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Vaginal estriol–lactobacilli combination and quality of life in endocrine-treated breast cancer

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Key words: BREAST CANCER, AROMATASE INHIBITORS, VAGINAL ATROPHY, SEXUALITY, QUALITY OF LIFE, VAGINAL ESTRIOL, LACTOBACILLI

ABSTRACT

Objective We investigated the effect of a combination of vaginal ultra-low-dose estriol with lactobacilli on the sexual functioning domain of quality of life during the treatment of breast cancer survivors on an aromatase inhibitor with vaginal atrophy.

Subjects and methods This was an open-label, bicentric, exploratory, clinical study in 16 postmenopausal breast cancer survivors on aromatase inhibitors suffering from vaginal atrophy-induced sexual disorders. Atrophy symptoms were assessed by scoring with an 11-point estimation scale (0 = not at all, 10 = worst imaginable feeling). Sexuality parameters of quality of life and medication adherence were recorded in a patient's diary and in the Female Somatic Sexual Experience Instrument (FSSEI) questionnaire. Patients underwent an initial treatment for 4 weeks (one vaginal tablet of Gynoflor® containing 0.03 mg estriol daily), followed by maintenance therapy (three vaginal Gynoflor® tablets weekly) for 8 weeks.

Results Vaginal dryness continuously improved from a median score of 8 at entry to a score of 4 at the end of initial therapy, and a median score of 2 at the end of maintenance therapy. Normal sexual activity before breast cancer diagnosis was reported by 14 women (88%). At study entry, only three women (19%) were sexually active. At the end of the Gynoflor® regimen, ten women (63%) reported sexual activity, of which seven (44%) reported sexual intercourse. The FSSEI demonstrated a non-significant trend of improvement of parameters related to sexuality.

Conclusions Local vaginal therapy with Gynoflor® in breast cancer survivors on aromatase inhibitors reporting atrophic vaginitis could be considered as a useful treatment for the quality of sexual life.

INTRODUCTION

The use of an aromatase inhibitor (AI) in hormone receptor-positive breast cancer patients often induces or enhances symptoms of vaginal atrophy[1]. This side-effect dramatically impacts quality of life, thereby hampering adherence and, as a consequence, affecting long-term survival rates[2]. Furthermore, atrophic vulvovaginitis interferes with other aspects of life, such as relationships, rehabilitation, and enjoyment of the remaining life span of these women[3].

Quality of life is a multidimensional construct that encompasses various areas of functioning. Four primary domains of quality of life have been suggested: mental, physical, social, and sexual[4]. Sexual quality of life generally refers to body image distress, changes in sexual desire, and perceived sexual functioning. From a medical viewpoint, sexuality encompasses more than genital functioning[5]. Women surviving breast cancer and treated with AIs may feel that their altered sexuality is not a medically legitimate complaint, and their treating physicians often emphasize disease-free survival more than

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such side-effects, which are often seen as insignificant and minor. However, sexual dysfunction is well known severely to interfere with quality of life and with the strong need for intimacy during cancer diagnosis and treatment.

Various models have been used to describe the female sexual response[6]. In 1966, Masters and Johnson proposed a model consisting of four successive phases: excitement, plateau, orgasmic, and resolution phases. In 1979, Kaplan proposed the three-phase model, consisting of desire, arousal, and orgasm, with desire being the factor inciting the overall response cycle. Recently, it has been suggested that sexual function should be considered as a circuit, with four main domains: libido, arousal, orgasm, and satisfaction[7,8]. Each aspect may overlap and negatively or positively feedback on the next[6]. Anyhow, normal sexuality includes adequate sexual desire, arousal with orgasm which leads to relaxation and induces a feeling of sexual pleasure, fulfilment, and satisfaction.

The best treatment for vaginal atrophy is local estrogen therapy[9,10]; however, evidence to support the use of conventional local estrogen therapy among breast cancer patients is conflicting[11]. Interestingly, some scientific data[12] suggest that estrogen therapy (including application of local vaginal estrogen) also improves local genital sensitivity and sexual response, thereby potentially improving a woman's sexuality, although some authors disagree with this[13].

