



## Full Length Article

## Pregnancy and non-pregnancy related ovarian vein thrombosis: Clinical course and outcome

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## ABSTRACT

**Objective:** To collect and summarize demographic, clinical, laboratory and radiologic characteristics, as well as management and follow-up data, of patients diagnosed with ovarian vein thrombosis.**Methods:** A multicenter retrospective review of all patients diagnosed with ovarian vein thrombosis between January 2000 and May 2015 at three university hospitals.**Results:** Data of 74 women were analyzed. Mean age was  $31 \pm 9$  years. Sixty (81.1%) cases were pregnancy-related. The presence of at least one underlying risk factor (most commonly active infection or surgery) was more common among pregnancy than non-pregnancy related cases (61.7% vs. 14.3%,  $P = 0.002$ ). Anticoagulation therapy was administered in 98.6% of patients and adjunctive antibiotic therapy in 39 (52.7%). At a median follow-up of  $40 \pm 38$  months, only one recurrent thrombotic event was observed, and no events of death. Median duration of anticoagulation treatment tended to be longer among patients with non-pregnancy related OVT (6 months [3–14] vs. 3 months [3–6],  $P = 0.1$ ). Thrombophilic evaluation detected any thrombophilic risk factor in 12 (20%) and 6 (42.9%) women with pregnancy and non-pregnancy related ovarian vein thrombosis, respectively ( $P = 0.09$ ).**Conclusion:** Pregnancy-related ovarian vein thrombosis is characterized by a provoked nature and a high rate of resolution after short term treatment. Treatment of three months duration of anticoagulation following this condition appeared in this study to be safe, with no recurrences encountered during a median follow up of 40 months. Thrombophilia seems to have an important role in ovarian vein thrombosis and should be evaluated in non-pregnancy related cases.

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## 1. Introduction

Ovarian vein occlusion due to thrombosis was first described in 1909 by Vineberg [1]. Ovarian vein thrombosis (OVT) occurs in 0.05–0.18% of pregnancies; most often encountered in the setting of the postpartum period [2]. Nevertheless, OVT is also associated with other causes such as prior pelvic surgery, malignancy, inflammatory bowel disease, and pelvic inflammatory disease [3–4]. Much of the available data on OVT are based on older publications and scattered case reports [3,5–8]. The clinical course, management strategies, and the role of thrombophilia among patients with OVT are poorly characterized, and conflicting results reported. Moreover, the natural history of OVT, in terms of

recurrence and expected survival, has not been well-described. Given the paucity of literature regarding clinical presentation, management and outcome of OVT, we performed this multicenter retrospective study of patients diagnosed with OVT in three large university hospitals in Israel. We also aimed to investigate whether the underlying etiology of OVT is related to the clinical course and treatment.

## 2. Materials and methods

## 2.1. Data collection

Three university hospitals in Israel participated in this study; each maintains an electronic database of all patients diagnosed with OVT. For all the patients included in this study the diagnosis of OVT was recorded in their electronic file. After hospital discharge, a special team of secretaries reviewed patient hospitalization files and added

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diagnoses that were not previously recorded. Between August and December 2015, we reviewed the electronic medical records of all cases of OVT managed between January 1, 2000 and May 31, 2015 at three hospitals. Data extracted included patient characteristics, clinical manifestations, laboratory findings, radiologic studies, and management and follow-up data from our thrombosis clinic. OVT was defined as 'acute' when all symptoms presented and persisted for <3 weeks; 'chronic' when at least one symptom persisted for >3 weeks; and 'asymptomatic' when none of the symptoms were present and OVT was diagnosed incidentally during radiologic evaluation. Thrombophilic evaluation, performed remotely from the thrombotic complication, included Prothrombin 20210, Factor V Leiden, Antithrombin, Protein C and S, anti-phospholipid antibodies and factor VIII. All patients who were diagnosed with antiphospholipid syndrome fulfilled the current diagnostic criteria-Sydney revision of Sapporo criteria [9]. Antiphospholipid antibodies tested included lupus anticoagulant, anticardiolipin IgM and IgG, anti beta2-glycoprotein1 IgM and IgG. The diagnosis of protein S deficiency was accepted only when testing was performed at least twice, from 6 months following pregnancy, following a period of time off anticoagulation. Institutional review board approval waiving informed consent was obtained for this retrospective study (No. HMO 0501-15) from Hadassah Medical Center Helsinki Committee.

## 2.2. Statistical analysis

Patient characteristics are described as means  $\pm$  SD and medians with interquartile range for continuous variables and as proportions for categorical variables. Significance between pregnancy and non-pregnancy related cases was assessed using the chi-square and Fisher's exact tests for categorical variables, while the Mann-Whitney *U* test was used for continuous variables without a normal distribution. Results are reported using *P*-values. A 2-sided *P*-value < 0.05 indicated statistical significance. SPSS 17.0 for Windows (IBM SPSS, New York, NY) was used for data management and analysis.

