

## ORIGINAL STUDY

# The European Vulvovaginal Epidemiological Survey (EVES): impact on sexual function of vulvovaginal atrophy of menopause

Martire Particco, MD,<sup>1</sup> Stora Djumaeva, MD,<sup>1</sup> Rossella E. Nappi, MD, PhD,<sup>1,2</sup>  
Nick Panay, BSc, FRCOG, MFSRH,<sup>3</sup> Santiago Palacios, MD, PhD,<sup>4</sup> on behalf of the EVES Study investigators

### Abstract

**Objective:** To estimate the impact of vulvovaginal atrophy (VVA) on sexual function in a clinical population of postmenopausal women.

**Methods:** Women 45 to 75 years old and more than 12 months after the last menstruation, who attended menopausal/gynecological centers in Italy and Spain, were included. Women with at least one VVA symptom completed the following questionnaires: Day-to-Day Impact of Vaginal Aging (DIVA), Female Sexual Function Index (FSFI), and Female Sexual Distress Scale revised (FSDS-R). A physical gynecological examination was performed to confirm the VVA diagnosis. Data were analyzed by chi-square and Student's *t* tests.

**Results:** In all, 2,160 evaluable women were included in the study. VVA was confirmed in 90% of the included participants. The negative impact on sexual function was significantly higher in women with than in women without confirmed VVA, as evaluated with the sexual function component (DIVA-C) of the DIVA questionnaire ( $P = 0.013$ ). Statistically significant differences ( $P < 0.0005$ ) were also detected in the scores of overall FSDS-R, the overall FSFI, and of all the FSFI subdomains (desire, arousal, lubrication, orgasm, satisfaction, and pain).

**Conclusion:** For postmenopausal women with at least one VVA symptom, the presence of physician-confirmed VVA is associated with significant impaired sexual function, as shown by unadjusted analyses. Given the impact on quality of life and the prevalence of VVA, further research to improve and reduce VVA is warranted.

**Key Words:** DIVA – FSDI – FSDS – Gynecological examination – Menopause – Sexual function – Vulvovaginal atrophy.

Vulvovaginal atrophy (VVA) of menopause (recently named more appropriately genitourinary syndrome of menopause [GSM]) develops as a direct consequence of the decline of plasmatic levels of estrogens, which results in anatomical and functional changes in the estrogen-receptor enriched mucosa and the bladder epithelium of the lower genital and urinary tracts. Collagen and mucopolysaccharides play a role in the maintenance of the thickness and moisture of the epithelium in premenopausal women.<sup>1</sup> Several changes are observed in the vagina at the onset of menopause as a consequence of the conversion to a

hypoestrogenic environment: the vaginal epithelium switches from glandular to squamous and stratified; the vaginal wall becomes thin and loses its elasticity; blood flow is reduced and changes in the vaginal flora lead to a pH >5.<sup>2</sup> All these changes lead to vaginal dryness, which is the most frequent symptom of VVA. Dryness is also one of the major contributors to the sexual dysfunction associated with VVA.<sup>3</sup> In addition, dryness, together with other symptoms of VVA such as dyspareunia, and decreased vaginal lubrication during intercourse or postcoital bleeding, are key factors impairing the quality of life of the affected women.<sup>4,5</sup>

Received September 16, 2019; revised and accepted November 13, 2019. From the <sup>1</sup>Shionogi Europe, London, UK; <sup>2</sup>Research Center for Reproductive Medicine, Gynecological Endocrinology and Menopause, IRCCS San Matteo Foundation, University of Pavia, Pavia, Italy; <sup>3</sup>Imperial College London, London, UK; and <sup>4</sup>Palacios Institute of Women's Health, Madrid, Spain.

Funding/support: The study was sponsored by Shionogi Ltd.

Financial disclosure/conflicts of interest: M.P. and S.D. are employees of Shionogi Europe. R.E.N. has financial relationships (as a lecturer, member of advisory boards and/or consultant) with Bayer-Schering Pharma, Endoceutics, Exceltis, Gedeon-Richter, HRA Pharma, Merck Sharp & Dohme, Novo Nordisk, Pfizer Inc., Shionogi Limited, and Teva Women's Health Inc/Theramex. N.P. has received honoraria for lecturing and acting in an advisory capacity for a number of pharma companies, including Abbott, Bayer, Besins, Kora, Lawley, Mithra, MSD, Mylan,

Novo Nordisk, Pfizer, SeCur, Shionogi, and Theramex. S.P. has financial relationships (as a lecturer, member of advisory boards and/or consultant) with Pfizer, Servier, Amgen, MSD, Preglem, Gynea, Sandoz, Procare Health, Bayer, Serelys, and Shionogi. He has also been a symposium speaker or advisory board member and has received research grants and/or consulting fees from Servier, Pfizer, GSK, Abbott, Ferrer, Bioiberica, Shionogi, Amgen, Novo Nordisk, Teva, Bayer Healthcare, Serelys, and Gedeon Richter.

Supplemental digital content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's Website ([www.menopause.org](http://www.menopause.org)).

