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Review

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Ovarian Vein Thrombosis

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Abstract

Ovarian vein thrombosis (OVT) is a rare type of venous thromboembolism most common diagnosed in the postpartum period and peaking around 2-6 days after delivery. Clinical symptoms are not specific including fever and abdominal pain and the right ovarian vein is more frequently involved (70-80% of cases). The diagnosis of OVT is a clinical challenge because there are multiple other conditions that can present similarly, including ovarian torsion, tubo-ovarian abscess, pelvic inflammatory disease, puerperal endometritis, appendicitis, inflammatory bowel disease and pyelonephritis. Ultrasound Doppler is the first-line imaging; however, most cases are confirmed with computed tomography or magnetic resonance imaging. Mortality related to ovarian vein thrombosis is low due to the combination treatment of broad-spectrum antibiotics and anticoagulation. Extension of thrombus to inferior vena cava or renal veins and rarely pulmonary embolism could also occur. OVT is actually a type of deep vein thrombosis that could be life-threatening however mortality is low due to the combination treatment of broad-spectrum antibiotics and anticoagulation. Anticoagulant treatment duration of 3 to 6 months has been recommended like typical cases of venous thromboembolism.

Key words: Anticoagulation, ovarian vein, postpartum, thrombosis

Introduction

Ovarian vein thrombosis (OVT) is a rare condition most often seen in the immediate postpartum period that has been reported in approximately 0.01–0.18% of vaginal and in 2% of caesarian births. Although most cases occur in puerperal patients, OVT could also occur in other conditions like pelvic inflammatory diseases, malignancy, sepsis, pelvic surgeries and hypercoagulable states including autoimmune diseases or inherited thrombophilia factors. However, in 4 to 16% of cases, it can be classified as idiopathic.[1-3]

OVT remains poorly understood with no consensus regarding its importance and the best treatment approach. In this review article an attempt is made to highlight the risk factors that predispose to OVT, the common symptoms, the diagnostic approach, the complications and the recommended treatment.

Review of the Literature

A Pubmed search of English literature was performed in order to review reported cases of non-malignant OVT during the period 1980-2021.

Demographic Data – Risk Factors (Table 1)

Review of the literature revealed 208 patients with median age 31 years (range, 15-73 years). Cases with insufficient data were not analyzed.

Most cases (74.6%) were diagnosed postpartum;[3-118] 52.5% after vaginal delivery[4,5,7,9,13-15,18,19,21-24,27,29-34,36,38,41-48,50,51,55,60,62-64,66,71,74,76,77,79,80,84,86,88,92,93,96-101,105,108,111,113-115,118] and the rest after caesarian section.[3,6,8,10-12,16,19,20,26,28,35,37,39,40,42,49,52,53,57-59,61,65,67,70,73,78,88-91,95-97,102,106,107,109,116,117] The analysis of puerperal patients shown 17 cases with multiple pregnancies (mostly twin)[18,19,40,42,52,53,88,91,92,94,96,97,99,107,109,112] and in 28 cases a pregnancy complication was reported like urgent or preterm delivery, HELLP (Hemolysis, Elevated Liver Enzymes and low Platelets) syndrome, or other less frequent complications.[8,17,30,39,49,54,56,57,61,67,73,75,82,87,88,90,93,97,99,102,106,115,116]

In non-puerperal related cases a possible endometrial reason was reported most common fibroids (11 cases)[4,23] or intrauterine device (IUD) (4 cases).[112] Twenty-one patients underwent pelvic surgery or other gynecological procedures, mostly hysterectomy (11 cases).[10,16,21,25,26,59,60,120,122,124,125]

Thrombophilia screening was performed only in a minority of cases. The most common inherited risk factor was heterozygocity of *FV-Leiden.* Other procoagulant risk factors included the presence of antiphospholipid antibodies or other risk factors including past medical history of thromboembolic disease or use of oral contraceptive pills (OCP).[11,28,31,36,39,47,62,68,70,73,88]

During COVID-19 pandemic, 7 cases have already been reported within a recent infection and more cases are expected to be published within 2022.[7,13,128]

