Journal of
Women's Health and Gynecology

Research Article Open Access

Effect of Ospemifene on Cardiometabolic Risk in Postmenopausal Women Reporting Vulvo and Vaginal Atrophy (VVA): Results of a 12-Month Prospective Study

Silvia Maffei[1*], Angela Papa[2], Pietro Di Cecco[2] and Letizia Guiducci[3]

[1]Department of Cardiovascular Endocrinology and Metabolism, Gynecological and Cardiovascular Endocrinology Unit, "Gabriele Monasterio" Foundation and Italian National Research Council (CNR) Pisa, Italy
[2]Department of Laboratory Medicine, Fondazione Toscana "Gabriele Monasterio", Pisa, Italy
[3]Laboratory of Biochemistry and Molecular Biology, Institute of Clinical Physiology, CNR, Pisa, Italy

***Corresponding author:** Silvia Maffei, Department of Cardiovascular Endocrinology and Metabolism, Gynecological and Cardiovascular Endocrinology Unit, "Gabriele Monasterio" Foundation and Italian National Research Council (CNR) Pisa, Italy, Tel: + 39 050 3152216, E-mail: silvia.maffei@ftgm.it

Received Date: July 26, 2021 **Accepted Date:** August 26, 2021 **Published Date:** August 28, 2021

Citation: Silvia Maffei (2021) Effect of Ospemifene on Cardiometabolic Risk in Postmenopausal Women Reporting Vulvo and Vaginal Atrophy (VVA): Results of a 12-Month Prospective Study. J Womens Health Gyn 8: 1-12.

Abstract

Vulvovaginal atrophy (VVA) is a common and disabling post-menopausal disorder. Ospemifene (OSP) is a selective estrogen receptor modulator (SERM) indicated for the treatment of VVA in postmenopausal women. Although the endometrial, breast and thromboembolic safety profile has been confirmed in numerous studies, the possible effects of OSP relative to its cardiovascular and metabolic profile have rarely been investigated. This study evaluates the cardio-metabolic effects of OSP in a sample of postmenopausal women reporting VVA.

The study was conducted on 53 women treated for 12 months (60mg OSP / day). Anthropometric measurements, blood pressure, anamnestic data, relative to VVA, climacteric symptoms, comorbidities and familiar history were evaluated at recruitment (T0) and after 3 (T1) and 12 months (T2) of therapy. The Vaginal Health Index, Greene Climacteric Scale and Insomnia-Severity Index, were used for the evaluation of VVA, postmenopausal symptoms and sleep quality, respectively. The cardiovascular and metabolic risk profile was assessed by blood samples at T0, T1 and T2.

VVA at T0 was present in 58.4% of patients and significantly improved at T1 and T2. Vasomotor symptoms, sleep and mood disorders significantly improved at T2. Blood pressure, systolic and diastolic, decreased at T1 and T2. No changes were found in heart rate and anthropometric parameters. Total cholesterol, fibrinogen, CRP and coagulation protein S levels significantly improved at T1 and T2; coagulation protein C only improved at T2. There was no negative impact either on triglyceride values or glucose and insulin values or on other parameters relating to cardio-vascular and metabolic risks.
Overall, in addition to improving VVA symptoms, OSP also appears to improve vasomotor symptoms, sleep pattern and mood, and has a protective and safety effect on cardiometabolic and thrombotic risk markers in long-term treatment.

OSP can therefore be considered a safe therapeutic option for postmenopausal women.

Keywords: VVA; Ospemifene; Menopausal Women; Cardio-metabolic risk; Coagulation and thrombotic risk

List od Abbreviations: ALT: Alanine aminotransferase; APC Resistance: Resistance to activated Protein C; aPTT: Activated partial thromboplastin time; AST: Aspartate aminotransferase; ATT: Anti Thrombin Third; BMI: Body Mass Index; HDL: High density lipoprotein; LDL: Low density lipoprotein; EMA: European Medicines Agency; FDA: Food and Drug Administration; GCS: Greene Climacteric Scale; GGT: Gamma Glutamyl Transferase; GSM: genitourinary syndrome of menopause; IL-6: Interleukin 6; INR: International Normalized Ratio; PCR: C reactive protein; SERM: Selective estrogen receptor modulators; VHI: Vaginal Health Index; VVA: Vulvo-vaginal atrophy

Introduction

Vulvovaginal atrophy (VVA) is one of the most widespread and disabling post-menopausal disorders [1]. Vaginal dryness and dyspareunia are the most common symptoms of VVA reported by post-menopausal women [2]. Unlike some symptoms that tend to regress in late postmenopause, VVA is also frequent in elderly women because although it begins around menopause, mainly as a consequence of estrogen deficiency [3], it is a chronic condition that progresses with aging [4].

Objectively detectable clinical changes and subjective symptoms are present in approximately 50% of all postmenopausal women [5]. VVA is often associated with vasomotor symptoms, and both sleep and mood disorders [6]. This results in an overall deterioration in the quality of life of women and couples [7].

