

The Role of Ovarian Varicose Veins and Varicocele in Cancer and Venous Thrombosis

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Abstract

Varicose veins next to the testicles and the ovaries are associated with oxidative stress, which can change the phenotype of germinating glands, provoking abnormalities in the hypothalamic-pituitary-gonadal axis. This creates an interference that can express itself in the form of gene mutations in patients with cancer and venous thrombosis. In this study, we made it our goal to evaluate the prevalence of ovarian varicose veins and varicocele in patients with cancer and venous thrombosis and to further investigate this association. In order to achieve this objective, 54 patients with cancer and 98 patients in the control group diagnosed with venous thrombosis were included in this study. All of these patients were examined through ultrasound with vascular Doppler as a means to investigate varicocele in men and ovarian varicose veins in women. Out of a total of 14,800 patients, 152 with cancer and venous thrombosis were selected (1.02%). The group with cancer presented a significantly ($p = 0.0029$) higher proportion of varicose veins (96.3%) next to the germinating glands than the group with venous thrombosis (84.7%).

Keywords: Varicose Veins; Varicocele; Cancer; Venous Thrombosis

Introduction

Varicocele characterizes itself in the form of dilated, congested and tortuous veins. It is extensively referred to as “varicose veins next to the testicles”, and it is a phenomenon that is found in 15% of adult men [1]. There is an association between varicocele and testicular dysfunction, and it has been seen to alter hormone production, cause semen abnormalities, provoke testicular atrophy and ultimately change the phenotype of the testicular gland [2,3].

Scientists support the hypothesis that hydrostatic pressure in varicose veins next to the testicles decreases microcirculation, inducing damage in germinating cells and in the testicular stroma [4]. In some infertile patients, varicocele can be a cause for imbalance in the hypothalamic-pituitary-gonadal axis and for the reduction of testosterone levels in the peripheral blood [5-7].

Recent studies have shown that male infertility and semen abnormality increase the risk of cancer and venous thrombosis [8,9]. It has also been discovered that varicocele is the most common cause of infertility in men [10,11].

Similar to varicocele in men, ovarian varicose veins also characterize themselves in the form of dilated, tortuous and congested veins next to the ovarian gland, often causing chronic pelvic pain and a feeling of heaviness in the pelvis in women [12,13]. Studies have shown that ovarian varicose veins are prevalent in 12 to 15% [12,14] of the general female population.

Increased oxidative stress (OS) in varicose dilations next to the testicles can reduce fertility in patients with varicocele and change this gland's phenotype [15-18]. Similarly, two experimental studies performed in female rats have demonstrated that increased OS present in ovarian varicose veins provokes histologic damage in the ovaries and suggests a negative effect related to fertility [19,20].

While it is true that physiological levels of OS in the ovaries are necessary for several biological functions, high levels can impair oocyte maturation [21], provoke DNA fragmentation in sperm and be related to the birth of children with embryonic defects and cancer [22-24].

The change in phenotype with morphologic as well as hormonal production alterations in both the ovaries [25] and the testicles [26] is associated to the increase in risk of cancer and venous thrombosis [8,9,25-28]. It has also been reported that ovarian varicose veins can evolve with venous thrombosis, pulmonary embolisms [29,30], and infertility [19,20].

Moreover, researchers have also evidenced that female infertility may increase the risk of cancer and other pathologies [31,32].

In patients with ovarian varicose veins, it has been observed that the level of female hormones in the blood collected from veins of the inguinal region was twice as large as the levels present in the blood collected from arm veins [33]. These women tend to have a larger uterus and more ovarian cysts [34].

Galkin *et al* have described 19 cases of patients who were considered infertile, out of which 14 became pregnant after treating their ovarian varicose veins through embolization. These results suggest the possibility of an association between infertility and this pathology [35], in a way similar to that in which it is associated to varicocele [15-18].

