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Title of protocol

Impact of combined hormonal contraceptive on vulvar vestibule in patients with vestibulodynia: an ultrasound vestibular thickness and electrodiagnostic functional sensory evaluation

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Synopsis

Title	Impact of combined hormonal contraceptive on vulvar vestibule in patients with vestibulodynia: an ultrasound vestibular thickness and electrodiagnostic functional sensory evaluation
Type	Case-control study
Rationale and Research Hypothesis	The vulvar vestibule, a thin band of tissue marking the entrance to the vagina, contains a high density of sensory nerve endings with dense and superficial branching, making this skin highly sensitive. Vulvodynia encompasses patients experiencing vulvar pain or discomfort persisting for at least three months, often lacking clear identifiable causes but potentially associated with factors such as genetics, immune function, hormones, inflammation, and neuropathic changes. Localized provoked vulvodynia at the vestibule, referred to as vestibulodynia (VBD), represents the most prevalent form of the condition. Various factors have been proposed to contribute to the onset and/or persistence of VBD. Hypersensitivity of the vulvar vestibule stands out as a defining feature of VBD. It has been suggested that alterations in the biochemical environment may enhance peripheral pain perception, affecting nerve fiber conduction and reducing nociceptor thresholds. Combined estrogen-progestin contraception enable control over family planning, which has immense social, economic, and political impact. Although the social advantages and medical benefits and risks regarding combined oral contraceptives (COCs) are imparted in medical training, incorporated in prescribing decisions, and utilized in patient counseling, the vulvar or vestibular effects of these medications are often unknown or overlooked.

	Historically, estrogen and progesterone have been the primary focus in female physiology, and testosterone in male physiology. However, androgens are also vital hormones in females, and their role in sexual health has been under-appreciated. It has been long known that COCs reduce androgen levels, with blood levels of testosterone decreasing by up to 60% and similar decreases observed in DHEA and DHEA-S levels. The hormonal changes associated with COCs may alter the function of the vestibular glands, potentially impacting arousal, and lubrication. Not all patients respond uniformly to the same COCs; it has indeed been demonstrated that individuals with longer CAG repeats demonstrated significantly lower levels of free testosterone compared to those with shorter polymorphisms. Some studies have investigated how the intake of COCs may influence the course of vulvodynia and how formulations containing more androgenic progestins might have a worsening effect. Studies have indeed suggested that women taking COCs containing 20µg of ethinyl estradiol (EE) or less may experience increased rates of sexual arousal disorder, vaginal dryness, VBD, and low sexual desire. These findings highlight the importance of considering the potential side effects and individual responses when prescribing contraceptives. The Research Hypothesis for the present study is to assess whether different COCs can influence the course of vulvodynia in affected patients or cause any vestibular alterations in healthy controls.

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Objectives	<u>The primary objective</u> is to evaluate the effect that different COCs type may have on vulvar vestibule in patients with or without VBD in terms of: - vestibular trophism (evaluated with VeTH score), - changes vestibular thickness measured through ultrasound - evaluation of current perception threshold (CPT) testing, a technique which quantifies the sensitivity of vestibular nerve fibers. <u>The secondary objectives</u> are to assess changes after COC assumption in: - symptoms like vulvar burning/pain and dyspareunia (evaluated through a 0- 10 visual scale VAS scale), - the q-tip test (Swab test) on the vestibule on 0- 10 visual scale