There are various - both local and systemic, hormonal and non-hormonal - treatments to improve "vaginal health" [8]. The selective estrogen receptor modulator (SERM), Ospemifene (OSP) has recently become available as a new therapeutic option for the treatment of VVA in postmenopausal women [9,10]. OSP is specifically indicated for the treatment of VVA due to the particular stimulating effect on the hormone receptors of the vaginal mucosa, but with a neutral effect on the estrogen receptors in the breast and uterus [11,12]. Some studies have compared the effects of OSP versus local treatments with 17β-estradiol, or estriol in gel form, or ova, or estradiol administered through the vaginal ring. The results have shown that OSP has an efficacy, safety and tolerability profile comparable, or better than local vaginal estrogen in the treatment of VVA [13-15].

Ospemifene is also currently the only drug with FDA and EMA [12] approval for the treatment of female "breast cancer survivors" after five years of adjuvant anti-hormonal therapy [16,17].

The menopausal transition is often associated with the appearance of cardiovascular and metabolic risk factors (weight gain, arterial hypertension, impaired glucose / insulin homeostasis, dyslipidemia) [18].

Although the endometrial, mammary and thromboembolic safety profile of OSP has been confirmed in numerous studies with large patient populations [13,19-21], little is known about the possible effects on the cardiometabolic risk factors.

Our study evaluated the long-term effects of Ospemifene on the metabolic cardiovascular risk profile in a sample of postmenopausal women reporting VVA / GSM.

Materials and Methods

The study was conducted at the Endocrinological-Cardiovascular Gynecology Outpatient Clinic and the Osteoporosis Study Center of the Italian National Research Council Gabriele Monasterio Tuscan Foundation in Pisa, Italy. The execution of the study was authorized by the local ethics committee (Prot No. 37981, study 3605, 20/06/2012). The study was registered at ClinicalTrials.gov with identification code: NCT03699150.

A total of 86 postmenopausal women were included who reported symptoms related to VVA (vaginal dryness, irritation / burning / itching of the vulva or vagina, decreased lubrication and dyspareunia). Of these, 53 women participated in the study for at least 12 months. Women with current cancer, thromboembolic disease, current or previous liver disease, or who had used steroids in the previous three months or who had received hormonal therapies in the six months prior to the start of the study, were excluded. In addition, women with a BMI greater than or equal to 30 kg / m2 were excluded, since there are no data in the literature relating to the effects of Ospemifene in obese patients or with risk factors for thromboembolism.

Study Design

In this interventional and prospective study, Ospemifene was administered continuously at a daily dose of 60 mg orally to postmenopausal women.

All study parameters were evaluated at recruitment (T0), and after 3 (T1) and 12 months (T2) of treatment.

The presence of climacteric symptoms, sleep and mood disorders was assessed through a dichotomous questionnaire administered at the baseline visit and at the 3-month and 12-month controls after the start of the study.

VVA was assessed using the Vaginal Health Index, (VHI) [2]. This index is composed of five parameters evaluated during the gynecological examination: vaginal hydration, type / consistency of the vaginal fluid, overall elasticity, the appearance of the vaginal mucosa, and vaginal pH. Each of these elements is rated on a scale of 1 to 5 so that the total VHI can vary from 5 to 25. Low scores correspond to clinical condition with greater urogenital atrophy: if the score is <15, the vagina is considered atrophic.

The Greene Climacteric Scale (GCS) was used to assess postmenopausal symptoms at the baseline visit and at the 3 and 12 month controls after the start of the study (22). This consists of 21 items with a rating scale from 0 (''not at all") to 3 (''extremely"). This questionnaire investigates psychosocial symptoms (11 items), somatic / physical symptoms (7 items), vasomotor symptoms (2 items), and sexual dysfunctions (1 item).

The Insomnia Severity Index (ISI) was used to assess the perceived quality of sleep (23,24), which consists of a 7-item questionnaire with a total score ranging from 0 to 28 (0-7: insomnia not clinically relevant; 8-14: below threshold insomnia, 15-21: moderate insomnia; 22-28: severe insomnia).

In addition, data were collected on comorbidities (obesity, hypertension, glucose intolerance / diabetes, dyslipidemia and thyroid disease), family history (glucose intolerance / diabetes, obesity, ischemic events, thrombosis, dyslipidemia, neoplasms, thyroid disease, osteoporosis and early menopause) and changes in anthropometric and hemodynamic measurements were assessed in the recruited women.

To evaluate the cardiovascular-metabolic risk profile, blood samples were taken at T0, and after 3 and 12 months of therapy.