The diagnosis of varicocele [36-38] and ovarian varicose veins [14] can be made through ultrasound technology and vascular Doppler. However, the golden standard method for the diagnosis is the phlebography of pelvic veins in women [39-41] as well as in men [42].

Studies show that when comparing ultrasonography to phlebography, the sensitivity in women [39-41] was of 96.2% and the specificity was of 100%. In men, the sensitivity was of 98% and the specificity was of 100% [42].

In light of the fact that ovarian varicose veins and varicocele with increased concentrations of OS cause changes in these glands' phenotype, we have decided to perform a retrospective study to investigate the prevalence in these two pathologies.

Materials and Methods

The sample was selected from a universe of 14,800 patients that were treated in my private practice specialized in vascular surgery, from the 1st of April 2012 to the 30th of June 2015, in Rio de Janeiro – Brazil. 152 (1, 02%) male and female patients diagnosed with cancer and venous thrombosis were selected. 98 of them were diagnosed with venous thrombosis and 54 with cancer. This study followed the Helsinki criteria and the rules of the medical code of ethics. All patients were informed about the study and signed their consent, giving authorization. The 54 patients who had cancer had their diagnosis confirmed by biopsy in hospitals with oncological reference, just as the patients with venous thrombosis were diagnosed by vascular eco-color Doppler and treated by specialists in this pathology.

The patients were examined by a radiologist specialized in image diagnosis and ultrasound and were monitored by the authors of this study. For the ultrasound, we worked with an instrument by Phillips, HD 7, in Rio de Janeiro, Brazil, with a C8-4v minuscule system, with a transvaginal transducer of 4 to 8 MHz for the ovarian varicose veins in women. We also used a 7.5 MHz transducer for varicocele in the scrotum in men. Before the exams, the female patients all excreted all liquid from their bladders and lay down in supine position. Female patients bent their knees and male patients stretched their knees. The transvaginal transducer was coated with a lubricated condom and introduced into the vaginal canal of the patient, which allowed identification of the ovaries and the vascular structures of each adnexal region. The researchers were looking to identify anechoic, circular, linear and non-pulsatile structures in the broad ligament of the uterus. When anechoic structures were found with a diameter equal to or larger than 4 mm, the color scale and pulsed-wave Doppler were used. We simulated three possibilities in the diagnostic investigation of ovarian varicose veins.

There is no absolute consensus in medical literature regarding the minimum diameter of varicose dilations next to the ovaries [38-41]. Since values vary from 4.0 to 7.0 mm, in order to define constraints for diameter values in our study, we adopted 3 criteria. The first criteria establishes the parameters for this diameter to be from 4.0 to 4.9 mm, criteria 2 establishes it as 5.0 mm to 5.9 mm and criteria 3 establishes it as over 6.0mm. Significant reflux was defined as the retrograde flux lasting equal to or longer than 0.5s, [43-45] monitored by Doppler pulse wave.

The transducer was introduced cautiously into the topography of the inguinal channel in men, where the artery was identified. Then, the spermatic veins in the external orifice of this channel were also identified and followed to the posterolateral region of the scrotum, where the veins of the venous plexus pampiniform were found. This was how the visualization of these structures (in mode B) and measurement of the diameter were done. Next, we used the scale of colors with Valsalva maneuvers and the pulsed Doppler effect to confirm or discard the presence of the varicose veins. Once again, we simulated three possibilities in the diagnostic investigation of varicocele, since there is no absolute consensus in medical literature regarding the minimum diameter of varicose dilations next to the testicles. It was considered in veins with diameter between 2.0mm and 2.49mm, 2.5 to 2.99 mm, and above 3.0mm, with reflux greater than or equal to 0.5 seconds in the veins next to the testicle [36-38].

Statistical analysis

The descriptive analysis presented in table form the observed data expressed by the frequency (n) and percentage (%). The comparison between the groups with cancer and venous thrombosis was evaluated by the χ^2 test or the Fisher exact. The significance criteria adopted was the level of 5%. The statistical analysis was processed by the statistics software SAS® System, version 6.11 (SAS Institute, Inc., Cary, North Carolina).

