Turkish Journal of Vascular Surgery 2021;30(Supp. 1):S22-S26

Invited Review

DOI: 10.9739/tjvs.2021.S56894
www.turkishjournalofvascularsurgery.org

Pelvic venous thrombosis

Sergio Gianesini[1], Erica Menegatti[1,2], Oscar Bottini[3], Yung-Wei Chi[4]

[1]*Department of Translational Medicine, University of Ferrara, Ferrara, Italy*
[2]*Department of Surgery, Uniformed Services University of Health Sciences, Bethesda, USA*
[3]*Division of Phlebology, German Hospital, Argentina*
[4]*Department of Cardiovascular Medicine, University of California Davis, California, USA*

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:

Received: September 15, 2020 ***Accepted:*** September 15, 2020 ***Published online:*** October 22, 2021

Correspondence: Sergio Gianesini, MD, PhD, FACS. Department of Translational Medicine, University of Ferrara, 44121 Ferrara, Italy.
e-mail: gnssrg@unife.it

Citation:
Gianesini S, Menegatti E, Bottini O, Chi YW. Pelvic venous thrombosis. Turk J Vasc Surg 2021;31(Supp. 1):S22-S26

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).[30]
- 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 glycocalyx, 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, glycocalyx has been recently identified as an innovative treatment target. Literature data have shown that sulodexide, a heparinoid, can reconstruct the endothelial glycocalyx 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 periuterine venous plexus may be an underdiagnosed and undertreat condition. Further larger-scale investigations are needed to develop a proper objective ultrasound protocol for the detection of PVD thrombosis, including the uterine venous plexus. Indeed, diagnosis and management of PVD-related thrombosis still remain a challenging scenario in the everyday clinical practice.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Jurga-Karwacka A, Karwacki GM, Schoetzau A, Zech CJ, Heinzelmann-Schwarz V, Schwab FD. A forgotten disease: Pelvic congestion syndrome as a cause of chronic lower abdominal pain. PLoS One 2019;14:e0213834.
2. Antignani PL, Lazarashvili Z, Monedero JL, Ezpeleta SZ, Whiteley MS, Khilnani NM, et al. Diagnosis and treatment of pelvic congestion syndrome: UIP consensus document. Int Angiol 2019;38:265-83.
3. Khilnani NM, Meissner MH, Learman LA, Gibson KD, Daniels JP, Winokur RS, et al. Research priorities in pelvic venous disorders in women: Recommendations from a Multidisciplinary Research Consensus Panel. J Vasc Interv Radiol 2019;30:781-9.
4. Amin T, Cohen H, Wong M, Goodhart V, Pointer SL, Jurkovic D. The prevalence of incidental uterine venous plexus thrombosis in women attending a gynecology clinic. J Thromb Haemost 2020;18:2557-65.
5. Bombeli T, Basic A, Fehr J. Prevalence of hereditary thrombophilia in patients with thrombosis in different venous systems. Am J Hematol 2002;70:126-32.
6. Chang SL, Huang YL, Lee MC, Hu S, Hsiao YC, Chang SW, et al. Association of varicose veins with incident venous thromboembolism and peripheral artery disease. JAMA 2018;319:807-17.
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;172:45-7.
8. Assal A, Kaner JD, Danda N, Cohen HW, Billett HH. Risk factors and prognosis of ovarian vein thrombosis. Blood Coagul Fibrinolysis 2017;28:468-74.
9. Harris K, Mehta S, Iskhakov E, Chalhoub M, Maniatis T, Forte F, et al. Ovarian vein thrombosis in the nonpregnant woman: An overlooked diagnosis. Ther Adv Hematol 2012;3:325-8.
10. Hafsa C, Golli M, Jerbi-Omezzine S, Salem R, Kriaa S, Zbidi M, et al. A rare aetiology of the post-partum fever: Ovarian vein thrombophlebitis. Ann Fr Anesth Reanim 2006;25:286-90. French.
11. Wysokinska EM, Hodge D, McBane RD 2nd. Ovarian vein thrombosis: Incidence of recurrent venous thromboembolism and survival. Thromb Haemost 2006;96:126-31.
12. Di Nisio M, Carrier M. Incidental venous thromboembolism: Is anticoagulation indicated? Hematology Am Soc Hematol Educ Program 2017;2017:121-7.
13. Riva N, Calleja-Agius J. Ovarian vein thrombosis: A narrative review. Hamostaseologie 2021;41:257-66.
14. Padberg F Jr, Cerveira JJ, Lal BK, Pappas PJ, Varma S, Hobson RW 2nd. Does severe venous insufficiency have a different etiology in the morbidly obese? Is it venous? J Vasc Surg 2003;37:79-85.
15. Willenberg T, Schumacher A, Amann-Vesti B, Jacomella V, Thalhammer C, Diehm N, et al. Impact of obesity on venous hemodynamics of the lower limbs. J Vasc Surg 2010;52:664-8.
16. Nanavati R, Jasinski P, Adrahtas D, Gasparis A, Labropoulos N. Correlation between pelvic congestion syndrome and body mass index. J Vasc Surg 2018;67:536-41.

