Maturitas 183 (2024) 107950

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Original article

Vulvovaginal atrophy in women with and without a history of breast cancer: Baseline data from the PatiEnt satisfactiON studY (PEONY) in Italy

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ARTICLE INFO

Keywords:
Vulvovaginal atrophy
Local estrogens
Nonhormonal local treatments
Ospemifene
Breast cancer

ABSTRACT

Objectives: To assess clinical characteristics of postmenopausal women with moderate/severe vulvovaginal atrophy, as well as its impact on sexual function, well-being, and quality of life, and to provide an overview of most used treatments.

Study design: Ongoing longitudinal, observational study conducted in 17 Italian gynecology centers, involving women already treated or initiating a local vaginal estrogen therapy or ospemifene. We report baseline data for women with and without a history of breast cancer. Participants filled in self-reported questionnaires at study entry.

Main outcome measures: Severity of vulvovaginal atrophy; ongoing treatments; patient-reported outcomes, including severity of symptoms, Day-to-Day Impact of Vaginal Aging (DIVA), Female Sexual Function Index (FSFI), Female Sexual Distress Scale-Revised (FSDS-R), and SF-12® Health Survey.

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https://doi.org/10.1016/j.maturitas.2024.107950
Received 31 July 2023; Received in revised form 22 January 2024; Accepted 20 February 2024
Available online 5 March 2024
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Results: Overall, 334 women (20.4 % with a history of breast cancer) started or continued local therapy (61.1 %) or ospemifene (38.8 %) at study entry. Vulvovaginal atrophy was severe in 28.6 %, and was responsible for severe symptoms, particularly vulvar dryness with burning or irritation and pain during sexual intercourse. Both sexual dysfunction (FSFI≤26) (81.5 %) and sexual distress (FSDS-R ≥ 11) (74.4 %) were common. A reduction in the SF-12 mental component score was documented. Women with breast cancer more often had severe vulvovaginal atrophy (41.2 %), had more severe symptoms, and the impact of vaginal symptoms on emotional well-being, sexual functioning and self-concept/body image was greater. The majority of them (83.8 %) received ospemifene as a treatment.
Conclusions: Moderate/severe vulvovaginal atrophy is a common, often neglected condition with an impact on QoL and sexuality, particularly in women with a history of breast cancer. It is important to alleviate the burden associated with the disease.

1. Introduction

Both hormonal deprivation and senescence contribute to significant changes in the functional anatomy of urogenital tissues giving origin to signs and symptoms of vulvovaginal atrophy (VVA) [1]. Main symptoms of VVA (vaginal dryness, irritation, itching, and dyspareunia) were included into the new definition of genitourinary syndrome of menopause [2] and ranged from 13 % to 87 % according to different study samples [3]. For instance, in a cohort of women with a history of breast cancer (BC), vaginal dryness was present in 61.5 % of postmenopausal women [4].

VVA is a chronic and progressive condition with a profound impact on sexual function and quality of life (QoL) of postmenopausal women [5]. Recent data from the European Vulvovaginal Epidemiology Survey (EVES) indicated that the amount of distress associated with VVA was significantly higher in those women reporting more severe symptoms [6,7]. No significant difference in term of burden of disease was present according to a positive history of BC, but the sample of these women was relatively small in comparison with those with no history of BC [8]. In the same study conducted in a total of 2412 postmenopausal women, less than half of them (42.5 %) have received at least one treatment to relieve VVA [9], a finding in line with the evidence that HCPs seemed not proactive in initiating the conversation on VVA symptoms [10]. Of note, the poor management of VVA translated into the evidence that women on VVA treatment presented with more severe symptoms [9]. These results were quite surprising in light of the common knowledge that VVA symptoms might be alleviated by the use of appropriate treatment [1,11]. Indeed, various local estrogen treatments (LET), alone or even combined with systemic hormones therapy, seem equally effective in alleviating VVA symptoms, including dyspareunia, and other associated conditions [12]. Local androgens, dehydroepiandrosterone (DHEA) pessaries and testosterone cream, represent additional options available in some countries [13]. Another effective possible treatment of moderate to severe VVA in postmenopausal women is the oral medication ospemifene, a third-generation selective estrogen receptor modulator approved in Europe in 2015 [14]. Given the recent availability of real-world data on efficacy and safety, ospemifene can now be considered a first-line pharmacological treatment option together with LET and vaginal DHEA for the management of moderate to severe VVA in postmenopausal women [15].

In Italy, compliance to available therapeutic options for VVA, including non-hormonal lubricants and moisturizers applied to the vagina, has been found quite low [16]. Barriers to adherence have been related to messiness of vaginal products, fears of hormones and unsatisfactory improvement of the condition [17]. Ensuring long-term adherence to treatment represents an important goal in clinical practice, since objective signs and subjective symptoms tend to return to pretreatment levels after approximately 1–3 months following treatment discontinuation [18]. Recent expert considerations suggest that offering patients a strategy that uses one or more medications for a long enough time to achieve the desired benefits with minimal risk and maximum adherence is mandatory [19]. This is even more relevant in women with a history of BC who remain untreated due to the low comfort of HCPs in making prescriptions [20], in spite of new and safer options available [21].