For the cardio-metabolic risk profile, blood triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol, GGT, ASL, ALT, homocysteine, nt-proBNP, glucose, and insulin values were measured. Creatinine and uric acid were measured for renal function. As nonspecific indices of inflammation, fibrinogen, PCR and IL-6 were measured. Coagulation and thrombotic risk were assessed by measuring: ATT, INR, aPTT, antithrombin III, APC resistance, protein C, and protein S.

Citrated blood samples were centrifuged at 3500 rpm for 15 minutes to obtain platelet-poor plasma for the determination of prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, antithrombin, activated protein C resistance, protein C and protein S using the Werfen commercial coagulation reagents, ReadiPlasTin, SynthASil, Q.F.A thrombin, liquid antithrombin, protein C and free protein S, respectively. Homocysteine serum levels were measured using an Architect i1000sr analyzer (Abbott Diagnostics, Abbott Park, IL).

Triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol, GGT, ASL, ALT, nt-proBNP, glucose, insulin, creatinine, uric acid PCR and IL-6 were evaluated by standard automated laboratory instruments (COBAS 6000 analyzer, Roche Diagnostics).

Patients

A total of 53 women with a mean age at the start of treatment of 54.9 ± 3.3 years were enrolled in the study. The mean age of menopause was 49.2 ± 4.2 years, with an average BMI of 22.9 ± 3.6 kg / m^2. The presence of comorbidities in the total population, expressed as a percentage, was 10.8% for obesity, 5.4% for hypertension, 0% for glucose intolerance / diabetes, 2.7% for dyslipidemia, and 18.9% for thyroid disease.

The presence of familiar history of diabetes was 15.1%, obesity 0%, ischemic events 27.3%, thrombosis 15.1%, dyslipidemia 21.2%, hypertension 23.5%, neoplasia 46.9%, thyroid disease 15.1%, osteoporosis 36.4%, and early menopause 9.1%.

Statistical Analysis

Continuous variables were reported as the mean ± standard deviation. When necessary, the logarithmic transformation of the parameters was carried out. The values transformed into logs for the analysis were then reconverted for the presentation of the data.

Student's t-test was used to compare baseline values with follow-up values (3 and 12 months). A bidirectional t test for independent samples by ANOVA was used to compare intergroup demographics and clinical data. All the analyses were carried out using IBM-SPSS software. The result was considered statistically significant when $p < 0.05$.

Results

All assessments were carried out at baseline (T0) measurement, and at T1 and T2.

VVA at T0 was clinically present in 58.4% of patients (N = 31), but decreased significantly to 22.7% and 8.3% at T1 and T2, respectively ($p = 0.03$, $p < 0.001$).

The VHI during the study is shown in Table 1.

At T0, the total group (N = 53) showed a mean score of 13.4 ± 6.2, which improved significantly at T1 and T2 (17.3 ± 3.4, 19.5 ± 2.7; $p < 0.001$, $p < 0.001$). This improvement was more evident in the subgroup of subjects (N = 31) who showed a VHI lower than 15. In particular, the VHI of this subgroup at T0 was 8.5 ± 2.0, which increased significantly already at T1 and was even higher at T2 (15.6 ± 1.7; 17.9 ± 2.9; $p < 0.001$, $p < 0.001$).

Table 2 presents the percentage of patients who reported vasomotor symptoms, sleep disturbances and mood disorders at T0, T1 and T2.

A total of 33.3% and 36.3% of subjects reported mood and sleep disorders, respectively at enrollment. These disturbances and their trends were measured using the Greene Scale and ISI Index, respectively. The psychological domain, which combines the anxiety cluster score (items 1-6) with the depression cluster score (items 7-11), showed an improvement trend at T1 and a statistically significant improvement at T2; as did the somatic domain (Figure 1). The vasomotor symptomatology score decreased significantly at 12 months of treatment, and similarly, sleep disturbances decreased significantly at T2 (Figure 1).

Table 1: VHI score for the entire population studied and in the subgroup with baseline VHI <15 diagnosed for atrophic vaginitis at baseline (T0), and after 3 and 12 months of treatmentrespectively (T1 and T2)

	T0	T1	T2	p T0 vs T1	p T0 vs T2
VHI Score (Total N = 53)	13.4 ± 6.2	17.3± 3.4	19.5 ±2.7	<0.001	<0.001
VHI Score (in the subgroup with baseline VHI <15; N = 31)	8.5 ± 2.0	15.6± 1.7	17.9 ±2.9	<0.001	<0.001

Table 2: Percentage of patients who reported vasomotor symptoms, sleep disturbances and mood disorders, at baseline (T0), and after 3 and 12 months of treatment respectively (T1 and T2)

SYMPTOM	T0	T1	T2	p T0 vs T1	p T0 vs T2
Vasomotor symptoms	44.5%	40.9%	12.5%	NS	0.001
Sleep disorders	33.3%	22.7%	12.5%	NS	0.005
Mood disturbances	36.3%	13.6%	8.3%	0.083	0.005