Results

Of a total of 14,800 patients, 152 with cancer (breast cancer, n=16, prostate cancer, n=11, skin cancer, n=5, bowel cancer, n=5, thyroid cancer, n=5, cervix cancer, n=2, brain cancer, n=3, lymphoma, n=2, bone cancer, n=1, stomach cancer, n=1, larynx cancer, n=1, bladder cancer, n=1, sarcoma, n=1) and venous thrombosis (in the lower limb veins, n=92, in the portal vein, n=1, in the

central venous sinus, n=2, in the ovarian vein, n=1, in the subclavian vein, n=1, in the upper limb veins, n=1) were selected (1.02%).

We have used 3 minimum dilation criteria for varicose veins next to the germinating glands in men and in women.

According to Table 1, the mean age in the group with cancer patients was of 63.8 years. In the group with venous thrombosis, the mean age was of 57.4 years. The mean minimum diameter in the entire sample of males was of 2.79mm for varicocele to the right of the gland, and of 3.07mm for varicocele to the left of the gland. In women, for varicose veins next to the left ovary, the mean diameter was of 5.11 mm, while for varicose veins next to the right ovary, the mean diameter was of 4.87mm.

	ALL		Cancer		Venous Thrombosis	
	mean	SD	Mean	SD	Mean	SD
In Men						
Right Varicocele (mm)	2.76	0.99	2.59	0.81	2.81	1.06
Left Varicocele (mm)	3.07	1.28	2.82	1.06	3.19	1.37
In Women						
Right Varicocele (mm)	4.87	1.69	5.06	1.24	4.75	1.91
Left Varicocele (mm)	5.11	1.92	5.46	1.52	4.89	2.10
Total Samples						
Age (years)	59.6	15.5	63.8	13.3	57.4	16.2

SD: Standard Deviation

Table 1: This table provides the mean average and the standard deviation (SD) of veins (in mm) in the total sample and by group (cancer and thrombosis)

In accordance with Table 2, when using criteria 1, we have found an increased prevalence of varicose veins next to the germinating glands in the entire sample. The group with cancer has presented a significantly ($p = 0.0029$) higher proportion of venous dilation (96.3%) than the group with venous thrombosis (84.7%).

	All		Cancer		Venous Thrombosis		P-value
	n	%	n	%	n	%	
Total sample							
Criteria 1	135	88.8	52	96.3	83	84.7	0.029
Criteria 2	107	70.4	39	72.2	68	69.4	0.71
Criteria 3	70	46.1	24	44.4	46	49.9	0.77
In Men							
Criteria 1	59	96.7	20	100	39	95.1	0.99
Criteria 2	51	83.6	15	75.0	36	87.8	0.27
Criteria 3	34	55.7	8	40.0	26	63.4	0.084
In Women							
Criteria 1	76	83.5	32	94.1	44	77.2	0.035
Criteria 2	56	61.5	24	70.6	32	56.1	0.17
Criteria 3	36	39.6	16	47.1	20	35.1	0.26
In Elders							
Criteria 1	66	89.2	32	97.0	34	82.9	0.068
Criteria 2	49	61.5	23	69.7	26	63.4	0.57
Criteria 3	33	44.6	14	42.4	19	46.3	0.74
In not Elders							
Criteria 1	69	88.5	20	95.2	49	86.0	0.43
Criteria 2	58	74.4	16	76.2	42	73.7	0.82
Criteria 3	37	47.4	10	47.6	27	47.4	0.98

Criteria 1: Varicocele: between 2.0mm and 2.49mm and Ovarian Varicocele Veis: between 4.0mm and 4.99mm

Criteria 2: Varicocele: between 2.50mm and 2.99mm and Ovarian Varicocele Veis: between 5.0mm and 5.99mm

Criteria 3: Varicocele \geq 3mm and Ovarian Varicocele Veis: \geq 6mm

χ^2 test or Fisher exact.

