



Vaginal dryness: individualised patient profiles, risks and mitigating measures

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Received: 5 February 2019 / Accepted: 14 February 2019

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Abstract

Vaginal dryness (VD) affects both pre- and postmenopausal women at any age. Since the hormonal regulation changes during the climacteric period are considered as being the main course of the VD, affected women prefer not to talk about the problem. However, the problem does exist, and unfortunately if any, relatively minor group in the population possesses the health literacy at sufficient level to understand that VD is a suboptimal health condition which carries a multi-factorial character. Thereby, some of the contributing factors are clearly preventable and, therefore, if treated properly, have a potential to milden the VD. Current chapter demonstrates specific signs and symptoms of Flammer syndrome in women suffering from vaginal dryness, although individualised patient profiles clearly discriminate between pre- and postmenopausal women regarding the subgroup-specific symptoms. Noteworthy, about 20% of the VD patients involved in the study notify a delayed or even impaired wound healing observed for themselves over a couple of years.

Optimising modifiable risk factors accompanying FS phenotype at the level of primary prevention is strongly recommended. Individualised patient profiles provide important information for VD mitigating measures tailored to the person. Further, future projects should essentially deal with the complexity of vulvar-vaginal dryness as part of the Sicca syndrome in individuals with FS phenotype, in order to prevent genital female cancers which may occur at any age. In contrast to the human papilloma virus as possible trigger of the disease, the role of the vulvar-vaginal dryness as an important risk factor is strongly underestimated in currently applied diagnostic and treatment approaches.

Keywords Vaginal dryness · Vaginal dysfunction · Vasoconstriction · Dehydration · Sicca · Stress · Altered sense regulation · Blood pressure · Menopause · Hormonal regulation · Microbiome · Pain · Sexual intercourse · Headache · Psychological aspects · Life quality · Dyspareunia · Vulva cancer · Flammer syndrome

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Vaginal dryness is a problem which women reluctantly speak about: what is behind the issue?

Vaginal dryness (VD) affects both pre- and postmenopausal women at any age. Since the hormonal down regulation during the climacteric period is considered as being the main course of the VD, affected women prefer not to talk about the problem. However, the problem does exist, and unfortunately if any, relatively minor group in the population possesses the health literacy at sufficient level to understand that VD is a suboptimal health condition which carries a multifactorial character. Furthermore, some of the contributing factors are clearly preventable, the mitigation of which therefore has a potential to milden the VD manifestation.

VD is a widespread problem negatively impacting the life quality

Some statistics

According to several population studies, more than half of postmenopausal women aged over 51 years suffer from mild or severe VD related to specific changes in menopausal hormonal regulation linked to the decreasing level of oestrogen. On the other hand, it is also true that around 17% of premenopausal women aged 17–50 years do experience problems with a sexual intercourse, due to vaginal dryness and painful sex [1].

Diagnosis

Usual symptoms of the VD are skin irritation, burning, itching and/or simply discomfort in the area—all primarily of non-bacterial origin that should be determined by gynaecologist.

Severe consequences

Painful intercourse strongly contributes to the lost sexual desire. Dyspareunia and anxiety towards regular sexual intercourse are severe consequences negatively impacting the life quality of the affected females and couples [2, 3]. Further, severe VD strongly influence daily life of the affected individuals by causing uncomfortable or even painful sit, stand, sport and exercise etc. [4]. Finally, dry vaginal tissue in a long-term is strongly predisposed to frequent infections affecting and diminishing physiologic functioning of the urogenital tract. Therefore, normal vaginal lubrication, acidic vaginal pH and normal vaginal microbiome are the life-important physiologic conditions which effectively help defending against permanent attacks by pathologic microbial contamination. Contextually, VD is associated with microbiome alterations demonstrating low abundance of *Lactobacillus* [5].

Known VD triggers and contributors

Main contributors known triggering VD and worsening the condition are summarised below. Amongst them, the best acknowledged is the hormonal down regulation of oestrogen; all other factors are strong contributors which, however, are much less investigated.