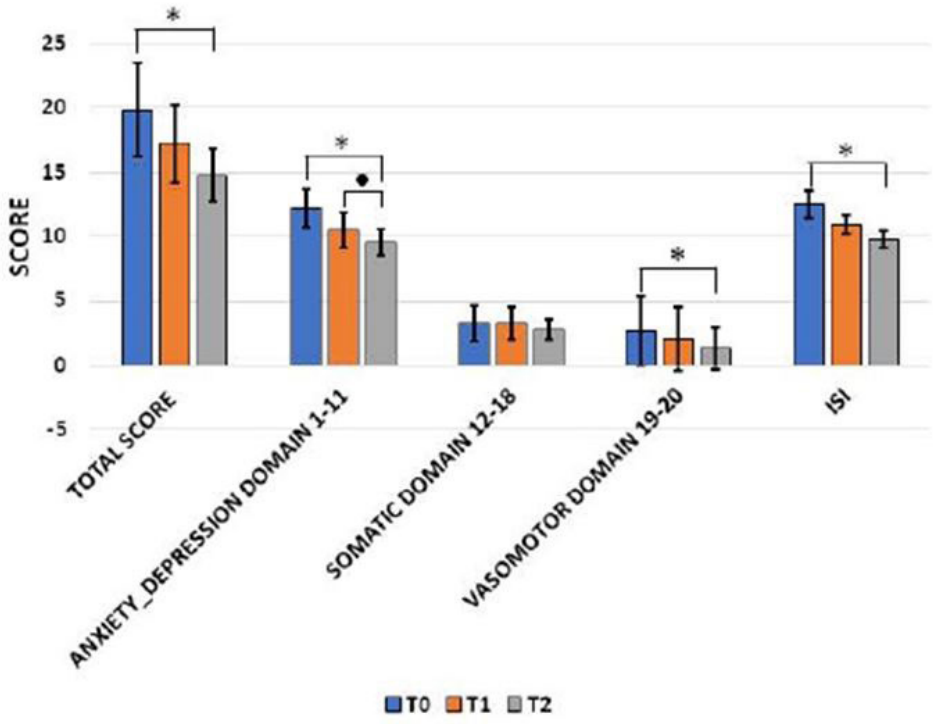

Figure 1: Trend of the total score of the Greene Scale and its domains: the psychological one that combines items 1to 11, the somatic domain relating to the sum of items 12-18 and the vaso motor domain. The Figure also shows the ISI trend, a score relating to the quality of sleep (N =53; *p≤0.05, •p=0.1)

The changes in the haemodynamic and anthropometric measurements after 3 and 12 months of treatment with Ospemifene are shown in Table 3. Table 4 shows the trend in concentrations of the haematochemical parameters relating to various panels: (metabolism / liver; renal function and non-specific indices of inflammation) of the subjects at T0, T1 and T2.

Table 5 shows the trend in concentrations of blood chemistry parameters relating to coagulation and thrombotic risk at T0, T1 and T2.

Table 3: Changes in hemodynamic and anthropometric measurements at baseline (T0), and after 3 and 12 months of Ospemifene treatment respectively (T1 and T2)

Hemodynamic and anthropometric measurements	**T0**	**T1**	**T2**	**p T0 vs T1**	**p T0 vs T2**
Systolic blood pressure (mmHg)	128.6 ± 15.0	120.0 ± 12.6	119.95±11.3	0.001	0.006
Diastolic blood pressure (mmHg)	76.0 ± 9.3	70.7 ± 9.1	70.2 ± 8.7	0.013	0.011
Heart rate (beats/min)	77.0 ± 10.1	75.1± 9.0	76.3 ±8.7	NS	NS
BMI (kg/m^2)	22.2 ± 3.6	22.2 ± 3.1	22.4 ± 2.7	NS	NS
BSA(m^2)	1.62 ± 0.10	1.62 ± 0.11	1.62 ± 0.11	NS	NS

Table 4: Concentrations of haematochemical parameters related to various panels: (metabolism / liver; renal function, non-specific indices of inflammation) of the subjects at baseline (T0), and after 3 and 12 months of Ospemifene treatment respectively (T1 and T2)

