Vascular Diseases in Women

Subjects: Cardiac & Cardiovascular Systems

Contributor: Katalin Farkas, Agata Stanek, Stephanie Zbinden, Barbara Borea, Simina Ciurica, Vanessa Moore, Peggy Maguire, Maria Teresa B. Abola, Elaine B. Alajar, Antonella Marcoccia, Dilek Erer, Ana I. Casanegra, Hiva Sharebiani, Muriel Sprynger, Maryam Kavousi, Mariella Catalano

According to the World Health Organization, cardiovascular disease (CVD) is the leading cause of death among women worldwide, yet its magnitude is often underestimated. Biological and gender differences affect health, diagnosis, and healthcare in numerous ways. The lack of sex and gender awareness in health research and healthcare is an ongoing issue that affects not only research but also treatment and outcomes. The importance of recognizing the impacts of both sex and gender on health and of knowing the differences between the two in healthcare is beginning to gain ground. There is more appreciation of the roles that biological differences (sex) and sociocultural power structures (gender) have, and both sex and gender affect health behavior, the development of diseases, their diagnosis, management, and the long-term effects of an illness.

Keywords: women ; vascular diseases ; risk factors ; gender differences

1. Cerebrovascular Disease

The WHO reports that, globally, there are more than 77 million people who are currently living and have had a stroke, and almost two-thirds of these were due to ischemic stroke. Annually, 55% of all ischemic strokes occur in women and fifty-two percent of all stroke-related deaths are among women [1]. One of the important risk factors for stroke incidence and mortality is advanced age. Men have a higher lifetime risk of ischemic stroke but, beyond the age of 85, stroke risk is higher in women [2]. Elderly women have more severe strokes, poorer outcomes, and more difficult access to stroke care [3]. Beyond the age of 60, changes in vascular function, such as endothelial dysfunction and arterial stiffness, are accelerated in women [4].

Atherosclerotic carotid artery disease is one of the treatable causes of cerebrovascular disease. In 1999, the Tromsø study, which was among the first to describe sex differences in the prevalence of atherosclerotic carotid artery disease, reported that more women beyond the age of 75 had more carotid plaques [5]. More contemporary data on women aged 30–79 years report that the estimated prevalence rates of increased carotid intima-media thickness, carotid plaque, and carotid stenosis are lower among women versus men: 23.2% vs. 32.1%, 17.1% vs. 25.2%, and 1.2% vs. 1.8%, respectively [6].

Sex differences in carotid plaque morphology and composition based on histology and non-invasive imaging have been reported. Women were found to have higher rates of stable fibrous/fibrocalcific plaques, while men had higher rates of unstable plaques, with high-risk features such as large intraplaque hemorrhage, thin fibrous cap, large lipid core, and more inflammatory cells [7].

The role of sex hormones in the development of atherosclerosis, plaque instability, and stroke risk has been reported. Estradiol appears to have a protective effect in women against stroke that decreases after menopause [8]. Thus, it is believed that estradiol can slow the progression of atherosclerosis if hormone therapy is started soon after menopause when the endothelium is relatively healthier [9].

Sex differences in the management of carotid disease have also been described, with a greater reduction in stroke risk observed in women when medical management was offered in large trials of carotid stenosis trials; however, women were reported to be less likely to receive preventive medical therapy. On the other hand, women were underrepresented in carotid surgery trials and only post-hoc analyses suggested that women benefited less from surgical intervention, although medical management at that time was not as optimal as what current medical treatment can offer. Furthermore, postoperative outcomes have been reported to be less favorable among women and it has been hypothesized that this may be due to smaller mean diameters of the carotid arteries in women, which may present greater technical difficulty during carotid endarterectomy [10].

2. Abdominal Aortic Aneurysms

Gender-based differences in prevalence, diagnosis and management have been reported in abdominal aortic aneurysms (AAA). In a cross-sectional study of 1.5 million women and 0.8 million men tested in clinics, the overall prevalence of AAA was 0.6%, and it more common in men (1.5%) compared to women (0.25%), with higher prevalence in smokers. Compared to nonsmokers, the risk of AAA among those with a smoking history was 15 times greater in women (RR 15, 13.2–17.0), with significant associations in women <75 years (RR 26.4, 20.3–34.2) [11].