Table 2: This table provides descriptive data (frequency and percentage) of the criteria (1,2 and 3) for varicose dilation in total according to the group (cancer and venous thrombosis) and the correspondent descriptive level (p value) of the χ^2 test or the Fisher exact, stratified by sex (men and women) and age group (≥ 60 e < 60 years)

When we increased the required values for minimum diameter, as in criteria 2 and 3, we did not find any significant differences in the proportion of varicose dilation. However, the prevalence of ovarian varicose veins and varicocele was persistently high in both pathologies.

In the sub-sample of women, the group with cancer presented a proportion of varicose dilation by criteria 1 (94.1%) significantly ($p = 0.035$) higher than the group with venous thrombosis (77.2%).

We have proven that the group with cancer presented a significantly ($p = 0.023$) higher proportion of elders (61.1%) than the group with venous thrombosis (41.8%), according to Table 3.

	ALL		Cancer		Venous Thrombosis		P-value
	%	n	%	n	%	n	
Sex							
Male	61	40.1	20	37.0	41	41.8	0.56
Female	91	59.9	34	63.0	57	58.2	
Age Group							
≥ 60 years	74	48.7	33	61.1	41	41.8	0.023
< 60 years	78	51.3	21	38.9	57	58.2	
χ^2 test							

Table 3: This table provides the characterization of the sample in total and according to the group (cancer and venous thrombosis) and the correspondent descriptive level (p value) of the χ^2 test

Discussion

Several studies have shown that varicocele and ovarian varicose veins can increase the risk for phenotypic changes (in the germinating glands), hormonal alterations and infertility [15-18,19,20]. Other researches have also reported that infertility and changes to the hormonal milieu also increase the risk for cancer and venous thrombosis [8,9,25-28].

Beatson and Charles Huggins noticed the role of the ovaries and the testicles in cancer even before sexual hormones were known. In 1895, Beatson [46] performed an oophorectomy in a woman with advanced breast cancer and Charles Huggins, [47] half a century later, executed the removal of the testicles in a man who had advanced prostate cancer. Both noticed the important improvement in their patients as a result of the procedures. This played a fundamental role in the development of hormonal therapy (tamoxifen and aromatase inhibitors) to treat and prevent cancer.

Some other authors have also reinforced the importance of the role played by germinating glands in cancer. This is substantiated by epidemiologic studies that have been performed in the past which featured castrated men and highlighted the role of the testicles in the pathogenesis of prostate [48]. In addition, it has also been seen that the removal of the ovaries decreases the risk of breast cancer in carriers of the BRCA1 gene (for cancers attributable to the BRCA1 mutation) by approximately 50% [49].

In addition, it has been reported that changes to the testicles' and ovaries' phenotypes [25,28] increases the risk of cancer and venous thrombosis [8,9,25-28,50]. Likewise, epidemiologic data have also demonstrated that venous thrombosis is very frequent in patients with cancer [51].

Furthermore, it is important to highlight that both varicose veins in the lower limbs and varicose veins next to the testicles can be associated to OS [15-18,52-54]. Additionally, varicose veins in the lower limbs may also change the phenotypes of the skin, cause the formation of ulcers, lead to hyperpigmentation and trigger the destruction of tissues [52,53]. Also, varicose veins next to the testicles have been seen to trigger OS, inflammatory processes, decrease glandular volume, alter hormone production, provoke semen abnormalities, cause infertility and change the gland's phenotype [15-18,55,56].

Although there are few studies, it has also been demonstrated that varicose veins next to the ovaries are also associated to OS and to tissue lesions that can cause infertility and hormonal alterations [19,20].

