

## P-1.

### **The Vulvovaginal Atrophy Questionnaire (VVAQ): A Novel Patient-Reported Outcome (PRO) for Assessing Symptoms of Vulvovaginal Atrophy in Menopausal Women**

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**Objective:** Symptoms of vulvovaginal atrophy (VVA), a principal component of the genitourinary syndrome of menopause (GSM), are commonly reported in studies of menopausal women; however, the lack of a validated self-report measure of symptomatic VVA has greatly limited our ability to quantify its prevalence and associated outcomes in women. Given the prevalence of VVA symptoms and potential impact on women's health, quality of life and interpersonal relationships, there is an urgent clinical and research need for a patient-based, culturally-sensitive, validated instrument for assessing VVA symptoms and their impact on women's lives. We present results from the first four phases of development of a novel PRO measure for assessing VVA symptoms in menopausal women. **Design:** The overall goal of this project is to develop and validate a new PRO measure for assessing symptomatic VVA in both research and clinical settings. Following established standards and guidelines, this new PRO measure has been developed in four discrete stages. The first phase involved an extensive literature review with input from an expert advisory panel to develop a working conceptual model. In the second phase, concept elicitation interviews were conducted in 36 post-menopausal women with clinically confirmed, symptomatic VVA. Based on qualitative interview findings, a draft questionnaire was developed during the third phase. The draft questionnaire was then evaluated for comprehension and relevance (content validity) by means of cognitive debriefing interviews in focus groups of women with and without symptomatic VVA (N=26 with VVA, N=15 without VVA). Participants were recruited from three clinical sites. All interviews were performed by a trained qualitative interviewer and transcribed and coded for content analysis according to well-established coding procedures and analysis methods. **Results:** Based on findings from both phases of qualitative interviewing, the draft questionnaire was modified and a revised conceptual model proposed. The revised VVAQ questionnaire consists of 14 individual items that assess vaginal and urinary health, impact on sexual function, and associated distress. The revised conceptual model and questionnaire includes the following domains: sensations, severity, perceived distress/bother, activities/function associated with symptomatic VVA and patient perception and experience of GSM/VVA. The sensation domain includes questions on dryness, burning, and pain during daily activities and urination. Pain during sexual activity is also addressed. Severity of GSM/VVA symptoms is also captured. In the perceived distress/bother domain, patients are asked if they have experienced any relief of their symptoms. Activities/Function domain includes items on sexuality (sexual function and spontaneity), other activities (clothing selection) and quality of life (relationships with partner(s)). Lastly, the patient perception and experience of GSM/VVA is addressed. Results from the cognitive debriefing phase confirmed that all of these items are comprehensible and relevant to women with and without symptomatic VVA. In the next phase of development, the draft questionnaire will be further evaluated in a quantitative validation study in women with and without diagnosed symptomatic VVA. **Conclusion:** In response to the urgent need for a patient-based, validated questionnaire of symptomatic VVA, a novel PRO measure has been developed based on qualitative responses of post-menopausal women with and without VVA. This new PRO measure was developed in close accordance with FDA's Guidance for PRO development and validation, and based also on expert advice from clinicians and researchers. Further clinical validation is planned, along with broader use of the measure in research and clinical settings.

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**Efficacy of vaginal misoprostol before diagnostic hysteroscopy in postmenopausal women: a randomized double-blind placebo-controlled clinical trial**

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**Objective:** To evaluate the efficacy and safety of prior use of misoprostol or placebo for postmenopausal women undergoing diagnostic hysteroscopy. **Design:** Randomized double-blind placebo-controlled clinical trial of 158 postmenopausal women who received either 200µg of misoprostol or placebo by vaginal route before diagnostic hysteroscopy. Indication for the exam, duration of the procedure, need for additional cervical dilatation, pain intensity, complications and adverse effects were studied. **Results:** Abnormal bleeding and endometrial thickening were the most common indications of the exam in both groups ( $p=0.4974$ ). The duration of hysteroscopy was similar in both groups ( $p=0.43$ ). Additional cervical dilatation was needed in 11 women in misoprostol group *versus* 9 in placebo group ( $p=0.6323$ ). In both groups, there was no significant difference in pain intensity and complications. Adverse effects were reported by 25.3% of women using misoprostol and were vaginal bleeding in 11.3%, cramping in 12.6% and diarrhea in 2.5% while one reported both vaginal bleeding and cramping. In the placebo group, only 2.5% of women presented adverse effects ( $p=0.0001$ ). **Conclusion:** Misoprostol does not reduce duration of the procedure, need for additional cervical dilatation, pain intensity and causes more adverse effects when used in postmenopausal women prior diagnostic hysteroscopy.

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### **Cortisol Response to Acute Stress in Midlife Women with Vasomotor Symptoms**