PatiEnt satisfactiON studY (PEONY) is a descriptive, real-world study designed with the aim to provide a comprehensive picture of postmenopausal women with moderate to severe VVA in Italy. The study aims to: a) assess clinical characteristics (signs and symptoms) and impact on sexual function along with well-being related to VVA and QoL and b) provide an overview of the most used treatments for VVA, in order to discuss margins of improvement in terms of appropriateness and acceptability by means of patient-reported outcomes (PROs) over time. In here, we report the baseline data of our study population including also women with a history of BC.

2. Methods

PEONY is an ongoing longitudinal, observational study conducted in 17 gynecology centers throughout Italy. A 12 months follow-up was planned.

Two different cohorts were identified: women with and without BC history.

Inclusion criteria were: age ≥ 18 years; post-menopausal state; moderate to severe VVA based on clinical judgment; already treated or initiating LET or ospemifene at study entry, irrespective of other concomitant treatments for VVA (moisturizers, lubricants, laser, and radiofrequency).

Exclusion criteria were: ongoing hormone replacement therapy, administered by pill or patch.

Baseline characteristics included: age, post-menopausal state, history of BC and related treatments and procedures, symptoms of VVA, severity of VVA, duration of VVA, weight, height, history of abortion/childbirths, hysterectomy, prolapse and urinary incontinence, relevant comorbidities, current chronic therapies, prescribed treatment for VVA. The vaginal health index (VHI) was used to evaluate vaginal elasticity, secretions, pH, the presence of petechiae on the epithelial mucosa, and hydration [22]. The score can vary between 5 and 25, with a cut-off <15 representing an index of atrophic vagina. The vulvar health index (VuHI) was used to evaluate the vulva status, including vulvar inflammation, musculature contraction, pain at speculum insertion, and epithelial integrity [23]. The score can vary from 0 to 24, with a cut-off >8 representing an index of atrophic vulva.

Participating women were administered self-reported questionnaires at study entry.

The baseline questionnaire contained information about sociodemographic characteristics, lifestyle, and the last prescribed treatment for VVA. Information on QoL, satisfaction, psychological and physical impact of VVA was collected using the following questionnaires:

- Symptoms of VVA were assessed using the specific section of the European Vulvovaginal Epidemiological Survey (EVES) [24]. Women were asked to score their symptoms of VVA, based on a list of

19 potentially VVA-related complaints on a four-point severity scale (absent, mild, moderate or severe). Vaginal symptoms included vaginal dryness (internal), pain during intercourse (internal), pain during intercourse at penetration, bleeding during intercourse, bleeding during sexual contact, burning or irritation (internal), itching (internal), vaginal discharge; vulvar symptoms include vaginal dryness (external), burning or irritation (external), itching (external) and pain during exercise; urinary symptoms include urinary incontinence, urinary urgency, urinary frequency, urinary difficulties, recurrent urinary tract infections, and post-coital cystitis. In addition, a single question investigated the presence and severity of abdominal pain.

- The Day-to-Day Impact of Vaginal Aging (DIVA) questionnaire is a structured, validated, self-administered instrument assessing the multidimensional impact of vaginal symptoms on functioning and well-being [25]. The DIVA instrument consists of four multi-item domain scales addressing major dimensions of functioning and well-being affected by postmenopausal vaginal symptoms: (1) activities of daily living (five items), (2) emotional wellbeing (four items), (3) self-concept and body image (five items), and (4) sexual functioning (nine items for a long version appropriate for sexually active women, and five items for a shorter version appropriate for women without a recent history of sexual activity). The questionnaire addresses symptom impact in the four weeks prior to survey self-administration. Each scale is designed to be scored from 0 to 4, with higher scores indicating greater impact of symptoms on the relevant domain.
- The Female Sexual Function Index (FSFI) is a 19-item self-reported measure of female sexual function over the past four weeks [26]. The instrument provides scores on six domains of sexual function as well as a total score. The domains include: desire (2 items), arousal (4 items), lubrication (4 items), orgasm (3 items), satisfaction (3 items), and pain (3 items). The full-scale score ranges from 2.0 to 36.0, where a higher score is associated with lower severity of sexual dysfunction.
- The Female Sexual Distress Scale-Revised (FSDS-R) is a self-administered questionnaire consisting of 13 items that relate to different aspects of sexual distress [27]. Every item requires an answer that is rated as 0–4 (never [0], rarely [1], occasionally [2], frequently [3], always [4]). The total score, ranging from 0 to 52, provides a measure of sexual distress, in which the higher the score, the higher the level of sexual distress. The FSDS-R is identical to the FSDS except for the addition of one question that asks women to rate their level of distress related to low sexual desire.
- The SF-12® Health Survey (SF-12) is a 12-item questionnaire used to assess generic health outcomes from the patient's perspective [28]. The SF-12 consists of a subset of 12 items from the SF-36® Health Survey (SF-36). A Physical Component Summary Score (PCS) and a Mental Component Summary Score (MCS) can be calculated. PCS and MCS are standardized so that in the normal population a value of 50 with a standard deviation of 10 is expected. SF-12 summary measures are scored so that a higher score indicates a better health state.

A summary of the questionnaires used in our study is available in Appendix 1.

In addition to validated questionnaires, the extent to which VVA symptoms interfered with different aspects of daily life was investigated through specific questions, with the answers ranging from 1 (no impact) to 10 (extreme impact).

