

Relationship between deep vein thrombosis and its risk factors in the female population*Relación entre la trombosis venosa profunda y sus factores de riesgo en la población femenina**Relação entre trombose venosa profunda e seus fatores de risco na população feminina***Patricia Bossolani Charlo¹**

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The aim was to identify the risk factors related to the development of deep venous thrombosis in the female population of Maringá. This is a quantitative research, carried out with the female population attending two vascular surgery outpatient clinics in a municipality in the northwest of Paraná, from November 2019 to March 2020, with a structured collection instrument. Data analysis was performed with the aid of the software and description of absolute and relative frequency. The results found showed a high prevalence of deep venous thrombosis in women over 66 years of age, and a significantly higher number of cases in white people. Systemic arterial hypertension was shown to be the main comorbidity in the population studied, followed by venous insufficiency and heart disease. Were concluded that there is a significant relationship between several risk factors and deep vein thrombosis in the female population, as well as an important understanding of each of these factors, a fact that is necessary for an adequate transfer of information to this target population.

Descriptors: Women's Health; Risk Population; Thrombus.**Resumen**

El objetivo fue identificar los factores de riesgo relacionados con el desarrollo de trombosis venosa profunda en la población femenina de Maringá. Esta es una investigación cuantitativa, realizada con la población femenina que asiste a dos clínicas ambulatorias de cirugía vascular en un municipio en el noroeste de Paraná, desde noviembre de 2019 hasta marzo de 2020, con un instrumento de recolección estructurado. El análisis de los datos se realizó con la ayuda del software y la descripción de la frecuencia absoluta y relativa. Los resultados encontrados mostraron una alta prevalencia de trombosis venosa profunda en mujeres mayores de 66 años y un número significativamente mayor de casos en personas de raza blanca. Se demostró que la hipertensión arterial sistémica es la principal comorbilidad en la población estudiada, seguida de insuficiencia venosa y enfermedad cardíaca. Concluimos una relación significativa entre varios factores de riesgo y trombosis venosa profunda en la población femenina, así como una comprensión importante de cada uno de estos factores, un hecho que es necesario para una transferencia adecuada de información a esta población objetivo.

Descriptores: Salud de la Mujer; Población en Riesgo; Trombo**Resumo**

Objetivou-se identificar os fatores de risco relacionados ao desenvolvimento da trombose venosa profunda na população feminina de Maringá. Trata-se de uma pesquisa quantitativa, realizada com a população feminina frequentadora de dois ambulatórios de cirurgia vascular em um município do noroeste do Paraná, de novembro de 2019 a março de 2020, com um instrumento de coleta estruturado. A análise dos dados foi feita com auxílio do software e descrição de frequência absoluta e relativa. Os resultados encontrados mostraram uma alta prevalência de trombose venosa profunda em mulheres acima dos 66 anos, e um número de casos significativamente maior na etnia branca. A hipertensão arterial sistêmica mostrou-se como comorbidade principal na população estudada, seguida de insuficiência venosa e cardiopatias. Concluiu-se uma relação significativa entre vários fatores de risco e a trombose venosa profunda na população feminina, bem como um importante entendimento de cada um desses fatores, fato que se faz necessário para um repasse adequado de informações para esta população alvo.

Descritores: Saúde da Mulher; População em Risco; Trombo

Introduction

Deep venous thrombosis (DVT) is characterized by the presence of thrombi that obstruct the deep veins, especially in the lower limbs, caused by the junction of the three components of the Virchow triad: endothelial injury, venous stasis and hypercoagulability. This occlusion of the deep venous system can be partial or total, with the main complication being the detachment of the thrombus, with the formation of emboli that can obstruct other arteries, especially the pulmonary artery, resulting in pulmonary embolism. In addition, post-thrombotic syndrome occurs as an important complication of the disease, which appears in up to 50% of patients with DVT. This syndrome is characterized by the chronicity of the symptoms of the disease, and is diagnosed from the sum of signs (pre-tibial edema, hyperpigmentation, erythema, venous ectasia) and symptoms (cramping, pain, feeling of heaviness, itching), by the scale of Villalta, with a score greater than or equal to 5 points¹⁻⁴.