## 3. Results

### 3.1. Patient characteristics

A total of 74 women with OVT were identified, mean age 32  $\pm$  9 years (range 19–68). Sixty (81.1%) cases were pregnancy-related and the remaining 14 (18.9%) were non-pregnancy related. The mean age of the group of patients with pregnancy-related OVT was significantly lower than that of patients with non-pregnancy related OVT (mean 31  $\pm$  6 vs. 40  $\pm$  15 years, *P* = 0.05).

### 3.2. Clinical features

Most patients (89.2%) had acute presentation, whereas 6.8% and 4.1% had chronic and asymptomatic courses, respectively. The most common symptom was lower abdominal pain (78.4%), followed by constitutional symptoms such as nausea, vomiting, or anorexia (14.9%), and malaise (8.1%). Fever was present in 52.7% of patients. On examination, abdominal tenderness was noted in 57 (77%). Palpable abdominal mass was found in one patient (1.4%).

Compared to non-pregnancy related cases, patients with pregnancy-related OVT tended to present with fever (*P* = 0.02) and acute symptomatology (acute presentation: 93.3% vs. 71.4%, chronic: 3.3% vs. 21.4%, asymptomatic: 3.3% vs. 7.1%, *P* = 0.04). Symptoms such as nausea, vomiting, anorexia, and malaise were more common among non-pregnancy related cases (*P* = 0.004 and *P* = 0.08, respectively) (Table 1).

In 60 (81.1%) patients, OVT occurred in the setting of pregnancy, mostly in the puerperium (*n* = 54), and the remaining during the first trimester of pregnancy (*n* = 3), or following first trimester elective

abortion (*n* = 3). The mean number of children among these women was 3.6 (range 0–12).

During the study period, the approximate total number of births at the 3 participating hospitals was 500,000, resulting in a rate of 0.01% of puerperal OVT. Among puerperal cases, symptoms appeared after a median of 6 days (range 2–37) following delivery. Most of these cases (85%) occurred following singleton pregnancy, 13.3% following twin pregnancy, and one (1.7%) following triplet pregnancy. The mode of delivery was vaginal and caesarean in 50% of the cases each. The median week of delivery was 38 (range 27–42), and the median birth weight 3050 (range 875–4300) grams.

### 3.3. Clinical risk factors

In 24 patients (32.4%), OVT occurred in the course of an acute infection: lower urinary tract infection (*n* = 8), Gram positive or negative sepsis (*n* = 4), endometritis (*n* = 4), chorioamnionitis (*n* = 3), pyelonephritis (*n* = 2), extensive wound infection (*n* = 1), CMV-positive infectious mononucleosis (*n* = 1), and *Clostridium difficile* associated diarrhea (*n* = 1). Microorganisms that were cultured included *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Enterococcus*, group A streptococci, *Staphylococcus aureus*, *Bacteroides fragilis*, and *Clostridium difficile*.

In 33 patients (44.6%), OVT occurred postoperatively after caesarean section (*n* = 27), total abdominal hysterectomy (*n* = 2), dilation and curettage (*n* = 2), small bowel resection (*n* = 1), and surgical hysterectomy (*n* = 1). Evidence of preceding trauma was present in two women (2.7%). Only one patient (1.4%) had active cancer at the time of diagnosis.

Nine patients (12.2%) had a personal history of an unprovoked venous thrombotic event (4 pulmonary embolism, 4 deep vein thrombosis, and one mesenteric venous thrombosis); the rate was higher among non-pregnancy related cases (28.6% vs. 8.3%, *P* = 0.06). In all five pregnancy related cases low molecular weight heparin prophylaxis was administered at the time of diagnosis. The remaining four patients with non-pregnancy related OVT, were not receiving anticoagulation therapy when OVT was diagnosed.

At least one underlying risk factor for OVT was found in 37 (61.7%) of pregnancy-related cases compared to 2 (14.3%) non-pregnancy related cases (*P* = 0.002) (Table 1).

### 3.4. Laboratory findings

Mild anemia was present in 40 (54.1%) patients at presentation. Only 8 (10.8%) presented with thrombocytopenia (platelet count < 150,000/mm<sup>3</sup>).

Elevated white blood cell count was found in 39 (52.7%) patients. A 2–4-fold increase in lactate dehydrogenase was detected in 37.8% of patients. Both of the latter findings were more common in pregnancy-related cases (*P* = 0.001 and *P* = 0.01, respectively). Increased inflammatory markers (elevated C-reactive protein or erythrocyte sedimentation rate) were observed in 13 of 25 patients (52%) in whom they were tested. Only one patient (1.4%) had impaired kidney function at the time of diagnosis.

### 3.5. Diagnosis

Diagnostic imaging was performed in all patients. Computed tomography (CT) served as the diagnostic modality in 68 (91.9%). In the remaining six patients, the diagnosis of OVT was confirmed by means of Doppler ultrasonography (*n* = 4, 5.4%) and magnetic resonance imaging (*n* = 2, 2.7%). OVT was unilateral in 73 (98.6%) patients, affecting mostly the right side (*n* = 61, 82.4%). Extension of thrombus beyond the affected ovarian vein occurred in 19 patients (25.7%); and involved the inferior vena cava (*n* = 7), renal vein (*n* = 4) and iliac vein (*n* = 2). Non-fatal pulmonary embolism was diagnosed in association with OVT

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