All information was collected on electronic case report forms and data were anonymous.

During the follow-up at 3, 6, and 12 months, we expect to collect information on persistency in therapy and satisfaction with treatment, discontinuation rates and reasons for treatment discontinuations, and changes in PROs.

The study protocol was approved by local ethics committees and all patients signed the informed consent. All procedures were conducted in compliance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013.

2.1. Statistical analysis

The study has purely descriptive purposes. As such, no formal sample size estimation was performed, and all consecutive eligible women seen in participating centres during 12 months were enrolled, irrespective of the ongoing treatment for VVA.

Descriptive data were summarized as mean and standard deviation or percentages. Characteristics of the study population were assessed overall and by history of BC.

Comparisons between groups (patients with and without BC history) were performed using the unpaired *t*-test or the Mann-Whitney *U* test in case of continuous variables and the chi-square test or Fisher exact test for categorical variables, as appropriate.

3. Results

3.1. Overall population

Between September 2021 and December 2022, we observed 414 postmenopausal patients with VVA and 334 of them (80.7 %) started or continued LET or ospemifene at study entry, and, therefore, were included in the present analysis. Among eligible women, 68 (20.4 %) had a history of BC and 266 (79.6 %) had no history of BC (Fig. 1).

Baseline characteristics are reported in Table 1. Participating women had a mean age of 57.5 years. Mean BMI was 23.4 kg/m^2. The vast majority of the study population was Italian; women of other nationalities were able to understand the content of the questionnaires. Physiological menopause was reported by 78.6 % of the study sample. Most of participants had at least a high school education level, were married, and employed. The most frequently reported comorbidities were urinary incontinence, hypertension and osteoporosis. One in ten women were smokers, one in twenty regularly drunk alcohol, one in seven drunk >3 coffee cups per day, and 38 % were sedentary.

Data relative to VVA severity and treatment are reported in Table 2. At enrollment, VVA was moderate in 61.7 % of the cases and severe in 28.6 % of the cases. Vaginal atrophy, as defined by a VHI <15, was present in 80.5 % of women, while vulvar atrophy, as defined by a VuHI score > 8, was present in 72.4 % of the cases. Mean VVA duration was 1.2 ± 8.4 months.

Before study entry (T-1), 147 (44.0 %) women were untreated, 84 (25.0 %) were treated with LET and 21 (6.3 %) with ospemifene. Furthermore, 42 (12.6 %) were treated with lubricants, 47 (14.1 %) with moisturizers, 24 (7.2 %) with laser therapy, and 6 (1.8 %) with radiofrequency (Table 2).

At study entry (baseline, T0), 204 (61.1 %) women were prescribed LET and 130 (38.9 %) ospemifene. In detail, 51 (15.3 %) were treatment naive and started ospemifene, 96 (28.7 %) were treatment naive and started LET, 53 (15.9 %) were already treated with LET or ospemifene and continued their previous treatment, while 134 (40.1 %) were already treated and changed therapy. Among those changing therapy, the main 3 reasons for change were: lack of efficacy ($N = 111$; 82.8 %), poor compliance ($N = 20$; 14.9 %), and adverse events ($N = 7$; 5.2 %).

Table 3 shows the burden of VVA in women's life. The first section of the table, which reports the items derived from the EVES questionnaire, shows that VVA was responsible for severe symptoms, particularly those regarding vulvar dryness with burning or irritation and pain during sexual intercourse. The second section of Table 3 describes impact on several aspects of life. In particular, the highest scores (i.e. greater impact) were documented for the acceptance of lack of spontaneity in the relationship, the acceptance of pain during sexual intercourse, and

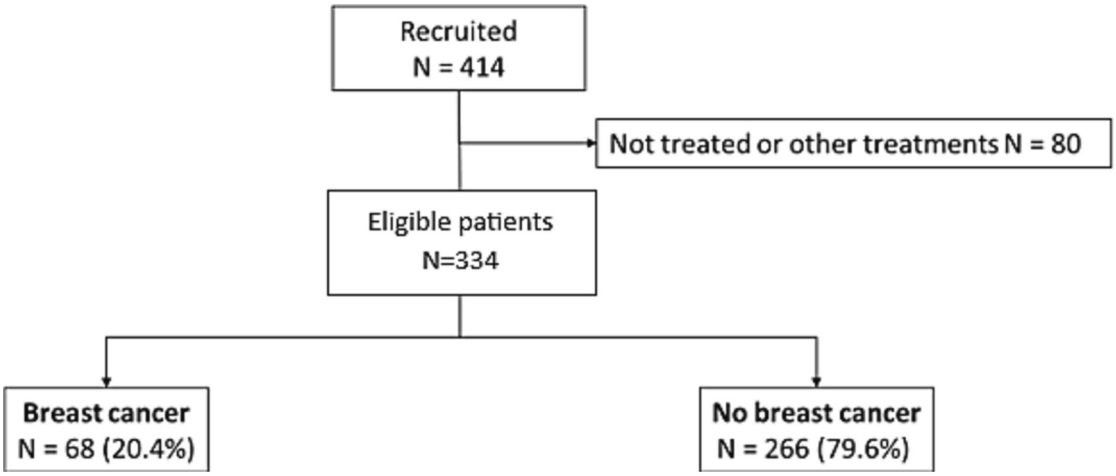

Fig. 1. Study flow-chart.

the loss of enjoyment of life and relationships. In the section of Table 3 relative to the validated questionnaires, we found that the highest DIVA scores (i.e., greater impact of vaginal symptoms) were documented in the domains of sexual functioning and self-concept/body image. Interestingly, the full FSFI score (a higher score is associated with lower severity of sexual dysfunction) suggested that 81.5 % of the overall population had a risk for sexual dysfunction (FSFI≤26), while sexual distress (FSDS-R ≥ 11) was found in 3 out of 4 participants (74.4 %). Finally, SF-12 scores suggest a reduction in the mental component score (mean value of 41.6 as compared to a normative value of 50).

