Pelvic venous thrombosis

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ABSTRACT

While the thrombotic risk associated with lower limb venous reflux has been clearly reported in the literature, evidence is lacking on the potentially similar procoagulant effect generated by a venous incompetence in the pelvic region. A recent publication identified an incidental periuterine venous plexus thrombosis in 3% of the women undergoing a gynaecological consultation for whatever reason, suggesting a potentially underestimated condition worthy of further investigation. The present paper analyses the available literature on the topic, providing an insight covering both pathophysiological and clinical aspects.

Keywords: Pelvic, thrombosis, venous.

Pelvic venous disease (PeVD) represent a frequent, but too often overlooked or inappropriately managed disease, as reported by the interesting paper of Jurga-Karwacka et al.[1]

A constantly growing interest on the topic has been recently demonstrated by the international community, with dedicated consensus documents,[2] even focusing on the unmet needs.[3] A topic not included in unmet needs, but surely worthy to be mentioned, is the thrombotic risk associated with pelvic refluxes. A recent publication by Amin et al.[4] showed an incidental uterine venous plexus thrombosis (UVPT) in 3% of all the patients undergoing a gynecological consult.

Although venous thrombosis in unusual sites (i.e., vena cava, pelvic and genitourinary veins, upper extremities, cerebral veins, and splanchnic veins) has been reported, given the lack of extensive studies, its management has often been extrapolated from the experience of lower limbs venous thromboembolism (VTE).[5] Lower limb varicose veins and reflux-induced endothelial inflammation have been associated with a significant thrombotic risk increase.[6] To the best of our knowledge, the literature lacks the investigation of the pelvic reflux-induced endothelial mechanotransduction into a potential thrombotic trigger. This article focuses on evidence-based data related to pelvic venous thrombosis, including a pathophysiology perspective.

OVARIAN VEIN THROMBOSIS FINDINGS

Ovarian vein thrombosis (OVT) has been described after post-abortion infection, pelvic inflammatory disease, and recent pelvic surgery complicated by infection. It is frequently detected incidentally in patients undergoing total abdominal hysterectomy:
Pelvic venous thrombosis

up to 80% of patients develop unilateral OVT after 3 to 20 months from surgery.[7]

More interestingly, this condition is described in the context of the venous “reservoir” resection following the same hysterectomy procedure: a condition hemodynamically similar to the lower limb varicose veins reservoir. Ovarian vein thrombosis remains poorly understood with no consensus regarding its importance or treatment. Assal et al.[8] in a retrospective study investigated 223 women with OVT to identify clinical features, risk factors, treatment patterns, and prognosis of the disease. Risk factors such as peripartum, gynecological cancer, hysterectomy, gynecological surgery were considered in the study. Only 36.6% of the patients had abdominal pain and 61.4% had a history of gynecologic surgery. However, pelvic reflux was not considered in the study as a risk factor for OVT development.

There are only few cases of OVT reported to date in healthy individuals with no known etiology. Idiopathic OVT excludes conditions such as postpartum, malignancies, recent surgeries, and any other risk factors predisposing to a hypercoagulable state[9] and, to date, only nine cases of idiopathic OVT have been reported. Despite representing a rare diagnosis, OVT can potentially cause fatal complications and symptoms can be non-specific and include pelvic pain, fever, and abdominal discomfort.[10] Complications can be fatal and include septic thrombophlebitis, an extension of the thrombus into the inferior vena cava, and pulmonary embolism (PE), with an incidence of 25% in untreated OVT patients and a mortality of 4%. [9] Therefore, early recognition and prompt treatment are of utmost importance. Ovarian vein thrombosis can resolve spontaneously, but, considering the potentially dangerous consequences, anticoagulation treatment is usually recommended.[11] However, there is no definite guideline regarding the dosing and duration of anticoagulation therapy.

Wysokinska et al,[12] examined the incidence and the recurrence of OVT compared to lower extremity deep vein thrombosis (DVT). None of 35 patients in the OVT group were idiopathic and the recurrence rate was comparable to the patients diagnosed with lower extremity DVT (3/100 patient-years of follow-up). The mean treatment duration with anticoagulation was 5.3±3.2 and 6.9±6.8 months for OVT and lower extremity DVT, respectively. Based on these findings, the authors suggested the application of lower extremity guidelines for the treatment of OVT.