The present assessment of sexual life improvement is a part of a broader exploratory, pharmacokinetic, clinical study[14] ($n = 16$) wherein we investigated the pharmacokinetics, safety, and efficacy of a ultra-low-dose vaginal estriol–lactobacilli combination therapy in breast cancer survivors on an AI suffering from vaginal atrophy. This product, Gynoflor®, contains 10^8 cfu viable lyophilized *Lactobacillus acidophilus* KS400 bacteria and 0.03 mg estriol (E3). The latter is not only given at ultra-low dose (0.03 mg), but is also a much less potent estrogen than estradiol (E2). Its dose is 16–32 times lower than used in conventional E3 vaginal preparations (0.5–1 mg). All women during the mentioned study applied a daily vaginal tablet for 4 weeks followed by a maintenance therapy of three tablets weekly for 8 weeks. Primary outcomes were serum concentrations and pharmacokinetics of E3, E2 and estrone (E1) using highly sensitive gas chromatography–mass spectrometry (GC/MS). Compared with baseline, serum E1 and E2 did not increase in any of the women at any time following vaginal application. Serum E3 transiently increased after the first application in 15 of 16 women, with a maximum 2–3 h post-insertion of 168 pg/ml; after 4 weeks, serum E3 was slightly increased in eight women with a maximum of 44 pg/ml, i.e. application of the low-dose 0.03 mg E3 and *Lactobacillus acidophilus* vaginal tablets in postmenopausal breast cancer patients during AI treatment suffering from vaginal atrophy leads only to small and transient increases in serum E3, but not E1 or E2.

Gynoflor® has been proven to be safe and efficacious in the restoration of disturbed vaginal flora[15,16] and in treatment of postmenopausal atrophic vaginitis[17–19]. The current clinical study demonstrated that an initial daily dose of a vaginal tablet for 4 weeks followed by one tablet every second day as maintenance therapy led only to small and transient increases in serum E3, but not E1 or E2 in women with breast cancer on AIs with severe atrophy[14]. Therefore, ultra-low-dose 0.03 mg E3 and *Lactobacillus acidophilus* vaginal tablets can be considered safe and efficacious for treatment of atrophic vaginitis in breast cancer patients taking AIs.

This article describes the study results with regard to the sexual domain of quality of life during treatment of breast cancer survivors on AIs suffering from symptomatic vaginal atrophy and dyspareunia with the ultra-low-dose estriol–lactobacilli combination (Gynoflor®).

METHODS

From April 2011 to July 2012, 16 postmenopausal breast cancer survivors on AIs suffering from sexual dysfunction related to vaginal atrophy were included in an open-label, clinical trial conducted at two centers in Belgium and in Germany. The study was approved by both Ethical Committees and the national authorities as appropriate (EudraCT No: 2010–022007-22) and all patients signed informed consent before any study action was taken, according to GCP guidelines and the Declaration of Helsinki.

This small ($n = 16$) open study with subjective evaluation of both signs and symptoms of vaginal atrophy assessed also sexual quality of life of during the pharmacokinetic clinical study as reported elswhere[14]. For the pharmacokinetic study, 16 women where statistically sufficient to detect the systemic effects of locally applied E3. Due to the fact that most of the breast cancer patients under endocrine therapy suffer from significant side-effects with a major impact on daily life, the study protocol also included an extended work-up concerning sexual quality of life issues. Of course, for this question, the number of patients was clearly insufficient to demonstrate clear statistical changes but, since this topic is of high clinical relevance, the generated sexual quality of life data trends are published here as a separate publication.

Included women were postmenopausal as defined as either aged 52 years or older or ≥ 46 years after bilateral oophorectomy with cessation of menses for at least 12 months. Furthermore, in women with intact ovaries following hysterectomy, follicle stimulating hormone levels had to be above 30 IU/l. All women had started AIs for adjuvant treatment of breast cancer at least 6 months ago. Additional criteria were presence of clinical symptoms of vaginal atrophy, and a Karnofsky score $\geq 80\%$. Women had the right to withdraw from the study at any time.

