjects in our study, which is much lower than the 25% complication rate that has been previously reported. Seven (14%) of the patients identified in our study were diagnosed with DVTs or PEs in other locations at the time of OVT diagnosis. Such patients should be treated as per guidelines for treatment of their respective clots.

There was no statistically significant correlation found between treatment and no treatment in terms of overall outcomes for patients diagnosed with OVT. The limitations of our study include, but are not limited to, the small sample size, the retrospective nature of the study, a primary outcome (resolution of thrombosis) of questionable significance, and that treatment choice was not randomly allocated. Three of the 4 prior studies cited have similarly shown no difference in outcomes between those treated with anticoagulation and those not treated with anticoagulation, although these studies were observational or not adequately powered. The fourth study's findings were extrapolated to argue for treatment because patients with OVT had similar recurrence rates to patients with DVT when OVT extension was included in recurrence rates. Based on our findings, unless an OVT is symptomatic, septic in nature, or discovered with a coexisting DVT or PE, an incidentally detected OVT does not necessarily warrant anticoagulation therapy. This topic likely would be better explored with a registry study or a population-based study given the low apparent occurrence rate.

Acknowledgment: Zackory Burns significantly contributed to the data analysis in this paper; this research could not have been completed without his efforts.

Contribution: T.P. designed research, performed research, and wrote the paper; D.H. designed research; and K.D. performed research.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

ORCID profiles: T.P., 0000-0003-1844-8957.

Correspondence: Trisha Plastini, Pennsylvania Hospital, 1 Pine West, 800 Spruce St, Philadelphia, PA 19107; e-mail: trisha.sterlicchi@uphs.upenn.edu.

References

1. Jacoby WT, Cohan RH, Baker ME, Leder RA, Nadel SN, Dunnick NR. Ovarian vein thrombosis in oncology patients: CT detection and clinical significance. *AJR Am J Roentgenol*. 1990;155(2):291-294.
2. Harris K, Mehta S, Iskhakov E, et al. Ovarian vein thrombosis in the nonpregnant woman: an overlooked diagnosis. *Ther Adv Hematol*. 2012;3(5):325-328.
3. Wysokinska EM, Hodge D, McBane RD II. Ovarian vein thrombosis: incidence of recurrent venous thromboembolism and survival. *Thromb Haemost*. 2006;96(2):126-131.
4. Dunnihoo DR, Gallaspy JW, Wise RB, Otterson WN. Postpartum ovarian vein thrombophlebitis: a review. *Obstet Gynecol Surv*. 1991; 46(7):415-427.
5. Takach TJ, Cervera RD, Gregoric ID. Ovarian vein and caval thrombosis. *Tex Heart Inst J*. 2005;32(4):579-582.
6. Klima DA, Snyder TE. Postpartum ovarian vein thrombosis. *Obstet Gynecol*. 2008;111(2 Pt 1):431-435.
7. Yassa NA, Ryst E. Ovarian vein thrombosis: a common incidental finding in patients who have undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy with retroperitoneal lymph node dissection. *AJR Am J Roentgenol*. 1999;172(1):45-47.
8. Dessole S, Capobianco G, Arru A, Demurtas P, Ambrosini G. Postpartum ovarian vein thrombosis: an unpredictable event: two case reports and review of the literature. *Arch Gynecol Obstet*. 2003; 267(4):242-246.
9. Castaman G. Changes of von Willebrand factor during pregnancy in women with and without von Willebrand disease. *Mediterr J Hematol Infect Dis*. 2013;5(1):e2013052.
10. Ortin X, Ugarriza A, Espax RM, et al. Postpartum ovarian vein thrombosis. *Thromb Haemost*. 2005;93(5):1004-1005.
11. Kominiarek MA, Hibbard JU. Postpartum ovarian vein thrombosis: an update. *Obstet Gynecol Surv*. 2006;61(5):337-342.
12. Simons GR, Piwnica-Worms DR, Goldhaber SZ. Ovarian vein thrombosis. *Am Heart J*. 1993;126(3 Pt 1):641-647.
13. Salomon O, Apter S, Shaham D, et al. Risk factors associated with postpartum ovarian vein thrombosis. *Thromb Haemost*. 1999;82(3): 1015-1019.
14. Kubik-Huch RA, Hebisch G, Huch R, Hilfiker P, Debatin JF, Krestin GP. Role of duplex color Doppler ultrasound, computed tomography, and MR angiography in the diagnosis of septic puerperal ovarian vein thrombosis. *Abdom Imaging*. 1999;24(1):85-91.
15. Twickler DM, Setiawan AT, Evans RS, et al. Imaging of puerperal septic thrombophlebitis: prospective comparison of MR imaging, CT, and sonography. *AJR Am J Roentgenol*. 1997;169(4):1039-1043.
16. Benfayed WH, Torreggiani WC, Hamilton S. Detection of pulmonary emboli resulting from ovarian vein thrombosis. *AJR Am J Roentgenol*. 2003;181(5):1430-1431.
17. Clarke CS, Harlin SA. Puerperal ovarian vein thrombosis with extension into the inferior vena cava. *Am Surg*. 1999;65(2):147-150.
18. Maull KI, van Nagell JR, Greenfield LJ. Surgical implications of ovarian vein thrombosis. *Am Surg*. 1978;44(11):727-733.
19. Duff P, Gibbs RS. Pelvic vein thrombophlebitis: diagnostic dilemma and therapeutic challenge. *Obstet Gynecol Surv*. 1983;38(6): 365-373.
20. Chen K. Septic pelvic thrombophlebitis. UpToDate. 2016. http://www.uptodate.com/contents/septic-pelvic-thrombophlebitis. Accessed 1 June 2017.
21. Brown CE, Stettler RW, Twickler D, Cunningham FG. Puerperal septic pelvic thrombophlebitis: incidence and response to heparin therapy. *Am J Obstet Gynecol*. 1999;181(1):143-148.

DOI 10.1182/bloodadvances.2017006577