Yet, in 17 cases a causal related-factor could not

Table 1. Causative factors of OVT

ETIOLOGY	NO* CASES
Pregnancy related**	155
Vaginal delivery	80
Caesarian section	48
Urgent delivery - preterm birth	13
Multiple pregnancy (twins)	17
HELLP	3
Endometrial lesion	
Fibroids	11
IUD	4
Endometriosis	1
Cyst	2
Prolapse	1
Pelvic operations /procedures	
Hysterectomy	11
Salpingectomy	3
Other	4
Hysteroscopy	1
Intraabdominal inflammation	
Hydronephrosis	17
Pyelonephritis	4
Other nephropathy	3
Behcet	3
IBD	2
Gallstones - ERCP	4
Thrombophilia - Hypercoagulable state	
OCP	4
Thrombotic history	4
Venous thromboembolism	1
Stroke	5
Positive Family history	1
APS	2
Lupus anticoagulant	1
APS triple positive	5
Recurrent abortions possible APS	3
Inherited Thrombophilia Factors	2
FV-Leiden	6
Low protein C and/or S	
Hyperhomocysteinemia	
Multiple factors	
COVID-19 infection	7
Idiopathic	19

* Number of reported cases, ** 8 cases antepartum
APS: Antiphospholipid Syndrome, ERCP: Endoscopic Retrograde Cholangiopancreatography, HELLP: Hemolysis, Elevated Liver Enzymes and Low Platelets, IBD: Inflammatory Bowel Disease, IUD: Intrauterine Device, OCP: Oral contraceptive pills, OVT: Ovarian vein thrombosis

be prescribed and the case was reported as idiopathic.[14,64,132]

Symptoms

Symptoms are nonspecific. They include mainly lower abdominal tenderness with or without flank pain and fever that could be associated with tachycardia, chills, nausea and vomiting.

Diagnosis (Table 2)

In 84% of patients the diagnosis was made with non-invasive imaging techniques, mainly by computer tomography (CT) with contrast augmentation. In 15% of patients the diagnosis was made intraoperatively.[4,30,38,42,43,46,47,54,59,71,76,83,86,87,92-94,99,101,103,111,112,114-116,118,136,140] 88% of patients for whom the diagnosis was made during operation were postpartum and there was a highly suspicion of acute abdomen due to appendicitis before the diagnosis of OVT.

The localization was the right ovarian vein in 54% of reported cases,[3,5-8,10,11,15,16,18,20,23-28,30-32,35,37,38,40-56,60-66,69,71-74,76-78,82,86,89,90-94,96-98,102,107,108,111,115,119,123,125,126,128-131,134-136,138,140,141,146,149] the left in 37%[4,14,19,21,29,34,39,57,67,70,73,80,83,93,120,121,122,124,127,133,139,143,145] and both veins in 9%.[17,19,22,36,52,59,79,86,87,93,95,132,137,142]

Table 2. Diagnosis of OVT and thrombus localization/extension

	NO CASES
Diagnosis	
US-Doppler	5
CT	90
MRI	9
Combination of imaging techniques	5
Operation	33
Localization	
Right	112
Left	31
Both	18
Thrombus extension	
IVC	81
Renal	27
PE	25
Iliac	11

CT: Computed Tomography, IVC: Inferior vena cava, MRI: Magnetic Reasonance Imaging, OVT: Ovarian vein thrombosis, PE: Pulmonary embolism, US: Ultrasound

Extension of thrombus in inferior vena cava (IVC) was observed in 81 cases,[5,6,9,11,12,16,18,20,22-28,31,35,37-42,45,46,48,50,53,55,56,61-67,71,73-75,77-79,85-90,93,96-99,102,105-109,115,118-120,126,129,132,140,146,149,154,157,161,162,164] in renal veins in 27 cases,[21,22,28,29,39-41,59,66,70,77,93,96-98,103,106,109,124,127,133,149,157,158,164] iliac veins 11 cases.[40,42,62,65,71,79,88,93,98,105] In 25 patients pulmonary embolism (PE) was also diagnosed.[11,20,26,40,42,48,61,62,65,71,73,79,89,98,119,120,126,132,139,140,149,157,161,162]