PARAMETER	T0	T1	T2	p T0 vs T1	p T0 vs T2
Blood metabolic/hepatic markers					
Triglycerides (mg/dL)	71.6±4.5	70.4±6.2	67.5±5.4	NS	NS
Total Cholesterol (mg/dL)	204.7±6.6	196.7±5.3	192.6±6.8	0.008	0.05
HDL (mg/dL)	78.0±3.1	77.6±2.7	76.4±2.5	NS	NS
LDL (mg/dL)	110.5±8.3	104.2±6.7	95.9±13.1	0.064	NS
gGT (IU/L)	16.7±2.6	16.7±2.0	17.7±32.9	NS	NS
AST (IU/L)	19.9±1.6	20.3±2.1	20.2±1.2	NS	NS
ALT (IU/L)	16.9±1.6	15.2±1.1	15.8±1.3	NS	NS
Glucose (mg/dL)	89.5±1.5	89.0±1.6	87.5±1.8	NS	NS
Insulin (mU/L)	6.8±1.1	5.6±01.1	5.4±0.3	NS	NS
Renal function					
Creatinine (mg/dL)	0.69±0.02	0.71±0.12	0.73±0.03	NS	NS
Uric acid (mg/dL)	3.8±0.3	3.9±0.4	3.9±0.4	NS	NS
Non-specific indices of inflammation					
Fibrinogen (mg/dL)	325.9±18.1	291.7±16.4	294.1±11.5	0.010	0.018
PCR (mg/dL)	0.19±0.08	0.13±0.02	0.11±0.03	0.001	0.001
IL-6 (ng/L)	1.20±0.22	1.30±0.21	1.33±0.27	NS	NS
Vit B12 (pg/mL)	404.8±52.8	579.6±156.2	444.9±128.5	NS	NS

Table 5: Trend in the concentration of blood chemistry parameters related to coagulation and thrombotic risk at baseline (T0), and after 3 and 12 months of Ospemifene treatment respectively (T1 and T2)

PARAMETER	T0	T1	T2	p T0 vs T1	p T0 vs T2
ATT_PT (%)	105.3±2.6	106.3±2.8	107.0±3.2	NS	NS
INR	0.98±0.01	0.98±0.02	0.98±0.01	NS	NS
aPTT (sec)	30.1±0.6	29.0±0.6	29.0±0.6	NS	NS
AT III (%)	111.8±4.6	107.5±2.6	105.1±3.4	NS	NS
APC Resistance	3.2±0.4	2.9±0.4	3.2±0.3	NS	NS
Protein C (%)	117.2±0.7	123.4±5.9	124.4±6.9	NS	0.034
Protein S (%)	85.2±3.4	96.3±2.7	95.0±3.1	0.003	0.012
Homocysteine (umol/L)	9.0±0.6	10.1±0.5	9.1±0.6	NS	NS
nt-proBNP (ng/L)	53.2±9.1	57.4±25.3	53.1±10.6	NS	NS

Discussion

The aim of the study was to evaluate the effects of Ospemifene at a dose of 60 mg daily for 12 months on cardio-metabolic and thromboembolic risk markers in a population of healthy postmenopausal women reporting VVA.

The enrolled patients represent an unselected population of patients who contacted the clinical center (real-life data).

Postmenopausal women belonging to the Cardiovascular Endocrinological Gynecology Outpatient Clinic and the Osteoporosis Study Center in Pisa, Italy participated in the study. VVA was assessed using the VHI, which is a standard validated questionnaire. Treatment with Ospemifene significantly improved the VVA score in all patients at both 3 and 12 months, demonstrating the early efficacy and maintenance of the treatment effect over time. These data on Ospemifene efficacy in VVA are in line with previous studies [25,13].

Approximately half of the women (58.4%) had vasomotor symptoms at enrollment. Ospemifene therapy significantly improved vasomotor symptoms: the Green Scale vasomotor symptom domain score was halved between 0 and 12 months. These results are in line with the post hoc analysis by Constantine et al. who described the alleviation of hot flashes after four weeks of Ospemifene treatment in women with moderate to severe symptoms [26]. This finding is also confirmed in the randomized double-blind trial by Rutanen et al. conducted in 160 symptomatic postmenopausal women using the Kupperman Index, [27]. Likewise, Komi, *et al*. [28] demonstrated a gradual decrease in the Kupperman Index at 4, 8 weeks and 3 months of treatment with Ospemifene in 118 healthy postmenopausal women, noting that this improvement was maintained even after the end of the study.

Mood disorders and sleep pattern disorders were evaluated in our population with the GCS and ISI index. A total of 33.3% and 36.3% of our population were affected by these disorders at enrollment respectively. In particular, the psychological domain of the GCS, which combines the anxiety cluster score (items 1-6) with the depression cluster score (items 7-11), showed an improvement trend at three months and a significant improvement at 12 months of treatment, as did the somatic domain (items 12-18).

It is difficult to compare these data with others since, to our knowledge, the published studies evaluated the psychological profile only before and after three months of treatment [27], but not for longer periods and without using such specific tools.

In our study, sleep quality had improved at 12 months of treatment, confirming the positive contribution to the overall improvement in the quality of life of the women treated. To the best of our knowledge, our study is the only one to have evaluated the sleep pattern with a specific validated test.

Significant changes in heart rate, BMI and BSA (body surface area) values were not observed in the 12 months of treatment. Although all the studies that have evaluated the effects of Ospemifene treatment reported baseline BMI values, none have compared them after 12 months of therapy. We also found no comparison studies related to body surface area. Ylikorkala, *et al*. reported no change in heart rate at the third month of treatment with Ospemifene at doses of 30, 60, and 90 mg versus placebo. Our study is thus the only one to demonstrate the neutrality of Ospemifene on body mass composition together with the neutrality of effects on heart rhythm during 12 months of therapy. However, our population sample had a BMI in the normal range. Further studies are needed to evaluate the effects of Ospemifene in overweight or obese patients.

