ORIGINAL RESEARCH—PAIN

Polymorphisms of the Androgen Receptor Gene and Hormonal Contraceptive Induced Provoked Vestibulodynia

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ABSTRACT

Aim. Women who developed vestibulodynia (vulvar vestibulitis) while taking combined hormonal contraceptives (CHCs) and a control group of women were tested for polymorphisms of the gene coding for the androgen receptor (AR) that is located on the X chromosome.

Study Design. DNA from 30 women who developed vestibulodynia while taking CHCs and 17 control women were tested for the number of cytosine–adenine–guanine (CAG) trinucleotide repeats in the AR. In addition, serum-free testosterone was tested in both groups.

Results. The mean number of CAG repeats in the study group was significantly greater than the control group (22.05 ± 2.98 vs. 20.61 ± 2.19, respectively; $P = 0.025$). This significant difference persisted when analyzing the CAG repeats from the longer allele from each subject. Among those who were taking drospirenone-containing CHCs, the mean calculated free testosterone was 0.189 ± 0.115 ng/dL in the study group and 0.127 ± 0.054 ng/dL in the control group, all of whom were taking drospirenone-containing CHCs ($P = 0.042$).

Conclusion. In the study cohort, women who developed vestibulodynia while taking CHCs are more likely to have longer CAG repeats in the AR than women who took the same type of CHC but did not develop vestibulodynia. We speculate that the risk of developing CHC-induced vestibulodynia may be due to lowered free testosterone combined with an inefficient AR that predisposes women to vestibular pain. **Goldtein AT, Belkin ZR, Krapf JM, Song W, Khera M, Jutrzonka SL, Kim NN, Burrows LJ, and Goldstein I. Polymorphisms of the androgen receptor gene and hormonal contraceptive induced provoked vestibulodynia. J Sex Med 2014;11:2764–2771.**

Key Words. Dyspareunia; Vestibulitis; Provoked Vestibulodynia; Vulva; Vulvodynia

Introduction

Provoked vestibulodynia (formerly called vulvar vestibulitis syndrome) is the most common cause of painful sexual intercourse, affecting 12% of premenopausal women in the general population [1]. Provoked vestibulodynia is characterized by severe, burning/sharp pain that occurs in response to pressure applied to the vulvar vestibule. Dyspareunia (painful intercourse) is the defining symptom of provoked vestibulodynia. The results of research examining the underlying etiology of provoked vestibulodynia can be challenging to interpret and even contradictory. As the diagnosis of provoked vestibulodynia is based on signs and symptoms, not from a defined pathophysiology, it is likely that there are multiple causes of this disorder.

This study was conducted at the Center for Vulvovaginal Disorders, Washington, DC. Genetic analysis was performed at the Baylor College of Medicine, Houston, TX.

Recent studies have elucidated at least four possible distinct subtypes of provoked vestibulodynia: (i) provoked vestibulodynia secondary to hormonal changes [2–4]; (ii) provoked vestibulodynia secondary to neuroproliferation [5,6]; (iii) provoked vestibulodynia secondary to inflammation [7–9]; and (iv) provoked vestibulodynia secondary to hypertonic pelvic floor muscles [10,11].

One potential cause of hormonally mediated provoked vestibulodynia is use of combined hormonal contraceptives (CHCs). Several studies have shown that CHC use significantly increases the risk of developing provoked vestibulodynia by four- to 11-fold [2,12,13]. In addition, it has been demonstrated that CHCs induce morphologic changes in the vestibular mucosa, making it "more vulnerable to mechanical strain" [14]. Furthermore, CHC use decreases mechanical pain thresholds in women taking them [3].

Studies have noted decreased lubrication induced by CHCs [15]. During arousal, women become lubricated through a combination of vaginal transudate of serum from the submucosal vasculature and mucin secretion from the vestibular glands which include the Bartholin's, Skene's, and minor vestibular glands. These glands are the embryologic analogues of the Cowper's glands, prostate, and the glands of Littré in males. Consequently, in women, as in men, these mucin-secreting glands are androgen dependent [16]. It is well-known that CHC use leads to a reduction in serum-free testosterone (FT) by decreasing ovarian production of total testosterone and by inducing the liver to produce increased levels of sex hormone binding globulin (SHBG) [15]. In addition, some CHCs contain synthetic progestins that act as testosterone antagonists at the androgen receptor (AR) [17]. Therefore, we postulate that due to antiandrogenic effects, CHCs may cause dysfunction of the vestibular glands, which in turn could cause provoked vestibulodynia in some women.

Testosterone exerts its effects on gene expression through the AR. The AR gene is located on the X chromosome at Xq11-12. The amino terminal transactivating domain of the AR contains a highly polymorphic cytosine–adenine–guanine (CAG) trinucleotide repeat sequence and regulates androgen signaling in steroid hormone-sensitive cells [18]. This polymorphism in the AR gene ranges in size and may contain 11–32 repeats [19]. The length of the polymorphism is *inversely* associated with androgen-induced gene transcription [20]. Specifically, fewer CAG repeats are associated with high intrinsic AR activity (e.g., a more efficient receptor), and more repeats are associated with weak AR activity. In women, mutations and polymorphisms have been identified in the AR gene that are associated with various disorders including premature ovarian failure [21,22], ovarian cancer [23], and breast cancer [24]. Therefore, we further postulate that certain polymorphisms in the AR gene (i.e., AR with more CAG repeats) might predispose women to develop provoked vestibulodynia while on CHCs. This study was designed to differentiate between the number of CAG repeats in the AR in women who developed provoked vestibulodynia while taking CHCs vs. women taking CHCs who have not developed provoked vestibulodynia.

Study Design and Methods

This study comprised two groups of women: a study group and a control group. The study group consisted of 30 women with provoked vestibulodynia secondary to hormonal changes and who were referred by the faculty of the medical center. Women in this group developed provoked vestibulodynia while taking CHCs and had resolution of symptoms with cessation of CHCs and treatment with topical estradiol and testosterone applied to the vestibule (Figure 1). All women in this group were taking CHCs at their initial presentation. Of these 30 women, 21 were taking a CHC that contained the progestin drospirenone.

The control group consisted of 17 women who were currently taking CHCs containing the progestin drospirenone and who did neither complain of dyspareunia nor show any evidence of provoked vestibulodynia on physical exam. Subjects were recruited from healthy women coming for routine gynecological exams that included general medical history; reproductive history; breast examination; abdominal examination; inspection of the external genitalia, vagina, and cervix; bimanual examination of the uterus and adnexa; and appropriate testing which may have included a Pap smear, vaginal cultures, and testing for sexually transmitted infections. Control subjects were of similar age as the study group. No extraordinary measures were taken in recruiting this group as women using hormonal contraceptives commonly fall within this age range.

Women were excluded from the study if they had any known hormonal disease that might affect serum estradiol or testosterone, such as polycystic