3.2. Population stratified by BC history

Baseline patients' characteristics stratified by BC history are reported in Table 1. Women with BC were had a lower age at menopause. Furthermore, menopause was physiological in 90.4 % of women without BC as compared to 31.8 % among women with BC. As for previous BC therapy, almost all patients (98.5 %) had undergone surgery, 42.6 % had been treated with chemotherapy, 39.7 % with tamoxifen, 27.9 % with aromatase inhibitors, 50 % with radiotherapy, 8.8 % with other treatments, and 4.4 % of the sample was not treated. No major differences between the two groups emerged as for comorbidities, with the only exception of a significantly higher prevalence of treatment for osteoporosis in women with BC (23.5 % vs. 10.5 %; $p = 0.0047$). No major differences emerged relative to lifestyle habits (Table 1).

Table 2 reports information about VVA severity in the subgroups. According to physician evaluation, women with BC had more often severe VVA at study entry (41.2 % vs. 25.4 % in women without BC; $p = 0.008$). No significant differences between the two groups were documented as for VHI; in both groups about 80 % of women suffered from vaginal atrophy (VHI <15). On the other hand, women with BC had a significantly higher VuHI mean score ($p = 0.03$) and more frequently suffered from vulvar atrophy, although statistical significance was not reached (80.6 % vs. 70.3 % in women without BC; $p = 0.09$).

Before study entry, women with BC were less likely to be treated with LET and more likely to be treated with lubricants, moisturizers, and laser (Table 2). At study entry, women without BC were prevalently treated with LET (72.6 %), while women with BC were prevalently treated with ospemifene (83.8 %) (Table 3). Of note, 11 (16.2 %) women with BC were treated with local hormonal therapy despite the general contraindication of using this treatment. A focus on this latter subgroup showed that median (interquartile range) time from BC diagnosis was 7 (5–11) years and that local therapy type was prasterone in 54.6 % of cases and estrogen vaginal cream in 45.4 % of cases.

Table 3 shows the burden of VVA in life of women with or without a history of BC. As compared to women without BC, women with BC history were significantly more likely to report severe symptoms relative to dryness on the outside/external genitalia, bleeding during sexual intercourse and during sexual contact, burning or irritation, and recurrent urinary tract infections. In addition, the impact of VVA on lifestyle was significantly higher in women with BC history as regards going to the gym, riding a bike, and enjoying life and relationships. Also, the DIVA questionnaire indicated that women with a history of BC showed significantly higher scores (i.e. greater impact of vaginal symptoms) in the domains of emotional well-being, sexual functioning and self-concept/body image. As far as sexual function and distress were concerned, the total score of the FSFI suggested that 83.8 % of women with BC history vs. 88.5 % among those without BC had a risk for sexual dysfunction (FSFI total score ≤ 26; $p = 0.29$). Sexual distress (FSDS-R ≥ 11) was found in 85.3 % of women with BC history vs. 71.5 % among those without BC ($p = 0.02$). Finally, women with BC history reported a significantly lower SF-12 physical component score than women without BC ($p = 0.04$), while no difference emerged as for the mental component score, which was reduced in both groups.

4. Discussion

The PEONY study provides a comprehensive overview of treatment for moderate to severe VVA and its physical and psychological burden in a large sample of Italian post-menopausal women referring to gynecological centers. Based on physician judgment, the vast majority of women had vaginal and vulvar atrophy and over one fourth had severe VVA. Symptoms most often reported as severe by the patients were pain during sexual intercourse (one out of two women), and dryness inside (44.8 %) and outside the vagina (32.7 %). VVA has an impact on PROs. In particular, 9 out of 10 women had FSFI values indicative of sexual dysfunction and 3 out of 4 had FSDS-R values indicative of sexual distress. As for generic quality of life measures, women attending the gynecological clinic for VVA problems had only slightly reduced physical well-being compared to the normative values, while the reduction in psychological well-being was marked.

Baseline data show that VVA is still a neglected problem for many women. In fact, over 40 % of patients with moderate/severe VVA had never been treated for this condition, one in four had been treated with LET, and only a small minority was prescribed ospemifene. The present results are in line with the evidence that Italian gynecologists do not effectively manage VVA and in their clinical experience <50 % of patients continue therapy after 12 months, due to the discomfort in vaginal application, the cost of oral therapies and the fear of possible side-effects [29]. Interestingly enough, in the present study a specialized counselling on the most suitable treatment of VVA led to individualized choices, especially in women with BC history who received a high rate of

Table 1
Baseline patients' characteristics in the overall population and by breast cancer (BC) history.