In cases in which phenotypic changes (which could potentially evolve into cancer) cannot be attributed to ovarian varicose veins, but rather to wholly different etiological factors, recent studies have demonstrated that treatment with the chemotherapeutic drug Cisplatin [57-61] can cause premature ovarian and testicular failure and is associated to a high risk of venous thrombosis [62]. This drug also decreases ovarian and testicular reserve by OS [60,61], creating a possibility for the development histologic injuries, infertility, changes in the phenotype of germinating glands and alterations in the hypothalamic-pituitary-gonadal axis.

OS can provoke organ dysfunction, genetic mutations and alterations in angiogenesis [63,64]. Studies have shown that there are several genes involved in biological functions, including the regulation of the hypothalamic-pituitary-gonadal axis, the regulation of oncogenes and the coordination of germinating cells. All of these play important roles in the endocrinal system [65,66]. This gain or loss of gene function can be decisive in the development of cancer [67-69].

The mutation of the BRCA 1 gene is associated to the reduction of the oocyte and follicle reserve, occult ovarian insufficiency and infertility [70]. We can at least think and pursue further research to investigate if ovarian varicose veins cause most cases of primary ovarian insufficiency, since Pacheco et al have reported that in treating ovarian varicose veins next to the ovaries in two patients with an established diagnosis of premature ovarian failure, both patients began menstruating again [71]. By analogy, the same way varicose veins next to the testicles caused testicular insufficiency [5-7] they could have the same effect on the ovaries.

Three recent studies have shown that OS is higher in varicose veins with insufficient valves [54,72,73]. High levels of OS impair oocyte maturation and contribute to oophoritis and premature ovarian failure [57,74].

A study has also demonstrated that over 50% of patients with ovarian varicose veins have polycystic ovaries [75] and that the morphologic and functional change in the polycystic ovary syndrome increases the risk of cancer [25], venous thrombosis [76], infertility and cardiovascular problems [77], as well as decreasing the ovarian reserve [25].

This research has demonstrated an expressive prevalence of varicose veins next to the germinating glands, both in the group with cancer patients and in the group with venous thrombosis, regardless of the criteria used.

In the entire sample, the group with cancer has presented a significantly higher ($p = 0.029$) proportion of varicose dilation in accordance to criteria 1 (96.3%) than the group with venous thrombosis (84.7%).

Furthermore, some studies have been showing epidemiologic data which highlight the differences in the prevalence of varicocele in men according to the specific pathology, demonstrating a percentage of 40% in infertile men(1), 41.7% in men with increased mean platelet volume (MPV) [78,79], 53% in men with benign prostate hyperplasia [80], 62% in men with aneurysms in coronary arteries (ectasia of the coronary arteries) [81] and of 100% in men prostate cancer [27].

Some authors have demonstrated the frequency of ovarian varicose veins in women by pathology. In women who suffered from chronic pelvic pain, the prevalence was of 50% [82,83]. In women with endometriosis, the prevalence was of 80% [84]. In women who had endometriomas in the left ovary, the prevalence was of 100% [85].

In this study, the authors evidence that the group with cancer contained a significantly ($p = 0.023$) higher proportion of elders (61.1%) with varicose veins than the group with venous thrombosis (41.8%). This data can be supported by two other studies which have shown that with increasing age, comes an increasing prevalence of varicocele [86,87]. There are also hypotheses that suggest that varicocele can cause a progressive decline in testicular function with increasing age [2]. Medical literature as a whole has also already extensively demonstrated that both aging [2,28] and varicose veins next to the germinating glands [15-18,33] favor hormonal alterations. With that being said, it can be seen that changes in the hormonal milieu could provide important alterations for cancer and venous thrombosis [88-94].

Several authors have reported positive results in treating varicocele in elders with surgery or embolization. The varicolectomy resulted in an increase of testosterone level [7,95] and the treatment of patients with prostate tumors through embolization resulted in decreases in PSA level, nocturia [95,96], and the volume of the gland. It also has been shown to contribute to the absence of cancer cells in 5 out of 6 patients who have had prostate cancer [27]. Additionally, low serum testosterone levels have also been reported in patients with prostate cancer, especially when the cancer is more aggressive [27,98,99].