Main exclusion criteria were use of any other sex hormones or use of any other vaginal medication 6 months before or during the study, use of steroidal AIs, any severe genital diseases or conditions. Women with a body mass index (BMI) lower than 18.5 kg/m^2 or higher than 30 kg/m^2 were also excluded.

Gynoflor® vaginal tablets (100 million viable *Lactobacillus acidophilus* KS400 and 0.03 mg E3) were supplied by Medinova AG, Switzerland. Recruited women underwent an

initial treatment for 4 weeks by inserting one tablet deeply into the vagina while in the recumbent position before going to sleep, followed by maintenance therapy (three vaginal tablets weekly) for 8 weeks.

Clinical examinations were performed at screening (S = week [– 1]), at entry (E = Day 0) and at days 14 (C1 = week 2), 28 (C2 = week 4), 56 (C3 = week 8) and 84 (C4 = week 12) to assess hormone levels, efficacy, and safety (Figure 1)[14].

Clinical vaginal atrophy symptoms were assessed by a visual analog scale with an 11-point estimation scale (0 = not at all, 10 = worst imaginable feeling). Additionally, symptoms, sexuality parameters of quality of life, and medication adherence were recorded in a patient's diary and in the Female Somatic Sexual Experience Instrument (FSSEI), version 'breast cancer', sexual questionnaire (at E and C4). The FSSEI is a validated sexual questionnaire used by the University Hospitals Leuven, Belgium[20]; it consists of 30 questions (qualitative and quantitative types, in the native patient's language) covering the main topics of women's sexual domain of quality of life: sexual history, desire, arousal/lubrication, orgasm and sexual satisfaction (Table 1).

At each control visit, the global efficacy and tolerability were assessed by both investigator and patient. Treatment adherence was assessed by asking women about their medication, checking the medication, and by reviewing the diaries.

The individual subject values were tabulated with descriptive statistics. Values between visits were compared using the Wilcoxon signed rank sum test, the McNemar test or the sign test. All continuous parameters were summarized using standard summary statistics as appropriate.

RESULTS

From 19 screened women, 16 were included in this study, eight from each center. One protocol violation was noted: a woman, who was treated with the steroidal AI exemestane before she switched to a non-steroidal AI, was recruited as the investigator was not aware of that.

All 16 patients were Caucasian, with a mean age of 57.0 (range 52.0–63.0) years and a BMI of 23.5 ± 3.0 kg/m^2. The diagnosis of breast cancer had been a median of 2.6 years ago with one subject diagnosed with the disease 28.2 years ago; the median duration of AI therapy was 2.1 years with one subject having it for 7.7 years. The daily AI dose was either 1 mg letrozole ($n = 11$) or 2.5 mg anastrozole ($n = 5$). The mean Karnofsky score was $98.1 \pm 5.4\%$. The most frequently used concomitant medications were taken for gastrointestinal conditions (56%) and for improving the function of the musculoskeletal system, such as antiphlogistics (44%).

Treatment adherence was very good during both initial (range 92.9–100.0%) and maintenance therapy (range 95.8–100.0%).

During treatment, the subjective improvement of all clinical signs and symptoms of vaginal atrophy were statistically not significant due to the small number of patients. Vaginal dryness improved continuously from a median score of 8 at entry to a score of 4 at the end of initial therapy, and a score of 2 at the end of maintenance therapy. Dryness and soreness improved from entry to control visits ($p < 0.001$), while statistical evaluation of the improvement in dyspareunia and other symptoms was hampered by low subject numbers (Table 2).