Hormonal regulation changes

Hormonal regulation changes by low and/or decreasing level of oestrogen usually occurs in peri- and postmenopause but also during breastfeeding—both are physiologic processes.

Menopausal symptoms including VD may result also from non-physiologic events such as intensive vaginal douching, cigarette smoking, cold medications, surgical removal of the ovaries, anti-oestrogen medication (e.g. to treat endometriosis and uterine fibroids), application of some anti-depressants (e.g. tricyclics), as well as irradiation and chemotherapy implemented to cancer patients.

Finally, several relevant pathologic conditions may lead to onset of VD such as immune system related disorders (allergies and Sjögren syndrome) [6] and application of antihistamines, as well as premature ovarian insufficiency (e.g. due to accelerated ageing) [7] and diabetes, amongst others.

Dehydration

Sufficient liquid intake is essential for the proper vaginal lubrication [8]. The whole body dehydration may strongly contribute to the Sicca syndrome including VD and headache amongst others [9]. Artificial lubrication with the vaginal moisturising gels is one of the most effective treatments against vaginal dryness.

Excessive vasoconstriction

Some studies have demonstrated that a lack of lubrication may be caused by significantly decreased blood flow to the vaginal walls demonstrated particularly due to excessive primary vascular dysregulation, secondary vasoconstriction (e.g. due to cancer treatment), ageing, abnormal metabolism related pathologies such as diabetes, and changes in vaginal innervation also augmenting vasoconstriction and promoting vaginal dryness [10].

Psychologic factors and stress overload

Psychologic factors play an important role in VD development and secondary complications [11]. For example, it is evident that not enough foreplay before sex frequently causes VD in both—pre- and postmenopausal women. Further, significant stress overload and anxiety negatively impacts both libido and vaginal lubrication [2, 3].

Hypothesised relationship between the Flammer syndrome phenotype and VD predisposition

The above summarised facts strongly support the hypothesis that both pre- and postmenopausal women demonstrating Flammer syndrome phenotype may be strongly predisposed to vaginal dryness. In particular,

- On the one hand, excessive vasoconstriction plays the central role in expression of the Flammer syndrome (FS) phenotype and, on the other hand, strongly contributes to the VD onset
- Specific psychological aspects are characteristic for FS such as meticulous personality with a particularly pronounced tendency to perfectionism that can result in significant stress overload demonstrated as a strong contributor to the VD development
- An altered sensation regulation is typical for the FS affected individuals such as strongly reduced feeling of thirst, amongst others; in this condition, if the sufficient liquid intake is not well controlled, it may lead to significant body dehydration and consequent Sicca syndrome including VD manifestation [6, 7, 9, 12].

Materials and methods

Study design

Patients with VD

Vaginal dryness was determined utilising patient self-reports and confirmed by gynaecologic examination of otherwise healthy patients introduced for check-up. The grade of the VD was evaluated by using a visual analogue scale (VAS) 0–10, where 0 means the absence of VD and 10—intolerable VD.

Altogether, 54 patients suffering from vaginal dryness, both premenopausal and postmenopausal ones, have been recruited. Menopausal status has been considered as an important stratification criterion; corresponding statistical evaluations are presented in the subchapter “Results”.

VD symptoms-free controls

Altogether 52 VD symptoms-free individuals—both premenopausal and postmenopausal ones, have been clinically examined attesting an absence of gynaecological pathologies and complains. The investigated women have been interviewed personally for the study during their hospital outpatients visits.

15-Item questionnaire to characterise the Flammer syndrome (FS) phenotype

The FS phenotype has been characterised earlier [12]. The FS questionnaire (see Table 2) applied to the actual study has been developed at the University Ophthalmologic Hospital Basel, Switzerland [13]. The actual version of the FS-questionnaire has been recently applied to analyse the FS symptoms in related health conditions such as “dry mouth” [14], Sicca and Sjögren syndromes [6], as well as gynaecological diseases such as several subtypes of breast cancer and metastatic disease [15–17].

