

Proposal for a protocol for sex hormones level sampling in patients with varices to evidence pelvic reflux

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Abstract Sex hormonal direct action on venous system has been advocated for explaining further dilatation of already present limb varices, or stimulate recurrences after varicose veins removal, or even dilate normal veins inducing valves incompetence, typically in women, but also in men. Hormones can directly reach leg vein trough Pelvic Veins Incontinence. This event is frequent and quite well evidenced by Ultrasound or Radiology. Blood sampling of hormones from antecubital vein (as a control) compared with blood from varicose veins could more easily (and less costly) make possible to evidence this hormonal discrepancy whose ratio could become the index of this hormonal influence and, indirectly, pelvic reflux. Many clinical situations could benefit from this study, which may provide reasons for taking a less aggressive approach, for directing attention to leaking points and the identification of cases at risk of recurrences, suggesting a regular use of compression stockings.

Keywords Pelvic veins reflux, pelvic leak points, varices recurrence, sex hormones action, leg-arm hormones ratio

Introduction

Evidence exist that pelvic veins incompetence¹⁻⁶, through well described escape points⁷⁻¹⁰ feeds the venous network of the lower limbs. This haemodynamic phenomenon has been associated with recurrences of VV after GSV surgery, typically in women affected by pelvic congestion syndrome (PCS)¹¹⁻¹³, but recently signalled

also in men through varicocele pathway¹⁴. The direct action of sex hormones on venous system has been advocated as an explanation of further dilatation limb varices that are already present, or as stimulating recurrences after the removal of varicose veins, or even as causing the dilation of normal veins and thereby inducing valves incompetence¹⁵⁻¹⁷. In spite of this, only a few studies concerning hormonal blood levels has been undertaken. However, they do confirm the existence of this effect showing a surprising correspondence between varices and high levels of hormones.

In fact, in Asciutto's study¹⁶ in PVI patients, the median oestradiol level in GSV samples was 121 pg mL⁻¹, while in the VV subjects without PVI the median level was 75 pg mL⁻¹ while, in both, the upper limb level was identical (68 pg mL⁻¹); similarly, in Oswald's study¹⁷ oestrogen level were two to nine higher in varicose veins of women with pre-menstrual syndrome; this Author also found a testosterone increase of 294% average, in 52% of men with varicose veins. Kendler made a similar observation¹⁸.

Basing on these premises we suggest assessing the lower limb vs. systemic sex hormone level ratio (SHR) in patients with CVI before treatment as a routine and cheap laboratory test, that can be used for determining the most appropriate diagnostic management and successive operative choices, and for better defining prognostic expectations and follow up.

Method

All the subjects should be submitted to (See data form table 1):

- Standard set of clinical information
- CEAP classification. Reflux investigation by Ultrasound in conventional complete appliance (UIP) with special attention to the saphenous femoral junction (SFJ) behaviour during Valsalva manoeuvre. (See (*) in data form)
- Exclusions : Hormone intake, Cancer, Elevated liver enzymes, Superficial thrombophlebitis, Deep venous system impairment, pregnancy. AGE: under 18-above 70
- Blood sampling, (5 mL) from ante-cubital vein as a baseline; fasting.
- Blood sampling, (5 mL) from thigh varices for local/systemic comparison and ratio calculation. The sampling site, identified and registered by duplex assessment, should be as near as possible to the varicose vein receiving the pelvic flow, and taken standing¹⁷, in upright position + Valsalva¹⁶ (If the Valsalva effect is implemented standing, it is easier to manage). The sitting position could also be considered¹⁸
- 1st sample during sustained Valsalva manoeuvre (maintained for 5 seconds)= pelvic origin hormonal content.
- 2nd sample (optional, from the same access) after subsequent manoeuvres of compression/release or muscular contraction movements for analysis of hormonal level without pelvic component.

According to authors¹⁶⁻¹⁷, hormone ratios rather than absolute hormone levels should be considered as most interesting data. However, absolute hormonal level could also be interesting, provided that sampling time, menstrual periods, contraceptives or medical intake are registered. Although individual hormone levels may vary considerably over time, the local/systemic ratio would remain constant.

Material

Sampling should be performed in all the varicose patients presenting for treatment. All Centres involved in varicose veins correction are invited to participate. Pathological situations to analyze:

- **Male: testosterone**
 - Patients with varices
 - from saphenous incontinence due to the SFJ reflux without

evidently dilated superior (control, as free from hormonal contribution) or refluxing afferents.