The 2022 AHA/SVS [12] and 2019 [13] ESVS Guidelines recommend repair in unruptured aneurysms with a diameter of 5.0 cm in women, with recommendation levels of class IA and class IIB, respectively. In a Swedish registry of 32,393 AAA patients, the proportion of treated versus untreated women was lower (17% versus 23%), and treated women were older compared to men (76.1 [8.5] years versus 73.0 [8.5] years) and more frequently suffered from COPD. Although the median times to rupture and death were similar at approximately 2.8 years, there was a higher risk of rupture and poorer survival among untreated female patients at all time points up to 5 years after diagnosis [14]. In a retrospective cohort of 16,386 patients with AAA, surgical repair was performed in 27% of women compared to 18% of men ($p < 0.001$). Women were more likely to undergo open surgical repair (RR 1.65; 95% CI 1.51–1.80), with open repair indicated for elective (RR, 1.82, 95% CI, 1.65–1.99) and symptomatic (RR, 1.46, 95% CI, 1.15–1.81) aneurysm. In those who had endovascular repair, women were more likely to have traditional risk factors such as smoking, older age, hypertension, and a family history of AAA. A similar trend was observed with open repair.

Women presented with smaller aneurysms (mean [SD], 57 [11.7] mm vs. 59 [17.7] mm in men; $p < 0.001$). Among those where aortic anatomy data was collected during endovascular repair (EVR), aortic neck lengths and neck diameters were shorter while aorta-neck angles and neck-AAA angle were larger in women. Between 2003 and 2015, sex-specific treatment practices changed, with increased use of EVR in women over time. Women who underwent EVR were more likely to be poor candidates for open repair ($p < 0.001$). Short-term (1 year) and long-term (10 year) survival rates were poorer in women after both open and endovascular repair, although sex-based differences were more significant after the latter. Although no significant sex differences were observed with open repair for elective or symptomatic aneurysms, women who underwent open repair for ruptured AAA had a greater risk of death, which was not statistically significant with endovascular intervention [15].

3. Lower Extremity Arterial Disease

Lower extremity arterial disease (LEAD), also called lower extremity peripheral artery disease (LEPAD), is the third component of the manifestations of systemic atherosclerosis [16]. Moreover, it is the main cause of lower limb amputation and a major risk factor for cardiovascular mortality [17][18]. Women with LEAD are on average 10–20 years older than men. It pertains to the diminished vascular benefits of estrogen, leading to a reduction in vasodilation and the absence of its antioxidant properties. Common risk factors for LEAD persist across sex, encompassing smoking, hypertension, diabetes mellitus, and dyslipidemia. However, in the case of women, the duration of smoking emerged as a risk factor for LEAD after just 10 years, in contrast to the 30-year threshold observed in men [19]. Despite that, other risk factors associated with LEAD in women have been shown to include obesity, osteopenia/osteoporosis, hypothyroidism, use of oral contraceptives, hormone replacement therapy, and complications associated with pregnancy (pre-eclampsia, gestational hypertension, placental abruption, and placental infarction) [20]. In addition, women with diabetes exhibit an increased hypercoagulable state, impaired endothelium-dependent vasodilation, more pronounced atherogenic dyslipidemia, and a higher prevalence of metabolic syndrome compared to diabetic men [21].

Recent epidemiological investigations indicate that women exhibit a prevalence of LEAD comparable to, if not higher than, that observed in men. This pattern is evident across diverse populations, encompassing women from low- and middle-income countries (LMIC) and those in socioeconomically disadvantaged groups. Nevertheless, it is crucial to acknowledge the potential underestimation of these figures, given that women frequently display asymptomatic or atypical symptoms in contrast to men, posing challenges in accurate diagnosis [22][23]. Symptoms in women, often resembling arthritis, neuropathy, or spinal stenosis, can be misconstrued as atypical manifestations of LEAD [24].

Furthermore, there is evidence indicating a higher prevalence of asymptomatic LEAD in women compared to men [20][21][24]. Moreover, women also have twice the prevalence of limb-threatening ischemia (CLTI) and more multilevel arterial occlusive disease [25][26]. Porras et al. [27], in their systematic review and meta-analysis, revealed that women diagnosed with LEAD tend to experience rest pain more frequently, with a lower prevalence of intermittent claudication.

Women have a greater functional impairment of the lower extremities, with a shorter distance from the treadmill to intermittent claudication, a shorter maximum distance from the treadmill, and a poorer quality of life compared to men [20][28]. The diminished treadmill claudication distances observed in women with LEAD may be attributed to their lower cardiopulmonary fitness and a self-perceived ability to climb stairs that is inferior to that of men. Consequently, Gardner et al. emphasize the importance of prioritizing exercise rehabilitation for women with intermittent claudication as a subgroup of LEAD patients, aiming to enhance their physical function [28]. Furthermore, the typical presentation of intermittent claudication in women generally occurs about 10–20 years later in age than men, and post-menopause [29].