Address correspondence to: Rossella E. Nappi, MD, PhD, Research Center for Reproductive Medicine, Section of Obstetrics and Gynecology IRCCS Policlinico San Matteo, Piazzale Golgi 2, 27100 Pavia, Italy. E-mail: [renappi@tin.it](mailto:renappi@tin.it)

Furthermore, symptoms of VVA are also associated with increased psychosocial distress.<sup>6-8</sup> Although these symptoms are troublesome, they are frequently accepted by menopausal women as the normal outcome of age and menopausal status, which discourages them from consulting their healthcare providers (HCP),<sup>9,10</sup> thus resulting in under-reporting.<sup>11</sup> In addition, the embarrassment of women when discussing sexual questions with physicians makes sexual function disorder a condition strongly associated with communication issues between patients and physicians.<sup>12</sup>

The prevalence of VVA confirmed by physical examination or pH measurement has been described to be between 69% and 98% in menopausal women.<sup>13,14</sup> As evidenced by several studies, the prevalence of vulvovaginal symptoms in menopausal women is approximately 50%,<sup>14,15</sup> leading to decreased sexual activity and reflecting on the troublesome consequences of this condition on women's quality of life.<sup>6,7</sup> Therefore, both the VVA prevalence and its substantial impact on women's sexual function and quality of life make VVA management a priority.

The European Vulvovaginal Epidemiology Survey (EVES) was designed to describe the prevalence of VVA confirmed by gynecological clinical assessment among all women attending menopause/gynecologic centres. Other secondary objectives were aimed at assessing the impact of VVA on quality of life and the association between signs and symptoms of VVA with sexual function. The results on overall incidence, symptoms, and quality of life have been published elsewhere. The present report focuses on the impact that VVA, as confirmed by objective gynecological examination, may play on sexual function of postmenopausal women. It should be highlighted that most surveys on these issues have been performed in an online-based environment. Therefore, the performance of a confirmatory gynecological examination, together with the face-to-face survey, may be of added value for this study.

## METHODS

### Design and participants

A cross-sectional multinational survey was performed in menopausal centers or gynecological clinics in Italy and Spain. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the participant centers. All participants provided written informed consent before study entry. The women included in the study were postmenopausal aged 45 to 75 years. For this study, postmenopausal status was defined as more than 12 months after the last menstrual period.

### Study procedures

Women attending menopausal/gynecological centers were asked to participate in the survey. Investigators performed an assessment of their menopause status and screened for symptoms related to VVA. Women who reported at least one VVA symptom also provided data on demographic information, and scored their symptoms, based on a list of 19 potentially VVA-related complaints, on a 4-score severity scale (absent, mild,

moderate, and severe). In addition, the participants completed two parts of the Day-to-Day Impact of Vaginal Aging (DIVA),<sup>16</sup> one on quality of life and the other on sexual function; the Female Sexual Function Index (FSFI)<sup>17</sup>; and the Female Sexual Distress Scale-revised 2005 (FSDS-R).<sup>18</sup> A gynecological clinical assessment was performed by the investigator to confirm the presence of VVA, consisting of a gynecological examination and additional tests carried out in accordance with routine clinical practice. The investigators evaluated the signs of VVA to calculate the Vaginal Health Index<sup>19</sup> and the Vulva Health Index.<sup>20</sup> The Vaginal Health Index Score is a tool that, by evaluating five parameters (vaginal elasticity, vaginal secretions, pH, epithelial mucous membrane, vaginal hydration) and by assigning a single score to each parameter, provides a final score defining the degree of atrophy in the genitourinary tract. Scores range from 5 to 25 with lower scores corresponding to greater urogenital atrophy. Vulva Health Index evaluates pain during intercourse (as classified by the women in severity intensities ranging from "none" to "moderate during intercourse with any discomfort intensity beyond intercourse"), labia, urethra, clitoris, introitus, and elasticity; scores from 0 to 24 with higher scores corresponding with greater vulvar atrophy. If the Vulva Health Index is over 8 or there is a score of 3 (severe) in any category, vulvar atrophy is suggested. The results of the questionnaires (DIVA, FSFI, FSDS-R) were analyzed versus the severity of VVA symptoms recorded in three categories (vaginal, vulvar, and urinary symptoms). For each of the symptoms in these three groups and for the nonclassified symptom "abdominal pain," women assigned an intensity, which was transformed into a points score (none = 0; mild = 1; moderate = 2; severe = 3). Both the distribution of severity within each symptom and the total sum of individual scores per category were analyzed. The three questionnaires (DIVA, FSFI, and FSDS-R) are designed with a Likert closed-answer structure. DIVA measures sexual function with nine questions on frequency, arousal, and satisfaction of sexual activity. In addition, DIVA measures quality of life with other different questions. The FSFI contains 19 questions on desire, arousal, lubrication, satisfaction, and uncomfortable symptoms during sexual activity. In turn, FSDS-R contains 13 questions measuring the concerns and distress related to sexual activity.

### Statistical analyses

With the intention to recruit a representative sample size from each of the countries involved in the survey (Italy and Spain), we planned to recruit approximately 1,000 women in each country. For continuous variables, descriptive statistics were performed with means, standard deviation (SD), and range for normally distributed variables, otherwise medians and interquartile range. Categorical variables were summarized with counts and percentages. Association between confirmed diagnosis of VVA, as per gynecological clinical assessment, and demographic characteristics was performed with chi-square test. Student's *t* test was used to compare quantitative variables. Positive or negative correlation

between quantitative variables was assessed with the Pearson's correlation coefficient for normally distributed data and the Spearman's correlation coefficient if the data were not normally distributed.