In total, 16 breast cancer patients completed the FSSEI (sexual questionnaire) and were included in the evaluation and analysis. In addition to a clinical examination at baseline, patients were asked whether they were sexually active before and during breast cancer diagnosis as a question in the FSSEI. Before breast cancer diagnosis, 14 women (88%) reported having sexual activity. At entry, only three women (19%) were sexually active, indicating the severity of the side-effects of AIs and the impact of the breast cancer diagnosis. At visit C4, ten women (63%) reported sexual activity (FSSEI analysis), of whom seven (43%) reported normal, regular penetrative vaginal sexual intercourse. A trend to correlation between improvement of vaginal atrophy symptoms and improvement of sexual functioning could be considered (Figure 2).

The FSSEI analysis (Table 3, Figure 3) demonstrated a trend for improvement of all main domains of sexual quality of life (desire, arousal, orgasm, and satisfaction), being statistically significant for 'body image' ($p = 0.0009$) and 'sexual desire' ($p = 0.0042$), but not for the others (due to the small number of subjects).

Symptom dynamics based on patient diary data showed a median time of 11 days (range 4–24 days) until improvement of vaginal dryness, and 27 days (range 4–89 days) until complete disappearance of this symptom. So the 28-day initial therapy was, on average, sufficient to treat the symptomatic vaginal atrophy in the investigated subjects. It should be noted that increased discharge was observed immediately after initiation of estriol–lactobacilli combination therapy. However, it was unclear whether this indicated some remnants of the tablets, enhanced lubrication (physiological discharge), or pathological discharge.

Figure 1 Study design. Clinical examinations were performed at screening (S = week – 1)), at entry (E = Day 0) and at days 14 (C1 = week 2), 28 (C2 = week 4), 56 (C3 = week 8) and 84 (C4 = week 12) to assess hormone levels, efficacy, and safety. Signs and symptoms were reported at every visit. The patient's questionnaire was fulfilled by patient every week. Female Somatic Sexual Experience Instrument (FSSEI) was used to describe the patient's status at E and C4

Table 1 Female Somatic Sexual Experience Instrument (FSSEI), version breast cancer