17. Canonico M, Plu-Bureau G, O'Sullivan MJ, Stefanick ML, Cochrane B, Scarabin PY, et al. Age at menopause, reproductive history, and venous thromboembolism risk among postmenopausal women: The Women's Health Initiative Hormone Therapy clinical trials. Menopause 2014;21:214-20.
18. Fletcher H, Wharfe G, Williams NP, Gordon-Strachan G, Pedican M, Brooks A. Venous thromboembolism as a complication of uterine fibroids: A retrospective descriptive study. J Obstet Gynaecol 2009;29:732-6.
19. Steenbeek MP, van der Vleuten CJM, Schultze Kool LJ, Nieboer TE. Noninvasive diagnostic tools for pelvic congestion syndrome: A systematic review. Acta Obstet Gynecol Scand 2018;97:776-86.
20. Labropoulos N, Jasinski PT, Adrahtas D, Gasparis AP, Meissner MH. A standardized ultrasound approach to pelvic congestion syndrome. Phlebology 2017;32:608-19.
21. Goodacre S, Sampson F, Thomas S, van Beek E, Sutton A. Systematic review and meta-analysis of the diagnostic accuracy of ultrasonography for deep vein thrombosis. BMC Med Imaging 2005;5:6.
22. Leibovitz Z, Degani S, Shapiro I, Tal J, Paz B, Levitan Z, et al. Diagnosis of pregnancy-associated uterine venous plexus thrombosis on the basis of transvaginal sonography. J Ultrasound Med 2003;22:287-93.
23. Mavrelos D, Cohen H, Pateman K, Hoo W, Foo X, Jurkovic D. Diagnosis of uterine vein thrombosis on transvaginal ultrasound. Ultrasound Obstet Gynecol 2013;42:480-3.
24. Line BR. Pathophysiology and diagnosis of deep venous thrombosis. Semin Nucl Med 2001;31:90-101.
25. Fletcher H, Wharfe G, Williams NP, Gordon-Strachan G, Pedican M, Brooks A. Venous thromboembolism as a complication of uterine fibroids: A retrospective descriptive study. J Obstet Gynaecol 2009;29:732-6.
26. Malone PC, Agutter PS. To what extent might deep venous thrombosis and chronic venous insufficiency share a common etiology? Int Angiol 2009;28:254-68.
27. Malone PC, Agutter PS. Deep venous thrombosis: The valve cusp hypoxia thesis and its incompatibility with modern orthodoxy. Med Hypotheses 2016;86:60-6.
28. Naramore S, Aziz F, Alexander CP, Methratta S, Cilley R, Rocourt D. Fecal impaction causing pelvic venous compression and edema. Pediatr Rep 2015;7:5999.
29. Chien S. Mechanotransduction and endothelial cell homeostasis: The wisdom of the cell. Am J Physiol Heart Circ Physiol 2007;292:H1209-24.
30. Lu D, Kassab GS. Role of shear stress and stretch in vascular mechanobiology. J R Soc Interface 2011;8:1379-85.
31. Givens C, Tzima E. Endothelial mechanosignaling: Does one sensor fit all? Antioxid Redox Signal 2016;25:373-88.
32. Yamashiro Y, Yanagisawa H. The molecular mechanism of mechanotransduction in vascular homeostasis and disease. Clin Sci (Lond) 2020;134:2399-418.
33. Weinbaum S, Tarbell JM, Damiano ER. The structure and function of the endothelial glycocalyx layer. Annu Rev Biomed Eng 2007;9:121-67.
34. Li T, Liu X, Zhao Z, Ni L, Liu C. Sulodexide recovers endothelial function through reconstructing glycocalyx in the balloon-injury rat carotid artery model. Oncotarget 2017;8:91350-61.
35. Bikdeli B, Chatterjee S, Kirtane AJ, Parikh SA, Andreozzi GM, Desai NR, et al. Sulodexide versus control and the risk of thrombotic and hemorrhagic events: Meta-analysis of randomized trials. Semin Thromb Hemost 2020;46:908-18.
36. Petersdorf RG, Beeson PB. Fever of unexplained origin: Report on 100 cases. Medicine (Baltimore) 1961;40:1-30.
37. Fernandez C, Beeching NJ. Pyrexia of unknown origin. Clin Med (Lond) 2018;18:170-4.
38. Aburahma AF, Saiedy S. Deep vein thrombosis as probable cause of fever of unknown origin. W V Med J 1997;93:368-70.