The incidence of this pathology, according to some studies, is shown in the general population as 5 cases per 10,000 individuals annually, and in Brazil around 0.6 per 1000 inhabitants annually. Proximal DVT progresses to pulmonary embolism in 46% of cases, and if left untreated, it can progress to death 4% of the time. In Europe, the rates reach 600 thousand cases of deep vein thrombosis and pulmonary embolism annually. In the United States of America, 300 thousand cases of thrombosis are registered per year, with DVT being the third most common cause within cardiovascular pathologies. In Brazil, studies show 122,096 hospitalizations for thrombosis, registered in 2014, and a decrease of this index to 113,817, in 2015^{1,3,5}.

The DVT mortality is represented by about 25% of cases, due to organ damage, with sudden death being the first symptom, which affects 10 to 30% of the North American population in the first thirty days after diagnosis. It has acquired risk factors, highlighting surgeries and immobilizations, mainly related to hospitalization, a factor that places DVT as the main cause of stable death in a hospital environment, since the time of pathophysiological evolution is directly proportional to the time of immobilization of the patient. individual^{6,7}.

In addition to this factor, advanced age, especially over 60 years of age, increases the chance of pathology, as well as obese patients, with body mass index (BMI) above 30 kg / m². Serious injuries are also included in this group, either by the trauma mechanism itself, or by its follow-up, such as the presence of fractures, associated infection, and prolonged immobilization. However, hereditary risk factors are of significant importance in the development of the pathology, such as mutations in the prothrombin gene, increased fibrinogen and increased factor VIII, which are responsible for coagulation, as well as deficiency of protein C and protein S, both members of the anticoagulation process. These situations, therefore, end up compromising the process and causing changes in the coagulation cascade

and, consequently, thrombus formation².

Contraceptives and pregnancy are two other important topics related to DVT, since the use of synthetic hormones such as estrogen and progesterone, whether in the form of oral contraceptives or as hormonal treatments, show signs of development in the female population. The National Health Surveillance Agency (ANVISA) notified 267 cases involving the use of oral contraceptives in 2011, 177 of which were related to circulatory system problems. Contraceptives work on the female body by increasing clotting factors and reducing its inhibitors. In addition, women using contraceptives are 2 to 6 times more likely to develop the disease compared to non-users¹.

During pregnancy, the chance of developing DVT ranges from 0.7 to 1.7 cases in 1000 pregnant women, increasing mainly in the third trimester of pregnancy and in the puerperal period. In this period, we found situations of hypercoagulability, in which there is hepatic synthesis of coagulation factors; blood stasis, whose condition develops due to the venous compression of the pregnant uterus and the decrease in vascular tone due to the action of progesterone; and the endothelial lesion that occurs in the process of nesting and placental discharge, facts that are related to the increase of five to ten times in the occurrence of thromboembolism in this population, reaching up to twenty times in the puerperium^{6,8,9}.

The registered cases emphasize the importance of thromboprophylaxis, especially in hospitalized patients, who make up an important risk group in the development of the pathology. Prophylaxis can be performed by using compression elastic stockings, as well as performing anticoagulation in these patients, according to medical recommendations⁷. Studies are scarce, which demonstrates the need for studies to emphasize the preventive measures of risk factors and clarify them to the target population, in order to reduce the incidence or worsening of this important circulatory problem, especially in the female population. This study aimed to relate the occurrence of deep venous thrombosis to existing risk factors.

Methodology

The study is characterized by quantitative and documentary research, carried out in two vascular surgery clinics, of low and high complexity in a municipality in the northwest of Paraná. The female population served from January 2018 to July 2019 in high complexity was included in the survey, and patients attended from the years 2015-2017 in low complexity, an analysis justified by the lack of recent medical records for the evaluation of this population. Residents of the municipality's metropolitan region were included in the survey. Exclusion factor being under 18 years old and medical records incorrectly filled in or with blank information.