## RESULTS

In all, 2,412 postmenopausal women were included in the EVES survey, between May, 2015 and March, 2016, in 46 outpatient menopausal ( $n = 1,519$ ; 63%) or gynecological centers ( $n = 893$ ; 37%) in Italy and Spain. Among them, 2,403 were evaluable for symptoms screening and 2,160 were women with at least one symptom related to VVA. This last group of women moved on to the next step of the survey by filling in the questionnaire on symptoms, and also the FSFI, FSDS-R, and DIVA questionnaires, and underwent a gynecological clinical examination.

Mean age  $\pm$  SD of the women was  $59.0 \pm 6.8$  years, being menopausal for  $9.9 \pm 7.1$  years. Among 2,403 evaluable women, 2,074 (86.3%) experienced physiological menopause, 228 (9.5%) had a surgically induced menopause, and 101 (4.2%) a menopause induced by medications. Demographic characteristics of the women are summarized in Table 1. In the group of participants evaluable for the study ( $n = 2,160$ ), the prevalence of confirmed clinical evidence of VVA by objective assessment with gynecological examination was 90.5% ( $n = 1,954$ ). The most common symptom was dryness (87.6%), followed by pain during intercourse (66.8%) (Table, Supplemental Digital Content 1, <http://links.lww.com/MENO/A527>, which shows the prevalence of symptoms referred by the participants). Median Vaginal Health Index was 13, and overall vaginal atrophy, as defined by a Vaginal Health Index  $< 15$ , was observed in 70.5% of the women. Median Vulva Health Index was 9.0 and overall severe vulvar atrophy (Vulva Health Index  $> 8$  or a score of 3/“severe” in any category) was observed in 58.9% of women.

Results of the questionnaires DIVA, FSFI, and FSDS-R were compared between women with or without confirmed VVA (Table 2). The impact on sexual function was significantly higher in women with confirmed versus not confirmed VVA according to the sexual functioning component (DIVA-C) of the DIVA score (1.39 vs 1.21;  $P = 0.013$ ), the overall FSDS-R (10.9 vs 7.2;  $P < 0.0005$ ), the percentage of women with FSDS-R score  $\geq 11$  (38.3% vs 27.7%;  $P = 0.003$ ), the overall FSFI score (15.7 vs 19.8;  $P < 0.0005$ ), and all the individual FSFI components ( $P < 0.0005$ ) of desire, arousal, lubrication, orgasm, satisfaction, and pain.

Among the evaluable women, 1,415 (65.9%) were currently sexually active. There was a nonsignificant trend for a lower sexual activity assessed as a dichotomic (yes/no) category in the group of women with confirmed VVA as compared with the women without confirmed VVA (65.4% vs 70.7% respectively;  $P = 0.114$ ). Among those women who were deemed sexually active, there was a nonsignificant trend for a lower median number of intercourse by month in the group with confirmed VVA (3.8 vs 4.4 respectively;  $P = 0.086$ ). There was no association between percentage of women with severe vulvar

( $P = 0.099$ ) or urinary ( $P = 0.920$ ) symptoms and the percentage of sexually active women; in the group of women with vaginal symptoms, there was a significant trend for those who had severe vaginal symptoms to be more sexually active (67.9% vs 63.0%;  $P = 0.022$ ). However, there was an association between being sexually active and the severity of certain particular symptoms, especially those related with intercourse such as pain or bleeding (see Table and Fig., Supplemental Digital Content 2, <http://links.lww.com/MENO/A528> and Supplemental Digital Content 3, <http://links.lww.com/MENO/A529>, which illustrate the association of symptoms and treatments with sexual activity). Symptoms were more severe in the sexually nonactive population. In addition, as compared with the sexually nonactive group, the group of sexually active women had a higher number of previous treatments for VVA ( $P < 0.0005$ ) and more frequently used lubricants instead of moisturizers ( $P < 0.0005$ ).

Reported severity states of vaginal atrophy were related with DIVA-C, the sexual functioning component of the DIVA questionnaire; women with severe vaginal atrophy also scored lower in DIVA-C ( $P < 0.0005$ ). The same association was observed with FSFI total and with all its individual components ( $P < 0.0005$ , for all results) and FSDS-R ( $P < 0.0005$ ) (Table, Supplemental Digital Content 4, <http://links.lww.com/MENO/A530>, which shows the associations between sexual function scores and severity of vaginal atrophy).

Correlation between symptoms score, signs score, and results of questionnaires was also addressed (Table 3). The DIVA global score correlated moderately with vaginal symptoms severity score (Spearman's  $\rho = 0.484$ ), vulvar symptoms severity score ( $\rho = 0.427$ ), and with overall symptoms severity score ( $\rho = 0.504$ ). FSDS-R score was moderately correlated with vaginal symptoms ( $\rho = 0.454$ ) and with overall symptoms score (0.431), but only slightly with other symptoms or signs (Vaginal Health Index and Vulva Health Index). No moderate or strong correlations were found between either symptoms, or signs scores and FSFI scores. A moderate linear correlation between DIVA total and FSDS-R was observed ( $\rho = 0.532$ ). No further moderate or strong linear correlations were observed between results of questionnaires with each other (DIVA, FSFI, and FSDS-R).