Outcomes	Primary outcomes: - Vestibular trophic health (VeTH), which assessed five criteria: petechiae, pallor, thinning, dryness and redness - Vestibular thickness analyzed by ultrasound measurements (Samsung ultrasound scan with a 20 MHz probe) - CPT evaluation. The CPT values will be measured using the Neurometer CPT/C electrodiagnostic neurostimulator (Neurotron,Inc., Baltimore, MD), which emits constant alternating sinusoid waveform current stimuli at frequencies of 2000 Hz (specific for large, myelinated Ab fibers), 250 Hz (specific for Ad fibers), and 5Hz (specific for C fibers), at intensity levels from 0.001 to 9.99mA. Vulvar vestibule CPT values (1=0.01 mA) will be determined using a G-trode Vaginal/ Rectal Electrode (Neurotron, Inc., Baltimore, MD). (Murina F, Bianco V, Radici G, et al. Electrodiagnostic functional sensory evaluation of patients with generalized vulvodynia: a Pilot Study. J Low Genit Tract Dis 2010;14:221Y4.) Secondary outcomes: assessment of: - 0-10 point visual scale (VAS) related to: dyspareunia and vulvo-vaginal pain/burning - Vestibular cotton swab test (small cotton-tipped applicator lightly rolled over the surfaces of the vestibule) on 0-10 visual scale
Design	Women enrolled in this case-control study, regardless of being affected by VBD (VBD Group) or not (Control Group), will be each randomized in 5 subgroups based on the assumption of 5 differents COCs type: A. 30 μg of EE and 3 mg of drospirenone B. 20 μg of EE and 3 mg of drospirenone C. 30 μg of EE and 2 mg of dienogest D. 30 μg of EE and 100 μg of levonorgestrel E. 1,5 mg E2 and 2,5 mg of nomegestrol acetate
Inclusion Criteria	- Women who wish to undergo to COCs - Women at least 18 years of age and before the menopause (absence of menstruation for 12 months) - Women affected by VBD

Exclusion Criteria	- Active vulvo-vaginal infections at the time of their gynecological examination - Genital bleeding of unknown origin - Patients who use topical therapies for VBD - Patients concomitantly included in different interventional clinical trials - Pregnant or breastfeeding patients - Women with contraindications to assumption of COCs - Patients who have used any type of hormonal contraceptive in the last 6 months - Unwillingness to provide the informed consent to the trial
Protocol	The original intent-to treat will include a total of 150 patients, with 75 in Group 1 consisting of patients with VBD and 75 in Group 2 consisting of healthy controls. Each group will be randomized into 5 homogeneous subgroups (from A to E) based on the assumption of 5 different COCs (appendix 1): A. 30 μg of EE and 3 mg of drospirenone B. 20 μg of EE and 3 mg of drospirenone C. 30 μg of EE and 2 mg of dienogest D. 30 μg of EE and 100 μg of levonorgestrel E. 1,5 mg E2 and 2,5 mg of nomegestrol acetate

Procedures	**a) Screening and Visit 1** - Physical examination and medical history will be collected - Evaluation of symptoms: 0-10 point visual scale (VAS) related to dyspareunia and vulvo-vaginal pain/burning - Vulvoscopy with evaluation of vestibular trophic health (VeTH), which assessed five criteria: petechiae, pallor, thinning, dryness and redness - Evaluation of vestibular cotton swabtest on 0-10 visual scale - Vestibular thickness analyzed by ultrasound measurements. -Assessment of vestibular CPT evaluation using the Neurometer CPT/C, electrodiagnostic neurostimulator Subject meeting inclusion and exclusion criteria will enroll in this trial. Then women included in each group will be randomized into 5 subgroups for the assumption of different types of COCs for 3 months. b) **Visit 2 (**90 ± 15 days) - Physical examination and assessment of any adverse events. - Evaluation of symptoms: 0-10 point visual scale (VAS) related to dyspareunia and vulvo-vaginal pain/burning - Vulvoscopy with evaluation of vestibular trophic health (VeTH), which assessed five criteria: petechiae, pallor, thinning, dryness and redness - Evaluation of vestibular cotton swabtest on 0-10 visual scale - Vestibular thickness analyzed by ultrasound measurements with a 20 MHz system. -Assessment of vestibular CPT evaluation using the Neurometer CPT/C, electrodiagnostic neurostimulator

Appendix 1. Subgroup of randomization of the women enrolled.

A. COCs 30 µg of EE and 3 mg of drospirenone:

B. COCs 20 µg of EE and 3 mg of drospirenone:

C. COCs 30 µg of EE and 2 mg of dienogest: NOVADIEN

D. COCs 20 µg of EE and 100 µg of levonorgestrel: MIRANOVA O LOETTE

E. COCs 1,5 mg E2 and 2,5 mg of nomegestrol acetate: ZOELY