Data collection was carried out exclusively from the analysis of the medical records of these patients, with identification, in terms of age, ethnicity, profession, precedence, presence of comorbidities, use of medication,



personal history, family history, and obstetric history, as well like life habits.

Data analysis was performed, first, from the tabulation of these using Microsoft Excel 2018 software, and the results were statistically analyzed and described using absolute and relative frequency. Subsequently, the crucial points found in the collection were discussed in order to understand the occurrence of the disease, the risk factors related to it, and the possible preventive measures for its development, in order to prevent future conditions.

Among the limitations of the study, we can report the lack of information in the medical records of each patient, whether in habitual, socioeconomic factors, and mainly personal history of each one of them, factors necessary to understand the pathophysiological condition of the patients, leading, therefore, to a difficulty in interpreting and relating risk factors in this population to the development of deep vein thrombosis.

The study was developed in accordance with the disciplinary guidelines of Resolution No. 466/12 of the National Health Council¹⁰. The research respected all ethical precepts, in which it was approved by the Ethics Committee

in research with human beings under the number of the opinion: 3,614,722. It was referred and authorized by the Center for Training and Research in Social Projects (CECAPS), as well as to the municipal ambulatories.

Results and Discussion

From the analysis of medical records, a total population of 796 (N = 796) patients was identified, 370 of whom were female, after applying the inclusion criteria resulted in a sample of 79 (n = 79) medical records of women with pathology, who attended the Vascular Surgery Outpatient Clinics of two hospitals in the city of Maringá. From the selection of patients, their most relevant characteristics, and their risk factors for the development of deep vein thrombosis were divided into 2 tables. First, its main socioeconomic aspects were evaluated, showing the profile of each patient in terms of age, with an emphasis on 32.9% over 66 years old, with a predominance of white color 37.9%, from the city of Maringá 64.5% , and 25.3% develop activities focused on general services, according to Table 1.

Table 1. Relationship between epidemiological profile and deep vein thrombosis, Maringá, PR, Brazil, 2020

Profile Variables	N	%
AGE		
18 – 30	9	11,3
31 – 40	8	10,1
41 – 50	18	22,7
51 – 65	16	20,2
Over 66	26	32,9
ETNIA		
White	30	37,9
Latin	7	8,8
Black	3	3,7
ORIGIN		
Maringá	51	64,5
Nova Esperança	2	2,5
Flórida	2	2,5
Munhoz de Melo	2	2,5
Paçandu	2	2,5
Nossa Senhora das Graças	1	1,2

Mandaguaçu	1	1,2
Astorga	1	1,2
Sarandi	1	1,2
Paranavaí	1	1,2
Alto Paraná	1	1,2
Uniflor	1	1,2
Floraí	1	1,2
Ourizona	1	1,2
Mandaguari	1	1,2
Querência do Norte	1	1,2
Itambé	1	1,2
Santa Izabel do Ivaí	1	1,2
PROFESSIONAL ACTIVITY		
General Services	20	25,3
From home	16	20,2
Retired	14	17,7
Student	1	1,2

Evaluating the identification criteria of each patient, we can observe DVT pictures in women ranging from 18 to 94 years old, with an average age of 53.7 years. This fact goes against the study¹¹ which shows the relationship between advanced age and the onset of the pathology, since in aging there is a decrease in fibrinolytic activity, increased vascular resistance and venous dilation, with a consequent reduction in the speed of blood flow, as well as the current clinical scenario of this population, the from the increase in hospitalizations for chronic degenerative diseases resulting from population aging. All these factors go against the pathophysiology of the disease. In addition, a study¹² also demonstrated advanced age as a risk factor, with patients with the pathology averaging 65.1 years with a range of +/- 19.1 years.