## DISCUSSION

The results of the EVES study show that VVA confirmed by objective gynecologic examination is associated with impaired sexual function in European postmenopausal women from Italy and Spain who were visiting a gynecology or menopause clinic, and who had at least one VVA symptom. This observation has been made across all domains of the FSFI and FSDS-R questionnaires, and also for the sexual domain of the DIVA questionnaire. This result is consistent with previous observations that suggested a strong association between VVA and sexual dysfunction.<sup>3</sup> Of note, almost two thirds of the women in the EVES study were sexually active. This percentage compares favorably with the observation of a large survey—the Women's Health Initiative—of more than

TABLE 1. Baseline characteristics of the participants

	Screened (n=2,403) (%)	With $\geq 1$ VVA symptom and VVA assessment (N=2,160)		<i>P</i> <sup>a</sup>
		No-VVA confirmed (n=206) (%)	VVA confirmed (n=1954) (%)	
Age (y), mean $\pm$ SD [range]	59.0 $\pm$ 6.8 [45-76]	55.5 $\pm$ 6.2 [45-75]	59.3 $\pm$ 6.7 [45-76]	<0.0005
Age at last menstruation (y), mean $\pm$ SD [range]	49.1 $\pm$ 4.6 [10-65]	48.5 $\pm$ 5.3 [17-59]	49.1 $\pm$ 4.5 [10-65]	0.083
Time since menopause (y), mean $\pm$ SD [range]	9.9 $\pm$ 7.1 [1-48]	7.0 $\pm$ 6.6 [1-36]	10.2 $\pm$ 7.1 [1-48]	<0.0005
Type of menopause, n (%)				
Natural	2,074 (86.3)	172 (83.5)	1,687 (86.3)	0.086
Induced by medications	101 (4.2)	15 (7.3)	78 (4.0)	
Surgical	228 (9.5)	19 (9.2)	189 (9.7)	
Body mass index, mean $\pm$ SD [range]	25.6 $\pm$ 4.5 [15.3-49.3]	25.6 $\pm$ 4.8 [16.8-43.7]	25.7 $\pm$ 4.5 [15.3-49.3]	0.853
Relationship status, n (%)				
Married	1,549 (76.0)	137 (69.5)	1,409 (76.7)	0.003
Single	173 (8.5)	24 (12.2)	149 (8.1)	
Widowed	135 (6.7)	8 (4.1)	127 (6.9)	
In a relationship	180 (8.8)	28 (14.2)	152 (8.3)	
Ethnic group: white, n (%)	1,946 (94.3)	198 (96.6)	1,741 (94.1)	0.629
Treatments to reduce VVA symptoms, n (%)				
None	1,290 (57.5)	130 (63.1)	1,079 (55.2)	0.021
At least one treatment used	953 (42.5)	76 (36.9)	875 (44.8)	
Number of treatments used				
1	754 (33.6)	61 (29.6)	691 (35.4)	
2	181 (8.1)	11 (5.3)	170 (8.7)	
3	18 (0.8)	4 (1.9)	14 (0.7)	
Nonhormonal therapy applied vaginally, n (%)	755 (31.4)	55 (26.7)	698 (35.7)	0.010
Hormonal (estrogen-containing) vaginally, n (%)	274 (11.4)	13 (6.3)	261 (13.4)	0.004
Hormonal (estrogen-containing) systemic, n (%)	118 (4.9)	26 (12.6)	92 (4.7)	<0.0005
Effectiveness, n (%)				
No relief	47 (5.9)	4 (6.2)	43 (5.9)	0.001
Low relief	199 (25.1)	6 (9.2)	193 (26.5)	
Moderate relief	226 (28.5)	19 (29.2)	206 (28.5)	
Good relief	243 (30.6)	21 (32.3)	222 (30.5)	
High relief	79 (9.9)	15 (7.3)	64 (8.8)	
Treatment period, n (%)				
1 wk or less	41 (5.2)	1 (1.6)	39 (5.4)	0.202
1-4 wks	105 (13.4)	14 (22.2)	91 (12.7)	
1-3 mos	130 (16.6)	10 (15.9)	120 (16.7)	
3-6 mos	96 (12.3)	8 (12.7)	88 (12.2)	
Over 6 mos	411 (52.5)	30 (47.6)	381 (53.0)	
Overall satisfaction with the treatment, n (%)				
Very low satisfaction	47 (5.7)	4 (6.2)	43 (5.7)	0.001
Low satisfaction	167 (20.4)	4 (6.2)	163 (21.6)	
Moderate satisfaction	318 (38.8)	20 (30.8)	297 (39.4)	
High satisfaction	223 (27.2)	28 (43.1)	195 (25.9)	
Very high satisfaction	64 (7.8)	9 (13.8)	55 (7.3)	
Reason for not being satisfied, n (%)				
Not effective enough	190 (41.3)	11 (42.3)	179 (51.3)	0.509
Worried about side effects	56 (12.2)	6 (23.1)	50 (11.5)	
Too expensive	42 (9.1)	0 (0.0)	40 (9.2)	
Difficult or unable to apply vaginally	21 (4.6)	2 (7.7)	21 (4.8)	
Messiness of treatment	85 (18.5)	4 (15.4)	80 (18.5)	
Other	66 (14.3)	3 (11.5)	63 (14.5)	
Intercourse (n/mo), mean $\pm$ SD [range]	3.8 $\pm$ 3.1 [0-30]	4.4 $\pm$ 3.4 [0-16]	3.8 $\pm$ 3.1 [0-30]	0.086
Childbirth (yes), n (%)	1,783 (83.3)	177 (85.9)	1,601 (83.0)	0.291
Abortion/miscarriage, n (%)	587 (28.0)	61 (29.9)	526 (27.9)	0.550
Chronic diseases (yes), n (%) <sup>b</sup>	1,576 (72.7)	148 (71.8)	1,425 (72.9)	0.740
Hypertension	531 (22.1)	41 (19.9)	489 (25.0)	
Hypercholesterolemia	405 (16.9)	40 (19.4)	364 (18.6)	
Hypothyroidism	292 (12.2)	23 (11.2)	267 (13.7)	
Osteoporosis	275 (11.4)	24 (11.7)	251 (12.8)	
Anxiety	242 (10.1)	35 (17.0)	207 (10.6)	
Arthrosis	222 (9.2)	22 (10.7)	200 (10.2)	
Surgery for prolapse/urinary incontinence, n (%)	90 (4.2)	8 (3.9)	82 (4.3)	0.789
Breast disease (yes), n (%)	319 (15.0)	36 (17.5)	282 (14.7)	0.269
If yes, benign <sup>c</sup>	117 (36.7)	20 (55.6)	97 (34.4)	0.028
If yes, malignant <sup>c</sup>	176 (55.2)	15 (41.7)	160 (56.7)	
Hysterectomy, n (%)	347 (16.4)	23 (11.3)	323 (17.0)	0.039