	Overall	BC history	No BC history	p-Value
Socio-demo characteristics				
N group	334	68	266	
Age at recruitment (years)	57.5 ± 6.1	56.2 ± 6.9	57.8 ± 5.9	0.07
Age at diagnosis (years)	57.3 ± 6.2	56.0 ± 7.0	57.7 ± 6.0	0.06
Nationality (%)				
Italian	98.7	100	98.4	0.59
Other	1.3	0	1.6	
Education (%)				**0.049**
<High school	19.3	11.3	21.4	
≥High school	80.7	88.7	78.6	
Marital status (%)				0.08
Married	77.3	77.0	77.3	
Single	8.7	3.3	10.1	
Widow	1.7	0	2.1	
Relation	12.4	19.7	10.5	
Employment (%)				0.25
Employed	60.6	70.0	58.2	
Unemployed/housewife	21.5	16.7	22.8	
Retired	17.8	13.3	19.0	
Clinical characteristics				
Age at menopause (years)	49.4 ± 4.5	47.7 ± 5.0	49.8 ± 4.3	**0.0005**
Menopause type (%)				
Physiological	78.6	31.8	90.4	**<0.0001**
Surgical	8.6	18.2	6.1	
Treatment-related	12.8	50.0	3.4	
BMI (kg/m^2)	23.4 ± 3.6	23.5 ± 3.1	23.3 ± 3.7	0.67
At least 1 abortion (%)	25.4	28.8	24.5	0.48
Deliveries type (%)				
No	26.1	25.8	26.2	0.96
Spontaneous	32.4	33.9	32.0	
Cesarean	41.5	40.3	41.8	
Comorbidities (%):				
Hysterectomy	6.4	7.6	6.1	0.59
Prolapse	6.1	7.6	5.7	0.57
Urinary incontinence	23.9	28.4	22.8	0.34
Other chronic diseases	32.0	27.5	33.2	0.43
Chronic therapies (%)				
None	36.8	38.2	36.5	0.78
Urinary urgency treatment	0.3	0	0.4	1.00
Antihypertensive drugs	18.6	14.7	19.5	0.36
Lipid-lowering drugs	12.9	13.2	12.8	0.92
Glucose-lowering drugs	3.9	2.9	4.1	1.00
Osteoporosis treatment	13.2	23.5	10.5	**0.0047**
Other	35.0	27.9	36.8	0.17
Lifestyle				
Smoke (%)				
No	73.8	71.4	74.5	0.58
Ex	16.6	20.6	15.5	
Yes	9.6	7.9	10.0	
If yes, number of cigarettes/day	9.5 ± 5.4	7.4 ± 2.8	9.9 ± 5.8	0.35
Alcohol (%)				0.89
No	61.5	59.7	62.0	
Sometimes	33.1	35.5	32.5	
Regularly	5.4	4.8	5.6	
Coffee (%)				0.35
No	19.1	17.5	19.6	
≤3 cups a day	66.0	61.9	67.1	
>3 cups a day	14.9	20.6	13.3	
Physical exercise (%)				0.07
No	38.1	25.8	41.4	
1–2 times a week	41.1	46.8	39.7	
≥3 times a week	20.7	27.4	19.0	

Data are means and standard deviations or proportions. p-Values derived from unpaired *t*-test or the Mann-Whitney *U* test in case of continuous variables and the chi-square test or Fisher exact test for categorical variables, as appropriate. Statistically significant p-values ($p < 0.05$ are in bold).

Table 2
VVA severity and treatments in the overall population and by breast cancer (BC) history.

	Overall	BC history	No BC history	p-Value
N group	334	68	266	
VVA severity				
VVA duration (months)	1.2 ± 8.4	2.4 ± 10.8	1.2 ± 7.2	0.52
Severity degree at enrolment by physician judgment (%)				**0.008**
Mild	9.6	5.9	10.6	
Moderate	61.7	52.9	64.0	
Severe	28.6	41.2	25.4	
VHI				
Score	12.3 ± 2.8	12.0 ± 2.8	12.4 ± 2.7	0.19
VHI <15	80.5	82.4	80.0	0.66
VuHI				
Score	11.4 ± 4.6	12.5 ± 4.8	11.1 ± 4.5	**0.03**
VuHI >8	72.4	80.6	70.3	0.09
VVA treatments				
Treatments at T-1 (%)				
No treatment	44.0	35.3	46.2	0.10
Local estrogen therapy	25.0	8.8	29.3	**0.0005**
Ospemifene	6.3	7.6	6.0	0.78
Lubricants	12.6	20.6	10.5	0.03
Moisturizers	14.1	29.4	10.1	**<0.0001**
Laser	7.2	19.1	4.1	**0.0001**
Radiofrequency	1.8	4.4	1.1	0.10
Treatments at T0 (%)				**<0.0001**
Ospemifene	38.9	83.8	27.4	
LT	61.1	16.2	72.6	
Concomitant treatments at T0 (%)				
Lubricants	2.7	2.9	2.6	1.00
Moisturizers	2.1	1.5	2.3	1.00
Laser	0.6	0.0	0.8	1.00
Radiofrequency	0.3	0.0	0.4	1.00