Regarding the ethnicity of those surveyed, the majority is white, followed by brown race, and with less incidence, black women. This fact, regarding the occurrence of major pathology in white women, goes in opposite to another study, such as Renni's¹³, which demonstrates a higher incidence of the pathology in African American individuals; and Almeida¹⁴, who had a higher occurrence of venous thrombosis in black women compared to white and Asian women, and reports that this race is a predictor for fatal thromboembolic events.

The origin was also a factor evaluated in the medical records of the patients, observing a much higher total attendance for women residing in the municipality, around 64.5%, while the patients residing in other municipalities of the 15th Regional Health, which Maringá is inserted, 20.8%



were added. The remaining 4.8% were precedents of the 14th Regional Health, which includes Paranavaí, Alto Paraná, Querência do Norte and Santa Izabel do Ivaí. This fact demonstrates the importance of the city of Maringá, and of its referral services to patients with the pathology in question.

In addition to these topics, we were able to assess the professional activity of each patient in the identification of medical records. An important number of retired women and home workers were demonstrated, both factors that,

even in opposition, lead to important characteristics for the development of the pathology, such as, respectively, blood stasis due to physical inactivity, and a lot of standing, a fact that prevents venous return, and predisposes to the formation of thrombi.

After identifying the patients, data on comorbidities, medication use, lifestyle, personal and family history, and obstetric history of each one were analyzed, analyzed in the Table 2.

Table 2. Main comorbidities and risk factors, Maringá, PR, Brazil, 2020

Variables	N	%			
COMORBIDITIES			Pulmonary thromboembolism (PTE)	6	11,3
Hypertension	20	25,3	Hospitalization history	6	11,3
Venous insufficiency	9	11,39	Gastrointestinal surgery	5	6,3
Heart disease	6	7,5	Stroke	4	5,0
Asthma / COPD	5	6,3	Post-thrombotic syndrome	3	3,7
Diabetes	4	5,0	DVT after unspecified surgery	2	2,5
Dyslipidemia	4	5,0	Gynecological surgery	2	2,5
Kidney disease	4	5,0	Repeating DVT	2	2,5
Neurological disease	4	5,0	DVT in local injury	2	2,5
May Thurner Syndrome	3	3,7	Otorhinolaryngological surgery	1	1,2
Obesity	2	2,5	DVT after catheter passage	1	1,2
Thrombophilia	2	2,5	Long trip	1	1,2
Anemia	1	1,26	FAMILY BACKGROUND		
Liver disease	1	1,26	Thrombosis	7	8,8
MEDICATION			Cancer	6	7,5
Antihypertensive	14	17,7	Diabetes / Hypertension	6	7,5
Contraceptive	13	16,4	History of stroke and / or AMI	4	5,0
Anticonvulsant	5	6,3	Venous insufficiency	3	3,7
Antiarrhythmic	4	5,0	OBSTETRIC HISTORY		
Phlebotonic	4	5,0	Cesarean	12	15,1
Opioid	3	3,7	Abortions	5	6,3
Antidiabetic	2	2,5	Normal deliveries	4	5,0
Antineoplastic	1	1,26	Use of elastic stockings	3	3,7
PERSONAL BACKGROUND			DVT in pregnancy	2	2,5
History of cancer	13	16,45	Premature labor	1	1,2
Cardiovascular surgery	10	12,65	LIFE HABITS		
Oncological surgery	9	11,3	Smoking	16	20,0
Chemotherapy	9	11,3	Sedentary lifestyle	2	2,5
Orthopedic surgery	6	11,3			

In the comorbidities item, most patients had a previous pathology, with a higher incidence of arterial hypertension, venous insufficiency, and heart disease. Two comorbidities of greater relevance for the development of deep venous thrombosis can be highlighted: the presence of thrombophilia in 2.5% of patients, which significantly increases the risk of developing thrombosis, and the May Thurner Syndrome by 3.7% patients. This pathology, of vascular origin, also known as Cockett's Syndrome, occurs from an anatomical vascular alteration that leads to an obstruction of the deep venous system, mainly altering the local blood flow, and increasing the chances of developing deep venous thrombosis, being demonstrated in some studies with a much higher incidence, approximately 80% in the female population compared to the male¹⁵.