Calculations based on available responses for each variable.

Information regarding treatments refers to those used to reduce VVA symptoms.

n/mo, number by month; SD, standard deviation; VVA, vulvovaginal atrophy; y, years.

<sup>a</sup>No-VVA versus VVA confirmed comparisons.

<sup>b</sup>Diseases with 10% or more are shown.

<sup>c</sup>Percentages calculated among the total of participants with breast disease.

**TABLE 2.** Comparison of sexual function between women with VVA confirmed and those with no-VVA confirmed

	With ≥1 VVA symptom and VVA assessment (n = 2,160)	No-VVA confirmed (n = 206)	VVA confirmed (n = 1,954)	P
Sexually active (yes), %	65.9	70.9	65.4	0.114
Intercourse (n/mo), mean ± SD	3.8 ± 3.2	4.4 ± 3.4	3.8 ± 3.1	0.086
Questionnaires				
DIVA—total, mean ± SD	0.92 ± 0.64	0.77 ± 0.61	0.94 ± 0.65	<0.0005
DIVA—sexual functioning, mean ± SD	1.37 ± 0.96	1.21 ± 0.94	1.39 ± 0.96	0.013
FSFI total, mean ± SD	16.1 ± 9.8	19.8 ± 10.8	15.7 ± 9.7	<0.0005
Desire	2.6 ± 1.2	3.0 ± 1.2	2.6 ± 1.1	<0.0005
Arousal	2.5 ± 1.8	3.0 ± 1.9	2.5 ± 1.7	<0.0005
Lubrication	2.6 ± 2.0	3.4 ± 2.2	2.5 ± 1.9	<0.0005
Orgasm	2.9 ± 2.1	3.5 ± 2.2	2.8 ± 2.1	<0.0005
Satisfaction	3.2 ± 1.9	3.6 ± 2.2	3.1 ± 1.9	<0.0005
Pain	2.7 ± 2.1	3.6 ± 2.2	2.6 ± 2.1	<0.0005
FSDS-R	10.5 ± 12.6	7.2 ± 10.5	10.9 ± 12.7	<0.0005
FSDS-R score ≥11, %	37.3	27.7	38.3	0.003

DIVA, Day-to-Day Impact of Vaginal Aging; FSFS-R, Female Sexual Distress Scale-revised 2005; FSFI, Female Sexual Function Index; n/mo, number by month; SD, standard deviation; VVA, vulvovaginal atrophy.

45,000 women aged 50 to 79 years, among which only half of the women were sexually active.<sup>21</sup> The population of the EVES survey is 5 years younger at both ends of the range, which may explain this apparent difference.