Treatment

Anticoagulation treatment was given in the majority of cases (97%). Unfractionated heparin (UFH) or low molecular weight heparin (LMWH) was initiated in 70% of the cases and subsequently bridging to vitamin K antagonists (VKAs) in 40%.[4,7,9,10,12,14,17,19,21,23-28,30,34,36,39,42-46,48,51,55,59,60,64,65,67,73,74,79,82,89,91,96,98,99,102,105,106,109,115,118,120,121,122,129,138,144-147,152,154,159,161] In 14 patients novel direct oral anticoagulants (DOACs) were used.[11,16,20,119,125,128,132,134,136,140-143,150] Thrombolysis with alteplase (tissue-type plasminogen activator-tPA) was given in 8 patients.[66,71,77,78,90,105,133,149] One patient was treated with antiplatelet treatment with aspirin.[101] IVC filter was implanted in 6 patients[40,42,58,75,85,133,164] and surgical treatment with ligation was performed in 23 patients.[22,38,53,61,63,76,80,83,84,88,95-97,100,113,114,116,117,123,160,163]

Septic thrombophlebitis was demonstrated in few cases with positive cultures (Table 3). However, antibiotics were administered in 123 patients (59%).[4-7,9-12,15,17-19,22-34,37,38,41,43-48,51-53,56-60,62,63,65-67,71,72,74-80,82,84-86,88-99,101,102,105-109,111,114-118,120-124,126-128,135,144,154,156,160] In 4 patients a ureteral intervention was performed (either aspiration, stent insertion or nephrostomy).[36,42,50,131] Three patients were also treated with immunosuppressive drugs.[150,159,161]

Table 3. Septic thrombophlebitis and microorganisms dectected from cultures *(Blood, urine, vagina, cervix, placenta)*

Microorganisms
Staphylococci spp
MRSA
Staphylococcus aureus
Streptococci spp
Streptococci pyogenes
Streptococci group A
Streptococci group B
Enterococci spp
Enterococcus faecalis
Peptostreptococci
Bacteroides spp
Bacteroids bivius
Camplylobacter fetus
Fusobacterium necrophorum
Candida
Escherichia coli

Follow-Up

The duration of anticoagulation treatment varied from less than one month to more than a year and in most of the cases there were no data about actual duration. Improvement was observed in 115 patients[4,5,7,9,12,14-23,25-32,34,36,37,39-44,46-51,54,55,60,62-67,69-80,82-84,86,87,90,91,96-99,101,106-109,111,15,116,118-123,127,129,130,132-134,136,138,140,143,145-147,149,150,152,159-162] and adverse events in 6 patients[53,84,93,95,126,139] including death in 3 patients.[84,126,139]

Discussion

Austin described the first known case of OVT in the postpartum setting in 1956.[165] With the improvement in antiseptic techniques and the use of antibiotics, mortality has improved, but complications of OVT continue to be reported and include thrombus extension, PE, and ureteral obstruction.[166]

The pathogenesis of postpartum OVT is not clearly understood. The changes in fibrinolysis and coagulation during pregnancy are possibly the most important factors resulting in hypercoagulability in combination with the increase in the diameter and the capacity of the ovarian veins during pregnancy. It has also been demonstrated that the velocity of the blood flow in the ovarian veins decreases considerably immediately following delivery.[1,166] History of thromboembolic disease, inherited thrombophilia or other concomitant diseases associated with hypercoagulability have not been directly correlated. In the majority of reported cases of OVT, screening for thrombophilia risk factors was not performed. Salomon et al. retrospectively analyzed 22 patients with postpartum OVT and reported inherited prothrombotic risk factors in 50% of them; Five had heterozygocity of *FV-Leiden* and the rest either protein S deficiency or *MTHFR C677T* homozygocity. However, it should be noted that 73% had a caesarian section delivery.[167] In present review of the literature, thrombophilia screening was performed in a minority of reported cases and the most common reported inherited prothrombotic risk factor was heterozygocity of *FV-Leiden*.