Of the medications used, antihypertensive medication comes in first place, in 17.7% of patients, which relates shows the relevance of arterial hypertension, as

described in the paragraph above, with a history of thrombosis. The relationship between DVT and hypertensive disease is due to the latter, when uncontrolled, leading to the onset of acute myocardial infarction. This pathology can lead to the appearance of endothelial damage to blood vessels, and consequently, it becomes a risk factor for DVT¹².

Thirteen users of oral contraceptives were also observed, some of whom stopped the medication after a thrombogenic episode. It is known that the occurrence of thrombosis is 2 to 6 times higher in women using combined hormonal contraceptives compared to non-users, because both estrogen and progesterone generate changes in the coagulation cascade. Progestogens are divided into 4 generations, and studies have proven the directly proportional relationship between the occurrence of thrombosis and the generation of medication. Since third generation progestogens, such as desogestrel and gestodene, lead to changes in hemostasis twice as much as



those of second generation, such as levonogestrel. They develop resistance to protein C, and decrease in protein S, both responsible for anticoagulant mechanism, which results, respectively, in an increase in factors of the coagulation cascade, and inhibition of fibrinolysis. Like progestogens, estrogens also have thrombogenic potential, from the formation of thrombin and coagulation factors, as well as inhibition of natural anticoagulant factors (the proteins mentioned above)^{1,16}.

In the personal history, it is possible to observe that 16.45% of the patients with DVT reported a history of cancer. This fact is related to the pathophysiology of neoplastic cells for the evolution of thrombosis. These cells activate the coagulation mechanism from pro-inflammatory substances, as well as producing pro-coagulant substances, such as the tissue factor, which is a major component of the extrinsic pathway of the coagulation cascade. It circulates in an increased amount in cases of cancer, and has been correlated with increased tumor angiogenesis, rapid growth rate, metastases, and ultimately, propensity for deep venous thrombosis. In patients with neoplasms, there is damage to the defense mechanisms of vascular endothelial cells, as well as an increase in adhesive interactions between them and neoplastic cells. These mechanisms from tumor cells then lead to the appearance of a local lesion and, consequently, to a process of hypercoagulability, one of the main tripods in the genesis of deep venous thrombosis^{13,17}.

Approximately 10% of patients with a history of cancer underwent prophylactic or curative treatment with chemotherapy and radiotherapy, which can make us think about a possible relationship between the medications used in these treatments, and the development of DVT, since 11, 3% of patients with the condition reported having undergone chemotherapy. It is worth remembering that cytotoxic therapies are responsible for 13% of thrombosis episodes in the oncological population, with a six-fold increase in risk compared to the healthy population. The substances present in chemotherapy lead to important abnormalities in the walls of blood vessels, and consequently, alter venous homeostasis. Chemotherapeutics reduce plasma levels of physiological anticoagulants, and increase the expression of tissue factor and its pro-coagulant activity, similar to the mechanism of neoplastic cells in the vascular system^{13,18}.

In addition to oncological factors and their treatment, major surgeries proved to be very relevant in appearance, cardiovascular surgeries were shown to be a risk factor in 12.65% of patients, followed by oncological and orthopedic surgeries (11.3%), gastrointestinal surgeries (6.3%), and gynecological surgeries (2.5%). This demonstrates the relationship of DVT with surgeries that require a longer surgical time, a greater metabolic supply, and a normally longer postoperative period, resulting in increased blood stasis, for a long period of immobilization, and, consequently, disease development.

It is also important to highlight the post-thrombotic syndrome in the personal history of patients with DVT. According to some studies, this syndrome occurs in 20 to 40% of patients with thrombosis in the first two years of

diagnosis, and in 5 to 10% of patients it is considered severe. Fact that differs from the number found in the present research, with 3 patients with this evolution, corresponding to 3.7%^{4,19,20}.