Although all the VVA-associated symptoms might impair sexual activity,<sup>22,23</sup> the symptoms more directly involved were dyspareunia and bleeding during intercourse, as reported by the participants. Dyspareunia, which was observed in just over two-thirds of the women in the EVES study, is of the utmost importance because it has been described as the most troublesome symptom.<sup>20</sup> Furthermore, it is a major cause of decreased frequency of intercourse,<sup>24</sup> impaired sexual function, and lower satisfaction in both women<sup>5</sup> and partners.<sup>25</sup> The largest study to date on the association of VVA and sexual dysfunction is the CLarifying vaginal atrophy's impact On SEx and Relationships (CLOSER) study, a survey of women with VVA and their male partners, which confirmed that the most frequent cause of avoidance of intimacy was painful sex.<sup>26</sup> The results of this study were consistent among countries,<sup>27-29</sup> including Northern and Southern Europe.<sup>4</sup> The CLOSER study focused mainly on the emotional impact of the impairment of sexual function due to VVA. Our results on the FSFS-R which measures distress associated with hypoactive sexual desire disorder<sup>18</sup> are in line with the CLOSER study results, thus confirming that VVA-related sexual dysfunction is associated with high emotional distress.

The EVES survey included an objective gynecological VVA confirmation by physical examination, which seems essential for correct interpretation of the findings. Indeed, although the symptoms related to intercourse such as pain or bleeding were associated with lower sexual activity, the EVES survey failed to show a strong linear correlation between symptom severity and sexual function, and also a clear association between severity of symptoms and sexual activity. In marked contrast, presence or absence of confirmed VVA resulted in highly significant differences in the scores of the questionnaires directed towards the assessment of sexual function (DIVA-C, FSFI, and FSFS-R). Furthermore, in practice, this fact means that requirement of an objective clinical confirmation as a cardinal feature for the diagnosis of VVA provides new insights that would otherwise have been missed. Another study that used the objective confirmation was the Italian Atrophy of the vaGina in womAn in postT-menopause in itAly (AGATA) survey, which included 913 women and reported dyspareunia in 77% of the women. However, the AGATA study did not perform specific evaluation of sexual function using questionnaires.<sup>30</sup> Regarding the management of sexual dysfunction associated with VVA, albeit not without controversy, some data show that local estrogens may facilitate restart of intercourse.<sup>26</sup> In turn, ospemifene—an oral selective estrogen receptor modulator (SERM)—has been shown to reduce the severity of

**TABLE 3.** Linear correlations between symptoms, signs, and sexual function (Spearman-rho values)

	Spearman correlations coefficients		
	FSFI	FSFS-R	Total DIVA
Symptoms with questionnaires			
Vaginal symptoms	-0.187	0.454	0.484
Vulva symptoms	-0.213	0.344	0.427
Urinary symptoms	-0.097	0.156	0.199
All symptoms	-0.226	0.431	0.504
Signs with questionnaires			
Vaginal Health Index	0.269	-0.110	-0.116
Vulva Health Index	-0.243	0.141	0.185

All correlations are statistically significant at level  $P < 0.01$  (bilateral).

DIVA, Day-to-Day Impact of Vaginal Aging; FSFS-R, Female Sexual Distress Scale-revised 2005; FSFI, Female Sexual Function Index.

dyspareunia as compared with placebo in women with VVA.<sup>31,32</sup> Ospemifene is approved in Europe for the treatment of moderate to severe VVA in postmenopausal women with other menopausal symptoms, and for whom local vaginal estrogens are not appropriate,<sup>33</sup> whereas in the United States, it is indicated for the treatment of symptoms of vulvar and vaginal atrophy due to menopause.

This study has some weaknesses. First, we used the FSFI questionnaire, which has not been validated in women with VVA, despite having previously been used to evaluate this condition.<sup>32</sup> Second, results may be flawed by methodology issues such as the intrinsic bias selection, characteristic of nonrandomized studies, and the lack of a control group. Third, the EVES study does not assess serum hormone levels and therefore fails to analyze the possible complex interactions between VVA, hormone levels, and sexual aspects such as arousal or desire.<sup>34</sup> Finally, adjusted analyses would be required to confirm the independent association of VVA with sexual function symptoms. On the contrary, two main strengths deserve to be mentioned. First, the face-to-face appointment instead of the online environment of most surveys of this issue provides additional quality and reliability to the survey. The second main strength of the EVES study is the performance of gynecological clinical assessment of VVA with an objective physical examination. Indeed, this point was marked as an a priori asset of the study, but ultimately it has resulted in the best discriminator factor for predicting FSDI and FSDS-R scores, as we have outlined above.

Future studies should approach the communication problems between women and HCP, and between sexual partners, to deal with both embarrassment and concerns regarding discussions of sexual function.<sup>26</sup> Clear and early communication of their sexual problems might allow women to benefit from therapeutic innovations such as local low-dose hormonal treatments<sup>35,36</sup> or SERMs.<sup>37</sup> The notion that sexual dysfunction associated with VVA is a treatable condition should be explained to women by their HCP in the setting of an improved educational policy. Given its impact on quality of life, VVA is certainly more than a physiologic condition, which, along with increased general life expectancy, will increase its prevalence. Thus, further investigations are needed to reduce VVA incidence and severity, a syndrome with a broad presence in the elderly population.

### CONCLUSIONS

Sexual dysfunction associated with VVA should be a priority for health policymakers because of its high prevalence. In this study, the objective gynecological examination confirmation has been the best tool to assess the severe impact of VVA on sexual function. Objective gynecological confirmation also allows the exclusion of other reasons for the observed VVA symptoms and initiation of an early therapeutic approach, despite the absence of obvious VVA signs. Postmenopausal women and their partners need to be empowered with proper educational policy to approach their troubles and worries about VVA-related sexual dysfunction without embarrassment,

particularly in view of the availability of new and improved treatments.