The values of systolic and diastolic blood pressure decreased significantly (Table 3) after 3 and 12 months of treatment with a net improvement in the blood pressure profile in the examined population. In contrast to our data, in the study by Ylikorkala, *et al.* conducted in a subgroup of 60 women (15 per group), 24 h blood pressure monitoring was unaffected by treatment with Ospemifene at a dose of 30, 60, 90 mg versus placebo at the third month of therapy [29].

Since menopause induces an average increase in systolic and diastolic values, Ospemifene contributes to the improvement in blood pressure by promoting a cardiovascular safety profile. However, in the sample of women who participated in the study, only 5.4% of the total population had arterial hypertension. No conclusions can therefore be drawn regarding our data in terms of the effect of Ospemifene in hypertensive women. A specific study would need to investigate this.

In our study, the circulating levels of total cholesterol significantly decreased at the 3rd and 12th months of treatment. We also observed a decreasing trend in circulating levels of LDL and stable levels of HDL. Similarly, the circulating triglycerides values did not change during the treatment. Regarding the lipid profile, it is known that oral hormone replacement therapies even at low doses, induce an increase in circulating triglyceride values [30-32]. The neutrality of Ospemifene on the concentra-

tion of TG should therefore be understood as a protective effect [33] since circulating TG levels represent a cardiovascular risk factor for coronary heart disease and acute myocardial infarction [34] with greater weight in women [35]. The improvement in the total cholesterol profile, the decreasing LDL-C trend and the neutral effect on triglyceridemia are in agreement with the results presented by Archer in a post hoc analysis of five clinical trials of phases 2 and 3 [36].

The net lipid profile in the women evaluated in our study showed an overall improvement with treatment at 3 and 12 months, thus implying cardiovascular protection.

In our study Ospemifene also appeared to have a neutral effect on hepatic (transaminase, GGT) and renal (creatinine, uric acid) metabolism throughout the entire treatment.

Furthermore, Ospemifene did not modify fasting blood glucose and insulin levels evaluated at the 3rd and 12th months of treatment. The neutral effect on glucose / insulin homeostasis was also described in the study by Ylikorkala et al. where the glucose and insulin levels both when fasting and after carbohydrate loading were not modified by the treatment [29].

Since menopause is often accompanied by IGT (37), the neutral effect of Ospemifene on glycemia and insulinemia should be considered positively. However, we cannot extend this effect on the glucose profile to women with a BMI corresponding to overweight, obese or glucose intolerant women, since our population sample had a BMI in the normal range, without IGT or diabetes.

In menopause there is an increase in the circulating values of nonspecific markers of inflammation, reflecting the increase in the inflammatory climate as an effect of estrogen deficiency [38,39]

Our study showed a significant decrease in the values of nonspecific markers of inflammation, such as fibrinogen and CRP, at both 3 and 12 months of treatment. Although significant, the decrease in fibrinogen levels detected remained within the normal range. Similarly, in their respective studies, Ylikorkala and Archer described the decrease in CRP and fibrinogen values at three and 12 months of treatment with a dose of 60 mg / day [29,34].

Since high levels of fibrinogen and CRP [40] represent biochemical markers of cardiovascular risk in particular for myocardial infarction, the reduction in these biomarkers appears to be protective, thus contributing to the safety profile of Ospemifene treatment.

In our study, the coagulation panel and thrombotic risk values (ATT-PT, INR, aPTT, ATIII, APC resistance and homocysteine) at 3 and 12 months of treatment did not show changes. In particular, the levels of all the coagulation factors analyzed remained within the normal range throughout the 12 months of the study. These data confirm the neutrality of Ospemifene treatment on coagulation markers.

On the other hand, the circulating values of protein S increased significantly at 3 and 12 months of treatment, while the protein C values increased significantly at the 12th month. This in agreement with findings reported by Archer, *et al.* [34], who found an improvement in the circulating levels of protein C evaluated at three months of treatment.

Overall, our data confirm the positive effect of Ospemifene on the thrombo-embolic risk. This effect could help justify the lower incidence of venous thromboembolic events with Ospemifene compared to other SERMs or to patients not treated for VVA [41].

The strengths and weaknesses of the study

The strengths of our study lie in the completeness of the characterization of each individual patient, both from clinical-anamnestic and biohumoral points of view and in the length of the observation period (12 months). None of the patients left the study.

A further strength is the fact that our sample represents an unselected population of patients who contacted the clinical center (real-life data). The only fundamental criterion for inclusion was that the patient reported symptoms of VVA.