Question 1a	How satisfied were you with your body image during the last 4 weeks? (0 = Completely dissatisfied; 10 = Completely satisfied)
Question 1b	How much stress did you experience during the last 4 weeks? (0 = Absolutely no stress; 10 = Very much stress)
Question 1c	How strong was your desire for physical contact during the last 4 weeks? (0 = Absolutely no desire; 10 = Very strong desire)
Question 1d	How strong was your sexual desire during the last 4 weeks? (0 = Absolutely no desire; 10 = Very strong sexual desire)
Question 2	Are there currently any other medical issues besides the breast cancer diagnosis?
Question 3	Are you taking any medications on a regular basis?
Question 4	Are you regularly using hygienic products, such as sanitary napkins or panty liners?
Question 5	Is it possible for you to insert a tampon into the vagina?
Question 6	Did you ever have a traumatic sexual experience?
Question 7	Were you sexually active before the diagnosis of breast cancer?
Question 8	How satisfied were you with your sex life before the breast cancer diagnosis? (0 = Completely dissatisfied; 10 = Very satisfied)
Question 9	Was intercourse painful before the breast cancer diagnosis?
Question 10	Before the diagnosis of breast cancer, did you use a lubricant to avoid pain during intercourse?
Question 11	Was your last menstrual period (menopause) already before the breast cancer diagnosis?
Question 12	Are you currently in the menopause, i.e. after the last menstrual period?
Question 13	Were you sexually active during the last 4 weeks?
Question 13a	How did your sexual life and your satisfaction with your sex life change when compared to the time before the diagnosis of breast cancer?
Question 14	How satisfied were you, in general, with your sex life during the last 4 weeks? (0 = Completely dissatisfied; 10 = Very satisfied)
Question 15	Is it possible for you to get an orgasm?
Question 15a	To what extent is this a problem for you? (0 = No problem; 10 = Very large problem)
Question 15b	How easy was it for you to get an orgasm during the last 4 weeks? (0 = Very difficult; 10 = Very easy)
Question 15c	During the last 4 weeks, how satisfied were you with the time needed to reach an orgasm? (0 = Completely dissatisfied; 10 = Very satisfied)
Question 16	Did you get vaginally wet during sexual activities in the last 4 weeks?
Question 16a	How fast did you get vaginally wet during sexual activities on average in the last 4 weeks? (0 = Very slowly; 10 = Very fast)
Question 16b	How often did you stay vaginally wet during sexual activities in the last 4 weeks? (0 = Never; 10 = Always)
Question 17	During the last 4 weeks, did you use a lubricant during sexual activity?
Question 18	Does your partner have sexual problems?
Question 19	How often did you have intercourse during the last 4 weeks?
Question 19a	Personal assessment of intercourse frequency (0 = Too little; 10 = Too much)
Question 20	How fast was intercourse for you during the last 4 weeks? (0 = Very slow; 10 = Very fast)
Question 21	Intercourse was too painful for me during the last 4 weeks
Question 21a	I have pain in the height of the vagina
Question 21b	Reason for pain
Question 22	Was the initiation of intercourse painful during the last 4 weeks? Type of pain at intercourse initiation
Question 22a	How painful was the initiation of sexual intercourse? (0 = Completely painless; 10 = Very painful)
Question 22b	How often did you have pain upon initiation of sexual intercourse? (0 = Never; 10 = Always)
Question 23	How did the pain develop during intercourse in the last 4 weeks? Type of pain
Question 24	Did you experience pain after intercourse during the last 4 weeks? Type of pain after intercourse
Question 24a	How much pain did you have after sexual intercourse? (0 = Completely painless; 10 = Very painful)
Question 24b	How often did you have pain after sexual intercourse? (0 = Never; 10 = Always)
Question 24c	Please indicate how long you were in pain after intercourse?
Question 25	Did you use a cream or ointment in the last 4 weeks to alleviate the pain during sexual intercourse?
Question 26	Did you perceive the pain during intercourse as a problem during the last 4 weeks? (0 = No problem; 10 = Very large problem)
Question 27	Would you start a therapy, if you knew that you had sexual problems?
Question 28	Have you already been treated for sexual problems?
Question 28a	Type of treatment
Question 29	When do you think sexual problems after breast cancer treatment must be given attention?
Question 30	Can we contact you to capture your future course of the disease?

Table 2 Signs and symptoms

	E		*C1*		*C2*		*C3*		*C4*	
	n	*Median (range)*	*n*	*Median (range)*	*n*	*Median (range)*	*n*	*Median (range)*	*n*	*Median (range)*
Signs										
Paleness of vaginal walls										
yes	12		4		4		4		2	
no	4		12		12		12		14	
p									0.2188	
Redness of vaginal walls										
yes	4		3		6		5		6	
no	12		13		10		11		10	
p									0.6875	
Vaginal ulceration(s)										
yes	1		0		0		1		0	
no	15		16		16		15		16	
p									na	
Decreased vaginal rugae										
yes	8		4		4		4		3	
no	8		12		12		12		13	
p									0.2266	
Symptoms										
Vaginal dryness	16	8.0 (3.0–10.0)	16	5.0 (0.0–8.0) *p = 0.0024*	16	4.0 (0.0–8.0) *p = 0.0029*	16	3.0 (0.0–9.0)	16	2.0 (0.0–9.0) *p = 0.0005*
Vaginal soreness	16	7.5 (0.0–10.0)	16	2.0 (0.0–6.0) *p = 0.0011*	16	1 (0.0–7.0) *p = 0.0001*	16	1 (0.0–7.0)	16	0.0 (0.0–10.0) *p = 0.0016*
Vaginal discharge	16	0.0 (0.0–6.0)	16	4.5 (0.0–10.0) *p = 0.0003*	16	3.0 (0.0–9.0) *p = 0.0017*	16	2.5 (0.0–8.0)	16	2.0 (0.0–7.0) *p = 0.0115*
Dyspareunia**	3	8.0 (8.0–9.0)	7	7.0 (0.0–10.0) *p = 0.5000*	7	4.0 (0.0–10.0) *p = 1.0000*	7	5.0 (0.0–8.0)	7	2.0 (0.0–9.0) *p = 0.5000*