Statistical analysis

For analytical and statistical evaluations, the data have been transferred to Microsoft Excel. SPSS Statistics v20.0.0 software (IBM, Armonk, New York, USA) has been applied. The prevalence of individual symptoms in groups of comparison has been evaluated and expressed in percentages. Pearson’s chi-square test of associations has been applied. *P* values below 0.05 have been considered as statistically significant.

Results

Specialised questionnaire analysing the prevalence of the VD patients versus controls has been used to investigate, whether women suffering from VD demonstrate specific features of the FS-phenotype as hypothesised here. VD patients recruited in the study have been stratified in subgroups according to their menopausal status, in order to answer the questions, whether the VD contributing factors are similar for or differ between pre- and postmenopausal patients—statistical analysis is provided in the Table 1.

Table 2 summarises the evaluation of the symptoms’ prevalence in the groups of comparison; corresponding statistical

Table 1 Age distribution amongst premenopausal and postmenopausal vaginal dryness (VD) patients, and healthy controls

Number of patients	Premenopausal VD	Postmenopausal VD	Healthy controls
	34	20	52
Patients age mean (min-max), [years]	40.62 (27–49)	59.9 (50–77)	54.62 (25–89)

Table 2 15-item Flammer syndrome questionnaire evaluated for the groups of comparison; systemic effects linked to the individuals symptoms as well as their relevance for the VD risks are notified

Nr:	More prevalent in VD vs controls?	Questions towards specific symptom/signs	Systemic effects and regulation alterations	VD relevant risks
1	Yes, statistically significant, $P = 0.007$	Do you suffer from cold hands and/or feet?	<ul style="list-style-type: none"> - Vascular regulation - Blood flow regulation - Potential hypoxic effects 	<ul style="list-style-type: none"> - Excessive vasoconstriction - Cold stress provocation
2	Yes, statistically significant, $P = 0.021$	Do you feel cold when you are not moving for a while?	<ul style="list-style-type: none"> - Vascular regulation - Blood flow regulation - Thermoregulation 	<ul style="list-style-type: none"> - Excessive vasoconstriction - Cold stress provocation
3	Yes, statistically close to significant, $P = 0.082$	Do/did you have low blood pressure?	<ul style="list-style-type: none"> - Cardiovascular regulation 	<ul style="list-style-type: none"> - Potential cardiovascular risks
4	Slightly more prevalent in VD	Do you ever feel dizzy when you suddenly stand up from a lying or resting position?	<ul style="list-style-type: none"> - Cardiovascular regulation - Vascular regulation - Blood flow regulation 	<ul style="list-style-type: none"> - Impacts by systemic hypoxic effects
5	More prevalent in post-VD than in premenopausal VD and controls; statistically non-significant	Do you need a relatively long time to fall asleep?	<ul style="list-style-type: none"> - Potential hypoxic effects - Sleep pattern regulation 	<ul style="list-style-type: none"> - Altered circadian rhythms - Abnormal stress reaction
6	Yes, statistically significant, $P = 0.03$	How is your feeling of thirst?	<ul style="list-style-type: none"> - Sense regulation 	<ul style="list-style-type: none"> - Potential dehydration
7	Yes, statistically significant, $P = 0.002$	How often do you have headache?	<ul style="list-style-type: none"> - Sense regulation - Sensation regulation - Hormonal regulation - Pain sensitivity 	<ul style="list-style-type: none"> - Hormonal regulation changes
8	More prevalent in post- than in premenopausal VD and controls; statistically non-significant	In case you suffer from migraine attacks, do you have accompanying symptoms (e.g. visual disturbances, transiently altered sensation such as crribbing in your arms or legs etc.)? If you have to take medications (other than painkillers), do you have a feeling that you react very strongly towards them and/or that you would feel better, if you would take a lower dosage than that is usually prescribed?	<ul style="list-style-type: none"> - Vascular regulation - Collateral complications (e.g. increased stroke risk) 	<ul style="list-style-type: none"> - Potential impacts by collateral complications
9	More prevalent in both pre- and postmenopausal VD; statistically non-significant	Do you suffer from any type of pain which you need to take painkillers for?	<ul style="list-style-type: none"> - Metabolic regulation - Drug sensitivity 	<ul style="list-style-type: none"> - Metabolic alterations
10	More prevalent in postmenopausal than in premenopausal VD; statistically non-significant	How well can you smell: can you smell odours which other people do not smell at all or to much lesser extent? Were/are you particularly slim at the age of 20–30 years?	<ul style="list-style-type: none"> - Sense regulation - Pain sensitivity - Collateral complications (e.g. chronic inflammation of any nature) - Sense regulation - Stress sensitivity 	<ul style="list-style-type: none"> - Collateral complications - Altered sense regulation - Psychological aspects
11	More prevalent in pre-menopausal VD than in postmenopausal VD and controls; statistically non-significant	Were/are you particularly slim at the age of 20–30 years?	<ul style="list-style-type: none"> - Metabolic regulation - Genetic predisposition 	<ul style="list-style-type: none"> - Metabolic alterations - Genetic component
12	Slightly more prevalent in VD	If you would judge your attitude (e.g. in job), would you recognise a tendency towards perfectionism?	<ul style="list-style-type: none"> - Disordered eating with collateral complications (e.g. psychologic stress, altered microbiome etc.) - Genetic predisposition - Psychologic pressure - Stress regulation 	<ul style="list-style-type: none"> - Impacts by collateral complications - Psychological aspects
13	No difference			

