

Oestradiol Levels in Varicose Vein Blood of Patients with and without Pelvic Vein Incompetence (PVI): Diagnostic Implications

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Abstract Purpose: To assess the difference in the oestradiol levels of blood taken from varicose veins in patients with and without pelvic vein incompetence (PVI).

Materials and methods: Women of child-bearing age with symptomatic primary or recurrent varicose veins of the great saphenous vein (GSV) were included in a prospective study. Patients underwent duplex ultrasonography and pelvic vein phlebography. They were divided into a group with PVI (PVI group) and a control group with GSV reflux alone (VV group). Blood samples were collected from the GSV at the sapheno-femoral junction or lower in the thigh as well as from the arm. Oestradiol levels were determined by electroluminescence.

Results: Between January and December 2007, 40 women were studied, of which 19 showed phlebographic evidence of PVI (PVI group), while 21 were included in the VV group. Phlebography revealed an incompetent ovarian vein in 14 (74%) patients of the PVI group, dilated uterine and ovarian plexuses in 12 (63%) and an incompetent internal iliac vein in six cases (32%). In the PVI group, the median oestradiol level in GSV samples was 121 pg ml^{-1} (range: 12–4300), while in the VV group the median level was 75 pg ml^{-1} (range: 9–1177). In the upper limb, the PVI group patients had a median level of 78 pg ml^{-1} (range: 15–121) and the VV group patients 68 pg ml^{-1} (range: 13–568). The ratio of lower limb/upper extremity was significantly higher ($p < 0.002$) in patients of PVI group (median: 1.9; range: 0.7–33) than in those of the VV group (median: 1.1; range: 0.8–13). A threshold ratio of 1.4 showed the highest combined sensitivity and specificity in differentiating patients with PVI from those without.

Conclusions: In patients with varicose veins arising from the GSV, oestradiol levels were significantly higher in the lower limb than in the upper extremity in the subgroup with associated PVI. It may be possible to use this observation as a diagnostic test in patients with suspected PVI. This deserves further study.

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The term pelvic vein incompetence (PVI) describes pathological reflux in pelvic veins. It is often associated with pelvic pain, dyspareunia and pelvic heaviness and might also play a role in the development of varicose veins.^{1,2} Invasive and non-invasive diagnostic methods have been used to detect pelvic reflux. The detection of reflux at the sapheno-femoral junction (SFJ) originating in the pelvis on ultrasonography (US) might lead to the suspicion of PVI.³ However, only diagnostic methods requiring the use of contrast media guarantee reliable detection of pelvic reflux pathways.^{4–6} Female sex hormones are mostly produced in the ovary. Incompetence of pelvic veins could allow reflux of hormone-rich blood to the SFJ and reach the great saphenous vein (GSV).

Oswald et al.⁷ have already measured the hormone content of varicose veins to assess the role of ovarian vein incompetence as a source of varicose veins. Building on this experience, we assumed that if high sex hormone levels could be detected in the lower limb in patients with phlebographic signs of PVI, this could help to select patients who should undergo contrast media examinations, reducing diagnostic costs and increasing patient acceptance.

We therefore conducted a prospective study analysing oestradiol blood levels in the lower and upper limbs in female patients with primary or recurrent GSV varicose veins and phlebographic evidence of PVI. We compared these findings to a control group of patients with isolated GSV varices.

Materials and methods

Female patients of child-bearing age with symptomatic primary or recurrent GSV varicose veins were recruited between January and December 2007 at our vascular centre. The study protocol was approved by our local ethics committee. Patients were divided into two subgroups: a PVI and a VV group, depending on the presence of PVI on phlebography. Not all patients underwent phlebography, which was only undertaken in those where clinical or duplex ultrasound scanning suggested that this might be present. The decision to perform phlebography of the pelvic veins was based on clinical signs typical of PVI: a history of vulval varicosities during pregnancy, an increase in venous congestion symptoms related to the menstrual period, dyspareunia, lower abdominal pain of unknown origin as well as a history of repeated surgery for recurrent varicose veins at the SFJ. PVI was also suspected if varicose veins were found at atypical sites (buttock, perineal or vulval region). Duplex ultrasound examinations were performed in all patients and if reflux was detected in the groin originating from cranial (epigastric) and/or medial (pubic and pudendal) veins, PVI was also suspected and pelvic venography was performed regardless of the above-mentioned symptoms. All patients gave written informed consent for their inclusion in this study.