In some cases, in women, making a diagnosis of LEAD can be a challenge. Women exhibit distinct fat distribution patterns in the lower body, limbs, and hips compared to men. This unique distribution can pose challenges for conducting precise physical examinations, including the assessment of pulses and bruits [30]. Additionally, duplex ultrasound may have some limitations in the examination of women. The high calcified arteries reported in women with diabetes and the elderly can cause difficulty in assessing the lumen of the artery. Moreover, in certain instances of obesity, the precision of this approach may be compromised, particularly in the proximal aorto-iliac arterial segments. Additionally, women demonstrate a higher susceptibility to adverse drug reactions associated with iodinated contrast media compared to men. This susceptibility may impose limitations on the utilization of CT and contrast angiography for the diagnosis of LEAD in women. In addition, some women having ABI > 1.4, as a consequence of arterial stiffness (patients with diabetes and end-stage renal disease, which occur more frequently in women) require alternative tests to diagnose LEAD [30].

Moreover, it was also reported that women with peripheral vascular diseases have low levels of knowledge and awareness about vascular diseases [31]. There are also differences between women and men concerning the use of guideline-directed medical therapy (GDMT)/optimal medical treatment. Women face a lower likelihood of being prescribed statins, antiplatelet agents, and angiotensin-converting enzyme inhibitors compared to men [32][33]. Even among high-risk patients with concurrent diabetes mellitus or chronic kidney disease, women are less likely to receive ACEi/ARB than men. Additionally, among individuals with diabetes, women exhibit inferior glycemic control compared to men. Furthermore, Black women are less frequently prescribed guideline-directed medical therapy (GDMT) compared to White women [34]. Additionally, fewer women undergo surgical intervention for LEAD [35]. They often have endovascular procedures. Nonetheless, women experience increased in-hospital complications following endovascular surgery, marked by elevated occurrences of bleeding, complications at the vessel access site, hematoma, or pseudoaneurysm [35]. In addition, women, after endovascular intervention, also have a higher risk of myocardial infarction, dissection, amputation, and death [36]. In the study by Hasan et al., it was shown that in women with LEAD who underwent peripheral vascular intervention (PVI), female gender was an independent predictor of major adverse cardiovascular events (MACE), mortality, non-fatal stroke, major bleeding, and higher cost. In turn, there were no significant differences in the rates of myocardial infarction, vascular complications, limb amputation, acute kidney injury, or length of stay [37]. However, Parvar et al. showed higher mortality and MACE rates in men with LEAD despite other accepted gender disparities [38].

A report from VASCUNET and the International Consortium of Vascular Registry presented data on symptomatic LEAD open surgical revascularization and peripheral vascular intervention (PVI) from 2010 to 2017. The information was gathered from administrative and registry data in the populations of 11 countries. Notable differences between women and men were evident in terms of patient age (72 vs. 70 years), the percentage of octogenarians (28% vs. 15%), the prevalence of claudication (45% vs. 51%), the incidence of PVI (57% vs. 51%), and the duration of hospital stay (7 days vs. 6 days) [39].

4. Vasculitis

Vasculitis is a heterogenous group of diseases defined by the presence of leucocytic inflammatory infiltrate in the vessel walls with reactive damage to the mural structures and necrosis. The endothelial injury can lead to thrombosis and ischemic tissue damage while the damage to endothelial wall can cause aneurysm and perforation with subsequent hemorrhage [40]. The most frequently observed vasculitis in women is Takayasu Arteritis (TAK), also known as ‘pulseless women’ disease, which is a systemic inflammatory condition leading to damage to the medium and large arteries and their branches. It is a rare disease with a reported worldwide incidence rate of only 1 to 2 per million. It occurs predominantly in young Asian girls and women under 40 years of age. Female preponderance is characteristic of TAK (9:1). TAK exhibits a panarteritis pattern, initiating around the vasa vasorum and the medioadventitial junction. Early stages show active inflammation with mononuclear cell infiltration, elastic fiber fragmentation, and giant cell granulomatous reaction. Later phases involve reactive fibrosis, increased ground substance, mural thrombus, and neovascularization. Severe inflammation can lead to smooth muscle cell loss, medial weakening, vascular dilatation, and aneurysm formation. In the healed phase, adventitial fibrosis, scarring, and laminar medial necrosis become prominent, surpassing those seen in other aortic inflammatory disorders. Clinical manifestations of TAK vary with disease stage and vascular region

involvement. The disease progresses through three stages: Stage I, the “prepulseless” phase, marked by constitutional symptoms; Stage II, the “pulseless” phase, characterized by vascular inflammation symptoms; and Stage III, the “fibrotic” stage, involving complications from vascular damage. Few patients reach the third stage, and only 19% follow a triphasic progression through all three stages [41].