Diagnosis requires a very high index of suspicion owing to its rarity and non-specific presentation. In the past, before the introduction into clinical practice of modern imaging techniques, diagnosis in most cases was based only on laparotomy. Nowadays, the diagnosis of OVT has become easier with non-invasive imaging techniques. Ultrasound is the initial imaging study of choice as it is inexpensive, free of radiation and doesn't require intravenous contrast. However, detection rates for OVT are poor, because it may not show the entire length of the vein in most cases secondary to obesity and/or overlying bowel gas.[168] In those cases the diagnosis could be made by CT with contrast augmentation or magnetic resonance imaging (MRI). On the other hand, symptomatic presentations are less common than those who are asymptomatic that makes the suspicion of OVT even

more difficult. The rise in the use of imaging may identify OVT that may not have been otherwise clinically evident. The incidence of OVT is higher in the right ovarian vein, with 70–90% of cases occurring on the right side, whereas 11–14% is bilateral. This is apparently from the longer length and the lack of competent valves on the right side.[151] Equivalent percentages are also observed in this review article and in almost 90% of cases the OVT occurred in the right ovarian vein. However, in the analysis by Assal et al. there was a similar incidence of right and left OVT (44.6 versus 41.4%, respectively) with a high percentage of bilateral thrombi (14.0%). Though, when the peripartum group was examined separately, a significantly higher incidence of right OVT (60%) and bilateral OVT (25%) was noted (P. 0.03).[166]

OVT is usually managed conservatively and most patients respond to antibiotics, anticoagulation, hydration and bed rest. Appropriate medical treatment should be started soon after diagnosis is confirmed to prevent serious complications. Heparin and warfarin have been traditionally used even in the postpartum period because are considered safe during lactation. To date, there are no data to support the use of DOACs in OVT. Single case reports and small series of patients have demonstrated good efficacy and safety in patients with portal vein thrombosis and cerebral venous thrombosis. These results are promising and may possibly extend the use of DOACs in other rare types of thrombosis as OVT. In literature there are few reports of patients with OVT treated with DOACs that showed similar efficacy with traditional treatment. However, in postpartum cases DOACs are contraindicated during lactation as they are excreted into breast milk. Thrombolytic drugs (alteplase, urokinase) have been used in few cases but are associated with a high risk of bleeding therefore they should be reserved for patients with massive thrombosis. Retrievable IVC filters can be used in cases of active bleeding including emergent surgical cases where anticoagulation is contraindicated or who have had a PE while on therapeutic anticoagulation. Surgical treatment with ovarian vein excision or ligation is rarely performed nowadays and is indicated only after the failure of conservative therapy or when the risk of PE is high. Initiation and appropriate duration of anticoagulation are also a matter of debate. Some argue that incidentally found OVT related to surgery may not need anticoagulation unless complications are noted[116] while a majority of experts believe rare thrombosis should be treated like lower extremity deep vein thrombosis (DVT).[169] There are no definitive guidelines for duration of anticoagulation. Some case reports suggest repeating imaging after 40 or 60 days and stopping anticoagulation if the resolution of thrombus or calcification is noted on follow-up imaging.

Even if prompt administration of anticoagulation is administered, thrombus expansion into the IVC and PE may develop. In fact, the risk of PE is up to 13% in cases with mortality of approximately 4%.[170] In the cohort of Assal et al. 9.9% of patients experienced recurrent VTE events, mostly DVT (82%) with average time to recurrence 409 days. All patients with recurrence were not during postpartum period and there recurrence was more common in patients with left OVT and bilateral OVT as compared with right OVT (P 0.01). The VTE recurrence rate in patients with a history of VTE was almost twice that of the overall group (18.2%), but was not statistically significant. Conversely, no statistically significant association between recurrence rate and a predisposing factor has been found. Moreover, even if there was a reduction in venous thromboembolism recurrence in the group that received anticoagulation, the results were not significant.[171]

OVT associated with septic pelvic thrombophlebitis could evolve into septic shock or emboli, which have a high mortality rate. Thus, physicians should consider OVT in any woman in the peripartum pe-

riod, after pelvic operations or in the setting of gynecological malignancy, with unexplained fever and lower abdominal pain not responding to antibiotics and analgesics and suggestive of acute appendicitis, endometritis, hydronephrosis, or ovarian torsion. A high index of suspicion and the ability to rule out other processes that may produce similar symptoms is important, because untreated OVT could even prove fatal. Prompt diagnosis and management especially in cases that mimic acute abdomen especially in the current endemic context of COVID-19 where thromboembolic complications are common. With the ongoing pandemic, the number of such cases is only expected to rise, and OVT should be a part of the differential.

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