Table 2 (continued)

Nr.	More prevalent in VD vs controls?	Questions towards specific symptom/signs	Systemic effects and regulation alterations	VD relevant risks
14	More prevalent in both pre- and postmenopausal VD; statistically non-significant	Do you notice ringing in your ears (tinnitus) from time to time?	- Stress reaction - Collateral complications	- Increased stress - Impacts by collateral complications
15	No difference	Do you notice reversible blotches (white or red) on your skin when you are very excited or angry (e.g. in stress situations)?	- Vascular regulation - Pronounced systemic effects - Stress sensitivity	- Systemic stress reaction

significance is noted. Systemic effects linked to the individual symptoms of the FS-phenotype are notified. Their relevance for the VD risks is presented.

The most significant differences between the VD subgroups as well as between VD patients and healthy controls are presented in Fig. 1.

Data interpretation

The results of the pilot study strongly support the hypothesis that both pre- and postmenopausal women suffering from vaginal dryness demonstrate symptoms and signs characteristic for the FS phenotype. The most significant differences recorded in the study are presented in Fig. 1 and concluded below.

FS symptoms and signs with similar profiles for both pre- and postmenopausal VD patients

- Major role of the vascular component by *excessive vasoconstriction* (symptoms 1 and 2)
- Low blood pressure (symptom 3)
- Altered sense regulation such as smell perception (symptom 11); in particular, decreased perception of thirst (symptom 6) may play an important role leading to insufficient liquid intake and body dehydration that is strongly supported by another FS-symptom 7, namely much more frequent headache in VD patients compared to the control group. To this end, frequent headache has been demonstrated as one of the typical symptoms of the *body dehydration* and as linked to that an increased risk of stroke even at young age [18].
- Although being statistically non-significant, following FS-symptoms have been demonstrated as more prevalent in VD patients than in controls: *dizziness, altered sleep patters, increased drug sensitivity, slim body shape and tinnitus*.