The 2018 EULAR guidelines for the pharmacological treatment of TAK recommend a two-phase strategy, with a combination of conventional glucocorticoid and synthetic DMARD in phase I, and a biologic DMARD in phase II if relapse occurs [42]. The 2021 American College of Rheumatology guidelines also recommend glucocorticoid combination therapy with DMARDs but differ in recommending tumor necrosis factor inhibitors as an option in initial therapy; tocilizumab is recommended in refractory disease [43]. Antiplatelet therapy is associated with a lower frequency of ischemic events but with an increase in bleeding. It is recommended in critical cerebrovascular disease or in vertebrobasilar involvement, but not routinely [43]. Vascular lesions in TAK are responsible for most of the morbidity and mortality associated with the disease, but current guidelines favor restricting invasive therapy (open surgery or endovascular treatment) in TAK to life- or organ-threatening situations, refractory hypertension, or when patient activities are significantly affected [41].

5. Vasospastic Diseases

Vascular dysregulation, the so-called vasospastic syndrome (VSS), occurs in the context of subjects who have a tendency to respond to stimuli such as coldness or emotional stress with inappropriate vasoconstriction or insufficient vasodilation in the microcirculation. Individuals experiencing vasospastic syndrome typically exhibit cold hands and feet along with abnormal vasoconstriction following exposure to local cold. Women are more commonly affected than men, and the initial symptoms often manifest during puberty, diminishing with age, particularly after menopause. The syndrome appears to have a hereditary component. Key symptoms include cold hands and, occasionally, cold feet. Elevated plasma ET-1 levels have been noted in those with vascular dysregulation [44]. Diagnosis methods for vasospastic syndrome include nailfold capillaroscopy combined with cold provocation. Vasospastic diseases like Raynaud’s syndrome, acrocyanosis, and erythromelalgia vary in prevalence, clinical presentation, therapy, prognosis, and impact on quality of life. **Raynaud’s syndrome**, affecting 5 to 20% of the European population, is more common in women, typically emerging around the age of 40. Attacks involve transient white-blue-red or white and blue discoloration of fingers and toes, triggered by cold or stress, lasting minutes to hours. Primary, secondary (with known causes), and suspected secondary Raynaud’s syndromes are differentiated. Treatment options include vasodilators, particularly long-acting calcium channel blockers. **Acrocyanosis**, a vasospastic acral disorder, results in persistent reddish-livid discoloration, primarily in hands and feet, with a higher incidence in women before the age of 25. Primary acrocyanosis lacks an identifiable cause, whereas secondary forms may respond to vasodilators and long-acting calcium channel blockers. Primary and secondary **erythromelalgia**, a rare condition, involves paroxysmal burning pain and redness in the legs, feet, and occasionally hands, triggered by warmth. Onset typically occurs between 40 and 55 years, with various therapeutic approaches that are occasionally successful [45].

6. Chronic Venous Insufficiency

Chronic venous insufficiency (CVI) is a vein disorder affecting millions of people every year. Women are more commonly affected than men [46]. Long-term inadequate venous function in the lower limbs presents a diverse range of clinical manifestations, spanning from asymptomatic cosmetic concerns to severe symptoms [47][48][49]. These can include telangiectases, reticular veins, varicose veins, edema, pigmentation and/or eczema, lipodermatosclerosis, atrophie blanche, and venous ulceration. Irregular venous flows in the lower extremities are detected in about 50% of individuals, with the estimated prevalence of Chronic Venous Insufficiency (CVI) varying depending on population studies [49].

Both men and women share common risk factors, including age, deep vein thrombosis, obesity, smoking, cancer, occupation, muscle weakness, leg injury, inactivity, family history, phlebitis, and footwear choices [50]. However, women, particularly during pregnancy and due to poor biomechanics related to footwear, are more susceptible to chronic venous insufficiency compared to men.

The main pathophysiological cause of the clinical manifestation of CVI of the lower extremities is ambulatory venous hypertension, which is caused by venous valve reflux, venous flow obstruction, or both [47][49][51].

To understand the pathophysiology of CVI or varicose veins, as well as their therapeutic options, such as endovenous ablations, one should know the anatomy and variations of the veins [37][38]. The venous system can be divided into three major components: the superficial venous system, the deep venous system, and perforating veins. The superficial veins are most frequently affected in patients with chronic venous disease [49][51].