*, *p* values = E – C1, or C2, or C4; **, only seven patients reporting actual sexual intercourse have been evaluated
na, not available

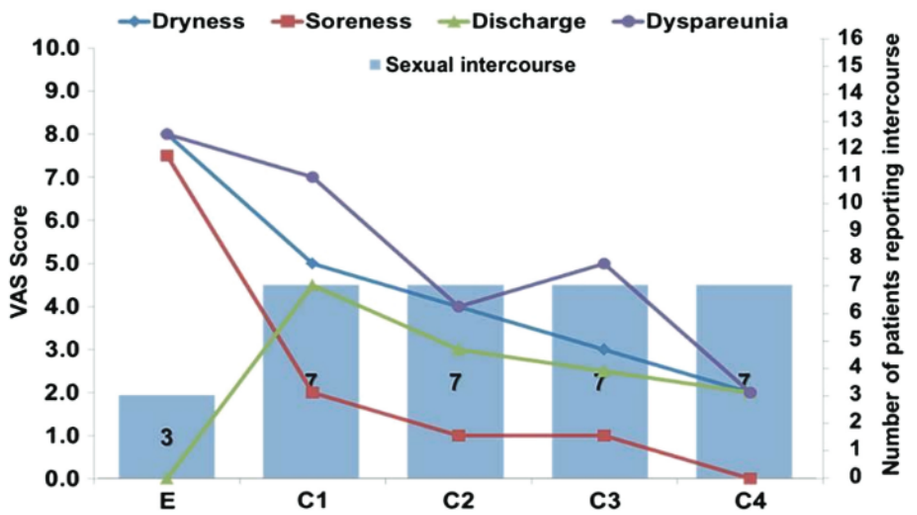

Figure 2 Comparison of dynamic of symptoms and sexual intercourse at entry (E = Day 0) and at days 14 (C1 = week 2), 28 (C2 = week 4), 56 (C3 = week 8) and 84 (C4 = week 12). VAS, visual analog scale

Table 3 Results of Female Somatic Sexual Experience Instrument (FSSEI)

		E					*C4*				
Question	*p*	*n*	*Yes*	*No*	*Median*	*Range*	*n*	*Yes*	*No*	*Median*	*Range*
1a. Body image	0.0009	16			6.6	0.0–9.6	16			8.4	7.2–10.0
1b. Distress level	0.1403	16			5.1	0.4–10.0	16			1.7	0.0–8.4
1c. Physical contact	0.4110	16			2.9	0.0–9.2	16			4.7	0.4–10.0
1d. Sexual desire	0.0042	16			1.1	0.0–5.5	16			3.8	0.4–10.0
13. Sexual activity* (4 weeks**)		16	3	13			16	10	6		
14. Sex satisfaction (4 weeks)	0.1250	6			1.1	0.0–2.6	10			4.6	1.1–10.0
15a. Orgasm problem	1.0000	2			7.2	4.3–10.0	4			6.6	0.0–8.4
15b. Getting orgasm	0.5000	4			3.2	0.2–7.3	8			6.2	0.3–10.0
15c. Time to orgasm (4 weeks)	0.7500	4			3.1	0.3–6.5	8			6.6	0.2–10.0
16. Lubrication	0.5000	3	1	2			9	7	2		
16a. Lubrication speed (4 weeks)	0.5000	2			1.2	0.1–2.3	8			5.8	1.6–10.0
16b. Staying lubricated (4 weeks)	1.0000	2			2.2	0.2–4.2	8			7.0	3.5–10.0
17. Lubricant use (4 weeks)		3	3	0			10	4	6		
19. Intercourse number (4 weeks)	0.5000	5	2	3			10	7	3		
19a. Frequency assessment	1.0000	5			0.7	0.0–1.1	7			3.4	0.0–5.5
20. Intercourse tempo (4 weeks)	0.5000	3			0.4	0.2–5.0	7			4.4	0.6–10.0
21. Intercourse painfulness (4 weeks)			4	0			8	2	6		
21a. Vaginal pain		3	3	va			2	2	va		
22. Painful initiation		3	3	va			5	2	3		
22a. Initiation painfulness	1.0000	3			9.3	2.1–9.5	2			5.7	3.6–7.8
22b. Initial pain frequency	1.0000	3			9.7	1.4–9.9	2			6.4	3.1–9.7
23. Pain development (4 weeks)		3	3	0			4	3	1		
24. Pain after intercourse (4 weeks)		2	2	va			4	1	3		
24a. Intensity of pain after	1.0000	3			8.7	2.1–9.7	2			1.5	1.0–1.9
24b. Frequency of pain after	1.0000	3			9.5	1.9–9.9	2			1.8	1.6–2.0
24c. Duration of pain after		3					2				
25. Cream use (4 weeks)		3	0	3			3	1	2		
26. Pain problem (4 weeks)	1.0000	3			9.7	7.1–9.8	4			3.9	0.0–8.8
27. Therapy wish		13	4	va			16	2	va		
28. Previous treatment		16	2	va			15	0	va		
29. (Immediate) attention wish		16	7	va			16	12	va		
30. Future contact		15	14	va			16	16	va		