VHI: the score can vary between 5 and 25, with a cut-off < 15 representing an index of atrophic vagina; VuHI: the score can vary between 0 and 24, with a cut-off > 8 representing an index of atrophic vulva.
T-1: last therapy before enrollment; T0: date of enrollment.
Data are means and standard deviations or proportions.
p-Values derived from the Mann-Whitney *U* test in case of continuous variables and the chi-square test or Fisher exact test for categorical variables, as appropriate.
Statistically significant p-values ($p < 0.05$ are in bold).

ospemifene prescription in keeping with its safety profile [30]. Of note, 16.2 % women with BC were treated with local hormonal therapy despite the general contraindication of using this treatment. However, guidelines suggest that low dose topical estrogens also in patients with a history of BC unresponsive to lubricants and moisturizers, provided that they are not in treatment with aromatase inhibitors [1,31].

Baseline data also show that severe VVA was more common in women with BC history (41.2 %) than in those without BC (25.4 %). Women with history of BC more frequently reported severe symptoms regarding dryness, pain and bleeding during sexual intercourse, burning or irritation on external genitalia. Of note, one in ten women with BC history reported severe recurring urinary tract infections (RUI) as compared to 2.3 % among women without BC. Compared to women without BC, those with history of BC deserve consideration since their quality of life is poorer in many different generic and disease-specific domains, despite being slightly younger than women without BC. BC history increases the impact of VVA on the performance of daily activities, on emotional well-being, sexual functioning, and self-concept of

Table 3
Quality of life of women living with VVA in the overall population and by breast cancer (BC) history.

	Overall	BC history	No BC history	p-Value
N group	334	68	266	
VVA symptoms				
Dryness (inside the vagina) (%)				0.06
Absent	4.0	0.0	5.0	
Mild	12.8	9.0	13.8	
Moderate	38.4	34.3	39.5	
Severe	44.8	56.7	41.8	
Dryness (on the outside/external genitalia) (%)				**0.04**
Absent	7.6	3.0	8.8	
Mild	17.4	16.4	17.7	
Moderate	42.2	34.3	44.2	
Severe	32.7	46.3	29.2	
Pain during sexual intercourse (inside the vagina) (%)				0.06
Absent	8.0	3.0	9.3	
Mild	12.0	6.0	13.5	
Moderate	29.1	28.4	29.3	
Severe	50.9	62.7	47.9	
Pain during sexual intercourse (on penetration) (%)				0.08
Absent	6.7	4.5	7.3	
Mild	12.6	4.5	14.7	
Moderate	25.5	25.4	25.5	
Severe	55.2	65.7	52.5	
Genital discomfort during physical activity (%)				0.38
Absent	54.0	47.8	55.6	
Mild	27.6	26.9	27.8	
Moderate	14.7	19.4	13.5	
Severe	3.7	6.0	3.1	
Bleeding during sexual intercourse (%)				**0.002**
Absent	61.2	44.8	65.5	
Mild	24.0	34.3	21.3	
Moderate	11.4	11.9	11.2	
Severe	3.4	9.0	1.9	
Bleeding during sexual contact (%)				**0.02**
Absent	69.5	62.7	71.3	
Mild	20.6	26.9	19.0	
Moderate	7.1	3.0	8.1	
Severe	2.8	7.5	1.6	
Burning or irritation (inside the vagina (%)				0.07
Absent	20.5	11.9	22.7	
Mild	26.3	20.9	27.7	
Moderate	31.8	40.3	29.6	
Severe	21.4	26.9	20.0	
Burning or irritation (on the outside/external genitalia) (%)				**0.045**
Absent	23.5	16.4	25.4	
Mild	28.1	28.4	28.1	
Moderate	30.9	26.9	31.9	
Severe	17.4	28.4	14.6	
Itching (inside of the vagina) (%)				0.65
Absent	50.5	50.7	50.4	
Mild	21.4	17.9	22.3	
Moderate	18.3	17.9	18.5	
Severe	9.8	13.4	8.8	
Itching (on the outside/external genitalia) (%)				0.07
Absent	43.1	40.3	43.8	
Mild	27.2	23.9	28.1	
Moderate	22.3	20.9	22.7	
Severe	7.3	14.9	5.4	
Vaginal discharge (%)				0.77
Absent	63.9	65.7	63.5	
Mild	25.1	25.4	25.0	
Moderate	8.9	6.0	9.6	
Severe	2.1	3.0	1.9	
Urinary incontinence (%)				0.78
Absent	64.5	62.7	65.0	
Mild	23.2	26.9	22.3	
Moderate	9.8	7.5	10.4	
Severe	2.4	3.0	2.3	
Urinary urgency (%)				0.40
Absent	49.5	53.7	48.5	
Mild	29.4	31.3	28.8	
Moderate	17.4	10.4	19.2	
Severe	3.7	4.5	3.5	
Urinary frequency (%)				0.99
Absent	41.6	41.8	41.5	
Mild	26.3	26.9	26.2	
Moderate	28.4	28.4	28.5	
Severe	3.7	3.0	3.8	
Difficult urination (%)				0.70
Absent	82.6	79.1	83.5	
Mild	12.5	16.4	11.5	
Moderate	3.4	3.0	3.5	
Severe	1.5	1.5	1.5	
Recurring urinary tract infections (%)				**0.003**
Absent	66.1	71.6	64.6	
Mild	19.6	13.4	21.2	
Moderate	10.4	4.5	11.9	
Severe	4.0	10.4	2.3	
Cystitis associated with sexual intercourse (%)				0.08
Absent	67.8	61.2	69.5	
Mild	12.9	9.0	13.9	
Moderate	12.6	17.9	11.2	
Severe	6.7	11.9	15.4	
Abdominal pain (%)				0.12
Absent	66.1	55.2	68.8	
Mild	21.1	31.3	18.5	
Moderate	9.5	10.4	9.2	
Severe	3.4	3.0	3.5	
Lifestyle impact of VVA: in a scale from 1 (=totally disagree) to 10 (=totally agree), how would you rate your overall agreement with the following statements? Please, check NA if the question is not applicable. Due to VVA….				
I can't go to the gym anymore	2.0 ± 2.1	2.6 ± 2.6	1.8 ± 1.8	**0.01**
I can't ride a bike	2.5 ± 2.5	3.2 ± 3.1	2.3 ± 2.3	**0.03**
It is uncomfortable to sit for too long	2.8 ± 2.6	3.2 ± 2.9	2.7 ± 2.5	0.15
I go late to bed so my husband is already sleeping	3.4 ± 3.2	3.9 ± 3.6	3.2 ± 3.1	0.26
I don't like taking day trips and having to use public restrooms	3.1 ± 2.8	3.1 ± 2.8	3.1 ± 2.8	0.86
I have constantly to change and wash my underwear	2.9 ± 2.8	2.8 ± 2.6	3.0 ± 2.8	0.94
I accept the lack of spontaneity in my relationship	3.9 ± 3.2	4.0 ± 3.2	3.9 ± 3.2	0.76
I accept the pain I experience in sexual intercourse	3.9 ± 3.2	4.1 ± 3.5	3.9 ± 3.1	0.68
I have lost the enjoyment of life and relationships	3.8 ± 3.2	4.5 ± 3.4	3.6 ± 3.2	**0.02**
Validated questionnaires				
DIVA				
Activities of daily living	0.7 ± 0.8	0.8 ± 0.7	0.7 ± 0.8	0.42
Emotional wellbeing	1.5 ± 1.1	1.7 ± 1.1	1.4 ± 1.1	0.047
Sexual functioning	2.1 ± 1.0	2.5 ± 1.0	2.0 ± 1.0	**0.0002**
Self-concept and body image	1.9 ± 1.2	2.4 ± 1.1	1.8 ± 1.2	**0.0003**
FSFI				
Score	18.6 ± 6.8	19.3 ± 6.4	18.5 ± 6.8	0.36
FSFI≤26	87.5	83.8	88.5	0.29