Clinical manifestations of CVI encompass discomfort, swelling, varicose veins, and skin alterations or ulceration. Venous leg discomfort is commonly characterized as a dull ache, throbbing, heaviness, or pressure sensation, especially after prolonged standing, and can be alleviated by measures that reduce venous pressure, such as leg elevation, compression stockings, or walking. However, approximately 20% of patients with other CVI clinical features do not experience leg discomfort, while around 10% solely present with this symptom [33]. In individuals with varicose veins, tenderness may arise due to venous distension. Cutaneous changes involve skin hyperpigmentation, stasis dermatitis, and ulceration. Hemosiderin deposition causes hyperpigmentation. Notably, hyperpigmentation in nonvenous conditions, like acanthosis nigricans or hemosiderosis, tends to be more diffuse or affects other body areas. Lipodermatosclerosis denotes inflammation of subcutaneous fat. Distinguishing a venous ulcer from an ischemic ulcer involves noting that ischemic ulcers are typically deeper, often exhibiting gangrenous edges or a gangrenous base [49][51].

Establishing an accurate diagnosis of CVI relies on a thorough history and physical examination. The physical examination should be conducted in an upright position to maximize vein distension. Both non-invasive and invasive diagnostic tests play crucial roles in supporting the diagnosis. In patients with CVI, the DUS examination should reveal both the anatomical patterns of veins and abnormalities in venous blood flow within the limbs.

Conservative management is the initial approach for all patients displaying signs and/or symptoms of CVI. The primary component of conservative management is the use of compression stockings. Additionally, encouraging risk modifications, such as weight reduction in obese individuals, regular walking exercise, and smoking cessation, is essential as part of conservative treatment [49][51].

The use of medical treatment for CVD has been a practice for many years, although there is some debate about its precise role in the treatment approach. Venoactive drugs (VADs) find extensive prescriptions in certain countries but are not universally available. These drugs fall into two categories: natural and synthetic. The primary mechanisms of action for VADs include reducing capillary permeability, minimizing the release of inflammatory mediators, or enhancing venous tone [52]. Numerous compounds have undergone testing with varying degrees of success, but among the most promising drugs are Ruscus extracts, micronized purified flavonoid fraction, calcium dobesilate, horse chestnut extract, hydroxyethylrutosides, red vine leaf extract, and sulodexide [49][51].

Open surgical therapy of varicose veins with high ligation and stripping of the GSV combined with the excision of large varicose veins has been the standard of care for more than a century. During the past decade, endovenous ablation therapy has largely replaced this classic ligation and stripping.

There are two types of thermal ablation therapy: EVLA and RFA. Both are guided by ultrasound. The mechanism involves a heat generator that causes local thermal injury to the vein wall leading to thrombosis and fibrosis. EVLA and RFA showed the same safety and efficacy in terms of quality of life, occlusion, thrombophlebitis, hematoma, and recanalization after 1 year [49][51][52]. The most common complication is bruising, which is observed in up to 75% of patients who receive ablation therapy. Other potential but rare complications include superficial vein thrombosis, DVT (especially EHIT), skin burns, pigmentation, and nerve injury.

Sclerotherapy is the least invasive percutaneous technique, using chemical irritants to close unwanted veins. Telangiectases, reticular veins, small varicose veins, and venous segments with reflux can be treated with sclerotherapy [49][51].

Women must be mindful of chronic venous insufficiency, as lower extremity venous disease is a relatively common yet frequently overlooked medical issue. Given its association with a broad clinical spectrum, it is essential to approach patients with suspicion of this condition. A comprehensive understanding of the normal anatomy and functioning of the venous system is necessary to accurately comprehend and diagnose the pathophysiology of CVI. Functional assessment through Doppler ultrasound (DUS) is indispensable for diagnosing patients with CVI. Although compression stockings serve as a cornerstone in conservative management, low compliance poses a significant challenge to this therapy. Considering the symptomatic nature, earlier adoption of venous ablation therapy should be contemplated for these patients.

7. Venous Thromboembolism

The most important acute venous pathology is venous thromboembolism (VTE), which is the combined name for deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is the third most common cardiovascular disease, with an annual incidence of 100–200 per 100,000 people. The reported annual incidence rates of PE ± MVT and MVT-only cases vary from 29–78 and 45–117 per 100,000 population, respectively, according to different surveys. The prevalence of VTE

increases with age, with a higher percentage in women at younger ages and in men at older ages. In women of reproductive age, VTE is a specific risk.

VTE is a major cause of morbidity and mortality during pregnancy and the postpartum period. The relative risk of VTE increases 5-fold during pregnancy and 60-fold in the puerperium (6 weeks postpartum) [53]. Incidence of VTE increases slightly above that of the general population in the first trimester, rises to a greater degree during the third trimester, and peaks in the first two weeks after delivery. Approximately half of all pregnancy-associated VTEs occur postpartum. Pregnancy-associated risk factors for VTE include cesarean delivery, assisted reproductive technology, stillbirth, preterm birth, preeclampsia, obstetric hemorrhage, and postpartum infection. Medical conditions associated with antepartum or postpartum VTE include preexisting diabetes mellitus, inflammatory bowel disease, systemic lupus erythematosus, and sickle cell disease. More than half of pregnancy-related VTEs are associated with an underlying thrombophilia [54].