*, Besides sexual intercourse includes also other (not described) sexual activities.**, during last 4 weeks
va, various answers possible. Only answers demonstrating sexual quality-of-life dynamics are shown, general questions on sexual history are not shown

DISCUSSION

The impact of estrogen deprivation on vaginal health during treatment with AIs is broadly recognized; however, the indirect effect on sexuality and quality of life is still underestimated[21]. Estrogen deficiency disrupts many of the physiological responses which characterize sexual arousal, including smooth muscle relaxation, vasocongestion and lubrication[13,22]. Vaginal dryness, dyspareunia and loss of sexual desire are the main factors destroying the sexual life of affected women. Therefore, support and information are needed not only by younger but also by older, postmenopausal women taking these drugs[3].

Estrogen receptors are heavily concentrated in the vulvovaginal area, making this body region extremely sensitive to estrogen deprivation[23]. Low estrogen levels result in a reduction of squamous epithelial cell layers of the vaginal epithelium, leading to a predominance of parabasal and basal cells, while levels of collagen, glycogen, mucopolysaccharides, and hyaluronic acid significantly decline[23,24]. Concomitantly, a severe reduction of the vaginal lactobacilli is seen, which in turn leads to an increased vaginal pH and further contributes to the greater risk for urogenital tract infections[25]. The resulting vaginal atrophy is a main contributor to sexual dysfunction: lubrication and tissue elasticity are reduced, and the vagina becomes shorter and narrower, leading to dyspareunia. Furthermore, the diminished sensory response reduces the orgasmic intensity, decreases libido, and leads to loss of sexual satisfaction[22,26].

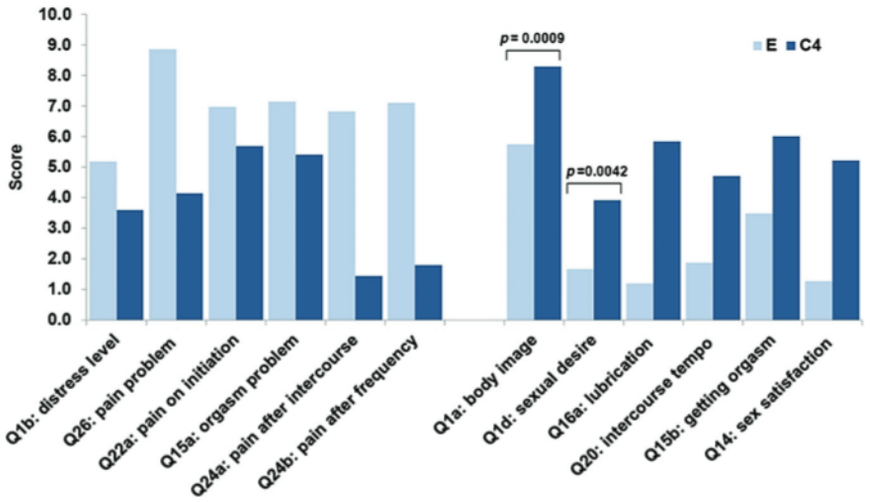

Figure 3 Sexual quality-of-life dynamics. E, entry visit (before treatment); C4, after 12 weeks of treatment, of which 4 weeks daily and 8 weeks three times a week