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**Objective:** Hot flashes and night sweats, or vasomotor symptoms (VMS), have been linked with altered diurnal cortisol secretion patterns in midlife women. These patterns are similar to those observed in individuals with insomnia. While resting-state cortisol levels have been investigated in women with VMS, previous studies have not examined if the presence of VMS also leads to perturbed cortisol release in response to acute stressors. Individuals with underlying chronic stress conditions (such as PTSD and depression) have been found to have both abnormally blunted and hyper-reactive cortisol release related to experimentally induced stress. Because women with significant VMS have more psychological distress and report more stress, we examined whether women with VMS also experience abnormal cortisol release patterns in response to an acute experimental stress paradigm compared to women without VMS. We also investigated if abnormal cortisol response was intensified by the presence of insomnia as these conditions are frequently linked. **Design:** 37 midlife women completed the Montreal Imaging Stress Task (MIST), a stress paradigm derived from the Trier Mental Challenge Test that includes a computerized arithmetic task combined with a social evaluative threat. 27 (73%) women reported VMS (mean 12.9 VMS events per 24hr) during screening and 10 (27%) reported none or <1 VMS event per 24 hours. All subjects completed questionnaires assessing insomnia (ISI), depressive (PHQ-8), and anxiety symptoms (HAM-A). Before and after completing the task, salivary cortisol, blood pressure, heart rate, and acute psychological responses (frustration, stress, anxiety, pain, comfort, calm, confidence) on a Visual Analog Scale (VAS) were measured. Within-person change in each of these measures was compared between those with and without VMS using Student's t-tests. To examine the impact of comorbid insomnia (defined as ISI $\geq$ 14, threshold score for clinical insomnia), we also examined differences between subjects without VMS (n=10), with VMS but no insomnia (n=16), and with both VMS and insomnia (n=11) using the non-parametric test for trend between the 3 groups. **Results:** Women with VMS had a smaller cortisol change in response to the MIST stress task compared to women without VMS (mean: 0.02  $\mu$ g/dl, 54% increase vs 0.07  $\mu$ g/dl, 83% increase, p=0.039, respectively). Mean baseline cortisol did not differ between those with and without VMS (0.1  $\mu$ g/dl vs. 0.09  $\mu$ g/dl; p=0.74). Time of day, and time from wake had no significant effect on baseline cortisol or cortisol response. Women with VMS had a diminished stress response on all VAS items, particularly on domains of confidence (p=0.08) and calm feelings (p<0.01) compared to women without VMS. When the VMS group was divided according to the presence or absence of insomnia symptoms, women with both VMS and insomnia had the smallest cortisol elevation in response to the acute stressor (mean cortisol increase 0.01 vs. 0.03 vs. 0.07  $\mu$ g/dl for VMS plus insomnia vs. VMS but no insomnia vs. no VMS/no insomnia, respectively; p=0.09). Women with VMS also reported higher depressive (PHQ-8, p<0.01) and anxiety symptoms (HAM-A, p<0.01). No group differences were observed in cardiovascular responses to the task. **Conclusion:** Results of this study show that women with VMS have a blunted acute response to a cognitive and social stressor task. This association was more pronounced when VMS were comorbid with insomnia symptoms. These findings suggest that chronic exposure to VMS is associated with an abnormal adrenal acute stress response, similar to that observed in people with other chronic stress conditions such as PTSD.

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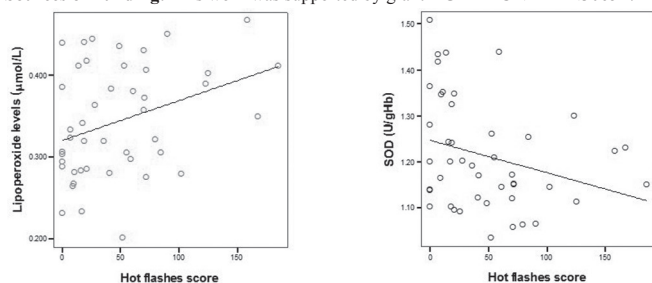
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**Liperoxide levels increase and superoxide dismutase decreases, as oxidative stress biomarkers, with hot flashes severity after menopause**

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**Objective:** To determine the relationship among different oxidative stress biomarkers and the hot flashes severity in postmenopausal women. **Design:** We carry out a cross-sectional study with 90 postmenopausal women of Mexico City, 48-57 yr (52.2±3.5 yr). We measured plasma lipoperoxides (LPO) by the TBARS assay, erythrocyte superoxide dismutase (SOD) and glutathione peroxidase (GPx), and total plasma antioxidant status with Randox kits, all as oxidative stress biomarkers. The hot flashes were evaluated by Hot Flush Weekly Weighted Score, developed and evaluated by Sloan J et al., and strengthen the concepts pictorially. In this test, the amount and intensity of the hot flashes in 24 hours, during 1 week, were registered by each woman. For the evaluation, we classified 5 categories of hot flashes intensity (0= no, 1= mild, 2= moderate, 3= severe and 4= very severe), we added the total of hot flashes per day, and then we multiplied each category by the number of times that was presented to the week. After, we obtained the scores and it was stratified into 3 groups per the intensity of the hot flashes as: mild (<17), moderate (17-59) and severe ≥60). **Results:** A positive correlation between LPO and hot flashes score was observed ( $r=0.342$ ,  $p<0.05$ ) [Figure A] and, a negative correlation between SOD and the test score ( $r=-0.286$ ,  $p<0.05$ ) [Figure B]; other oxidative stress markers were not related. LPO levels increase with hot flashes severity (mild  $0.309\pm0.06$ , moderate  $0.351\pm0.07$  and severe  $0.372\pm0.06$   $\mu\text{mol/L}$ ,  $p<0.05$ ) and SOD activity diminished (mild  $1.29\pm0.13$ , moderate  $1.19\pm0.11$  and severe  $1.16\pm0.07$  U/gHb,  $p<0.05$ ). **Conclusion:** Our findings suggest that LPO levels increase and SOD activity decreases with the severity of hot flashes, showing high oxidative stress in postmenopausal women with severe hot flashes.

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**Figure. A. Correlation between lipoperoxides levels and hot flashes score; B. SOD and hot flashes score.**