Another important factor in the personal history analyzed was the presence of endothelial injury as a predisposing factor in thrombosis found in two patients, this factor being an important criterion in the pathophysiology of the disease. One of the cases showed the development of DVT after the passage of a central venous catheter, and the other, progression to thrombosis after direct injury to the blood vessel. Both situations are related to the damage to the blood vessel wall, activating the coagulation cascade, and evolving to a pathological condition.

An isolated case was observed, among all the studied antecedents, of deep venous thrombosis after prolonged travel. Even with a reduced percentage in the present study (1.2%), it is necessary to consider it as a risk factor for pathology. Other studies show this relationship, directly proportional, between thrombosis and travel time, mainly by plane, with the evolution of the condition normally two weeks after²¹.

Among the 79 patients, 11.3% had a relationship between pulmonary thromboembolism (PTE) and deep venous thrombosis. This fact reinforces the important relationship between these two pathologies, since most pulmonary emboli originate in the deep veins of the pelvis, and in the lower extremities²².

In the assessment of life habits, there was a significant presence of smoking among the patients analyzed. This factor appears in 20% of these women, two of whom are users of heavy smoking, corresponding to 46 packs / year and 40 packs / year. This fact confirms the harmful relationship between thrombosis and cigarettes, since it generates damage to the vascular wall, with reduction of local oxygen, elevation of plasma fibrinogen levels, activation of the coagulation cascade and, from some substances that composes, like nicotine, induction of a prothrombotic state by platelet activation, leading to the emergence of deep venous thrombosis^{23,24}.

Finally, the topic of obstetric history in patients with deep venous thrombosis showed truly relevant results. We can observe a history of abortion in patients with DVT (6.3%), as well as a thrombogenic episode during pregnancy (2.5%). These events are like studies that relate pregnancy to a state of hypercoagulability, from the activation of coagulation factors, increased platelet aggregation, and reduced fibrinolytic factors, responsible for thrombus degradation⁹. It is also important to mention that, among the performed routes of delivery, cesarean section is the main obstetric antecedent in the development of the disease, affecting 15.1% of patients, a much higher prevalence of thrombosis when compared to patients undergoing normal delivery. This makes us think of cesarean section as an important thrombogenic risk factor, and even more, of the importance of caring for pregnant women and women who have recently given birth by cesarean section, reinforcing compression stockings and early postpartum walking,



reducing the likelihood of evolution of the picture for a thrombotic disease.

Conclusion

Based on the present study, from all the patients analyzed, we were able to conclude that there is a significant relationship between several risk factors for deep vein thrombosis, as demonstrated by their relationship with each patient and with previous studies. In view of the identification of these factors, it is necessary and essential to pass on information to the female population regarding the risks of certain therapies, regarding the modification of life habits, especially smoking cessation, better health care in order to prevent or delay the onset of cancer, especially those that already have a risk factor for it. Reinforce the care of women during pregnancy, by significantly increasing the risk of thrombosis while pregnant. And mainly for the continuation and important observation in hospitalized patients, using not only medication for the prophylaxis of

thrombosis, but also possible measures of early ambulation, use of compression boots, and greater care for patients of older age.

In addition, it is necessary to emphasize the importance of a good anamnesis during the medical consultation, as well as paying attention to the patient's age and socioeconomic condition. A thorough history of her comorbidities and those of her family members, such as screening for thrombosis in close relatives, use of medications, knowledge of the patient's type of work, whether due to a sedentary lifestyle or increased physical effort, observing a possible relationship with pathology. And, finally, a good obstetric history, the search for thrombophilia, unexplained abortions, number of pregnancies and choice of delivery method, with the patient's knowledge about the greatest risks of thrombosis in a cesarean section, when compared to normal delivery. Thus, it will be possible to further increase the transfer of relevant information to the female population to prevent the onset of deep venous thrombosis.

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