The 'gold standard' treatment for these problems in healthy postmenopausal women is application of vaginal estrogen preparations, but in breast cancer survivors such treatment is in general contraindicated due to safety concerns. Earlier reported results of the current study[14] have demonstrated that therapy with ultra-low-dose 0.03 mg E3 and *Lactobacillus acidophilus* vaginal tablets (Gynoflor®) can be considered as a safe and efficacious treatment of atrophic vaginitis in breast cancer patients taking AIs. Only a few studies have evaluated the effects of vaginal estrogen for improvement in sexual function of postmenopausal women. Gast and colleagues[27] demonstrated that local estrogen therapy was also associated with improvement in sexual desire, frequency of orgasm, and sexual satisfaction; however, there was no effect on coital frequency. Cayan and colleagues[28] evaluated, with a 19-item Sexual Function Index questionnaire, sexual desire, arousal, lubrication, orgasm, satisfaction, and pain during various estrogen application regimens. In this study, the vaginal therapy-only group did not have a favorable response in desire, arousal, orgasm or satisfaction compared to the oral group. It could be stated that the effect of local vaginal estrogen application on the sexuality of women still needs more in-depth investigations[13]. Nonetheless, it seems that the restoration of vaginal epithelial health with local estrogen application results in increased vaginal compliance, decreased vaginal pH, increased vaginal blood flow, and lubrication[12,29]. Women subsequently report decreased vaginal irritation, soreness, dryness, and pain during intercourse, resulting in increased sexual desire, arousal, i.e. subjective improvement in the sexual domain of quality of life[12,29,30].

Our study demonstrated similar findings for postmenopausal breast cancer patients taking AIs. We have seen that, even in the absence of a systemic increase in circulating estrogen levels (as reported earlier[14]), symptoms of vaginal atrophy and sexual functioning both improved and approached the level of functioning that was present before diagnosis (75% vs. 88%). The FSSEI demonstrated a trend for improvement of all main domains of sexual quality of life (desire, arousal, orgasm, satisfaction); however, statistics failed to show significance due to small subject numbers (only seven of 16 patients reported normal sexual intercourse).

The results of our study also support the positive role of local vaginal E3 and probably other estrogens in achieving better results in sexuality[27,28] as E3 really succeeds in transforming the pelvic tissues into better shape for intercourse[12,29,30], and it seems that this is especially relevant in the AI-treated breast cancer women suffering from vaginal atrophy with dyspareunia. It still remains unclear and could be further investigated whether this concept could be adapted for other, especially postmenopausal, women with dyspareunia-induced sexual problems. The strengths of the present study were the precise study design and comprehensive evaluation of various relevant parameters in the investigated patient population. The weaknesses of the study were the small numbers of subjects for the testing of some parameters of sexuality, but this will probably be the only study looking at the quality of life in women with an endocrine treatment of breast cancer. Hence, for consolidation of these exploratory findings, larger studies including more women are needed.

In conclusion, it was demonstrated that local Gynoflor® therapy of postmenopausal breast cancer survivors treated with a non-steroidal AI reporting atrophic vaginitis could be considered as a useful treatment opportunity having probably a positive impact on the sexual domain of quality of life of affected women.

Conflict of interest Dr Gilbert Donders is a member of the Global Advisory Board of Medinova AG, Switzerland. Dr Philipp Grob and Dr Valdas Prasauskas are employees of Medinova AG, Switzerland. The authors alone are responsible for the content and writing of the paper.

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