Menopausal-specific difference in FS-related profiles

- No feeling of thirsty is more strongly pronounced in premenopausal VD patients
- Also smell perception is stronger in premenopausal VD patients
- Vasoconstriction is more pronounced in premenopausal VD patients
- In contrast, longer sleep onset is reported by postmenopausal VD patients who also to 100% suffer from frequent headache and more frequently report on accompanying symptoms such as an impaired vision, deafness appeared in the extremities
- Painkillers are taken more frequently by postmenopausal VD patients who also more frequently report on low BMI in early adulthood than premenopausal VD patients

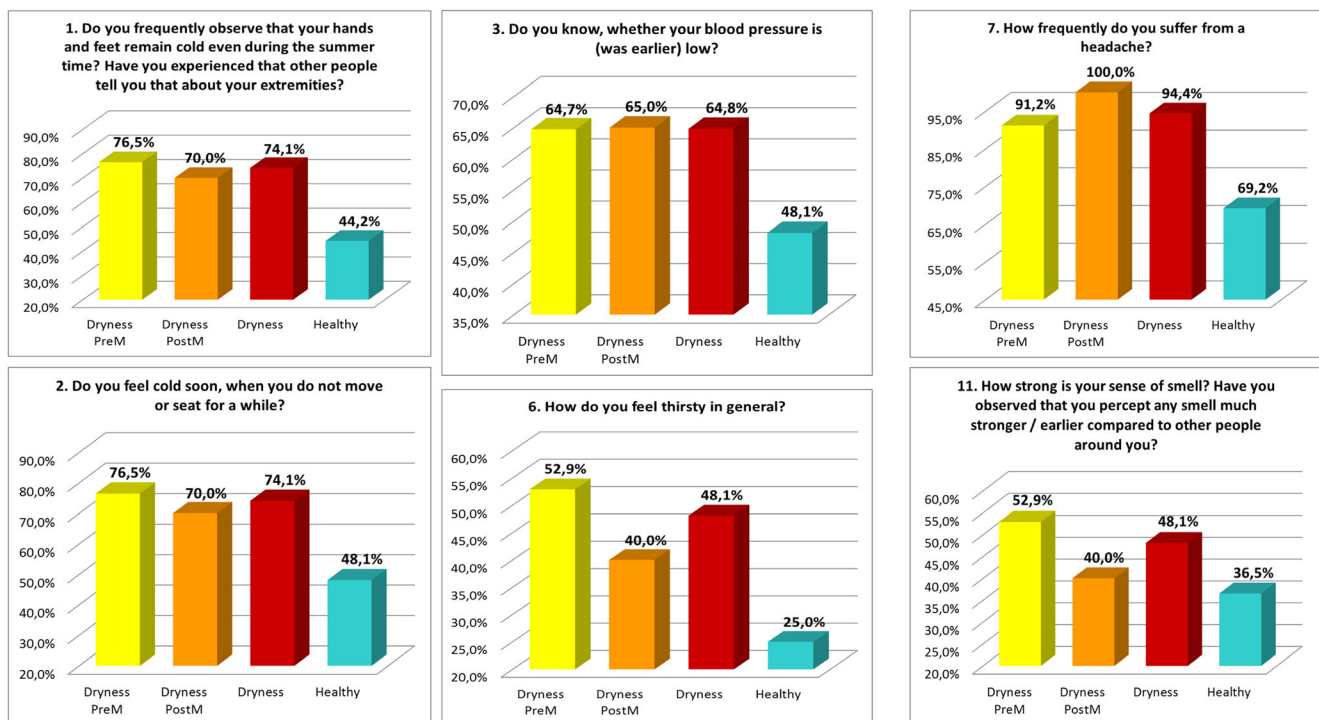


Fig. 1 The most pronounced prevalence of individual symptoms characteristic for the FS-phenotype in VD patients versus controls is demonstrated. “Dryness PreM” - premenopausal VD patients, “Dryness

PostM” - postmenopausal VD patients. “Dryness” combines both VD sub-groups; “Healthy” = control group; specifically to the question 6, the answer “I do not feel thirsty” is displayed

- Tinnitus is more frequent in premenopausal VD patients than in postmenopausal counterpart.