In women, hormonal contraception also significantly increases the risk of VTE, especially when combined with other risk factors such as obesity, smoking, or hereditary thrombophilia. Increased risk of thrombosis is also associated with ovarian stimulation therapy, in the background of which studies have demonstrated the effect of supraphysiological estrogen levels on various coagulation factors [55].

Once the acute trigger has disappeared, the associated increased risk of thrombosis disappears, whereas persistent predisposing risk factors play an important role in the recurrence of VTE.

VTE recurs in about 30% of patients in the 10 years following an acute event, regardless of the length of acute treatment. Independent predictors of recurrence are age, male sex, active malignancy, and neurological disease with lower limb paralysis. Other predictors of recurrence include idiopathic VTE, lupus anticoagulant or antiphospholipid antibody, antithrombin, protein C or protein S deficiency, hyperhomocysteinemia, persistently elevated plasma D-dimer in idiopathic VTE, and residual venous thrombosis [56]. Various VTE recurrence-prediction scores have been developed to assess the risk of recurrence, particularly in patients with idiopathic or cancer-related VTE. In women with idiopathic VTE, if up to one of the following risk factors was identified, the risk of recurrence of VTE was significantly lower: (1) older age (≥65 years), (2) obesity (BMI ≥ 30 kg/m^2), (3) increased D-dimer before stopping warfarin therapy, and (4) signs of post-thrombotic syndrome. The risk of recurrence after discontinuation of anticoagulation for a combined oral contraceptive-associated VTE was low, and this was lower than after an unprovoked VTE [57]. Persistently elevated D-dimer after discontinuation of anticoagulant therapy, age group over 50 years, male sex, and VTE unrelated to hormonal therapy (in women) increased the risk of recurrence of idiopathic VTE in the DASH prediction score [58].

Typical symptoms of lower limb DVT include swelling, pain, redness, and dilatation of the superficial veins in the affected limb, although sometimes the disease may be asymptomatic. Scoring systems (most commonly the Wells score) used to determine the probability of DVT play an important role in its diagnosis, with DVT being classified as high, medium, or low probability. The “gold standard” for objective confirmation of DVT is the compression ultrasound (CUS). Pregnant patients with normal proximal CUS results should have dedicated iliac vein testing (typically Doppler/duplex ultrasonography or, rarely, non-contrast MRI) if they have symptoms of iliac vein DVT [54]. For the evaluation of PE, computed tomography pulmonary angiography (CTPA) has become the diagnostic-imaging standard. Planar lung ventilation/perfusion scintigraphy is a common test in pregnancy. Most young pregnant women do not have significant lung disease, and guidelines support the use of perfusion-only scintigraphy (i.e., no ventilation scan) in pregnant patients with normal chest radiographs to reduce maternal and fetal radiation exposure [54]. Among the laboratory tests, an elevated (>0.5 mg/mL) quantitative D-dimer level supports but does not confirm the diagnosis of VTE, as it can be elevated in many other conditions (postoperative, infectious, liver disease, heart failure, cancer, pregnancy, and DIC).

Treatment of DVT is based on anticoagulation. The agent used in the acute phase may be subcutaneous LMWH, intravenous or subcutaneous unfractionated heparin (UFH), or subcutaneous fondaparinux. In parallel to being given oral vitamin K antagonist (VKA) treatment, parenteral anticoagulation should be continued until the INR is between 2 and 3 on two consecutive days, but for at least 5 days. There are also new or direct (DOAC) oral anticoagulants available for the treatment of VTE, which act by inhibiting fibrin (dabigatran) or activated factor X (apixaban, edoxaban, and rivaroxaban). They have the advantage of not requiring INR control, having no food interactions, and having significantly reduced drug interactions. The duration of anticoagulant treatment is known, with 3 months for transient cause, at least 6 months for unknown cause, and at least 12 months for recurrent DVT. The duration of treatment is also influenced by the degree of recanalization detectable by duplex ultrasound examination. Most cases of pregnancy-related VTE can be treated with low molecular weight heparin, but cases of limb- or life-threatening VTE require consideration of thrombolysis and other reperfusion therapies [59].

Obstetricians–gynecologists, infertility, and menopausal specialists have key roles in the prevention of VTE in women, and in taking into account the increased risk of VTE in treated women.