- with saphenous incontinence without reflux at the SFJ or with dissociated reflux (Valsalva negative, compression/relaxation (C/R) positive) (= reflux from pelvic veins)
- fed directly by branches of pelvic origin
- as recurrences in the presence of branches of pelvic origin
- with the presence of dilated/refluxing superior afferents at the SFJ.
- in the presence of varicocele.
- with thigh GSV isolated dilatations associated to upper tributary intake
- varices appearing soon after puberty

Female: estrogen, progesterone

- Patients with varices
 - from saphenous incontinence due to the SFJ reflux without evidently dilated superior (control, as free from hormonal contribution) or refluxing afferents
 - with saphenous incontinence without reflux at the SFJ or with dissociated reflux (Valsalva negative, C/R positive) (= reflux from pelvic veins)
 - fed directly by branches of pelvic origin
 - as recurrences in the presence of branches of pelvic origin
 - with the presence of dilated/refluxing superior afferents at the SFJ
 - with symptoms from PCS, (especially pre-menstrual syndrome)

- with the presence of pelvic reflux escape points.
- multiparous (≥ 2 pregnancies)
- with ultrasound diagnosis of ovarian/pelvic vein dilation
- and history of vulvar varices
- with thigh GSV isolated dilatation associated to upper tributary intake
- post treatment matting

Discussion

Sex hormones are mostly produced in the ovary and testicle. Pelvic vein Incompetence (PVI) could allow reflux of hormone-rich blood to the lower limb venous system¹⁶ through well-known anatomically leaking points¹⁹. In women, these hormones are normally transported through the ovarian veins to the left renal vein as well as to the inferior vena cava and, after liver inactivation, they are eliminated through the kidneys, but in pelvic veins incompetence (PVI) they pass directly into the lower limbs network flow.

Direct (non-genomic) vascular action on the vein wall associated with oestrogens and testosterone favours dilatation through several mechanisms (NO mediation, L-calcium channel blocker and potassium channel activation in vascular smooth muscle cells)²⁰⁻²¹.

Notoriously, very high oestradiol levels during pregnancy are associated with the clinical appearance of varicose veins and their regression immediately after childbirth²². High levels of oestradiol in non-pregnant women could lead to varicose veins because of increased vein distensibility (the production of oestradiol causes the relaxation of smooth muscle and softening of collagen fibres)¹⁵.

Symptoms of venous stasis often worsen during menstruation¹⁵, have higher prevalence in multiparous women⁴ and positive therapeutic effects of hormonal replacement on symptoms suggest that sex hormones might play an important, although still not clear, role in the pathophysiology of venous dilatation¹⁶.

As consequence, in varicose veins patients with pelvic veins insufficiency (PVI) direct hormones saturated blood action could contribute to further dilate already present limb varices, or stimulate recurrences after varicose veins removal, or even dilate normal veins inducing valves

incompetence. Clinically, this event can be related to pre-menstrual syndrome (PS), veins dilatation, thin-walled aneurysmatic, VV recurrence, GSV stem recanalization, post treatment matting, menstrual symptoms, overheating, pain when subjected to heat, inclination for swelling and possible inclination for bleeding²³. Although typically occurring in female where oestrogen cycling is natural, there is evidence that, analogous to what happens in females a similar (testosterone based) hormonal mechanism is active also in men^{14,23}, through cremasteric, pudendal and deferential veins via varicocele.

So, according to Oswald²³, there are apparently two forms of varicose veins:

- varicose veins without sex hormone increase and
- varicose veins with sex hormone increase

On this base, the presence of a high sex hormones level and in particular their arm/leg ratio in varicose network prior to correction, independently from the method employed, should at least be investigated and in any case monitored for the purpose of avoiding recurrences or any other related adverse effect.

In the presence symptoms and signs of PVI, the passage of blood from the pelvis to the limb network through the leaking points is relatively easy to identify by ultrasound. However, it is not possible to quantify the hormones level: the assessment of SHR could be a simple solution.