- Pain
- Low BMI in early adulthood

Most frequent combination of the FS-symptoms in premenopausal VD patients

- Excessive vasoconstriction
- Feeling cold soon
- Low blood pressure
- Dizziness
- Strongly reduced thirst perception
- Headache
- Strong smell perception
- Perfectionistic personality
- Tinnitus

Most frequent combination of the FS-symptoms in postmenopausal VD patients

- Excessive vasoconstriction
- Feeling cold soon
- Low blood pressure
- Dizziness
- Prolonged sleep onset
- Headache and migraine with accompanying symptoms

Expert recommendations

Optimising modifiable risk factors at the level of VD primary prevention is strongly recommended. The above presented profiles provide a lot of information for the targeted prevention. Corresponding measures should be tailored to the individual. However, general measures consider regulation of vaginal pH and microbiota depending on the hormonal status, microbiota composition and the phase of menstrual cycle. Regarding the microbial composition, dietary interventions may be suggested supporting the primary colonisation by Lactobacilli to the vaginal microbiota [19].

Finally, future projects should essentially deal also with vulvar-vaginal dryness as part of the Sicca syndrome in females with FS phenotype predisposed to lichen sclerosus of vulva (LSV). LSV demonstrates clear symptoms of the tissue dryness (skin sensitivity and irritation, burning, itching, pain, etc.) and step-by-step leads to vulvar atrophy, fibrosis and dysplasia that may result in a manifestation of the vulvar carcinoma, if not effectively treated well in time. To this end, in the USA, women have a 1 in 333 chance of developing vulvar cancer at some point during their life. The American Cancer Society reports on

about 6190 cancers of the vulva in USA in 2018, and about 1200 women die of this cancer [14]. In contrast to the human papilloma virus as possible trigger of the disease, the role of the vulvar dryness as an important risk factor is strongly underestimated in currently applied diagnostics and treatment.

Authors' contributions Olga Golubnitschaja is the coordinator of the international project, who has created the main scientific concepts and hypotheses presented in the article; she has drafted the manuscript. Vadym Goncharenko and Rostyslav Bubnov have coordinated the research, patient recruitment, data analysis and interpretation performed in Ukraine. Pavol Zubor has coordinated the research, patient recruitment, data analysis and interpretation performed in Slovakia. Jiri Polivka Jr. has performed data evaluation and statistical analysis. Walther Kuhn, Kamil Biringer and Tibor Bielik have contributed to the project by conceptual development of the publication. All the authors have read and approved the final manuscript.

Funding This multi-centre study has been supported by the following organisations: European Association for Predictive, Preventive and Personalised Medicine, EPMA, Brussels, Belgium; Centre of excellence for perinatology research II co-financed from EU sources (ITMS: 26220120036), Slovak Republic; and the National Sustainability Program I (NPU I) Nr. LO1503, Ministry of Education Youth and Sports, Czech Republic and MH CZ-DRO (Faculty Hospital in Plzen-FNPI, 00669806).

Compliance with ethical standards All procedures performed in the current study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study-relevant ethical committees have approved the approach and involvement of the local patients into the international multi-centre study, namely in Ukraine—Bogomolets National Medical University/Clinical Hospital “Pheophania”, Kyiv, Ukraine (protocol number 85, issued 11.02.2015) by the ethics committee of institutional review board and Special Academic Council on Doctoral Thesis of D.K. Zabolotny Institute of Microbiology and Virology of the National Academy of Sciences of Ukraine (protocol N 7 issued 03.07.2018), and in Slovak Republic—Department of Obstetrics and Gynaecology, Jessenius Faculty of Medicine, Martin University Hospital, Martin, (protocol number IRB 1927/2016).

Competing interests The authors declare that they have no competing interests.

Informed consent statement All subjects, who have been involved in the study, agreed to participate and signed the “informed consent” form.

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