8. Lymphedema

Lymphedema is a prevalent (2–4/1000) [60] but frequently overlooked disease caused by an imbalance between the production and reabsorption of lymphatic fluid due to disruption or overload of the lymphatic system. It can be a primary manifestation of congenitally abnormal lymphatic vessels or can be secondary to other conditions that damage the lymphatic vessels or lymph nodes. Although multiple factors intervene in its pathophysiology, the lymphatic endothelium expresses estrogen receptors, suggesting a role of estrogen in the lymphatic function that may explain the higher prevalence in females (60–80% of the population) [60][61][62][63].

Individuals born with agenesis or hypogenesis of the lymphatic vessels will develop lymphedema at a different age, either alone or within a syndrome (Noonan, Turner, etc.). Primary lymphedema is rare (1–10%) and more prevalent in females after puberty, suggesting hormonal influence [61][64]. Penetrance is variable, and in some patients it may develop after a triggering event [65].

Worldwide, it is caused most by filarial infection. In developed countries, common causes of secondary lymphedema include cancer and cancer therapies, followed by obesity, infection, and inflammatory disorders. It can appear years after the initiating event. Cancer-associated lymphedema is more common in females: prevalence is high in breast cancer (13–20%) and gynecological malignancies (20–37%) compared to other malignancies equally distributed by gender [66][67]. The risk of lymphedema is influenced by the therapy, being higher for lymph node resection and radiation. Tamoxifen, a partial estrogen receptor agonist used in hormone-dependent breast cancer has been associated with lymphatic dysfunction and may predispose to lymphedema [64].

Edema affecting one or both limbs is the main clinical finding. Patients describe tightness, heaviness, or discomfort. Initially, the edema is soft, pitting, and improves with elevation. As lymphedema progresses, it becomes constant and non-pitting due to cutaneous fibrosis and adipose deposition. The skin thickens, as evidenced by Stemmer’s sign (the inability to pinch the skin below the second toe) and develops hyperkeratosis with verrucose lesions. In females with breast cancer-associated lymphedema, more than 60% reported that it affected their body imaging and sexuality [68]. A common theme in patient forums revolves around finding suitable options for clothing to accommodate for the size discrepancy of the limbs and compression garments.

Lipedema, almost exclusively affecting females, can be mistaken for lymphedema; however, both conditions may overlap. Lipedema impacts quality of life, social, and emotional functioning. Its diagnosis is frequently delayed, as is the appropriate management and support [69]. The presence of port-wine stains or limb discrepancy should raise concern for Klippel–Trenaunay–Weber syndrome, vascular malformations, or hemihypertrophy.

Diagnosis can be delayed, as often body changes are attributed to obesity. Typical clinical features in the right clinical setting establish the diagnosis of lymphedema. Surveillance of patients at risk, (breast cancer, gynecological malignancies) may help to reduce time lapses in diagnosis and treatment.

Objective measurements of the volume of the affected limb obtained with water displacement methods, circumferential measurements, or electronic volumetry are helpful for assessing the effectiveness of therapies [67]. Lymphoscintigraphy is commonly used to assess the lymphatic flow. It obtains serial images after administration of a radiolabeled agent, distally, in the affected limb.

Complex decongestive therapy is the cornerstone of lymphedema therapy regardless of the underlying reason, and its goal is to achieve and maintain maximal volume reduction in the affected limb. This multi-modality therapy is performed by a specialized therapist in multiple sessions and it includes manual lymphatic drainage, multilayer bandaging, decongestive exercises, and chronic use of compression garments. Pneumatic pumps providing intermittent compression specially designed for lymphedema therapy can be used for maintenance, in addition to compression garments. These treatment modalities are time consuming and require lifelong commitment.

Surgical therapy can be considered in selected patients, directed at restoring lymphatic flow in the early stages of the disease [67] or at reducing the limb size, in severe forms of lymphedema, in addition to compression garments [70].

Most studies focusing on quality of life and psychosocial consequences of lymphedema have been conducted in women with lymphedema after breast cancer and its treatment. Among breast cancer survivors, patients with lymphedema had

significantly higher medical costs, hospitalizations, and medical visits than those without lymphedema [71][72]. Among female survivors of other cancers, those with lymphedema reported lower physical function and required more assistance for activities of daily living [73]. Lifting restrictions, limited mobility, and fear of infections restrict the possibilities of actively participating in work, hobbies, or sports. Other recurring themes that describe the impacts of lymphedema on daily life include altered body image, sleep disturbances (avoiding the affected site, elevation of the limb during sleep), burden of self-care (economic cost, time-consuming tasks, and need to alter their wardrobe), and the impact of living with a chronic disease [74][75].