In addition, all the GSV incompetence cases with a competent SFJ terminal valve, (about 30% of the cases in a study of 2019 legs)²⁴ could benefit from the SHR evaluation if a pelvic origin is suspected. The same is true for isolated non-saphenous refluxes (44% from the pelvis in a study of 835 legs)²⁵, and for recurrences not due to groin stump recanalization, abnormal GSV dilatation connected to a tributary, and all further situations where pelvic venous blood may directly discharge the limb venous network.

In women in particular, SHR study could be significant in multiparous (≥ 2 pregnancies?), in those recalling vulvar varices that disappeared after delivery, those with PCS, and especially with pre-menstrual varicose pain.

Also post treatment rapid occurrence of telangiectating matting should be taken into consideration.

Moreover, many patients could still have a concealed non-suspected PVI with an abnormal SHR, like, for example, in men with a non-apparent varicocele or in sudden appearance post puberal period varices.

Assigned ID (by the program) _____ Place _____ date _____
 Patient nRef _____ Gender [M] [F] Age _____ Menstrual Phase _____
 Exclusions: Hormone intake, Cancer, Elevated liver enzymes, Superficial thrombophlebitis, Deep venous system impairment, pregnancy. AGE: under 18-above 70.

Main veins pathology requesting visit (if any) _____
 Weigh, height, BMI, _____
 Associated pathologies _____
 Administered medicaments _____
 Past surgery (not venous) _____
 Past treatments (venous – date and kind of last procedure): _____
 Present Pathology related to varices: _____
 Varicocele (male) _____
 Vulvar veins (present or past) _____
 Recurrences (causal treatment/s and description present state): _____
 Post treatment telangiectating matting _____
 Primary: CEAP _____

Ultrasound Duplex limb complete assessment, standing; in particular: _____
 GSV reflux presence and distance _____
 GSV calibre (SFJ, 10-15 cm, Knee) _____
 Dilatations _____

SFJ reflux presence (*) _____
 Valsalva manoeuvre _____
 Compression/release or other activation manoeuvres _____
 SFJ upper tributaries reflux at Valsalva _____
 Dilated thigh tributaries from pelvis _____
 Pelvic escape points incompetence _____
 Other findings _____
 Transvaginal US assessment _____
 Other radiology diagnostics _____

Dosage of testosterone in male (samples taken at the same session) _____
 oestrogens (17- β -oestradiol) and progesterone in female _____
 1-Baseline Blood sampling, (5 mL) from ante-cubital vein, fasting. _____
 2-Blood sampling (5 mL) from thigh varices (pelvic origin hormonal content) (**) _____
 3- Blood sampling (5 mL) from same access after vein wash-out (***) _____

Table I - Data form for sex hormones level sampling in patients with varices. () Remind to assess GSV reflux during Valsalva placing the sample volume just in front of the GSV orifice inside the Femoral vein perpendicular to flow in transverse position; same, placing the sample volume over the tributary. (**) the sampling site, identified and registered by duplex assessment, should be as near as possible to the varicose vein receiving the pelvic flow during a sustained (5 seconds) Valsalva manoeuvre. (***) after subsequent manoeuvres of compression/release or muscular contraction movements for analysis of hormonal level without pelvic component.*

If ratio importance of hormonal blood level were confirmed, more invasive diagnosis procedures could be limited or enhanced; it would be possible also¹⁹ to:

- State which cases are at risk of recurrence. A grading in two or more clinical groups could be created
- Address treatments over more conservative methods
- Be more aggressive in the obliteration of leaking points
- Verify the effect and duration of treatment by monitoring hormone levels
- Limit aggressive procedure or, at the contrary, indicate further treatment
- Find chemical antagonist to the effects of local hormones and mediators
- Develop some kind of conservative treatments (compression pants limiting leaking flow)²⁶

- Analyse possible temporary ovary function blocking, limited to post-operative period

Conclusion

The passage of blood rich in sex hormones from the pelvic network directly to the lower limb venous system through several refluxing pathways could be related to varicose veins pathology probably as a concurrent effect in a consistent number of cases, not only in women but also in men. As a consequence, varices could be grouped in high or low hormones associated. The knowledge of this condition through the measurement of sex hormone levels in the lower limb and ratios with systemic levels in patients could have consequences for diagnosis and treatment and could be done with simple low cost laboratory tests. Data collected could help to integrate the modern SVP classification to assess pelvic vein disorders²⁷. A study protocol (still imprecise since it is at the purely theoretical stage) is proposed as a project base for setting up a multicentre study.

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