Exclusion criteria included age under 18 years; known vascular malformation in the abdomen or lower limb; pregnancy; thrombophlebitis of the GSV; a history of deep vein thrombosis (DVT) in the lower limb; and previous allergic reactions to radiological contrast medium. Patients who met the inclusion criteria underwent a meticulous

clinical examination. Previous surgery due to lower limb varicosity, pregnancies as well as clinical extension of varicosities (based on Clinical–Etiology–Anatomy–Pathophysiology (CEAP) classification⁸) were recorded.

Phlebography was performed using an imaging technique based on the descriptions of Ahlberg.⁹ The examination proceeded in a standardised fashion with visualisation of the ovarian veins (OVs) and the common iliac veins (CIVs) in an antero-posterior projection and of the internal iliac veins (IIVs) in an oblique projection (30° left or right anterior oblique).

The presence and the extent of any reflux were documented and the names of the pelvic veins affected by reflux were recorded. PVI was considered to be present if one of the following criteria was fulfilled:

- pelvic reflux toward the ipsi- or contralateral proximal thigh;
- visualisation of a dilated OV throughout its entire course;
- retrograde filling of the main stem of the IIV and at least one tributary (gluteal, ischiadic or obturator veins); or
- retrograde filling of contrast medium across the midline.

Based on our previous experience,¹⁰ an OV was considered to be dilated if its diameter was at least 1.5 times that of the contralateral vessel. If the vein was dilated without reflux, it was not considered incompetent. In selected cases, the main ovarian trunk and/or the IIV were embolised with the use of standard spring coils (Gianturco spring embolisation coils; Cook). Complications were of investigation and treatments were recorded.

Blood samples were collected after venous duplex ultrasound imaging and diagnosis of GSV incompetence leading to varicose veins. The GSV was marked with the help of US at the groin or the proximal part of the medial thigh. Blood samples were collected as near to the SFJ as possible using a 23-gauge needle with the patients in upright position and performing a Valsalva manoeuvre. In the upper limb, blood was taken from an ante-cubital vein.

The levels of the active form 17-beta-oestradiol were determined by sandwich electrochemiluminescent immunoassay (ECLIA) using the Elecsys 2010 system (Roche, Mannheim, Germany – coefficient of variation 2–8%). The time of blood sampling with reference to the menstrual cycle, hormone replacement therapy or oral contraception was considered irrelevant due to the intention to compare oestradiol levels in the upper and lower limbs and not to analyse absolute values.

Statistical analysis

To compare the study and the control groups, we used the Mann–Whitney *U*-test for ordinal data (assuming non-normal distribution of data in view of the wide scatter of results) and Fisher's exact test categorical data. Descriptors for ordinal data in this study are the median, interquartile range and range of data. Regarding the comparison of oestradiol levels, in patients with bilateral varicose

Table 1 Demographic data.

	PVI group	VV group	p-Value
Age mean (range)	42 (29–55)	36 (18–52)	0.043 (+)
Primary varicosity	9 (47%)	4 (19%)	0.091 (×)
Recurrence	10 (53)	17 (81%)	
CEAP			
Class C1	7 (37%)	3 (14%)	0.15 (×)
Class C2	12 (63%)	18 (86%)	

(+) Mann–Whitney-*U*-test, (×) Fisher's exact test.

veins, the higher value measured in the lower limb was considered for analysis. The maximum difference between lower limb measurements accepted as reliable was 5%. A difference of less than 20% between varicose vein blood and upper limb blood oestradiol levels was considered non-significant.

In order to define the most predictive lower limb/upper extremity ratio for the diagnosis of PVI, we calculated specificity and sensitivity for a range of values of this ration and plotted a receiver operating characteristic (ROC) curve.

Results

Between January and December 2007, 40 female patients were included in this study, of which 19 (48%) patients had clinical signs and symptoms as well as US findings of PVI and were included in PVI group, while 21 (52%) patients were assigned to the VV group. Demographic data are shown in Table 1. Amongst all patients, there were 13 cases of varicose vein recurrence after previous stripping of the GSV and in 27 cases of primary varicose veins (see Table 1: demographic data). The mean number of pregnancies was 2.5 per patient (range: 0–5). Thirty (75%) patients presented with CEAP clinical class C2 and 10 (25%) with class C1. There was no case of oedema of the legs or venous ulceration. Varicose veins in the thigh and the calf were the main clinical findings. In the PVI group, 10 patients (53%) had varicose tributaries originating in the gluteal or groin region and connecting to varicose veins on the thigh or on the calf.