9. Pelvic Congestion Syndrome

Pelvic congestion syndrome (PCS) is a venous disorder characterized by chronic non-cyclic pelvic pain caused by venous insufficiency predominantly associated with pelvic varicosities in women [76]. Environmental factors such as pregnancy, obesity, jobs associated with prolonged standing or heavy lifting, some treatment interventions such as pelvic surgery and estrogen therapy, some anomalies in pelvic venous anatomy, and a genetic basis are risk factors involved in the pathology of PCS [77][78][79].

There are four anatomical zones in the abdomen and pelvis that are related to the pathophysiology and consequently symptoms of PCS, including the left renal vein; the gonadal, internal iliac and pelvic veins; the pelvic origin extra-pelvic veins; and the lower extremity veins. The pathophysiology of PCS is considered in three domains of the anatomic, hemodynamic, and etiologic. Based on the SVP classification, which includes symptoms (S), varices (V), and a pathophysiologic domain, which is a composite anatomic-hemodynamic-etiologic domain (P), the inferior vena cava, left renal vein, gonadal veins, iliac veins, and pelvic escape veins are anatomic segments of this classification. Also, the underlying pathological hemodynamic can be reflux or obstruction, and the etiology can be thrombotic, non-thrombotic, or congenital [78][80]. In addition, there are other factors involved in the pathogenesis of PCS, including estrogen, inflammation, vasoactive peptides such as endothelin, calcitonin gene-related peptide (CGRP) and substance P (SP), and nociceptive mechanism, which activates the autonomic nervous system by sexual and non-sexual stimuli, and neuropathic and psychogenic mechanisms [81][82].

According to anatomical zones, there are three categories of symptoms, including venous renal symptoms, chronic pelvic pain, and extra-pelvic pain. Left renal vein compression (usually associated with nutcracker syndrome) can lead to renal venous hypertension, microhematuria or macrohematuria, and left flank or abdominal pain that is worsened by activities such as standing, sitting, or walking. Symptoms of this category are more prevalent on the left side. The second category of symptoms are characterized by chronic pelvic pain characterized as a dull unilateral or bilateral pain associated with negative cognitive, behavioral, sexual, and emotional consequences and symptoms related to lower urinary tract, sexual, bowel, pelvic floor, myofascial, or gynecologic dysfunction. Symptoms are often worse with activities such as walking and prolonged standing and improve with lying down. Symptoms of this category are sensitive but non-specific. The third group of symptoms is subdivided into symptoms localized to the external genitalia or lower extremities, including reflux-related symptoms, symptoms related to posteromedial thigh, sciatic/tibial nerve varices, and venous claudication associated with iliocaval venous obstruction. Also, renal hilar varices, pelvic varices, and pelvic origin extra-pelvic varices are varices classifications related to the anatomical zones [76][78][80].

In addition to considering the clinical manifestations as a spectrum and performing SVP classification, the first line of diagnosis includes non-invasive approaches, including pelvic ultrasound, cross-sectional computed tomography (CT) and magnetic resonance (MR) imaging, whereas conventional venography is the gold standard procedure for PCS diagnosis [76][83]. Depending on the SVP class, which is diagnosed and confirmed by imaging, there are different options for treatment, including pharmacological and hormonal therapy, endovascular therapy, and surgery [83][84].

PCS diagnosis is common in young women of reproductive age. Chronic pain and reduced physical activities are the main factors that affect the quality of life of PCS patients by limiting their social activity and the possibility of regular work. Furthermore, there is no explanation for the chronic pelvic pain of about 61% of patients. The fact that these patients do not know the reason for their pain makes their life harder than the group that is aware of their diagnosis [81][85].

In addition to social life, they have major challenges in family life with sexual challenges, infertility, and pregnancy. Symptoms such as dysmenorrhea, dysuria, and dyspareunia can affect sexual function [85]. In addition, some case reports indicate that persistent genital arousal can be associated with PCS [86][87]. Infertility is another challenge for PCS patients due to ovarian varices or pelvic congestion caused by inferior vena cava obstruction [76][88][89]. As mentioned below, pregnancy is a risk factor for PCS. Compression of the iliac veins by the gravid uterus, elevation of blood volume, and dilation of the ovarian and pelvic veins during pregnancy are the factors that make multiparous women prone to PCS [76]

[79][90]. In addition, the pain that worsens during pregnancy makes pregnancy difficult for PCS patients [91]. There is a lack of knowledge about the risk of deep vein thrombosis during pregnancy in PCS patients. These limitations and challenges in different aspects of the life of the PCS patient can affect their quality of life and induce psychological pressures that can not only affect their mental health, but also affect the circulation of the pelvis due to vasodilation [82][85].

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