(*continued on next page*)

Table 3 (*continued*)

	Overall	BC history	No BC history	p-Value
FSDS-R				
Score	22.6 ± 14.7	28.5 ± 14.0	21.1 ± 14.6	**0.0002**
FSDS-R ≥ 11	74.4	85.3	71.5	**0.02**
SF-12				
PCS	48.0 ± 8.5	46.1 ± 8.2	48.5 ± 8.5	**0.04**
MCS	41.6 ± 10.3	42.6 ± 10.4	41.3 ± 10.3	0.33

Questionnaire interpretation: Lifestyle impact of VVA: the higher the score, the higher the level of agreement on each item. DIVA: range 0–4, the higher scores, the greater impact of vaginal symptoms. FSFI: range 2–36, the higher the score, the less severity of sexual dysfunction. Female Sexual Distress Scale – Revised (FSDS-R): range 0–52, the higher the score, the higher the level of sexual distress. Score ≥ 11 discriminates women with sexual distress. SF-12: normalized to 50 ± 10, the higher the score, the higher the level of mental or physical health.

Data are means and standard deviations or proportions.

p-Values derived from the Mann-Whitney *U* test in case of continuous variables and the chi-square test or Fisher exact test for categorical variables, as appropriate.

Statistically significant p-values ($p < 0.05$ are in bold).

body image as assessed with the DIVA questionnaire. The greater negative impact of VVA on the sexual life of women with BC history is further supported by the finding that 85.3 % had FSDS-R scores indicative of sexual distress. Women with BC history also showed a poorer physical well-being at SF-12. Overall, these results confirm the multifactorial impact of the disease on women's life with BC history [32]. Moreover, they also deserve a significant attention in light of the poor accuracy that has been shown in documenting VVA symptoms in BC survivors [33] and the paucity of information delivered by oncologists on the possible consequence of premature menopause induced by adjuvant treatments [34].