Di Nisio and Carrier[12] suggested an anticoagulation therapy to treat OVT, considering that the incidentally detected splanchnic vein thrombosis is similar to clinically suspected splanchnic vein thrombosis in terms of prognosis. In the multivariate analysis performed by Riva et al.[13] a decrease of the incidence of thrombotic events was observed (hazard ratio [HR]: 0.85, 95% confidence interval [CI]: 0.76-0.96) without increasing the risk of major bleeding (p<0.05) using anticoagulation treatment, although further studies are needed to corroborate this evidence.

**Uterine Venous Plexus Thrombosis Findings**

Little information is available regarding UVPT. To shed light on this, Amin et al.[4] studied the clinical prevalence and the risk factors related to incidental UVPT in 1,383 non-pregnant women, 39 of whom had an incidental UVPT with 3.0% of prevalence. Several risk factors were identified such as multiparity (odds ratio [OR]: 5.75, 95% CI: 2.10-15.7), recent surgery (OR: 3.10, 95% CI: 1.19-8.07), and presence of leg varicose veins (OR: 3.15, 95% CI: 1.32-7.49).

Another important risk factor for UVPT is the family history of VTE (OR: 8.74, 95% CI: 1.65-46.4), which must be considered for the correct identification of the risk profile of each patient. Also, body mass index (BMI) is considered a risk factor due to the correlation between obesity and venous hypertension, even in the absence of a venous disease.[14,15] The role of BMI in PVD is of particular interest, considering it has also been recently identified as a protective factor for pelvic refluxes.[16] In the aforementioned study, no correlation was identified between postmenopausal status and UVPT (OR: 0.36, 95% CI: 0.13-0.95),[4] even if an increased risk of developing VTE in women over the age of 55 was previously reported (HR: 1.5, 95% CI: 1.0-2.4).[17]

A higher proportion of women with UVPT involved in the study of Amin et al.[4] showed pelvic pain and menorrhagia. Menorrhagia may be associated with polycythemia and reactive thrombocytosis which could lead to a prothrombotic state that is closely associated with VTE.[18]

**Pelvic Venous Thrombosis Diagnosis**

Venography is considered the reference standard test for the diagnosis of PeVD. Although it is a valid
method for diagnosing, it is invasive, and time- and cost-consuming.\[19\]

Venous ultrasound protocols for PVD detection are available in the literature, yet have focused on the reflux identification rather than on the thrombosis diagnosis.\[20\] The diagnosis of thrombosis by compression ultrasound is limited by the absence of nearby rigid anatomical structures and by the intestinal gas. The transvaginal ultrasound technique is considered a more optimal method for identifying a pelvic venous thrombosis due to the ability to get very close to the pelvic veins by the use of a Doppler.\[21\]

Clinical series have shown that thrombosis in uterine veins can be detected by transvaginal ultrasound examination. A study comparing transvaginal ultrasonography with venography techniques showed 91% specificity in identifying veins >5 mm in diameter (95% CI; 77-98%).\[19\]

Leibovitz et al.\[22\] described a case of incidental pelvic vein thrombosis owing to the description of the dilation of the pelvic veins. The few data reported in the literature are controversial, indicating a range of expansion of the vessels between 10 and 16 mm or between 5 and 15 mm.\[22,23\]

PELVIC VENOUS THROMBOSIS PATHOPHYSIOLOGY CONSIDERATIONS

Thrombosis can be associated with vessel wall damage, venous stasis, and a clotting disorder.\[24\] In PVD, venous reflux and pooling-induced stasis can lead to vein wall inflammation and consequent thrombosis, in a hemodynamic scenario similar to the lower limb chronic venous disease one.\[6,25\]

The literature data suggest the possible role of hypoxia on the vein wall distension with an impact on the vasa venarum perfusion impairment; this event would result in unusual endothelial hypoxia.\[26\] As a consequence, leukocytes would migrate in the area affected by the damage, the vessel wall would remodel, and a thrombotic event may occur.