The standardised phlebography protocol was completed at the time of hospitalisation in all 19 patients in the PVI group and confirmed PVI in all cases. There were no adverse events due to the contrast agent nor was there any case of bleeding or pelvic vein thrombosis. An incompetent OV was recognised in 14 (74%) patients of the PVI group, dilated plexuses in 12 (63%) and an incompetent IIV in six cases (32%). Endovascular treatment with coil obliteration of the incompetent veins was performed in 10 cases.

The oestradiol measurements are summarised in Table 2, including the lower limb/upper limb ratios. These data have been plotted in Fig. 1a and b, confirming that the lower limb/upper limb ratios are higher in the PVI group. In order to define the most predictive ratio for diagnosis of PVI, we plotted the ROC curve (Fig. 2). A threshold ratio of 1.4 showed the highest combined sensitivity and specificity in differentiating patients with PVI from those without.

Discussion

In 1947, Taylor¹¹ used the term 'venous congestion syndrome of the pelvis' to describe a combination of symptoms consisting of pelvic varicosities, dysmenorrhoea, post-coital pain and pelvic pain. This classical tetrad of symptoms is associated with a typical pattern of varicosities.^{1,2} In some cases, incompetent pelvic veins may carry reflux to the venous system of the lower limb, resulting in primary varicosities and/or in recurrence after surgical treatment of varicose veins.^{2,12} Symptoms often worsen during menstruation,¹³ the higher prevalence in multiparous women³ as well as the positive therapeutic effects of hormonal replacement on symptoms^{14–16} suggest that sex hormones might play a crucial role in the pathophysiology of this peculiar clinical entity.

High oestradiol levels can result from an excessive medical treatment,¹⁷ at the beginning of the menopause¹⁸ and rarely due to oestradiol-producing tumours.¹⁹ By contrast, lower oestradiol levels can be caused by an endocrine disease.²⁰ In addition, hormonal regulation is influenced by psychiatric diseases, chronic stress, extreme sport or anorexia.^{21–23} Oestradiol is transported through the ovarian veins to the left renal vein as well as to the inferior vena cava. After liver inactivation, it is eliminated through the kidneys. In patients with incompetent pelvic or ovarian veins, the oestradiol-rich blood may flow to the lower limb veins through multiple connections between the pelvic and the lower limb venous systems.

In our study population, hormone levels were higher in the lower limb than in the upper limb only in patients where PVI was associated with varicose veins. The patients with PVI were slightly older than the VV group patients. These data confirm the observations reported by Oswald et al.,⁷ who assessed hormone levels of varicose veins to detect the incompetence of the OV as a source of varices. These authors measured the concentration of hormones such as oestrogen, corticoids and oestradiol in varicose vein blood of 10 patients with pre-menstrual pain and 10 without. In this group of patients, there was no significant difference between the hormone concentration levels in any of the samples in the group without pain. In the symptomatic group, there was no

Table 2 Oestradiol levels (pg ml⁻¹). In patient with bilateral varicosities, the higher oestradiol level in the lower limbs was considered for comparison. See text for explanation. All data are median (range).

	PVI group	VV group	p-Value (+)
Lower limb	121 (12–1177)	75 (9–4300)	N.S.
Upper extremity	68 (13–568)	68 (15–121)	N.S.
Lower limb/upper extremity ratio	1.1 (0.7–33)	1.9 (0.8–13)	0.002
Modified lower limb/upper extremity ratio	1.1 (0.7–1.8)	1.9 (0.8–4.7)	0.001

(+) Mann–Whitney-*U*-test.