The EVES study had already demonstrated that the most commonly reported symptoms associated with VVA were vaginal dryness (87.6 %) and pain during sexual intercourse (66.8 %), with a significant impact on quality of life of postmenopausal women attending menopause and/or gynecology clinics [24]. Even the European REVIVE Study conducted on a surveyed sample of 3768 postmenopausal women aged 45–75 years found that the most common VVA symptom was vaginal dryness (70 %), and that VVA significantly influenced the ability to be intimate, to enjoy sexual intercourse, and to feel sexual spontaneity, with an overall reduction of sexual drive [10]. In the PEONY sample, the number of women with severe VVA measured by VHI and VuHI is quite high likely because it includes symptomatic BC women candidate to treatment. The evidence of a higher rate of RUIs in the Peony sample with a positive history of BC is in keeping with an estimate of 4.25 additional cases/100/yr of UTI in BC with VVA versus a non-VVA-matched population [35]. The relevance of lower urinary tract symptoms (LUTS), especially RUIs has been already documented in a younger clinical population of Italian women with VVA [36]. Indeed, the presence of LUTS was related to dyspareunia, and distress from LUTS was inversely related to sexuality [36]. Even in a large study involving over 18,000 patients a higher incidence of RUIs was found in women with VVA as compared to women without VVA [37].

The baseline PEONY data have several implications for research and clinical practice. First, our study has the aim to gain a deep insight into the current therapeutic strategies adopted for VVA treatment in Italy and its results can represent a basis for discussing strategies to improve effectiveness, appropriateness and acceptability of care [38]. In addition, given the evidence that VVA may worsen in the absence of appropriate treatment, leading to progressive sexual dysfunction and potentially severe uro-gynecological consequences in the aging population [39], PEONY data contribute to raise awareness on the active role of gynecologists in individualizing treatment taking into account women's preferences which are important determinants of adherence and satisfaction [40]. Indeed, a recent multicenter cross-sectional study conducted in 29 public and private hospitals in Spain confirmed a better quality of life [41] and a higher rate of satisfaction depending on the type of VVA treatment [42]. Finally, the evidence that BC women carry a significant burden of disease in comparison to postmenopausal women with no history of BC will contribute to implement treatment protocols to address symptoms specific to this special population of women with VVA [43].

We await for longitudinal PEONY data to assess changes in quality of life and satisfaction with different types of VVA treatments in Italian clinical practice.

4.1. Strengths and limitations

This study has strengths and limitations. Among the strengths, to the best of our knowledge, this is one of the largest real-world study available on VVA and its treatment. Other strengths are represented by the multicenter nature of the study and the use of many validated tools to collect data in routine care. Among the limitations, the study may be representative only of the women attending specialized centers in Italy. In fact, the low rate of overweight/obesity and the high rate of women with high level of school education suggest that women of low socioeconomic status are less likely to seek care for problems related to VVA.

4.2. Conclusions

In conclusion, moderate/severe VVA is a common, often neglected condition which impacts on daily activities, relationships, and quality of life at menopause. It is important to alleviate the burden associated with this condition in different populations of postmenopausal women with VVA, including those with a history of BC.

Contributors

Maria Cristina Meriggiola contributed to conception and design of the study, acquisition, analysis and interpretation of data, and drafting and revising the article for important intellectual content.

Paola Villa contributed to conception and design of the study, acquisition, analysis and interpretation of data, and drafting and revising the article for important intellectual content.

Silvia Maffei contributed to conception and design of the study, acquisition, analysis and interpretation of data, and drafting and revising the article for important intellectual content.

Angelamaria Becorpi contributed to conception and design of the study, acquisition, analysis and interpretation of data, and drafting and revising the article for important intellectual content.

Tiziana Di Paolantonio contributed to conception and design of the study, acquisition, analysis and interpretation of data, and drafting and revising the article for important intellectual content.

Antonio Nicolucci contributed to conception and design of the study, acquisition, analysis and interpretation of data, and drafting and revising the article for important intellectual content.

Stefano Salvatore contributed to conception and design of the study, acquisition, analysis and interpretation of data, and drafting and revising the article for important intellectual content.

Rossella E. Nappi contributed to conception and design of the study, acquisition, analysis and interpretation of data, and drafting and revising the article for important intellectual content.

All authors gave final approval of the submitted manuscript. Authors received editorial assistance (CORESEARCH, Pescara, Italy).

Funding

The study was funded by SHIONOGI S.r.l., Roma, Italy. The funding sources were not involved in the study design or the data collection, analysis and interpretation.

Ethical approval

The study protocol was approved by local ethics committees and all patients signed the informed consent. All procedures were conducted in compliance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available on request.

Declaration of competing interest

REN had past financial relationships (lecturer, member of advisory boards and/or consultant) with Boehringer Ingelheim, Ely Lilly, Endoceutics, Palatin Technologies, Pfizer Inc., Procter & Gamble Co, TEVA Women's Health Inc. and Zambon SpA. At present, she has on-going relationship with Abbott, Astellas, Bayer HealthCare AG, Besins Healthcare, Exeltis, Fidia, Gedeon Richter, HRA Pharma, Merck Sharpe & Dohme, Novo Nordisk, Organon & Co, Shionogi Limited, Theramex, and Viatris. TDP is an employee of SHIONOGI S.r.l. AN has financial relationships (support to research, lecturer, consultant) with AlfaSigma, Astra Zeneca, Eli Lilly, Novo Nordisk, Sanofi, Shionogi, Theras, SOBI. PV has financial relationship (presentations, speakers bureaus, manuscript writing or educational events) with PharmExtracta, Bromatech. Shionogi, Amgen. MCM had financial relationship (lecturer, consultant) with Bayer HealthCare AG, Exeltis, Gedeon Richter, Organon & Co, Sandoz, Shionogi Limited and Theramex. The other authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.maturitas.2024.107950.

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