**Acknowledgments:** Manuscript writing and editorial support was provided by Emili González-Pérez, PhD of TFS, S.L., with financial support provided by Shionogi Ltd.

The complete list of EVES Study investigators is as follows: C. Argudo Prieto (Gijón, Spain), L. Baquedano Mainar (Zaragoza, Spain), A. M. Becorpi (Firenze, Italy), P. Benedetti Panici (Roma, Italy), C. Benedetto (Torino, Italy), N. Biglia (Torino, Italy), M. Busacca (Milano, Italy), A. Cagnacci (Modena, Italy), J. Calleja Abu-Amshah (Madrid, Spain), M. J. Cancelo Hidalgo (Guadalajara, Spain), C. Castelo Branco i Flores (Barcelona, Spain), A. Cianci (Catania, Italy), E. Cicinelli (Bari, Italy), P. Coronado Martin (Madrid, Spain), M. Correa Rancel (Santa Cruz de Tenerife, Spain), F. De Seta (Trieste, Italy), C. Di Carlo (Napoli, Italy), M. Fernández Abellán (Málaga, Spain), J. M. Fernández Moya (Madrid, Spain), M. Gambacciani (Pisa, Italy), P. García Alfaro (Barcelona, Spain), M. González Fernández (Barcelona, Spain), S. González Rodríguez (Madrid, Spain), M. Guida (Salerno, Italy), E. Iglesias Bravo (Sevilla, Spain), P. Llaneza Coto (Oviedo, Spain), S. Luisi (Siena, Italy), M. Manubens Grau (Barcelona, Spain), D. Marchesoni (Udine, Italy), P. Marín Sánchez (El Palmar, Spain), N. Mendoza Ladrón de Guevara (Granada, Spain), R. E. Nappi (Pavia, Italy), B. Otero García-Ramos (Baracaldo, Spain), A. M. Paoletti (Cagliari, Italy), S. Palacios (Madrid, Spain), A. Pellegrino (Lecco, Italy), J. C. Presa Lorite (Jaén, Spain), V. Remorgida (Genova, Italy), S. Salvatore (Milano, Italy), R. Sánchez Borrego (Barcelona, Spain), S. Sánchez Méndez (Sant Cugat del Vallés, Spain), R. Seracchioli (Bologna, Italy), M. Stomati (Brindisi, Italy), N. Surico (Novara, Italy), F. Vázquez Fernández (Lugo, Spain) and P. Villa (Roma, Italy).

### REFERENCES

- Castelo-Branco C, Cancelo MJ, Villero J, Nohales F, Juliá MD. Management of post-menopausal vaginal atrophy and atrophic vaginitis. *Maturitas* 2005;52 (Suppl 1):S46-52.
- Pandit L, Ouslander JG. Postmenopausal vaginal atrophy and atrophic vaginitis. *Am J Med Sci* 1997;314:228-231.
- Levine KB, Williams RE, Hartmann KE. Vulvovaginal atrophy is strongly associated with female sexual dysfunction among sexually active postmenopausal women. *Menopause* 2008;15 (4 Pt 1):661-666.
- Nappi RE, Mattsson L-Å, Lachowsky M, Maamari R, Giraldi A. The CLOSER survey: impact of postmenopausal vaginal discomfort on relationships between women and their partners in Northern and Southern Europe. *Maturitas* 2013;75:373-379.
- Kingsberg SA, Wysocki S, Magnus L, Krychman ML. Vulvar and vaginal atrophy in postmenopausal women: findings from the REVIVE (REal Women's Views of Treatment Options for Menopausal Vaginal ChangEs) survey. *J Sex Med* 2013;10:1790-1799.
- Nappi RE, Palacios S, Panay N, Particco M, Krychman ML. Vulvar and vaginal atrophy in four European countries: evidence from the European REVIVE Survey. *Climacteric* 2016;19:188.
- Nappi RE, Kokot-Kierepa M. Vaginal Health: Insights, Views & Attitudes (VIVA): results from an international survey. *Climacteric J Int Menopause Soc* 2012;15:36-44.
- Nappi RE, Cucinella L, Martella S, Rossi M, Tiranini L, Martini E. Female sexual dysfunction (FSD): Prevalence and impact on quality of life (QoL). *Maturitas* 2016;94:87-91.
- Nappi RE, Kokot-Kierepa M. Women's voices in the menopause: results from an international survey on vaginal atrophy. *Maturitas* 2010;67:233-238.
- Bachmann GA, Nevadunsky NS. Diagnosis and treatment of atrophic vaginitis. *Am Fam Physician* 2000;61:3090-3096.
- Gandhi J, Chen A, Dagur G, et al. Genitourinary syndrome of menopause: an overview of clinical manifestations, pathophysiology, etiology, evaluation, and management. *Am J Obstet Gynecol* 2016;215:704-711.
- Latif EZ, Diamond MP. Arriving at the diagnosis of female sexual dysfunction. *Fertil Steril* 2013;100:898-904.