The need to exclude obese patients, for safety reasons, prevents us from drawing any conclusions for this group.

In this study, a control group was not set up as each patient acted as a control for herself.

Conclusions

The present study evaluated the effects of Ospemifene at a dose of 60 mg per day orally on cardio-metabolic and thromboembolic risk markers in healthy postmenopausal women with VVA.

The data obtained demonstrated that long-term treatment, in addition to improving the symptoms of VVA, also improved the vasomotor symptoms, sleep pattern and mood, basal systolic and diastolic blood pressure values, lipid profile, and the thrombotic and inflammatory profile. The therapy did not change the coagulation parameters, or the hepatic and renal profile and glucose / insulin homeostasis but had a neutral effect on these indicators.

Overall, Ospemifene therapy was demonstrated to exert a protective and safety effect on cardiometabolic and thrombotic risk markers.

We thus believe that ospemifene can be considered a safe treatment option for postmenopausal women.

References

1. Nappi RE, Martini E, Cucinella L, Martella S, Tiranini L, et al. (2019) Addressing Vulvovaginal Atrophy (VVA)/Genitourinary Syndrome of Menopause (GSM) for Healthy Aging in Women. Front Endocrinol (Lausanne) 10: 561.

2. Bachmann G (1995) Urogenital ageing: An old problem newly recognized. Maturitas 22: S1–S5.

3. Nappi RE, Palacios S (2014) Impact of vulvovaginal atrophy on sexual health and quality of life at postmenopause. Climacteric17: 3–9.

4. Mitchell CM, Waetjen LE (2018) Genitourinary changes with aging. Obstet Gynecol Clin North Am 45: 737–50.

5. Parish SJ, Nappi RE, Krychman ML (2013) Impact of vulvovaginal health on postmenopausal women: a review of surveys on symptoms of vulvovaginal atrophy. Int J Womens Health 5: 437–47

6. Nappi RE, Di Carlo C, Becorpi AM, Gambacciani M, De Seta F, et al. (2019) investigators of the EVES Study. The effect of vulvovaginal atrophy on women's quality of life from an Italian cohort of the EVES study. J Obstet Gynaecol 40: 512-9.

7. Panay N, Palacios S, Bruyniks N, Particco M, Nappi RE (2019) EVES Study investigators. Symptom severity and quality of life in the management of vulvovaginal atrophy in postmenopausal women.Maturitas 124: 55-61.

8. Naumova I, Castelo-Branco C (2018) Current treatment options for postmenopausal vaginal atrophy.Int J Womens Health 10: 387-95.

9. Bachmann GA, Komi JO (2010) Ospemifene Study Group. Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study. Menopause 17: 480–6.

10. Palacios S, Cancelo MJ (2016) Clinical update on the use of ospemifene in the treatment of severe symptomatic vulvar and vaginal atrophy.Int J Womens Health 8: 617-26.

11. DeGregorio MW, Zerbe RL, Wurz GT (2014) Ospemifene: a first-in-class, non-hormonal selective estrogen receptor modulator approved for the treatment of dyspareunia associated with vulvar and vaginal atrophy. Steroids 90: 82-93.

12. European Public Assessment Report (2014) European Medicines Agency.

13. Goldstein SR, Bachmann GA, Koninckx PR, Lin VH, Portman DJ, Ylikorkala O (2014) Ospemifene 12-month safety and efficacy in post- menopausal women with vulvar and vaginal atrophy. Climacteric 17: 173-82.

14. Bruyniks N, Biglia N, Palacios S, Mueck AO (2017) Systematic indirect comparison of ospemifene versus local estrogens for vulvar and vaginal atrophy. Climacteric20: 195-204.

15. Archer DF, Simon JA, Portman DJ, Steven R, Goldstein SR, et al. (2019) Ospemifene for the treatment of menopausal vaginal dryness, a symptom of the genitourinary syndrome of menopause. Review Expert Rev Endocrinol Metab 14: 301-14.

16. Wurz GT, Soe LH, DeGregorio MW (2012) Ospemifene, vulvovaginal atrophy, and breast cancer. Maturitas 74: 220-5.

17. Cai B, Simon J, Villa P, Biglia N, Panay N, et al. (2020) No increase in incidence or risk of recurrence of breast cancer in ospemifene-treated patients with vulvovaginal atrophy (VVA). Maturitas 142: 38-44.

18. Maffei S, Guiducci L, Cugusi L, Cadeddu C, Deidda M, et al. (2019) Women-specific predictors of cardiovascular disease risk - new paradigms.Int J Cardiol 286: 190-7.

19. Wurz GT, Kao CJ, DeGregorio MW (2014) Safety and efficacy of ospemifene for the treatment of dyspareunia associated with vulvar and vaginal atrophy due to menopauseClin Interv Aging 9: 1939-50.