Maloni et al.\[27\] showed the pathophysiological role of reflux associated with thrombotic events through hypoxia theory with active venous hypertension related to the activation of the muscle pump. Interestingly, venous hypertension in pelvic venous disease is also associated with constipation. Indeed, the prolonged standing of the feces in the intestine causes an increase in the intra-abdominal pressure which generates an increment in the capillary pressure which forces the fluid into the interstitial spaces. Therefore, venous stasis can produce a risk of thrombosis or edema affecting the pelvic venous system.\[28\]

There is also a “passive” hypertension strictly correlated with pelvic reflux through molecular mechanosensory biosignaling in which physical forces are translated into biochemical signals. Endothelial cells are constantly exposed to two vascular forces: shear stress, which is the frictional force carry out by blood flow, and circumferential stretch, due to blood flow pulsating. Vessels stretch is normal, but can arise also from hypertension, causing thickening of arterial walls.\[29,30\]

Endothelial cells have many mechanosensors to sense the blood flow. These sensors can be divided into three main categories:

- Luminal sensors: G protein-coupled receptors (GPCRs, S1P1 and bradykinin receptor B2) and heterotrimeric G proteins; ion channels (TRPV4, TRPP2, TRPC1, Piezo1 and Piezo2); cilia (associated with PKD1 and PKD1 channels); the glycocalyx (composed of glycoproteins, hyaluronan, and proteoglycan such as Syndecan-1 and -4); protein-coated membrane called caveolae (structure given by Caveolin 1-3 and Cavin 1-3).
- Junctional sensors: PECAM-1, VE-Cadherin, and VEGFR2 proteins, which form a complex which generate many signaling pathways as a response to cutting.\[31\]
- Basal sensors: integrins, that are the link between extracellular matrix and actin cytoskeleton, and responding to shear stress forces or changes in cytoskeletal tension.

Review of the literature reveals that an alteration of this signal transduction pathway by abnormal signal/mechanical stimuli can induce vascular disorders such as atherosclerosis, aortic aneurysm, and hypertension.\[32\]

Recently, glycocalyx has been identified as an innovative treatment target. It dampens the force of shear stress that reaches the surface of blood vessels.\[33\]

Syndecans, in complex with glyocalyx, link to the cytoskeleton through their cytoplasmic termini, providing a possible mechanism for force transfer from shear stress to the cytoskeleton. The removal of syndecan causes the inhibition of shear stress responses of endothelial cells, disrupting actin dynamics. As a
result, endothelial cells are not able to form new stress fibers after application of shear.[33]

Due to its role in the regulation of shear stress vessels, glyocalyx has been recently identified as an innovative treatment target. Literature data have shown that sulodexide, a heparinoid, can reconstruct the endothelial glyocalyx after damage in a rat carotid artery model.[34]

The clinical translation benefit was demonstrated by the review of Bikdeli et al.[35] on sulodexide molecule with a positive impact in venous and arterial thrombo-inflammation process.

A final consideration is about fever with unknown origin identified in patients with pelvic venous reflux.[36] The causes of hyperpyrexia can be divided into four categories: infective (17 to 35%), inflammatory (24 to 36%), neoplastic (10 to 20%), and miscellaneous (3 to 15%).[31] Inflammatory disorders, solid tumors, hematological malignancies, and miscellaneous are non-infective causes of pyrexia of unknown origin;[37] however, no pelvic reflux or pelvic thrombosis has been reported among non-infective causes, even if hyperpyrexia has been described in patients with pelvic venous reflux. Nonetheless, it has been demonstrated that DVT is the main cause of unknown hyperpyrexia in 6% of cases.[38] Further investigations should be addressed to explore the eventual role of PVD-associated pelvic thrombosis as a cause for the hyperpyrexia of unknown origin in these patients.

In conclusion, pelvic venous thrombosis, particularly in the peritumoral venousplexus may be an underdiagnosed and undertreatment condition. Furtherlarger-scale investigations are needed to develop a proper objective ultrasound protocol for the detection of PVD thrombosis, including the uterine venousplexus. Indeed, diagnosis and management of PVD-related thrombosis still remain achallenging scenario in the everyday clinical practice.

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REFERENCES