13. Freedman MA. Vaginal pH, estrogen and genital atrophy. *Menopause Manag* 2008;9:13.
14. Nappi RE, Palacios S. Impact of vulvovaginal atrophy on sexual health and quality of life at postmenopause. *Climacteric J Int Menopause Soc* 2014;17:3-9.
15. Parish SJ, Nappi RE, Krychman ML, et al. Impact of vulvovaginal health on postmenopausal women: a review of surveys on symptoms of vulvovaginal atrophy. *Int J Womens Health* 2013;5:437-447.
16. Huang AJ, Gregorich SE, Kuppermann M, et al. Day-to-Day Impact of Vaginal Aging questionnaire: a multidimensional measure of the impact of vaginal symptoms on functioning and well-being in postmenopausal women. *Menopause* 2015;22:144-154.
17. Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. *J Sex Marital Ther* 2005;31:1-20.
18. Derogatis LR, Rosen R, Leiblum S, Burnett A, Heiman J. The Female Sexual Distress Scale (FSDS): initial validation of a standardized scale for assessment of sexually related personal distress in women. *J Sex Marital Ther* 2002;28:317-330.
19. Bachmann G. Urogenital ageing: an old problem newly recognized. *Maturitas* 1995;22 (Suppl):S1-5.
20. Palacios S, Cancelo MJ, Castelo Branco C, Llana P, Molero F, Borrego RS. Vulvar and vaginal atrophy as viewed by the Spanish REVIVE participants: symptoms, management and treatment perceptions. *Climacteric J Int Menopause Soc* 2017;20:55-61.
21. McCall-Hosenfeld JS, Jaramillo SA, Legault C, et al. Correlates of sexual satisfaction among sexually active postmenopausal women in the Women's Health Initiative-Observational Study. *J Gen Intern Med* 2008; 23:2000-2009.
22. Santoro N, Komi J. Prevalence and impact of vaginal symptoms among postmenopausal women. *J Sex Med* 2009;6:2133-2142.
23. Mac Bride MB, Rhodes DJ, Shuster LT. Vulvovaginal atrophy. *Mayo Clin Proc* 2010;85:87-94.
24. Thomas HM, Bryce CL, Ness RB, Hess R. Dyspareunia is associated with decreased frequency of intercourse in the menopausal transition. *Menopause* 2011;18:152-157.
25. Smith KB, Pukall CF. Sexual function, relationship adjustment, and the relational impact of pain in male partners of women with provoked vulvar pain. *J Sex Med* 2014;11:1283-1293.
26. Nappi RE, Kingsberg S, Maamari R, Simon J. The CLOSER (CLarifying Vaginal Atrophy's Impact On SEx and Relationships) survey: implications of vaginal discomfort in postmenopausal women and in male partners. *J Sex Med* 2013;10:2232-2241.
27. Simon JA, Nappi RE, Kingsberg SA, Maamari R, Brown V. Clarifying Vaginal Atrophy's Impact on Sex and Relationships (CLOSER) survey: emotional and physical impact of vaginal discomfort on North American postmenopausal women and their partners. *Menopause* 2014; 21:137-142.
28. Domoney C, Currie H, Panay N, Maamari R, Nappi RE. The CLOSER survey: impact of postmenopausal vaginal discomfort on women and male partners in the UK. *Menopause Int* 2013;19:69-76.
29. Guidozzi F, Thomas C, Smith T, Nappi RE. CLarifying vaginal atrophy's impact On SEx and Relationships (CLOSER) survey in South Africa. *Climacteric J Int Menopause Soc* 2017;20:49-54.
30. Palma F, Della Vecchia E, Cagnacci A; as the Writing Group of the AGATA study. Medical and patient attitude towards vaginal atrophy: the AGATA study. *Climacteric J Int Menopause Soc* 2016; 19:553-557.
31. Portman DJ, Bachmann GA, Simon JA; Ospemifene Study Group. Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy. *Menopause* 2013;20:623-630.
32. Constantine G, Graham S, Portman DJ, Rosen RC, Kingsberg SA. Female sexual function improved with ospemifene in postmenopausal women with vulvar and vaginal atrophy: results of a randomized, placebo-controlled trial. *Climacteric J Int Menopause Soc* 2015;18: 226-232.
33. Senshio; INN-ospemifene - WC500182775.pdf [Internet]. [cited 2017 Mar 4]. Available at: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/002780/WC500182775.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002780/WC500182775.pdf). Accessed March 4, 2017.
34. Goldstein SR, Bachmann GA, Koninckx PR, et al. Ospemifene 12-month safety and efficacy in postmenopausal women with vulvar and vaginal atrophy. *Climacteric J Int Menopause Soc* 2014;17:173-182.
35. Labrie F, Archer DF, Koltun W, et al. Efficacy of intravaginal dehydroepiandrosterone (DHEA) on moderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy, and of the genitourinary syndrome of menopause. *Menopause* 2016;23: 243-256.
36. Caruso S, Cianci S, Amore FF, et al. Quality of life and sexual function of naturally postmenopausal women on an ultralow-concentration estriol vaginal gel. *Menopause* 2016;23:47-54.
37. Wurz GT, Kao C-J, DeGregorio MW. Safety and efficacy of ospemifene for the treatment of dyspareunia associated with vulvar and vaginal atrophy due to menopause. *Clin Interv Aging* 2014;9: 1939-1950.