20. Portman D, Palacios S, Nappi RE, Mueck AO (2014) Ospemifene, a non- oestrogen selective oestrogen receptor modulator for the treatment of vaginal dryness associated with postmenopausal vulvar and vaginal atrophy: a randomised, placebo-controlled, phase III trial. Maturitas 78: 91-8.

21. Simon JA, Lin VH, Radovich C, Bachmann GA (2013) Ospemifene Study Group. One-year long-term safety extension study of ospemifene for the treatment of vulvar and vaginal atrophy in postmeno- pausal women with a uterus. Menopause 20: 418–27.

22. Greene JG, Hart DM (1987) Evaluation of a psychological treatment programme for climacteric women. Maturitas, 9: 41-8.

23. Morin CM (1993) Insomnia, psychological assessment and management. The Guilford, New York.

24. Bastien CH, Vallieres A, Morin CM (2001) Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Medicine 2: 297-307.

25. Simon J, Portman D, Mabey RG Jr. Long-term safety of ospemifene (52-week extension) in the treatment of vulvar and vaginal atrophy in hysterectomized postmenopausal women. Maturitas 77: 274-81.

26. Constantine GD, D Archer DF, Pollycove R, Jiang W, Altomare C, et al. (2016) Ospemifene's effect on vasomotor symptoms: a post hoc analysis of phase 2 and 3 clinical data Menopause 23: 957-64.

27. Rutanen EM, Heikkinen J, Halonen K, Komi J, Lammintausta R, et al. (2003) Clinical Trial. Effects of ospemifene, a novel SERM, on hormones, genital tract, climacteric symptoms, and quality of life in postmenopausal women: a double-blind, randomized trial. Menopause 10: 433-9.

28. Komi J, Lankinen KS, Härkönen P, DeGregorio MW, Voipio S, et al. (2005) Effects of ospemifene and raloxifene on hormonal status, lipids, genital tract, and tolerability in postmenopausal women. Menopause 12: 202-9.

29. Ylikorkala O, Cacciatore B, Halonen K, Lassila R, Lammintausta R, et al. (2003) Effects of ospemifene, a novel SERM, on vascular markers and function in healthy, postmenopausal women. Menopause 10: 440-7.

30. Clinical Trial Writing Group for the PEPI Trial (1995) Effects of estrogen or estrogen/ progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial. JAMA 273: 199-208.

31. Rossouw JE, Cushman M, Greenland P (2008) Inflammatory, lipid, thrombotic, and genetic markers of coronary heart disease risk in the Women's Health Initiative trials of hormone therapy. Arch Intern Med 168: 2245-53.

32. Mercuro G, Vitale C, Fini M, Zoncu S, Leonardo F, et al. (2003) Lipid profiles and endothelial function with low-dose hormone replacement therapy in postmenopausal women at risk for coronary artery disease: a randomized trial. Int J Cardiol 89: 257–65.

33. Anagnostis P, Stevenson JC, Crook D, Johnston DG, Godsland IF (2016) Effects of gender, age and menopausal status on serum apolipoprotein concentrations Clin Endocrinol (Oxf) 85: 733-40.

34. Budoff M (2016) Triglycerides and Triglyceride-Rich Lipoproteins in the Causal Pathway of Cardiovascular Disease. Am J Cardiol 118: 138-45.

35. Austin MA, Hokanson JE, Edwards KL (1998) Hypertriglyceridemia as a cardiovascular risk factor.Am J Cardiol 81: 7B-12B.

36. Archer DF, Altomare C, Jiang W (2017) Cort S.Ospemifene's effects on lipids and coagulation factors: a post hoc analysis of phase 2 and 3 clinical trial data. Menopause 24: 1167-74.

37. Mauvais-Jarvis F (2017) Menopause, Estrogens, and Glucose Homeostasis in Women. Adv Exp Med Biol1043: 217-25.

38. Conroy SM, Neilson HK, O'Reilly R, Woolcott CG, Stanczyk FZ, et al. (2017) Friedenreich CM. Associations between postmenopausal endogenous sex hormones and C-reactive protein: a clearer picture with regional adiposity adjustment? Menopause 24: 1040-8.

39. Lau ES, Paniagua SM, Guseh JS, Bhambhani V, Zanni MV, et al. (2019) Sex Differences in Circulating Biomarkers of Cardiovascular Disease. J Am Coll Cardiol 74: 1543-53.

40. Kaptoge S, Di Angelantonio E, Pennells L, Wood AM, White IR, et al. (2012) C-reactive protein, fibrinogen, and cardiovascular disease prediction. Emerging Risk Factors Collaboration, N Engl J Med 367: 1310-20.

41. Nordstrom BL, Cai B, De Gregorio F, Dhalwani N, Fraeman KH, et al. (2020) Incidence of venous thromboembolism among postmenopausal women prescribed ospemifene, selective estrogen receptor modulators for noncancer indications, or untreated vulvar and vaginal atrophy. Menopause 27: 864-71.