The change in ovarian phenotype in menopause [28] and in ovarian insufficiency [89] is associated with increased levels of gonadotropin, decreased ovarian function and a possibility of increasing the risk of cancer [28], endocrine pathologies (such as diabetes and thyroid diseases, among others) and non-endocrine pathologies (such as Lupus and auto-immune hemolytic anaemia, among others) [31,89].

Hormonal interference in the ovary provoked by modern oral contraceptives are able not only to help with contraception but also with other positive effects, such as reducing the rates of endometrial, ovarian and colon rectal cancer [100].

What calls one's attention is the fact that the stimulation of the ovaries for purposes of ovulation with gonadotropin provokes thrombosis in atypical anatomic regions, such as in the jugular vein, the central retinal vein and even in the arteries [94,95].

On the other hand, androgen deficiency with elevated gonadotropin levels and impairment in spermatogenesis increase venous thromboembolisms [26,101].

In this research, in the female subsample, the group with cancer presented a significantly ($p = 0.035$) higher proportion of varicose dilation in accordance to criteria 1 (94.1%) than the group with venous thrombosis (77.2%). By criteria 2 and 3 there was no significant difference, even though the prevalence was still expressive (Table II). It has also already been reported that varicose dilations next to the germinating glands are associated to hormonal alterations [5-7,33]. The rupture of this hormonal balance can exert a fundamental role in the development of cancer and venous thrombosis [8,9,25-28].

In other pathologies (that is, cases of endometrioses that have been associated to hormonal alterations, infertility and cancer) [31], a high prevalence of ovarian varicose veins has been found [85]. Pacheco *et al.* have also found in patients with endometriosis that the mean minimum diameter of the varicose veins next to the right ovary was of 6.2mm ($p=0.0016$) and that the mean diameter of the varicose veins next to the left ovary was of 5.8mm ($p=0.0001$). In this research, in female patients in the group with cancer and venous thrombosis, the mean minimum diameter in the right ovary was of 4.87 mm and in the left ovary of 5.11mm.

The therapeutic test suggests that varicose veins cause destruction of tissue and organs, OS in endothelial cells and, as a result of these damages, the alteration of the expression of several genes [52-54].

For varicose veins in the lower limbs, surgical treatment and the use of compression stockings lead to a decrease in OS and even in the scarring of ulcers [52,53].

In cases of varicocele, varicocelectomies decrease OS next to the testicles, leading to a possibility of the testicles resuming growth [55,102]. Moreover, hormone production, sperm production and fertility rates all increase as a result of this procedure [55,102].

The treatment of pelvic varicose veins through embolization has resulted in an improvement in clinic symptomatology and 23 cases of pregnancy reported by several authors [35,39,40,103-105]. These studies suggest that once these pathologies are treated; there is a decrease in OS, an improvement in hormone production, and an increase in ovarian reserve and fertility.

OS present in cancer [25], venous thrombosis [78], varicose veins [52,53,54] and endometriosis [106] plays an important role in these pathologies, interfering with genetics, angiogenesis and in the chronic inflammatory process [52,53,66]. However, further research is still needed to confirm that the treatment of varicose veins next to the ovaries and the testicles can prevent, delay, stop or even revert the development of cancer and venous thrombosis and several other pathologies in some patients.

Conclusion

The group with cancer presented a significantly higher proportion of varicose dilation by criteria 1 than the group with venous thrombosis.

OS present in varicose dilations next to the ovaries and the testicles can alter the phenotype of these glands and interfere in the hypothalamic-pituitary-gonadal axis, leading to changes in the hormonal milieu. This can favour gene mutation in patients with cancer and venous thrombosis.

Information published in medical literature as well as the expressive prevalence of varicocele and ovarian varicose veins in the group of patients with cancer and venous thrombosis made clear to us the necessity of defending a new theory that varicocele and ovarian varicose veins plays an important role in the development of these pathologies.

This article warrants future studies to confirm this theory.

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