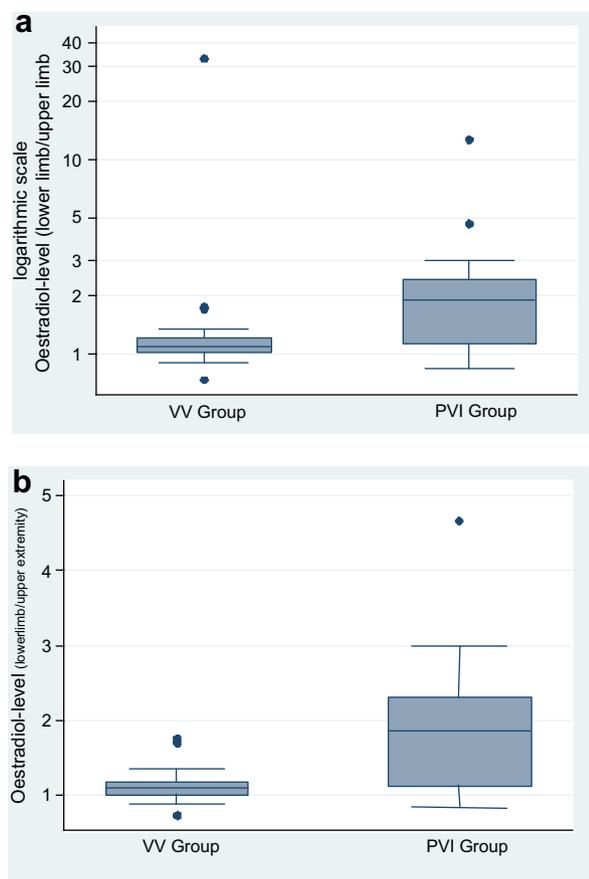


Figure 1 Oestradiol levels in the study groups. Depicted is the ratio lower limb/upper extremity. Fig. 1a includes all patients, while in Fig. 1b patients with the highest levels of both groups were excluded (see text for explanation). Box and whisker plots show median (central line), upper and lower quartiles (box) and range excluding outliers (whiskers).

difference between the oestrogen and corticoid blood concentration. However, in the symptomatic group, the concentration level of oestradiol in the sample from painful varicose veins was two to nine times higher compared with samples from the non-affected leg and brachial vein. Oswald speculated that the higher concentration of oestradiol was due to an incompetent ovarian vein, which follows a route through the pelvis to the varicose veins and which may explain the high oestrogen content. The severity of PVI was not be classified in our study so we were unable to analyse the correlation between the severity of PVI and oestradiol levels. We cannot speculate as to whether higher oestradiol levels may be helpful in detection of PVI without phlebography.

We observed a wide range of oestradiol levels but it is likely that this may have arisen in part because of the different menstrual phase in which blood samples were collected. Failing to record this aspect should be considered a drawback of this study. Patients were not asked about medical intake of hormones and/or oral contraceptives, which would also influence absolute hormones levels. Unrecognised endocrine diseases may also have played a role. We aimed to minimise these differences by basing our conclusions on hormone ratios rather than absolute hormone levels. Other limitations of our study include

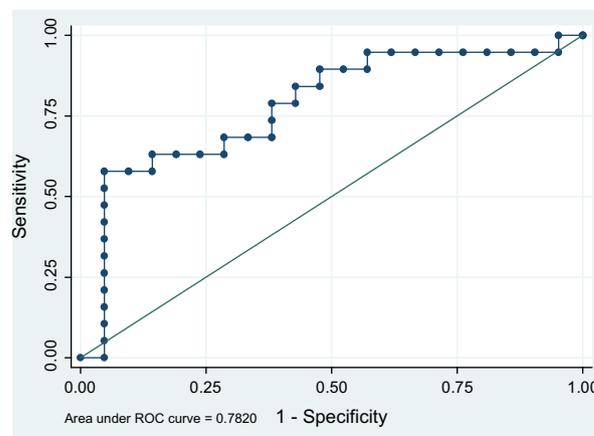


Figure 2 ROC curve. Sensitivity and specificity of ratios are reported. The distance of the curve from the middle values is correlated to the predictive value of the ratio as tool to differentiate patients with PVI from patients without PVI. A threshold ratio of 1.4 showed the highest combined sensitivity and specificity in differentiating patients with PVI from those without.

omission of transvaginal ultrasound imaging. Due to a lack of experience with transvaginal US of the OV, we decided not to rely on this diagnostic tool. Some authors have reported that combined trans-abdominal and transvaginal US is potentially useful for non-invasive screening to determine which patients with chronic pelvic pain may benefit from selective ovarian venography.²⁴ We avoided undertaking phlebography in patients without signs and symptoms of PVI so we cannot be sure that all patients in the VV group were free of pelvic vein incompetence. The consequences of exposing women of child-bearing age to radiation and the already-reported high sensitivity and specificity of US³ in detecting PVI were the main reasons for avoiding the use of phlebography in asymptomatic patients. It is also unclear whether there is any value in treating asymptomatic pelvic vein reflux. Finally, our study involved relatively few patients and a much larger cohort would have been required to provide more exact data in view of the variability of oestradiol levels.

Conclusions

These preliminary data indicate that blood samples taken from the GSV in the lower limb could help to identify those patients with clinical signs and symptoms of PVI who should undergo phlebography. If our findings can be confirmed in larger cohorts of patients, it may be possible to minimise the costs of diagnosis for patients with PVI, avoiding exposure to radiation and contrast media.

Conflict of interest

None.

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